DAVID Y. IGE
GOVERNOR

VIRGINIA PRESSLER, M.D.
DIRECTOR OF HEALTH

State of Hawaii
DEPARTMENT OF HEALTH
1250 Punchbowl Street
Honolulu, HI 96813-2416
doh.testimony@doh.hawaii.gov

Testimony in SUPPORT of HB0585
RELATING TO THE REGULATION OF ELECTRONIC SMOKING DEVICES

REPRESENTATIVE DELLA AU BELATTI, CHAIR
HOUSE COMMITTEE ON HEALTH
Hearing Date: January 30, 2015 Room Number: 329

Fiscal Implications: None

Department Testimony: The Department of Health (DOH) supports this measure, which prohibits the use of electronic smoking devices (ESDs) in places where smoking is already illegal and also updates signage requirements. The public health concern is for the protection from the unregulated use of these potentially hazardous products.

The use of ESDs in existing smoke-free locations has the potential to expose non-smokers and vulnerable populations such as children and pregnant women to aerosolized nicotine and other toxic substances. ESDs pose serious threats to adolescents and fetuses.[1] The use of ESDs in traditionally smoke-free areas causes confusion in the enforcement of smoke-free laws; it creates distractions in work environments; and it renormalizes smoking behavior.

The revised definitions are consistent with *Sottera, Inc. v. U.S. Food ond Drug Administration* (FDA), 627 F.3d 891 (D.C. Cir. 2010) case ruling, upheld on appeal in the U.S. court, which found that the FDA does have the authority to regulate electronic smoking devices or any product made or derived from tobacco that is intended for human consumption as tobacco products. The federal government has determined that electronic smoking devices are considered tobacco products.

ESDs have become increasingly prevalent and widely available since their introduction to the U.S. market. Since 2005, the ESD industry has grown from one manufacturer in China to an estimated market value of $3 billion in global business with 466 brands. It has become a profitable business that the tobacco industry is gradually taking over.

ESDs produce an aerosol that is not merely "water vapor." The aerosol contains several carcinogens, such as formaldehyde, acetaldehyde, lead, nickel, and chromium and other hazardous

[1] World Health Organization (2014) Electronic nicotine delivery systems: Report of the Conference to the WHO Framework Convention on Tobacco Control Sixth Session, October 13-18, 2014 Moscow Russian Federation. Provisional agenda 4.4.2 Available at: http://apps.who.int/gb/fctc/PDF/cop6/FCTC_COP6_10-en.pdf

substances cited by the Agency for Toxic Substances and Disease Registry which are associated with a range of negative health effects such as skin, eye, and respiratory irritation.[2,3,4,5,6] In recent months, significant international research has increased the understanding of ESDs as harmful, carcinogenic devices. In November 2014, researchers at the Japanese Ministry of Health announced that they found ESDs contained greater levels of cancer-causing agents than found in traditional cigarettes.[7]

ESD companies, and their parent tobacco companies, encourage their use "anywhere," and promote their social acceptability. The World Health Organization has called for the regulation of ESDs and urges that their use indoors be "banned" until exhaled vapor is proven to be not harmful to bystanders and reasonable evidence exists that smoke-free policy enforcement is not undermined.[8]

The FDA currently does not have the authority to regulate where ESDs are used; that is the domain of state and local governments. To protect the health of the public, and provide clarity on smoke-free regulations, 274 municipalities and three states have now included ESDs in their smoke-free laws. In January 2014, the DOH adopted its own internal policy banning ESD use on all DOH properties and occupied premises. As of September 2014, the State Department of Accounting and General Services further prohibited ESD use in and around all state buildings under its jurisdiction. Most recently, Hawaii County enacted Bill 302, prohibiting the use of ESDs wherever tobacco products are already illegal, and there currently is a similar bill being heard by the City and County of Honolulu.

The DOH supports this measure to provide protection from ESDs for the state. The proposed revision in signage is appropriate, and the DOH will assist in the public education and distribution of the new signs.

Offered Amendments: None.

Thank you for the opportunity to testify.

---

[2] Jensen, R. et al. (2015). Hidden Formaldehyde in E-Cigarette Aerosols. New England Journal of Medicine 2015;372:392-394. Available at : *www.nejm.org/doi/full/10.1056/NEJMc1413069*

[3] Lerner, C.A., et al. (2015). Environmental health hazards of e-cigarettes and their components: Oxidants and copper in e-cigarette aerosols
Environ Pollut. 2015 Jan 8;198C:100-107

[3] State of California Environmental Protection Agency Office of Environmental Health Hazard Assessment Safe Drinking Water and Toxic Enforcement Act of 1986. (2013). Chemicals known to the State of California to cause cancer or reproductive toxicity. Available at: *http://oehha.ca.gov/prop65/prop65_list/files/P65single091313.pdf*

[5] German Cancer Research Center. (2013). Red Series Tobacco Prevention and Tobacco Control Volume 19: Electronic Cigarettes - An Overview. Available at:
www.dkfz.de/de/tabakkontrolle/download/Publikationen/RoteReihe/Band_19_ecigarettes_an_overview.pdf

[6] Goniewicz, M. et al. (2013). Levels of selected carcinogens and toxicants in vapour from electronic cigarettes. Tob. Control. 1:1–8. Available at: *www.ncbi.nlm.nih.gov/pubmed/23467656*

[7] AFP, November 27, 2014. Scientists Say E-Cigs Contain 10 Times As Many Cancer Chemicals As Cigarettes. Retrieved from http://www.businessinsider.com/afp-e-cigarettes-contain-10-times-amount-of-carcinogens-japan-2014-11

[8] World Health Organization (see footnote 1).

UNIVERSITY OF HAWAI'I SYSTEM
Legislative Testimony

Written Testimony Presented Before the
House Committee on Health
January 30, 2015, 10:10 am
By
Robert Bley-Vroman, Chancellor
and
Jerris Hedges, MD, MS, MMM
Dean, John A. Burns School of Medicine
Interim Director, University of Hawai'i Cancer Center
University of Hawai'i at Mānoa

HB 585 – RELATING TO THE REGULATION OF ELECTRONIC SMOKING DEVICES

Chair Belatti, Vice Chair Creagan, and Members of the Committee:

The University of Hawai'i at Mānoa John A. Burns School of Medicine and the University of Hawai'i Cancer Center support this bill.

The UH Cancer Center is one of only 68 institutions in the U.S. that hold the prestigious National Cancer Institute (NCI) designation, and is the only NCI-designated center in the Pacific. The NCI designation provides greater access to federal funding and research opportunities. More importantly, it gives the people of Hawai'i and the Pacific region access to innovative and potentially life-saving clinical trials without the necessity of traveling to the mainland.

Our passion at the UH Cancer Center is to be a world leader in eliminating cancer through research, education, and improved patient care. Because tobacco consumption is a leading preventable cause of cancer, we take all issues related to tobacco in Hawai'i very seriously. Whereas the UH Cancer Center always has supported strong tobacco control measures in Hawai'i, the recent emergence of e-cigarettes presents new challenges for tobacco control and tobacco-related legislation.

Our perspective on e-cigarettes is informed by the scientific literature, including original published research by our own faculty. Despite the complexities of the larger debate regarding e-cigarettes, we believe this bill represents reasonable legislation that balances the rights of adults to use e-cigarettes in appropriate venues while restricting the use of e-cigarettes in public places where conventional cigarettes also are banned.

As scientific research on e-cigarettes progresses, we will have a stronger basis to adjust laws according to evidence. At the present time, however, caution is warranted. As others have noted, the FDA currently does not regulate e-cigarettes, and thus the consumer has no assurances regarding e-cigarette ingredients. Further, because of the novelty of e-cigarettes, the long term effects of using these devices are unknown. A further concern, not often discussed, is the potential for e-cigarettes to be used as drug delivery devices for substances other than nicotine.

For these reasons, we respectfully urge you to pass this bill.

January 29, 2015

To: The Honorable Representative Della Au Belatti, Chair
Members, House Committee on Health

From: Cory Smith, VOLCANO Fine Electronic Cigarettes®
CEO and Owner

RE: HB 585 – oppose.

Thank you for the opportunity to submit testimony.

VOLCANO Fine Electronic Cigarettes® is the largest manufacturer and retailer of vapor products (commonly referred to as "electronic cigarettes") and vaping accessories in the State of Hawaii. We currently own and operate 11 locations statewide and employ over 100 full-time workers to support sales of our products not only here in Hawaii, but to all 50 states as well as Japan and the UK. We stand in opposition to HB 585 for the following:

- Although electronic cigarettes emit NO smoke, the bill **falsely defines vapor products as "electronic smoking devices" and deceptively redefines "smoking" to include the use of electronic cigarettes** in an attempt to restrict their usage in the same places as tobacco cigarettes. Vapor products contain no tobacco, produce no smoke, and have not been demonstrated to have the detrimental effects of combustible tobacco products. In fact, the FDA has taken appropriate and proportional regulation seriously and to date has not issued regulations for the product because they seemingly understand the potential this product has to switch people over from actual tobacco, which kills 480,000 people per year. Further, Mitch Zeller, Director of the Center for Tobacco Products at the FDA recently stated:
    - "If a current smoker, otherwise unable or unwilling to quit, completely substituted all of the combusting cigarettes that they smoked with an electronic cigarette at the individual level, that person would probably be significantly reducing their risk." (http://thedianerehmshow.org/shows/2014-01-21/new-health-risks-cigarette-smoking/transcript)

- In sharp contrast to indoor smoke free policies/laws (which are largely self enforced because of broad public support), please note that **it is also impossible to enforce an e-cigarette usage ban** (since the products can be used discreetly without anyone else knowing). By simply waiting a few seconds before exhaling, no visible vapor is exhaled by e-cigarette users, and as such, nobody will know that anyone is even using an e-cigarette. Despite widespread usage in

cities and states that have banned e-cigarette use where smoking is banned, there is no record of any fine or citation being given. **Enacting unwarranted and unenforceable regulations carries the risk of unintended consequences like sending former smokers back to combustible tobacco products; harming their health and undermining the mandate of the state to promote viable alternatives to known killers.**

- Numerous studies conducted on e-cigarettes have found that e-cigarettes emit no hazardous levels of any constituents, and that levels of nitrosamines in e-cigarettes are nearly identical (i.e. very little if any) to those in nicotine gums and patches. Those studies are attached to this presentation.
    - Burstyn, I. Peering through the mist: What does the chemistry of contaminants in electronic cigarettes tell us about health risks? *BMC Public Health.* January 2014. (concluding that there is no risk to bystanders exposed to electronic cigarette vapor) http://www.biomedcentral.com/1471-2458/14/18/abstract
    - Goniewicz ML, et al. Levels of selected carcinogens and toxicants in vapour from electronic cigarettes. *Tobacco Control*. March 2013. (testing of the vapor from twelve different electronic cigarettes, cigarette smoke, and the aerosol of the FDA-approved nicotine inhaler revealed that electronic cigarette vapor contains 9-450x less toxicants and chemicals when compared to secondhand smoke, with the authors noting that the trace levels present were comparable to what is released from the nicotine inhaler) http://tobaccocontrol.bmj.com/content/early/2013/03/05/tobaccocontrol-2012-050859.abstract
    - Siegel, M, et. al. Electronic cigarettes as a harm reduction strategy for tobacco control: A step forward or a repeat of past mistakes. Journal of Public Health Policy. December 2010. (reviewing the evidence and concluding that there is no evidence electronic cigarettes pose risks to users and bystanders that is in any way comparable to cigarettes) http://www.palgrave-journals.com/jphp/journal/v32/n1/full/jphp201041a.html
    - Trehy, et. al. Analysis of electronic cigarette cartridges, refill solutions, and smoke for nicotine and nicotine related impurities. August 2011. (finding no harmful levels of any chemical in electronic cigarettes) http://www.tandfonline.com/doi/abs/10.1080/10826076.2011.572213

Thank you for your time and consideration. If you have any questions, please feel free to contact me or Volcano's representative Celeste Nip at nipfire@me.com.

Sincerely,
Cory Smith
CEO and Owner

VOLCANO Fine Electronic Cigarettes®

1003 Sand Island Access Rd. Suite #1260, Honolulu, HI 96813

BMC Public Health

BioMed Central
The Open Access Publisher

Peering through the mist: systematic review of what the chemistry of contaminants in electronic cigarettes tells us about health risks

BMC Public Health 2014, **14**:18 doi:10.1186/1471-2458-14-18

Igor Burstyn (igor.burstyn@drexel.edu)

ISSN 1471-2458

Article type Research article

Submission date 26 August 2013

Acceptance date 2 January 2014

Publication date 9 January 2014

Article URL http://www.biomedcentral.com/1471-2458/14/18

Peering through the mist: systematic review of what the chemistry of contaminants in electronic cigarettes tells us about health risks

Igor Burstyn[1*]
[*] Corresponding author
Email: igor.burstyn@drexel.edu

[1] Department of Environmental and Occupational Health, School of Public Health, Drexel University, Nesbitt Hall, 3215 Market St. Floor 6, Office 614, Philadelphia, PA 19104, USA

Abstract

Background

Electronic cigarettes (e-cigarettes) are generally recognized as a safer alternative to combusted tobacco products, but there are conflicting claims about the degree to which these products warrant concern for the health of the vapers (e-cigarette users). This paper reviews available data on chemistry of aerosols and liquids of electronic cigarettes and compares modeled exposure of vapers with occupational safety standards.

Methods

Both peer-reviewed and "grey" literature were accessed and more than 9,000 observations of highly variable quality were extracted. Comparisons to the most universally recognized workplace exposure standards, Threshold Limit Values (TLVs), were conducted under "worst case" assumptions about both chemical content of aerosol and liquids as well as behavior of vapers.

Results

There was no evidence of potential for exposures of e-cigarette users to contaminants that are associated with risk to health at a level that would warrant attention if it were an involuntary workplace exposures. The vast majority of predicted exposures are < <1% of TLV. Predicted exposures to acrolein and formaldehyde are typically <5% TLV. Considering exposure to the aerosol as a mixture of contaminants did not indicate that exceeding half of TLV for mixtures was plausible. Only exposures to the declared major ingredients -- propylene glycol and glycerin -- warrant attention because of precautionary nature of TLVs for exposures to hydrocarbons with no established toxicity.

Conclusions

Current state of knowledge about chemistry of liquids and aerosols associated with electronic cigarettes indicates 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*) creates personal exposures that would justify surveillance of health among exposed persons in conjunction with investigation of means to keep any adverse health effects as low as reasonably achievable. Exposures of bystanders are likely to be orders of magnitude less, and thus pose no apparent concern.

Keywords

Vaping, e-cigarettes, Tobacco harm reduction, Risk assessment, Aerosol, Occupational exposure limit

Background

Electronic cigarettes (also known as e-cigarettes) are generally recognized as a safer alternative to combusted tobacco products (reviewed in [1]), but there are conflicting claims about the degree to which these products warrant concern for the health of the vapers (e-cigarette users). A vaper inhales aerosol generated during heating of liquid contained in the e-cigarette. The technology and patterns of use are summarized by Etter [1], though there is doubt about how current, complete and accurate this information is. Rather conclusive evidence has been amassed to date on comparison of the chemistry of aerosol generated by electronic cigarettes to cigarette smoke [2-8]. However, it is meaningful to consider the question of whether aerosol generated by electronic cigarettes would warrant health concerns on its own, in part because vapers will include persons who would not have been smokers and for whom the question of harm reduction from smoking is therefore not relevant, and perhaps more importantly, simply because there is value in minimizing the harm of those practicing harm reduction.

One way of approaching risk evaluation in this setting is to rely on the practice, common in occupational hygiene, of relating the chemistry of industrial processes and the emissions they generate to the potential worst case of personal exposure and then drawing conclusions about whether there would be interventions in an occupational setting based on comparison to occupational exposure limits, which are designed to ensure safety of unintentionally exposed individuals. In that context, exposed individuals are assumed to be adults, and this assumption appears to be suitable for the intended consumers of electronic cigarettes. “Worst case” refers to the maximum personal exposure that can be achieved given what is known about the process that generates contaminated atmosphere (in the context of airborne exposure considered here) and the pattern of interaction with the contaminated atmosphere. It must be noted that harm reduction notions are embedded in this approach since it recognizes that while elimination of the exposure may be both impossible and undesirable, there nonetheless exists a level of exposure that is associated with negligible risks. To date, a comprehensive review of the chemistry of electronic cigarettes and the aerosols they generate has not been conducted, depriving the public of the important element of a risk-assessment process that is mandatory for environmental and occupational health policy-making.

The present work considers both the contaminants present in liquids and aerosols as well as the declared ingredients in the liquids. The distinction between exposure to declared ingredients and contaminants of a consumer product is important in the context of comparison to occupational or environmental exposure standards. Occupational exposure limits are developed for unintentional exposures that a person does not elect to experience. For example, being a bread baker is a choice that does not involve election to be exposed to

substances that cause asthma that are part of the flour dust (most commonly, wheat antigens and fungal enzymes). Therefore, suitable occupational exposure limits are created to attempt to protect individuals from such risk on the job, with no presumption of "assumed risk" inherent in the occupation. Likewise, special regulations are in effect to protect persons from unintentional exposure to nicotine in workplaces (http://www.cdc.gov/niosh/docs/81-123/pdfs/0446.pdf; accessed July 12, 2013), because in environments where such exposures are possible, it is reasonable to protect individuals who do not wish to experience its effects. In other words, occupational exposure limits are based on protecting people from involuntary and unwanted exposures, and thus can be seen as more stringent than the standards that might be used for hazards that people intentionally choose to accept.

By contrast, a person who elects to lawfully consume a substance is subject to different risk tolerance, as is demonstrated in the case of nicotine by the fact that legally sold cigarettes deliver doses of nicotine that exceed occupational exposure limits [9]: daily intake of 20 mg of nicotine, assuming nearly 100% absorption in the lungs and inhalation of 4 m^3 of air, corresponds to roughly 10 times the occupational exposure limit of 0.5 mg/m^3 atmosphere over 8 hours [10]. Thus, whereas there is a clear case for applicability of occupational exposure limits to contaminants in a consumer product (e.g. aerosol of electronic cigarettes), there is no corresponding case for applying occupational exposure limits to declared ingredients desired by the consumer in a lawful product (e.g. nicotine in the aerosol of an electronic cigarette). Clearly, some limits must be set for voluntary exposure to compounds that are known to be a danger at plausible doses (e.g. limits on blood alcohol level while driving), but the regulatory framework should reflect whether the dosage is intentionally determined and whether the risk is assumed by the consumer. In the case of nicotine in electronic cigarettes, if the main reason the products are consumed is as an alternative source of nicotine compared to smoking, then the only relevant question is whether undesirable exposures that accompany nicotine present health risks, and the analogy with occupational exposures holds. In such cases it appears permissible to allow at least as much exposure to nicotine as from smoking before admitting to existence of new risk. It is expected that nicotine dosage will not increase in switching from smoking to electronic cigarettes because there is good evidence that consumers adjust consumption to obtain their desired or usual dose of nicotine [11]. The situation is different for the vapers who want to use electronic cigarettes without nicotine and who would otherwise not have consumed nicotine. For these individuals, it is defensible to consider total exposure, including that from any nicotine contamination, in comparison to occupational exposure limits. In consideration of vapers who would never have smoked or would have quit entirely, it must be remembered that the exposure is still voluntary and intentional, and comparison to occupational exposure limits is legitimate only for those compounds that the consumer does not elect to inhale.

The specific aims of this review were to:

1. Synthesize evidence on the chemistry of liquids and aerosols of electronic cigarettes, with particular emphasis on the contaminants.
2. Evaluate the quality of research on the chemistry of liquids and aerosols produced by electronic cigarettes.
3. Estimate potential exposures from aerosols produced by electronic cigarettes and compare those potential exposures to occupational exposure standards.

Methods

Literature search

Articles published in peer-reviewed journals were retrieved from *PubMed* (http://www.ncbi.nlm.nih.gov/pubmed/) available as of July 2013 using combinations of the following keywords: “electronic cigarettes”, “e-cigarettes”, “smoking alternatives”, “chemicals”, “risks”, “electronic cigarette vapor”, “aerosol”, “ingredients”, “e-cigarette liquid”, “e-cig composition”, “e-cig chemicals”, “e-cig chemical composition”, “e-juice electronic cigarette”, “electronic cigarette gas”, “electronic cigars”. In addition, references of the retrieved articles were examined to identify further relevant articles, with particular attention paid to non-peer reviewed reports and conference presentations. Unpublished results obtained through personal communications were also reviewed. The Consumer Advocates for Smoke-free Alternatives Association (CASAA) was asked to review the retrieved bibliography to identify any reports or articles that were missed. The papers and reports were retained for analysis if they reported on the chemistry of e-cigarette liquids or aerosols. No explicit quality control criteria were applied in selection of literature for examination, except that secondary reporting of analytical results was not used. Where substantial methodological problems that precluded interpretation of analytical results were noted, these are described below. For each article that contained relevant analytical results, the compounds quantified, limits of detection, and analytical results were summarized in a spreadsheet. Wherever possible, individual analytical results (rather than averages) were recorded (see Additional file 1). Data contained in Additional file 1 is not fully summarized in the current report but can be used to investigate a variety of specific questions that may interest the reader. Each entry in Additional file 1 is identified by a *Reference Manage ID* that is linked to source materials in a list in Additional file 2 (linked via *RefID*); copies of all original materials can be requested.

Comparison of observed concentrations in aerosol to occupational exposure limits

For articles that reported mass or concentration of specific compounds in the aerosol (generated by smoking machines or from volunteer vapers), measurements of compounds were converted to concentrations in the “personal breathing zone”,[a] which can be compared to occupational exposure limits (OELs). The 2013 Threshold Limit Values (TLVs) [10] were used as OELs because they are the most up to date and are most widely recognized internationally when local jurisdictions do not establish their own regulations (see http://www.ilo.org/oshenc/part-iv/occupational-hygiene/item/575; accessed July 3, 2013). TLVs are more protective that of US Occupation Safety and Health Administration’s Permissible Exposure Limits because TLVs are much more often updated with current knowledge. However, all OELs generally agree with each other because they are based on the same body of knowledge. TLVs (and all other OELs) aim to define environmental conditions to which nearly all persons can be exposed to all day over many years without experiencing adverse health effects. Whenever there was an uncertainty in how to perform the calculation, a “worst case” scenario was used, as is the standard practice in occupational hygiene, where the initial aim is to recognize potential for hazardous exposures and to err on the side of caution. The following assumptions were made to enable the calculations that approximate the worst-case personal exposure of a vaper (Equation 1):

1. Air the vaper breathes consists of a small volume of aerosol generated by e-cigarettes that contains a specific chemical plus pristine air;
2. The volume of aerosols inhaled from e-cigarettes is small compared to total volume of air inhaled;
3. The period of exposure to the aerosol considered was 8 hours for comparability to the standard working shift for which TLVs were developed (this does not mean only 8 hours worth of vaping was considered but, rather, a day's worth of exposure was modeled as being concentrated into just 8 hours;
4. Consumption of 150 puffs in 8 hours (an upper estimate based on a rough estimate of 150 puffs by a typical vaper in a day [1]) was assumed. (Note that if vaping over 16 hours "day" was considered then air into which contaminants from vaping are diluted into would have to increase by a factor of 2, thereby lowering estimated exposure; thus, the adopted approach is entirely still in line with "worst case" assessment.);
5. Breathing rate is 8 liters per minute [12,13];
6. Each puff contains the same quantity of compounds studied.

$$\left[\text{mg}/\text{m}^3\right] = \text{mg}/\text{puff} \times \text{puffs}/\left(8\,\text{hr day}\right) \times 1/\left(\text{m}^3\text{air inhaled in 8 hr}\right) \quad (1)$$

The only exception to this methodology was when assessing a study of aerosol emitted by 5 vapers in a 60 m^3 room over 5 hours that seemed to be a sufficient approximation of worst-case "bystander" exposure [6]. All calculated concentrations were expressed as the most stringent (lowest) TLV for a specific compound (i.e. assuming the most toxic form if analytical report is ambiguous) and expressed as "percent of TLV". Considering that all the above calculations are approximate and reflecting that exposures in occupational and general environment can easily vary by a factor of 10 around the mean, we added a 10-fold safety factor to the "percent of TLV" calculation. This safety factor accounts for considerable uncertainty about the actual number and volume of puffs since the number of puffs is hard to estimate accurately with reports as high as 700 puffs per day Farsalinos [14]. Details of all calculations are provided in an Excel spreadsheet (see Additional file 3).

No systematic attempt was made to convert the content of the studied liquids into potential exposures because sufficient information was available on the chemistry of aerosols to use those studies rather than making the necessary simplifying assumptions to do the conversion. However, where such calculations were performed in the original research, the following approach was used: under the (probably false – see the literature on formation of carbonyl compounds below) assumption of no chemical reaction to generate novel ingredients, composition of liquids can be used to estimate potential for exposure if it can be established how much volume of liquid is consumed in given 8 hours, following an algorithm analogous to the one described above for the aerosols (Equation 2):

$$\left[\text{mg}/\text{m}^3\right] = \text{mg}/\left(\text{mL liquid}\right) \times \left(\text{mL liquid}\right)/\text{puff} \times \text{puffs}/\left(8\text{ hr day}\right) \times 1/\left(\text{m}^3\text{air inhaled in 8 hr}\right) \quad (2)$$

Comparison to cigarette smoke was not performed here because the fact that e-cigarette aerosol is at least orders of magnitude less contaminated by toxic compounds is uncontroversial [2-8].

The study adhered to the PRISMA guidelines for systematic reviews (http://www.prisma-statement.org/).

Results and discussion

General comments on methods

In excess of 9,000 determinations of single chemicals (and rarely, mixtures) were reported in reviewed articles and reports, typically with multiple compounds per electronic cigarette tested [2-8,15-43]. 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 e-cigarette liquids and aerosols. The only report that was excluded from consideration was work of McAuley et al. [24] 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 polycyclic aromatic hydrocarbons (PAH) are not since it is incredible that cigarette smoke would contain fewer PAHs, which arise from incomplete combustion of organic matter, than aerosol of e-cigarettes that do not burn organic matter [24]. 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. When in doubt, we erred on the side of trusting that proper quality controls were in place, a practice that is likely to increase appearance of atypical or erroneous results in this review. From this perspective, assessment of concordance among independent reports gains higher importance than usual since it is unlikely that two experiments would be flawed in the same exact manner (though of course this cannot be assured).

It was judged that the simplest form of publication bias – disappearance of an entire formal study from the available literature – was unlikely given the exhaustive search strategy and the contested nature of the research question. It is clearly the case that only a portion of all industry technical reports were available for public access, so it is possible that those with more problematic results were systematically suppressed, though there is no evidence to support this speculation. No formal attempt was made to ascertain publication bias *in situ* though it is apparent that anomalous results do gain prominence in typical reviews of the literature: diethylene glycol [44,45] detected at non-dangerous levels (see details below) in one test of 18 of early-technology products by the US Food and Drugs Administration (FDA) [23] and one outlier in measurement of formaldehyde content of exhaled air [4] and aldehydes in aerosol generated from one e-cigarette in Japan [38]. It must be emphasized that the alarmist report of aldehydes in experiments presented in [38] is based on the concentration in generated aerosol rather than air inhaled by the vaper over prolonged period of time (since vapers do not inhale only aerosol). Thus, results reported in [38] cannot be the basis of any claims about health risk, a fallacy committed both by the authors themselves and commentators on this work [45].

It was also unclear from [38] what the volume of aerosol sampled was – a critical item for extrapolating to personal exposure and a common point of ambiguity in the published reports. However, in a personal exchange with the authors of [38] [July 11, 2013], it was clarified that the sampling pump drew air at 500 mL/min through e-cigarette for 10 min, allowing more appropriate calculations for estimation of health risk that are presented below. Such misleading reporting is common in the field that confuses concentration in the aerosol (typically measured directly) with concentration in the air inhaled by the vaper (never determined directly and currently requiring additional assumptions and modeling). This is

important because the volume of aerosol inhaled (maximum ~8 L/day) is small compared to the volume of air inhaled daily (8 L/min); this point is illustrated in the Figure 1.

Figure 1 Illustrating the difference between concentrations in the aerosol generated by vaping and inhaled air in a day. *Panel **A*** shows a black square that represents aerosol contaminated by some compound as it would be measured by a "smoking machine" and extrapolated to dosage from vaping in one day. This black square is located inside the white square that represents total uncontaminated air that is inhaled in a day by a vaper. The relative sizes of the two squares are exaggerated as the volume of aerosol generated in vaping relative to inhaled air is much smaller than is illustrated in the figure. *Panel **B*** shows how exposure from contaminated air (black dots) is diluted over a day for appropriate comparison to occupational exposure limits that are expressed in terms of "time-weighted average" or average contamination over time rather than as instantaneous exposures. Exposure during vaping occurs in a dynamic process where the atmosphere inhaled by the vaper alternates between the smaller black and larger white squares in *Panel **A***. Thus, the concentration of contaminants that a vaper is exposed to over a day is much smaller than that which is measured in the aerosol (and routinely improperly cited as reason for concern about "high" exposures).

A similar but more extreme consideration applies to the exposure of bystanders which is almost certainly several orders of magnitude lower than the exposure of vapers. In part this is due to the absorption, rather than exhalation, of a portion of the aerosol by the vapers: there is no equivalent to the "side-stream" component of exposure to conventional cigarettes, so all of the exposure to a bystander results from exhalation. Furthermore, any environmental contamination that results from exhalation of aerosol by vaper will be diluted into the air prior to entering a bystander's personal breathing zone. Lastly, the number of puffs that affect exposure to bystander is likely to be much smaller than that of a vaper unless we are to assume that vaper and bystander are inseparable.

It is unhelpful to report the results in cigarette-equivalents in assessments that are not about cigarette exposure, as in [43], because this does not enable one to estimate exposures of vapers. To be useful for risk assessment, the results on the chemistry of the aerosols and liquids must be reported in a form that enables the calculations in Equations 1 and 2. It must be also be noted that typical investigations consisted of qualitative and quantitative phases such that quantitative data is available mostly on compounds that passed the qualitative screen. In the qualitative phase, presence of the compounds above a certain limit of detection is determined. In the quantitative phase, the amount of only the compounds that are detected in the qualitative phase is estimated. This biased all reports on concentration of compounds towards both higher levels and chemicals which a particular lab was most adept at analyzing.

Declared Ingredients: comparison to occupational exposure limits

Propylene glycol and glycerin

Propylene glycol and glycerin have the default or precautionary 8-hour TLV of 10 mg/m^3 set for all organic mists with no specific exposure limits or identified toxicity (http://www.osha.gov/dts/chemicalsampling/data/CH_243600.html; accessed July 5, 2013). These interim TLVs tend to err on the side of being too high and are typically lowered if evidence of harm to health accumulates. For example, in a study that related exposure of theatrical fogs (containing propylene glycol) to respiratory symptoms [46], "mean personal

inhalable aerosol concentrations were 0.70 mg/m^3 (range 0.02 to 4.1)" [47]. The only available estimate of propylene concentration of propylene glycol in the aerosol indicates personal exposure on the order of 3–4 mg/m^3 in the personal breathing zone over 8 hours (under the assumptions we made for all other comparisons to TLVs) [2]. The latest (2006) review of risks of occupational exposure to propylene glycol performed by the Health Council of the Netherlands (known for OELs that are the most protective that evidence supports and based exclusively on scientific considerations rather than also accounting for feasibility as is the case for the TLVs) recommended exposure limit of 50 mg/m^3 over 8 hours; concern over short-term respiratory effects was noted [http://www.gezondheidsraad.nl/sites/default/files/200702OSH.pdf; accessed July 29, 2013]. Assuming extreme consumption of the liquid per day via vaping (5 to 25 ml/day and 50-95% propylene glycol in the liquid)[b], levels of propylene glycol in inhaled air can reach 1–6 mg/m^3. It has been suggested that propylene glycol is very rapidly absorbed during inhalation [4,6] making the calculation under worst case scenario of all propylene glycol becoming available for inhalation credible. It must also be noted that when consuming low-nicotine or nicotine-free liquids, the chance to consume larger volumes of liquid increases (large volumes are needed to reach the target dose or there is no nicotine feedback), leading to the upper end of propylene glycol and glycerin exposure. Thus, estimated levels of exposure to propylene glycol and glycerin are close enough to TLV to warrant concern. However, it is also important to consider that propylene glycol is certainly not all absorbed because visible aerosol is exhaled in typical vaping. Therefore, the current calculation is in the spirit of a worst case assumption that is adopted throughout the paper.

Nicotine

Nicotine is present in most e-cigarette liquids and has TLV of 0.5 mg/m^3 for average exposure intensity over 8 hours. If approximately 4 m^3 of air is inhaled in 8 hours, the consumption of 2 mg nicotine from e-cigarettes in 8 hours would place the vaper at the occupational exposure limit. For a liquid that contains 18 mg nicotine/ml, TLV would be reached upon vaping ~0.1-0.2 ml of liquid in a day, and so is achieved for most anyone vaping nicotine-containing e-cigarettes [1]. Results presented in [25] on 16 e-cigarettes also argue in favor of exceedance of TLV from most any nicotine-containing e-cigarette, as they predict >2 mg of nicotine released to aerosol in 150 puffs (daily consumption figure adopted in this report). But as noted above, since delivery of nicotine is the purpose of nicotine-containing e-cigarettes, the comparison to limits on unintended, unwanted exposures does not suggest a problem and serves merely to offer complete context. If nicotine is present but the liquid is labeled as zero-nicotine [25,44], it could be treated as a contaminant, with the vaper not intending to consume nicotine and the TLV, which would be most likely exceeded, is relevant. However, when nicotine content is disclosed, even if inaccurately, then comparison to TLV is not valid. Accuracy in nicotine content is a concern with respect to truth in advertising rather than unintentional exposure, due to presumed (though not yet tested) self-regulation of consumption by persons who use e-cigarettes as a source of nicotine.

Overall, the declared ingredients in the liquid would warrant a concern by standards used in occupational hygiene, provided that comparison to occupational exposure limits is valid, as discussed in the introduction. However, this is not to say that the exposure is affirmatively believed to be harmful; as noted, the TLVs for propylene glycol and glycerin mists is based on uncertainty rather than knowledge. These TLVs are not derived from knowledge of toxicity of propylene glycol and glycerin mists, but merely apply to any compound of no known toxicity present in workplace atmosphere. This aspect of the exposure from e-

cigarettes simply has little precedent (but see study of theatrical fogs below). Therefore, the exposure will provide the first substantial collection evidence about the effects, which calls for monitoring of both exposure levels and outcomes, even though there are currently no grounds to be concerned about the immediate or chronic health effects of the exposure. The argument about nicotine is presented here for the sake of completeness and consistency of comparison to TLVs, but in itself does not affect the conclusions of this analysis because it should not be modeled as if it were a contaminant when declared as an ingredient in the liquid.

Contaminants

Polycyclic aromatic hydrocarbons

Polycyclic aromatic hydrocarbons (PAH) were quantified in several reports in aerosols [5,6,43] and liquids [7,19,42]. These compounds include well-known carcinogens, the levels of which are not subject to TLV but are instead to be kept "as low as reasonably achievable" [10]. For PAH, only non-carcinogenic pyrene that is abundant in the general environment was detected at 36 ng/cartridge in 5 samples of liquid [7]; PAHs were not detected in most of the analyses of aerosols, except for chrysene in the analysis of the aerosol of one e-cigarette [43].

Tobacco-specific nitrosamines

The same risk assessment considerations that exist for PAH also hold for carcinogenic tobacco-specific nitrosamines (TSNAs) [48] for which no occupational exposure limits exist because (a) these exposures do not appear to occur in occupational settings often enough to warrant development of TLVs, and (b) it is currently accepted in establishing TLVs that carcinogens do not have minimal thresholds of toxicity. As expected, because the TSNAs are contaminants of nicotine from tobacco leaf, there is also evidence of association between nicotine content of the liquid and TSNA concentrations, with reported concentrations <5 ng/cartridge tested [7]. Smaller studies of TSNA content in liquids are variable, with some not reporting any detectable levels [18,33,35] and others clearly identifying these compounds in the liquids when controlling for background contamination (n = 9) [23]. Analyses of aerosols indicate that TSNAs are present in amounts that can results in doses of < ng/day [5,33] to μg/day [8] (assuming 150 puffs/day) (see also [43]). The most comprehensive survey of TSNA content of 105 samples of liquids from 11 manufactures indicates that almost all tested liquids (>90%) contained TSNAs in μg/L quantities [36]. This is roughly equivalent to 1/1000 of the concentration of TSNAs in modern smokeless tobacco products (like snus), which are in the ppm range [48]. For example, 10 μg/L (0.01 ppm) of total TSNA in liquid [36] can translate to a daily dose of 0. 025–0. 05 μg from vaping (worst case assumption of 5 ml liquid/day); if 15 g of snus is consumed a day [49] with 1 ppm of TSNAs [48] and half of it were absorbed, then the daily dose is estimated to be 7.5 μg, which is 150–300 times that due to the worst case of exposure from vaping. Various assumptions about absorption of TSNAs alter the result of this calculation by a factor that is dwarfed in magnitude compared to that arising from differences considered above. This is reassuring because smokeless tobacco products, such as snus, pose negligible cancer risk [50], certainly orders of magnitude smaller than smoking (if one considers the chemistry of the products alone). In general, it appears that the cautious approach in face of variability and paucity of data is to seek better understanding of the predictors of presence of TSNA in liquids and aerosols so that measures for minimizing exposure to TSNAs from aerosols can be devised.

This can include considering better control by manufactures who extract the nicotine from tobacco leaf..

Volatile organic compounds

Total volatile organic compounds (VOC) were determined in aerosol to be non-detectable [3] except in one sample that appeared to barely exceed the background concentration of 1 mg/m^3 by 0.73 mg/m^3 [6]. These results are corroborated by analyses of liquids [19] and most likely testify to insensitivity of employed analytic methods for total VOC for characterizing aerosol generated by e-cigarettes, because there is ample evidence that specific VOC are present in the liquids and aerosols.[c] Information on specific commonly detected VOC in the aerosol is given in Table 1. It must be observed that these reported concentrations are for analyses that first observed qualitative evidence of the presence of a given VOC and thus represent worst case scenarios of exposure when VOC is present (i.e. zero-level exposures are missing from the overall summary of worst case exposures presented here). For most VOC and aldehydes, one can predict the concentration in air inhaled by a vaper to be < <1% of TLV. The only exceptions to this generalization are:

Table 1 Exposure predictions based on analysis of aerosols generated by smoking machines: Volatile Organic Compounds

Compound	N#	Estimated concentration in personal breathing zone		Ratio of most stringent TLV (%)		Reference
		PPM	mg/m^3	Calculated directly	Safety factor 10	
Acetaldehyde	1	0.005		0.02	0.2	[5]
	3	0.003		0.01	0.1	[4]
	12	0.001		0.004	0.04	[8]
	1	0.00004		0.0001	0.001	[3]
	1	0.0002		0.001	0.008	[3]
	150	0.001		0.004	0.04	[40,41]
	1	0.008		0.03	3	[38]
Acetone	1	0.002		0.0003	0.003	[38]
	150	0.0004		0.0001	0.001	[40,41]
Acrolein	12	0.001		1	13	[8]
	150	0.002		2	20	[40,41]
	1	0.006		6	60	[38]
Butanal	150	0.0002		0.001	0.01	[40,41]
Crotonaldehyde	150		0.0004	0.01	0.1	[40,41]
Formaldehyde	1	0.002		0.6	6	[5]
	3	0.008		3	30	[4]
	12	0.006		2	20	[8]
	1	<0.0003		<0.1	<1	[3]
	1	0.0003		0.1	1	[3]
	150	0.01		4	40	[40,41]
	1	0.009		3	30	[38]
Glyoxal	1		0.002	2	20	[38]
	150		0.006	6	60	[40,41]
o-Methylbenzaldehyde	12		0.001	0.05	0.5	[8]
p,m-Xylene	12		0.00003	0.001	0.01	[8]
Propanal	3	0.002		0.01	0.1	[4]
	150	0.0006		0.002	0.02	[40,41]
	1	0.005		0.02	0.2	[38]
Toluene	12	0.0001		0.003	0.03	[8]
Valeraldehyde	150		0.0001	0.0001	0.001	[40,41]

average is presented when N > 1.

(a) acrolein: ~1% of TLV (average of 12 measurements) [40] and measurements at a mean of 2% of TLV (average of 150 measurements) [41] and

(b) formaldehyde: between 0 and 3% of TLV based on 18 tests (average of 12 measurements at 2% of TLV, the most reliable test) [40] and an average of 150 results at 4% of TLV [41].

Levels of acrolein in exhaled aerosol reported in [6] were below 0.0016 mg/m^3 and correspond to predicted exposure of <1% of TLV (Table 2). It must re-emphasized that all calculations based on one electronic cigarette analyzed in [38] are best treated as qualitative in nature (i.e. indicating presence of a compound without any particular meaning attached to the reported level with respect to typical levels) due to great uncertainty about whether the

manner in which the e-cigarette was operated could have resulted in overheating that led to generation of acrolein in the aerosol. In fact, a presentation made by the author of [38] clearly stated that the "atomizer, generating high concentration carbonyls, had been burned black" [40,41]. In unpublished work, [40] there are individual values of formaldehyde, acrolein and glyoxal that approach TLV, but it is uncertain how typical these are because there is reason to believe the liquid was overheated; considerable variability among brands of electronic cigarettes was also noted. Formaldehyde and other aldehydes, but not acrolein, were detected in the analysis one e-cigarette [43]. The overwhelming majority of the exposure to specific VOC that are predicted to result from inhalation of the aerosols lie far below action level of 50% of TLV at which exposure has to be mitigated according to current code of best practice in occupational hygiene [51].

Table 2 Exposure predictions for volatile organic compounds based on analysis of aerosols generated by volunteer vapers

Compound	N[#]	Estimated concentration in personal breathing zone (ppm)	Ratio of most stringent TLV (%)		Reference
			Calculated directly	Safety factor 10	
2-butanone (MEK)	3	0.04	0.02	0.2	[4]
	1	0.002	0.0007	0.007	[6]
2-furaldehyde	3	0.01	0.7	7	[4]
Acetaldehyde	3	0.07	0.3	3	[4]
Acetic acid	3	0.3	3	30	[4]
Acetone	3	0.4	0.2	2	[4]
Acrolein	1	<0.001	<0.7	<7	[6]
Benzene	3	0.02	3	33	[4]
Butyl hydroxyl toluene	1	4E-05	0.0002	0.002	[6]
Isoprene	3	0.1	7	70	[4]
Limonene	3	0.009	0.03	0.3	[4]
	1	2E-05	0.000001	0.00001	[6]
m,p-Xyelen	3	0.01	0.01	0.1	[4]
Phenol	3	0.01	0.3	3	[4]
Propanal	3	0.004	0.01	0.1	[4]
Toluene	3	0.01	0.07	0.7	[4]

average is presented when N > 1.

Finding of an unusually high level of formaldehyde by Schripp *et al.* [4] – 0.5 ppm predicted vs. 15-minute TLV of 0.3 ppm (not given in Table 2) – is clearly attributable to endogenous production of formaldehyde by the volunteer smoker who was consuming e-cigarettes in the experimental chamber, since there was evidence of build-up of formaldehyde prior to vaping and liquids used in the experiments did not generate aerosol with detectable formaldehyde. This places generalizability of other findings from [4] in doubt, especially given that the only other study of exhaled air by vapers who were not current smokers reports much lower concentrations for the same compounds [6] (Table 2). It should be noted that the report by Romagna *et al.* [6] employed more robust methodology, using 5 volunteer vapers (no smokers) over an extended period of time. Except for benzene, acetic acid and isoprene, all calculated concentrations for detected VOC were much below 1% of TLV in exhaled air [6]. In summary, these results do not indicate that VOC generated by vaping are of concern by standards used in occupational hygiene.

Diethylene glycol and ethylene glycol became a concern following the report of their detection by FDA [44], but these compounds are not detected in the majority of tests performed to date [3,15,17,19,23]. Ten batches of the liquid tested by their manufacture did not report any diethylene glycol above 0.05% of the liquid [42]. Methods used to detect diethylene glycol appear to be adequate to be informative and capable of detecting the compound in quantities < <1% of TLV [15,17,23]. Comparison to TLV is based on a worst case calculation analogous to the one performed for propylene glycol. For diethylene glycol, TLV of 10 mg/m^3 is applicable (as in the case of all aerosols with no know toxicity by inhalation), and there is a recent review of regulations of this compound conducted for the Dutch government by the Health Council of the Netherlands (jurisdiction with some of the most strict occupational exposure limits) that recommended OEL of 70 mg/m^3 and noted lack of evidence for toxicity following inhalation [http://www.gezondheidsraad.nl/sites/default/files/200703OSH.pdf; accessed July 29; 2013]. In conclusion, even the quantities detected in the single FDA result were of little concern, amounting to less than 1% of TLV.

Inorganic compounds

Special attention has to be paid to the chemical form of compounds when there is detection of metals and other elements by inductively coupled plasma mass spectrometry (ICP-MS) [8,26]. Because the parent molecule that occurs in the aerosol is destroyed in such analysis, the results can be misleading and not interpretable for risk assessment. For example, the presence of sodium (4.18 μg/10 puffs) [26] does not mean that highly reactive and toxic sodium metal is in the aerosol, which would be impossible given its reactivity, but most likely means the presence of the ubiquitous compound that contains sodium, dissolved table salt (NaCl). If so, the corresponding daily dose of NaCl that arises from these concentrations from 150 puffs is about 10,000 times lower than allowable daily intake according to CDC (http://www.cdc.gov/features/dssodium/; accessed July 4, 2013). Likewise, a result for presence of silica is meaningless for health assessment unless the crystalline form of SiO_2 is known to be present. When such ambiguity exists, a TLV equivalence calculation was not performed. We compared concentrations to TLVs when it was even remotely plausible that parent molecules were present in the aqueous solution. However, even these are to be given credence only in an extremely pessimistic analyst, and further investigation by more appropriate analytical methods could clarify exactly what compounds are present, but is not a priority for risk assessment.

It should also be noted that one study that attempted to quantify metals in the liquid found none above 0.1-0.2 ppm levels [7] or above unspecified threshold [19]. Table 3 indicates that most metals that were detected were present at <1% of TLV even if we assume that the analytical results imply the presence of the most hazardous molecules containing these elements that can occur in aqueous solution. For example, when elemental chromium was measured, it is compared to TLV for insoluble chromium IV that has the lowest TLV of all chromium compounds. Analyses of metals given in [43] are not summarized here because of difficulty with translating reported units into meaningful terms for comparison with the TLV, but only mercury (again with no information on parent organic compound) was detected in trace quantities, while arsenic, beryllium, chromium, cadmium, lead and nickel were not. Taken as the whole, it can be inferred that there is no evidence of contamination of the aerosol with metals that warrants a health concern.

Table 3 Exposure predictions based on analysis of aerosols generated by smoking machines: Inorganic Compounds[#]

Element quantified	Assumed compound containing the element for comparison with TLV	N[##]	Estimated concentration in personal breathing zone (mg/m^3)	Ratio of most stringent TLV (%)		Reference
				Calculated directly	Safety factor 10	
Aluminum	Respirable Al metal & insoluble compounds	1	0.002	0.2	1.5	[26]
Barium	Ba & insoluble compounds	1	0.00005	0.01	0.1	[26]
Boron	Boron oxide	1	0.02	0.1	1.5	[26]
Cadmium	Respirable Cd & compounds	12	0.00002	1	10	[8]
Chromium	Insoluble Cr (IV) compounds	1	3E-05	0.3	3	[26]
Copper	Cu fume	1	0.0008	0.4	4.0	[26]
Iron	Soluble iron salts, as Fe	1	0.002	0.02	0.2	[26]
Lead	Inorganic compounds as Pb	1	7E-05	0.1	1	[26]
		12	0.000025	0.05	0.5	[8]
Magnesium	Inhalable magnesium oxide	1	0.00026	0.003	0.03	[26]
Manganese	Inorganic compounds, as Mn	1	8E-06	0.04	0.4	[26]
Nickel	Inhalable soluble inorganic compounds, as Ni	1	2E-05	0.02	0.2	[26]
		12	0.00005	0.05	0.5	[8]
Potassium	KOH	1	0.001	0.1	1	[26]
Tin	Organic compounds, as Sn	1	0.0001	0.1	1	[26]
Zinc	Zinc chloride fume	1	0.0004	0.04	0.4	[26]
Zirconium	Zr and compounds	1	3E-05	0.001	0.01	[26]
Sulfur	SO_2	1	0.002	0.3	3	[26]

The actual molecular form in the aerosol unknown and so worst case assumption was made if it was physically possible (e.g. it is not possible for elemental lithium & sodium to be present in the aerosol); there is no evidence from the research that suggests the metals were in the particular highest risk form, and in most cases a general knowledge of chemistry strongly suggests that this is unlikely. Thus, the TLV ratios reported here probably do not represent the (much lower) levels that would result if we knew the molecular forms.
average is presented when N > 1.

Consideration of exposure to a mixture of contaminants

All calculations conducted so far assumed only one contaminant present in clean air at a time. What are the implications of small quantities of various compounds with different toxicities entering the personal breathing zone at the same time? For evaluation of compliance with exposure limits for mixtures, Equation 3 is used:

$$\mathrm{OEL}_{\mathrm{mixture}} = \sum_{i-1}^{n} \left(C_i / TLV_i \right), \tag{3}$$

where C_i is the concentration of the i^{th} compound ($i = 1,\ldots,n$, where n > 1 is the number of ingredients present in a mixture) in the contaminated air and TLV_i is the TLV for the i^{th} compound in the contaminated air; if $OEL_{mixture} > 1$, then there is evidence of the mixture exceeding TLV.

The examined reports detected no more than 5–10 compounds in the aerosol, and the above calculation does not place any of them out of compliance with TLV for mixture. Let us imagine that 50 compounds with TLVs were detected. Given that the aerosol tends to contain various compounds at levels, on average, of no more than 0.5% of TLV (Tables 1 and 3), such a mixture with 50 ingredients would be at 25% of TLV, a level that is below that which warrants a concern, since the "action level" for implementation of controls is traditionally set at 50% of TLV to ensure that the majority of persons exposed have personal exposure below mandated limit [51]. Pellerino et al. [2] reached conclusions similar to this review based on their single experiment: contaminants in the liquids that warrant health concerns were present in concentrations that were less than 0.1% of that allowed by law in the European Union. Of course, if the levels of the declared ingredients (propylene glycol, glycerin, and nicotine) are considered, the action level would be met, since those ingredients are present in the concentrations that are near the action level. There are no known synergistic actions of the examined mixtures, so Equation 3 is therefore applicable. Moreover, there is currently no reason to suspect that the trace amounts of the contaminants will react to create compounds that would be of concern.

Conclusions

By the standards of occupational hygiene, current data do not indicate that exposures to vapers from contaminants in electronic cigarettes warrant a concern. There are no known toxicological synergies among compounds in the aerosol, and mixture of the contaminants does not pose a risk to health. However, exposure of vapers to propylene glycol and glycerin reaches the levels at which, if one were considering the exposure in connection with a workplace setting, it would be prudent to scrutinize the health of exposed individuals and examine how exposures could be reduced. This is the basis for the recommendation to monitor levels and effects of prolonged exposure to propylene glycol and glycerin that comprise the bulk of emissions from electronic cigarettes other than nicotine and water vapor. From this perspective, and taking the analogy of work on theatrical fogs [46,47], it can be speculated that respiratory functions and symptoms (but not cancer of respiratory tract or non-malignant respiratory disease) of the vaper is of primary interest. Monitoring upper airway irritation of vapers and experiences of unpleasant smell would also provide early warning of exposure to compounds like acrolein because of known immediate effects of elevated exposures (http://www.atsdr.cdc.gov/toxprofiles/tp124-c3.pdf; accessed July 11, 2013). However, it is questionable how much concern should be associated with observed concentrations of acrolein and formaldehyde in the aerosol. Given highly variable assessments, closer scrutiny is probably warranted to understand sources of this variability, although there is no need at present to be alarmed about exceeding even the occupational exposure limits, since occurrence of occasional high values is accounted for in established TLVs. An important clue towards a productive direction for such work is the results reported in [40,41] that convincingly demonstrate how heating the liquid to high temperatures generates compounds like acrolein and formaldehyde in the aerosol. A better understanding about the sources of TSNA in the aerosol may be of some interest as well, but all results to date consistently indicate quantities that are of no more concern than TSNA in smokeless tobacco or nicotine replacement therapy (NRT) products. Exposures to nicotine from

electronic cigarettes is not expected to exceed that from smoking due to self-titration [11]; it is only a concern when a vaper does not intend to consume nicotine, a situation that can arise from incorrect labeling of liquids [25,44].

The cautions about propylene glycol and glycerin apply only to the exposure experienced by the vapers themselves. Exposure of bystanders to the listed ingredients, let alone the contaminants, does not warrant a concern as the exposure is likely to be orders of magnitude lower than exposure experienced by vapers. Further research employing realistic conditions could help quantify the quantity of exhaled aerosol and its behavior in the environment under realistic worst-case scenarios (i.e., not small sealed chambers), but this is not a priority since the exposure experienced by bystanders is clearly very low compared to the exposure of vapers, and thus there is no reason to expect it would have any health effects.

The key to making the best possible effort to ensure that hazardous exposures from contaminants do not occur is ongoing monitoring of actual exposures and estimation of potential ones. Direct measurement of personal exposures is not possible in vaping due to the fact the aerosol is inhaled directly, unless, of course, suitable biomarkers of exposure can be developed. The current review did not identify any suitable biomarkers, though cotinine is a useful proxy for exposure to nicotine-containing liquids. Monitoring of potential composition of exposures is perhaps best achieved though analysis of aerosol generated in a manner that approximates vaping, for which better insights are needed on how to modify "smoking machines" to mimic vaping given that there are documented differences in inhalation patterns [52] that depend on features of e-cigarettes [14]. These smoking machines would have to be operated under a realistic mode of operation of the atomizer to ensure that the process for generation of contaminants is studied under realistic temperatures. To estimate dosage (or exposure in personal breathing zone), information on the chemistry of the aerosol has to be combined with models of the inhalation pattern of vapers, mode of operation of e-cigarettes and quantities of liquid consumed. Assessment of exhaled aerosol appears to be of little use in evaluating risk to vapers due to evidence of qualitative differences in the chemistry of exhaled and inhaled aerosol.

Monitoring of liquid chemistry is easier and cheaper than assessment of aerosols. This can be done systematically as a routine quality control measure by the manufacturers to ensure uniform quality of all production batches. However, we do not know how this relates to aerosol chemistry because previous researchers did not appropriately pair analyses of chemistry of liquids and aerosols. It is standard practice in occupational hygiene to analyze the chemistry of materials generating an exposure, and it is advisable that future studies of the aerosols explicitly pair these analyses with examination of composition of the liquids used to generate the aerosols. Such an approach can lead to the development of predictive models that relate the composition of the aerosol to the chemistry of liquids, the e-cigarette hardware, and the behavior of the vaper, as these, if accurate, can anticipate hazardous exposures before they occur. The current attempt to use available data to develop such relationships was not successful due to studies failing to collect appropriate data. Systematic monitoring of quality of the liquids would also help reassure consumers and is best done by independent laboratories rather than manufactures to remove concerns about impartiality (real or perceived).

Future work in this area would greatly benefit from standardizing laboratory protocols (e.g. methods of extraction of compounds from aerosols and liquids, establishment of "core" compounds that have to be quantified in each analysis (as is done for PAH and metals),

development of minimally informative detection limits that are needed for risk assessment, standardization of operation of "vaping machine", etc.), quality control experiments (e.g. suitable positive and negative controls without comparison to conventional cigarettes, internal standards, estimation of%recovery, etc.), and reporting practices (e.g. in units that can be used to estimate personal exposure, use of uniform definitions of limits of detection and quantification, etc.), all of which would improve on the currently disjointed literature. Detailed recommendations on standardization of such protocols lie outside of scope of this report.

All calculations conducted in this analysis are based on information about patterns of vaping and the content of aerosols and liquids that are highly uncertain in their applicability to "typical" vaping as it is currently practiced and says even less about future exposures due to vaping (e.g. due to development of new technology). However, this is similar to assessments that are routinely performed in occupational hygiene for novel technology as it relied on "worst case" calculations and safety margins that attempt to account for exposure variability. The approach adopted here and informed by some data is certainly superior to some currently accepted practices in the regulatory framework in occupational health that rely purely on description of emission processes to make claims about potential for exposure (e.g. [53]). Clearly, routine monitoring of potential and actual exposure is required if we were to apply the principles of occupational hygiene to vaping. Detailed suggestions on how to design such exposure surveillance are available in [54].

While vaping is obvious not an occupational exposure, occupational exposure standards are the best available option to use. If there were a standard for voluntary consumer exposure to aerosols, it would be a better fit, but no such standard exists. The only candidate standard is the occupational standard, which is conservative (more protective) when considered in the context of voluntary exposures, as argued above, and any suggestion that another standard be used needs to be concrete and justified.

In summary, analysis of the current state of knowledge about the chemistry of contaminants in liquids and aerosols associated with electronic cigarettes indicates that there is no evidence that vaping produces inhalable exposures to these contaminants at a level that would prompt measures to reduce exposure by the standards that are used to ensure safety of workplaces. Indeed, there is sufficient evidence to be reassured that there are no such risks from the broad range of the studied products, though the lack of quality control standards means that this cannot be assured for all products on the market. However, aerosol generated during vaping on the whole, when considering the declared ingredients themselves, if it were treated in the same manner as an emission from industrial process, creates personal exposures that would justify surveillance of exposures and health among exposed persons. Due to the uncertainty about the effects of these quantities of propylene glycol and glycerin, this conclusion holds after setting aside concerns about health effects of nicotine. This conclusion holds notwithstanding the benefits of tobacco harm reduction, since there is value in understanding and possibly mitigating risks even when they are known to be far lower than smoking. It must be noted that the proposal for such scrutiny of "total aerosol" is not based on specific health concerns suggested by compounds that resulted in exceedance of occupational exposure limits, but is instead a conservative posture in the face of unknown consequences of inhalation of appreciable quantities of organic compounds that may or may not be harmful at doses that occur during vaping.

Key conclusions:

- Even when compared to workplace standards for involuntary exposures, and using several conservative (erring on the side of caution) assumptions, the exposures from using e-cigarettes fall well below the threshold for concern for compounds with known toxicity. That is, even ignoring the benefits of e-cigarette use and the fact that the exposure is actively chosen, and even comparing to the levels that are considered unacceptable to people who are not benefiting from the exposure and do not want it, the exposures would not generate concern or call for remedial action.
- Expressed concerns about nicotine only apply to vapers who do not wish to consume it; a voluntary (indeed, intentional) exposure is very different from a contaminant.
- There is no serious concern about the contaminants such as volatile organic compounds (formaldehyde, acrolein, etc.) in the liquid or produced by heating. While these contaminants are present, they have been detected at problematic levels only in a few studies that apparently were based on unrealistic levels of heating.
- The frequently stated concern about contamination of the liquid by a nontrivial quantity of ethylene glycol or diethylene glycol remains based on a single sample of an early-technology product (and even this did not rise to the level of health concern) and has not been replicated.
- Tobacco-specific nitrosamines (TSNA) are present in trace quantities and pose no more (likely much less) threat to health than TSNAs from modern smokeless tobacco products, which cause no measurable risk for cancer.
- Contamination by metals is shown to be at similarly trivial levels that pose no health risk, and the alarmist claims about such contamination are based on unrealistic assumptions about the molecular form of these elements.
- The existing literature tends to overestimate the exposures and exaggerate their implications. This is partially due to rhetoric, but also results from technical features. The most important is confusion of the concentration in aerosol, which on its own tells us little about risk to heath, with the relevant and much smaller total exposure to compounds in the aerosol averaged across all air inhaled in the course of a day. There is also clear bias in previous reports in favor of isolated instances of highest level of chemical detected across multiple studies, such that average exposure that can be calculated are higher than true value because they are “missing” all true zeros.
- Routine monitoring of liquid chemistry is easier and cheaper than assessment of aerosols. Combined with an understanding of how the chemistry of the liquid affects the chemistry of the aerosol and insights into behavior of vapers, this can serve as a useful tool to ensure the safety of e-cigarettes.
- The only unintentional exposures (i.e., not the nicotine) that seem to rise to the level that they are worth further research are the carrier chemicals themselves, propylene glycol and glycerin. This exposure is not known to cause health problems, but the magnitude of the exposure is novel and thus is at the levels for concern based on the lack of reassuring data.

Endnotes

[a]Atmosphere that contains air inhaled by a person.

[b]This estimate of consumption was derived from informal reports from vaping community; 5 ml/day was identified as a high but not rare quantity of consumption and 25 ml/day was the high end of claimed use, though some skepticism was expressed about whether the latter

quantity was truly possible. High-quality formal studies to verify these figures do not yet exist but they are consistent with report of Etter (2012).

[c]The term "VOC" loosely groups together all organic compounds present in aerosol and because the declared ingredients of aerosol are organic compounds, it follows that "VOC are present".

Competing interests

Funding for this work was provided by The Consumer Advocates for Smoke-free Alternatives Association (CASAA) Research Fund. CASAA is an all-volunteer, donation-funded, non-profit organization devoted to defending consumer access to and promoting tobacco harm reduction; it is a consumer (not industry) advocacy NGO. For more information, see http://casaa.org/. CASAA exercised no editorial control over the author's writing or analysis: the author, not the funder, had full control of the content.

Author's contribution

IB is responsible for all aspects of the report and was the sole contributor.

Author's information

IB is trained in both occupational hygiene and epidemiology and thus is an expert in bring information that these two fields contribute to risk assessment and policy-making. IB does not and never has used any tobacco products. Current research was completed by him as independent research contract during otherwise unpaid summer months. IB is an Associate Professor at Drexel University and felt obliged to disclose his primary academic appointment but this work was completed outside of the structures of Drexel University.

Acknowledgements

The author is thankful to Dr Carl V Phillips, the CASAA Scientific Director, for frank discussion of relevant scientific matters. The contribution of Charity Curtis, Masters of Public Health student at Drexel University to the initial literature search was greatly appreciated. Lastly, the author is deeply indebted to pre-publication peer review that occurred upon release of the content of this article as technical report -- Burstyn I: *Peering through the mist: What does the chemistry of contaminants in electronic cigarettes tell us about health risks?* July - August 2013, Drexel University School of Public Health, Philadelphia, PA (http://publichealth.drexel.edu/~/media/files/publichealth/ms08.pdf) – all the feedback is greatly appreciated and the remaining flaws in the report are author's sole responsibility.

References

1. Etter JF: *The electronic cigarette: an alternative to tobacco? Jean-François Etter.* 2012.

2. Pellegrino RM, Tinghino B, Mangiaracina G, Marani A, Vitali M, Protano C, *et al*: **Electronic cigarettes: an evaluation of exposure to chemicals and fine particulate matter (PM).** *Ann Ig* 2012, **24:**279–288.

3. eSmoking Institute: *Assessment of e-cigarette safety by comparing the chemical composition of e-cigarette aerosol and cigarette smoke from reference traditional cigarette.* http://www.esmokinginstitute.com/en/node/31. 2013. Ref Type: Electronic Citation.

4. Schripp T, Markewitz D, Uhde E, Salthammer T: **Does e-cigarette consumption cause passive vaping?** *Indoor Air* 2013, **23:**25–31.

5. Lauterbach JH, Laugesen M: *Comparison of toxicant levels in mainstream aerosols generated by Ruyan® electronic nicotine delivery systems(ENDS) and conventional cigarette products.* ; 2012.

6. Romagna G, Zabarini L, Barbiero L, Boccietto E, Todeschi S, Caravati E, *et al*: *Characterization of chemicals released to the environment by electronic cigarettes use (ClearStream-AIR project): is passive vaping a reality?*. Helsinki, Finland: XIV Annual Meeting of the SRNT Europe 2012; 2012. Ref Type: Report.

7. Laugesen M: In *Safety report on the Ruyan® e-cigarette cartridge and inhaled aerosol.* Edited by Health New Zealand Ltd. 2008. Ref Type: Report.

8. Goniewicz ML, Knysak J, Gawron M, Kosmider L, Sobczak A, Kurek J, *et al*: **Levels of selected carcinogens and toxicants in vapour from electronic cigarettes.** *Tob Control* 2013 [Epub ahead of print].

9. Benowitz NL, Jacob P III: **Daily intake of nicotine during cigarette smoking.** *Clin Pharmacol Ther* 1984, **35:**499–504.

10. The American Conference of Governmental Industrial Hygienists: *2013 threshold limit values for chemical substances and physical agents & biological exposure indices.* Cincinnati, OH: ACGIH; 2013.

11. Scherer G: **Smoking behaviour and compensation: a review of the literature.** *Psychopharmacol (Berl)* 1999, **145:**1–20.

12. Ganong WF: *Review of medical physiology.* 15th edition. London: Prentice Hall; 1995.

13. Holmes JR: *How much air do we breathe? Research note 94–11.* California: California Environmental Protection Agency; 1994. Ref Type: Report.

14. Farsalinos KE, Romagna G, Tsiapras D, Kyrzopoulos S, Voudris V: **Evaluation of electronic cigarette use (vaping) topography and estimation of liquid consumption: implications for research protocol standards definition and for public health authorities' regulation.** *Int J Environ Res Public Health* 2013, **10:**2500–2514.

15. Alliance Technologies L: *Chemical composition of "Instead" electronic cigarette smoke juice and vapor.* 2009. Ref Type: Report.

16. Alliance Technologies L: *Characterization of liquid "Smoke Juice" for electronic cigarettes.* 2009. Ref Type: Report.

17. Alliance Technologies L: *Characterization of Regal cartridges for electronic cigarettes.* 2009. Ref Type: Report.

18. Alliance Technologies L: *Characterization of regal cartridges for electronic cigarettes - Phase II.* 2009. Ref Type: Report.

19. eSmoking Institute: *Identifying the concentration of chemical compounds and heavy metals in liquids.* http://www.esmokinginstitute.com/en/node/32. 2013. Ref Type: Electronic Citation.

20. Evans Analytical Group: *Gas chromatography mass spectroscopy(GC-MS) analysis report; JOB NUMBER C09Y8961.* 2009. Ref Type: Report.

21. Coulson H: In *Analysis of components from Gamucci electronic cigarette cartridges, tobacco flavour regular smoking liquid; Report number: E98D.* Edited by LPD Laboratory Services, Blackburn MicroTech Solutions Ltd. 2009. Ref Type: Report.

22. Ellicott M: In *Analysis of components from "e-Juice XX HIGH 36mg/ml rated Nicotine Solution" ref S 55434; Report Number: E249A.* Edited by LPD Laboratory Services, Blackburn MicroTech Solutions Ltd. 2009. Ref Type: Report.

23. Westenberger BJ: In *Evaluation of e-cigarettes; DPATR-FY-09-23.* Edited by US Food and Drug Administration. 2009. Ref Type: Report.

24. McAuley TR, Hopke PK, Zhao J, Babaian S: **Comparison of the effects of e-cigarette vapor and cigarette smoke on indoor air quality.** *Inhal Toxicol* 2012, **24:**850–857.

25. Goniewicz ML, Kuma T, Gawron M, Knysak J, Kosmider L: **Nicotine levels in electronic cigarettes.** *Nicotine Tob Res* 2013, **15:**158–166.

26. Williams M, Villarreal A, Bozhilov K, Lin S, Talbot P: **Metal and silicate particles including nanoparticles are present in electronic cigarette cartomizer fluid and aerosol.** *PLoS One* 2013, **8:**e57987.

27. Laugesen M: *Ruyan® E-cigarette bench-top tests.* Dublin: Society for Research on Nicotine and Tobacco; 2009. Ref Type: Abstract.

28. Tytgat J: In *"Super Smoker" expert report.* Edited by Catholic University L. 2007. Ref Type: Report.

29. Valance C, Ellicott M: In *Analysis of chemical components from high, med & low nicotine cartridges; Report Number: D318.* Edited by LPD Laboratory Services, Blackburn MicroTech Solutions Ltd. 2008. Ref Type: Report.

30. Kubica P, Kot-Wasik A, Wasik A, Namiesnik J: **"Dilute & shoot" approach for rapid determination of trace amounts of nicotine in zero-level e-liquids by reversed phase liquid chromatography and hydrophilic interactions liquid chromatography coupled**

with tandem mass spectrometry-electrospray ionization. *J Chromatogr A* 2013, **1289:**13–18.

31. Trehy ML, Ye W, Hadwiger ME, Moore TW, Allgire JF, Woodruff JT, *et al*: **Analysis of electronic cigarette cartridges, refill solutions, and smoke for nicotine and nicotine related impurities.** *J Liquid Chromatogr Relat Technol* 2011, **34:**1442–1458.

32. Graves I: *Report no. 468304. 60 ml sample of mist from 11 mg nicotine e-cigarette cartridge. Thermal desorption tubes. 468304.* Hamilton, New Zealand: Hill Laboratories; 2008. Ref Type: Report.

33. Pattison J, Valenty SJ: *Material characterization report. 0910.14.* Analyze Inc; 2009. Ref Type: Report.

34. Sodoma A, Caggiano CM: *Material characterization report. 0706.04.* Analyze Inc; 2007. Ref Type: Report.

35. Anspach T: *Determination of tobacco-specific nitrosamines (TSNA) in aroma fluid for e-cigarettes. 11–57021.* Eurofins Dr.Specht Laboratorien; 2011. Ref Type: Report.

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

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

38. Uchiyama S, Inaba Y, Kunugita N: **Determination of acrolein and other carbonyls in cigarette smoke using coupled silica cartridges impregnated with hydroquinone and 2,4-dinitrophenylhydrazine.** *J Chromatogr A* 2010, **1217:**4383–4388.

39. Uchiyama S: *Determination of acrolein and other carbonyls in cigarette smoke using coupled silica cartridges impregnated with hydroquinone and 2,4-dinitrophenylhydrazine.* ; 2013. Ref Type: Personal Communication.

40. Uchiyama S: *unpublished concentrations from experiments presented in https://www.jstage.jst.go.jp/article/bunsekikagaku/60/10/60_10_791/_pdf; through personal communications.* 2013. Ref Type: Unpublished Work.

41. Ohta K, Uchiyama S, Inaba Y, Nakagome H, Kunugita N: **Determination of carbonyl compounds generated from the electronic cigarette using coupled silica cartridges impregnated with hydroquinone and 2,4-dinitrophenylhydrazine.** *BUNSEKI KAGAKU* 2011, **60:**791–797.

42. eSmoke: *Analytical reports on batches of e-liquids.* 2009. http://www.esmoke.net/pages.php?pageid=20 Ref Type: Electronic Citation.

43. Murphy J, Wong E, Lawton M: *Chemical and operational assessment of the Ruyan classic e-cigarette. Report P.474.* British American Tobacco; 2010. Ref Type: Report.

44. Trtchounian A, Talbot P: **Electronic nicotine delivery systems: is there a need for regulation?** *Tob Control* 2011, **20:**47–52.

45. Etter JF, Bullen C, Flouris AD, Laugesen M, Eissenberg T: **Electronic nicotine delivery systems: a research agenda.** *Tob Control* 2011, **20:**243–248.

46. Varughese S, Teschke K, Brauer M, Chow Y, van NC, Kennedy SM: **Effects of theatrical smokes and fogs on respiratory health in the entertainment industry.** *Am J Ind Med* 2005, **47:**411–418.

47. Teschke K, Chow Y, Van NC, Varughese S, Kennedy SM, Brauer M: **Exposures to atmospheric effects in the entertainment industry.** *J Occup Environ Hyg* 2005, **2:**277–284.

48. Hecht SS, Hoffmann D: **Tobacco-specific nitrosamines, an important group of carcinogens in tobacco and tobacco smoke.** *Carcinogenesis* 1988, **9:**875–884.

49. Digard H, Errington G, Richter A, McAdam K: **Patterns and behaviors of snus consumption in Sweden.** *Nicotine Tob Res* 2009, **11:**1175–1181.

50. Phillips CV, Sargent C, Rabiu D, Rodu B: **Calculating the comparative mortality risk from smokeless tobacco vs. smoking.** *Am J Epidemiol* 2006, **163**(11)**:**S189. Ref Type: Abstract.

51. Liedel NA, Busch KA, Crouse WE: *Exposure measurement action level and occupational environmental variability. HEW Publication No. (NIOSH) 76–131.* Cincinnati, OH: US Departement of Health, Education, and Welfare, Public Health Service, Center for Disease Control, National Institute for Occupational Safety and Health, Division of Laboatories and Criteria Development; 1975. Ref Type: Report.

52. Trtchounian A, Williams M, Talbot P: **Conventional and electronic cigarettes (e-cigarettes) have different smoking characteristics.** *Nicotine Tob Res* 2010, **12:**905–912.

53. Tischer M, Bredendiek-Kamper S, Poppek U, Packroff R: **How safe is control banding? Integrated evaluation by comparing OELs with measurement data and using monte carlo simulation.** *Ann Occup Hyg* 2009, **53:**449–462.

54. British Occupational Hygiene Society, Nederlandse Vereniging voor Arbeidshygiëne: *Testing compliance with occupational exposure limits for airborne substances.* 2011. Ref Type: Report.

Additional files

Additional_file_1 as XLSX

Additional file 1 Summary of chemical analyses of e-cigarettes extracted from the literature.

Additional_file_2 as RTF

Additional file 2 Key to identifying articles listed in *Additional file 1.*

Additional_file_3 as XLSX

Additional file 3 Calculations conducted to compare reported results to threshold limit values. Spreadsheet that implemented calculations summarized in the article.

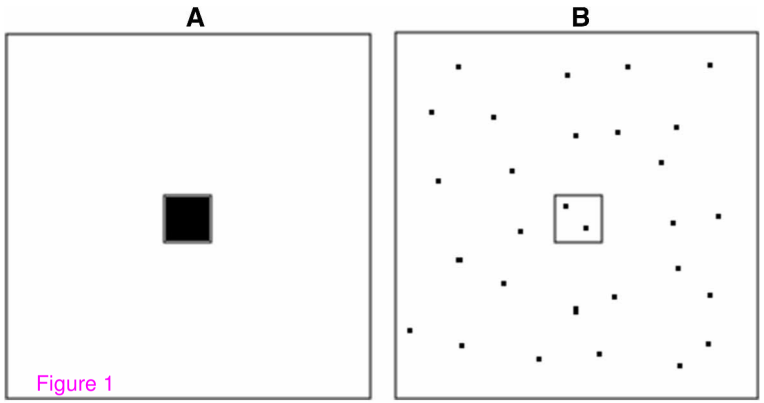


Figure 1

Additional files provided with this submission:

Additional file 1: 9759835901066082_add1.xlsx, 57K
http://www.biomedcentral.com/imedia/1731529015118196/supp1.xlsx
Additional file 2: 9759835901066082_add2.rtf, 60K
http://www.biomedcentral.com/imedia/1581997989118196/supp2.rtf
Additional file 3: 9759835901066082_add3.xlsx, 70K
http://www.biomedcentral.com/imedia/1576899991181967/supp3.xlsx

TC Online First, published on March 6, 2013 as 10.1136/tobaccocontrol-2012-050859

Levels of selected carcinogens and toxicants in vapour from electronic cigarettes

Maciej Lukasz Goniewicz,[1,2,3] Jakub Knysak,[3] Michal Gawron,[3] Leon Kosmider,[3,4] Andrzej Sobczak,[3,4] Jolanta Kurek,[4] Adam Prokopowicz,[4] Magdalena Jablonska-Czapla,[5] Czeslawa Rosik-Dulewska,[5] Christopher Havel,[6] Peyton III Jacob,[6] Neal Benowitz[6]

▶ Additional material is published online only. To view please visit the journal online (http://dx.doi.org/10.1136/tobaccocontrol-2012-050859).

[1]Department of Health Behavior, Division of Cancer Prevention and Population Sciences, Roswell Park Cancer Institute, Buffalo, New York, USA
[2]Tobacco Dependence Research Unit, Queen Mary University of London, London, UK
[3]Department of General and Analytical Chemistry, Medical University of Silesia, Sosnowiec, Poland
[4]Department of Chemical Hazards, Institute of Occupational and Environmental Health, Sosnowiec, Poland
[5]Polish Academy of Science, Institute of Environmental Engineering, Zabrze, Poland
[6]Division of Clinical Pharmacology and Experimental Therapeutics, Departments of Medicine and Bioengineering & Therapeutic Sciences, University of California, San Francisco, California, USA

Correspondence to
Dr Maciej L Goniewicz, Department of Health Behavior, Division of Cancer Prevention and Population Sciences, Roswell Park Cancer Institute, Elm & Carlton Streets / Carlton House A320, Buffalo, NY 14263, USA; maciej.goniewicz@roswellpark.org

Received 24 October 2012
Accepted 31 January 2013

To cite: Goniewicz ML, Knysak J, Gawron M, *et al*. *Tob Control* Published Online First: [*please include* Day Month Year] doi:10.1136/tobaccocontrol-2012-050859

ABSTRACT

Significance Electronic cigarettes, also known as e-cigarettes, are devices designed to imitate regular cigarettes and deliver nicotine via inhalation without combusting tobacco. They are purported to deliver nicotine without other toxicants and to be a safer alternative to regular cigarettes. However, little toxicity testing has been performed to evaluate the chemical nature of vapour generated from e–cigarettes. The aim of this study was to screen e-cigarette vapours for content of four groups of potentially toxic and carcinogenic compounds: carbonyls, volatile organic compounds, nitrosamines and heavy metals.

Materials and methods Vapours were generated from 12 brands of e-cigarettes and the reference product, the medicinal nicotine inhaler, in controlled conditions using a modified smoking machine. The selected toxic compounds were extracted from vapours into a solid or liquid phase and analysed with chromatographic and spectroscopy methods.

Results We found that the e-cigarette vapours contained some toxic substances. The levels of the toxicants were 9–450 times lower than in cigarette smoke and were, in many cases, comparable with trace amounts found in the reference product.

Conclusions Our findings are consistent with the idea that substituting tobacco cigarettes with e-cigarettes may substantially reduce exposure to selected tobacco-specific toxicants. E-cigarettes as a harm reduction strategy among smokers unwilling to quit, warrants further study. (To view this abstract in Polish and German, please see the supplementary files online.)

INTRODUCTION

An electronic cigarette, also known as e-cigarette, is a type of nicotine inhaler, imitating ordinary cigarettes. Although the majority of e-cigarettes look similar to other tobacco products, such as cigarettes or cigars, certain types resemble pens, screwdrivers or even harmonicas. E-cigarettes contain nicotine solution in a disposable cartridge. The cartridge is replaced when the solution is finished or might be refilled by the e-cigarette user. In contrast with ordinary cigarettes, which involve tobacco combustion, e-cigarettes use heat to transform nicotine solution into vapour. Processed and purified nicotine from tobacco leaves, suspended in a mixture of glycerin or propylene glycol with water, is vapourised. Nicotine present in such vapour enters the respiratory tract, from where it is absorbed to the bloodstream.[1–4]

Distributors of e-cigarettes promote the product as completely free of harmful substances. The basis for the claim of harmlessness of the e-cigarettes is that they do not deliver toxic doses of nicotine and the nicotine solution lacks harmful constituents. E-cigarettes are new products and, as such, require further testing to assess their toxic properties. Currently, the scientific evidence on the lack or presence of toxic chemicals in the vapour generated from e-cigarettes, and inhaled by their users is very limited. In August 2008, Ale Alwen, the Assistant Director-General for Non-communicable Diseases and Mental Health, stated that 'the electronic cigarette is not a proven nicotine replacement therapy. WHO has no scientific evidence to confirm the product's safety and efficacy. However, WHO does not discount the possibility that the electronic cigarette could be useful as a smoking cessation aid. The only way to know is to test.[5] Douglas Bettcher, Director of the WHO's Tobacco Free Initiative stated that only clinical tests and toxicity analysis could permit considering e-cigarettes a viable method of nicotine replacement therapy.[6]

The majority of tests carried out on e-cigarettes until now consist of analysing the chemicals in the cartridges or nicotine refill solutions.[7–18] The current tests show that the cartridges contain no or trace amounts of potentially harmful substances, including nitrosamines, acetaldehyde, acetone and formaldehyde. However, using e-cigarettes requires heating the cartridges and under such conditions chemical reactions may result in formation of new compounds. Such a situation takes place in the case of ordinary cigarettes, where a number of toxic compounds are formed during combustion. The US Department of Health and Human Services of the Food and Drug Administration agency carried out tests which showed the presence of trace amounts of nitrosamines and diethylene glycol in e-cigarette vapour. These tests were conducted in a manner which simulated the actual use of the products.[19]

We developed analytical methods and measured concentrations of selected compounds in the vapour generated by different brands and types of e-cigarettes. We focused our study on the four most important groups of toxic compounds present in the tobacco smoke: carbonyl compounds, volatile organic compounds (VOCs), tobacco-specific nitrosamines and metals (table 1).

MATERIALS AND METHODS

Electronic cigarettes and reference product (Nicorette inhalator)

Since the internet is currently the main distribution channel for the products, we searched price

Table 1 Selected toxic compounds identified in tobacco smoke [20–23]

Chemical compounds	Toxic effects
Carbonyl compounds	
Formaldehyde*, acetaldehyde*, acrolein*	Cytotoxic, carcinogenic, irritant, pulmonary emphysema, dermatitis
Volatile organic compounds (VOCs)	
Benzene*, toluene*, aniline	Carcinogenic, haematotoxic, neurotoxic, irritant
Nitrosamines	
N′–nitrosonornicotine (NNN)*, 4-(methylnitrosoamino)-1-(3-pyridyl)-1-butanone (NNK)*, N′-nitrosoethylomethyloamine	Carcinogenic
Polycyclic aromatic compounds (PAHs)	
Benzo(a)pyrene, benzo(a)anthracene, dibenzo(a)anthracene	Carcinogenic
Free radicals	
Methyl radical, hydroxyl radical, nitrogen monoxide	Carcinogenic, neurotoxic
Toxic gases	
Carbon monoxide, hydrogen sulfide, ammonia, sulfur dioxide, hydrogen cyanide	Cardiovascular toxicants, carcinogenic, irritant
Heavy metals	
Cadmium (Cd)*, lead (Pb)*, mercury (Hg)*	Carcinogenic, nephrotoxic, neurotoxic, haematotoxic
Other toxicants	
Carbon disulfide	Neurotoxic

*Indicates compounds analysed in this study.

comparison websites, online marketplace (Allegro.pl auction service) and internet discussion forums for e–cigarette users to identify the most popular brands of e–cigarettes distributed from within Poland. The searching was limited to web pages from Poland, and only Polish language was allowed for in retrieval options. Some 30 brands were identified. The brands were entered into Google.pl, and ranked according to the number of hits they generated. The number of hits in the search engine for the selected 30 models allowed selection of the 11 most popular e-cigarettes brands. Additionally, one e-cigarette model purchased in Great Britain was used in the study. All e–cigarette models selected for the study were purchased online. Characteristics of the product tested in the study are shown in table 2.

The suitable cartridges of the same brand name were used for the study. They were purchased from the same sources as that of the e-cigarette and were matched to selected models. All cartridges were characterised by high nicotine content (16–18 mg). As a reference product the medicinal nicotine inhalator was used (Nicorette 10 mg, Johnson&Johnson, Poland). The inhalator for the study was purchased in one of the local pharmaceutical warehouses.

Generation of vapour from e-cigarettes and reference product

Vapour from e-cigarettes was generated using the smoking machine Palaczbot (Technical University of Lodz, Poland) as described previously.[3] This is a one-port linear piston-like smoking machine with adjustable puffing regimes in a very wide range, controlled by computer interface.

Pilot samples demonstrated that it was impossible to generate vapour from e–cigarettes in standard laboratory conditions assumed for conventional cigarettes testing (International Organization for Standardization (ISO) 3808).[24] Inhalation of a volume of 35 ml anticipated in conventional cigarette standard is insufficient for activation of most of the e-cigarettes. Thus, we decided to generate vapour in conditions reflecting the actual manner of e-cigarettes using, determined based on the results of inhalation topography measurement among 10 ‘e–smokers’, who declared that they regularly use e-cigarettes for a period

Table 2 Characteristics of products tested in the study

Product code	Brand name	Model	Cartridge type	Flavour	Labelled nicotine content (mg or mg/ml)	Measured nicotine content (mg) [3]	Retailer	Country
EC01	Joye	510	Cartridge	Marlboro	4	4	Inspired s.c.	Poland
EC02	Janty	eGo	Cartridge	Marlboro	16	5	Janty	Poland
EC03	Janty	Dura	Cartridge	Marlboro	16	5	Janty	Poland
EC04	DSE	901	Cartridge	Regular	16	9	Fausee	Poland
EC05	Trendy	808	Cartridge	Trendy	18	2	Damhess	Poland
EC06	Nicore	M401	Cartridge	Marlboro	18	5	Atina Poland	Poland
EC07	Mild	201	Cartridge	Marlboro	18	19	Mild	Poland
EC08	Colinss	Age	Cartomizer	Camel	18	11	Colinss	Poland
EC09	Premium	PR111	Cartomizer	Tobacco	16	12	Premium	Poland
EC10	Ecis	510	Cartridge	Menthol	11	5	Arcotech	Poland
EC11	Dekang	Pen	Cartridge	Regular	18	18	Ecigars Polska	Poland
EC12	Intellicig	Evolution	Cartridge	Regular	8	8	Intellicig	UK

longer that 1 month.[3] All testing procedures in this work were carried out using the same averaged puffing conditions: puff duration of 1.8 s, intervals between puffs of 10 s, puff volume 70 ml and number of puffs taken in one puffing session was 15. A total of 150 puffs were taken from each e-cigarette in 10 series of 15 puffs with intervals between series of 5 min each. Each e-cigarette was tested three times on three following days after batteries were recharged during nights. A fresh cartridge was placed on the e-cigarettes each day they were tested. Vapour was visibly being produced during the full 150 puffs taken from each product tested.

Analytical chemistry

Note: The details of the sample preparation and analysis are given in the online supplementary materials.

It was planned to absorb the analysed vapour components in bulbs containing an organic solvent (extraction to liquid) or on suitable sorbents (extraction to solid phase). This required the modification of the system described above, in such a manner to enable quick connection of desirable sorption system. Carbonyl compounds and organic compounds due to their volatility were trapped in tubes packed with solid adsorbent. Metals and nitrosamines in turn, which are characterised by lower volatility, were to be absorbed in two gas washing bottles with methanol (50 ml in each bottle). Both washing bottles were immersed in acetone-dry ice bath in order to avoid any losses of volatile solvent. A picture of the set for vapour generation from e–cigarette and metals or nitrosamines absorption is presented in online supplementary figure S2.

The samples, after the preparation and condensation procedure, were analysed using analytical methods with high specificity and sensitivity allowing detection of even trace amounts of analysed compounds. Figure 1 shows the sample preparation procedure; and all analytical methods are described in details in the online supplementary materials. The following carbonyl compounds were analysed in this work using high-performance liquid chromatography with diode array detector (HPLC-DAD): formaldehyde, acetaldehyde, acrolein, acetone, propionic aldehyde, crotonaldehyde, butanol, benzaldehyde, isovaleric aldehyde, valeric aldehyde, m-methylbenzaldehyde, o-methylbenzaldehyde, p-methylbenzaldehyde, hexanal, 2,5-dimethylbenzaldehyde. VOCs included benzene, toluene, chlorobenzene, ethylbenzene, m,p-xylene, o-xylene, styrene, 1,3-dichlorobenzene, 1,4-dichlorobenzene, 1,2-dichlorobenzene, naphthalene and were analysed with gas chromatography-mass spectrometry. Among tobacco-specific nitrosamines two compounds were measured: N′–nitrosonornicotine (NNN) and 4-(methylnitrosoamino)-1-(3-pyridyl)-1-butanone (NNK) with ultra-performance liquid chromatography-mass spectrometry. An inductively coupled plasma mass spectrometry technique was used to quantify following metals: cobalt (Co), nickel (Ni), copper (Cu), zinc (Zn), cadmium (Cd), lead (Pb), arsenic (As), chromium (Cr), selenium (Se), manganese (Mn), barium (Ba), rubidium (Rb), strontium (Sr), silver (Ag), thallium (Tl) and vanadium (V). All analytical methods used in this work were validated as per the International Conference on Harmonisation guideline Q2(R1).[25]

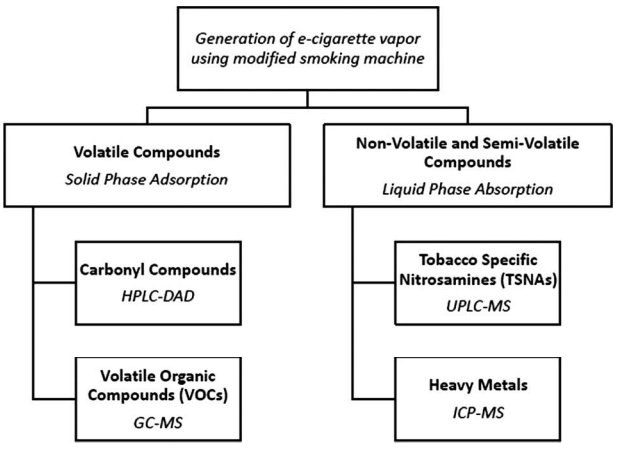


Figure 1 Analytical procedures applied in the study to test carcinogens and selected toxicants in vapour from e-cigarettes. GC-MS, gas chromatography-mass spectrometry; HPLC-DAD, high-performance liquid chromatography with diode array detector; ICP-MS, inductively coupled plasma-mass spectrometry; TSNA, tobacco-specific nitrosamine; UPLC-MS, ultra-performance liquid chromatography-mass spectrometry; VOC, volatile organic compound.

Statistical analysis

Results were presented as mean±SEM levels of selected compounds in vapour generated from e–cigarettes (per 150 puffs). The study aimed to compare the results obtained for aerosol from Nicorette inhalator with the results obtained for all examined e–cigarette models. Due to the small size of the groups, the difference between the mean from two groups was assessed based on Student's t test. All statistical analyses were conducted using the software for statistical data analysis Statistica V.9.0 (StaftSoft, Tulsa, USA). The significance level was established as $p<0.05$.

RESULTS

Carbonyl compounds

Among 15 carbonyls analysed, only 4 were found in vapour generated from e–cigarettes (table 3); and these compounds were identified in almost all examined e–cigarettes. The exception was one e-cigarette marked with code EC09, where acrolein was not detected. Three of the carbonyls have known toxic and irritating properties: formaldehyde, acetaldehyde and acrolein. The content of formaldehyde ranged from 2.0 μg to 56.1 μg, acetaldehyde from 1.1 μg to 13.6 μg, and acrolein from 0.7 μg to 41.9 μg per one e-cigarette (150 puffs). Trace amounts of formaldehyde, acetaldehyde and o-methylbenzaldehyde were also detected from the Nicorette inhalator. None of these compounds were detected in blank samples.

Volatile organic compounds

Among 11 VOCs analysed, only two were found in samples of vapour generated from e-cigarettes (table 3), and these compounds were identified in almost all examined e–cigarettes. The only one exception was e-cigarette marked with code EC02, where toluene and m,p-xylene were not detected. The content of toluene ranged from 0.2 μg to 6.3 μg per one e–cigarette (150 puffs). Although the m,p-xylene levels found in analysed samples of e–cigarette vapours ranged from 0.1 μg to 0.2 μg, it was also found on the same level in blank samples. In Nicorette inhalator in turn, none of the compounds analysed in that group were noted.

Tobacco-specific nitrosamines

Both nitrosamines analysed in the study were identified in all but three vapours generated from e-cigarettes (table 3). NNN was not found in e–cigarettes marked with codes EC01, EC04 and EC05 and NNK was not identified in products EC04, EC05 and EC12. The content of NNN ranged from 0.8 ng to 4.3 ng, and NNK from 1.1 ng to 28.3 ng per one e–cigarette

Table 3 Levels of selected compounds in vapour generated from e–cigarettes (per 150 puffs)

Compound	BS	Levels in vapour from electronic cigarettes†												Reference product
		Product code												
		EC01	EC02	EC03	EC04	EC05	EC06	EC07	EC08	EC09	EC10	EC11	EC12	Inhalator
Carbonyl compounds (μg)														
Formaldehyde	ND	44.2±4.1*	23.6±8.7*	30.2±2.3*	47.9±0.2*	56.1±1.4*	35.3±2.7*	19.0±2.7*	6.0±2.0	3.2±0.8	3.9±1.5	23.9±11.1	46.3±2.1*	2.0±1.1
Acetaldehyde	ND	4.6±0.2*	6.8±3.2	8.2±2.5*	11.5±2.0*	3.0±0.2*	13.6±2.1*	11.1±3.3*	8.8±1.6*	3.5±0.3*	2.0±0.1	3.7±1.5	12.0±2.4*	1.1±0.6
Acrolein	ND	41.9±3.4*	4.4±2.5	16.6±2.5*	30.1±6.4*	22.0±1.6*	2.1±0.4*	8.5±3.6	0.7±0.4	ND	2.7±1.6	1.1±0.6	7.4±3.2*	ND
o-methylbenzaldehyde	ND	1.9±0.5	4.4±1.2*	3.2±1.0*	4.9±1.2*	1.7±0.1*	7.1±0.4*	1.3±0.8	5.5±0.0*	6.0±0.7*	3.2±0.5*	5.1±0.1*	2.2±0.6*	0.7±0.4
Volatile Organic Compounds (VOCs) (μg)														
Toluene	ND	0.5±0.1*	ND	0.2±0.0*	0.6±0.1*	0.2±0.0*	ND	0.3±0.2	0.2±0.1	6.3±1.5*	0.2±0.1*	0.5±0.1*	0.5±0.0*	ND
p,m-xylene	0.1	0.1±0.0*	ND	0.1±0.0*	0.2±0.1*	0.1±0.0	ND	0.1±0.1	0.1±0.0	0.1±0.0*	0.1±0.0*	0.1±0.1*	0.1±0.0	ND
Tobacco-Specific Nitrosamines (TSNAs) (ng)														
NNN	ND	ND	2.7±2.2	0.8±0.8	ND	ND	0.9±0.4	4.3±2.4	1.9±0.3*	1.2±0.6	2.0±1.1	3.2±0.6*	1.3±0.1	ND
NNK	ND	2.0±2.0	3.6±1.8	3.5±1.8	ND	ND	1.1±1.1	21.1±6.3*	4.6±0.4*	28.3±13.2	2.1±2.1	13.0±1.4*	ND	ND
Metals (μg)														
Cd	0.02	0.17±0.08	0.15±0.03*	0.15±0.05	0.02±0.01	0.04±0.01	0.22±0.16	0.02±0.01	0.08±0.03	0.01±0.01	0.17±0.10	0.03±0.03	ND	0.03±0.01
Ni	0.17	0.28±0.22	0.29±0.08	0.21±0.03	0.17±0.07	0.14±0.06	0.11±0.06	0.23±0.09	0.26±0.10	0.19±0.09	0.12±0.04	0.11±0.08	0.11±0.05	0.19±0.04
Pb	0.02	0.06±0.01	0.06±0.03	0.07±0.01	0.03±0.01	0.05±0.01	0.03±0.01	0.04±0.01	0.57±0.28	0.09±0.04	0.06±0.02	0.04±0.03	0.03±0.03	0.04±0.01

Values are mean±SEM.
*Significant difference with Nicorette inhalator ($p<0.05$).
†Units are μg, except for nitrosamines units are ng.
BS, blank sample; ND, not detected; NNK, N′-nitrosonornicotine (NNN) and 4-(methylnitrosoamino)-1-(3-pyridyl)-1-butanone; NNN, N′-nitrosonornicotine; DL, detection limit.

(150 puffs). In Nicorette inhalator or in blank samples in turn, none of these compounds was noted.

Metals

Among 12 metals analysed in the study, cadmium, nickel and lead were identified, and were present in all vapours generated from e-cigarettes (except cadmium, which was not detected in a product of code EC12; table 3). The content of cadmium ranged from 0.01 μg to 0.22 μg, nickel from 0.11 μg to 0.29 μg and lead from 0.03 μg to 0.57 μg per one e-cigarette (150 puffs). The same metals in trace amounts were detected in Nicorette inhalator and in blank samples.

DISCUSSION

We examined vapours generated from 12 models of e-cigarettes for the presence of four groups of toxic compounds found in tobacco smoke. The Nicorette inhalator was used as a reference product. Such a choice was dictated by the premise that a therapeutic product like Nicorette inhalator should fulfil specified safety standards and should not contain significant levels of any of the analysed toxic compounds.

Our results confirm findings from the previous studies, in which small amounts of formaldehyde and acetaldehyde were detected in cartridges. [9 18] However, the presence of acrolein in a cartridge or nicotine solution has not been reported so far. Formaldehyde and acetaldehyde were also found in vapour exhaled to test chamber by volunteers who used e–cigarette filled with three various nicotine solutions.[26] Recently, Uchiyama *et al*[27] demonstrated that vapour generated from a single brand of e–cigarette contained low levels of formaldehyde, acetaldehyde and acrolein. There is a possibility that acrolein is present in vapour only, since this compound may be formed as a result of heating glycerin which is a component of the solution. Pyrolysis of glycerin has been studied in steam with acrolein, formaldehyde and acetaldehyde observed as the major products.[28 29] These products appear to result from dehydration and fragmentation of glycerin. Although energy calculations of the dehydration of glycerin by the neutral mechanisms indicate that these processes can only occur at relatively high temperatures such as in pyrolysis or combustion, the addition of acids allows substantially lower dehydration temperatures.[30]

All three carbonyl compounds found in the study and discussed above have been shown to be toxic in numerous studies: formaldehyde is classified as carcinogenic to humans (group 1 by International Agency for Research on Cancer, IARC)[31]; acetaldehyde as possibly carcinogenic to humans (group 2B),[31] and acrolein causes irritation to the nasal cavity, and damage to the lining of the lungs and is thought to contribute to cardiovascular disease in cigarette smokers.[32] Exposure to carbonyl compounds found in vapour might cause mouth and throat irritation which is the most frequently reported adverse event among e–cigarette users.[1 33] A study by Cassee *et al*[34] showed that sensory irritation in rats exposed to mixtures of formaldehyde, acetaldehyde and acrolein is more pronounced than that caused by each of the compounds separately. Future studies should evaluate possible adverse health outcomes of short term and long term exposure to these compounds among users of e–cigarettes and people involuntarily exposed to exhaled vapours.

We found that the vapour of some e-cigarettes contains traces of the carcinogenic nitrosamines NNN and NNK, whereas neither was detected in aerosol from the Nicorette inhalator. The studies conducted previously reported the presence of NNN and NNK in e–cigarette cartridges in amounts of 3.9–8.2 ng per cartridge,[18 19] which corresponds with the results on vapour obtained in the present paper. However some other studies have reported that some cartridges are free of nitrosamines.[12] This inconsistency of findings of various studies might be due to different analytical methodologies of variable sensitivity applied in the studies discussed above.

Two of the analysed VOCs were detected: toluene and m, p-xylene. None of the studies conducted until now reported the presence of these compounds in a cartridge, nicotine solution or e–cigarette vapour. None of these compounds were found in a study by Schripp *et al*[26] on passive exposure to e–cigarette vapours. Three toxic metals, cadmium, nickel and lead, were detected in the vapour of analysed e–cigarettes. Since the same elements were also detected in trace amounts in Nicorette inhalator and in blank samples it is possible that there were other sources of these metals. This limitation of the study does not allow us to conclude whether e–cigarette alone may be a significant source of exposure to these chemicals.

Recently, we published a study on tests for nicotine delivery of Polish and UK e–cigarette brands.[3] Many of the same brands in that paper have also been included in this study and tested for toxicants delivery. It should be mentioned that the leading brands with the highest nicotine delivery did not have the highest yields for toxicant delivery. This is important as while selecting the brands for nicotine the worst brands for toxicants generally can be avoided.

The results allowed us to compare the content of harmful substances between various e–cigarette models and conventional cigarettes (based on literature data).[35] To compare levels of selected toxins in e-cigarette vapour and mainstream smoke of a conventional cigarette we assumed that users of e-cigarettes take on overage 15 puffs during one session of product use, and it would correspond to smoking one conventional cigarette. In our study the vapours from e-cigarettes were generated from 150 puffs (10 series of 15 puffs each). For comparison purposes, we assumed that 150 puffs of an e-cigarette correspond to smoking 10 cigarettes. The comparison of toxic substance levels between conventional cigarettes and e-cigarettes is presented in table 4.

Table 4 Comparison of toxins levels between conventional and electronic cigarettes

Toxic compound	Conventional cigarette (μg in mainstream smoke) [35]	Electronic cigarette (μg per 15 puffs)	Average ratio (conventional vs electronic cigarette)
Formaldehyde	1.6–52	0.20–5.61	9
Acetaldehyde	52–140	0.11–1.36	450
Acrolein	2.4–62	0.07–4.19	15
Toluene	8.3–70	0.02–0.63	120
NNN	0.005–0.19	0.00008–0.00043	380
NNK	0.012–0.11	0.00011–0.00283	40

NNK, N′-nitrosonornicotine (NNN) and 4-(methylnitrosoamino)-1-(3-pyridyl)-1-butanone; NNN, N′-nitrosonornicotine.

As shown in table 4 levels of selected toxic compounds found in the smoke from a conventional cigarette were 9–450-fold higher than levels in the vapour of an e–cigarette. Smoking an e-cigarette (also referred to as 'vaping') can result in exposure to carcinogenic formaldehyde comparable with that received from cigarette smoking. Formaldehyde was also found in the vapour of medicinal inhalators, at levels that overlapped with those found in e-cigarette vapour. Exposure to acrolein, an oxidant and respiratory irritant thought to be a major contributor to cardiovascular disease from smoking, is 15 times lower on average in e-cigarette vapour compared with cigarette smoke. The amounts of toxic metals and aldehydes in e-cigarettes are trace amounts and are comparable with amounts contained in an examined therapeutic product.

The results of the study support the proposition that the vapour from e–cigarettes is less injurious than the smoke from cigarettes. Thus one would expect that if a person switched from conventional cigarettes to e-cigarettes the exposure to toxic chemicals and related adverse health effects would be reduced. The confirmation of that hypothesis however, requires further studies involving people using e-cigarette devices.

The primary limitation of our research is that the puffing profile we used may not reflect actual user puff topography. Hua *et al*[36] reported that e–cigarette users take longer puffs, and that puff duration varied significantly among e–cigarette brands and users. This suggests that actual doses of toxicants inhaled by e–cigarette users might be higher than measured in our study. Similarly to results of tobacco cigarette testing with smoking machines (International Organization for Standardization (ISO), Federal Trade Commission (FTC)) the values obtained in our study should be interpreted with caution. The other limitation of our research is that we have tested only 12 brands of e-cigarettes. There are numerous different brands in the market, and there is little information on their quality control.

CONCLUSIONS

The vapour generated from e-cigarettes contains potentially toxic compounds. However, the levels of potentially toxic compounds in e-cigarette vapour are 9–450-fold lower than those in the smoke from conventional cigarettes, and in many cases comparable with the trace amounts present in pharmaceutical preparation. Our findings support the idea that substituting tobacco cigarettes with electronic cigarettes may substantially reduce exposure to tobacco-specific toxicants. The use of e-cigarettes as a harm reduction strategy among cigarette smokers who are unable to quit, warrants further study.

What this paper adds

- Distributors of e–cigarettes promote the product as completely free of harmful substances. Currently, there is no comprehensive research on the presence of toxic chemicals in the vapour generated from e-cigarettes and inhaled by their users.
- This study of chemical composition of vapour generated from 12 brands of e-cigarettes revealed that the vapour contained some toxic substances.
- The levels of potentially toxic compounds in e-cigarette vapour were found to be from ninefold to almost 450-fold lower compared with smoke from conventional cigarettes, and in many cases comparable with trace amounts present in pharmaceutical preparations.

Contributors MLG and NB designed the study and wrote the paper. JK, MG and LK tested the products using smoking machine. AS and JK developed the analytical method and measured carbonyl compounds and VOCs. AP, MJC, and CRD developed the analytical method and measured metals. CH and PJ developed the analytical method and measured TSNAs. MLG and JK analysed the data. All contributors approved the final version of the manuscript.

Funding This study was conducted while the first author was at Medical University of Silesia, Poland and was supported by the Ministry of Science and Higher Education of Poland under grant number N N404 025638. The study sponsor had no involvement in the study design, collection, analysis and interpretation of data, the writing of the manuscript or the decision to submit the manuscript for publication. Analysis of nitrosamines at the University of California, San Francisco was supported by grants P30 DA012393 and S10 RR026437 from the National Institutes of Health.

Competing interests MLG received research funding from Pfizer, manufacturer of stop smoking medication and is currently funded by the UK Centre for Tobacco Control Studies (UKCTCS), UK Public Health Centre of Excellence. UKCTCS receives it funding from the Economic and Social Research Council (ESRC), British Heart Foundation (BHF), Cancer Research UK, National Institute for Health Research (NIHR), and Medical Research Council (MRC). Dr Benowitz is a consultant for several companies that market smoking cessation medications and has been a paid expert in litigation against tobacco companies. The other authors declare they have no actual or potential competing financial interests.

Provenance and peer review Not commissioned; externally peer reviewed.

Data sharing statement Data could be made available to qualified researchers by request to the corresponding author.

REFERENCES

1 Bullen C, McRobbie H, Thornley S, *et al*. Effect of an electronic nicotine delivery device (e–cigarette) on desire to smoke and withdrawal, user preferences and nicotine delivery: randomised cross-over trial. *Tob Control* 2010;19:98–103.
2 Cahn Z, Siegel M. Electronic cigarettes as a harm reduction strategy for tobacco control: a step forward or a repeat past mistakes? *J Public Health Policy* 2011;32:16–31.
3 Goniewicz ML, Kuma T, Gawron M, *et al*. Nicotine levels in electronic cigarettes. *Nicotine Tob Res* 2013;15:158–66.
4 Vansickel AR, Cobb CO, Weaver MF, *et al*. A clinical laboratory model for evaluating the acute effects of electronic "cigarettes": nicotine delivery profile and cardiovascular and subjective effects. *Cancer Epidemiol Biomarkers Prev* 2010;19:1945–53.
5 World Health Organization (WHO). *Marketers of electronic cigarettes should halt unproven therapy claims. News release*. Geneva, Switzerland. 19 September 2008. http://www.who.int/mediacentre/news/releases/2008/pr34/en/index.html (accessed 2 Oct 2012).
6 World Health Organization (WHO). *WHO says there is no evidence that the electronic cigarette helps smokers to quit smoking. WHO this week asked manufacturers and marketers to stop their unproved therapy claims. Transcript of WHO podcast*. Geneva, Switzerland. 26 September 2008. http://www.who.int/mediacentre/multimedia/podcasts/2008/transcript_48/en/ (accessed 2 Oct 2012).
7 Laugesen M. Ruyan nicotine electronic inhaler/e-cigarette: bench-top tests. *Poster POS5-11. Poster presented at the 2009 Joint Conference of SRNT and SRNT-Europe*; 27–30 April 2009, Dublin, Ireland: Saggart, Co.. http://www.healthnz.co.nz/DublinEcigBenchtopHandout.pdf (accessed 1 Oct 2012).
8 Alliance Technologies LLC. *Characterization of liquid "smoke juice" for electronic cigarettes*. 2009. http://truthaboutecigs.com/science/4.pdf (accessed 16 Mar 2012).
9 Coulson H. *Analysis of components from Gamucci electronic cigarette cartridges, tobacco flavor regular smoking liquid 2009*. Report number: E98D. LPD Lab Service. 3 March 2009. http://truthaboutecigs.com/science/7.pdf (accessed 16 Mar2012).
10 Exponent. *NJOY e-cigarette health risk assessment*. http://truthaboutecigs.com/science/5.php (accessed 16 Mar 2012).
11 Alliance Technologies LLC. *Characterization of Regal cartridges for electronic cigarettes*. 2009. http://truthaboutecigs.com/science/8.pdf (accessed 16 Mar 2012).
12 Alliance Technologies LLC. *Characterization of Regal cartridges for electronic cigarettes—Phase II*. 2009. http://truthaboutecigs.com/science/9.pdf (accessed 16 Mar 2012).
13 Ellicott M. *Analysis of components from "e-juice XX high 36mg/ml rated nicotine solution" ref S 55434. Report number: E249A*. LPD Lab Service. 11 June 2009. http://truthaboutecigs.com/science/11.pdf (accessed 16 Mar. 2012).
14 Valance C, Ellicott M. *Analysis of chemical components from high, med and low nicotine cartridges*. Report number: D318. LPD Lab Service. 10 September 2008. http://truthaboutecigs.com/science/12.pdf (accessed 16 Mar 2012).
15 Alliance Technologies LLC. *Chemical composition of "Instead" electronic cigarette smoke juice and vapor*. 2009. http://truthaboutecigs.com/science/13.pdf (accessed 16 Mar 2012).

16 Cai X, Kendall MW. *Gas chromatography mass spectrometry (GC-MS) analysis report*. Job number C09Y8961. EAG Evans Analytical Group. 21 July 2009. http://truthaboutecigs.com/science/14.pdf (accessed 16 Mar 2012).
17 Tytgat J. *"Super Smoker" Expert report*. Final Report. Toxicology Laboratory, Catholic University Leuven. 29 June 2007. http://truthaboutecigs.com/science/15.pdf (accessed 16 Mar 2012).
18 Laugesen M. *Safety report on the Ruyan e-cigarette cartridge and inhaled aerosol*. Christchurch, New Zealand: Health New Zealand Ltd., 30 October 2008. http://www.healthnz.co.nz/RuyanCartridgeReport30-Oct-08.pdf (accessed 21 May 2012).
19 Westenberger BJ. *Evaluation of e-cigarettes*. St Louis, MO: Department of Healthand Human Services, Food and Drug Administration, Center for Drug Evaluation and Research, Division of Pharmaceutical Analysis, 4 May 2009. http://www.fda.gov/downloads/Drugs/ScienceResearch/UCM173250.pdf (accessed 23 May 2012).
20 International Agency for Research on Cancer (IARC). *Evaluation of the carcinogenic risks to humans. Tobacco smoke and involuntary smoking. IARC Monographs.* Volume 38. Lyon, France. 2004. http://monographs.iarc.fr/ENG/Monographs/vol83/mono83-1.pdf (accessed 3 Oct 2012).
21 U.S. Department of Health and Human Services. *The health consequences of smoking: a report of the surgeon general*. Atlanta, GA: U.S. Department of Health and Human Services, Centers for Disease Control and Prevention, National Center for Chronic Disease Prevention and Health Promotion, Office on Smoking and Health, 2004. http://www.surgeongeneral.gov/library/reports/smokingconsequences/index.html (accessed 3 Oct 2012).
22 Perfetti TA, Rodgman A. The complexity of tobacco and tobacco smoke. *Beitr zur Tabakforsch Int* 2011;24:215–32.
23 Smith CJ, Livingston SD, Doolittle DJ. An international literature survey of IARC group I carcinogens reported in mainstream cigarette smoke. *Food Chem Toxicol* 1997;35:1107–30.
24 International Organization for Standardization (ISO). *Routine analytical cigarette-smoking machine—definitions and standard conditions. ISO 3308:2000*. Geneva, Switzerland, 2000.
25 International Conference on Harmonization (ICH). *Technical requirements for registration of pharmaceuticals for human use. Topic Q2 (R1): Validation of analytical procedures: text and methodology*. Geneva, Switzerland, 2005. http://www.ich.org/fileadmin/Public_Web_Site/ICH_Products/Guidelines/Quality/Q2_R1/Step4/Q2_R1__Guideline.pdf (accessed 8 Nov 2011).
26 Schripp T, Markewitz D, Uhde E, *et al*. Does e-cigarette consumption cause passive vaping? *Indoor Air* 2013;23:25–31.
27 Uchiyama S, Inaba Y, Kunugita N. Determination of acrolein and other carbonyls in cigarette smoke using coupled silica cartridges impregnated with hydroquinone and 2,4-dinitrophenylhydrazine. *J Chromatogr A* 2010;1217:4383–8.
28 Antal MJ, Mok WSL, Roy JC, *et al*. Pyrolytic sources of hydrocarbons from biomass. *J Anal Appl Pyrolysis* 1985;8:291–303.
29 Stein YS, Antal MJ, Jones MJ. A study of the gas-phase pyrolysis of glycerol. *Anal Appl Pyrolysis* 1983;4:283–96.
30 Nimlos MR, Blanksby SJ, Qian X, *et al*. Mechanisms of glycerol dehydration. *J Phys Chem A* 2006;110:6145–56.
31 International Agency for Research on Cancer (IARC). *Agents classified by the IARC Monographs, Volumes 1–105*. Geneva, Switzerland, 2012 http://monographs.iarc.fr/ENG/Classification/index.php (accessed: 10 September 2012).
32 U.S. Environmental Protection Agency (EPA). *Toxicological review of acrolein*. Washington, DC. May 2003. http://www.epa.gov/iris/toxreviews/0364tr.pdf (accessed 10 Sep 2012).
33 Goniewicz ML, Lingas EO, Hajek P. Patterns of electronic cigarette use and user beliefs about their safety and benefits: an internet survey. *Drug Alcohol Rev*. Published Online First 20 September 2012. doi:10.1111/j.1465-3362.2012.00512.x
34 Cassee FR, Arts JH, Groten JP, *et al*. Sensory irritation to mixtures of formaldehyde, acrolein, and acetaldehyde in rats. *Arch Toxicol* 1996;70:329–37.
35 Counts ME, Morton MJ, Laffoon SW, *et al*. Smoke composition and predicting relationships for international commercial cigarettes smoked with three machine-smoking conditions. *Regul Toxicol Pharmacol* 2005;41:185–227.
36 Hua M, Yip H, Talbot P. Mining data of usage of electronic nicotine delivery systems (ENDS) from YouTube videos. *Tob Control* 2013;22:103–6.

Original Article

Electronic cigarettes as a harm reduction strategy for tobacco control: A step forward or a repeat of past mistakes?

Zachary Cahn[a,*] and Michael Siegel[b]

[a]Department of Political Science, University of California at Berkeley, UC Berkeley Department of Political Science, 210 Barrows Hall #1950, Berkeley, CA 94720-1950, USA.

[b]Department of Community Health Sciences, Boston University School of Public Health, 801 Massachusetts Avenue, Boston, MA 02118, USA.

*Corresponding author.

Abstract The issue of harm reduction has long been controversial in the public health practice of tobacco control. Health advocates have been reluctant to endorse a harm reduction approach out of fear that tobacco companies cannot be trusted to produce and market products that will reduce the risks associated with tobacco use. Recently, companies independent of the tobacco industry introduced electronic cigarettes, devices that deliver vaporized nicotine without combusting tobacco. We review the existing evidence on the safety and efficacy of electronic cigarettes. We then revisit the tobacco harm reduction debate, with a focus on these novel products. We conclude that electronic cigarettes show tremendous promise in the fight against tobacco-related morbidity and mortality. By dramatically expanding the potential for harm reduction strategies to achieve substantial health gains, they may fundamentally alter the tobacco harm reduction debate.
Journal of Public Health Policy advance online publication, 9 December 2010; doi:10.1057/jphp.2010.41

Keywords: electronic cigarette; harm reduction; nicotine regulation; tobacco control

Introduction

Harm reduction is a framework for public health policy that focuses on reducing the harmful consequences of recreational drug use without necessarily reducing or eliminating the use itself.[1] Whereas harm reduction policies have been widely adopted

for illicit drug use (for example, needle exchange programs[2]) and alcohol use (for example, designated driver programs[3]), they have not found wide support in tobacco control. Many within the tobacco control community have embraced nicotine replacement therapy (NRT) and other pharmaceutical products, but these products are designed as cessation strategies rather than recreational alternatives. Recently, however, a new product that does not fit neatly into any previous category has entered the nicotine market: the electronic cigarette. Electronic cigarettes do not contain tobacco, but they are recreational nicotine devices and the user closely mimics the act of smoking. Thus, they are neither tobacco products nor cessation devices. The novel potential of electronic cigarettes warrants revisiting the harm reduction debate as it applies to these products.

In this article, we first explain what electronic cigarettes are and why they are difficult to categorize. Second, we examine the available evidence concerning the safety and efficacy of electronic cigarettes. Then, we review the most common arguments made against harm reduction in the tobacco control literature, followed by an analysis of each of these arguments in light of the recent emergence of electronic cigarettes. Finally, we identify conclusions from this analysis and their implications for the public health practice of tobacco control.

What are Electronic Cigarettes and Why are They Novel?

Electronic cigarettes are hand-held devices that deliver nicotine to the user through the battery-powered vaporization of a nicotine/propylene-glycol solution. The act of 'smoking' an electronic cigarette is called 'vaping' and it mimics smoking; but, there is no combustion and the user inhales vapor, not smoke. Although the nicotine is derived from tobacco, electronic cigarettes contain no tobacco. Theoretically, we would expect *vaping* to be less harmful than smoking as it delivers nicotine without the thousands of known and unknown toxicants in tobacco smoke. Moreover, a product that mimics the act of smoking, in addition to delivering nicotine, can address both pharmacologic and behavioral components of cigarette addiction. Electronic cigarettes are not manufactured or distributed by the tobacco industry or by the

  0197-5897 **Journal of Public Health Policy** 1–16

pharmaceutical industry. Hundreds of small distributors market them over the internet and in shopping mall kiosks. They have been on the market in the United States for more than 3 years and have become increasingly popular.

Review of Evidence Regarding the Safety of Electronic Cigarettes

As ~5300 of the estimated 10 000–100 000 chemicals in cigarette smoke have ever been identified,[4] we already have more comprehensive knowledge of the chemical constituents of electronic cigarettes than tobacco ones. We were able to identify 16 studies[5–17] that have characterized, quite extensively, the components contained in electronic cigarette liquid and vapor using gas chromatography mass spectrometry (GC-MS) (Table 1). These studies demonstrate that the primary components of electronic cigarette cartridges are propylene glycol (PG), glycerin, and nicotine. Of the other chemicals identified, the FDA has focused on potential health hazards associated with two: tobacco-specific nitrosamines (TSNAs) and diethylene glycol (DEG).[5]

TSNAs have been detected in two studies at trace levels.[5,6] The maximum level of total TSNAs reported was 8.2 ng/g.[6] This compares with a similar level of 8.0 ng in a nicotine patch, and it is orders of magnitude lower than TSNA levels in regular cigarettes.[18] Table 2 shows that electronic cigarettes contain only 0.07–0.2 per cent of the TSNAs present in cigarettes, a 500-fold to 1400-fold reduction in concentration. The presence of DEG in one of the 18 cartridges studied by the US Food and Drug Administration (FDA) is worrisome, yet none of the other 15 studies found any DEG. The use of a non-pharmaceutical grade of PG may explain this contamination.

Other than TSNAs and DEG, few, if any, chemicals at levels detected in electronic cigarettes raise serious health concerns. Although the existing research does not warrant a conclusion that electronic cigarettes are safe in absolute terms and further clinical studies are needed to comprehensively assess the safety of electronic cigarettes, a preponderance of the available evidence shows them to be much safer than tobacco cigarettes and comparable in toxicity to conventional nicotine replacement products.

Table 1: Laboratory studies of the components in and safety of electronic cigarettes[5–17]

Study	*Brand tested*	*Main findings*
Evaluation of e-cigarettes (FDA laboratory report)[5]	NJOY, Smoking Everywhere	'Very low levels' of tobacco-specific nitrosamines (TSNAs) were detected in 5 of 10 cartridges tested. Diethylene glycol (DEG) was detected about 0.1% in 1 of 18 cartridges tested.
Safety Report on the Ruyan e-Cigarette Cartridge and Inhaled Aerosol[6]	Ruyan	Trace levels of TSNAs were detected in the cartridge liquid. The average level of TSNAs was 3.9 ng/cartridge, with a maximum level of 8.2 ng/cartridge. Polyaromatic hydrocarbon carcinogens found in cigarette smoke were not detectable in cartridge liquid. No heavy metals detected. Exhaled carbon monoxide levels did not increase in smokers after use of the e-cigarette. The study concluded that e-cigarettes are very safe relative to cigarettes and safe in absolute terms on all measurements applied.
Ruyan E-cigarette Bench-top Tests[7]	Ruyan	None of the 50 priority-listed cigarette smoke toxicants were detected. Toxic emissions score for e-cigarette was 0, compared to 100–134 for regular cigarettes.
Characterization of Liquid 'Smoke Juice' for Electronic Cigarettes[8]	Liberty Stix	No compounds detected via gas chromatography mass spectrometry (GC-MS) of electronic cigarette cartridges or vapors other than propylene glycol (99.1% in vapor), glycerin (0.46%), and nicotine (0.44%).
Analysis of Components from Gamucci Electronic Cigarette Cartridges, Tobacco Flavour Regular Smoking Liquid[9]	Gamucci	GC-MS detected propylene glycol (77.5%), glycerin (14.0%), nicotine (8.5%), and cyclotene hydrate (0.08%) in e-cigarette liquid. Levels of cyclotene hydrate were not believed to be of concern.
Analysis of Components from Gamucci Electronic Cigarette Cartridges, Tobacco Flavour Light Smoking Liquid[9]	Gamucci	GC-MS detected propylene glycol (80.4%), glycerin (14.4%), and nicotine (5.3%) in e-cigarette liquid. No other compounds detected.

Analysis of Components from Gamucci Electronic Cigarette Cartridges, Ultra Light Smoking Liquid[9]	Gamucci	GC-MS detected propylene glycol (85.5%), glycerin (11.2%), and nicotine (3.3%) in e-cigarette liquid. No other compounds detected.
Analysis of Components from Gamucci Electronic Cigarette Cartridges, Tobacco Flavour Zero, Smoking Liquid[9]	Gamucci	GC-MS detected propylene glycol (84.3%), glycerin (7.6%), 1,3-bis(3-phenoxyphenoxy)Benzene (7.0%), 3-Isopropoxy-1,1,1,7,7,7-hexamethyl-3,5,5-tris(trimethylsiloxy)tetrasiloxane (0.77%), and α,3,4-tris[(trimethylsilyl)oxy]Benzeneacetic acid (0.39%) in e-cigarette liquid. No other compounds were detected. 1,3-bis(3-phenoxyphenoxy) Benzene is non-hazardous. The other two chemicals have an unknown safety profile, but are present at nominally low levels.
NJOY e-Cigarette Health Risk Assessment[10]	NJOY	The vapor constituents detected were propylene glycol, glycerin, nicotine, acetaldehyde, 1-methoxy-2-propanol, 1-hydroxy-2-propanone, acetic acid, 1-menthone, 2,3-butanediol, menthol, carvone, maple lactone, benzyl alcohol, 2-methyl-2-pentanoic acid, ethyl maltol, ethyl cinnamate, myosamine, benzoic acid, 2,3-bipyridine, cotinine, hexadecanoic acid, and 1'1-oxybis-2-propanol. No TSNAs, polyaromatic hydrocarbons, or other tobacco smoke toxicants were detected. On the basis of the amounts of these components present and an examination of the risk profile of these compounds, the report concludes that the only significant side effect expected would be minor throat irritation resulting from the acetaldehyde.
Characterization of Regal Cartridges for Electronic Cigarettes[11]	inLife	No DEG was detected in the cartridge liquid or vapors.
Characterization of Regal Cartridges for Electronic Cigarettes – Phase II[12]	inLife	No TSNAs were detected in the e-cigarette liquid (limit of detection was 20 ppm).

Table 1 *continued*

Study	*Brand tested*	*Main findings*
Analysis of Components from "e-Juice XX High 36 mg/ml rated Nicotine Solution": ref S55434[13]	e-Juice	GC-MS detected propylene glycol (51.2%), 1,3-bis(3-phenoxy phenoxy)Benzene (20.2%), glycerin (15.0%), nicotine (10.0%), vanillin (1.2%), ethanol (0.5%), and 3-cyclohexene-1-menthol,.α.,.α.4-trimethyl (0.4%). No other compounds detected. 1,3-bis(3-phenoxyphenoxy)Benzene is non-hazardous. Vanillin and 3-cyclohexene-1-menthol,.α.,.α.4-trimethyl have unknown safety profiles.
Analysis of Chemical Components from High, Med & Low Nicotine Cartridges[14]	The Electronic Cigarette Company (UK)	The compounds detected by GC-MS were propylene glycol, water, nicotine, ethanol, nitrogen, and triacetin. Triacetin is not known to be hazardous. No other compounds were detected.
Chemical Composition of "Instead" Electronic Cigarette Smoke Juice and Vapor[15]	Instead	No DEG was detected in e-cigarette liquid or vapor for the two products tested.
Gas Chromatography Mass Spectrometry (GC-MS) Analysis Report[16]	Not specified	GC-MS detected propylene glycol, glycerin, nicotine, caffeine, tetra-ethylene glycol, pyridine, methyl pyrrolyl, pyridine, methyl pyrrolidinyl, butyl-amine, and hexadecanoic acid in the e-cigarette liquid.
Super Smoker Expert Report[17]	Super Smoker	GC-MS detected propylene glycol, glycerin, nicotine, ethanol, acetone ethyl acetate, acetals, isobutyraldehyde, essential oils, and 2-methyl butanal in the e-cigarette liquid. No other compounds were detected.

Table 2: Maximum tobacco-specific nitrosamine levels[a] in various cigarettes and nicotine-delivery products (ng/g, except for nicotine gum and patch that are ng/patch or ng/gum piece)[6]

Product	*NNN*	*NNK*	*NAT*	*NAB*	*Total*
Nicorette gum (4 mg)[18]	2.00	ND	ND	ND	2.00
NicoDerm CQ patch (4 mg)[18]	ND	8.00	ND	ND	8.00
Electronic cigarettes[6]	**3.87**	**1.46**	**2.16**	**0.69**	**8.18**
Swedish snus[18]	980	180	790	60	2010
Winston (full)[18]	2200	580	560	25	3365
Newport (full)[18]	1100	830	1900	55	3885
Marlboro (ultra-light)[18]	2900	750	1100	58	4808
Camel (full)[18]	2500	900	1700	91	5191
Marlboro (full)[18]	2900	960	2300	100	6260
Skoal (long cut straight)[18]	4500	470	4100	220	9290

[a]The concentrations here represent nanograms (ng) of toxin detected in 1 ruyan 16-mg multi-dose cartridge (which contains approximately 1 gm of e-liquid). They are compared to the amount of toxin contained in approximately one tobacco cigarette (approximately 1 gm of tobacco) or one unit of nicotine replacement product.
Abbreviations: NNN=4-(methylnitrosamino)-1-(3-pyridyl)-1-butanone; NNK=N′-nitrosonornicotine; NAT=N′-nitrosoanatabine; NAB=N′-nitrosoanabasine.
ND=Not detected.

Review of Evidence about the Effectiveness of Electronic Cigarettes in Smoking Cessation

No studies have measured directly the effectiveness of electronic cigarettes in helping smokers cease smoking. Two published studies have examined the effectiveness of the product by measuring their effect on cravings and other short-term indicators. We summarize them briefly in Table 3.[19,20] Bullen *et al*[19] demonstrated that electronic cigarettes deliver nicotine effectively, more rapidly than a nicotine inhaler. In this study, electronic cigarette use significantly reduced craving, a similar effect to what was observed with a nicotine inhaler. Nicotine delivery and reduction in cigarette craving was much less than with a regular cigarette. Eissenberg[20] found that 10 puffs on one brand of electronic cigarettes delivered a small amount of nicotine, again far less than a tobacco cigarette, whereas another brand delivered little to none. The first brand was able to significantly reduce cigarette craving.

Taken together, this evidence suggests that electronic cigarettes are capable of reducing cigarette craving, but that the effect is not due exclusively to nicotine. Bullen *et al* observe that 'the reduction in

Table 3: Studies of the effectiveness of electronic cigarettes in reducing cigarette craving and other nicotine withdrawal symptoms[19,20]

Study	*Brand tested*	*Summary of findings*
Effect of an E-Cigarette on Cravings and Withdrawal, Acceptability and Nicotine Deliver: Randomized Cross-Over Trial[19]	Ruyan	The 16 mg electronic cigarette delivered nicotine more rapidly than a nicotine inhaler, but less rapidly than cigarettes. Electronic cigarette use significantly reduced craving, but less than cigarettes. The reduction of craving was similar to that observed with the nicotine inhaler. The electronic cigarettes produced fewer minor side effects than the nicotine inhaler.
Electronic Nicotine Delivery Devices: Ineffective Nicotine Delivery and Craving Suppression after Acute Administration[20]	NJOY and Crown Seven	After 10 puffs on an electronic cigarette, one of the two brands tested significantly reduced the craving for a cigarette. Nicotine delivery was found to be minimal.

desire to smoke in the first 10 min[utes] of [electronic cigarette] use appears to be independent of nicotine absorption' (p. 100).[19] The sizable craving reduction achieved by the 'placebo' – a nicotine-free electronic cigarette – demonstrates the ability of physical stimuli to suppress cravings independently.[19] Many studies have established the ability of *denicotinized* cigarettes to provide craving relief.[21,22] Barrett[21] found that denicotinized cigarettes reduce cravings more than a *nicotinized* inhaler, supporting Buchhalter *et al*'s[22] conclusion that although some withdrawal symptoms can be treated effectively with NRT, others, such as intense cravings, respond better to smoking-related stimuli.

Although more research is needed before we will know how effective electronic cigarettes are at achieving smoking abstinence, there is now sufficient evidence to conclude that these products are at least capable of suppressing the urge to smoke. There is also reason to believe that they offer an advantage over traditional nicotine delivery devices '[t]o the extent that non-nicotine, smoking-related stimuli alone can suppress tobacco abstinence symptoms indefinitely' (p. 556).[22]

The Most Common Arguments against Harm Reduction

Our review of the existing literature identified five primary arguments against harm reduction as a tobacco control strategy. These arguments explain why, in the past, harm reduction has not been accepted as a tobacco control strategy.

Promotion of safer alternatives will inhibit smoking cessation/ prevention efforts

The core fear is that smokers who might otherwise have quit smoking altogether will instead become addicted to another harmful product. In addition, a product that reduces harm to the individual may attract new, nonsmoking users, and thus undermine efforts to prevent tobacco use.[23]

Skepticism about the role of combusted products in harm reduction

The argument here, based on numerous related concerns, is that the combustion of tobacco produces inherently dangerous exposures and thus the search for a 'safer' cigarette is futile. It is impossible to assess the risks of a new product using machine measured delivery of smoke constituents, because there is no good way to simulate actual smoking behavior.[23] We cannot, moreover, easily infer human risk from chemical measurements because no reliable toxicity indices exist.[24] A widespread school of thought in tobacco control holds that the very nature of tobacco combustion precludes safer cigarettes, and therefore attempts to develop them should be abandoned.[25]

Alternatives promoted as safer may prove more dangerous, or they may be equally dangerous, leading to false or unsupported claims and to the misleading of the public

Experience with potentially reduced exposure products in the past has revealed that products promoted by the tobacco industry as potentially safer have ended up either not being safer or resulted in increased toxicant exposures.[23] In particular, a broad consensus within the public health community holds that 'light' cigarettes

misled consumers into thinking that they were being exposed to lower levels of toxic chemicals.[26] Smokers ended up compensating for the reduced nicotine in 'lights' by smoking with greater frequency and intensity, resulting in higher exposures than originally reported.[23]

NRT has not been effective, meaning that harm reduction equals harm maintenance

Pierce[27] argued that using NRT for tobacco harm reduction is, in fact, harm maintenance because NRT is so ineffective that it essentially ensures that Big Tobacco (the large tobacco industry companies) will not lose its customers. Smokers simply do not like products that merely deliver nicotine, and therefore 'we should not assume that smokers would be willing and able to substitute a nicotine maintenance product for their cigarette smoking' (p. S54).

Big Tobacco cannot be trusted to develop and market a safer tobacco alternative

The final argument is that the tobacco companies, based on their history of lies and deception, simply cannot be trusted to develop and market a safer tobacco alternative.[28] Fairchild and Colgrove[28] make a related point, that 'prioritizing the reduction of harm, however great or minimal, may necessitate some level of cooperation with the tobacco industry and will *certainly prove lucrative for it*' (our emphasis added, p. 201) Thus, tobacco harm reduction will necessarily benefit the tobacco industry regardless of what else might be achieved.

Analysis of Arguments in Light of the Emergence of Electronic Cigarettes

With the emergence of electronic cigarettes, the harm reduction debate in tobacco control has changed. We now address the five major arguments against harm reduction in light of the emergence of electronic cigarettes.

Promotion of safer alternatives will inhibit smoking cessation/ prevention efforts

In contrast to reduced risk cigarettes or smokeless tobacco products, electronic cigarettes are not tobacco products. Thus, switching to electronic cigarettes is not an alternative to smoking cessation, but rather a form of smoking cessation akin to long-term use of NRT. Moreover, because 'low absolute abstinence rates suggest that nicotine alone may not be sufficient to suppress … abstinence symptoms effectively' (p. 551),[22] higher abstinence rates are likely to obtain from a product that better addresses these symptoms. Crucially, electronic cigarettes could entice smokers who were not otherwise inclined, to attempt to quit. Although the use of electronic cigarettes by nonsmokers is a theoretical concern, there is no existing evidence that youths or nonsmokers are using the product. Regulations can address the sale and marketing of these products to minors.

Skepticism about the role of combusted products in harm reduction

Electronic cigarettes, such as NRT, are not tobacco products and no combustion takes place.

Alternatives promoted as safer may actually be equally or more dangerous

Thus far, none of the more than 10 000 chemicals present in tobacco smoke,[4] including over 40 known carcinogens, has been shown to be present in the cartridges or vapor of electronic cigarettes in anything greater than trace quantities. No one has reported adverse effects, although this product has been on the market for more than 3 years. Still, the FDA struck a more ominous tone in its July 2009 press release, warning of the presence of carcinogens at 'detectable' levels.[29] Yet it failed to mention that the levels of these carcinogens was similar to that in NRT products (Table 2). Whereas electronic cigarettes cannot be considered safe, as there is no threshold for carcinogenesis, they are undoubtedly safer than tobacco cigarettes.

NRT is unappealing and ineffective

Pharmaceutical products for dispensing nicotine are unappealing 'by design' (p. S123)[30] to avoid 'abuse-liability'.[30] Electronic cigarettes, on the other hand, were designed with the express purpose of replicating the act of smoking, without using tobacco.[31] An investment newsletter reports that demand thus far has been explosive.[32] Intense consumer interest in electronic cigarettes has already spawned a vibrant online community of 'vapers' who compare and contrast the performance of various brands and models according to their durability, battery life, thickness of vapor, and other criteria.[33] No non-tobacco nicotine product has heretofore elicited such dedication among its users, suggesting the rare promise of the electronic cigarette as a smoking cessation tool.

Big Tobacco cannot be trusted

Electronic cigarettes are not tobacco products and not produced by tobacco companies. They were invented in Beijing by a Chinese pharmacist Hon Lik, whose employer, Golden Dragon Holdings, 'was so inspired that it changed its name to Ruyan (meaning "like smoke") and started selling abroad'.[31] Rather than being helpful to cigarette makers, electronic cigarettes compete directly against them.[32] Thus David Sweanor, adjunct law professor specializing in tobacco control issues at the University of Ottawa, says they are 'exactly what the tobacco companies have been afraid of all these years'.[31]

Conclusion

Tobacco cigarettes are the leading cause of disease in the United States, which is why the 'primary goal of tobacco control is to reduce mortality and morbidity associated with tobacco use' (p. 326).[23] Electronic cigarettes are designed to mitigate tobacco-related disease by reducing cigarette consumption and smoking rates. The evidence reviewed in this article suggests that electronic cigarettes are a much safer alternative to tobacco cigarettes. They are likely to improve upon the efficacy of traditional pharmacotherapy for smoking cessation.

In light of this evidence, it is unfortunate that in the United States, the American Cancer Society, American Lung Association, American

  0197-5897 **Journal of Public Health Policy** 1–16

Heart Association, Campaign for Tobacco-Free Kids, Action on Smoking and Health, American Legacy Foundation, American Academy of Pediatrics, and the Association for the Treatment of Tobacco Use and Dependence have all issued statements supporting FDA efforts to take them off the US market.[34] In the United States, the courts will ultimately determine whether the FDA has the legal authority to do this, but we question the ethical and health policy merits of this approach.

Do products with established user bases warrant a different regulatory approach than entirely new products? This would seem to follow from consistent application of the principal of nonmaleficence – 'do no harm.' Products yet to enter the market have only *potential* beneficiaries, people who can only speculate about what the precise therapeutic effects of the product will be for them. In contrast, products already on the market have users who may already be deriving benefits. By definition, enacting a ban will harm current users, unless the evidence suggests that the harms outweigh the benefits *for those already using the product*. The burden of proof is on the regulatory agency to demonstrate that the product is unreasonably dangerous for its intended use.

How does this principle apply to electronic cigarettes? For the many vapers who report using them in place of cigarettes,[33] the benefits of the product are readily observable, already established. Simply demonstrating that electronic cigarettes are 'not safe' may not be sufficient grounds to ban them. Unless the evidence suggests that vaping does not yield the anticipated *reduction* in harm to the user, enacting an electronic cigarette prohibition will do harm to hundreds of thousands of vapers already using electronic cigarettes in place of tobacco ones – a clear violation of nonmaleficence.

The essential rationale for the FDA's pre-market approval process – to keep dangerous products out of the marketplace – may not easily extend to new nicotine products because a range of extraordinarily deadly nicotine products is already grandfathered into the market. This has led to an awkward nicotine regulatory structure where dirty tobacco products face few barriers to market entry whereas cleaner products are subject to oft onerous hurdles. The FDA contends that they can and should regulate electronic cigarettes as 'drug-device combinations' that are required to meet stringent Federal Food Drug and Cosmetic Act (FDCA) safety standards. The FDA reasons that

electronic cigarettes do not qualify for the usual exemption from FDCA standards afforded to most other recreational nicotine products because 'much less is known about the safety of E-Cigarettes' and 'it may be possible for E-Cigarettes … to satisfy the FDCA's safety, effectiveness, and labeling requirements and obtain FDA approval' (p. 26).[35] Ironically, the only nicotine products exempted from FDCA safety requirements are those that are too obviously harmful to have any chance of meeting these requirements. Litigation presently before the US Court of Appeals for the District of Columbia may ultimately determine whether the FDA can legally regulate electronic cigarettes as drug-device combinations.[36] Regardless of the court's decision, we believe a better regulatory approach would not actively discourage producers of harm reduction products.

Fairchild and Colgrove[28] conclude that 'the later history of tobacco industry deception and manipulation was an important factor contributing to the erosion of public health support for harm reduction'(p. 201). With entrenched skepticism toward harm reduction now manifested as deep cynicism about electronic cigarettes – a distinct product that actually *does* reduce risk and threatens cigarette makers – the tobacco industry is ironically benefiting from its own past duplicity. The push to ban electronic cigarettes may repeat the mistakes of the past in the name of avoiding them. Regulatory policy for electronic cigarettes and other novel nicotine products must be guided by an accurate understanding of how they compare to tobacco cigarettes and NRT in terms of reducing toxic exposures and helping individual smokers quit.

About the Authors

Zachary Cahn is a graduate student in the political science department at the University of California at Berkeley. His research focuses on the political determinants of substance control policies.

Michael Siegel is a professor of community health sciences at Boston University School of Public Health, where he has studied tobacco epidemiology and public policy and evaluated tobacco-related policies at national, state, and local levels.

References

1. Alderman, J., Dollar, K.M. and Kozlowski, L.T. (2010) Commentary: Understanding the origins of anger, contempt, and disgust in public health policy disputes: Applying moral psychology to harm reduction debates. *Journal of Public Health Policy* 31(1): 1–16.
2. Des Jarlais, D.C., McKnight, C., Goldblatt, C. and Purchase, D. (2009) Doing harm reduction better: Syringe exchange in the United States. *Addiction* 104(9): 1441–1446.
3. Ditter, S.M., Elder, R.W., Shults, R.A., Sleet, D.A., Compton, R. and Nichols, J.L. (2005) Effectiveness of designated driver programs for reducing alcohol-impaired driving: A systematic review. *American Journal of Preventive Medicine* 28(Suppl. 5): 280–287.
4. Rodgman, A. and Perfetti, T.A. (2009) *The Chemical Components of Tobacco and Tobacco Smoke*. Boca Raton, FL: CRC Press.
5. Westenberger, B.J. (2009) *Evaluation of e-Cigarettes*. St Louis, MO: Department of Health and Human Services, Food and Drug Administration, Center for Drug Evaluation and Research, Division of Pharmaceutical Analysis, http://truthaboutecigs.com/science/2.pdf, accessed 16 March 2010.
6. Laugesen, M. (2008) *Safety Report on the Ruyan e-Cigarette Cartridge and Inhaled Aerosol*. Christchurch, New Zealand: Health New Zealand, http://www.healthnz.co.nz/RuyanCartridgeReport30-Oct-08.pdf, accessed 16 March 2010.
7. Laugesen, M. (2009) *Ruyan E-cigarette Bench-Top Tests*. Christchurch, New Zealand: Health New Zealand, http://www.healthnz.co.nz/DublinEcigBenchtopHandout.pdf, accessed 16 March 2010.
8. Alliance Technologies LLC (2009) *Characterization of Liquid "Smoke Juice" for Electronic Cigarettes*. Monmouth Junction, NJ: Alliance Technologies LLC, http://truthaboutecigs.com/science/4.pdf, accessed 16 March 2010.
9. Coulson, H. (2009) *Analysis of Components from Gamucci Electronic Cigarette Cartridges, Tobacco Flavour Regular Smoking Liquid*. Lancashire, UK: Blackburn MicroTech Solutions, http://truthaboutecigs.com/science/7.pdf, accessed 16 March 2010.
10. Exponent. (2009) *NJOY e-Cigarette Health Risk Assessment*. Menlo Park, CA: Exponent, http://truthaboutecigs.com/science/5.php, accessed 16 March 2010.
11. Alliance Technologies LLC. (2009) *Characterization of Regal Cartridges for Electronic Cigarettes*. Monmouth Junction, NJ: Alliance Technologies LLC, http://truthaboutecigs.com/science/8.pdf, accessed 16 March 2010.
12. Alliance Technologies LLC. (2009) *Characterization of Regal Cartridges for Electronic Cigarettes – Phase II*. Monmouth Junction, NJ: Alliance Technologies LLC, http://truthaboutecigs.com/science/9.pdf, accessed 16 March 2010.
13. Ellicott, M. (2009) *Analysis of Components from "e-Juice XX HIGH 36 mg/ml Rated Nicotine Solution" ref S 55434*. Lancashire, UK: Blackburn MicroTech Solutions, http://truthaboutecigs.com/science/11.pdf, accessed 16 March 2010.
14. Valance, C. and Ellicott, M. (2008) *Analysis of Chemical Components from High, Med & Low Nicotine Cartridges*. Lancashire, UK: Blackburn MicroTech Solutions, http://truthaboutecigs.com/science/12.pdf, accessed 16 March 2010.
15. Alliance Technologies LLC. (2009) *Chemical Composition of 'Instead' Electronic Cigarette Smoke Juice and Vapor*. Monmouth Junction, NJ: Alliance Technologies LLC, http://truthaboutecigs.com/science/13.pdf, accessed 16 March 2010.
16. Cai, X. and Kendall, M.W. (2009) *Gas Chromatography Mass Spectrometry (GC-MS) Analysis Report*. Sunnyvale, CA: Evans Analytical Group, http://truthaboutecigs.com/science/14.pdf, accessed 16 March 2010.
17. Tytgat, J. (2007) *"Super Smoker" Expert Report*. Leuven, Belgium: Catholic University of Leuven, http://truthaboutecigs.com/science/15.pdf, accessed 16 March 2010.

18. Stepanov, I., Jensen, J., Hatsukami, D. and Hecht, S.S. (2006) Tobacco-specific nitrosamines in new tobacco products. *Nicotine & Tobacco Research* 8(2): 309–313.
19. Bullen, C., McRobbie, H., Thornley, S., Glover, M., Lin, R. and Laugesen, M. (2010) Effect of an electronic nicotine delivery device (e cigarette) on desire to smoke and withdrawal, user preferences and nicotine delivery: Randomised cross-over trial. *Tobacco Control* 19(2): 98–103.
20. Eissenberg, T. (2010) Electronic nicotine delivery devices: Ineffective nicotine delivery and craving suppression after acute administration. *Tobacco Control* 19(1): 87–88.
21. Barrett, S.P. (2010) The effects of nicotine, denicotinized tobacco, and nicotine-containing tobacco on cigarette craving, withdrawal, and self-administration in male and female smokers. *Behavioral Pharmacology* 21(2): 144–152.
22. Buchhalter, A.R., Acosta, M.C., Evans, S.E., Breland, A.B. and Eissenberg, T. (2005) Tobacco abstinence symptom suppression: The role played by the smoking-related stimuli that are delivered by denicotinized cigarettes. *Addiction* 100(4): 550–559.
23. Zeller, M. and Hatsukami, D. (2009) The strategic dialogue on tobacco harm reduction: A vision and blueprint for action in the US. *Tobacco Control* 18(4): 324–332.
24. Pankow, J.F., Watanabe, K.H., Toccalino, P.L., Luo, W. and Austin, D.F. (2007) Calculated cancer risks for conventional and "potentially reduced exposure product" cigarettes. *Cancer Epidemiology, Biomarkers & Prevention* 16(3): 584–592.
25. Miller, G.H. (1985) The "less hazardous" cigarette: A deadly delusion. *New York State Journal of Medicine* 85(7): 313–317.
26. Kozlowski, L.T., Goldberg, M.E., Yost, B.A., White, E.L., Sweeney, C.T. and Pillitteri, J.L. (1998) Smokers' misperceptions of light and ultra-light cigarettes may keep them smoking. *American Journal of Preventive Medicine* 15(1): 9–16.
27. Pierce, J. (2002) Harm reduction or harm maintenance? [Editorial]. *Nicotine & Tobacco Research* 4(Suppl. 2): S53–S54.
28. Fairchild, A. and Colgrove, J. (2004) Out of the ashes: The life, death, and rebirth of the "safer" cigarette in the United States. *American Journal of Public Health* 94(2): 192–204.
29. US Food and Drug Administration. (2009) FDA and public health experts warn about electronic cigarettes. FDA news release, 22 July, http://www.fda.gov/NewsEvents/Newsroom/PressAnnouncements/ucm173222.htm, accessed 5 January 2010.
30. Shiffman, S., Gitchell, J.G., Warner, K.E., Slade, J., Henningfield, J.E. and Pinney, J.M. (2002) Tobacco harm reduction: Conceptual structure and nomenclature for analysis and research. *Nicotine & Tobacco Research* 4(Suppl. 2): S113–S129.
31. Denmick, B. (2009) A high-tech approach to getting a nicotine fix. *Los Angeles Times*, 25 April, http://articles.latimes.com/2009/apr/25/world/fg-china-cigarettes25, accessed 3 January 2010.
32. Mickey, A. (2009) Big tobacco beware, the next big stock story could involve e-cigarettes. *Seeking Alpha*, 12 April, http://seekingalpha.com/article/130595-big-tobacco-beware-the-next-big-story-stock-could-involve-e-cigarettes, accessed 2 January 2010.
33. E-cigarette Forum, http://www.e-cigarette-forum.com/forum/, accessed 16 March 2010.
34. Siegel, M. The rest of the story: Tobacco news analysis and commentary, http://tobaccoanalysis.blogspot.com, accessed 5 January 2010.
35. Food and Drug Administration. (2009) *Brief in Opposition to Motion for Preliminary Injunction*. Washington DC: United States Food and Drug Administration, 11 May 2009, http://www.fda.gov/downloads/NewsEvents/PublicHealthFocus/UCM173191.pdf, accessed June 2010.
36. Smoking Everywhere, Inc., *et al* v. United States Food and Drug Administration, *et al* (2010) United States Court of Appeals for the District of Columbia Circuit (No. 10-5032).

November 7, 2011

A Tool to Quit Smoking Has Some Unlikely Critics

By JOHN TIERNEY

If you want a truly frustrating job in public health, try getting people to stop smoking. Even when researchers combine counseling and encouragement with nicotine patches and gum, few smokers quit.

Recently, though, experimenters in Italy had more success by doing less. A team led by Riccardo Polosa of the University of Catania recruited 40 hard-core smokers — ones who had turned down a free spot in a smoking-cessation program — and simply gave them a gadget already available in stores for $50. This electronic cigarette, or e-cigarette, contains a small reservoir of liquid nicotine solution that is vaporized to form an aerosol mist.

The user "vapes," or puffs on the vapor, to get a hit of the addictive nicotine (and the familiar sensation of bringing a cigarette to one's mouth) without the noxious substances found in cigarette smoke.

After six months, more than half the subjects in Dr. Polosa's experiment had cut their regular cigarette consumption by at least 50 percent. Nearly a quarter had stopped altogether. Though this was just a small pilot study, the results fit with other encouraging evidence and bolster hopes that these e-cigarettes could be the most effective tool yet for reducing the global death toll from smoking.

But there's a powerful group working against this innovation — and it's not Big Tobacco. It's a coalition of government officials and antismoking groups who have been warning about the dangers of e-cigarettes and trying to ban their sale.

The controversy is part of a long-running philosophical debate about public health policy, but with an odd role reversal. In the past, conservatives have leaned toward "abstinence only" policies for dealing with problems like teenage pregnancy and heroin addiction, while liberals have been open to "harm reduction" strategies like encouraging birth control and dispensing methadone.

When it comes to nicotine, though, the abstinence forces tend to be more liberal, including Democratic officials at the state and national level who have been trying to stop the sale of e-cigarettes and ban their use in smoke-free places. They've argued that smokers who want an

alternative source of nicotine should use only thoroughly tested products like Nicorette gum and prescription patches — and use them only briefly, as a way to get off nicotine altogether.

The Food and Drug Administration tried to stop the sale of e-cigarettes by treating them as a "drug delivery device" that could not be marketed until its safety and efficacy could be demonstrated in clinical trials. The agency was backed by the American Cancer Society, the American Heart Association, Action on Smoking and Health, and the Center for Tobacco-Free Kids.

The prohibitionists lost that battle last year, when the F.D.A. was overruled in court, but they've continued the fight by publicizing the supposed perils of e-cigarettes. They argue that the devices, like smokeless tobacco, reduce the incentive for people to quit nicotine and could also be a "gateway" for young people and nonsmokers to become nicotine addicts. And they cite an F.D.A. warning that several chemicals in the vapor of e-cigarettes may be "harmful" and "toxic." But the agency has never presented evidence that the trace amounts actually cause any harm, and it has neglected to mention that similar traces of these chemicals have been found in other F.D.A.-approved products, including nicotine patches and gum. The agency's methodology and warnings have been lambasted in scientific journals by Dr. Polosa and other researchers, including Brad Rodu, a professor of medicine at the University of Louisville in Kentucky.

Writing in Harm Reduction Journal this year, Dr. Rodu concludes that the F.D.A.'s results "are highly unlikely to have any possible significance to users" because it detected chemicals at "about one million times lower concentrations than are conceivably related to human health." His conclusion is shared by Michael Siegel, a professor at the Boston University School of Public Health.

"It boggles my mind why there is a bias against e-cigarettes among antismoking groups," Dr. Siegel said. He added that it made no sense to fret about hypothetical risks from minuscule levels of several chemicals in e-cigarettes when the alternative is known to be deadly: cigarettes containing thousands of chemicals, including dozens of carcinogens and hundreds of toxins.

Both sides in the debate agree that e-cigarettes should be studied more thoroughly and subjected to tighter regulation, including quality-control standards and a ban on sales to minors. But the harm-reduction side, which includes the American Association of Public Health Physicians and the American Council on Science and Health, sees no reason to prevent adults from using e-cigarettes. In Britain, the Royal College of Physicians has denounced "irrational and immoral" regulations inhibiting the introduction of safer nicotine-delivery devices.

"Nicotine itself is not especially hazardous," the British medical society concluded in 2007. "If nicotine could be provided in a form that is acceptable and effective as a cigarette substitute, millions of lives could be saved."

The number of Americans trying e-cigarettes quadrupled from 2009 to 2010, according to the

Centers for Disease Control. Its survey last year found that 1.2 percent of adults, or close to three million people, reported using them in the previous month.

"E-cigarettes could replace much or most of cigarette consumption in the U.S. in the next decade," said William T. Godshall, the executive director of Smokefree Pennsylvania. His group has previously campaigned for higher cigarette taxes, smoke-free public places and graphic warnings on cigarette packs, but he now finds himself at odds with many of his former allies over the question of e-cigarettes.

"There is no evidence that e-cigarettes have ever harmed anyone, or that youths or nonsmokers have begun using the products," Mr. Godshall said. On a scale of harm from 1 to 100, where nicotine gums and lozenges are 1 and cigarettes are 100, he estimated that e-cigarettes are no higher than 2.

If millions of people switch from smoking to vaping, it would be a challenge to conventional wisdom about the antismoking movement. The decline in smoking is commonly attributed to paternalistic and prohibitionist social policies, and it's ritually invoked as a justification for crackdowns on other products — trans fats, salt, soft drinks, Quarter Pounders.

But the sharpest decline in smoking rates in the United States occurred in the decades before 1990, when public health experts concentrated on simply educating people about the risks. The decline has been slower the past two decades despite increasingly elaborate smoking-cessation programs and increasingly coercive tactics: punitive taxes; limits on marketing and advertising; smoking bans in offices, restaurants and just about every other kind of public space.

Some 50 million Americans continue to smoke, and it's not because they're too stupid to realize it's dangerous. They go on smoking in part because of a fact that the prohibitionists are loath to recognize: Nicotine is a drug with benefits. It has been linked by researchers (and smokers) to reduced anxiety and stress, lower weight, faster reaction time and improved concentration.

"It's time to be honest with the 50 million Americans, and hundreds of millions around the world, who use tobacco," Dr. Rodu writes. "The benefits they get from tobacco are very real, not imaginary or just the periodic elimination of withdrawal.

"It's time to abandon the myth that tobacco is devoid of benefits, and to focus on how we can help smokers continue to derive those benefits with a safer delivery system."

As a former addict myself — I smoked long ago, and was hooked on Nicorette gum for a few years — I can appreciate why the prohibitionists fear nicotine's appeal. I agree that abstinence is the best policy. Yet it's obviously not working for lots of people. No one knows exactly what long-term benefits they'd gain from e-cigarettes, but we can say one thing with confidence: Every time they light up a tobacco cigarette, they'd be better off vaping.

The New York Times

December 8, 2013

The Case for Tolerating E-Cigarettes

By AMY L. FAIRCHILD and JAMES COLGROVE

DEBATE over e-cigarettes — battery-powered cigarette look-alikes that heat liquid nicotine but emit a harmless vapor — is raging. New York City and Chicago are considering adding e-cigarettes to their bans on smoking in bars, restaurants and parks, and Los Angeles is moving to restrict e-cigarette sales, even though e-cigarettes don't generate smoke and, while not proved to be entirely safe for users, are undoubtedly less hazardous than tobacco cigarettes.

The evidence, while still thin, suggests that many e-cigarette users, hoping to kick the habit, use e-cigarettes as a safer alternative to tobacco. Research also suggests that e-cigarettes may be better at helping to sustain smoking cessation than pharmaceutical products like nicotine patches or gums.

No one believes nicotine addiction is a good thing, and our qualified support for e-cigarettes is not one we reach lightly. Although some e-cigarette manufacturers have no links to the tobacco industry, Big Tobacco is consuming an ever-greater share of the e-cigarette market. It is hard for public health advocates like us to look favorably on anything the industry wants. But history shows that harm reduction — the doctrine that many risks cannot be eradicated and that efforts are best spent on minimizing the resulting harm — has had an important place in antismoking efforts and suggests that regulation is better than prohibition.

It's been only a half-century since the federal government took an interest in making tobacco products safer. In 1964, Surgeon General Luther L. Terry issued a watershed report definitively linking smoking with lung cancer. But he also described research into new kinds of cigarettes as "a promising avenue for further development." In the early 1970s, the government spent some $6 million a year to try to develop safer tobacco products. Even the health secretary Joseph A. Califano Jr., who called smoking "Public Enemy No. 1," saw, in 1978, a place for "research aimed at creating a less hazardous cigarette." As late as 1981, the surgeon general advised smokers who couldn't or wouldn't quit to switch to low-tar and low-nicotine brands.

The American Cancer Society, while worried that the development of less hazardous cigarettes might derail efforts to deter people from smoking or getting them to quit, supported "frank scientific discussion about the possibilities of developing cigarettes that will be less harmful and still satisfying to smokers."

This effort came to a halt in the 1980s, when stunning revelations from high-profile court cases demonstrated that the tobacco industry had lied about the dangers of smoking for decades and

even manipulated the levels of nicotine in its products to ensure that smokers stayed hooked. The magnitude of the deception made it nearly impossible to consider the possibility of a "safer" tobacco product. It inspired, among advocates, opposition to anything less than total cessation.

This new stance was supported by the availability of over-the-counter nicotine replacement therapies and a focus on protection of bystanders from secondhand smoke. As the head of the American Heart Association put it in 2000: "There is no such thing as a safer cigarette."

The irony is that, during these same years, AIDS prompted public health advocates to support needle exchange for users of intravenous drugs, a harm-reduction approach that also drew fire from those who favored complete elimination of drug use. Fears that such programs would lead to greater illicit drug use have been definitively put to rest.

Of course the analogy is not exact: Unlike clean needles, which present no independent harms to injecting drug users, less risky alternatives to smoking, like smokeless chewing tobacco and the moist tobacco product known as snus, carry a grave risk: oral cancers.

E-cigarettes potentially overcome that barrier. Most experts consider nicotine harmful only at extremely high doses. Tobacco control advocates tolerate the long-term use of therapies like the nicotine patch and nicotine gum despite their approval only as temporary smoking-cessation aids. In 2000, the chairman of a Public Health Service panel called tobacco dependence a "chronic condition that warrants repeated treatment," even if that meant treating smokers "for the rest of their lives."

Advocates fear that e-cigarettes will serve as a gateway to deadly cigarettes — or sustain smokers in public settings where lighting up is banned. "Waiting to act," New York City's health commissioner, Thomas A. Farley, said, "is a risk we should not take."

But there is a price to such rigidity. Emotion should not rule out harm reduction, even if eradication of smoking is the ultimate goal. Banning vaping in public won't help. Instead, e-cigarettes should be regulated by the Food and Drug Administration as products "sold or distributed for use to reduce harm or the risk of tobacco-related disease." The industry can't be trusted to provide safer products. The historical mistake was not the pursuit of a safer cigarette, but championing that cause with dishonest partners.

If e-cigarettes can reduce, even slightly, the blight of six million tobacco-related deaths a year, trying to force them out of sight is counterproductive.

Amy L. Fairchild is a professor, and James Colgrove is an associate professor, of sociomedical sciences at the Mailman School of Public Health at Columbia.

Inhalation Toxicology

http://informahealthcare.com/iht
ISSN: 0895-8378 (print), 1091-7691 (electronic)

Inhal Toxicol, 2013; 25(6): 354–361

DOI: 10.3109/08958378.2013.793439

informa healthcare

RESEARCH ARTICLE

Cytotoxicity evaluation of electronic cigarette vapor extract on cultured mammalian fibroblasts (ClearStream-LIFE): comparison with tobacco cigarette smoke extract

Giorgio Romagna[1], Elena Allifranchini[1], Elena Bocchietto[1], Stefano Todeschi[1], Mara Esposito[1], and Konstantinos E. Farsalinos[2]

[1]*Abich srl, biological and chemical toxicology research laboratory, Verbania (VB), Italy and* [2]*Department of Cardiology, Onassis Cardiac Surgery Cente, Kallithea, Greece*

Abstract

Context: Electronic cigarettes (ECs) are used as alternatives to smoking; however, data on their cytotoxic potential are scarce.
Objective: To evaluate the cytotoxic potential of 21 EC liquids compared to the effects of cigarette smoke (CS).
Methods: Cytotoxicity was evaluated according to UNI EN ISO 10993-5 standard. By activating an EC device, 200 mg of liquid was evaporated and was extracted in 20 ml of culture medium. CS extract from one cigarette was also produced. The extracts, undiluted (100%) and in five dilutions (50%, 25%, 12.5%, 6.25% and 3.125%), were applied to cultured murine fibroblasts (3T3), and viability was measured after 24-hour incubation by 3-[4,5-dimethylthiazol-2-yl]-2,5-diphenyltetrazolium bromide assay. Viability of less than 70% was considered cytotoxic.
Results: CS extract showed cytotoxic effects at extract concentrations above 12.5% (viability: 89.1 ± 3.5% at 3.125%, 77.8 ± 1.8% at 6.25%, 72.8 ± 9.7% at 12.5%, 5.9 ± 0.9% at 25%, 9.4 ± 5.3% at 50% and 5.7 ± 0.7% at 100% extract concentration). Range of fibroblast viability for EC vapor extracts was 88.5–117.8% at 3.125%, 86.4–115.3% at 6.25%, 85.8–111.7% at 12.5%, 78.1–106.2% at 25%, 79.0–103.7% at 50% and 51.0–102.2% at 100% extract concentration. One vapor extract was cytotoxic at 100% extract concentration only (viability: 51.0 ± 2.6%). However, even for that liquid, viability was 795% higher relative to CS extract.
Conclusions: This study indicates that EC vapor is significantly less cytotoxic compared tobacco CS. These results should be validated by clinical studies.

Keywords

Cytotoxicity, electronic cigarette, fibroblasts, *in vitro*, nicotine, smoking, tobacco harm reduction

History

Received 8 January 2013
Revised 2 April 2013
Accepted 3 April 2013
Published online 6 June 2013

Introduction

There is overwhelming evidence that smoking is a major cause of respiratory and cardiovascular disease (Bartecchi et al., 1995). Even low cigarette consumption has significant effects on human health (Bjartveit & Tverdal, 2005). Complete cessation is the goal for all smokers; however, many of them are unwilling or unable to quit. Therefore, harm reduction strategies have been developed, aiming at substituting tobacco cigarettes with other products that deliver less harmful constituents to human organism (Stratton et al., 2001).

Electronic nicotine-delivery devices, commonly called electronic cigarettes (ECs), were invented in China and have been recently introduced to the market worldwide (Henningfield & Zaatari, 2010; Pauly et al., 2007) as an alternative and potentially safer habit. They consist of a battery-part, a cartridge containing liquid and an electrical resistance that gets warm by activation of the battery and evaporates the liquid. The liquid usually contains glycerol, propylene glycol, water, nicotine and a variety of flavors that the user can choose.

It is estimated that millions of people are using EC, and surveys suggest that they may be effective in smoking cessation (Etter, 2010). Although they do not contain or burn tobacco, which seems promising in avoiding delivery of harmful substances, no studies have specifically evaluated their toxicity. This has raised serious public health concerns (Cobb et al., 2010). Our research team has developed a series of protocols called ''ClearStream'' (CLarifying Evidence and Research on the Safety and The Risks of Electronic AtMos; atmos = vapor in Greek), to evaluate the toxicological, environmental and clinical effects of ECs. The purpose of this study (ClearStream-LIFE; LIFE = Living In-vitro Fibroblasts' Exposure) was to evaluate the *in vitro* cytotoxicity of vapor extract of 21 commercially available liquids used for EC and to compare it with the cytotoxicity of cigarette smoke (CS) extract.

Address for correspondence: Konstantinos E. Farsalinos, Onassis Cardiac Surgery Center, Sygrou 356, Kallithea 17674, Greece. Tel: +306977454837. Fax: +302109493373. E-mail: kfarsalinos@gmail.com

Materials and methods

Materials

A commercially available tobacco cigarette containing 1 mg of nicotine, 10 mg of tar and 10 mg of carbon monoxide was used for this experiment. Twenty-one commercially available liquids used for EC were obtained from the market in sealed bottles, each containing 10 ml of liquid (manufactured by FlavourArt s.r.l., Oleggio, Italy).The composition of EC liquids, as reported by the manufacturer, was (w/w) 46.17% propylene glycol USP, 44.92% glycerol USP, 8.11% water, 0.8% nicotine USP and <0.5% flavorings. The only difference between liquids composition was the flavorings used (Table 1). Twelve of the flavors were tobacco-like, while the rest were mostly fruit and sweet flavors. Each flavoring (including tobacco-like flavors) is a complex mixture of several physically extracted or chemically produced substances approved for use in food industry, for which no additional information was provided by the manufacturer. A commercially available EC device (510 T, Omega Vape, Manchester, UK) was used for vapor production. The device consists of a 3.7-volt lithium battery, an atomizer with a resistance of 2.2 Ohms wrapped over a fiberglass wick and a cartridge attached to the mouthpiece with a capacity of 1 ml of liquid. Care was taken to have the battery fully charged before each vapor extract was produced. Vacuum produced by inhalation (and by the vacuum pump during the experiment) leads to automatic activation of the battery, delivering 3.7 volts until the battery is discharged. The battery voltage was checked before and after use for the production of each EC extract with a digital voltmeter. A new atomizer was used for each vapor extract production; its resistance was measured with a digital multimeter and it was discarded if the resistance was found to differ by more than 0.1 volt. By applying 3.7 volts to a 2.2 Ohm resistance, the total energy for liquid evaporation in the experiment was 6.2 Watts.

An important issue was to test the function of the atomizer in conditions similar to the experimental setting, in order to ensure that no ''dry puff'' occurs. ''Dry puff'' is a phenomenon that occurs when the wick is insufficiently supplied with liquid, so that the evaporation rate is higher than the liquid supply rate to the wick; this leads to higher temperature of evaporation that is detected by the user as an unpleasant burning taste. This cannot be detected during any laboratory experiment. In addition, it is possible that the unpleasant taste is caused by substances that may form as a result of evaporation and that may or may not be toxic. Since the user detects and then avoids this phenomenon (by lowering device activation time and increasing puff intervals), the value of the experiment would be significantly undermined if ''dry puff'' was reproduced during the laboratory study. The only realistic way we found of testing this was to assign one of the researchers (who is a regular EC user) to test the EC device with three randomly selected atomizers from the pack delivered to the laboratory, using them in the same manner as during the experiment (2-second puffs, one puff every 60 s; see section ''*Production of extracts*''). Testing revealed that ''dry puff'' phenomenon was not reproduced when the EC atomizers were used in a way similar to the experimental setting.

Cell cultures

Cytotoxicity was measured by 3-[4,5-dimethylthiazol-2-yl]-2,5-diphenyltetrazolium bromide (MTT) assay on monolayer-cultured mouse BALB/3T3 fibroblasts derived from Swiss

Table 1. Fibroblast viability in electronic cigarette vapor and cigarette smoke extracts.

	Dilutions						
Extracts	100%[a]	50%[b]	25%[c]	12.5%[d]	6.25%[e]	3.125%[f]	*p**
Tuscan[g]	94.5 ± 2.8	99.8 ± 5.7	104 ± 1.5	101.4 ± 4.1	100.7 ± 5.9	98.6 ± 3.8	0.216
Black fire[g]	96.3 ± 9.9	93.4 ± 2.5	94.4 ± 1.6	104.6 ± 2.9	95.3 ± 4.3	97 ± 3.2	0.159
Ozone[g]	90.7 ± 9.9	95.9 ± 9.1	96.2 ± 4.3	94.9 ± 6	96.7 ± 5.1	97 ± 4.9	0.879
Reggae night[g]	81.3 ± 5.1	90.3 ± 3.7	89.5 ± 4.2	89.7 ± 3.4	90.2 ± 5.7	91.6 ± 4.2	0.132
Vanilla	100 ± 2.4	98.5 ± 3.5	100.3 ± 2.0	100.1 ± 0.8	104.1 ± 3.1	98.3 ± 3.3	0.183
7foglie[g]	81.4 ± 2.9	87.5 ± 1.5	89.4 ± 4.0	87.1 ± 8.3	89.6 ± 12.1	93.2 ± 10.7	0.587
Max blend[g]	96.2 ± 6.0	97 ± 6.9	102.1 ± 7.4	111.8 ± 4.5	114.3 ± 1.7	115.5 ± 5.3	0.003
Virginia[g]	78.4 ± 14.4	86.1 ± 13.5	91.3 ± 15.6	96.4 ± 16.2	106.3 ± 9.7	104.4 ± 10.7	0.478
Perique black[g]	79.3 ± 1.5	89.8 ± 2.4	94.7 ± 1.2	95.3 ± 5.2	95.1 ± 2.4	93.9 ± 3.4	<0.001
Layton blend[g]	101.1 ± 1.0	103.7 ± 0.8	102.7 ± 2.8	100.6 ± 2.1	103.4 ± 5.5	97.9 ± 4.2	0.295
Hypnotic[g]	93.8 ± 10.8	95.2 ± 14.0	106.2 ± 6.5	97.4 ± 5.1	100.6 ± 7.4	98.5 ± 3.9	0.579
Hazelnut	88.7 ± 1.4	90.1 ± 5.6	93.5 ± 6.7	91.5 ± 1.5	115.3 ± 8.0	117.8 ± 13.4	0.001
Shade[g]	83.6 ± 5.1	92.5 ± 3.9	94.6 ± 5.0	97.8 ± 5.9	101.5 ± 2.5	101.9 ± 1. 3	0.002
RY4[g]	88.4 ± 8.1	96.1 ± 3.7	98.7 ± 6.4	95.8 ± 7.4	98.9 ± 6.3	98.9 ± 5.9	0.378
Strawberry	85.8 ± 2.8	95.4 ± 2.3	97.5 ± 1.5	104.0 ± 6.2	99.6 ± 1.4	107.5 ± 1.2	<0.001
Managua	79.1 ± 2.4	79.9 ± 3.3	79.1 ± 3.1	85.8 ± 2.0	86.4 ± 1.7	88.5 ± 3.5	0.002
Burley	102.2 ± 3.4	95.8 ± 2.9	97.6 ± 1.3	97.3 ± 3.4	106.2 ± 8.3	100.5 ± 6.2	0.171
Apple	95.2 ± 1.2	87.4 ± 2.7	100.8 ± 8.2	95.6 ± 3.9	101.8 ± 3.1	106.6 ± 15.6	0.106
Licorice	95.4 ± 3.9	93.9 ± 2.8	96.5 ± 2.6	98.5 ± 4.4	98.9 ± 2.0	99.6 ± 2.5	0.252
Chocolate	87.6 ± 2.2	89.6 ± 0.6	93.2 ± 1.3	93.4 ± 1.5	93.7 ± 1.9	98.9 ± 1.2	<0.001
Coffee	51.0 ± 2.6	85.9 ± 11.8	92.0 ± 8.9	101.5 ± 3.1	112.2 ± 3.6	114.5 ± 1.1	<0.001
CS	5.7 ± 0.7	9.4 ± 5.3	5.9 ± 0.9	72.8 ± 9.7	77.8 ± 1.8	89.1 ± 3.5	<0.001

Values are presented as mean ± standard deviation. Viability is expressed as percent, compared to untreated cells.
CS = cigarette smoke.
For electronic cigarette liquid extracts, dilutions represent (w/v): [a]1%, [b]0.5%, [c]0.25%, [d]0.125%, [e]0.0625% and [f]0.03125%.
*p value for comparison between different extract concentrations in each liquid and in tobacco cigarette (ANOVA).
[g]Tobacco flavors.

albino mouse embryos (NIH 3T3 Batch 2 051163, NIH AIDS Research & Reference Reagent Program), according to UNI ISO 10993-5 standard. Cells were grown in Dulbecco's basal medium (Euroclone), supplemented with fetal bovine serum (Euroclone), penicillin–streptomycin 0.1 mg/ml (Euroclone), kanamycin 0.1 mg/ml (SIGMA, St Louis, MO), non-essential amino acid 0.1 mg/ml (SIGMA) and 4 mM glutamine (Euroclone). The doubling time of this cell line was 16–20 h.

Production of extracts

Vapor extract was produced by simulating EC use. The EC device was connected to a flask containing culture medium through a sealed tube. Horizontal orientation of the device was chosen, because this is the orientation of the device during real EC use. The other end of the tube was inside the flask, just above the culture medium level. A vacuum pump was connected to the flask; vacuum from the pump automatically triggered the EC device. The vapor was allowed to flow into the flask, over the medium. The EC cartridge was filled with 400 mg of liquid, and a number of inhalation simulations were performed in order to consume 200 mg of liquid, therefore having a theoretical concentration of 1% (w/v) into the culture medium of the flask (denoted as 100% EC extract). Weighting of the EC cartridge was performed before and during the experiment by a precision scale (Mettler, model AB104-S, precision of 0.1 mg), in order to make sure that the quantity of liquid consumed did not exceed 200 mg. Each inhalation simulation lasted 2 s, with 60 s between inhalations. The medium inside the flask was kept swirling during the experiment. CS extract was produced by using a similar method. Inhalation simulations, consisting of 2-second puffs every 60 s, were performed until one cigarette was consumed. The resulting solution was denoted as 100% CS extract. Immediately after preparation, all EC vapor and CS extracts were used in cell cultures.

Treatment and exposure

Cells were seeded in 96-well plate with Dulbecco's basal medium plus 10% fetal bovine serum and maintained in culture for 24 h (5% CO_2, 37 °C, >90% humidity) in order to form a semi-confluent monolayer. In each well, 100 µl of a cell suspension of 1×10^5 cells/ml was dispensed. A different plate was prepared for each extract testing. On the next day, each plate was examined under the microscope to ensure that cell attachment was even across the plate. Then, the medium was aspirated and replaced by medium containing the CS and EC liquid extracts in one undiluted (100%) and five diluted samples (50%, 25%, 12.5%, 6.25% and 3.125%). For the EC extract, 100% EC extract equals to a vapor extract concentration of 1%. Three different wells were treated with each dilution, and columns 2 and 11 were used to culture cells with normal medium (without extract, untreated cells); then, they were incubated for 24 h at 37 °C. Subsequently, cells were tested for viability by MTT assay. Untreated cells were used as controls.

MTT assay

The assay was performed according to the method developed by Mossman (1983). After incubation, the culture medium was removed and replaced with 10 µl of 1 mg/ml MTT. The cells were then incubated for 2 h. MTT is cleaved by mitochondrial dehydrogenases of viable cells, leading to the formation of purple crystals, representing formazan metabolism, which are insoluble in aqueous solutions. The solution was then removed and replaced with 200 µl/well of isopropanol to extract and solubilize the formazan. It was incubated for 30 min at room temperature under medium speed shaking. Then, the solution was measured spectrophotometrically. The absorbance at 570 nm was measured with a microplate reader (Tecan, model Sunrise Remote), and background subtraction was adjusted with absorbance readings at 690 nm. The absorbance values were normalized by setting the negative control group (untreated cells) in each row to 100%. Subsequently, the viability of the treated cells was expressed as a percent of untreated cells.

Quality check of assay

According to UNI ISO 10993-5 standard, a test meets acceptance criteria if the left (column 2) and the right (column 11) mean of the blanks do not differ by more than 15% from the mean of all blanks; this criterion was met in all our experiments. Sodium lauryl sulfate (SLS; SIGMA) was used as positive control in order to demonstrate an appropriate test system response. Historically, inhibitory concentration 50 (IC_{50}) of SLS is 0.093 mg/ml with 95% CI of 0.070–0.116 mg/ml (Spielmann et al., 1991). A test meets acceptance criteria if IC_{50} for SLS is within the 95% CI; in our experiment, IC_{50} for SLS was 0.100 mg/ml. Finally, the absolute value of optical density, OD_{570}, obtained in the untreated wells indicates whether the 1×10^4 cells seeded per well have grown exponentially with normal doubling time during the 2 days of the assay. In our experiments, OD_{570} of untreated cells were $\geq$0.2, meeting the acceptance criteria of UNI ISO 10993-5.

Statistical analysis

All data are reported as mean ± standard deviation. One-way analysis of variance (ANOVA) was used for comparison of percent viability between different extract concentrations of the same liquid. If statistically significant differences were found, post-hoc analysis was performed with Bonferroni test to determine which extract concentrations had different effects on viability. No observed adverse effects level (NOAEL) was defined as the lowest extract concentration that showed statistically significant lower viability compared to the 3.125% extract concentration. The difference in percent viability between CS extract and each EC vapor extract was also assessed with one-way ANOVA. Linear regression analysis was used to determine whether tobacco flavoring was associated with a statistically significant difference in viability. IC_{50} (the concentration of extract that produced 50% viability) was estimated from regression plots. According to UNI ISO 10993-5 standard, viability of less than 70% by MTT assay was considered cytotoxic. All analyses were performed with commercially available software (SPSS v18, Chicago, IL), and a two-tailed P value of ≤ 0.05 was considered statistically significant.

Results

Fibroblast viability measurements for each EC liquid and CS extracts at different dilutions are displayed in Table 1. From the 21 samples examined, only ''Coffee'' exhibited a cytotoxic effect; this was observed at the highest extract concentration only. Figures S1–S7 (supplemental material) display fibroblast viability for all EC liquids together with the respective viability for CS extract. The range of fibroblast viability for all EC liquids was 88.5–117.8% at 3.125%, 86.4–115.3% at 6.25%, 85.8–111.7% at 12.5%, 78.1–106.2% at 25%, 79.0–103.7% at 50% and 51.0–102.2% at 100% extract concentration. CS extract exhibited significant cytotoxicity at extract concentrations $>12.5\%$. The viability rate of CS extract at each dilution was $89.1 \pm 3.5\%$ at 3.125%, $77.8 \pm 1.8\%$ at 6.25%, $72.8 \pm 9.7\%$ at 12.5%, $5.9 \pm 0.9\%$ at 25%, $9.4 \pm 5.3\%$ at 50% and $5.7 \pm 0.7\%$ at 100% ($p < 0.001$ compared to every EC liquid extract at 100%, 50% and 25% concentration). Viability rate of ''Coffee'' flavor, the only EC liquid that showed cytotoxic potential (according to ISO 10993-5 definition), was $114.5 \pm 2.0\%$ at 3.125%, $112.2 \pm 3.6\%$ at 6.25%, $101.5 \pm 3.1\%$ at 12.5%, $92.0 \pm 8.9\%$ at 25%, $85.9 \pm 11.8\%$ at 50% and $51.0 \pm 2.6\%$ at 100% extract concentration. Figure 1 displays the relative difference in viability between CS extract and ''Coffee'' extract at each dilution; statistically significant higher fibroblast viability was observed for ''Coffee'' extract at all extract concentrations. IC_{50} and NOAEL for each EC and for the CS extracts are displayed in Table 2. IC_{50} could not be determined for EC vapor extracts, since viability was >50% at all extract concentrations. For the majority of EC liquids (13 of 21), viability was not statistically different between extract concentrations, thus NOAEL for these samples was defined as 100% concentration. Twelve of the EC liquids tested were flavors mimicking tobacco. However, they were not associated with a statistically significant difference in fibroblast viability.

Discussion

This is the first study that has evaluated the cytotoxic effects of vapor produced from commercially available EC liquids. The main result of our study is that the vapor from only 1 of the 21 EC liquids examined had cytotoxic effects on cultured fibroblast according to protocol definition. CS extract had significant cytotoxic effects, and fibroblast viability was significantly lower at all extract concentrations compared to EC vapor extracts. It is important to note that, we tested the EC liquids by simulating the way they are used by every user, that is, by activating a commercially available EC device and producing vapor, which was subsequently tested. In addition, we used standardized protocols and procedures such as UNI ISO 10993-5 standard and MTT-assay, with cytotoxicity defined according to UNI ISO 10993-5 standard as viability <70% compared to untreated cells. Moreover, we used cells that have been commonly used in studies evaluating tobacco cigarette cytotoxicity (Lu et al., 2007; Yu et al., 2006). Finally, we performed a cytotoxic study on CS extract using the same methodology to generate the test article. This is particularly important since EC are marketed for the smokers only as an alternative option. Therefore, the main scientific question is whether the EC is less harmful compared to regular tobacco cigarette, and this was evaluated in our study.

CS is a complex suspension that contains more than 4000 chemicals according to EPA report (1992). Several of these are linked to cancer or cardiovascular and lung disease from *in vitro* studies, including tobacco-specific nitrosamines (Hecht & Hoffmann, 1988; Wu et al., 2003), polycyclic aromatic hydrocarbons (Besaratinia et al., 2002; Zedeck, 1980), metals like cadmium and lead (Ronco et al., 2005) and

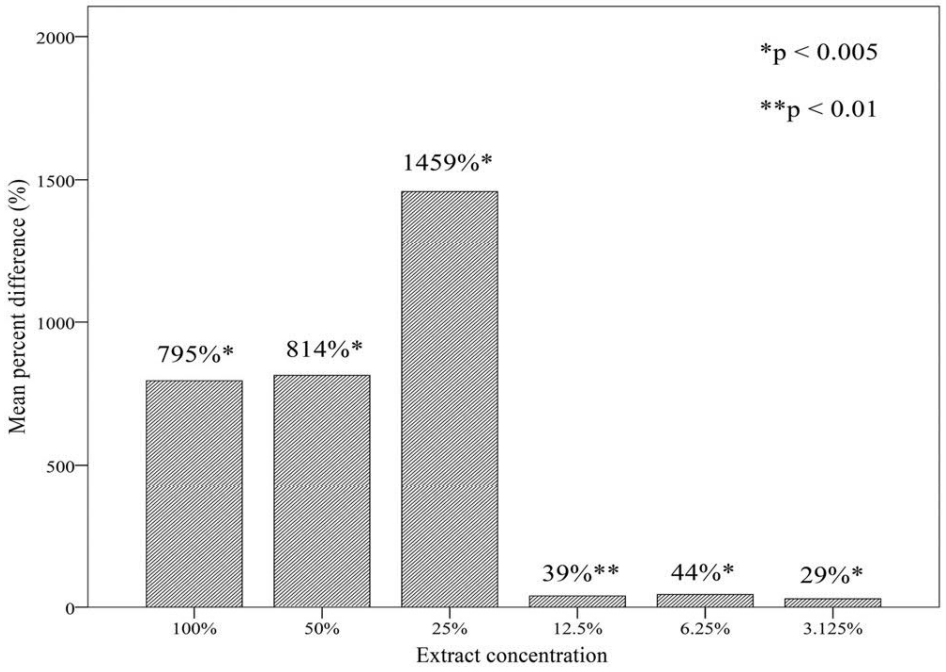


Figure 1. Relative mean differences between cigarette smoke extract viability and electronic cigarette ''Coffee'' vapor extract viability. Coffee was the only electronic cigarette liquid that showed cytotoxic effects according to the definition of UNI ISO 10993-5 standard.

Table 2. Inhibitory concentration 50 (IC_{50}) and no adverse effect level (NOAEL) for each electronic cigarette vapor extract and for the cigarette smoke (CS) extract.

Extracts	IC_{50}	NOAEL
Tuscan[a]	>100%	100%
Black fire[a]	>100%	100%
Ozone[a]	>100%	100%
Reggae night[a]	>100%	100%
Vanilla	>100%	100%
7foglie[a]	>100%	100%
Max blend[a]	>100%	25%
Virginia[a]	>100%	100%
Perique black[a]	>100%	50%
Layton blend[a]	>100%	100%
Hypnotic[a]	>100%	100%
Hazelnut	>100%	6.25%
Shade[a]	>100%	50%
RY4[a]	>100%	100%
Strawberry	>100%	12.5%
Managua	>100%	12.5%
Burley	>100%	100%
Apple	>100%	100%
Licorice	>100%	100%
Chocolate	>100%	3.125%
Coffee	>100%	12.5%
CS	16%	6.25%

[a]Tobacco flavors.

other compounds like acrolein, formaldehyde and phenol (Risner & Martin, 1994; Smith & Hansch, 2000). The major contributors to the *in vitro* cytotoxic effects of smoke are also responsible for the respiratory tract irritation in experimental animals and humans and cause histopathological changes in the upper respiratory tract (Lu et al., 2007). Therefore, in vitro cytotoxicity screening represents an important initial step in the toxicological evaluation of tobacco products.

There may be multiple mechanisms that lead to CS extract-induced cytotoxicity. For example, oxidative stress is an important mechanism that alters the balance between proliferation and apoptosis in fibroblasts (Müller & Gebel, 1998). Genetic damage is also induced by CS extract (Cui et al., 2012). Depletion of antioxidants by several CS extract components like acrolein and aldehydes compromises the defensive mechanisms of fibroblasts and promotes cell damage (Colombo et al., 2012; Ishii et al., 2003). Other chemicals cause direct cell-membrane damage (Thelestam et al., 1980). The end-result is fibroblast apoptosis and death (Kim et al., 2011; Park et al., 2010, 2008). This has important implications in the development of lung disease like emphysema (Baglole et al., 2006; Rennard et al., 2006).

We did not find any significant cytotoxic effects by any of the EC vapor extracts studied, except for ''Coffee'' at the highest extract concentration. Liquids consist mainly of glycerol, propylene glycol, water and nicotine; a wide variety of flavors are also available. Both glycerol and propylene glycol are classified by Food and Drug Administration and Flavor and Extracts Manufacturer Association (FEMA) as additives that are ''generally recognized as safe'' for use in food (FDA, 2012a,b-revised; FEMA GRAS numbers 2525 and 2940, respectively). Glycerol is also present in tobacco cigarettes and it is the main source of acrolein, produced by pyrolysis due to combustion. Acrolein has well-established cytotoxic effect on fibroblasts (Cattaneo et al., 2000; Jia et al., 2009). It is unlikely that acrolein can be produced by EC use because the temperature of liquid evaporation is considerably lower compared to combustion when smoking tobacco cigarette. Propylene glycol is a solvent used in oral, intravenous and topical pharmaceutical products. One study showed moderate cytotoxic effect on skin fibroblasts (Ponec et al., 1990). However, an animal study found that exposure to significant amounts of propylene glycol in air had no adverse effects on the respiratory system (Robertson et al., 1947). Propylene glycol is also present in tobacco cigarettes and is pyrolyzed to acetaldehyde during smoking, which has significant cytotoxic effects (Cattaneo et al., 2000; Krokan et al., 1985). Considering the fact that almost half of EC liquids content we examined was propylene glycol, the results of our study indicate that it is unlikely for propylene glycol to be pyrolyzed to acetaldehyde by EC use or to have any significant cytotoxic effect by itself. Concerning nicotine, there are studies showing that, at levels commonly found in cigarettes, it does not induce cell death (Laytragoon-Lewin et al., 2011) and may even have anti-apoptotic effects (Argentin & Cicchetti, 2006, 2004). It should be mentioned, however, that these effects have been suggested to facilitate the growth of tumors already initiated (Davis et al., 2009). Nicotine is not classified as a carcinogen by the International Agency for Research on Cancer (WHO-IARC, 2004), and the results of this study show that nicotine does not produce cytotoxic effects at the level present in the liquids tested.

Regarding the cytotoxicity observed for ''Coffee'', the manufacturer indicated that this flavor is a complex mixture of several natural and synthetic substances. Most of the natural substances come from roasted coffee beans. This processing of coffee beans may itself lead to production of some toxic elements, like ochratoxin A degradation products, which have cytotoxic and apoptotic properties (Cramer et al., 2008). Hegele et al (2009) found that coffee beans extract contains significant amounts of hydrogen peroxide, inducing cell death *in vitro*. It is possible that these substances are also present in the flavor used for preparing the ''Coffee'' EC liquid. However, we cannot exclude that the process of vapor formation from heating of the ''Coffee'' EC liquid may lead to production of other substances that have cytotoxic properties. It should be mentioned that the cytotoxic effect of this EC liquid extract was found only at the highest extract concentration, and, even at this concentration, fibroblast viability was 795% higher compared to CS extract.

Only one study has been published evaluating the cytotoxic effects of EC liquids (Bahl et al., 2012). Some of the liquids tested were found cytotoxic, mostly in embryonic cells and to a lesser extend in adult cells. This discrepancy in results may be attributed to several fundamental differences between the study by Bahl et al. and the study herein. The most crucial difference is that Bahl et al. tested the EC liquids in liquid form. It should be emphasized that the approach used by Bahl et al. does not deliver the EC liquid in the designated manner, which is less relevant than vapor generation of the liquid *via* activation of the electronic device. Herein, we simulated the exact mode of function of the EC and tested the extract of the resulting vapor. This may have significant implications on the results. Second, it is possible that not all liquid constituents evaporate at the same manner or in similar

concentrations. Furthermore, the concentrations of various constituents (for example, flavorings) may be different in vapor compared to liquid, and this may influence the results.

From a public health perspective, the field of tobacco harm reduction is particularly important. Smoking can produce subclinical dysfunction even at a young age (Farsalinos et al., 2013); therefore, attempts to quit smoking should be performed as soon as possible. However, quitting rates are relatively low with currently approved means (Rigotti et al., 2010). Until recently, only products containing tobacco were available in tobacco harm reduction (smokeless tobacco, like snus). Epidemiological studies have shown that use of such products is promising regarding cancer and cardiovascular disease risk reduction (Janzon & Hedblad, 2009; Lee & Hamling, 2009). Likewise, EC may have an important role in harm reduction. Unlike other products, EC contain no tobacco. In addition, the fact that nicotine is administered by a method that resembles tobacco cigarette use (hand-to-mouth movement, visible ''smoke'' exhaled) make them unique in dealing both with the chemical and psychological (behavioral) addiction to smoking. Several studies have characterized the chemicals contained in EC, with results showing that they do not contain any toxic substances (Ellicott, 2009; Tytgat, 2007; Valance & Ellicott, 2008). Even in studies where nitrosamines were detected (Laugesen, 2008; Westenberger, 2009), the levels were similar to a nicotine patch and 500 to 1400-fold lower compared to tobacco cigarettes (Stepanov et al., 2006). The results of this study are in line with these findings, showing significantly higher cytotoxicity of CS extract compared to EC vapor extracts.

Limitations

There are some limitations applicable to this study. Cytotoxicity studies on cultured cells have been developed in order to reduce the use of experimental animals. Extrapolating these results to the human *in vivo* toxicity should be done with caution. There is no consensus on the methodology of preparing and testing EC vapor extracts, and this is the first study that has attempted to evaluate the cytotoxic potential of EC vapor. However, we provided a comparative measure of toxicity with CS extract, which has well-established *in vivo* toxic effects. We did not use automated whole smoke exposure systems such as VitroCell or RM20s Borgwaldt systems, which offer more *in vivo*-like exposures since the cells are present inside the chamber where CS is delivered (Fukano et al., 2006; Maunders et al., 2007). Moreover, we did not use the standardized ISO method for CS extract (35 ml of air aspirated in 2-second per puff). This was done because we wanted to produce CS extract with the same method as EC liquid extract; aspiration of 35 ml air from the EC device produced very small amount of vapor, which was minimal compared to the amount generated by real EC use. Therefore, we preferred to use the same methodology in both EC and CS extract production. It should be mentioned that the ISO method for CS production significantly underestimates real smokers' exposure (Djordjevic et al., 2000).

We compared vapor extract from 200 mg of liquid with CS extract that was generated from one cigarette, both dissolved in 20 ml of culture medium. These are not similar exposure levels. In fact, there is no established method for comparing the amount of EC liquid and number of tobacco cigarettes. A practical and pragmatic way of comparing the two would be to measure how much liquid is consumed by users after using the EC device for similar time to that needed to smoke one cigarette. We have measured this as part of another protocol and we have found that the average EC liquid consumption was 60 mg. Therefore, we should have used the smoke extract of at least three cigarettes dissolved in 20 ml of culture medium in order to have a comparable exposure level to that of EC liquid extract we used. Unfortunately, this measurement was performed after the completion of this study. If three cigarettes had been used in this protocol, it is probable that the cytotoxicity of CS extract and the resulting differences in cell viability compared to effects induced by the EC liquid extracts would have been even higher than what was observed. However, this is an assumption and cannot be inferred unless explicitly tested.

It should be emphasized that our results do not necessarily apply to all EC liquids marketed. Nicotine is extracted from tobacco; therefore, if liquids contain non-pharmaceutical grade nicotine, several tobacco impurities may be present and adversely affect the results. The same applies for all other liquid constituents (Cahn & Siegel, 2011). We did not find an association between EC tobacco flavors and fibroblast viability. This was probably due to the fact that substances approved for food industry were used even for these flavors (according to manufacturer's report). However, it is possible to use natural tobacco extract to mimic tobacco flavor, and some companies may use or produce themselves such extracts for use in EC liquids. The cytotoxicity potential of these extracts is currently unknown, and they are not approved for use in food industry. In any case, regulation is needed and specific standards should be implemented in order to ensure that quality products are available in the market. Although no standards have been implemented by public health authorities, several industry associations like Electronic Cigarette Industry Trade Association and American E-Liquid Manufacturing Standards Association have developed such standards.

Finally, another important issue not addressed in this study is the effect of different, modified EC devices that deliver higher voltage and wattage to the resistance. This would accelerate the rate of evaporation; and if the resistance is not sufficiently supplied with liquid, it might possibly result in overheating and production of toxic chemicals. We tested the EC device used in the experiment to make sure that no ''dry puff'' phenomenon occurs, but it remains to be examined whether this phenomenon is associated with the production of toxic substances.

Conclusions

In conclusion, from the 21 commercially available EC liquids we tested in vapor form, only one was found to have cytotoxic effects on cultured mammalian fibroblast cells according to ISO 10993-5 definition. Overall, EC vapor extracts showed by far higher fibroblast viability compared to CS extract. This supports the concept that EC may be less harmful compared

to tobacco cigarettes and could be useful products in tobacco harm reduction. However, more research is needed, both in the laboratory with different cell lines and in clinical level, in order to better understand and evaluate the effects of EC use on human health.

Declaration of interest

No author has any financial interest in the outcome of this study.

The study was funded by FlavourArt s.r.l. No author has received any financial compensation for this study. The study was investigator-initiated and investigator-driven. The sponsor had no involvement in the study design, data collection, analysis and interpretation, writing or approving the manuscript and decision to submit the manuscript for publication.

References

Argentin G, Cicchetti R. (2004). Genotoxic and antiapoptotic effect of nicotine on human gingival fibroblasts. Toxicol Sci 79:75–81.

Argentin G, Cicchetti R. (2006). Evidence for the role of nitric oxide in antiapoptotic and genotoxic effect of nicotine on human gingival fibroblasts. Apoptosis 11:1887–97.

Baglole CJ, Bushinsky SM, Garcia TM, et al. (2006). Differential induction of apoptosis by cigarette smoke extract in primary human lung fibroblast strains: implications for emphysema. Am J Physiol Lung Cell Mol Physiol 291:L19–29.

Bahl V, Lin S, Xu N, et al. (2012). Comparison of electronic cigarette refill fluid cytotoxicity using embryonic and adult models. Reprod Toxicol 34:529–37.

Bartecchi CE, MacKenzie TD, Schrier RW. (1995). The global tobacco epidemic. Sci Am 272:44–51.

Besaratinia A, Kleinjans JC, Van Schooten FJ. (2002). Biomonitoring of tobacco smoke carcinogenicity by dosimetry of DNA adducts and genotyping and phenotyping of biotransformational enzymes: a review on polycyclic aromatic hydrocarbons. Biomarkers 7:209–29.

Bjartveit K, Tverdal A. (2005). Health consequences of smoking 1-4 cigarettes per day. Tob Control 14:315–20.

Cahn Z, Siegel M. (2011). Electronic cigarettes as a harm reduction strategy for tobacco control: a step forward of a repeat of past mistakes? J Public Health Policy 32:16–31.

Cattaneo V, Cetta G, Rota C, et al. (2000). Volatile components of cigarette smoke: effect of acrolein and acetaldehyde on human gingival fibroblasts in vitro. J Periodontol 71:425–32.

Cobb NK, Byron MJ, Abrams DB, Shields PG. (2010). Novel nicotine delivery systems and public health: the rise of the ''e-cigarette''. Am J Public Health 100:2340–2.

Colombo G, Dalle-Donne I, Orioli M, et al. (2012). Oxidative damage in human gingival fibroblasts exposed to cigarette smoke. Free Radic Biol Med 52:1584–96.

Cramer B, Königs M, Humpf HU. (2008). Identification and in vitro cytotoxicity of ochratoxin A degradation products formed during coffee roasting. J Agric Food Chem 56:5673–81.

Cui J, Zhao W, Xu X, et al. (2012). DNA polymerase beta is involved in the protection against the cytotoxicity and genotoxicity of cigarette smoke. Environ Toxicol Pharmacol 34:370–80.

Davis R, Rizwani W, Banerjee S, et al. (2009). Nicotine promotes tumor growth and metastasis in mouse models of lung cancer. PLoS One 4: e7524.

Djordjevic MV, Stellman SD, Zang E. (2000). Doses of nicotine and lung carcinogens delivered to cigarette smokers. J Natl Cancer Inst 92: 106–111.

Ellicott M. (2009). Analysis of components from ''e-Juice XX HIGH 36 mg/ml Rated Nicotine Solution'' ref S 55434. Lancashire, UK: Blackburn MicroTech Solutions. Available from: http://truthaboute-cigs.com/science/11.pdf. [Last accessed: 6 Aug 2012].

EPA EPA Report/600/6-90/006F. (1992). Respiratory health effects of passive smoking: lung cancer and other disorders. Washington, DC.

Etter JF. (2010). Electronic cigarettes: a survey of users. BMC Public Health 10:231.

Farsalinos K, Tsiapras D, Kyrzopoulos S, Voudris V. (2013). Acute and chronic effects of smoking on myocardial function in healthy heavy smokers: a study of Doppler flow, Doppler tissue velocity and two-dimensional speckle tracking echocardiography. Echocardiography 30:285–92.

FDA. (2012a) (revised). Code of federal regulations, Title 21, Part 184: direct food substances affirmed as generally recognized as safe. Section 184.1666 Propylene glycol. Available from: http://www.accessdata.fda.gov/scripts/cdrh/cfdocs/cfcfr/cfrsearch.cfm?fr=184.1666. [Last accessed: 6 Aug 2012].

FDA (2012b) (revised). Code of federal regulations Title 21, Part 182: substances generally recognized as safe. Section 182.90 Substances migrating to food from paper and paperboard products. Available from: http://www.accessdata.fda.gov/scripts/cdrh/cfdocs/cfcfr/CFRSearch.cfm?fr=182.90. [Last accessed: 2 Apr 2013].

Fukano Y, Yoshimura H, Yoshida T. (2006). Heme oxygenase-1 gene expression in human alveolar epithelial cells (A549) following exposure to whole cigarette smoke on a direct in vitro exposure system. Exp Toxicol Pathol 57:411–8.

Hecht SS, Hoffmann D. (1988). Tobacco-specific nitrosamines, an important group of carcinogens in tobacco and tobacco smoke. Carcinogenesis 9:875–84.

Hegele J, Münch G, Pischetsrieder M. (2009). Identification of hydrogen peroxide as a major cytotoxic component in Maillard reaction mixtures and coffee. Mol Nutr Food Res 53:760–9.

Henningfield JE, Zaatari GS. (2010). Electronic nicotine delivery systems: emerging science foundation for policy. Tob Control 19: 89–90.

Ishii T, Fujishiro M, Masuda M, et al. (2003). Depletion of glutathione S-transferase P1 induces apoptosis in human lung fibroblasts. Exp Lung Res 29:523–36.

Janzon E, Hedblad B. (2009). Swedish snuff and incidence of cardiovascular disease: a population-based cohort study. BMC Cardiovasc Disord 9:21.

Jia L, Zhang Z, Zhai L, Bai Y. (2009). Protective effect of lipoic acid against acrolein-induced cytotoxicity in IMR-90 human fibroblasts. J Nutr Sci Vitaminol (Tokyo) 55:126–30.

Kim SY, Lee JH, Huh JW, et al. (2011). Cigarette smoke induces Akt protein degradation by the ubiquitin-proteasome system. J Biol Chem 286:31932–43.

Krokan H, Grafstrom RC, Sundqvist K, et al. (1985). Cytotoxicity, thiol depletion and inhibition of O6-methylguanine-DNA methyltransferase by various aldehydes in cultured human bronchial fibroblasts. Carcinogenesis 6:1755–9.

Laugesen M. (2008). Safety report on the Ruyan e-cigarette cartridge and inhaled aerosol. Christchurch, New Zealand: Health New Zealand. Available from: http://www.healthnz.co.nz/RuyanCartridgeReport30-Oct-08.pdf. [Last accessed: 6 Aug 2012].

Laytragoon-Lewin N, Bahram F, Rutqvist LE, et al. (2011). Direct effects of pure nicotine, cigarette smoke extract, Swedish-type smokeless tobacco (snus) extract and ethanol on human normal endothelial cells and fibroblasts. Anticancer Res 31:1527–34.

Lee PN, Hamling J. (2009). Systematic review of the relation between smokeless tobacco and cancer in Europe and North America. BMC Med 7:36.

Lu B, Kerepesi L, Wisse L, et al. (2007). Cytotoxicity and gene expression profiles in cell cultures exposed to whole smoke from three types of cigarettes. Toxicol Sci 98:469–78.

Maunders H, Patwardhan S, Phillips J, et al. (2007). Human bronchial epithelial cell transcriptome: gene expression changes following acute exposure to whole cigarette smoke in vitro. Am J Physiol Lung Cell Mol Physiol 292:L1248–56.

Mossman T. (1983). Rapid colorimetric assay for cellular growth and survival: application to proliferation and cytotoxicity assays. J Immunol Methods 65:55–63.

Müller T, Gebel S. (1998). The cellular stress response induced by aqueous extracts of cigarette smoke is critically dependent on the intracellular glutathione concentration. Carcinogenesis 19:797–801.

Park JW, Kim HP, Lee SJ, et al. (2008). Protein kinase C alpha and zeta differentially regulate death-inducing signaling complex formation in cigarette smoke extract-induced apoptosis. J Immunol 180:4668–78.

Park JW, Yoon JY, Kim YJ, et al. (2010). Extracellular signal-regulated kinase (ERK) inhibition attenuates cigarette smoke extract (CSE) induced-death inducing signaling complex (DISC) formation in human lung fibroblasts (MRC-5) cells. J Toxicol Sci 35:33–9.

Pauly J, Li Q, Barry MB. (2007). Tobacco-free electronic cigarettes and cigars deliver nicotine and generate concern. Tob Control 16:357.

Ponec M, Haverkort M, Soei YL, et al. (1990). Use of human keratinocyte and fibroblast cultures for toxicity studies of topically applied compounds. J Pharm Sci 79:312–6.

Rennard SI, Togo S, Holz O. (2006). Cigarette smoke inhibits alveolar repair: a mechanism for the development of emphysema. Proc Am Thorac Soc 3:703–8.

Rigotti NA, Pipe AL, Benowitz NL, et al. (2010). Efficacy and safety of varenicline for smoking cessation in patients with cardiovascular disease: a randomized trial. Circulation 121:221–9.

Risner CH, Martin P. (1994). Quantitation of formaldehyde, acetaldehyde, and acetone in sidestream cigarette smoke by high-performance liquid chromatography. J Chromatogr Sci 32:76–82.

Robertson OH, Loosli CG, Puck TT, et al. (1947). Tests for the chronic toxicity of propylene glycol and triethylene glycol on monkeys and rats by vapor inhalation and oral administration. J Pharmacol Exp Ther 91:52–76.

Ronco AM, Arguello G, Munoz L, et al. (2005). Metals content in placentas from moderate cigarette consumers: correlation with new born birth weight. Biometals 18:233–41.

Smith CJ, Hansch C. (2000). The relative toxicity of compounds in mainstream cigarette smoke condensate. Food Chem Toxicol 38: 637–46.

Spielmann H, Gerner I, Kalweit S, et al. (1991). Interlaboratory assessment of alternatives to the Draize eye irritation test in Germany. Toxicol In Vitro 5:539–42.

Stepanov I, Jensen J, Hatsukami D, Hecht SS. (2006). Tobacco-specific nitrosamines in new tobacco products. Nicotine Tob Res 8: 309–13.

Stratton K, Shetty P, Wallace R, Bondurant S. (2001). Clearing the smoke: the science base for tobacco harm reduction-executive summary. Tob Control 10:189–95.

Thelestam M, Curvall M, Enzell CR. (1980). Effect of tobacco smoke compounds on the plasma membrane of cultured human lung fibroblasts. Toxicology 15:203–17.

Tytgat J. (2007). ''Super Smoker'' expert report. Leuven, Belgium: Catholic University of Leuven. Available from: http://truthaboutecigs.com/science/15.pdf. [Last accessed: 6 Aug 2012].

Valance C, Ellicott M. (2008). Analysis of chemical components from high, med & low nicotine cartridges. Lancashire, UK: Blackburn MicroTech Solutions. Available from: http://truthaboutecigs.com/science/12.pdf. [Last accessed: 6 Aug 2012].

WHO-IARC. (2004). IARC monographs on the evaluation of carcinogenic risks to humans. Volume 83, tobacco smoke and involuntary smoking. Avaialble from: http://monographs.iarc.fr/ENG/Monographs/vol83/mono83.pdf. [Last accessed: 2 March 2013].

Westenberger BJ. (2009). Evaluation of e-cigarettes. St Louis, MO: Department of Health and Human Services, Food and Drug Administration, Center for Drug Evaluation and Research, Division of Pharmaceutical Analysis. Available from: http://truthaboutecigs.com/science/2.pdf. [Last accessed: 6 Aug 2012].

Wu W, Ashley DL, Watson CH. (2003). Simultaneous determination of five tobacco-specific nitrosamines in mainstream cigarette smoke by isotope dilution liquid chromatography/electrospray ionization tandem mass spectrometry. Anal Chem 75:4827–32.

Yu R, Wu M, Lin S, Talbot P. (2006). Cigarette smoke toxicants alter growth and survival of cultured mammalian cells. Toxicol Sci 93: 82–95.

Zedeck MS. (1980). Polycyclic aromatic hydrocarbons: a review. J Environ Pathol Toxicol 3:537–67.

The Rest of the Story: Tobacco News Analysis and Commentary

...Providing the whole story behind tobacco news.

Tuesday, August 02, 2011

New Study Documents that Thousands of E-Cigarette Users are Having Success Quitting; Claim that E-Cigs are Ineffective is No Longer Tenable

A new study published online ahead of print in the journal *Addiction* suggests that electronic cigarettes have been effective in helping literally thousands of smokers to cut down or quit smoking entirely, refuting a claim in last week's *New England Journal of Medicine* that these devices are likely to be ineffective because they deliver very little nicotine (a claim which was based entirely on a single study in which subjects were instructed to take 10 puffs on an e-cig, but no more).

(see: Etter J-F, Bullen C. Electronic cigarette: users profile, utilization, satisfaction and perceived efficacy. *Addiction* 2011; doi:10.1111/j.1360-0443.2011.03505.x).

The study involved a survey of electronic cigarette usage patterns and results using two survey frames: one was subjects recruited through electronic cigarette-related web sites and forums. The other was subjects recruited though smoking or smoking cessation web sites having nothing to do with e-cigarettes. Although the first sampling frame would produce a biased sample (consisting of people with more successful experiences with e-cigarettes than in the population as a whole), the authors compared the results between the two samples to provide some indication of the extent to which the results were biased by the sampling scheme.

The most notable finding was that there were not marked differences between the experiences of e-cigarette users recruited via e-cigarette forums versus non-e-cigarette-related sites. Even among the subjects recruited from general smoking cessation sites or via Google, the overwhelming majority of ever users of electronic cigarettes (80.8%) reported that e-cigarettes helped them reduce smoking a lot (compared to 93.2% of subjects recruited via e-cigarette-related sites).

Among ex-smokers recruited at the general sites, 93.3% reported that e-cigarettes helped them quit smoking (compared to 96.1% of subjects recruited via e-cigarette sites).

About Me

Michael Siegel

Dr. Siegel is a Professor in the Department of Community Health Sciences, Boston University School of Public Health. He has 25 years of experience in the field of tobacco control. He previously spent two years working at the Office on Smoking and Health at CDC, where he conducted research on secondhand smoke and cigarette advertising. He has published nearly 70 papers related to tobacco. He testified in the landmark Engle lawsuit against the tobacco companies, which resulted in an unprecedented $145 billion verdict against the industry. He teaches social and behavioral sciences, mass communication and public health, and public health advocacy in the Masters of Public Health program.

View my complete profile

Among all e-cigarette users, 92.2% stated that the device helped them to reduce smoking a lot. An overwhelming majority (88.6) reported that it is easy to abstain from smoking when using the e-cigarette.

Interestingly, the overwhelming majority (82.7%) of electronic cigarette users are worried that these devices might be banned and 79.2% of those who quit smoking using e-cigarettes are afraid that they would return to smoking if such a ban occurred. Of those who stopped smoking while on e-cigarettes, 96.0% reported that the electronic cigarette played a definitive role in helping them quit smoking.

The paper's major finding is as follows: "e-cigarettes were used largely by former smokers as an aid to quit smoking, to avoid relapse and to deal with withdrawal symptoms, much as people use nicotine replacement therapy (NRT). ... Our data suggest that e-cigarettes may help smokers to quit smoking, reduce their cigarette consumption and attenuate craving and tobacco withdrawal symptoms. Users of nicotine-containing e-cigarettes reported only slightly superior effects on withdrawal than users of non-nicotine cigarettes, suggesting that nicotine delivery explains only part of the effect of these devices on withdrawal, and that sensory and behavioural components of the e-cigarette are also important."

Another important finding is that smokers who used e-cigarettes
and to deal with withdrawal symptoms, much as people use nicotine replacement therapy (NRT). ... Our data suggest that e-cigarettes
consequence of reduced smoking. This difference is substantial ... and very close to the difference ... reported previously between patients with moderate and severe COPD."

The paper concludes: "E-cigarettes were used mainly by former smokers as an aid to quit smoking and avoid relapse. These products were perceived as satisfactory, useful, and efficacious, and almost all users preferred nicotine-containing e-cigarettes."

The Rest of the Story

Despite the fact that the sample is non-representative and the true efficacy of electronic cigarettes is certainly lower than reported here, the findings of the study nevertheless provide strong evidence that electronic cigarettes are being used with success by many smokers to quit smoking or cut down substantially on the number of cigarettes they consume, and that e-cigarettes are being used with success by many ex-smokers to remain off cigarettes.

Based on this survey alone, there are more than 2,000 ex-smokers who are electronic cigarette users who claim that the device played an instrumental role in their success in quitting smoking. Nearly 80% of these ex-smokers fear they would return to smoking if they discontinued the use of electronic cigarettes, as recommended by Cobb and Abrams in their *New England Journal of Medicine* perspective article.

Given these findings, along with previous data from other surveys

No Effect of Graphi...
Physician's Argument for Banning Tobacco Sales in ...

and anecdotal evidence from numerous other sources, the claim that electronic cigarettes are completely ineffective in smoking cessation because they do not deliver nicotine effectively is now untenable.

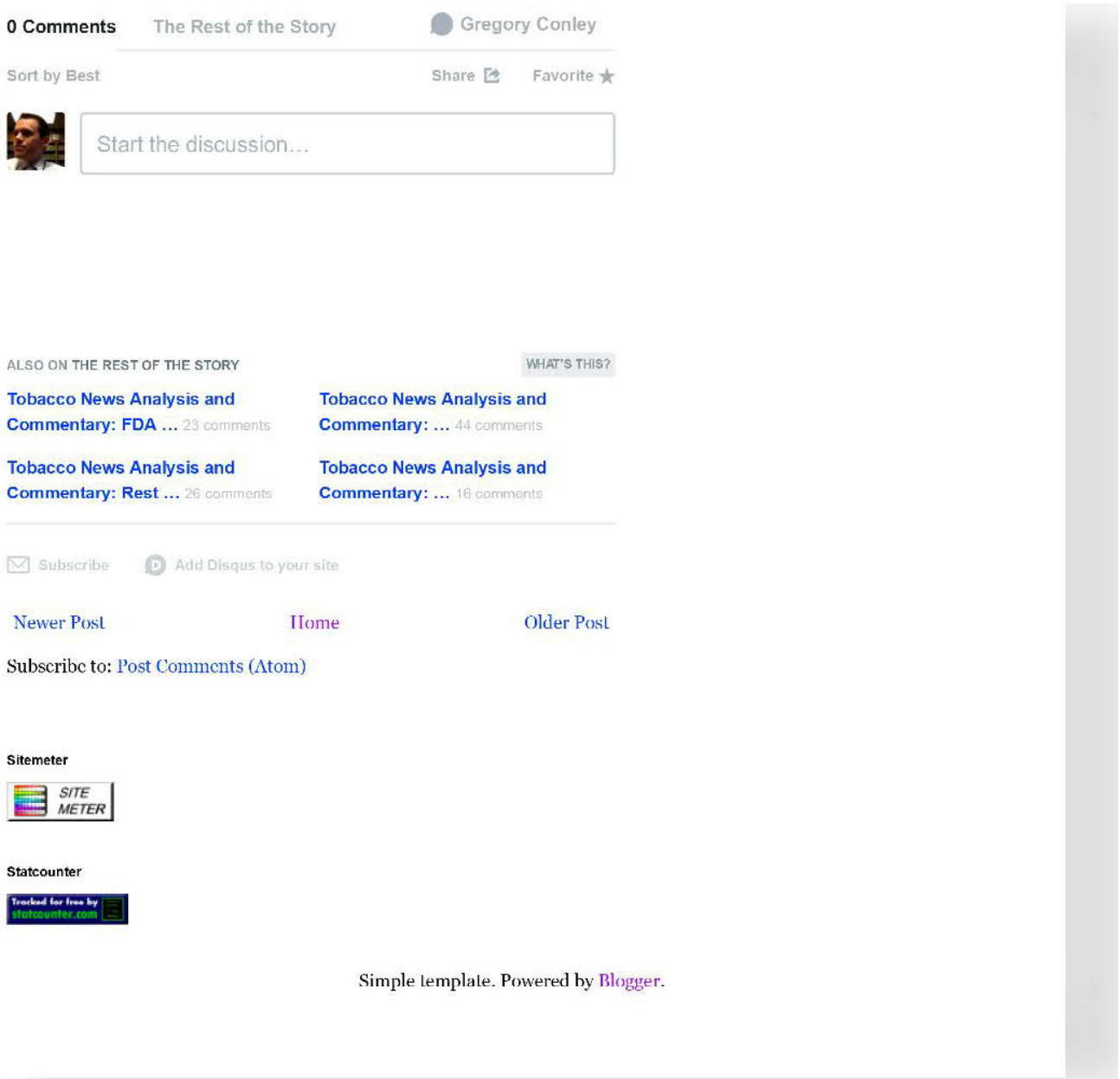
It is now clear that there are indeed thousands of ex-smokers who successfully quit smoking because of electronic cigarettes and who would likely return to smoking if persuaded to discontinue using electronic cigarettes in favor of an "approved" form of smoking cessation pharmacotherapy.

It is also clear that there are thousands of ex-smokers who successfully quit smoking because of electronic cigarettes and who would likely return to smoking if e-cigarettes were banned or taken off the market, as recommended by numerous anti-smoking groups, including the Campaign for Tobacco-Free Kids, American Heart Association, American Cancer Society, American Lung Association, and the American Legacy Foundation.

While there is no question that more rigorous research is needed to study the effectiveness of electronic cigarettes for smoking cessation (e.g., clinical trials), there is also no question that these products can be effective and are effective among thousands of users. This may not mean that the proportion of users who are successful is high, but it does mean that the number of people who would be harmed by taking e-cigarettes off the market or by persuading people to discontinue their use is substantial.

Thus, promoting the removal of electronic cigarettes from the market pending further research and recommending that people refrain from using the product pending further research are both strategies that will almost invariably cause substantial health harm to the population. Therefore, I do not find either of these approaches to be responsible and appropriate ones.

Posted by Michael Siegel at 11:19 AM 0 Comments


0 Comments
The Rest of the Story
Gregory Conley
Sort by Best
Share
Favorite
Start the discussion…
ALSO ON THE REST OF THE STORY
WHAT'S THIS?
Tobacco News Analysis and Commentary: FDA … 23 comments
Tobacco News Analysis and Commentary: … 44 comments
Tobacco News Analysis and Commentary: Rest … 26 comments
Tobacco News Analysis and Commentary: … 16 comments
Subscribe
Add Disqus to your site
Newer Post
Home
Older Post
Subscribe to: Post Comments (Atom)
Sitemeter
SITE METER
Statcounter
Tracked for free by statcounter.com
Simple template. Powered by Blogger.

Addiction
RESEARCH REPORT
doi:10.1111/j.1360-0443.2011.03505.x

Electronic cigarette: users profile, utilization, satisfaction and perceived efficacy

Jean-François Etter[1] & Chris Bullen[2]

Institute of Social and Preventive Medicine, Faculty of Medicine, University of Geneva, Geneva, Switzerland[1] and Clinical Trials Research Unit, School of Population Health, University of Auckland, Auckland, New Zealand[2]

ABSTRACT

Aims To assess the profile, utilization patterns, satisfaction and perceived effects among users of electronic cigarettes ('e-cigarettes'). **Design and Setting** Internet survey in English and French in 2010. **Measurements** Online questionnaire. **Participants** Visitors of websites and online discussion forums dedicated to e-cigarettes and to smoking cessation. **Findings** There were 3587 participants (70% former tobacco smokers, 61% men, mean age 41 years). The median duration of electronic cigarette use was 3 months, users drew 120 puffs/day and used five refills/day. Almost all (97%) used e-cigarettes containing nicotine. Daily users spent $33 per month on these products. Most (96%) said the e-cigarette helped them to quit smoking or reduce their smoking (92%). Reasons for using the e-cigarette included the perception that it was less toxic than tobacco (84%), to deal with craving for tobacco (79%) and withdrawal symptoms (67%), to quit smoking or avoid relapsing (77%), because it was cheaper than smoking (57%) and to deal with situations where smoking was prohibited (39%). Most ex-smokers (79%) feared they might relapse to smoking if they stopped using the e-cigarette. Users of nicotine-containing e-cigarettes reported better relief of withdrawal and a greater effect on smoking cessation than those using non-nicotine e-cigarettes. **Conclusions** E-cigarettes were used much as people would use nicotine replacement medications: by former smokers to avoid relapse or as an aid to cut down or quit smoking. Further research should evaluate the safety and efficacy of e-cigarettes for administration of nicotine and other substances, and for quitting and relapse prevention.

Keywords E-cigarette, electronic cigarette, electronic nicotine delivery systems (ENDS), internet, nicotine, smoking, tobacco use disorder.

Correspondence to: Jean-François Etter, Institute of social and preventive medicine, University of Geneva, CMU, case postale, CH-1211 Geneva 4, Switzerland. E-mail: jean-francois.etter@unige.ch
Submitted 8 February 2011; initial review completed 4 May 2011; final version accepted 11 May 2011

INTRODUCTION

Electronic cigarettes (referred hereafter as e-cigarettes and by some authorities as electronic nicotine delivery systems, ENDS) look like tobacco cigarettes, but do not contain tobacco. Instead, they comprise a metal casing within which a battery-powered atomiser produces a vapour for inhalation from cartridges that contain humectants (e.g. propylene glycol or glycerol), flavours, nicotine or in some cases other medications (rimonabant, amino-tadalafil) [1–3]. Their appearance, size, handling and oral inhalation characteristics resemble those of tobacco cigarettes and may be important in their popularity and in assisting smokers to quit.

E-cigarettes are popular. Google searches for 'electronic cigarettes' have increased by 5000% over the past 2 years [4], and 9% of UK smokers and 9% of Polish teenage smokers report having used them [5,6]. Many smokers report using them to quit smoking [7,8], or to 'smoke' in smoke-free places [7]. However, because there are no data supporting the marketers' claim that e-cigarettes help smokers to quit, the World Health Organization (WHO) and the US Food and Drug Administration (FDA) have asked them not to make therapeutic claims [9,10].

Conference presentation: This study was presented at the European Conference on Tobacco or Health, Amsterdam, the Netherlands, 28–30 March 2011.

Few research reports on e-cigarettes are available [11–19]. In clinical studies, e-cigarettes appear to attenuate craving for tobacco, despite delivering very little nicotine to the blood [16,17,20]. Laboratory testing has shown that some e-cigarette cartridges may contain toxic components, including low levels of carcinogens [12,14,19]. Many questions remain unanswered: are e-cigarettes safe, are they addictive, who uses them, why and how are they used, are they effective for smoking cessation or reduction [21,22]? Also unanswered are questions about their wider impact: are they used by young non-smokers, could they be a gateway to tobacco use or nicotine dependence, and could their use in public places undermine smoke-free laws [4,6,19,22–24]?

Conducting clinical trials of these devices is challenging: there is a lack of safety data, the regulatory environment makes conducting trials of such novel devices difficult [14,22,25] and trials are expensive and time-consuming to conduct. Therefore, until trials can be undertaken, user surveys are a means of gathering information about the effects of this product on a range of outcomes [5–7]. The aim of this study was to describe e-cigarette users, assess how and why they used this product, their satisfaction with the product and its perceived effects.

METHODS

We posted a questionnaire on the smoking cessation website Stop-Tabac.ch [26–28], in English and French, and used data collected between March and October 2010 (data collection will continue until December 2011). We contacted discussion forums and websites informing about e-cigarettes or selling them, and asked them to publish links to the survey (http://www.stop-tabac.ch/fr_hon/ECIG_EN). Participants were aged >18 years, and current, past and never-users of e-cigarettes were eligible. We recorded IP addresses (i.e. computer numbers) to identify and delete duplicate records, and collected saliva vials in a subsample of participants for cotinine analysis (results reported separately) [29]. The sample size expected initially was 1500, but participation was greater than expected. The survey was approved by the ethics committee of the Geneva University Hospitals.

The questionnaire, based on previous work by the authors [7,17,22], assessed:

- Prior or current use of e-cigarettes, and intention to use them.
- Dosage, puffs/day, brand, flavours, cost and where obtained.
- Duration of use, delivery of nicotine, ease in staying off cigarettes.
- Effect on smoking cessation and on tobacco withdrawal symptoms (Minnesota Withdrawal Form) [30], in participants who had used the e-cigarette during a quit attempt.
- Respiratory symptoms [clinical chronic obstructive pulmonary disease (COPD) questionnaire] [31,32].
- Reasons for using and reasons for stopping use.
- Side effects, acceptability and satisfaction.
- Use of smoking cessation medications (nicotine therapy, bupropion and varenicline).
- Smoking status, cigarettes per day and time to first cigarette.
- Currently trying to quit or reduce smoking, intention to quit, confidence in ability to quit.
- Age, sex, income, education, country and, from May 2010 onwards, where respondents learned about the survey.

Statistical analyses

We compared current and former smokers, and users of e-cigarettes containing nicotine with those using e-cigarettes without nicotine. There is a concern that participants enrolled on forums and websites that defend the rights of e-cigarette users may deliberately answer in a way that is favourable to their agenda (e.g. exaggerating satisfaction or under-reporting side effects). To test this hypothesis, we compared two groups: (i) the 1005 users who learned about the survey on websites where the right to use e-cigarettes is often debated and advocated: E-cigarette-forum.com ($n = 782$), Vapersforum.com ($n = 129$), Casaa.org ($n = 32$), the UK Vapers forum ($n = 23$), Vapersclub.com ($n = 20$) or Forum-ecigarette.com ($n = 19$), with (ii) the 83 participants who learned of the survey on more neutral sites, including Stop-tabac.ch ($n = 26$) (a smoking cessation website with some factual, neutral information on e-cigarettes), on Google ($n = 30$) or on other sites unrelated to e-cigarettes ($n = 27$).We used analyses of variance (ANOVAs) to compare means, Mann–Whitney *U*-tests to compare medians and χ^2 tests to compare proportions. For most variables, we reported medians rather than means, because medians are less sensitive to extreme values. We used linear regression models to test associations between continuous variables, with 95% confidence intervals (CI) around the point estimates as a measure of precision. Prices in currencies other than $US were converted to $US. A *P*-value of <0.05 was used as the cut-off for judging statistical significance.

RESULTS

Participant characteristics

The raw data file included 3659 records, but we deleted 66 double entries (i.e. duplicate answers by the same people identified by computer numbers) and six records of

people aged <18. The median age of the 3587 participants was 41 years (25th and 75th percentiles: 31 and 50 years), most were men (61%), former smokers (70%) and answered the English version of the questionnaire (79%) (Table 1). Distribution of respondents by country was: United States (62%), France (14%), United Kingdom (6%), Switzerland (4%), Canada (3%) and other countries (11%). Participants learned about the survey on the following websites: E-cigarette-forum.com (53%), Vapersforum.com (9%), the Sedansa website (3%), the Totally Wicked website (2%), Casaa.org (2%), Google (2%), Stoptabac.ch (2%), the UK Vapers forum (2%) and other websites (25%). Most participants (58%) had obtained a diploma that would give access to university, and household income tended to be above average. Among current smokers, most reported currently trying to quit or to reduce their tobacco use. Very few ($n = 4$) never smokers used nicotine-containing e-cigarettes, but of these, three said they used them to deal with their craving for tobacco and to avoid relapsing to smoking, indicating that they were actually former smokers misclassified as never smokers. Most participants were current users of e-cigarettes, but 15.2% were never users and 1.3% were past users.

Daily users versus never users of e-cigarettes

There were more men (65% versus 46%, $P < 0.001$) and more former smokers (77% versus 42%, $P < 0.001$) among daily e-cigarette users than among never users. Daily users were more likely to have ever used bupropion (30 versus 19%, $P < 0.001$) and nicotine therapy (70 versus 64%, $P < 0.001$), but not varenicline. Among current smokers, daily e-cigarette users smoked fewer cigarettes than never users (13 versus 16 cigarettes/day, $P < 0.001$). However, *before* they first started using the e-cigarette, daily e-cigarette users smoked more tobacco than never users (25 versus 16 cigarettes/day, $P < 0.001$). Among smokers, e-cigarette users were also more likely than never users to be currently trying to quit smoking (71 versus 51%, $P < 0.001$) or trying to reduce their tobacco use (96 versus 72%), more confident in their ability to quit ('very sure': 17 versus 6%, $P < 0.001$), and had lower scores on the clinical COPD questionnaire (total score: 1.25 versus 1.79, $P < 0.001$). Among former smokers, the duration of smoking abstinence was shorter in daily users than in never users (105 versus 150 days, $P = 0.001$).

Utilization

The most-used brands varied by country. Among daily users living in the United States, the most-used brands were: Joye (40.5%), Vapor4Life (9.2%), Janty (5.8%), Totally Wicked (5.8%) and PureSmoker (5.3%); in France: Janty (27.5%), Joye (19.8%), Sedansa (13.7%), Kyozen (6.9%) and CigLib (6.9%); and in the United Kingdom: TECC (19.9%), Totally Wicked (17.6%), Titan (13.2%), Joye (11.8%) and Screwdriver (9.6%). The most-used models (sold under various brand names) were the 510 (40.5% of daily e-cigarette users), the eGo (11.3%), the KR808 (9.1%), the 901 (6.4%) and the Tornado (5.1%). The flavours used most were tobacco (39% of users), mint–menthol (15%), various fruit flavours (14%), coffee (9%), vanilla (5%) and chocolate (3%). The tobacco flavour was rated lower (83% 'good' or 'very good') than for all other flavours combined (93%, $\chi^2 = 115$, $P < 0.001$). The models tested in previous studies [14–19,24,33] were seldom or never used by respondents: Njoy ($n = 10$, 0.3%), Liberty ($n = 8$, 0.3%), Ruyan ($n = 5$, 0.2%), Smoking Everywhere ($n = 4$, 0.1%), Gamucci ($n = 4$, 0.1%), Crown Seven ($n = 0$), inLife ($n = 0$), Supersmoker ($n = 0$) and VapCig ($n = 0$).

Among daily users of the e-cigarette, the median duration of the current episode of use was 3 months, but 15% had been using it for 1 or more years. Daily users drew an average of 120 puffs per day (Table 2). Almost all daily users (97%) said their e-cigarette contained nicotine. The median capacity of refill bottles was 20 ml and the median nicotine concentration in the liquid, uniform across brands and models, was 18 mg/ml (Table 2). Daily users used two bottles of refill liquid per month, refilled their e-cigarette five times a day, and each refill or cartridge lasted 2 hours. The average price per kit was 60 $US, and daily users spent 33 $US per month for their e-cigarettes (including refill liquid and cartridges, batteries, components). Almost all daily users (96%) bought their e-cigarettes on the internet and about half (45%) intended to continue using them for another year or more. Daily users used their e-cigarette mainly at home (98% 'often' and 'very often'), in their car (90%) and at work (71%), but less frequently in cafes/restaurants/bars/discos (43%), in public transport (15%) or during business meetings (13%).

Satisfaction

Most current smokers reported that the e-cigarette helped them to reduce their smoking (92%), and most former smokers (96%) said that it helped them to quit smoking. Most ever users (89%) said that it was easy to abstain from smoking while using the e-cigarette (Table 3). Most users (94%) were willing to recommend it to a friend, and satisfaction ratings were high (mean = 9.3 on a 0–10 scale). Few (10%) still experienced the urge to smoke while using the e-cigarette, and most former smokers (79%) feared that they would relapse to smoking if they stopped using it.

Most ever users (91%) liked the e-cigarette's taste and the sensation while inhaling (Table 3). However, 22%

Table 1 Characteristics of study participants: internet (English and French), March–October 2010.

	All	*Current smokers*	*Former smokers*	*Statistic*	*P-value*	*E-cigarette with nicotine*	*E-cigarette without nicotine*	*Statistic*	*P-value*
Number of respondents	3587	1051	2508			2850	112		
Version (% English)	78.9	65.0	84.8	$\chi^2 = 176$	<0.001	91.9	67.9	$\chi^2 = 76.4$	<0.001
Age (years)[a]	41 (31, 50)	42 (31, 52)	40 (32, 50)	$U = 115\,164$	0.11	41 (31, 50)	42 (31, 51)	$U = 145\,209$	0.75
Sex (men, %)	61.3	58.2	62.5	$\chi^2 = 5.7$	0.017	64.6	47.3	$\chi^2 = 14.0$	<0.001
Household income (%)									
Below average	27.7	31.2	26.2	$\chi^2 = 17.6$	0.004	28.1	28.5	$\chi^2 = 10.1$	0.071
Average	30.9	29.8	31.5			30.9	25.0		
Above average	36.4	32.9	37.9			36.5	36.6		
E-cigarette use				$\chi^2 = 372$	<0.001			$\chi^2 = 42.8$	<0.001
Daily	80.8	61.7	89.2			96.7	84.8		
Occasional (not daily)	2.7	6.3	1.0			2.5	11.6		
Past users	1.3	2.6	0.8			0.8	3.6		
Never users	15.2	29.5	9.0			–	–		
Ever used nicotine therapy (%)	68.1	62.9	70.5	$\chi^2 = 36.1$	<0.001	69.4	60.4	$\chi^2 = 8.8$	0.031
Ever used bupropion (%)	28.0	25.3	29.1	$\chi^2 = 7.5$	0.058	29.9	32.4	$\chi^2 = 0.7$	0.86
Ever used varenicline (%)	18.4	16.2	19.4	$\chi^2 = 20.6$	<0.001	18.6	22.0	$\chi^2 = 18.5$	<0.001
Smoking status									
Daily smokers	19.0					12.1	12.5	$\chi^2 = 14.7$	0.002
Occasional (non-daily)	10.5					12.0	9.8		
Former smokers	70.2					75.8	75.9		
Never smokers	0.3					0.1	1.8		
Daily smokers									
Tobacco cigarettes/day now[a]		15 (10, 20)				15 (8, 20)	12 (7, 20)	$U = 2027$	0.37
Cigarettes/day before using e-cigarette[a]		25 (20, 30)				25 (20, 30)	17 (11, 21)	$U = 1049$	0.001
Minutes to first cigarette of the day[a]		15 (5, 30)				10 (5, 30)	15 (9, 38)	$U = 1886$	0.25
Sure they could quit smoking if they tried (very sure, %)		11.2				15.0	23.1	$\chi^2 = 2.4$	0.48
Decided to quit next 30 days (%)		35.4				34.4	38.5	$\chi^2 = 1.7$	0.63
Now trying to quit smoking (%)		60.1				68.2	64.3	$\chi^2 = 0.1$	0.76
Currently trying to reduce cigarettes/day (%)		84.4				94.7	92.9	$\chi^2 = 0.1$	0.76
Duration of most recent quit attempt (days)[a]		21 (3, 122)				21 (2, 91)	21 (1, 274)	$U = 1255$	0.42
Former smokers									
Days since quit smoking[a]			107 (41, 251)			105 (42, 238)	112 (35, 254)	$U = 81\,142$	0.69

[a]Median (25th and 75th centiles).

Table 2 Utilization patterns among daily e-cigarette users.

	All daily e-cigarette users	*Current smokers*	*Former smokers*	*Statistic*	*P-value*	*E-cigarette with nicotine*	*E-cigarette without nicotine*	*Statistic*	*P-value*
n daily users	2896	647	2234			2757	95		
Duration current episode of use (days)[a]	91 (28, 274)	49 (14, 152)	152 (49, 274)	$U = 498\,148$	<0.001	91 (28, 274)	91 (16, 152)	$U = 108\,394$	0.18
Use e-cigarette minutes after waking[a]	20 (10, 45)	20 (10, 60)	20 (10, 45)	$U = 658\,777$	0.17	20 (10, 45)	30 (15, 90)	$U = 90\,702$	<0.001
Puffs per day drawn on e-cigarette[a]	120 (80, 200)	100 (70, 200)	120 (80, 200)	$U = 611\,447$	0.04	120 (80, 200)	100 (50, 200)	$U = 103\,405$	0.011
Capacity of refill bottles (ml)[a]	20 (10, 30)	15 (10, 30)	30 (10, 30)	$U = 478\,601$	<0.001	20 (10, 30)	15 (10, 30)	$U = 80\,939$	0.20
Nicotine in liquid (mg per ml)[a]	18 (12, 24)	18 (13, 24)	18 (12, 24)	$U = 568\,704$	0.88	18 (12, 24)	0 (0, 0)	$U = 4384$	<0.001
Bottles per month[a]	2 (1, 3)	2 (1, 3)	2 (1, 3)	$U = 517\,168$	0.001	2 (1, 3)	1.3 (0.5, 4)	$U = 82\,030$	0.003
Refills/cartridges per day[a]	5 (2, 10)	4 (2, 10)	5 (3, 10)	$U = 534\,495$	<0.001	5 (2, 10)	3 (1, 10)	$U = 91\,982$	0.001
Refill/cartridge lasts? (hours)[a]	2 (1, 5)	3 (1, 6)	2 (1, 5)	$U = 574\,500$	<0.001	2 (1, 5)	3 (1, 12)	$U = 102\,312$	0.019
Duration of battery (hours)[a]	6 (3, 10)	5 (3, 10)	6 (3, 10)	$U = 625\,419$	0.37	6 (3, 10)	6 (3, 12)	$U = 116\,736$	0.76
Price per kit ($US)[a]	60 (42, 80)	59 (40, 80)	65 (44, 80)	$U = 594\,056$	0.002	60 (42, 80)	67 (41, 106)	$U = 108\,436$	0.092
Monthly spending ($US)[a]	33 (20, 50)	30 (19, 50)	35 (20, 50)	$U = 483\,114$	0.004	35 (20, 50)	25 (16, 36)	$U = 65\,295$	<0.001
Intends to use for >1 year (%)	45.4	50.2	44.0	$\chi^2 = 21.2$	0.012	45.4	41.3	$\chi^2 = 44.8$	<0.001
Ever used e-cigarette and tobacco on the same day (%)	65.2	95.7	56.4	$\chi^2 = 707$	<0.001	65.7	50.0	$\chi^2 = 11.7$	0.11
If dual use: duration (days)[a]	5 (1, 19)	19 (5, 60)	1 (1, 5)	$U = 211\,625$	<0.001	5 (1, 19)	5 (1, 19)	$U = 39\,680$	0.71

[a]Median (25th and 75th centiles).

Table 3 Satisfaction with the e-cigarette, in ever users.

	All ever users	*Current smokers*	*Former smokers*	χ^2	*P-value*	*E-cigarette with nicotine*	*E-cigarette without nicotine*	χ^2	*P-value*
n ever users	3037	740	2279			2850	112		
E-cigarette helped reduce smoking? (a lot, %)	92.2	86.7	94.3	86.7	<0.001	99.0	88.7	33.0	<0.001
E-cigarette ever broke down? (often, %)	8.0	11.3	7.0	27.1	<0.001	8.0	5.4	3.9	0.27
Liquid leaks out? (sometimes + often, %)	18.4	21.9	17.2	17.8	0.001	18.1	24.9	9.2	0.057
Would recommend e-cigarette to a friend (absolutely, %)	94.3	89.9	95.8	44.0	<0.001	94.9	86.2	19.4	0.001
Satisfaction, 0–10 scale (mean)	9.3	8.7	9.5	$F = 261$	<0.001	9.4	9.1	$F = 8.8$	0.003
Burns throat (somewhat + strongly, %)	22.1	23.8	15.7	25.9	<0.001	18.0	10.8	8.9	0.012
Rather + strongly agree (%)									
Still feel urge to smoke when using it	9.5	22.5	5.4	545	<0.001	9.3	9.8	5.7	0.22
Easy to abstain from smoking when using e-cigarette	88.6	82.4	90.3	536	<0.001	89.3	75.7	32.6	<0.001
Fears that e-cigarette might be toxic	6.0	9.1	5.1	25.9	<0.001	5.8	8.9	8.4	0.077
Fear that e-cigarettes will be banned	82.7	80.2	83.5	5.2	0.27	83.6	64.3	36.8	<0.001
Wonders what is composition of e-liquid	25.7	32.2	23.7	35.1	<0.001	25.4	29.7	2.8	0.59
The battery is discharged too quickly	37.0	44.0	34.8	40.4	<0.001	36.9	35.1	4.8	0.31
Refill cartridges are emptied too quickly	44.2	51.2	41.8	28.0	<0.001	44.6	37.3	4.8	0.31
Difficult to adjust nicotine dose with it	8.3	12.9	6.7	119	<0.001	8.0	–	–	–
Likes the taste of e-cigarette	91.2	86.3	92.6	50.0	<0.001	91.7	85.7	10.3	0.036
Likes sensation when inhales vapour	91.4	87.3	92.8	79.7	<0.001	92.0	86.6	13.5	0.009
Uses it because it causes no bad odours	89.6	89.5	89.7	12.8	0.012	90.1	83.6	14.9	0.005
E-cigarette causes a dry mouth/throat	26.2	29.1	25.1	8.5	0.07	26.4	24.3	5.5	0.24
Should provide faster relief of craving	9.7	17.5	7.4	116	<0.001	9.6	9.3	8.3	0.080
E-cigarette should provide more nicotine	4.2	7.9	3.0	69.1	<0.001	4.4	0.9	32.8	<0.001
Vapour should be more concentrated	19.7	28.3	16.9	67.4	<0.001	19.2	27.0	12.1	0.017
It should be easier to draw on e-cigarette	20.4	29.3	17.5	75.7	<0.001	20.1	27.0	9.2	0.057
Is afraid of becoming addicted to e-cigarette	7.7	10.0	7.0	11.5	0.021	7.8	1.8	18.3	0.001
Former smokers: fears that will start smoking again if stopped using it	–	–	79.2	–	–	80.0	63.9	26.5	<0.001
Did e-cigarette help you stop smoking? (a lot + definitely, %)	–	–	96.0	–	–	96.4	90.6	62.2	<0.001

reported that it burned the throat or gave a dry mouth or dry throat (26%). Similar proportions suggested the vapour should be more concentrated (20%) and that it should be easier to draw (inhale) on the e-cigarette (20%). One-third thought that the cartridges and batteries ran out too quickly, 18% said that the liquid sometimes leaked from the device, and 8% reported that their e-cigarette had broken down at some stage. Only a small proportion expressed concerns that the e-cigarette might be toxic (6%) or could lead to dependence (8%), but most feared that it might one day be banned by authorities (83%).

Linear regression modelling showed that the price of e-cigarette kits was not associated with the length of battery life, but was associated with the duration that refill cartridges lasted: for each additional 10 $US spent per kit, refills lasted 0.5 hours longer ($t = 3.1$, 95% CI: 0.2–0.9 hours, $P = 0.002$). There were no statistically significant associations between price and technical problems such as breakdowns or leakage.

Reasons for use

E-cigarettes were used because they were perceived to be less toxic than tobacco (84%), to quit smoking or avoid relapsing (77%), to deal with craving for tobacco (79%) and tobacco withdrawal symptoms (67%), and because they were cheaper than smoking (57%) (Table 4). Other less common reasons were to avoid bothering other people with tobacco smoke (44%), to deal with smoke-free situations (39%) or to avoid having to go outside to smoke (34%). Fewer used the e-cigarette to reduce tobacco consumption (28%), and far fewer reported being unable to stop using it (4%).

Reasons for stopping use

Those who had stopped using e-cigarettes ($n = 47$) indicated that they had done so because they did not need them any more (41% 'rather' plus 'strongly agree'), because they thought they would not relapse to smoking even if they stopped (33%), because of the product's poor quality (35%), because it did not reduce cravings (33%), because they relapsed to smoking (25%), because it did not help them to quit smoking (21%), because they feared its side effects (21%) or because they replaced it with a smoking cessation medication (10%).

Withdrawal symptoms

For participants who had used the e-cigarette during a quit attempt and who reported withdrawal symptoms ('moderate' or 'severe') [30], Table 5 shows the proportion who also reported whether the e-cigarette relieved symptoms. Craving to smoke was the symptom most

Table 4 Reasons for using the electronic cigarette, among ever users.

Among ever e-cigarette users: I use (used) the e-cigarette . . . (very true, %)	*All ever users*	*Current smokers*	*Former smokers*	χ^2	*P-value*	*E-cigarette with nicotine*	*E-cigarette without nicotine*	χ^2	*P-value*
n ever users	3037	740	2279			2850	112		
E-cigarette less toxic than tobacco	83.5	81.1	84.3	5.2	0.16	84.5	64.2	55.3	<0.001
To deal with craving for tobacco	79.0	77.3	79.7	2.3	0.52	80.1	61.5	28.0	<0.001
To quit smoking or avoid relapsing	76.8	57.7	83.0	207	<0.001	77.2	69.6	6.9	0.075
To deal with withdrawal symptoms	66.5	60.2	68.7	17.8	<0.001	67.7	40.9	39.5	<0.001
E-cigarette cheaper than smoking	57.3	53.8	58.4	8.2	0.041	58.2	43.9	32.6	<0.001
To avoid bothering others with tobacco smoke	43.6	42.4	44.0	5.4	0.14	44.0	38.7	6.1	0.11
To deal with situations where one cannot smoke (at work, etc.)	39.4	45.6	37.4	22.5	<0.001	39.9	30.0	21.5	<0.001
To avoid having to go outside to smoke	34.4	36.9	33.6	14.0	0.003	34.9	29.1	24.7	<0.001
To reduce tobacco consumption in preparation of a quit attempt	27.8	42.4	23.0	169	<0.001	17.8	28.2	15.2	0.002
To reduce tobacco consumption with *no* intention to quit smoking	20.3	23.5	19.2	94.6	<0.001	20.5	15.6	13.7	0.003
Because is unable to stop using it	4.4	4.4	4.4	3.3	0.35	4.5	2.8	4.9	0.18

Table 5 Relief of withdrawal symptoms, in those who used e-cigarettes during an attempt to quit smoking.

In those reporting 'moderate' and 'severe' symptoms, did e-cigarette relieve it? % (n) 'a lot' on 5-point scale	*All ever users* % (n)	*Current smokers* % (n)	*Former smokers* % (n)	χ^2	*P-value*	*E-cigarette with nicotine* % (n)	*E-cigarette without nicotine* % (n)	χ^2	*P-value*
Craving to smoke	90.0 (1457)	75.7 (342)	94.5 (1112)	104	<0.001	90.7 (1378)	76.9 (52)	18.1	<0.001
Angry, irritable, frustrated	82.5 (1089)	70.5 (227)	85.8 (858)	30.6	<0.001	83.2 (1033)	78.1 (32)	3.4	0.33
Anxious, nervous	80.8 (1078)	64.5 (231)	85.4 (844)	52.8	<0.001	81.4 (1022)	71.4 (35)	11.7	0.009
Restless, impatient	77.9 (950)	65.0 (203)	81.6 (744)	42.2	<0.001	78.9 (889)	68.6 (35)	9.1	0.028
Difficulty concentrating	74.0 (773)	63.4 (161)	77.0 (609)	14.4	0.002	74.8 (731)	64.0 (25)	2.0	0.56
Depressed mood, sad	70.9 (622)	59.8 (123)	74.0 (497)	12.0	0.007	71.4 (581)	71.4 (21)	5.1	0.16
Insomnia, sleep problems	53.4 (573)	44.2 (114)	56.0 (455)	8.1	0.044	54.1 (532)	43.5 (23)	21.4	<0.001
Appetite, hungry, weight gain	52.7 (733)	42.1 (146)	55.7 (583)	9.5	0.023	52.8 (685)	48.4 (31)	0.7	0.87

relieved by the e-cigarette (90%). The effects of e-cigarettes on suppressing withdrawal symptoms were reported as being greater by former smokers than current smokers, and greater by users of nicotine-containing e-cigarettes than users of non-nicotine e-cigarettes (Table 5).

Use to inhale other substances

Very few ever users ($n = 27$, 0.9%) reported having used the e-cigarette to inhale other substances than the liquid designed for that purpose. The substances disclosed were cannabis ($n = 5$, 0.2%), vitamins ($n = 3$), flavours ($n = 2$), herbs ($n = 2$) and vodka ($n = 1$). The median duration of e-cigarette use to inhale these substances was five days, but only 1 day among those who used cannabis.

Comparing users of e-cigarettes containing or not containing nicotine

Compared with users of non-nicotine e-cigarettes, users of nicotine-containing e-cigarettes were more likely to be men and smoked more tobacco cigarettes per day before they first started using e-cigarettes (Table 1). However, there was no between-group difference for current smoking status. Those who used nicotine-containing e-cigarettes were more likely to be daily users, used their first e-cigarette of the day earlier in the day, drew more puffs on their e-cigarette, used more refills per day and more bottles per month, their refill cartridges lasted less, and more of them intended to use e-cigarettes for another year or more (Table 2). Users of nicotine-containing e-cigarettes were also more likely to answer that it helped them to quit or reduce their smoking, they were more satisfied with it, in particular with its taste and with the sensation while inhaling, more likely to say that they feared relapsing if they stopped using it, but they were also more likely to answer that e-cigarette use burned their throat (Table 3). Most of the reasons for using the e-cigarette were endorsed more frequently by users of nicotine-containing e-cigarettes than by users of non-nicotine e-cigarettes, in particular use to deal with craving and withdrawal (Table 4).

Comparing current and former tobacco smokers

Former smokers were more likely than current smokers to use the e-cigarette and to have ever used smoking cessation medications (Table 1). Among daily e-cigarette users, the duration of use was longer in former smokers than in current smokers (Table 2). Former smokers also took more puffs per day, were less likely to use the tobacco flavour, used larger refill bottles, their refills or cartridges lasted less and they spent more per month than current smokers. Former smokers were also more likely to say

that the e-cigarette helped them to quit or reduce their smoking, to report that it helped improve their respiratory symptoms, and to use e-cigarettes to deal with tobacco withdrawal symptoms (Table 3).

Comparing participants enrolled on e-cigarette forums with those enrolled on neutral sites

The 1005 participants enrolled on e-cigarette forums/websites were more likely to be former smokers than the 83 participants enrolled on 'neutral' websites (72 versus 43%, $P < 0.001$), more likely to be daily e-cigarette users (93 versus 31%, $P < 0.001$), had used the e-cigarette longer (current episode of use: 91 days versus 14 days [medians], $P = 0.003$), were generally more satisfied with the e-cigarette, but indicated the same reasons for using them (Table 6). When analyses were restricted to former smokers, differences in several satisfaction variables were smaller and often non-significant: e.g. satisfaction rating (0–10 scale): mean = 9.6 in both groups ($t = 0.2$, $P = 0.8$), 'e-cigarette burns the throat' (16.3 versus 25.0%, $\chi^2 = 0.8$, $P = 0.7$) and 'fear e-cigarette might be toxic' (6.1 versus 0%, $\chi^2 = 2.0$, $P = 0.75$).

DISCUSSION

The main finding of this survey, which enrolled predominantly self-selected visitors of websites dedicated to e-cigarettes, is that e-cigarettes were used largely by former smokers as an aid to quit smoking, to avoid relapse and to deal with withdrawal symptoms, much as

Table 6 Comparison of participants enrolled on e-cigarette forums with those enrolled on other websites.

Selected variables	*Enrolled on e-cigarette forums*	*Enrolled on Stop-tabac or Google*	*Statistic*	*P-value*
n	1005	83		
Smoking status (%)				
Daily smokers	14.5	48.8	$\chi^2 = 72.5$	<0.001
Occasional (non-daily)	13.0	4.9		
Former smokers	72.3	43.9		
Never smokers	0.3	2.4		
E-cigarette use (%)				
Daily	93.2	30.1	$\chi^2 = 456.8$	<0.001
Occasional (not daily)	3.1	1.2		
Past users	1.0	1.2		
Never users	2.7	67.5		
In daily e-cigarette users				
Use e-cigarette containing nicotine (%)	97.6	100	$\chi^2 = 0.6$	0.45
Duration current episode of use (days)[a]	91 (21, 274)	14 (5, 152)	$U = 6164$	0.003
Puffs per day drawn on e-cigarette[a]	100 (70, 200)	200 (65, 300)	$U = 7696$	0.15
Bottles of e-liquid per month[a]	1.5 (1, 3)	1.5 (1, 3)	$U = 7546$	0.94
Refill/cartridge lasts? (hours)[a]	3 (1, 6)	3.5 (2, 8)	$U = 8876$	0.17
In ever users				
E-cigarette helped reduce smoking? (a lot, %)	93.2	80.8	$\chi^2 = 13.1$	0.011
Satisfaction, scale 0–10 (mean)	9.4	8.9	$t = 2.1$	0.03
Would recommend e-cigarette to a friend (absolutely, %)	95.5	88.5	$\chi^2 = 49.7$	<0.001
Burns throat (somewhat + strongly, %)	17.9	41.6	$\chi^2 = 34.5$	<0.001
Fears that e-cigarette might be toxic	6.3	18.5	$\chi^2 = 9.4$	0.052
In ex-smokers: e-cigarette helped quit smoking (a lot + definitely, %)	96.1	93.3	$\chi^2 = 11.5$	0.02
Opinions (agree, %)				
Fear that e-cigarettes will be banned	86.0	84.6	$\chi^2 = 4.5$	0.34
E-cigarette causes a dry mouth/throat	23.9	33.3	$\chi^2 = 4.7$	0.32
Should provide faster relief of craving	6.7	4.3	$\chi^2 = 3.5$	0.32
Afraid of becoming addicted to e-cigarette	6.8	14.8	$\chi^2 = 11.9$	0.02
Reasons for using e-cigarette (very true, %)				
E-cigarette less toxic than tobacco	85.4	77.8	$\chi^2 = 4.7$	0.20
To deal with craving for tobacco	82.4	88.9	$\chi^2 = 1.7$	0.64
To quit smoking or avoid relapsing	76.8	84.6	$\chi^2 = 2.4$	0.49
To deal with withdrawal symptoms	66.5	76.9	$\chi^2 = 3.5$	0.33

[a]Median (25th and 75th centiles).

people use nicotine replacement therapy (NRT). Use of e-cigarettes in smoke-free places was cited relatively less frequently, but many participants used them because they were perceived to be less toxic and cheaper than tobacco. Daily users spent 33 $US per month for e-cigarettes, which is much cheaper than smoking one pack a day (incurring a cost of about 150–200 $US per month in the respondents' countries). This is also substantially cheaper than smoking cessation medications (which, at the recommended dosage, cost about the same as smoking one pack a day). Thus, an important reason for the popularity of e-cigarettes [5,6] is most probably their price.

Several other findings raise questions needing further research. For example, it would be interesting to investigate why e-cigarettes have more appeal to men than to women. Only one never smoker used nicotine-containing e-cigarettes, a finding that could reflect the fact that under-age consumers were ineligible for the survey, or that contrary to the hypothesis expressed by some authors [4,23,24], e-cigarettes do not facilitate initiation to nicotine use in young never smokers.

The duration of use in former smokers (5 months) was substantially longer than use of NRT (usually a few days to a few weeks) [34,35, Etter & Schneider; unpublished data]. This suggests either that our sampling method resulted in the self-selection of long-term users, or that e-cigarettes are actually used longer-term than NRT, for reasons that deserve investigation.

It is not clear why one brand (Joye) and one model (the 510) dominated the market. This may result from successful marketing, or perhaps users may communicate about their preferred brands in online forums, and the best brands may gain popularity this way. It may be that some brands were over-represented in this survey because of links from websites selling these brands, in particular Totally Wicked and Sedansa. The models used in previous studies were seldom or never used by participants in this study [14–19,24]. To ensure validity and generalizability, future studies should use the most popular models.

Very few respondents (3% of users) used e-cigarettes without nicotine. This could suggest that, despite two studies showing very low absorption of nicotine [16,17], it may be an important ingredient of this product, perhaps because of its taste in addition to its pharmacological properties on withdrawal relief. Alternatively, users might have greater expectations for nicotine-containing products, so these products are purchased more commonly. Interestingly, the concentration of nicotine in the liquid was uniform across the various brands (18 mg/ml), suggesting that manufacturers reached a consensus. It is not clear how this particular concentration was arrived at, but few users said that e-cigarettes should provide more nicotine, despite the low nicotine absorption observed in the two clinical studies noted above [16,17]. The uniformity of nicotine content across the different brands makes it possible to compare them. The average content of nicotine per bottle, 360 mg (20 ml × 18 mg/ml), is of concern because the fatal dose of nicotine is estimated to be 30–60 mg for adults and 10 mg for children [2]. Thus, these refill bottles are extremely dangerous and should be replaced by sealed, tamper-proof, leak-resistant cartridges.

Daily use (120 puffs and five refills per day, that is, 24 puffs per refill) was in the range of the number of puffs inhaled by daily cigarette smokers. However, the average 24 puffs per refill is considerably less than the 170–300 smokeable puffs reported from *in vitro* tests (i.e. the number of puffs before the aerosol density decreased) [18]. This could mean that users switch cartridges when the flavour or the nicotine taste fade out, and this may occur much sooner than a decrease in aerosol density. A dosage of 120 puffs/day suggests a more intense use than the 10 puffs or 5 minutes puffing tested in clinical reports [15–17]. An implication of this is that laboratory tests should allow users to puff substantially more before outcomes are measured, to mimic actual utilization by experienced users.

The flavour used most was tobacco, even though this flavour rated lowest for satisfaction, possibly because some users did not sample all available flavours before choosing one. The sensation of a burning throat and dry mouth or throat was due in part to nicotine; whether it is also due to the humectants should be investigated.

Perceived effect on smoking and withdrawal symptoms

Our data suggest that e-cigarettes may help smokers to quit smoking, reduce their cigarette consumption and attenuate craving and tobacco withdrawal symptoms. Users of nicotine-containing e-cigarettes reported only slightly superior effects on withdrawal than users of non-nicotine e-cigarettes, suggesting that nicotine delivery explains only part of the effect of these devices on withdrawal, and that the sensory and behavioural components of the e-cigarette are also important. Of interest, current smokers who used the e-cigarette had fewer respiratory symptoms than smokers who did not use it (a difference of 0.54 points on the clinical COPD questionnaire), which we speculate might be a consequence of reduced smoking. This difference is substantial, as it is larger than the minimally clinically important difference for this questionnaire (0.4 points) [32], and very close to the difference of 0.6 points reported previously between patients with moderate and severe COPD [31].

Use for other substances

E-cigarettes represent a new way to administer substances to the respiratory tract. However, very few people

reported using e-cigarettes to inhale substances other than the liquid designed for that purpose, and when they did, it was only briefly. Of course, some respondents may not have disclosed illicit drug use. Some e-cigarettes have been found to contain tadalafil analogues, rimonabant and several other substances and medications [3], with unknown effects.

Study limitations

This study was conducted in a self-selected sample of visitors of discussion forums and websites dedicated to e-cigarettes, some of which defend the right to use e-cigarettes in the face of mounting pressure for regulation or prohibition of this product [19,36,37]. However, organized multiple responding did probably not occur: a check of IP addresses showed that there were few double entries by the same participants, and double entries were deleted. Users enrolled on e-cigarette forums/websites differed from participants enrolled on 'neutral' sites on several accounts (mainly smoking status and current use of e-cigarettes), but when taking smoking status into account, the opinions of these two groups did not differ greatly. Nevertheless, it is still possible that some respondents gave the answers that they thought might help to defend their position (e.g. by reporting more satisfaction, more effects on smoking cessation, fewer concerns about safety). Whether we also over-sampled satisfied users, long-term users or heavy users of e-cigarettes is unknown. Thus, while our results provide new and interesting information, e-cigarettes are probably somewhat less satisfactory and less effective than reflected in these data, and our results should be interpreted with caution and may have limited generalizability. Finally, technology progresses rapidly, and our results may not apply to future models.

CONCLUSIONS

E-cigarettes were used mainly by former smokers as an aid to quit smoking and avoid relapse. These products were perceived as satisfactory, useful and efficacious, and almost all users preferred nicotine-containing e-cigarettes. Despite its limitations, this study adds to the still small body of knowledge about e-cigarettes and provides valuable additional information for smokers, clinicians, regulators and policy makers. Further research should address the safety and efficacy of using e-cigarettes to deliver nicotine and other substances, and assess their effectiveness as an aid to quitting and relapse prevention.

Declarations of interest

Jean-François Etter's salary is paid by the University of Geneva. He has served as an expert consultant for the World Health Organization regarding electronic nicotine delivery systems (ENDS). He consulted for Pfizer, a manufacturer of smoking cessation medications, in 2006–07 (on the Swiss varenicline advisory board), and received medications for a clinical trial from Pfizer in 2006; no competing interests since then. Chris Bullen's salary is paid by The University of Auckland and his research is supported by grants from the New Zealand Health Research Council (HRC), the University of Auckland and the NZ Heart Foundation. He has previously undertaken tobacco control research supported by the New Zealand Ministry of Health, and by Niconovum, Sweden, prior to the purchase of this company by RJ Reynolds. He is currently an investigator on a study involving reduced nicotine cigarettes in which the products were purchased by the University of Auckland from Vector Group Ltd, USA. He has previously undertaken research on ENDS funded by HealthNZ, in which the study products were supplied by Ruyan, Hong Kong; and he is the principal investigator on an HRC-funded efficacy trial of ENDS that will use products provided by a NZ-based ENDS retailer. Other than these relationships, he has no conflicts of interest to declare.

Acknowledgements

Vincent Baujard, from the HON Foundation, Geneva, Switzerland (http://www.hon.ch) developed the software for data collection.

References

1. Flouris A. D., Oikonomou D. N. Electronic cigarettes: miracle or menace? *BMJ* 2010; **340**: c311.
2. American-Legacy-Foundation. *Electronic Cigarette ('e-cigarette') Fact Sheet*. American Legacy Foundation, 2009. Available at: http://www.legacyforhealth.org/PDFPublications/ECIGARETTE_0909_temp.pdf (accessed 16 June 2011; archived by Webcite at http://www.webcitation.org/5zUApidHT).
3. Hadwiger M. E., Trehy M. L., Ye W., Moore T., Algire J., Westenberger B. Identification of amino-tadalafil and rimonabant in electronic cigarette products using high pressure liquid chromatography with diode array and tandem mass spectrometric detection. *J Chromatogr A* 2010; **1217**: 7547–55.
4. Yamin C. K., Bitton A., Bates D. W. E-cigarettes: a rapidly growing Internet phenomenon. *Ann Intern Med* 2010; **153**: 607–9.
5. Dockrell M. 'It sounds like the replacement I need to help me stop smoking': use and acceptability of 'e-cigarettes' among UK smokers, 2010. Paper presented at the *12th Annual Meeting of the Society for Research on Nicotine and Tobacco Europe*, Bath, UK, 6–9 September.
6. Zielinska-Danch W., Goniewicz M. L., Koszowski B., Czogala J., Sobczak A. Patterns of use and prevalence of new combustible and non-combustible tobacco products among adolescents in Southern Poland, 2010. Paper presented at the *12th Annual Meeting of the Society for Research on Nicotine and Tobacco Europe*, 6–9 September.

7. Etter J. F. Electronic cigarettes: a survey of users. *BMC Public Health* 2010; **10**: 231.
8. Goniewicz M. L. Patterns of use of electronic nicotine delivery devices (ENDS) among Polish e-smokers, 2010. Paper presented at the *12th Annual Meeting of the Society for Research on Nicotine and Tobacco Europe*, Bath, UK, 6–9 September.
9. World Health Organization (WHO). *Marketers of Electronic Cigarettes Should Halt Unproved Therapy Claims, Geneva, World Health Organization, September 2008*, 2008. Available at: http://www.who.int/mediacentre/news/releases/2008/pr34/en/index.html (accessed 16 June 2011; archived by Webcite at http://www.wecitation.org/5zUAainod).
10. Food and Drug Administration (FDA). FDA acts against 5 electronic cigarette distributors. Silver Spring, MD; US Food and Drug Administration; 2010.
11. Bullen C., Glover M., Laugesen M. *et al*. Effect of an e-cigarette on cravings and withdrawal, acceptability and nicotine delivery: randomised cross-over trial, 2009. Poster presented at the *Conference of the Society for Research on Nicotine and Tobacco*, Dublin, 27–30 April 2009.
12. Laugesen M. *Safety Report on the Ruyan E-Cigarette Cartridge and Inhaled Aerosol*. Christchurch, New Zealand: Health New Zealand Ltd; 2008.
13. Laugesen M. Ruyan e-cigarette bench-top tests, 2009. Poster presented at the *Conference of the Society for Research on Nicotine and Tobacco*, Dublin, 27–30 April 2009.
14. Food and Drug Administration (FDA). *Summary of Results: Laboratory Analysis of Electronic Cigarettes Conducted By FDA, US: Food and Drug Administration (FDA), July 2009*, 2009. http://www.fda.gov/NewsEvents/PublicHealthFocus/ucm173146.htm (accessed 16 June 2011; archived at http://www.webcitation.org.5zUAMMHkS).
15. Eissenberg T. Electronic nicotine delivery devices: ineffective nicotine delivery and craving suppression after acute administration. *Tob Control* 2010; **19**: 87–8.
16. Vansickel A. R., Cobb C. O., Weaver M. F., Eissenberg T. E. A clinical laboratory model for evaluating the acute effects of electronic 'cigarettes': nicotine delivery profile and cardiovascular and subjective effects. *Cancer Epidemiol Biomarkers Prev* 2010; **19**: 1945–53.
17. Bullen C., McRobbie H., Thornley S. *et al*. Effect of an electronic nicotine delivery device (e cigarette) on desire to smoke and withdrawal, user preferences and nicotine delivery: randomised cross-over trial. *Tob Control* 2010; **19**: 98–103.
18. Trtchounian A., Williams M., Talbot P. Conventional and electronic cigarettes (e-cigarettes) have different smoking characteristics. *Nicotine Tob Res* 2010; **12**: 905–12.
19. Cahn Z., Siegel M. Electronic cigarettes as a harm reduction strategy for tobacco control: a step forward or a repeat of past mistakes? *J Public Health Policy* 2011; **32**: 16–31.
20. Darredeau C., Campbell M., Temporale K., Barrett S. P. Subjective and reinforcing effects of electronic cigarettes in male and female smokers, 2010. Paper presented at the *12th Annual Meeting of the Society for Research on Nicotine and Tobacco Europe*, Bath, UK, 6–9 September.
21. Wang D., Connock M., Barton P. *et al*. 'Cut down to quit' with nicotine replacement therapies in smoking cessation: a systematic review of effectiveness and economic analysis. *Health Technol Assess* 2008; **12**: iii–iv, ix–xi, 1–135.
22. Etter J. F., Bullen C., Flouris A. D., Laugesen M., Eissenberg T. Electronic nicotine delivery systems: a research agenda. *Tob Control* 2011; **20**: 243–8.
23. Henningfield J. E., Zaatari G. S. Electronic nicotine delivery systems: emerging science foundation for policy. *Tob Control* 2010; **19**: 89–90.
24. Cobb N. K., Byron M. J., Abrams D. B., Shields P. G. Novel nicotine delivery systems and public health: the rise of the 'e-cigarette'. *Am J Public Health* 2010; **100**: 2340–2.
25. Office fédéral de la santé publique (FSP). Lettre d'information n°146: cigarettes électroniques [Information letter no. 146 : electronic cigarettes], 2009. *Office fédéral de la santé publique*, Berne, May 2009.
26. Wang J., Etter J. F. Administering an effective health intervention for smoking cessation online: the international users of Stop-Tabac. *Prev Med* 2004; **39**: 962–8.
27. Etter J. F. Internet-based smoking cessation programs. *Int J Med Inform* 2006; **75**: 110–6.
28. Etter J. F. Comparing computer-tailored, internet-based smoking cessation counseling reports with generic, untailored reports: a randomized trial. *J Health Commun* 2009; **14**: 646–57.
29. Etter J. F., Bullen C. Saliva cotinine levels in users of electronic nicotine delivery systems. *Eur Respir J* 2011; in press.
30. Hughes J. R., Hatsukami D. Signs and symptoms of tobacco withdrawal. *Arch Gen Psychiatry* 1986; **43**: 289–94.
31. van der Molen T., Willemse B. W., Schokker S. *et al*. Development, validity and responsiveness of the Clinical COPD Questionnaire. *Health Qual Life Outcomes* 2003; **1**: 13.
32. Kocks J. W., Tuinenga M. G., Uil S. M. *et al*. Health status measurement in COPD: the minimal clinically important difference of the clinical COPD questionnaire. *Respir Res* 2006; **7**: 62.
33. Trtchounian A., Talbot P. Electronic nicotine delivery systems: is there a need for regulation? *Tob Control* 2011; **20**: 47–52.
34. Bansal M. A., Cummings K. M., Hyland A., Giovino G. A. Stop-smoking medications: who uses them, who misuses them, and who is misinformed about them? *Nicotine Tob Res* 2004; **6**: S303–10.
35. Etter J. F., Perneger T. V. Attitudes toward nicotine replacement therapy in smokers and ex-smokers in the general public. *Clin Pharmacol Ther* 2001; **69**: 175–83.
36. World Health Organization (WHO). WHO study group on tobacco product regulation. Report on the Scientific Basis of Tobacco Product Regulation: Third Report of a WHO study group. *WHO Technical Report Series.* Geneva: WHO; 2009.
37. Wollscheid K. A., Kremzner M. E. Electronic cigarettes: safety concerns and regulatory issues. *Am J Health Syst Pharm* 2009; **66**: 1740–2.

Int. J. Environ. Res. Public Health **2013**, *10*, 7272-7282; doi:10.3390/ijerph10127272

OPEN ACCESS

International Journal of
Environmental Research and Public Health
ISSN 1660-4601
www.mdpi.com/journal/ijerph

Article

Impact of Flavour Variability on Electronic Cigarette Use Experience: An Internet Survey

Konstantinos E. Farsalinos [1,*], Giorgio Romagna [2], Dimitris Tsiapras [1], Stamatis Kyrzopoulos [1], Alketa Spyrou [1] and Vassilis Voudris [1]

[1] Onassis Cardiac Surgery Center, Sygrou 356, Kallithea 17674, Greece;
E-Mails: dtsiapras@hotmail.com (D.T.); stkyrz@gmail.com (S.K.); aspirou@gmail.com (A.S.); vvoudris@otenet.gr (V.V.)

[2] ABICH S.r.l, Biological and Chemical Toxicology Research Laboratory, Via 42 Martiri, 213/B-28924 Verbania (VB), Italy; E-Mail: giorgio.romagna@gmail.com

* Author to whom correspondence should be addressed; E-Mail: kfarsalinos@gmail.com; Tel.: +306-977-454-837; Fax: +302-109-493-373.

Received: 19 November 2013; in revised form: 11 December 2013 / Accepted: 12 December 2013 / Published: 17 December 2013

Abstract: *Background:* A major characteristic of the electronic cigarette (EC) market is the availability of a large number of different flavours. This has been criticised by the public health authorities, some of whom believe that diverse flavours will attract young users and that ECs are a gateway to smoking. At the same time, several reports in the news media mention that the main purpose of flavour marketing is to attract youngsters. The importance of flavourings and their patterns of use by EC consumers have not been adequately evaluated, therefore, the purpose of this survey was to examine and understand the impact of flavourings in the EC experience of dedicated users. *Methods:* A questionnaire was prepared and uploaded in an online survey tool. EC users were asked to participate irrespective of their current smoking status. Participants were divided according to their smoking status at the time of participation in two subgroups: former smokers and current smokers. *Results:* In total, 4,618 participants were included in the analysis, with 4,515 reporting current smoking status. The vast majority (91.1%) were former smokers, while current smokers had reduced smoking consumption from 20 to 4 cigarettes per day. Both subgroups had a median smoking history of 22 years and had been using ECs for 12 months. On average they were using three different types of liquid flavours on a regular basis, with former smokers switching between flavours more

frequently compared to current smokers; 69.2% of the former subgroup reported doing so on a daily basis or within the day. Fruit flavours were more popular at the time of participation, while tobacco flavours were more popular at initiation of EC use. On a scale from 1 (not at all important) to 5 (extremely important) participants answered that variability of flavours was "very important" (score = 4) in their effort to reduce or quit smoking. The majority reported that restricting variability will make ECs less enjoyable and more boring, while 48.5% mentioned that it would increase craving for cigarettes and 39.7% said that it would have been less likely for them to reduce or quit smoking. The number of flavours used was independently associated with smoking cessation. *Conclusions:* The results of this survey of dedicated users indicate that flavours are marketed in order to satisfy vapers' demand. They appear to contribute to both perceived pleasure and the effort to reduce cigarette consumption or quit smoking. Due to the fact that adoption of ECs by youngsters is currently minimal, it seems that implementing regulatory restrictions to flavours could cause harm to current vapers while no public health benefits would be observed in youngsters. Therefore, flavours variability should be maintained; any potential future risk for youngsters being attracted to ECs can be sufficiently minimized by strictly prohibiting EC sales in this population group.

Keywords: electronic cigarette; flavours; smoking; tobacco; nicotine; smoking cessation; public health

1. Introduction

Cigarette smoking is considered the single most preventable cause of disease, affecting several systems in the human body and causing premature death [1]. The World Health Organisation predicts more than 1 billion deaths within the 21st century related to tobacco cigarettes [2]. Although there is overwhelming evidence for the benefits of smoking cessation [3], it is a very difficult addiction to break. Currently available nicotine replacement therapy have low long-term success rate, which may be attributed solely to psychological support [4], while oral medications are more effective [5] but are hindered by reports of adverse neuropsychiatric effects [6]. In this context, the tobacco harm reduction strategy has been developed, with a goal of providing nicotine through alternative methods in order to reduce the amount of harmful substances obtained by the user [7].

Electronic cigarettes (ECs) have been marketed in recent years as alternative to smoking products. They consist mainly of a battery and an atomiser where liquid is stored and gets evaporated by energy supplied to an electrical resistance. The liquid contains mainly propylene glycol and glycerol, with the option to include nicotine. A major characteristic of the EC liquid market is the availability of a variety of flavourings. Besides tobacco-like flavours, the consumer can choose flavours consisting of fruits, sweets, drinks and beverages and many more. The availability of so many flavours has been criticized by authorities such as the Food and Drug Administration (FDA), stating that there is a potential to attract youngsters [8]. Such a concern was probably raised by the experience with tobacco products, with studies showing that flavoured cigarettes were more appealing to young users [9]. A recent survey

of electronic cigarette users found that almost half of participants were using non-tobacco flavours [10]. However, no survey was specifically designed to detect the impact of flavourings on EC experience by users. Therefore, the purpose of this survey was to evaluate the patterns of flavourings use and determine their popularity in a sample of dedicated adult EC users.

2. Methods

A questionnaire was prepared by the research team in two languages (English and Greek) and was uploaded in an online survey tool (www.surveymonkey.com). A brief presentation of the survey was uploaded in the website of a non-profit EC advocates group (www.ecigarette-research.com) together with informed consents in English and Greek. If the participant agreed with the informed consent, he was redirected to the questionnaire in the respective language by pressing the "I agree" button. The survey was available online for 15 days. The protocol was approved by the ethics committee of our institution.

EC users of any age, irrespective of current or previous smoking status, were asked to participate to the survey. The survey was communicated in internet social media and several EC users' forums and advocate groups worldwide. The IP address of the participants was recorded in order to remove double entries. There was an option for participants to report their email address for participation in future projects; unwillingness to report the email address was not a criterion for exclusion from the survey. Information about age, gender, country of residence and education level was requested. Past and present smoking status was asked and, based on the latter, participants were divided into two groups for the analysis: former smokers who had completely quit smoking and smokers who were still smoking after initiation of EC use. The questionnaire included questions about the type of flavours used regularly by the participants, whether the variety of flavourings was important in reducing or completely substituting smoking and defining the reasons for using multiple flavours. To assess difficulty in finding flavours of their preference at EC use initiation, the following question was asked: "Was it difficult to find the flavourings of your preference at initiation of EC use?". The answers were scored as: 1, "not at all difficult"; 2, "slightly difficult"; 3, "difficult"; 4, "very difficult"; and 5, "extremely difficult". To examine the importance of flavours variability in reducing or quitting smoking, the following question was asked: "Was the variability of flavourings important in your effort to reduce or completely substitute smoking?". The answer was scored as: 1, "not at all important"; 2, "slightly important"; 3, "important"; 4, "very important"; and 5, "extremely important".

3. Statistical Analysis

Participants were categorised into current smokers and former-smokers according to their reported status at the time of participation to the survey. Results are reported for the whole sample and for each of the subgroups. The sample size varied by variable because of missing data. In some questions, responders were allowed to choose more than one option; in these cases, each answer is presented separately and the sum of responses may exceed 100%. Kolmogorov-Smirnoff tests were performed to assess normality of distribution of variables. Continuous variables are reported as median (interquartile range [IQR]). Categorical variables are reported as number (percentage). Mann Whitney U test was used to compare continuous variables between current and former smokers, while cross tabulations with χ^2 test were used for categorical variables. Finally, a stepwise binary logistic regression analysis

was performed, with smoking status (former *vs.* current smoker) as the independent variable and age, gender, education level, smoking duration, number of flavourings used regularly, and EC consumption (ml liquid or number of prefilled cartomisers) as covariates. A two-tailed P value of <0.05 was considered statistically significant, and all analyses were performed with commercially available statistical software (SPSS v. 18, Chicago, IL, USA).

4. Results

4.1. Baseline Characteristics

After excluding double entries, 4,618 participants were included to the analysis, with 4,515 reporting current smoking status (current *vs.* former smokers). The baseline characteristics of the study group and subgroups are displayed in Table 1. More than 90% were former smokers. The mean age was 40 years, with male predominance. No difference between former and current smokers was observed in age, while more males were former smokers. The vast majority were from America and Europe, with a small proportion residing in Asia and Australia. More than half of participants were educated to the level of university/college. Smoking duration was similar between subgroups. Interestingly, former smokers reported higher daily cigarette consumption before initiation of EC use, although the difference was not statistically significant. Current smokers reported a substantial reduction in cigarette consumption, from 20 to 4 cigarettes per day. The median duration of EC use was 12 months, with higher consumption (ml liquid or number of cartridges) reported by former smokers. Higher nicotine concentration liquids were used by current smokers (P = 0.005). In total, 140 participants (3.0%) reported using non-nicotine liquids, 2.8% of former and 1% of current smokers (χ^2 = 4.5, P = 0.033); 21 users of non-nicotine liquids did not mention their current smoking status. Finally, more current smokers were using first (cigarette-like) and second generation (eGo-type) devices while more former smokers were using third generation devices (also called “Mods”, variable voltage or wattage devices).

4.2. Perceptions in Relation to Flavours

Responses to questions related to flavours are displayed in Table 2. At the time of participation, most commonly used flavours were fruits, followed by sweets and tobacco. Significant differences were observed between subgroups. Characteristically, more current smokers were using tobacco flavours compared to former smokers, while more of the latter were using fruit and sweet flavours. On a regular basis, participants reported using 3 (IQR: 2–4) different types of flavours. At initiation of EC use, most popular flavours were tobacco followed by fruit and sweet flavours. The median score for difficulty to find the flavours of their preference at EC initiation was 2 (IQR: 1–3), with no difference between subgroups. Most participants (68.3%) were switching between flavours on a daily basis or within the day, with former smokers switching more frequently. More than half of the study sample mentioned that they like the variety of flavours and that the taste gets blunt from long-term use of the same flavour. The average score for importance of flavours variability in reducing or quitting smoking was 4 (“very important”). Finally, the majority of participants stated that restricting variability of flavours would make the EC experience less enjoyable while almost half of them answered that it

would increase craving for tobacco cigarettes and would make reducing or completely substituting smoking less likely.

Table 1. Baseline characteristics of the study population and subgroups.

Characteristic	Total	Former Smokers	Current Smokers	Statistic	*P*
Participants, n (%)	4,618	4,117 (91.2)	398 (8.8)		
English translation	4,386 (95.0)	3,915 (95.1)	369 (92.7)		
Greek translation	232 (5.0)	202 (4.9)	29 (7.3)		
Region of residence, n (%)					
America	2,220 (48.5)	2,007 (48.7)	157 (39.4)		
Asia	76 (1.7)	58 (1.4)	16 (4.0)		
Australia	80 (1.7)	75 (1.8)	4 (1.0)		
Europe	2,197 (48.0)	1,939 (47.1)	217 (54.5)		
Education, n (%)					
High school or less	1,037 (22.7)	917 (22.3)	98 (24.6)		
Technical Education	1,099 (24.1)	993 (24.1)	86 (21.6)		
University/College	2,425 (53.2)	2,170 (52.7)	206 (51.8)		
Age (years)	40 (32–49)	40 (32–49)	40 (32–49)	U = 754,278	0.624
Gender (male)	3,229 (71.8)	2,922 (72.7)	246 (62.5)	χ^2 = 18.0	<0.001
Smoking duration (years)	22 (15–30)	22 (15–30)	22 (14–30)	U = 816,534	0.924
Cigarette consumption before EC use (/d)	24 (20–30)	25 (20–30)	20 (19–30)	U = 768,398	0.189
Cigarettes consumption after EC use (/d)			4 (2–6)		
EC use duration (months)	12 (6–23)	12 (6–23)	12 (5–23)	U = 790,219	0.373
EC consumption (ml or cartridges/d)	4 (3–5)	4 (3–5)	3 (2–5)	U = 677,862	<0.001
Nicotine levels in EC (mg/ml)	12 (6–18)	12 (6–18)	12 (8–18)	U = 722,563	0.005
EC devices used, n (%)					
Cigarette-like	84 (1.8)	61 (1.5)	20 (5.0)	χ^2 = 25.9	<0.001
eGo-type	1,123 (24.7)	966 (23.5)	133 (33.4)	χ^2 = 19.5	<0.001
"Mods" [a]	3,348 (73.5)	3,047 (74.0)	237 (59.5)	χ^2 = 38.3	<0.001

Notes: Values presented as median (interquartile range) or number (percentage). Abbreviations: EC, electronic cigarette. [a] New generation devices, usually hand-made or with the ability to manually set the voltage or wattage delivery.

Table 2. Patterns of flavourings use in the study population and subgroups.

Characteristic	Total	Former Smokers	Current Smokers	Statistic	*P*
Flavours used now, n (%) [a]					
Tobacco	1,984 (43.9)	1,773 (43.1)	211 (53.0)	χ^2 = 14.6	<0.001
Mint/menthol	1,468 (31.8)	1,339 (32.5)	129 (32.4)	χ^2 = 0.0	0.964
Sweet	2,836 (61.4)	2,629 (63.9)	207 (52.0)	χ^2 = 21.8	<0.001
Nuts	691 (15.0)	643 (15.6)	48 (12.1)	χ^2 = 3.5	0.060
Fruits	3,203 (69.4)	2,953 (71.7)	250 (62.8)	χ^2 = 14.0	<0.001
Drinks/beverages	1,699 (36.8)	1,562 (37.9)	137 (34.4)	χ^2 = 1.9	0.167
Other	1,028 (22.3)	946 (23.0)	82 (20.6)	χ^2 = 1.2	0.281

Table 2. *Cont.*

Flavours used at EC initiation, n (%) [a]					
Tobacco	3,118 (69.1)	2,846 (69.1)	272 (68.3)	$\chi^2 = 0.1$	0.746
Mint/menthol	1,086 (24.1)	1,004 (24.4)	82 (20.6)	$\chi^2 = 2.8$	0.092
Sweet	1,347 (29.8)	1,251 (30.4)	96 (24.1)	$\chi^2 = 6.8$	0.009
Nuts	203 (4.5)	186 (4.5)	17 (4.3)	$\chi^2 = 0.1$	0.821
Fruits	1,743 (38.6)	1,606 (39.0)	137 (34.4)	$\chi^2 = 3.2$	0.073
Drinks/beverages	808 (17.9)	748 (16.8)	60 (15.1)	$\chi^2 = 2.4$	0.124
Other	302 (6.7)	282 (6.8)	20 (5.0)	$\chi^2 = 1.9$	0.164
Switching between flavours, n (%)					
Daily/within the day	3,083 (68.3)	2,851 (69.2)	232 (58.3)	$\chi^2 = 20.1$	<0.001
Weekly	718 (15.9)	636 (15.4)	82 (20.6)	$\chi^2 = 7.2$	0.007
Less than weekly	465 (10.3)	412 (10.0)	53 (13.3)	$\chi^2 = 4.3$	0.038
At EC initiation, was it difficult to find the flavours of your preference? [b]	2 (1–3)	2 (1–3)	2 (1–3)	U = 760,068	0.054
Why do you feel the need to choose different flavours? n (%) [a]					
Like variety of choices	3,300 (73.1)	3,041 (73.9)	259 (65.1)	$\chi^2 = 14.3$	<0.001
They get "blunt" from long-term use	2,325 (51.5)	2,131 (51.8)	194 (48.7)	$\chi^2 = 1.3$	0.250
Other reasons	342 (7.6)	318 (7.7)	24 (6)	$\chi^2 = 1.5$	0.223
Was flavours variability important in reducing/quitting smoking? [b]	4 (3–5)	4 (3–5)	4 (3–5)	U = 731,547	0.455
How would your experience with EC change if flavours variability was limited? n (%) [a]					
Less enjoyable	3,111 (68.9)	2,886 (70.1)	225 (56.5)	$\chi^2 = 31.2$	<0.001
More boring	2,063 (45.7)	1,901 (46.2)	236 (40.7)	$\chi^2 = 4.4$	0.036
Increase craving for cigarettes	2,188 (48.5)	1,982 (48.1)	206 (51.8)	$\chi^2 = 1.9$	0.168
Less likely to reduce or quit smoking	1,793 (39.7)	1,617 (39.3)	176 (44.2)	$\chi^2 = 3.7$	0.054
No difference	285 (6.3)	253 (6.1)	32 (8.0)	$\chi^2 = 2.2$	0.138

Notes: Values presented as median (interquartile range) or number (percentage). Abbreviations: EC, electronic cigarette. [a] Participants were allowed to choose more than one answers. [b] Score reported (see text for details).

Binary logistic regression analysis showed that male gender (B = 0.373, $P = 0.001$), EC consumption (B = 0.046, $P = 0.044$) and number of flavours regularly used (B = 0.089, $P = 0.038$) were associated with complete smoking abstinence in this population of dedicated long-term vapers, while age, education level and smoking duration were not associated with smoking abstinence.

5. Discussion

This is the first survey that specifically focused on the issue of flavours and their impact in EC use. A substantial number of dedicated EC consumers participated; they reported that flavours play an important role in their EC use experience and in reducing cigarette consumption and craving, while the number of flavours regularly used was independently associated with complete smoking abstinence in this population.

The availability of a variety of flavours has been a controversial issue since the initial appearance of ECs to the market. Most companies offer a variety of flavours, from those resembling tobacco to a large

number commonly used in the food industry. Public health authorities have raised concerns about this issue, and several statements have been released suggesting flavours could attract youngsters [8,11,12]. Such concerns are probably rooted back to the marketing of the tobacco industry for flavoured tobacco cigarettes. Internal industry documents and published surveys indicated that flavoured tobacco products are more appealing to youngsters and may be a gateway to maintaining smoking as a long term habit, while use by adults was quite low [13–16]. This is the main reason why the FDA decided to implement a ban on characteristic flavours in tobacco cigarettes [17]. It was expected that such concerns would be raised for ECs, although current vapers are overwhelmingly adults. Anecdotal evidence from EC consumers' internet forums and results from surveys [10] have shown that different flavours are very popular among dedicated users. The results of this survey confirm previous observations by finding that dedicated users switch between flavours frequently and the variability of flavours plays an important role both in reducing cigarette craving and in perceived pleasure. Moreover, the number of flavours used was associated with smoking cessation. Therefore, flavours variability is needed to support the demand by current vapers, who are in their vast majority adults. This survey also indicated that there is a switch in flavours preference of EC consumers; tobacco is the preferred flavour when initiating EC use, probably because smokers are used to this flavour and feel the need to use something that resembles their experience from smoking. However, different choices are made as time of use progresses. This may be a way to distract them from the tobacco flavour in order to reduce smoking craving; alternatively, it could indicate that they just don't need the tobacco flavour any more, but feel the desire to experiment with new flavours. In some cases, tobacco flavour may even become unpleasant, especially in those who have completely quit smoking. The improvement in olfactory and gustatory senses in these people can lead to both more pleasure perceived from different flavours and an aversion to tobacco flavour (in a similar way that it is unpleasant for a non-smoker); the latter has been reported in EC consumers' forums (http://www.e-cigarette-forum.com/forum/polls/209041-do-you-vape-tobacco-flavors.html). Such a phenomenon may contribute to lower relapse to smoking and may prevent the EC from being a gateway to smoking; however, this should be specifically studied before making any conclusions. Finally, the issue of taste buds "tolerance", which is anecdotally mentioned by vapers, was reported by almost half of the sample as a reason to switch between flavours, although it is most probably a type of olfactory rather than gustatory tolerance.

Besides information on the use of flavourings, this survey provides information on other issues related to EC use. A small minority of participants were using first generation cigarette-like devices. This has been observed in other surveys [10]. There was a higher prevalence of third-generation devices used in the subgroup of former smokers compared to current smokers. Such devices have the ability to provide higher energy to the atomiser, thus producing more vapour and delivering more pleasure to the user [18,19]. Until now, two randomised studies evaluating the efficacy of EC use in smoking cessation have used first-generation cigarette-like devices [20,21]. It is possible that newer generation devices may be more effective in substituting smoking, and this should be evaluated in future studies. Additionally, former smokers were using lower nicotine-concentration liquids compared to current smokers. It has been observed from previous studies that EC users who have completely substituted smoking try to gradually reduce their nicotine use [18]. Despite that, only 2.8% of former smokers were using 0-nicotine liquids at the time of survey participation, indicating that nicotine is

important in smoking abstinence and that EC consumers remain long-term nicotine users. However, the possibility that several vapers may quit EC use shortly after switching to non-nicotine liquids cannot be excluded; such users would not participate to this survey, therefore overestimating the significance of nicotine on EC use. Finally, we observed a male predominance in participation to this survey, which is in line with previous studies [10,18]. In this survey, males were more likely to have completely quit smoking. Further studies are needed to explore this phenomenon and define whether females are less successful in smoking cessation with EC use, are less motivated long-term users or use ECs in the short term as smoking substitutes.

There are some limitations applicable to this study. The survey was announced and promoted in popular EC websites. Therefore, it is expected that dedicated users with positive experience with ECs would mainly participate, and the high proportion of former smokers confirms this. However, it is important to evaluate the patterns of use in smokers who have successfully quit smoking, since this can provide health officials with information on how to educate smokers into using ECs, especially during the initial period of use. Although a significant proportion stated that flavours play a major role in reducing or quitting smoking, this study was not designed to evaluate whether variability of flavours may promote smoking cessation in the general population; moreover our sample is not representative of the general population of smokers, who are generally less educated compared to the population evaluated here [22]. This should be evaluated in a randomised study. Finally, although the fact that flavours are important for existing EC users provides sufficient explanation for their current marketing, it does not exclude the possibility that they may also attract youngsters. However, currently available evidence indicates that regular use of ECs by non-smoking adults or youngsters is very limited [23–25]; thus, any restriction of flavours for the reason of protecting youngsters is currently not substantiated by evidence and no public health benefit would be derived. On the contrary, such a measure could have a negative impact and cause harm in current vapers, who are reporting that they enjoy flavours and that restrictions would make smoking reduction or cessation more difficult and would increase cigarette craving. Therefore, it would be more realistic and valuable to promote restrictions to the use of ECs by youngsters and to properly inform the public that ECs should be used only by smokers as a method to reduce cigarette consumption or completely substitute smoking.

6. Conclusions

The results of this survey indicate that EC liquid flavourings play a major role in the overall experience of dedicated users and support the hypothesis that they are important contributors in reducing or eliminating smoking consumption. This should be considered by the health authorities; based on the current minimal adoption of ECs by youngsters, it is reasonable to support that any proposed regulation should ensure that flavourings are available to EC consumers while at the same time restrictions to the use by youngsters (especially non-smokers) should be imposed in order to avoid future penetration of EC use to this population.

Acknowledgements

We would like to thank E-Cigarette Research Advocates Group for promoting the survey in their website (www.ecigarette-research.com). This is a non-profit group of electronic cigarette users with no

relation to the electronic cigarette or other industry. The website does not promote or present any electronic cigarette product and do not accept any advertisements. The sole purpose of the group is to inform about research conducted on electronic cigarettes. Konstantinos E. Farsalinos has been allowed to present studies and post comments concerning electronic cigarette research on this website, without providing or receiving any form of payment. We would also like to thank all other websites and internet forums for promoting the survey and encouraging electronic cigarette users to participate. None of the websites promoting the survey had any access to the data collected from participants. No funding was received for this study.

Conflicts of Interest

The authors declare no conflict of interest.

References

1. Doll, R.; Peto, R.; Boreham, J.; Sutherland, I. Mortality in relation to smoking: 50 years' observations on male British doctors. *BMJ* **2004**, *328*, 1519–1528.
2. World Health Organisation. Tobacco fact sheet No339. Updated, July 2013. Available online: http://www.who.int/mediacentre/factsheets/fs339/en/ (accessed on 14 November 2013).
3. Taylor, D.H.; Hasselblad, V; Henley, S.J.; Thun, M.J.; Sloan, F.A. Benefits of smoking cessation for longevity. *Am. J. Public Health* **2002**, *92*, 990–996.
4. Moore, D.; Aveyard, P.; Connock, M.; Wang, D.; Fry-Smith, A.; Barton, P. Effectiveness and safety of nicotine replacement therapy assisted reduction to stop smoking: Systematic review and meta-analysis. *BMJ* **2009**, *338*, b1024, doi:10.1136/bmj.b1024.
5. Rigotti, N.A.; Pipe, A.L.; Benowitz, N.L.; Arteaga, C.; Garza, D.; Tonstad, S. Efficacy and safety of varenicline for smoking cessation in patients with cardiovascular disease: A randomized trial. *Circ.* **2010**, *121*, 221–229.
6. Hays, J.T.; Ebbert, J.O. Adverse effects and tolerability of medications for the treatment of tobacco use and dependence. *Drugs* **2010**, *70*, 2357–2372
7. Rodu, B.; Godshall, W.T. Tobacco harm reduction: An alternative cessation strategy for inveterate smokers. *Harm Reduct. J.* **2006**, *3*, 37, doi:10.1186/1477-7517-3-37.
8. Food and Drug Administration. *FDA and Public Health Experts Warn About Electronic Cigarettes*; 2009. Available online: http://www.fda.gov/NewsEvents/Newsroom/PressAnnouncements/ucm173222.htm (accessed on 14 November 2013).
9. Lewis, M.J.; Wackowski, O. Dealing with an innovative industry: A look at flavored cigarettes promoted by mainstream brands. *Am. J. Public Health* **2006**, *96*, 244–251.
10. Dawkins, L.; Turner, J.; Roberts, A.; Soar, K. "Vaping" profiles and preferences: An online survey of electronic cigarette users. *Addiction* **2013**, *108*, 1115–1125.

11. Mayers, M.L. *FDA Acts to Protect Public Health from Electronic Cigarettes. Campaign for Tobacco-Free Kids Statement*; 2009. Available online: http://www.tobaccofreekids.org/press_releases/post/id_1166 (accessed on 14 November 2013).
12. National Association of Attorneys General. *FDA Regulation on E-Cigarettes*; 2013. Available online: http://www.naag.org/assets/files/pdf/E%20Cigarette%20Final%20Letter%20(5)(1).pdf (accessed on 14 November 2013).
13. Connolly, G.N. Sweet and spicy flavours: New brands for minorities and youth. *Tob. Control.* **2004**, *13*, 211–212.
14. Carpenter, C.M.; Wayne, G.F.; Pauly, J.L.; Koh, H.K.; Connolly, G.N. New cigarette brands with flavors that appeal to youth: Tobacco marketing strategies. *Health Aff.* **2005**, *24*, 1601–1610.
15. Klein, S.M.; Giovino, G.A.; Barker, D.C.; Tworek, C.; Cummings, K.M.; O'Connor, R.J. Use of flavored cigarettes among older adolescent and adult smokers: United States, 2004–2005. *Nicotine Tob. Res.* **2008**, *10*, 1209–1214.
16. Chung, P.J.; Garfield, C.F.; Rathouz, P.J.; Lauderdale, D.S.; Best, D.; Lantos, J. Youth targeting by tobacco manufacturers since the Master Settlement Agreement. *Health Aff.* **2002**, *21*, 254–263.
17. Food and Drug Administration. Overview of the family smoking prevention and tobacco control act. 2009. Available online: http://www.fda.gov/downloads/TobaccoProducts/GuidanceComplianceRegulatoryInformation/UCM336940.pdf (accessed on 14 November 2013).
18. Farsalinos, K.E.; Romagna, G.; Tsiapras, D.; Kyrzopoulos, S.; Voudris, V. Evaluating nicotine levels selection and patterns of electronic cigarette use in a group of "vapers" who had achieved complete substitution of smoking. *Subst. Abuse* **2013**, *7*, 139–146.
19. Farsalinos, K.E.; Romagna, G.; Allifranchini, E.; Ripamonti, E.; Bocchietto, E.; Todeschi, S.; Tsiapras, D.; Kyrzopoulos, S.; Voudris, V. Comparison of the cytotoxic potential of cigarette smoke and electronic cigarette vapour extract on cultured myocardial cells. *Int. J. Environ. Res. Public Health* **2013**, *10*, 5146–5162.
20. Caponnetto, P.; Campagna, D.; Cibella, F.; Morjaria, J.B.; Caruso, M.; Russo, C.; Polosa, R. EffiCiency and Safety of an eLectronic cigAreTte (ECLAT) as tobacco cigarettes substitute: A prospective 12-month randomized control design study. *PLoS One* **2013**, *8*, e66317, doi:10.1371/journal.pone.0066317.
21. Bullen, C.; Howe, C.; Laugesen, M.; McRobbie, H.; Parag, V.; Williman, J.; Walker, N. Electronic cigarettes for smoking cessation: A randomised controlled trial. *Lancet* **2013**, *382*, 1629–1637.
22. Centers for Disease Control and Prevention (CDC). Vital signs: Current cigarette smoking among adults aged ≥ 18 years with mental illness—United States, 2009–2011. *Morb. Mortal. Wkly. Rep.* **2013**, *62*, 81–87.
23. Dockrell, M.; Morrison, R.; Bauld, L.; McNeill, A. E-cigarettes: Prevalence and attitudes in Great Britain. *Nicotine Tob. Res.* **2013**, *15*, 1737–1744.
24. Camenga, D.R.; Delmerico, J.; Kong, G.; Cavallo, D.; Hyland, A.; Cummings, K.M.; Krishnan-Sarin, S. Trends in use of electronic nicotine delivery systems by adolescents. *Addict. Behav.* **2013**, doi:10.1016/j.addbeh.2013.09.014, published online.

25. Lee, S.; Grana, R.A.; Glantz, S.A. Electronic cigarette use among Korean adolescents: A Cross-Sectional Study of Market Penetration, Dual Use, and Relationship to Quit Attempts and Former Smoking. *J. Adolesc. Health* **2013**, doi: 10.1016/j.jadohealth.2013.11.003.

COALITION FOR A TOBACCO-FREE HAWAI'I

To: The Honorable Della Au Belatti, Chair, Committee on Health
The Honorable Richard Creagan, Vice Chair, Committee on Health
Members, House Committee on Health
From: Jessica Yamauchi, Executive Director
Date: January 30, 2015
Hrg: House Committee on Health; Friday. January 30, 2015 at 10:10 a.m. in Rm 329

Thank you for the opportunity to offer testimony in **strong support of** House Bill 585, which regulates electronic smoking devices (ESDs).

The Coalition for a Tobacco Free Hawaii (Coalition) is a program under the Hawai`i Public Health Institute working to reduce tobacco use through education, policy and advocacy. Our program consists of over 100 member organizations and 2,000 advocates that work to create a healthy Hawaii through comprehensive tobacco prevention and control efforts.

The Coalition supports including ESDs in Hawai`i State smoke-free air laws, which will provide for further consistency and protections of our residents and visitors.

HB 585 amends 328J and adds important definitions of the law, which are critical to allowing consistency among all of Hawai`i State smoking laws. ESDs, often referred to as e-cigarettes, heat and vaporize a solution that typically contains nicotine, and are often designed to mimic the look and feel of a real cigarette.[1]

Currently ESDs are not regulated at any level (federal or state); therefore all emissions and chemicals released in exhalation are also unregulated. ESDs do not emit only "harmless water vapor" as claimed by the industry. "Secondhand aerosol (incorrectly called vapor by the industry) from ESDs contains nicotine, ultrafine particles and levels of toxins."[2] It is vital that we protect everyone from the dangers of secondhand aerosol. According to Dr. Stanton Glantz, Director for the Center for Tobacco Control Research and Education at the University of California, San Francisco, "If you are around somebody who is using e-cigarettes, you are breathing an aerosol of exhaled nicotine, ultra-fine particles, volatile organic compounds, and other toxins."[3] The World Health Organization (WHO) recommends that "legal steps should be taken to end use of e-cigarettes indoors in public and work places. Evidence suggest that exhaled e-cigarette aerosol increases the background air level of some toxicants, nicotine and particles."[4]

The Coalition is concerned about e-cigarettes for several reasons, including secondhand aerosol, dual usage, and youth usage. Emerging research shows dual use where cigarette users switch to

---

[1] Americans for Nonsmokers' Rights, "Electronic Smoking Devices (ESDs) and Smokefree Laws", available at www.no-smoke.org/eigs.html.
[2] Americans for Nonsmokers' Rights, "Electronic Smoking Devices and Secondhand Aerosol", available at www.no-smoke.org/pdf/ecigarette-secondhand-aerosol.pdf.
[3] Ibid
[4] Noncommunicable diseases and mental health: Background on WHO report on regulation of e-cigarettes and similar products." Available at: http://www.who.int/nmh/events/2014/backgrounder-e-cigarettes/en

ESDs in locations they are not permitted to smoke.[5] Allowing the use of ESDs in locations where smoking is prohibited is problematic as ESD use puts innocent bystanders around the ESD user who breathe ESD aerosol at risk for illness, creates distractions in the workplace, threatens the social norm, and undercuts years of progress by tobacco control groups.

Restricting ESD use is a growing trend across the U.S. More than 225 municipalities and three states restrict the use of ESDs in smoke-free environments including New York City, Los Angeles, Long Beach, San Diego, and Boston.

Manufacturers and retailers acknowledge that ESDs contain nicotine, are addictive and habit-forming, are intended for committed smokers, and should not be used by women who are pregnant or persons with an elevated risk of any medical condition, including, but not limited to, heart disease, diabetes, high blood pressure or asthma.[6] According to Americans for Nonsmokers' Rights, "ESDs are not a proven smoking cessation device; they are an alternative nicotine delivery device that will maintain or restore the habit, and can hook a new generation addicted to nicotine."[7] A study, in the New England Journal of Medicine found formaldehyde in high voltage ESDs at significantly higher concentrations than even regular cigarettes. Liquid nicotine in the e-juice cartilage is also a concern as it can be absorbed through the skin and as little as 500 mg can be lethal. In 2014, a child in the US died from an overdose of liquid nicotine.

The Coalition is also extremely concerned about the rising trend of youth use. In Hawai`i, high school tobacco use rate has continued to drop over the last decade from 24.5% in 2000 to 8.7% in 2011, however the use of e-cigarettes is on the rise.[8] Youth usage of ESDs is at an alarming rate especially in the state of Hawai`i where teen use is twice as high as the national average. According to the Hawai`i Youth Tobacco Survey (2013) youth usage (at least once in the past 30 days) tripled (18%) among high school students and quadrupled (8%) among middle school students. The Centers for Disease Control and Prevention reports more than a quarter-million youth who had never smoked a cigarette used e-cigarettes in 2013.

ESDs have not been regulated by FDA and are not an FDA approved cessation device. In a synopsis of the WHO report, they concluded that "there was currently insufficient evidence to conclude that e-cigarettes help users quit smoking or not. Therefore, WHO currently recommends that smokers should first be encouraged to quit smoking and nicotine addiction by using a combination of already-approved treatments."[9] There is no way for users to know how

---

[5] Centers for Disease Control and Prevention (CDC). Notes from the field: electronic cigarette use among middle and high school students -- United States, 2011-2012. MMWR Morb Mortal Wkly Rep. 2013;62:729-730. Available at http://www.cdc.gov/mmwr/preview/mmwrhtml/mm6235a6.htm?s_cid=mm6235a6_w

[6] http://www.ejuiceusa.com/warnings---read-me.php; www.vapedudes.com/; http://www.vaportokers.com/; http://www.virginvapor.com/; http://www.volcanoecigs.com/about-us

[7] Americans for Nonsmokers' Rights, "Electronic Smoking Devices (ESDs) and Smokefree Laws", available at www.no-smoke.org/ecigs.html.

[8] The Hawaii Health Data Warehouse, State of Hawaii, Hawaii School Health Survey, Youth Tobacco Survey Module. Available at: http://www.hhdw.org/cms/uploads/Data%20Source_%20YTS/YTS_Prevalence_IND_00001.pdf.

[9] Noncommunicable diseases and mental health: Background on WHO report on regulation of e-cigarettes and similar products." Available at: http://www.who.int/nmh/events/2014/backgrounder-e-cigarettes/en

THE QUEEN'S HEALTH SYSTEMS

HB 585, Relating to the Regulation of Electronic Smoking Devices
House Committee on Health
January 30, 2015, 10:10 A.M.
Room 329

Dear Chairwoman Belatti and Members of the House Committee on Health:

My name is Paula Yoshioka, and I am a Senior Vice President at The Queen's Health Systems (QHS). I would like to express my strong support for HB 585, relating to the regulation of electronic smoking devices.

We are committed at QHS to making ensuring a safe, clean and healthy community environment for our staff, patients and families. Tobacco products have been proven to be harmful to the health of both the participant and bystanders. For that reason, we have banned smoking in or on our grounds. We are also committed to promoting tobacco use cessation by providing programs that help people to quit.

We fully support the state's current prohibitions on smoking in public places and feel that expanding that prohibition to electronic cigarettes is consistent with promoting community health. The U.S. Surgeon General has expressed his worry about the potential negative health impacts of electronic cigarettes[1] and the U.S. Food and Drug Administration is actively pursuing tighter restrictions on the sale of electronic cigarettes. Regulating public use of electronic cigarettes is also increasingly happening in a number of states and municipalities, including New York, Chicago and San Francisco.[2] It is for these reasons that I ask your support of this bill.

Thank you for your time and consideration of this matter.

---

[1] http://abc13.com/health/surgeon-general-desperate-need-of-clarity-on-e-cigarettes/493448/
[2] http://www.tobaccofreekids.org/tobacco_unfiltered/post/2014_04_29_ecigarettes

I am the Director of Operations for PC Gamerz, we are a eSports center and Vape lounge located in Aiea. We have hundreds of customers that visit our store on a weekly basis. That vape at our store, many of them used to smoke cigarettes. We are worried about the proposed legislation on banning vaping where cigarettes smoking is banned.

We feel that individual businesses should make the choice on their own. If they want to allow or not allow vaping.

Currently Most businesses do this, like movie theaters do not allow it. And have signage posted. Some restaurants allow it like buffalo wild wings in pearl highlands.

This allows businesses like mine the option of promoting to those that choose and support that lifestyle. Without forcing them to be with all the smokers they got away from.

Please consider all of the businesses that have opened and been successful in this struggling economy. If you ban vaping in all places cigarettes are currently banned, you will force all of the vape shops to be out of business. And all of their employee's will lose their jobs and livelihood.

Thank you for your consideration

Devin Wolery
Director of Operations
PC Gamerz, Inc.

creagan1 - Dannah

From: mailinglist@capitol.hawaii.gov
Sent: Thursday, January 29, 2015 12:56 PM
To: HLTtestimony
Cc: cory.chun@cancer.org
Subject: Submitted testimony for HB585 on Jan 30, 2015 10:10AM
Attachments: HB 585 1-30-15_1.docx

HB585
Submitted on: 1/29/2015
Testimony for HLT on Jan 30, 2015 10:10AM in Conference Room 329

Submitted By	Organization	Testifier Position	Present at Hearing
Cory Chun	American Cancer Society Cancer Action Network	Support	Yes

Comments:

Please note that testimony submitted less than 24 hours prior to the hearing, improperly identified, or directed to the incorrect office, may not be posted online or distributed to the committee prior to the convening of the public hearing.

Do not reply to this email. This inbox is not monitored. For assistance please email webmaster@capitol.hawaii.gov

American Cancer Society
Cancer Action Network
2370 Nu`uanu Avenue
Honolulu, Hawai`i 96817
808.432.9149
www.acscan.org

January 29, 2015

Representative Della Au Belatti, Chair
Representative Richard P. Creagan, Vice Chair
Members of the House Committee on Health

Public Hearing: January 30, 10:10 am

HB 585 - RELATING TO THE REGULATION OF ELECTRONIC SMOKING DEVICES.
Cory Chun, Government Relations Director – Hawaii Pacific
American Cancer Society Cancer Action Network

Thank you for the opportunity to provide testimony in support of HB 585, which amends the state's smoke-free workplace statute to prohibit the use of electronic smoking devices in enclosed and partially enclosed public places where smoking is prohibited.

The American Cancer Society Cancer Action Network (ACS CAN) is the nation's leading cancer advocacy organization. ACS CAN works with federal, state, and local government bodies to support evidence-based policy and legislative solutions designed to eliminate cancer as a major health problem.

Electronic smoking devices are often designed to look like cigarettes, right down to the glowing tip. When the user puffs on it, the system delivers an aerosol that is inhaled. A growing number of studies have examined the contents of electronic smoking device aerosol. Unlike a vapor, an aerosol contains fine particles of liquid, solid, or both. Propylene glycol, nicotine, and flavorings were most commonly found in electronic smoking device aerosol. Other studies have found the aerosol to contain heavy metals, volatile organic compounds and tobacco-specific nitrosamines, among other potentially harmful chemicals. The electronic smoking device is often marketed as a way for a smoker to get nicotine in places where smoking is not allowed.

While the health effects of electronic smoking devices are currently under study, there are still serious questions about the safety of inhaling the substances in an electronic smoking device aerosol. Studies have shown that the use of electronic smoking devices can cause short-term lung changes and irritations, while the long-term health effects are unknown. Both exposure to and health effects of secondhand aerosol from electronic

smoking devices require further research, but preliminary studies indicate nonusers can be exposed to the same potentially harmful chemicals as users, including nicotine, ultrafine particles and volatile organic compounds. This exposure could be especially problematic for vulnerable populations such as children, pregnant women, and people with heart disease depending on the level of exposure.

Since the introduction of electronic smoking devices to the U.S. market, the marketing and use of these products have significantly increased. A U.S. Centers for Disease Control survey published in 2013 showed that electronic smoking device usage in middle school and high school students doubled between 2011 and 2012, increasing from 3.3 to 6.8 percent.

While electronic smoking device manufacturers may claim the ingredients are just "water vapor" or "safe," without federal regulation there is no sure way for electronic smoking device users to know what they are consuming. Nor is there any way of knowing what nonusers are exposed to and the extent of the risk to their health. Additionally, there are hundreds of types of electronic smoking devices on the market today and the products vary considerably by ingredients, and quality control and assurance. Prohibiting the use of electronic smoking devices in workplaces, restaurants, and bars can protect the public health by preventing nonusers from being exposed to nicotine and other potentially harmful chemicals in these products.

Thank you for the opportunity to submit testimony on this matter.

Hearing on 1-30-15

Testimony in Strong Opposition to Bill 585

Dear House Health Committee,

The Hawaii Smokers Alliance STRONGLY OPPOSES HB 585) relating to attacks on constituents and visitors that enjoy e-cigarette.

A large number of anti-e-cigarette bills are currently being pushed at the legislature and city council, many states on the mainland, and overseas. As the old saying goes, if you want to find out the truth about something – follow the money.

At first it was a little surprising to see the anti-smoking lobby oppose these products that are a safe alternative to tobacco products and more shocking still to see the anti-smoking lobby opposing a product that has helped so many quit smoking tobacco.

Dr. Carmona, the Former Surgeon General from 2002-2006 recently made this statement. "I believe that it is essential that we provide adult smokers with high-quality, innovative alternatives to traditional cigarettes. The current data indicate that electronic cigarettes may have a very meaningful harm reduction potential, and NJOY [e-cigarettes] is committed to the further development of the science in this area. I look forward to working with NJOY in this important capacity."

However all is not well for giant pharmaceutical companies such as GSK/Johnson and Johnson, Pfizer and so on. Their expensive, unenjoyable, and sometimes dangerous NRT products are getting hit hard in sales by e-cigarettes. Let us keep in mind that the lobbyist ring called "Tobacco Free Hawaii" lists Pfizer as a "Major Funder" for their group. Other groups such as the American Lung Association and Heart Association also receive big bucks from Pharma. Most of the rest came from the settlement and from tax payers via the health dept. Pfizer is the manufacturer of Chantix, which carries a "Black Box Warning" due to significant dangers being found.

"Sophie Ragot, marketing manager at Glaxo Smith Klein laboratories [which markets J&J NRT products] confirms the latest figures, and adds that the situation of the NRT (nicotine replacement therapy) market in the last quarter alone is even worse. She claims sales in this time frame have dropped by 17% in general and 35% in the case of nicotine patches. The situation is

very similar in other European countries as well, and I'm sure NRT sales in the US aren't what they used to be either." http://vaperanks.com/how-e-cigarettes-are-killing-the-nicotine-patch-market-in-europe/

Take for example this article pinning down what's going on from the **Oklahoma Constitution** newspaper.

"The funds that our state receives each year from Tobacco Master Settlement Agreement is invested and managed by Tobacco Settlement Endowment Trust or TSET. So far, the tobacco Master Settlement Agreement has provided $1.04 billion in payouts to Oklahoma and 75% of those funds go directly to TSET.
TSET uses the profits from its investments of MSA money to fund a range of endeavors including the Oklahoma Tobacco Helpline. According to a 2006 Tobacco Cessation Leadership Network document featuring the tobacco control accomplishments of TSET, the purpose for integrating the anti-tobacco policies (higher taxation, public prohibitions and insurance coverage for pharmaceutical cessation products) with smoking cessation service is to increase demands for these services and to create new demand for them. According to TSET, Oklahoma has systematically integrated its anti-smoking policies with tobacco cessation promotion. TSET also funds the Oklahoma Insurance Department, Oklahoma Hospital Association, Oklahoma Dept. of Mental Health and Substance Abuse, and Oklahoma Healthcare Authority."
"The smoking cessation drug market has been a lucrative one for the pharmaceutical companies, but the popularity of electronic cigarettes has them worried. Already in England, electronic cigarettes have surpassed conventional cessation product sales. I could write a book on the pervasive pharmaceutical influence present throughout our state's public health system, but it's not necessary because you can see it plain enough in our state and local anti-tobacco policies. However, if you'd like to further investigate their role in Oklahoma health policy, start with the Oklahoma Turning Point Initiative and the Robert Wood Johnson Foundation. The Robert Wood Johnson Foundation is one of Johnson & Johnson's largest shareholders. Johnson & Johnson just happens to own or manufacture a variety of pharmaceutical drugs including some of the very same smoking cessation products promoted by the state through the Oklahoma Tobacco Helpline."
http://www.oklahomaconstitution.com/ns.php?nid=534&commentary=1

From Bloomberg News:

"GlaxoSmithKline Plc (GSK) is pushing for more stringent regulation of electronic cigarettes, which compete with its Nicorette gum and other smoking cessation products, according to e-mails from a company executive."

http://webcache.googleusercontent.com/search?q=cache:wYLRdF1XHOgJ:www.bloomberg.com/news/2014-02-19/glaxo-memo-shows-drug-industry-lobbying-on-e-cigarettes.html+&cd=1&hl=en&ct=clnk&gl=us

creagan3 - Karina

From: mailinglist@capitol.hawaii.gov
Sent: Thursday, January 29, 2015 3:23 PM
To: HLTtestimony
Cc: knguyen@ala-hawaii.org
Subject: Submitted testimony for HB585 on Jan 30, 2015 10:10AM
Attachments: HB 585 - ecigs where smoking prohibited, Jan 2015.pdf

HB585
Submitted on: 1/29/2015
Testimony for HLT on Jan 30, 2015 10:10AM in Conference Room 329

Submitted By	Organization	Testifier Position	Present at Hearing
Kim Nguyen	American Lung Association of the Mountain Pacific	Support	No

Comments:

Please note that testimony submitted less than 24 hours prior to the hearing, improperly identified, or directed to the incorrect office, may not be posted online or distributed to the committee prior to the convening of the public hearing.

Do not reply to this email. This inbox is not monitored. For assistance please email webmaster@capitol.hawaii.gov

O`ahu
810 Richards St Suite 750
Honolulu, HI 96813
Tel: (808) 537-5966
Fax: (808) 537-5971
www.ala-hawaii.org

Lung HelpLine
1-800- LUNG-USA
(586-4872)

Fighting for Air

January 29, 2015

AMERICAN LUNG ASSOCIATION. IN HAWAII

To: The Honorable Della Au Belatti, Chair
The Honorable Richard Creagan, Vice Chair
Members, House Committee on Health

Re: Strong Support for HB 585, Relating to Electronic Smoking Devices

Hrg: Friday, January 30, 2015 at 10:10 am, Room 329

Thank you for the opportunity to submit written testimony in strong support of HB 585. I serve as the Hawai`i director for the American Lung Association of the Mountain Pacific; our mission is to save lives by improving lung health and preventing lung disease.

We strongly support prohibiting the use of Electronic Smoking Devices (ESDs) in places open to the public and places of employment. We also support including "electronic smoking devices" in the definition of "tobacco product" and "smoke or smoking" in the smoke-free workplace law, and to prohibit the use of electronic smoking devices in the places where smoking is prohibited. Including electronic smoking devices will protect the public, reduce confusion within society, decrease distractions in the workplace, and create and maintain the social norm.

HB 585 is the first step to regulating ESDs and protecting employees, customers, our kama'aina, and the public from inadvertent exposure to nicotine and other chemicals and poisons. ESDs are not FDA approved smoking cessation devices and do not emit harmless water vapor. They are currently unregulated and emit nicotine, ultra-fine particles, and other toxins into the air. We urge you to pass HB 585 in order to provide protection for our Hawaii community.

I can be reached at 808-687-5375 or knguyen@ala-hawaii.org, should you have any questions.

Kind regards,

Kim Nguyen, MSW
Executive Director – Hawai`i
American Lung Association of the Mountain Pacific

creagan1 - Dannah

From: Stephanie Moir <smoir@kkv.net>
Sent: Thursday, January 29, 2015 11:01 AM
To: HLTtestimony
Subject: Strong Support for HB 585, Relating to Electronic Smoking Devices

Categories: Purple Category

January 28, 2015

To: The Honorable Della Au Belatti, Chair
The Honorable Richard Creagan, Vice Chair
Members, House Committee on Health

Re: Strong Support for HB 585, Relating to Electronic Smoking Devices

Hrg: Friday, January 30, 2015 at 10:10 am, Room 329

Thank you for the opportunity to submit testimony in strong support of HB 585. I strongly support prohibiting the use of Electronic Smoking Devices (ESDs) in places open to the public and places of employment.

I support including “electronic smoking devices” in the definition of “tobacco product” and “smoke or smoking” in the smoke-free workplace law, and to prohibit the use of electronic smoking devices in the places where smoking is prohibited. Including electronic smoking devices will protect the public, reduce confusion within society, decrease distractions in the workplace, and maintain the social norm.

HB 585 is the first step to regulating ESDs and protecting employees, customers, and the public from inadvertent exposure to nicotine and other chemicals and poisons. ESDs are not FDA approved smoking cessation devices and do not emit harmless water vapor. They are currently unregulated and emit nicotine, ultra-fine particles, and other toxins into the air. I urge you to pass HB 585 in order to provide protection for the public. Failing to act may set us back decades.

Mahalo for your time,
Steph

--
Stephanie Moir, MPH

Tobacco Control Program Coordinator
Tobacco Treatment Specialist
Kokua Kalihi Valley
Comprehensive Family Services
2239 N. School St.| Honolulu HI 96819

smoir@kkv.net

creagan3 - Karina

From:	mailinglist@capitol.hawaii.gov
Sent:	Thursday, January 29, 2015 11:43 AM
To:	HLTtestimony
Cc:	don.weisman@heart.org
Subject:	Submitted testimony for HB585 on Jan 30, 2015 10:10AM
Attachments:	American Heart Association testimony in SUPPORT of HB 585 Relating to the Regulation of Electronic Smoking Devices.docx
Categories:	Purple Category

HB585
Submitted on: 1/29/2015
Testimony for HLT on Jan 30, 2015 10:10AM in Conference Room 329

Submitted By	Organization	Testifier Position	Present at Hearing
Paul Ho, M.D.	American Heart Association Hawaii Division	Support	No

Comments:

Please note that testimony submitted less than 24 hours prior to the hearing, improperly identified, or directed to the incorrect office, may not be posted online or distributed to the committee prior to the convening of the public hearing.

Do not reply to this email. This inbox is not monitored. For assistance please email webmaster@capitol.hawaii.gov

American Heart Association | American Stroke Association

life is why™

Testimony in SUPPORT of HB 585,
"Relating to the Regulation of Electronic Cigarettes"

The American Heart Association SUPPORTS HB 585, "Relating to the Regulation of Electronic Cigarettes."

The AHA considers e-cigarettes that contain nicotine to be tobacco products and therefore supports their regulation under existing laws relating to the use and marketing of tobacco products. To prevent the potential negative public health impact of e-cigarettes, we strongly support laws and regulation that prohibit the sale and marketing of e-cigarettes to youth. We support effective regulation that addresses marketing, labeling, quality control of manufacturing, and standards for contaminants. We also support the inclusion of e-cigarettes in smoke-free air laws. Moreover, we consider it important to monitor and prevent these products from serving as gateway products or as an initiation to nicotine addiction in nonsmokers and re-initiation in smokers. These policy recommendations were developed by an expert advisory group and leading researchers in the field of tobacco control and prevention and e-cigarettes in tandem with a comprehensive review of the literature. The association's policy guidance will continue to be updated as rapidly evolving evidence emerges. We will continue to assess the scientific evidence relating to e-cigarettes long-term health effects and their efficacy as a smoking cessation aid and encourage the development of a robust research agenda to understand the public health impact of e-cigarettes, especially in at-risk populations.

Although the levels of toxic constituents in e-cigarette aerosol are much lower than those in cigarette smoke, there is still some level of passive exposure to organic compounds, nicotine, and fine particles. To date, there is insufficient evidence to support the notion that exposure to exhaled aerosol has a deleterious impact on bystanders. Some studies have found very low concentrations of air pollutants across different types, liquids, puff durations, and nicotine concentrations. The levels of particle and nicotine exposure vary with the composition of the liquids, the type of e-cigarette, size of the room, puff duration, interval between puffs, and the number of users.

Nevertheless, there is concern that nonsmokers will be involuntarily exposed to nicotine, which could be substantial where there is heavy e-cigarette use in confined spaces. Secondhand exposure to e-cigarette aerosol exposes a nonsmoker to nicotine, particulates, and several potentially toxic organic chemicals, but at much lower levels than from conventional cigarette smoke. The biological effects of such an exposure are expected to be much less than that of secondhand smoke, but nonsmokers are exposed to some nicotine, and the regular use of e-cigarettes has the potential to substantially contaminate the environment with nicotine.

Moreover, unregulated e-cigarette use has the potential to recreate a social norm around tobacco product use in public places, unraveling decades of work on comprehensive smoke-free air laws. It is not always easy to identify that a person is using an e-cigarette, because there is not the large plume of smoke or the strong detectable odor that comes from

conventional cigarettes. Therefore, the use of e-cigarettes creates enforcement issues for employees in restaurants, bars, airport terminals, planes, and other smoke-free public places. E-cigarette companies are marketing their products to be used in all the places where smoking is banned, including bars, restaurants, hotels, offices, and airplanes, which promotes unregulated use.

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

Respectfully submitted,

Paul Ho, M.D.
Cardiologist, American Heart Association Hawaii Division Board Member

creagan3 - Karina

From: mailinglist@capitol.hawaii.gov
Sent: Wednesday, January 28, 2015 2:50 PM
To: HLTtestimony
Cc: wintersnicholas@rocketmail.com
Subject: Submitted testimony for HB585 on Jan 30, 2015 10:10AM

HB585
Submitted on: 1/28/2015
Testimony for HLT on Jan 30, 2015 10:10AM in Conference Room 329

Submitted By	Organization	Testifier Position	Present at Hearing
Nicholas Winters	Individual	Oppose	Yes

Comments: There's nothing dangerous in vaping products that help people quit. If you pass this you'll have more people smoking tobacco again.

Please note that testimony submitted less than 24 hours prior to the hearing, improperly identified, or directed to the incorrect office, may not be posted online or distributed to the committee prior to the convening of the public hearing.

Do not reply to this email. This inbox is not monitored. For assistance please email webmaster@capitol.hawaii.gov

creagan3 - Karina

From: mailinglist@capitol.hawaii.gov
Sent: Wednesday, January 28, 2015 7:26 PM
To: HLTtestimony
Cc: awatanabe67@gmail.com
Subject: Submitted testimony for HB585 on Jan 30, 2015 10:10AM

HB585
Submitted on: 1/28/2015
Testimony for HLT on Jan 30, 2015 10:10AM in Conference Room 329

Submitted By	Organization	Testifier Position	Present at Hearing
Alan Watanabe	Individual	Oppose	No

Comments: Where's the evidence? Please vote no to h b 585.

Please note that testimony submitted less than 24 hours prior to the hearing, improperly identified, or directed to the incorrect office, may not be posted online or distributed to the committee prior to the convening of the public hearing.

Do not reply to this email. This inbox is not monitored. For assistance please email webmaster@capitol.hawaii.gov

creagan3 - Karina

From: mailinglist@capitol.hawaii.gov
Sent: Wednesday, January 28, 2015 7:01 PM
To: HLTtestimony
Cc: timlemke20@yahoo.com
Subject: Submitted testimony for HB585 on Jan 30, 2015 10:10AM

HB585
Submitted on: 1/28/2015
Testimony for HLT on Jan 30, 2015 10:10AM in Conference Room 329

Submitted By	Organization	Testifier Position	Present at Hearing
Tim Lemke	Individual	Oppose	No

Comments: I'm a non-smoker and I don't vape. Vaping products don't harm anyone and they help people quit. Most of all I think this bill is a ridiculous attack on civil liberties. I oppose it completely. Thanks for your time and understanding.

Please note that testimony submitted less than 24 hours prior to the hearing, improperly identified, or directed to the incorrect office, may not be posted online or distributed to the committee prior to the convening of the public hearing.

Do not reply to this email. This inbox is not monitored. For assistance please email webmaster@capitol.hawaii.gov

Chair Belatti, Vice-Chair Creagan, and members of the committee,

Thank you for the opportunity to testify in STRONG OPPOSITION to HB585. This bill is entirely wrongheaded and based on fallacious information. Electronic cigarette usage, or vaping, absolutely is NOT smoking, it does not involve tobacco, and the visual appearance of the activity is an invalid basis for the restrictions set forth in this bill. The legislature in putting forward this bill is promoting bad science, outdated information, and alarmist hysteria.

Current science finds that vaping produces little risk to the user and no significant toxic exposures to bystanders. Current studies are finding that vaping is likely the most effective means of quitting smoking. Studies also show there is no significant uptake of vaping among nonsmokers, and smoking rates continue to trend down as vaping becomes more popular. Vaping is a huge public health boon and must not be subjected to the same regulation as tobacco.

Furthermore, this law is completely unnecessary. All public and private entities can already choose to allow or disallow vaping on their premises. Employers should be allowed to make their own determinations regarding the impact of vaping on their business -- many have found an increase in productivity, contrary to the groundless assertions in the bill. The only thing this bill will do is take away the right to choose.

With estimates of ecigarettes being upwards of 95-99% safer than tobacco cigarettes, many thousands of lives around the state are put at risk by overregulation. The Hawaii state legislature will literally be harming people by curtailing the adoption of ecigarettes -- if not outright killing them.

I have attached a current comprehensive study on ecigarettes, which includes policy prescriptions. Ignorance can be no excuse for the bad information contained in this bill and the bad policy it represents.

P. Kuromoto

Ther Adv Drug Saf
2014, Vol. 5(2) 67–86
DOI: 10.1177/2042098614524430

Safety evaluation and risk assessment of electronic cigarettes as tobacco cigarette substitutes: a systematic review

Konstantinos E. Farsalinos and Riccardo Polosa

***Abstract*:** Electronic cigarettes are a recent development in tobacco harm reduction. They are marketed as less harmful alternatives to smoking. Awareness and use of these devices has grown exponentially in recent years, with millions of people currently using them. This systematic review appraises existing laboratory and clinical research on the potential risks from electronic cigarette use, compared with the well-established devastating effects of smoking tobacco cigarettes. Currently available evidence indicates that electronic cigarettes are by far a less harmful alternative to smoking and significant health benefits are expected in smokers who switch from tobacco to electronic cigarettes. Research will help make electronic cigarettes more effective as smoking substitutes and will better define and further reduce residual risks from use to as low as possible, by establishing appropriate quality control and standards.

Keywords: electronic cigarettes, e-liquid, e-vapor, harm reduction, nicotine, safety, tobacco

Introduction

Complete tobacco cessation is the best outcome for smokers. However, the powerful addictive properties of nicotine and the ritualistic behavior of smoking create a huge hurdle, even for those with a strong desire to quit. Until recently, smokers were left with just two alternatives: either quit or suffer the harmful consequences of continued smoking. This gloomy scenario has allowed the smoking pandemic to escalate, with nearly 6 million deaths annually and a predicted death toll of 1 billion within the 21st century [World Health Organization, 2013]. But a third choice, involving the use of alternative and much safer sources of nicotine with the goal to reduce smoking-related diseases is now available: tobacco harm reduction (THR) [Rodu and Godshall, 2006].

Electronic cigarettes (ECs) are the newest and most promising products for THR [Polosa *et al.* 2013b]. They are electrically-driven devices consisting of the battery part (usually a lithium battery), and an atomizer where liquid is stored and is aerosolized by applying energy and generating heat to a resistance encircling a wick. The liquid used mainly consists of propylene glycol, glycerol, distilled water, flavorings (that may or may not be approved for food use) and nicotine. Consumers (commonly called 'vapers') may choose from several nicotine strengths, including non-nicotine liquids, and a countless list of flavors; this assortment is a characteristic feature that distinguishes ECs from any other THR products. Since their invention in 2003, there has been constant innovation and development of more efficient and appealing products. Currently, there are mainly three types of devices available [Dawkins, 2013], depicted in Figure 1. (1) First-generation devices, generally mimicking the size and look of regular cigarettes and consisting of small lithium batteries and cartomizers (i.e. cartridges, which are usually prefilled with a liquid that bathes the atomizer). Batteries may be disposable (to be used once only) or rechargeable. (2) Second-generation devices, consisting mainly of higher-capacity lithium batteries and atomizers with the ability to refill them with liquid (sold in separate bottles). In the most recent atomizers you can simply change the atomizer head (resistance and wick) while keeping the body of the atomizer, thus reducing the operating costs. (3) Third-generation devices (also called 'Mods', from modifications),

Correspondence to:
Konstantinos E. Farsalinos, MD
Onassis Cardiac Surgery Center, Sygrou 356, Kallithea 17674, Greece
kfarsalinos@gmail.com

Riccardo Polosa, PhD
Centro per la Prevenzione e Cura del Tabagismo (CPCT) and Institute of Internal Medicine, Università di Catania, Catania, Italy

creagan3 - Karina

From: mailinglist@capitol.hawaii.gov
Sent: Thursday, January 29, 2015 3:03 AM
To: HLTtestimony
Cc: oakwoodh@hotmail.com
Subject: Submitted testimony for HB585 on Jan 30, 2015 10:10AM

HB585
Submitted on: 1/29/2015
Testimony for HLT on Jan 30, 2015 10:10AM in Conference Room 329

Submitted By	Organization	Testifier Position	Present at Hearing
Oakwood Hirata	Individual	Oppose	Yes

Comments: I wish to oppose SB585

Please note that testimony submitted less than 24 hours prior to the hearing, improperly identified, or directed to the incorrect office, may not be posted online or distributed to the committee prior to the convening of the public hearing.

Do not reply to this email. This inbox is not monitored. For assistance please email webmaster@capitol.hawaii.gov

creagan3 - Karina

From: mailinglist@capitol.hawaii.gov
Sent: Wednesday, January 28, 2015 5:14 PM
To: HLTtestimony
Cc: 4spiritnsoul@gmail.com
Subject: *Submitted testimony for HB585 on Jan 30, 2015 10:10AM*

HB585
Submitted on: 1/28/2015
Testimony for HLT on Jan 30, 2015 10:10AM in Conference Room 329

Submitted By	Organization	Testifier Position	Present at Hearing
Naomi C. Liu	Individual	Oppose	No

Comments:

Please note that testimony submitted less than 24 hours prior to the hearing, improperly identified, or directed to the incorrect office, may not be posted online or distributed to the committee prior to the convening of the public hearing.

Do not reply to this email. This inbox is not monitored. For assistance please email webmaster@capitol.hawaii.gov

creagan3 - Karina

From: mailinglist@capitol.hawaii.gov
Sent: Wednesday, January 28, 2015 7:05 PM
To: HLTtestimony
Cc: michrobins3@myself.com
Subject: *Submitted testimony for HB585 on Jan 30, 2015 10:10AM*

HB585
Submitted on: 1/28/2015
Testimony for HLT on Jan 30, 2015 10:10AM in Conference Room 329

Submitted By	Organization	Testifier Position	Present at Hearing
Michelle Robinson	Individual	Oppose	No

Comments:

Please note that testimony submitted less than 24 hours prior to the hearing, improperly identified, or directed to the incorrect office, may not be posted online or distributed to the committee prior to the convening of the public hearing.

Do not reply to this email. This inbox is not monitored. For assistance please email webmaster@capitol.hawaii.gov

creagan3 - Karina

From: mailinglist@capitol.hawaii.gov
Sent: Thursday, January 29, 2015 7:33 AM
To: HLTtestimony
Cc: 808aprilpacheco@gmail.com
Subject: *Submitted testimony for HB585 on Jan 30, 2015 10:10AM*

HB585
Submitted on: 1/29/2015
Testimony for HLT on Jan 30, 2015 10:10AM in Conference Room 329

Submitted By	Organization	Testifier Position	Present at Hearing
April Pacheco	Individual	Oppose	No

Comments:

Please note that testimony submitted less than 24 hours prior to the hearing, improperly identified, or directed to the incorrect office, may not be posted online or distributed to the committee prior to the convening of the public hearing.

Do not reply to this email. This inbox is not monitored. For assistance please email webmaster@capitol.hawaii.gov

creagan3 - Karina

From: mailinglist@capitol.hawaii.gov
Sent: Wednesday, January 28, 2015 9:23 PM
To: HLTtestimony
Cc: pipelinemax@outlook.com
Subject: *Submitted testimony for HB585 on Jan 30, 2015 10:10AM*

HB585
Submitted on: 1/28/2015
Testimony for HLT on Jan 30, 2015 10:10AM in Conference Room 329

Submitted By	Organization	Testifier Position	Present at Hearing
Kimo Cruz	Individual	Oppose	No

Comments:

Please note that testimony submitted less than 24 hours prior to the hearing, improperly identified, or directed to the incorrect office, may not be posted online or distributed to the committee prior to the convening of the public hearing.

Do not reply to this email. This inbox is not monitored. For assistance please email webmaster@capitol.hawaii.gov

creagan3 - Karina

From: mailinglist@capitol.hawaii.gov
Sent: Wednesday, January 28, 2015 8:15 PM
To: HLTtestimony
Cc: nguyenke60@gmail.com
Subject: *Submitted testimony for HB585 on Jan 30, 2015 10:10AM*

HB585
Submitted on: 1/28/2015
Testimony for HLT on Jan 30, 2015 10:10AM in Conference Room 329

Submitted By	Organization	Testifier Position	Present at Hearing
Ke Nguyen	Individual	Oppose	No

Comments:

Please note that testimony submitted less than 24 hours prior to the hearing, improperly identified, or directed to the incorrect office, may not be posted online or distributed to the committee prior to the convening of the public hearing.

Do not reply to this email. This inbox is not monitored. For assistance please email webmaster@capitol.hawaii.gov

creagan3 - Karina

From: mailinglist@capitol.hawaii.gov
Sent: Thursday, January 29, 2015 9:03 AM
To: HLTtestimony
Cc: jjw333333@gmail.com
Subject: *Submitted testimony for HB585 on Jan 30, 2015 10:10AM*

HB585
Submitted on: 1/29/2015
Testimony for HLT on Jan 30, 2015 10:10AM in Conference Room 329

Submitted By	Organization	Testifier Position	Present at Hearing
Jake J. Watkins	Individual	Oppose	No

Comments:

Please note that testimony submitted less than 24 hours prior to the hearing, improperly identified, or directed to the incorrect office, may not be posted online or distributed to the committee prior to the convening of the public hearing.

Do not reply to this email. This inbox is not monitored. For assistance please email webmaster@capitol.hawaii.gov

creagan3 - Karina

From: mailinglist@capitol.hawaii.gov
Sent: Thursday, January 29, 2015 9:19 AM
To: HLTtestimony
Cc: mauimoonflower@gmail.com
Subject: *Submitted testimony for HB585 on Jan 30, 2015 10:10AM*

HB585
Submitted on: 1/29/2015
Testimony for HLT on Jan 30, 2015 10:10AM in Conference Room 329

Submitted By	Organization	Testifier Position	Present at Hearing
Sabrina Spencer	Individual	Oppose	No

Comments:

Please note that testimony submitted less than 24 hours prior to the hearing, improperly identified, or directed to the incorrect office, may not be posted online or distributed to the committee prior to the convening of the public hearing.

Do not reply to this email. This inbox is not monitored. For assistance please email webmaster@capitol.hawaii.gov

creagan1 - Dannah

From: mailinglist@capitol.hawaii.gov
Sent: Thursday, January 29, 2015 11:57 AM
To: HLTtestimony
Cc: surfmaster008@gmail.com
Subject: Submitted testimony for HB585 on Jan 30, 2015 10:10AM

HB585
Submitted on: 1/29/2015
Testimony for HLT on Jan 30, 2015 10:10AM in Conference Room 329

Submitted By	Organization	Testifier Position	Present at Hearing
Sean Higa	Individual	Oppose	No

Comments: You guys already banned smoking at the beach and parks, Vaping was helping me cope and now you want to take that away too. UNFAIR!

Please note that testimony submitted less than 24 hours prior to the hearing, improperly identified, or directed to the incorrect office, may not be posted online or distributed to the committee prior to the convening of the public hearing.

Do not reply to this email. This inbox is not monitored. For assistance please email webmaster@capitol.hawaii.gov

creagan3 - Karina

From: mailinglist@capitol.hawaii.gov
Sent: Thursday, January 29, 2015 2:49 PM
To: HLTtestimony
Cc: starjenchan@gmail.com
Subject: Submitted testimony for HB585 on Jan 30, 2015 10:10AM

HB585
Submitted on: 1/29/2015
Testimony for HLT on Jan 30, 2015 10:10AM in Conference Room 329

Submitted By	Organization	Testifier Position	Present at Hearing
Jenny Chan	Individual	Oppose	No

Comments: I strongly oppose HB585

Please note that testimony submitted less than 24 hours prior to the hearing, improperly identified, or directed to the incorrect office, may not be posted online or distributed to the committee prior to the convening of the public hearing.

Do not reply to this email. This inbox is not monitored. For assistance please email webmaster@capitol.hawaii.gov

creagan3 - Karina

From: mailinglist@capitol.hawaii.gov
Sent: Thursday, January 29, 2015 6:41 PM
To: HLTtestimony
Cc: brianportal808@gmail.com
Subject: *Submitted testimony for HB585 on Jan 30, 2015 10:10AM*

HB585
Submitted on: 1/29/2015
Testimony for HLT on Jan 30, 2015 10:10AM in Conference Room 329

Submitted By	Organization	Testifier Position	Present at Hearing
Brian Santiago	Individual	Oppose	No

Comments:

Please note that testimony submitted less than 24 hours prior to the hearing, improperly identified, or directed to the incorrect office, may not be posted online or distributed to the committee prior to the convening of the public hearing.

Do not reply to this email. This inbox is not monitored. For assistance please email webmaster@capitol.hawaii.gov

creagan3 - Karina

From: mailinglist@capitol.hawaii.gov
Sent: Thursday, January 29, 2015 9:51 PM
To: HLTtestimony
Cc: jtenn10@aol.com
Subject: Submitted testimony for HB585 on Jan 30, 2015 10:10AM

HB585
Submitted on: 1/29/2015
Testimony for HLT on Jan 30, 2015 10:10AM in Conference Room 329

Submitted By	Organization	Testifier Position	Present at Hearing
Jolyn M. Tenn	Individual	Oppose	No

Comments: Aloha Legislators, I am in strong opposition to this proposed measure for the simple reason that it is unnecessary. The well funded organizations and individuals that keep calling for these ridiculous bans are targeting a percentage of the population who enjoy smoking, and vaping although a faux subsitute to actually smoking has been proven to be a far better alternative, no second hand smoke, no tar or combustion of plant burning materials which are the actual components that are covered by the smoking ban. Recent studies an d most of the medical profession would rather see people vaping then smoking an actual cigarette. The ones who are obsessed with banning these products do so because they simply do not want to have to see someone vaping and their aversions are psychological and not supported by science or even common sense. Aloha, Jolyn M. Tenn

Please note that testimony submitted less than 24 hours prior to the hearing, improperly identified, or directed to the incorrect office, may not be posted online or distributed to the committee prior to the convening of the public hearing.

Do not reply to this email. This inbox is not monitored. For assistance please email webmaster@capitol.hawaii.gov