HAWAII FOOD INDUSTRY ASSOCIATION

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TO:
SENATE COMMITTEES ON HEALTH and COMMERCE AND CONSUMER PROTECTION
Senator Josh Green and Senator Rosalyn Baker, Chairs
Senator Rosalyn Baker and Brian Taniguchi, Vice Chairs

FROM: HAWAII FOOD INDUSTRY ASSOCIATION
Lauren Zirbel, Executive Director

DATE: February 7, 2014
TIME: 9am
PLACE: Conference Room 229

RE:

Position:

The Hawaii Food Industry Association is comprised of two hundred member companies representing retailers, suppliers, producers and distributors of food and beverage related products in the State of Hawaii.

We ask that, if passed, the bill be revised to have the following section removed:
"Specifies that the revenue from electronic smoking device license fees shall be used to support smoking cessation programs in the State."

Tobacco education and cessation programs already have a dedicated funding source in the form of the settlement funds. These funds exist for the purpose of paying for these programs and should be sufficient to cover the costs.

There is no nexus between license fees and smoking cessation. Retailer license fees exist to pay for the licensing process and enforcement; these fees were not created to fund other programs. Using licensing fees to fund programs for which they were not intended creates a situation where fees are likely to rise unpredictably, this impedes retailers ability to budget and creates unnecessary financial and administrative burdens.

Thank you for the opportunity to testify.

February 6, 2014

To: The Honorable Josh Green, Chair
Members, Senate Committee on Health
The Honorable Rosalyn H. Baker, Chair
Members, Senate Committee on Commerce and Consumer Protection

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

RE: SB2495 – oppose.

Thank you for the opportunity to submit testimony.

VOLCANO Fine Electronic Cigarettes® is the largest manufacturer and retailer of electronic cigarettes and vaping accessories in the State of Hawaii and is widely considered one of the fastest growing companies in the state. 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 SB2495 for the following:

I. No Evidence Supports Restricting Electronic Cigarette Use by Adults

- Several million smokers in the US have quit smoking or sharply reduced their cigarette consumption by switching to or substituting with smoke-free electronic cigarettes. **To date, there is no evidence that electronic cigarette usage has harmed anyone**, which is logical since the product emits a tiny amount of vaporized nicotine and flavorings (similar to nicotine inhalers that are marketed as smoking cessation aids). 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. 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. 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. 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. http://www.tandfonline.com/doi/abs/10.1080/10826076.2011.572213

- 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.**

II. Requiring Face to Face Sales for Vapor Product Sales is Legislative Overreach

- SB2495 would prohibit our company from selling electronic cigarettes to customers through the Internet by requiring all sales of vapor products to take place in a direct, face to face transaction. **Enactment of this provision would at a minimum require us to move that portion of our**

business to the mainland, resulting in the loss of jobs here in Hawaii.

- Safeguards are appropriate to ensure that minors are not able to acquire nicotine products through the Internet, but there are narrowly tailored laws already in place in states across the U.S. that would achieve this end without decimating an entire sector of our business. For example, Illinois, South Carolina and North Carolina have recently required third-party age verification for Internet or other remote sales.[1] Bills pending in Mississippi and Ohio also have similar requirements.

- All electronic cigarettes are not created equally. Certain models of electronic cigarettes may be available in convenience stores across Hawaii, but there are countless models that are only available in two places; speciality e-cigarette stores (of which there are none in certain places in Hawaii) and Internet retailers like our company. Under SB2495, Hawaiians who wish to purchase an electronic cigarette online will continue to do so, but they will not be permitted to purchase a product from a company that is creating jobs here in their home state.

III. Vapor Product Businesses Should Not Have to Obtain Additional Business Licenses

- SB2495 puts in place the same regulatory framework for tobacco cigarettes for a product that contains **no tobacco, produces no smoke, and has been found to have a modified risk profile** in comparison to traditional tobacco products. Enactment of this provision will result in unnecessary additional business costs and may result in consumers having easier access to combustible cigarettes than smoke-free alternatives like electronic cigarettes.

- It is concerning that the responsibility of enforcing these undue restrictions would fall on the Department of Health, an agency that has become increasingly hostile to our business market in recent years.

- SB2495 would direct that all monies collected by the Department of Health as license fees be used to fund smoking cessation programs. These programs have not been proven to be effective and we object to our license fees being used to subsidize the purchase of products we compete with, namely the nicotine gum, nicotine patch, and nicotine lozenge.

- SB2495 places restrictions on promotional materials or advertisements regarding electronic

[1] Illinois' requirement reads: "[F]or sales made though the Internet or other remote sales methods, performing an age verification through an independent, third-party age verification service that compares information available from public records to the personal information entered by the person during the ordering process that establishes the person is 18 years of age or older." *See* Illinois Criminal Statutes, 720 ILCS 675.

cigarettes that includes public streets, parks and walkways. We believe this would amount to a violation of our First Amendment rights, especially in light of the dearth of evidence that the products we sell pose a threat to public health.

IV. The Bigger Picture: Electronic Cigarettes Are a Plus For Public Health

- The available evidence indicates that all noncombustible tobacco / nicotine products (including e-cigarettes, nicotine gums, lozenges, patches) are about 99% less hazardous alternatives to cigarettes. **The concept of tobacco and nicotine harm reduction is being embraced by more public health professionals and academics each year.** Indeed, last year the FDA Center for Drug Evaluation & Research recognized that nicotine, disconnected from smoke, is not the killer in cigarette smoke when it voted to permit the makers of nicotine replacement therapy products to label their products for long-term use by smokers looking to quit.

- VOLCANO supports appropriate and proportionate regulation, and asks that Hawaii await guidance from the FDA on regulatory parameters for this product. The Tobacco Control Act of 2009 was enacted to counteract the known harm caused by combustible tobacco products and was never intended to cover vaporizing products like e-cigarettes.

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 Celeste Nip at nipfire@me.com.

Sincerely,
Cory Smith
CEO and Owner
VOLCANO Fine Electronic Cigarettes®

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

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

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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.

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

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):

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

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:

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

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

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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.

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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.

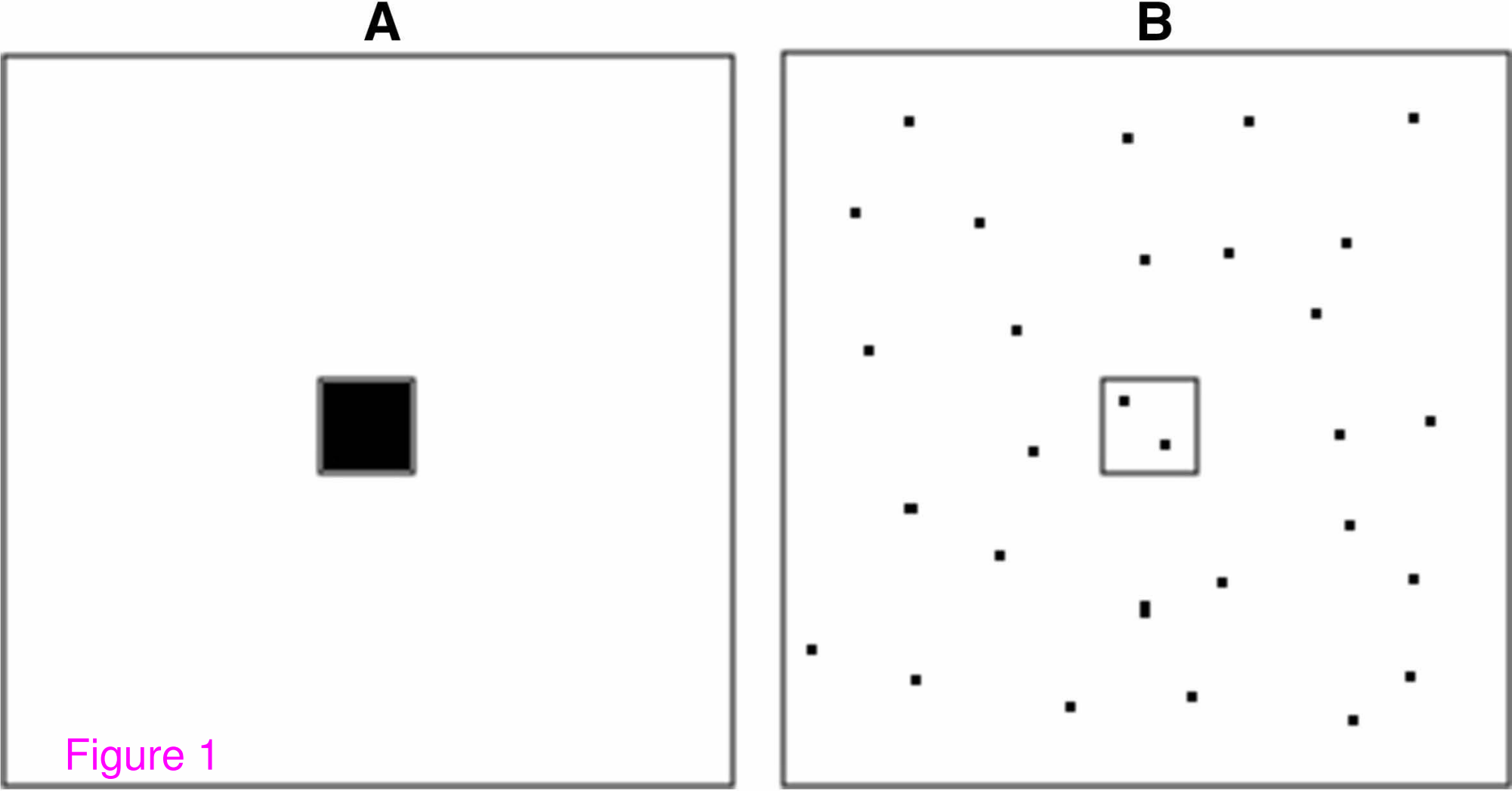

Figure 1

Additional files provided with this submission:

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Additional file 3: 9759835901066082_add3.xlsx, 70K
http://www.biomedcentral.com/imedia/1576899991181967/supp3.xlsx

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Levels of selected carcinogens and toxicants in vapour from electronic cigarettes

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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]

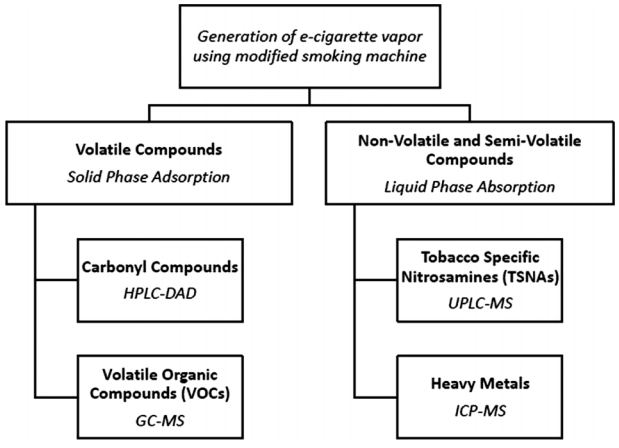

Figure 1 Analytical procedures applied in the study to test carcinogens and selected toxicants in vapour from e-cigarettes. GC-MS, gas chromatography-mass spectrometry; HPLC-DAD, high-performance liquid chromatography with diode array detector; ICP-MS, inductively coupled plasma-mass spectrometry; TSNA,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

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Original Article

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

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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.
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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

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

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

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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.

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RESEARCH ARTICLE

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

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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

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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.

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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

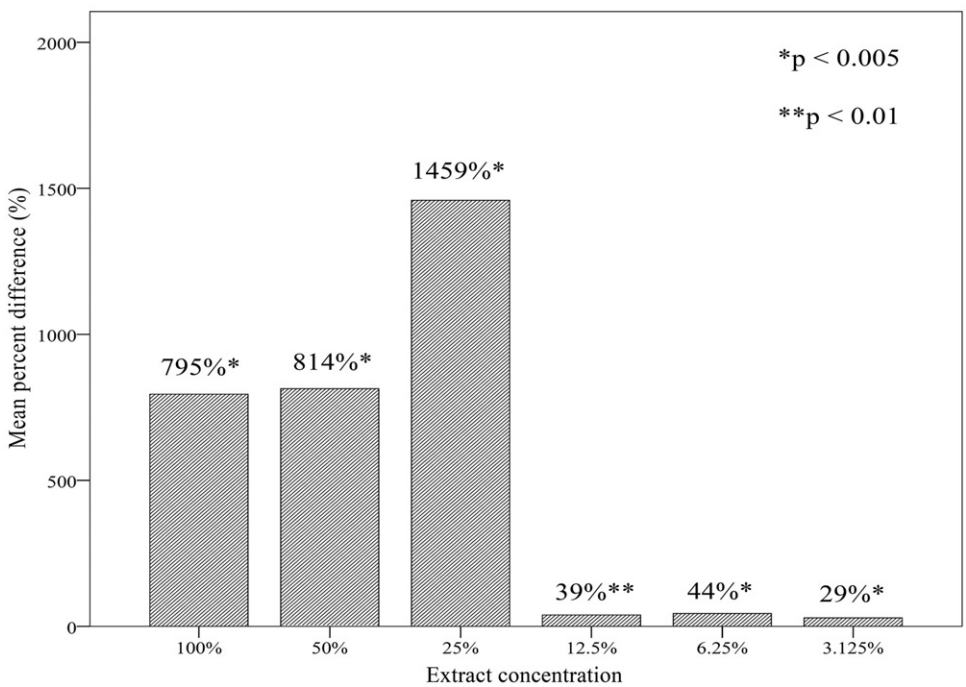

Figure 1. Relative mean differences between cigarette smoke extract viability and electronic cigarette ''Coffee'' vapor extract viability. Coffee was the only electronic cigarette liquid that showed cytotoxic effects according to the definition of UNI ISO 10993-5 standard.

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.

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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

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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.

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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 (but did not quit entirely) still improved their health: "current smokers who used the e-cigarette had fewer respiratory symptoms than smokers who did not use it ... which we speculate might be a 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

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► March (22)
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► 2010 (220)
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► 2008 (196)
► 2007 (250)
► 2006 (395)
► 2005 (281)

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.

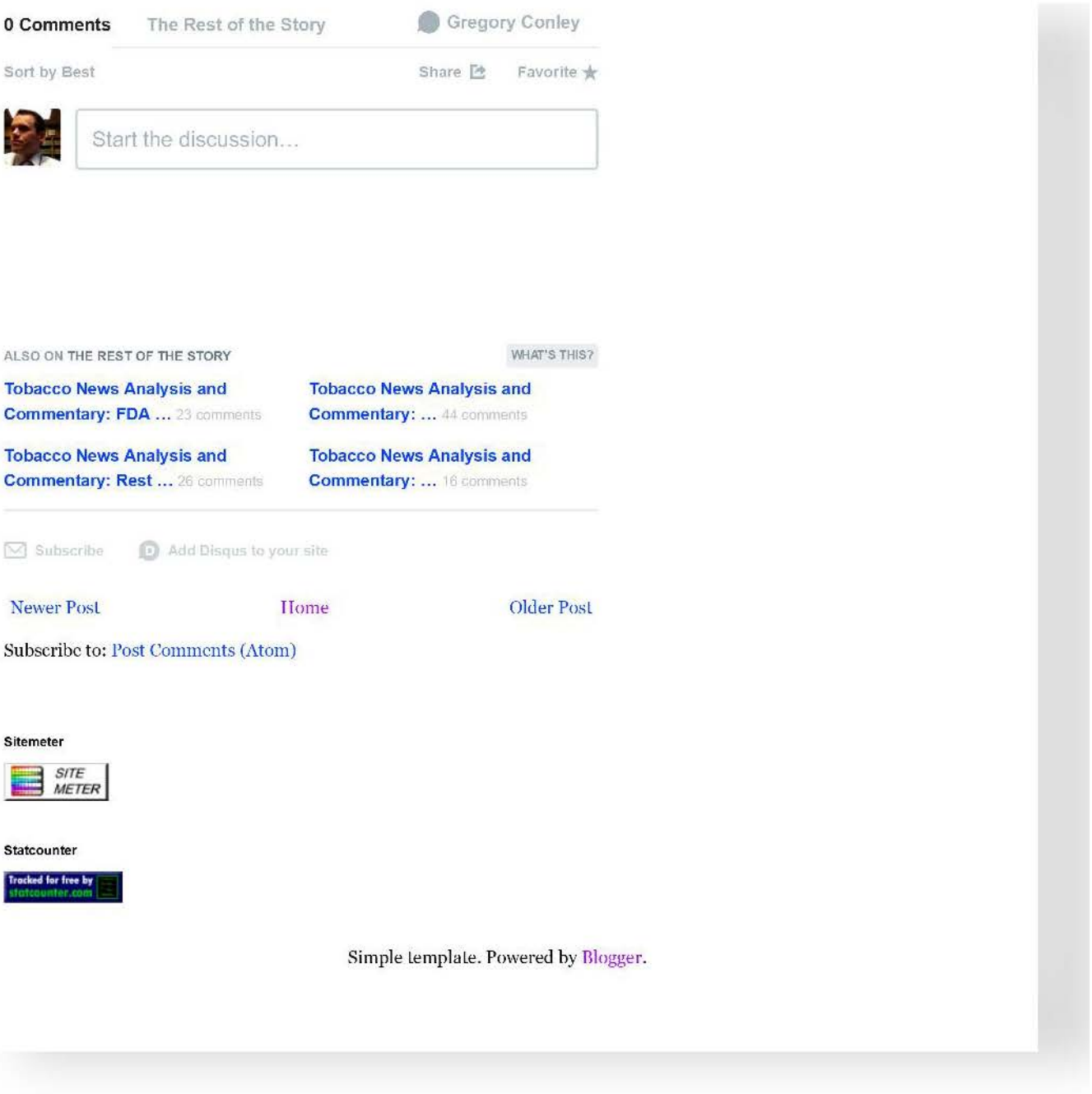
It is now clear that there are indeed thousands of ex-smokers who successfully quit smoking because of electronic cigarettes and who would likely return to smoking if persuaded to discontinue using electronic cigarettes in favor of an "approved" form of smoking cessation pharmacotherapy.

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



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

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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.

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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].

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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, $P \leq 0.001$). 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.

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Article

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

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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)	$\chi^2 = 18.0$	<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)	$\chi^2 = 25.9$	<0.001
eGo-type	1,123 (24.7)	966 (23.5)	133 (33.4)	$\chi^2 = 19.5$	<0.001
"Mods" [a]	3,348 (73.5)	3,047 (74.0)	237 (59.5)	$\chi^2 = 38.3$	<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)	$\chi^2 = 14.6$	<0.001
Mint/menthol	1,468 (31.8)	1,339 (32.5)	129 (32.4)	$\chi^2 = 0.0$	0.964
Sweet	2,836 (61.4)	2,629 (63.9)	207 (52.0)	$\chi^2 = 21.8$	<0.001
Nuts	691 (15.0)	643 (15.6)	48 (12.1)	$\chi^2 = 3.5$	0.060
Fruits	3,203 (69.4)	2,953 (71.7)	250 (62.8)	$\chi^2 = 14.0$	<0.001
Drinks/beverages	1,699 (36.8)	1,562 (37.9)	137 (34.4)	$\chi^2 = 1.9$	0.167
Other	1,028 (22.3)	946 (23.0)	82 (20.6)	$\chi^2 = 1.2$	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.

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Aloha,

I am the owner of HI Vapor Emporium and I have seen firsthand how ecigarette and vapor products have caused those that were long time smokers to quit when switching to ecigarettes. I have heard several testimonies from the vaping community on how they were able to stop using other narcotics like chrystal methamphetamine too. By passing the bill it will make it a lot more difficult for individuals to switch over to a healthier lifestyle. Please keep this in consideration.

Mahalo,

Nohi

From: mailinglist@capitol.hawaii.gov
To: HTHTestimony
Cc: sean@blacklavavape.com
Subject: Submitted testimony for SB2495 on Feb 7, 2014 09:00AM
Date: Wednesday, February 05, 2014 4:32:09 PM

SB2495
Submitted on: 2/5/2014
Testimony for HTH/CPN on Feb 7, 2014 09:00AM in Conference Room 229

Submitted By	Organization	Testifier Position	Present at Hearing
Sean Anderson	Black Lava Vape	Oppose	Yes

Comments: My name is Sean Anderson. I own Black Lava Vape in Kailua Kona. I employ 7 employees, and plan on expanding in the very near future. ALL of these E-Cig bills will put us out of business, and will leave my employees unemployed. The most confusing part about all these bills are, there is simply no reason for them. As a former smoker its really simple: If e-cigs aer classified in the eyes of Hawaii as a real cigarette, I will just start smoking again. This is something that I dont want. I found something that finally helped me stop smoking, and now the state of Hawaii wants to take that away from me. Why is this?

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SB2495
Submitted on: 2/5/2014
Testimony for HTH/CPN on Feb 7, 2014 09:00AM in Conference Room 229

Submitted By	Organization	Testifier Position	Present at Hearing
Michael Zehner	Hawaii Smokers Alliance	Oppose	No

Comments:

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Dear Chairs Green and Baker, Vice-Chair Taniguchi, and Members of the Committees,

Thank you for the opportunity to speak out STRONGLY AGAINST SB2495, which would impose tobacco regulations on businesses involving e-liquid and e-liquid vaporization equipment (AKA e-cigarettes or vaping products); regulate vaping as tobacco smoking; and appropriate fees levied on the industry to "smoking cessation programs." There is no justification for conflating tobacco and vaping, and doing so is against the interests of businesses and the public alike. Directing fees levied on vaping business to "smoking cessation programs" is practically Orwellian, since vaping is an effective smoking cessation tool.

Vaping is not smoking. There is a large and growing body of science showing that vaping produces little to none of the exposure to harmful substances found in tobacco smoke. This is in absolute terms, not just as compared to smoking. Studies have also shown that "secondhand vapor" is effectively nonexistent – no dangerous substances are detectable in room air, and even nicotine is undetectable.

Forcing vaping businesses to become tobacco businesses is bad. I am the proprietor of an e-liquid vaporizer manufacturing business, and it is important for the committees to know that Hawaii has a strong and burgeoning vaping industry. There are at least 3 hardware manufacturers and at least a half-dozen e-liquid manufacturers, in addition to the many retail outlets. Speaking for my business, we have no need or desire to market or sell tobacco products, however if we were required to get a retail tobacco license, we would be tempted to add tobacco products to our lineup to mitigate costs associated with such licensing. In other words *this could increase the prevalence of tobacco products in Hawaii, while not having such licensing requirements keeps vaping businesses out of the tobacco business*.

Businesses should be able to allow vaping if they choose. Indoor smoking bans are ostensibly based on the potential for harm to all people in the enclosed space from secondhand smoke. The downside is economic harm to businesses that would otherwise have chosen to allow their patrons to smoke. Since studies have shown there is no effective risk from "secondhand vapor," this eliminates any justification for an indoor ban. This is a win-win situation. Recreational use of nicotine per se is legal and unregulated; people are free to choose to do it and businesses should be able to serve that when there is no compelling reason to disallow it.

Vaping is smoking cessation. Studies have also shown that vaping is as effective, and likely more effective a tool for quitting smoking as other commonly accepted therapies. Anecdotally, vaping appears to be one of the most effective smoking cessation tools ever invented – ask around your constituencies and it will be clear. Many people statewide have quit long-term tobacco habits using vaping, when other methods simply didn't work. This should be encouraged, not discouraged.

The vaping industry does a good job of self-regulation. Because people by and large turn to vaping to escape the self-harm associated with smoking, the vaping industry has a highly functional self-regulating mechanism. Safety is a paramount concern for vaping consumers, and hardware and e-liquids are scrutinized closely. Vaping communities are preoccupied with safe use, and word gets around quickly when a manufacturer is not doing all it can. In fact, the industry is so safety-conscious *that even Chinese*

manufacturers are taking steps to make their devices and e-liquids as safe as possible. It is a competitive advantage for vaping businesses to be able to tout safety!

Teen vaping does not lead to teen smoking. Vaping is a new product segment that is exploding in popularity, so it is impossible for usage figures to NOT be up across all segments, including children. But the increase in vaping among children in 2012 is correlated with a *reduction in tobacco smoking among children in 2012*, making it difficult to suggest that teen vaping leads to teen smoking. In the absence of toxic exposure and effects, vaping may actually make teenage indiscretions – which no law can possibly end – safer.

I have attached studies outlining the current scientific knowledge of the safety of vaping, which show 1) toxin exposure to be negligible, 2) that purportedly dangerous "secondhand vapor" is basically nonexistent, and 3) that vaping is as effective or moreso than other therapies. Please legislate based on evidence, and in the public interest.

P. Kuromoto, Honolulu, HI

Peering through the mist: What does the chemistry of contaminants in electronic cigarettes tell us about health risks?

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Abstract

The aim of this paper is to review available data on chemistry of aerosols and liquids of electronic cigarettes and to make predictions about compliance with occupational exposure limits of personal exposures of vapers (e-cigarette users) to compounds found in the aerosol. Both peer-reviewed and "grey" literatures were accessed and more than 9000 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. The calculations reveal that 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 by approaching half of TLV. 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. Comparing the exposure to nicotine to existing occupational exposure standards is not valid so long as nicotine-containing liquid is not mislabeled as nicotine-free. It must be noted that the quality of much of the data that was available for these assessment was poor, and so much can be done to improve certainty in this risk assessment. However, the existing research is of the quality that is comparable with most workplace assessments for novel technologies. In summary, an analysis of 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*), if it were an emission from industrial process, creates personal exposures that would justify surveillance of health among exposed persons in conjunction with investigation of means to keep health effects as low as reasonably achievable. Exposures of bystanders are likely to be orders of magnitude less, and thus pose no apparent concern.

Keywords**:** vaping, e-cigarettes, tobacco harm reduction, risk assessment, aerosol, occupational exposure limit

Introduction

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 appropriately 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/) 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 electronic **Appendix A**:

https://dl.dropboxusercontent.com/u/4285761/CASAA/eAppendixA.xlsx). Data contained in **Appendix A** 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 **Appendix A is** identified by a *Reference Manage ID* that is linked to source materials in a list in **Appendix B** (linked via *RefID*: https://dl.dropboxusercontent.com/u/4285761/CASAA/AppendixB.rtf) and attached electronic copies of all original materials (**Biobliography.zip**: https://dl.dropboxusercontent.com/u/4285761/CASAA/bibliography.zip).

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). 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 negligible compared to total volume of air inhaled;
3. The period of exposure to the aerosol considered was normalized to 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 (see point 4) but rather that amount of breathing used to dilute the day's worth of vaping exposure was 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 to be conservative;
5. Breathing rate is 8 liters per minute [12,13];
6. Each puff contains the same quantity of compounds studied.

$$[mg/m^3] = mg/puff \times puffs/(8\ hr\ day) \times 1/(m^3\ air\ inhaled\ in\ 8\ hr) \qquad Eq.\ 1$$

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. Details of all calculations are provided in an Excel spreadsheet (see electronic **Appendix C**: https://dl.dropboxusercontent.com/u/4285761/CASAA/eAppendixC.xlsx).

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

[a] Atmosphere that contains air inhaled by a person

simplifying assumptions to do the conversion. However, where such calculations were performed in the original research, the following approach as 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):

$$[mg/m^3] = mg/(mL\ liquid) \times (mL\ liquid)/puff \times puffs/(8\ hr\ day) \times 1/(m^3\ air\ inhaled\ in\ 8\ hr) \qquad Eq.\ 2$$

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].

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 [2-8,14-42]. 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.[23] because of clear evidence of cross-contamination – admitted to by the authors – with cigarette smoke and, possibly, reagents. The results pertaining to non-detection of tobacco-specific nitrosamines (TSNAs) are potentially trustworthy, but those related to PAH are not since it is incredible that cigarette smoke would contain fewer polycyclic aromatic hydrocarbons (PAH; arising in incomplete combustion of organic matter) than aerosol of e-cigarettes that do not burn organic matter [23]. In fairness to the authors of that study, similar problems may have occurred in other studies but were simply not reported, but it is impossible to include a paper in a review once it is known for certain that its quantitative results are not trustworthy. 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[43,44] detected at non-dangerous levels (see details below) in one test of 18 of early-technology products by FDA[22] and one outlier in measurement of formaldehyde content of exhaled air [4] and aldehydes in aerosol generated from one e-cigarette in Japan [37]. It must be emphasized that the alarmist report of aldehydes in experiments presented in [37] 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 [37] cannot be the basis of any claims about health risk, a fallacy committed both by the authors themselves and commentators on this work [44].

It was also unclear from [37] 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 [37][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 negligible compared to the volume of air inhaled daily (8L/min); this point is illustrated in the **Figure**.

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 bystanders 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 affects 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 results in cigarette-equivalents, as in [42], because this does not enable one to estimate exposures of vapers . Moreover, there is no value in comparison of the content of e-cigarette aerosol to cigarette smoke when the two products produce emissions that are orders of magnitude apart. 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. 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 have default or precautionary TLV of 10 mg/m^3 over 8 hours 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 [45], "mean personal inhalable aerosol concentrations were 0.70 mg/m^3 (range 0.02 to 4.1)" [46]. 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

[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

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.

Nicotine is present in most 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 [24] on 16 e-cigarettes also argue in favor of exceedance of TLV from most any nicotine-containing e-cigarette, as they predict >2mg 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 [24,43], 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 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.

Polycyclic Aromatic Hydrocarbons

Polycyclic aromatic hydrocarbons (PAH) were quantified in several reports in aerosols [5,6,42] and liquids [7,18,41]. 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” (the so called ALARA principle)[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[42].

Tobacco-Specific Nitrosamines

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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).

The same risk assessment considerations that exist for PAH also hold for carcinogenic tobacco-specific nitrosamines (TSNAs)[47] 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 [17,32,34] and others clearly identifying these compounds in the liquids when controlling for background contamination (n=9)[22]. Analyses of aerosols indicate that TSNAs are present in amounts that can results in doses of <ng/day[5,32] to µg/day [8] (assuming 150 puffs/day) (see also [42]). 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 [35]. 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 [47]. The TSNA concentration of the liquids is orders of magnitude less than smokeless tobacco products, though the actual dosage from e-cigarettes vs. smokeless tobacco remains to be clearly understood. For example, 10 µg/L (0.01 ppm) of total TSNA in liquid[35] can translate to a daily dose of 0.000025-0.00005 µg from vaping (worst case assumption of 5 ml/day); if 15 g of snus is consumed a day [48] with 1 ppm of TSNAs [47] and half of it were absorbed, then the daily dose is estimated to be 0.008 µg, which is 160-320 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[49], 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 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 of the nicotine.

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[18] 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 1a**. 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 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:

(a) acrolein: ~1% of TLV (average of 12 measurements) and measurements at a mean of 2% of TLV (average of 150 measurements)[39,40] 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) and an average of 150 results at 4% of TLV [39,40].

[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"

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 [37] 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 [37] clearly stated that the "atomizer, generating high concentration carbonyls, had been burned black" [39,40]. In unpublished work,[39] 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 [42]. 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[50].

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[43], but these compounds are not detected in the majority of tests performed to date [3,14,16,18,22]. Ten batches of the liquid tested by their manufacture did not report any diethylene glycol above 0.05% of the liquid [41]. Methods used to detect diethylene glycol appear to be adequate to be informative and capable of detecting the compound in quantities <<1% of TLV[14,16,22]. 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)[8,25]. Because the parent molecule that occurs in the aerosol is destroyed in such analysis, the results can be alarmist and not interpretable for risk assessment. For example, the presence of sodium (4.18 µg/10 puffs)[25] 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 [18]. **Table 1b** 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 [42] 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, but 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.

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:

$$\text{OEL}_{\text{mixture}} = \sum_{i=1}^{n} (C_i / TLV_i), \qquad \text{Eq. 3}$$

where C_i is the concentration of the i^{th} compound (i=1,…,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 $\text{OEL}_{\text{mixture}} > 1$, 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 (**Table 1**), 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 [50]. 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 [45,46], 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 [39,40] 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 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[24,43].

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[51]. 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 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 have failed to 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. 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.[52]). 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 [53].

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.

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Figure: Illustrating the difference between concentrations in the aerosol generated by vaping and inhaled air in a day. *Panel A* shows 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 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 (with the exception of "ceiling limits" that do not affect the vast majority of comparisons in this report). 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).

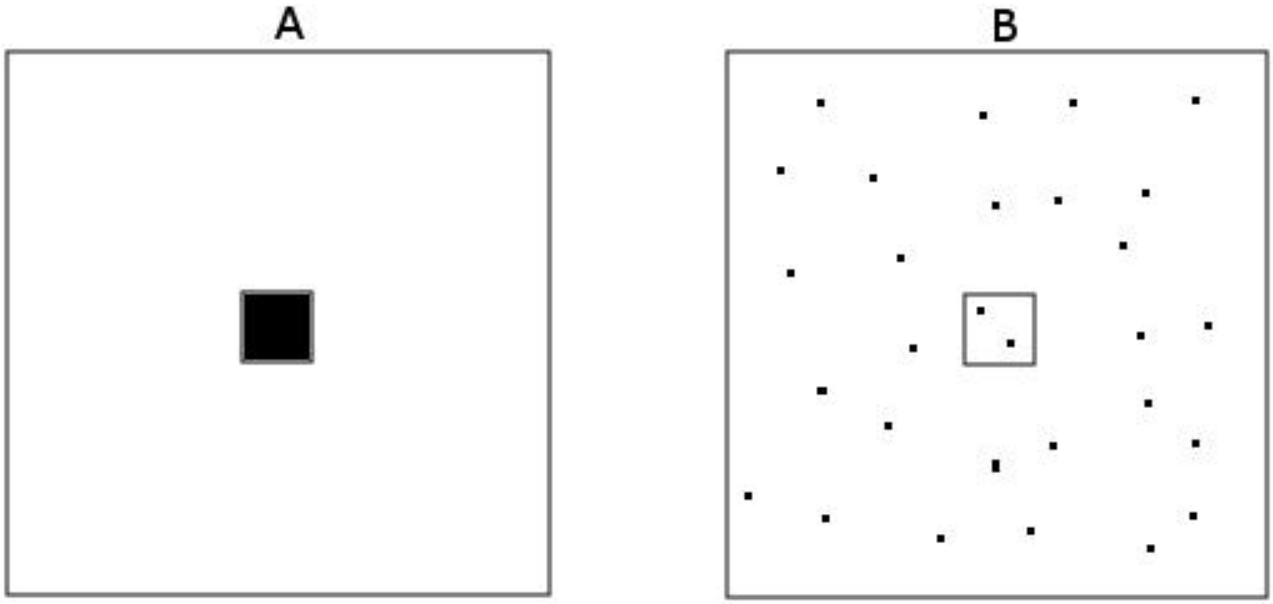

Table 1a: Exposure predictions based on analysis of aerosols generated by smoking machines: Volatile Organic Compounds

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**	[39,40]
	1	0.008		**0.03**	**3**	[37]
Acetone	1	0.002		**0.0003**	**0.003**	[37]
	150	0.0004		**0.0001**	**0.001**	[39,40]
Acrolein	12	0.001		**1**	**13**	[8]
	150	0.002		**2**	**20**	[39,40]
	1	0.006		**6**	**60**	[37]
Butanal	150	0.0002		**0.001**	**0.01**	[39,40]
Crotonaldehyde	150		0.0004	**0.01**	**0.1**	[39,40]
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**	[39,40]
	1	0.009		**3**	**30**	[37]
Glyoxal	1		0.002	**2**	**20**	[37]
	150		0.006	**6**	**60**	[39,40]
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**	[39,40]
	1	0.005		**0.02**	**0.2**	[37]
Toluene	12	0.0001		**0.003**	**0.03**	[8]
Valeraldehyde	150		0.0001	**0.0001**	**0.001**	[39,40]

average is presented when N>1

Table 1b: 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**	[25]
Barium	Ba & insoluble compounds	1	0.00005	**0.01**	**0.1**	[25]
Boron	Boron oxide	1	0.02	**0.1**	**1.5**	[25]
Cadmium	Respirable Cd & compounds	12	0.00002	**1**	**10**	[8]
Chromium	Insoluble Cr (IV) compounds	1	3E-05	**0.3**	**3**	[25]
Copper	Cu fume	1	0.0008	**0.4**	**4.0**	[25]
Iron	Soluble iron salts, as Fe	1	0.002	**0.02**	**0.2**	[25]
Lead	Inorganic compounds as Pb	1	7E-05	**0.1**	**1**	[25]
		12	0.000025	**0.05**	**0.5**	[8]
Magnesium	Inhalable magnesium oxide	1	0.00026	**0.003**	**0.03**	[25]
Manganese	Inorganic compounds, as Mn	1	8E-06	**0.04**	**0.4**	[25]
Nickel	Inhalable soluble inorganic compounds, as Ni	1	2E-05	**0.02**	**0.2**	[25]
		12	0.00005	**0.05**	**0.5**	[8]
Potassium	KOH	1	0.001	**0.1**	**1**	[25]
Tin	Organic compounds, as Sn	1	0.0001	**0.1**	**1**	[25]
Zinc	Zinc chloride fume	1	0.0004	**0.04**	**0.4**	[25]
Zirconium	Zr and compounds	1	3E-05	**0.001**	**0.01**	[25]
Sulfur	SO_2	1	0.002	**0.3**	**3**	[25]

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

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

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Characterization of chemicals released to the environment by electronic cigarettes use (ClearStream-AIR project): is passive vaping a reality?[3]

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Abstract

Background Electronic cigarettes (e-CIG) have been marketed as a safer alternative habit to tobacco smoking. We have developed a group of research protocols to evaluate the effects of e-CIG on human health, called ClearStream. No studies have adequately evaluated the effects of e-CIG use on the release of chemicals to the environment. The purpose of this study was to identify and quantify the chemicals released on a closed environment from the use of e-CIG (ClearStream-AIR).

Methods A 60 m^3 closed-room was used for the experiment. Two sessions were organized, the first using 5 smokers and the second using 5 users of e-CIG. Both sessions lasted 5 h. Between sessions, the room was cleaned and ventilated for 65 h. Smokers used cigarettes containing 0.6 mg of nicotine while e-CIG users used commercially available liquid (FlavourArt) with nicotine concentration of 11 mg/ml. We measured total organic carbon (TOC), toluene, xylene, carbon monoxide (CO), nitrogen oxides (NO_x), nicotine, acrolein, poly-aromatic hydrocarbons (PAHs) glycerin and propylene glycol levels on the air of the room.

Results During the smoking session, 19 cigarettes were smoked, administering 11.4 mg of nicotine (according to cigarette pack information). During the e-CIG session, 1.6 ml of liquid was consumed, administering 17.6 mg of nicotine. During the smoking session we found: TOC=6.66 mg/m^3, toluene=1.7 µg/m^3, xylene=0.2 µg/m^3, CO=11 mg/m^3, nicotine=34 µg/m^3, acrolein=20 µg/ml and PAH=9.4 µg/m^3. No glycerin, propylene glycol and NO_x were detected after the smoking session. During the e-CIG session we found: TOC=0.73 mg/m^3 and glycerin=72 µg/m^3. No toluene, xylene, CO, NO_x, nicotine, acrolein or PAHs were detected on room air during the e-CIG session.

Conclusions Passive vaping is expected from the use of e-CIG. However, the quality and quantity of chemicals released to the environment are by far less harmful for the human health compared to regular tobacco cigarettes. Evaporation instead of burning, absence of several harmful chemicals from the liquids and absence of sidestream smoking from the use of the e-CIG are probable reasons for the difference in results.

Introduzione

La rapida espansione, negli ultimi anni, del mercato della sigaretta elettronica, legata in parte alla possibilità di utilizzarla anche nei luoghi in cui è vietato fumare, ha fatto sorgere alcune perplessità sulla sua sicurezza in questi contesti. Ad oggi però queste perplessità si basano più su ragionamenti di tipo ipotetico che su valutazioni scientifiche. Scopo di questo esperimento, è quello di iniziare a comprendere e misurare qual è l'impatto del fumo elettronico sull'atmosfera di un ambiente chiuso, confrontandolo con il fumo tradizionale.

Protocollo

Per l'esperimento è stata predisposta una stanza, con un volume pari a circa $60\,m^3$, all'interno della quale sono stati allestiti dei sistemi di campionamento dell'aria.

Al fine di garantire una maggiore sensibilità e per rimuovere la variabile legata al ricircolo d'aria, l'esperimento è stato condotto in un ambiente senza rinnovo d'aria esterna.

I parametri analizzati sono stati:

- CO
- NO_x
- Acroleina
- Idrocarburi Policiclici Aromatici (IPA)
- Carbonio Organico Totale (COT)
- Sostanze Organiche Volatili (SOV)
- Nicotina
- Glicerina
- Glicole Propilenico

Alcuni di questi parametri (CO, NO_x, COT) sono stati monitorati in continuo. Per tutti gli altri sono state impiegate delle fiale e delle membrane specifiche per catturare le varie famiglie di composti in esame in modo cumulativo.

Procedura

L'esperimento si è svolto in 2 sessioni, una per i fumatori ed una per i *vaper*[1], della durata di 5 h ciascuna ed ha coinvolto, per ogni sessione, 5 volontari.

[1] Termine anglosassone gergale, utilizzato per indicare un utilizzatore abituale di sigaretta elettronica.

Introduction

The rapid expansion of the e-cigarette market in recent years, due in part to the fact that they can be used also in no smoking areas, has given rise to perplexities on their safety in these contexts. However, thus far, these perplexities are based more on hypothetical reasons rather than scientific evaluations. The aim of this experiment is to understand and to measure what kind of impact e-cigarettes use has on a closed environment atmosphere compared to traditional cigarette smoking.

Protocol

A $60\,m^3$ volume room was used for the experiment. This room was fitted with air sampling systems.

In order to guarantee a higher sensitivity and remove air recirculation-dependant variables, the experiment was performed without renewal of indoor air.

The following parameters were analyzed:

- CO
- NO_x
- Acrolein
- Polycyclic Aromatic Hydrocarbons (PAHs).
- Total Organic Carbon (TOC)
- Volatile Organic Compounds (VOCs)
- Nicotine
- Glycerine
- Propylene Glycol

Some of these parameters (CO, NO_x, TOC) were monitored continuously. For all the other parameters, in order to capture the various types of compounds cumulatively, vials and specific membranes were used.

Procedures

The experiment was divided in two sessions: one for vapers[1] and one for smokers. Each session lasted 5 h and involved 5 volunteers.

Between the sessions the room was cleaned and ventilated for 65 h, in order to restore the original

[1] English slang term indicating an electronic cigarette user.

Tra le due sessioni la stanza è stata pulita ed arieggiata per complessive 65 h al fine di ripristinare le condizioni di neutralità iniziali.

Sessioni di Campionamento

Nel corso delle due prove, dopo aver allestito la stanza per il campionamento e rilevato i parametri di partenza, 5 volontari hanno fumato le loro sigarette o usato la loro personale sigaretta elettronica, a seconda della sessione in corso.

Ai volontari è stato spiegato che avrebbero potuto fumare/*svapare*[2] nelle quantità e nei tempi più adatti alle loro personali esigenze, a condizione di svolgere questa attività sempre all'interno del locale predisposto per l'esperimento.

La permanenza nel locale è stata tassativamente limitata al tempo strettamente necessario a fumare/*svapare*.

L'accesso e la permanenza nel locale sono stati consentiti ad un massimo di 3 volontari contemporaneamente.

La porta della stanza è rimasta chiusa se non per il tempo necessario ad entrare o ad uscire.

Tutti i volontari hanno firmato un consenso informato prima di prendere parte allo studio.

Per la sessione fumatori, si è provveduto ad annotare il numero di sigarette fumate, mentre per la sessione *vaper* è stato valutato il peso del liquido consumato, con una bilancia di precisione.

Volontari

I volontari fumatori avevano un età media di circa 21 anni con una storia media di 6.5 anni di fumo ed un consumo medio giornaliero di circa 17 sigarette. Il contenuto di nicotina delle sigarette fumate era pari a 0.6 mg per sigaretta. Nel corso della sessione di campionamento sono state fumate complessivamente 19 sigarette, che hanno dispensato ai fumatori circa 11.4 mg di nicotina, basandosi su quanto riportato sul pacchetto.

I *vaper* hanno dichiarato di usare la sigaretta elettronica in maniera esclusiva da circa 3 mesi (min 1, max 6) con un consumo giornaliero di liquido[3] pari a 1.5 ml e un contenuto di nicotina medio di 11 mg/ml. Tutti i volontari, hanno usato un liquido commerciale (*Heaven Juice* tradizionale) prodotneutral conditions.

Sampling Sessions

For the two tests, the room was initially prepared for the sampling and analyzed for baseline conditions. Then, 5 volunteers smoked their cigarettes or e-cigarettes, depending on the session.

Volunteers were allowed to smoke/vape[2] as much as and whenever they wanted, provided that they used the room set for the experiment.

The time that volunteers spent in the room was strictly limited to smoking/vaping.

Only a maximum of 3 volunteers were allowed in the room at the same time.

The door of the room was opened only to let volunteers in or out.

Informed consent was obtained by all subjects before participating to the study.

During the smokers' session, the number of smoked cigarettes was noted down. During the vapers' session, the weight of consumed liquid, was evaluated using a precision scale.

Volunteers

The mean age of smokers was about 21 years and they were smoking on average 17 cigarettes per day for 6.5 years. The nicotine content in the smoked cigarettes was 0.6 mg per cigarette. During the sampling session, a total of 19 cigarettes were smoked which dispensed about 11.4 mg of nicotine, according to the information on cigarette packs.

Vapers declared that they had been using e-cigarettes exclusively for about 3 months (min 1, max 6), with a liquid[3] daily intake of 1.5 ml, and an average nicotine content of 11 mg/ml.

For e-cigarette users, a commercially available liquid (Heaven Juice traditional) produced by FlavourArt was used, and a commercial EGO Pulse device by Smokie's®.

During the sampling session, 1760 mg of liquid were vaporized, which is equal to 1.6 ml containing

[2] Termine gergale largamente usato, derivato dall'inglese *to vape*, ed impiegato per indicare l'azione di chi fuma una sigaretta elettronica.

[3] Tutti i liquidi per sigaretta elettronica utilizzati nell'esperimento erano del tipo *Heaven Juice Tradizionale* di FlavourArt, contenenti circa il 40% di glicerolo USP, circa il 50% di glicole propilenico USP, da 0.9% a 1.8% di nicotina USP, <1% di componente aromatica, acqua depurata, secondo quanto ricavato dalla documentazione fornita del produttore.

[2] English term *to vape* indicating the act of e-smoking.

[3] Heaven Juice Traditional e-cigarette liquids by Flavour Art were used during the experiment. They contained about 40% of USP glycerol, 50% of USP propylene glycol, from 0.9% to 1.8% of USP nicotine, <1% aromatic component, purified water, according to the information provided by the producer.

Composti Analizzati Analyzed compounds	Supporto di campionamento Sampling medium	Litri campionati (teorici) Sampled liters (theoretical)	Metodo Method
Nicotina **Nicotine**	Fiala XAD-2 XAD-2 vial	600	NIOSH 2544
Glicoli - Glicerina **Glycols - Glycerine**	Filtro in fibra di vetro + fiala XAD-7 Glass fiber filter + XAD-7 vial	600	NIOSH 5523
Idrocarburi Policiclici Aromatici (IPA) **Polycyclic Aromatic Hydrocarbons (PAHs)**	Filtro in fibra di vetro + fiala XAD-2 Glass fiber filter + XAD-2 vial	600	NIOSH 5515
Acroleina **Acrolein**	Fiala di Silica gel + DPNH Silica gel vial + DPNH	60	NIOSH 2018
SOV **VOCs**	Fiala di carbone attivo Activated carbon vial	60	UNI EN 13649

Tab. 1: Metodi utilizzati per il campionamento dei composti. / Methods used for substances sampling.

to da *FlavourArt* e un dispositivo EGO Pulse di Smokie's®.

Durante la sessione di campionamento, sono stati vaporizzati 1760 mg di liquido, pari a circa 1.6 ml e contenenti circa 17.6 mg di nicotina.

Materiali e Metodi

Per le metodiche di campionamento sono state adottate diverse procedure sia della normativa UNI che NIOSH, impiegando differenti fiale SKC specifiche per i diversi componenti da ricercare. Per alcune molecole sono state utilizzate anche delle membrane filtranti in fibra di vetro o in PTFE con porosità di 0.8 µm (Tab. 1).

Ogni fiala è stata collegata ad un campionatore aspirante portatile, calibrato e impostato per aspirare uno specifico volume, in funzione della durata dell'esperimento e delle specifiche della metodica in uso.

A questi sistemi di campionamento cumulativo, sono stati affiancati, un rilevatore di CO, CO_2, NO_x, e un rilevatore di COT a ionizzazione di fiamma FID.

A fine esperimento, le fiale e le membrane sono state sigillate e trasportate presso i laboratori ABICH S.r.l.[4] per le analisi.

Risultati

Le analisi dei campioni hanno evidenziato numerose e sostanziali differenze tra fumo di sigaretta e fumo elettronico, sia in termini di impatto sulla qualità dell'aria, sia anche in termini di tossicità. (Tab. 2).

Per il campionamento sono state impiegate delle membrane in PTFE e siamo rimasti colpiti dal co-

[4]ABICH S.r.l., Verbania (VB), Italia

about 17.6 mg of nicotine.

Materials and Methods

Considering the sampling methodologies different procedures both from UNI and NIOSH have been used. Different SKC vials specific for the different components to search were used. For some molecules, also fiberglass or PTFE 0.8 µm porosity membrane filters were used (Tab. 1).

Each vial was linked with a portable suction sampler, calibrated and set to aspirate a specific volume, depending on the duration of the experiment and on the method details.

In addition to these cumulative sampling systems, a CO and CO_2 and NO_x detector and a FID flame ionization TOC detector were used.

At the end of the experiment, the vials and the membranes were sealed and taken to the ABICH S.r.l.[4] labs for the analysis.

Results

The sampling analysis underlined many and fundamental differences between cigarette smoking and e-cigarette smoking, both in terms of impact on air quality and also on toxicity. (Tab. 2).

PTFE membranes have been used for the sampling. We were surprised by the colour of the mem-

[4]ABICH S.r.l.,Verbania (VB), Italy

Parametro Parameter	Volume Campionato* Sampled Volume* [L]	Concentrazione Media* Mean Concentration* [mg/m^3]	
		Sigaretta Tradizionale Traditional Cigarette	Sigaretta Elettronica Electronic Cigarette
Nicotina / Nicotine	600	0.034	< 0.001**
Glicerina / Glycerine	600	< 0.001**	0.072
Glicolene Propilenico / Propylene Glycol	600	< 0.01**	< 0.01**
Acroleina / Acrolein	60	0.020	< 0.0016**

Tempo di campionamento: 300 minuti. / Sampling time: 300 minutes.

* dati relativi alle condizioni operative di riferimento (20°C e 0.101 MPa) riprodotte dall'attrezzatura / values refer to ideal working conditions (20°C and 0.101 MPa) simulated by the equipment

** inferiore alla soglia rilevabile dalla metodica / below the instrument sensitivity

Tab. 2: Sostanze rilevate. / Detected substances.

lore assunto dalle membrane alla fine delle sessioni. Questo, pur non costituendo un dato analitico di per sé, in qualche modo ci ha dato un'idea dei risultati che avremmo ottenuto (Fig. 3 e 4).

branes at the end of the sessions. Even if this does not constitute analytic data as such, it has given us an idea of the results that we could expect (Fig. 3 and 4).

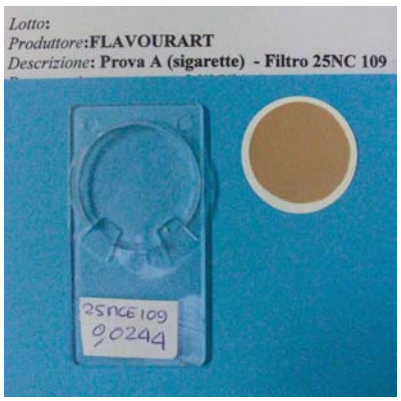

Fig. 3: Membrana in PTFE al termine della sessione di fumo tradizionale. / PTFE membrane at the end of the cigarette smoking session.

Fig. 4: Membrana in PTFE al termine della sessione di fumo elettronico. / PTFE membrane at the end of the e-cigarette session.

CO (Monossido di Carbonio) [12] Il monossido di carbonio non ha mostrato alcuna variazione con il fumo elettronico, rimanendo al di sotto dei limiti di rilevabilità dello strumento, mentre il fumo di sigaretta ha prodotto un costante incremento della sua concentrazione durante tutta la durata del campionamento, raggiungendo un picco di 11 mg/m^3, valore questo, al di sopra della soglia di legge (10 mg/m^3)[5] (Fig. 5).

Il monossido di carbonio è un gas tossico con una elevata affinità per l'emoglobina, compromettendo

CO (Carbon Monoxide) [12] The levels of carbon monoxide did not show any variation during e-cigarette smoking, remaining below the detection limits of the tool. On the contrary cigarette smoking produced a steady elevation in CO throughout the sampling period. It reached a peak of 11 mg/m^3, which is above the legal threshold (10 mg/m^3)[5] (Fig. 5).

Carbon monoxide is a toxic gas with a high affinity for haemoglobin, compromising its ability to transport oxygen. Smokers, continue to exhale out high levels of CO several hours after smoking their

[5]Decreto Legislativo 13 agosto 2010, n. 155. Attuazione della direttiva 2008/50/CE relativa alla qualità dell'aria ambiente e per un'aria più pulita in Europa.

[5]Legislative decree 13th August 2010, n.155. Application of the directive 2008/50/CE concerning the quality air in the environment for a clearer air in Europe.

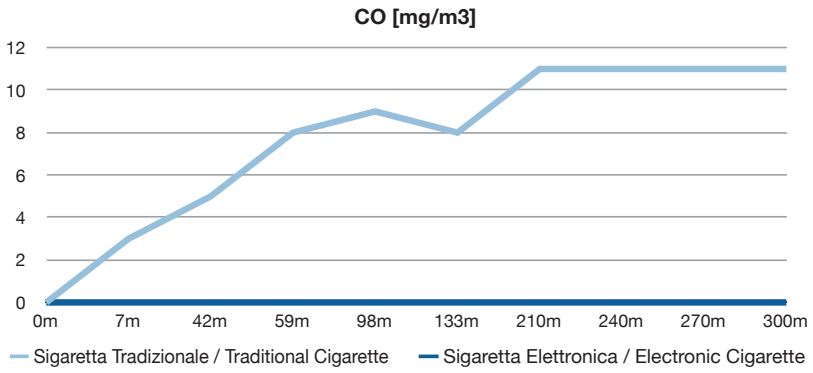

Fig. 5: Concentrazione di CO durante l'esperimento. / CO concentration during the experiment.

la sua capacità di trasportare ossigeno. Un fumatore continua ad emettere elevati livelli di monossido di carbonio, anche molte ore dopo aver fumato l'ultima sigaretta [5].

Nicotina Tra gli aspetti più interessanti, abbiamo osservato che la nicotina, pur presente nei liquidi utilizzati per l'esperimento, non è stata rilevata durante la sessione relativa al fumo elettronico. Per contro sono stati dosati 34 µg/m^3 di nicotina, con il fumo tradizionale. Va precisato che, stando a quanto riportato sui pacchetti, la quota di nicotina inalata dai fumatori, ammonta complessivamente a circa 11.4 mg, mentre i *vaper* hanno inalato nicotina per un totale di 17.6 mg. Tuttavia la quota di nicotina indicata sul pacchetto tiene conto solo della quota inalata, senza fornire alcuna informazione relativa a quella effettivamente presente nella sigaretta e liberata nell'aria durante la sua combustione.

Basandosi sui risultati osservati è possibile dedurre che il fumo di sigaretta produce una contaminazione da nicotina nell'aria, almeno 35 volte superiore a quella del fumo elettronico, il che equivale a dire che servono almeno 35 *vaper* per produrre un livello di nicotina equivalente a quello prodotto da un singolo fumatore.

Se inoltre avessimo bilanciato le prove, chiedendo ai fumatori, di consumare sigarette, in quantità tali da eguagliare il consumo di nicotina dei *vaper*, questi avrebbero dovuto fumare circa 29 sigarette, producendo una concentrazione di nicotina stimata in circa 52 µg/m^3.

Argomentare sulle ragioni di questi risultati è estremamente difficile, si potrebbe ipotizzare che esista per i *vaper* una differente cinetica di assorbimento della nicotina, o più semplicemente che le quantità in gioco siano estremamente contenute se paragonate a quelle effettivamente liberate dal fumo tradizionale. Ma al di là di queste ipotesi, tutte da verificare, il risultato in sé rimane un fatto: 5 *vaper* che utilizzano la sigaretta elettronica, per 5 h, in una last cigarette, even if the last cigarette was put out many hours before [5].

Nicotine Among all, the most interesting aspects we observed was that nicotine was not detected in air during the e-smoking session, although liquids used for experiments contained it. On the other hand, 34 µg/m^3 of nicotine were found during the smoking session. It should be made clear that, according to the information on packs, the amount of nicotine inhaled by smokers was about 11.4 mg, while the amount of nicotine inhaled by vapers was about 17.6 mg. However the amount of nicotine reported on packs is the inhaled amount. This information does not give details about the real amount of nicotine inside the cigarettes and released in the air during combustion and from side stream smoke.

Based on the observed results, we can conclude that cigarette smoking produces nicotine contamination in the air at least 35 times higher than e-smoking. This means that we need at least 35 vapers to produce nicotine level in air similar to the level produced by a single smoker.

Moreover if we had balanced the tests, asking cigarette smokers to consume the amount of cigarettes necessary to match the amount of nicotine used by vapers, the latter should have smoked about 29 cigarettes, producing an expected nicotine concentration of about 52 µg/m^3.

It's extremely difficult to discuss about the reasons for these results. We could suppose that there is a different absorption kinetics for nicotine. Or maybe the amount in play is extremely low, when compared to the nicotine amount released during traditional smoking. However beyond all these hypotheses, which have not been verified, there is one fact: 5 vapers using e-cigarettes for 5 h in a small room without renewal of indoor air do not produce detectable levels of nicotine in the air.

Parametro Parameter	Volume Campionato* Sampled Volume* [L]	Concentrazione Media* Mean Concentration* [µg/m³]	
		Sigaretta Tradizionale Traditional Cigarette	Sigaretta Elettronica Electronic Cigarette
Metiletilchetone / Methylethylketone	60	4.2	4.4
1-etil-3-metil benzene / 1-ethyl-3-methylbenzene	60	0.2	3.4
Limonene / Limonene	60	12.5	0.1
Decano / Decane	60	0.4	4.2
Undecano / Undecane	60	4.2	0.7
Dodecano / Dodecane	60	3.7	0.3
Cedrene / Cedrene	60	0.3	0.9
Longifolene / Longifolen	60	18.3	30.3
Toluene / Toluene	60	1.7	-
O,m,p – Xilene / o,m,p – Xylene	60	0.2	-
1-etil-2-metil benzene / 1-ethyl-2-methylbenzene	60	4.9	-
1,2,4-trimetil benzene / 1,2,4-Trimethylbenzene	60	0.3	-
Mentene / Menthene	60	0.5	-
BHT (Butilidrossitoluene / Butylhydroxytoluene)	60	-	0.4
Terpene / Terpene (u.s.)	60	-	2.3
Longiciclene / Longicyclene	60	-	2.2
Cariofillene / Caryophillene	60	-	1.0
n.i. totali / total u.s.	60	14.7	12.6

n.i. sostanza non identificabile / u.s. unidentifiable substance

Tempo di campionamento: 300 minuti. / Sampling time: 300 minutes.

* dati relativi alle condizioni operative di riferimento (20°C e 0.101 MPa) riprodotte dall'attrezzatura / values refer to ideal working conditions (20°C and 0.101 MPa) simulated by the equipment

** inferiore alla soglia rilevabile dalla metodica / below the instrument sensitivity

Tab. 6: Sostanze Organiche Volatili. / Volatile Organic Compounds.

stanza di piccole dimensioni e senza rinnovo d'aria, non producono livelli rilevabili di nicotina nell'aria.

Glicole Propilenico Altro parametro inatteso è il glicole propilenico, che non è stato rilevato durante la prova con il fumo elettronico, pur costituendo il 50% del liquido[3].

Questo curioso fenomeno è stato osservato anche in un altro studio simile [11]. Anche questo studio non ha rilevato nicotina nel vapore passivo di una stanza sperimentale (significativamente più piccola della stanza da noi utilizzata). Alcuni esperimenti suggeriscono che l'assorbimento del glicole propilenico per via inalatoria sia estremamente rapido [17] e questo potrebbe spiegare perché questa molecola pur così abbondante non è stata rilevata.

Glicerina e Acroleina Non è stata rilevata glicerina relativamente al fumo di sigaretta, mentre ne è stata rilevata una traccia con il fumo elettronico, pari a 72 µg, valore molto al di sotto della soglia di

Propylene Glycol Results on propylene glycol were also unexpected. During e-smoking tests, propylene glycol was not detected, although 50% of liquid[3] consisted of propylene glycol.

This curious phenomenon has also been observed in a similar study [11]. Even in that case, nicotine was not detected in an experimental room of the passive vaping (which was significantly smaller than the room we used). Some studies suggest that propylene glycol absorption via inhalation is extremely rapid [17]. This could explain why this molecule has not been detected even though it was present in significant amounts in the liquid used.

Glycerine and Acrolein No glycerine was detected in air during cigarette smoking. On the other hand, 72 µg/m^3 were detected during e-smoking. This amount is much lower than the threshold safety

Parametro Parameter	Volume Campionato* [L] Sampled Volume*	Concentrazione Media* [µg/m³] Mean Concentration*	
		Sigaretta Tradizionale Traditional Cigarette	Sigaretta Elettronica Electronic Cigarette
Naftalene / Naphthalene	600	**2.78**	< 0.02**
Acenaftilene / Acenaphthylene	600	< 0.02**	< 0.02**
Acenaftene / Acenaphthene	600	**0.19**	< 0.03**
Fluorene / Fluorene	600	**0.47**	< 0.06**
Fenantrene / Phenanthrene	600	**0.37**	< 0.08**
Antracene / Anthracene	600	< 0.04**	< 0.04**
Fluorantene / Fluoranthene	600	**0.13**	< 0.02**
Pirene / Pyrene	600	< 0.01**	< 0.01**
Benzo(a)antracene / Benzo(a)anthracene	600	< 0.16**	< 0.16**
Crisene / Chrysene	600	**5.46**	< 0.14**
Benzo(b)fluorantene / Benzo(b)fluoranthene	600	< 0.33**	< 0.33**
Benzo(k)fluorantene / Benzo(k)fluoranthene	600	< 0.74**	< 0.74**
Benzo(a)pirene / Benzo(a)pyrene	600	< 0.62**	< 0.62**
Indeno(1,2,3-cd)pirene / Indeno(1,2,3-cd)pyrene	600	< 1.47**	< 1.47**
Dibenzo(a,h)antracene / Dibenzo(a,h)anthracene	600	< 1.47**	< 1.47**
Benzo(ghi)perilene / Benzo(g,h,i)perylene	600	< 1.60**	< 1.60**

Tempo di campionamento: 300 minuti. / Sampling time: 300 minutes.

* dati relativi alle condizioni operative di riferimento (20°C e 0.101 MPa) riprodotte dall'attrezzatura / values refer to ideal working conditions (20°C and 0.101 MPa) simulated by the equipment

** inferiore alla soglia rilevabile dalla metodica / below the instrument sensitivity

Tab. 7: Idrocarburi Policiclici Aromatici. / Polycyclic Aromatic Hydrocarbons.

azione (TWA-TLV 10 mg/m^3) e ben al di sotto della soglia definita di rischio moderato o irrilevante [4].

Tuttavia, bisogna rilevare che l'acroleina, molecola che si forma della disidratazione ad elevate temperature della glicerina, era presente e ben rilevabile nell'aria della stanza, durante la prova dei fumatori (20 µg/m^3).

È noto infatti che la glicerina viene spesso aggiunta ai tabacchi come umettante e durante la combustione si trasformi in acroleina [3]. L'assenza di processi di combustione nel fumo elettronico, è di fondamentale importanza per comprendere come mai l'acroleina non sia stata rilevata nell'aria durante la prova.

L'acroleina è una sostanza notoriamente molto tossica e irritante, inoltre è attualmente sospetta per avere un ruolo nei processi di cancerogenesi [1].

limit (TWA-TLV 10 mg/m^3) and much lower than the threshold for moderate risk [4].

However, it's important to note that acrolein, a molecule formed by dehydration of glycerine due to high temperatures, was present in the air of the room during cigarette smoking test (20 µg/m^3).

In fact, it is well known that glycerine is often added to moisten tobacco. During combustion glycerine is transformed into acrolein [3]. The fact that no combustion is involved when using e-cigarettes probably plays a fundamental role in the absence of acrolein from indoor air during their use.

As everyone knows, acrolein is a very toxic and irritating substance. Moreover it is currently suspected of having a fundamental role in the carcinogenic process [1].

SOV Dall'analisi delle sostanze organiche volatili, sono state evidenziate fondamentalmente componenti aromatiche, in particolare il longifolene, tipico dell'aroma di pino, era presente in entrambe le prove. È probabile che questo composto facesse parte dei prodotti detergenti o deodoranti impiegati per pulire la stanza prima dell'esperimento. In merito

VOCs During the analysis of volatile organic compounds, aromatic components were detected, in particular longifolen, typical of pine aroma, in both tests. One of the detergents used to clean the room before the test could have contained this compound. Regarding cigarette smoking, xylene and toluene were detected. These are two very common toxic

al fumo di sigaretta, si rilevano comunque tracce di xilene e toluene, due composti tossici, normalmente presenti nel fumo di sigaretta. Il limonene, terpene dell'olio essenziale di limone, è stato rilevato solo durante la prova con il fumo tradizionale ed in effetti questa molecola è stata riscontrata anche da altri studi come componente del fumo di sigaretta [11] (Tab. 6).

IPA Tra i composti più rilevanti, in termini di tossicità cronica del fumo di tabacco, ci sono certamente gli idrocarburi policiclici aromatici. Questi composti, prodotti durante il processo di combustione, sono noti per gli effetti cancerogeni e mutageni.

La prova ha identificato 6 dei 16 IPA ricercati, durante la sessione con il fumo tradizionale, mentre non è stato rilevato nulla con il fumo elettronico (Tab. 7).

COT [15] L'analisi del carbonio organico totale, non ci dà informazioni specifiche sulla tossicità. È un modo per valutare globalmente la quantità di materia organica immessa nell'aria, senza distinguere tra sostanze tossiche e non tossiche. Tuttavia questo parametro ci fornisce una visione globale del grado di contaminazione dell'aria, durante tutta la durata dell'esperimento.

Nel grafico è possibile osservare l'andamento dei livelli di COT nell'aria durante le 5 h di campionamento.

Dal grafico è stato sottratto il valore di fondo presente all'inizio del campionamento ($1\,mg/m^3$).

Due aspetti sono interessanti a mio parere. In primo luogo i livelli massimi con il fumo di sigaretta sono oltre 9 volte più alti che con il fumo elettronico, in secondo luogo, il fumo impiega appena 11 minuti, a raggiungere il valore massimo raggiunto dalla sigaretta elettronica ($0.73\,mg/m^3$), nel tempo di 5 h (Fig. 8).

compounds in cigarette smoking. Limonene which is an oil lemon terpene, was detected only during the traditional smoking test. In fact this molecule was found as a component in cigarette smoke even in other studies [11] (Tab. 6).

PHAs Polycyclic aromatic hydrocarbons are, without doubt, among the most important compounds in terms of chronic toxicity caused by tobacco smoking. These substances, which are produced during the combustion process, are well known for their carcinogenic and mutagenic effects.

During the traditional cigarette smoking session, 6 out of 16 PAHs were identified. Nothing was identified during the e-cigarette session (Tab. 7).

TOC [15] The total organic carbon analysis does not give us specific information about toxicity. It is a measure of the overall amount of organic matter released in the air. There is no distinction between toxic and non-toxic substances. However this parameter gives us a global view of the degree of contamination of air, throughout the whole experiment.

The chart shows the TOC level trends in the air during the 5 h sampling.

The chart does not contain the original value of air at the beginning of the sample ($1\,mg/m^3$).

In my opinion there are two interesting aspects which should be underlined. Firstly, the maximum levels during cigarette smoking sessions are 9 times higher than the e-smoking session. Secondly, cigarette smoking takes just 11 minutes to reach a value similar to the maximum value measured for the e-cigarette ($0.73\,mg/m^3$), in 5 h (Fig. 8).

Conclusioni

L'esperimento su descritto ha evidenziato, limitatamente ai parametri osservati, che il fumo elettronico non comporta l'immissione nell'aria di un ambiente chiuso, di sostanze tossiche o cancerogene in quantità rilevabili. Ulteriori studi sono necessari, per approfondire e meglio definire tutti gli aspetti coinvolti, ma questa valutazione preliminare suggerisce che l'impatto del fumo elettronico passivo, se confrontato con quello del fumo di sigaretta, è talmente ridotto da essere appena rilevabile e non presenta le caratteristiche di tossicità e di cancerogenicità rilevate nel fumo di sigaretta. L'assenza di combustione e la mancanza di fumo secondario (*sidestream smoke*), noto per i suoi effetti tossici [2, 6], sono probabilmen-

Conclusions

The above experiment, within the limits of the observed parameters, has underlined that e-smoking does not produce detectable amounts of toxic and carcinogenic substances in the air of an enclosed space. Further studies are needed to better understand all the involved aspects. However this preliminary assessment indicates that passive vaping impact, when compared to the traditional cigarette smoking, is so low that it is just detectable, and it does not have the toxic and carcinogenic characteristics of cigarette smoking. The absence of combustion and the lack of sidestream smoking, with its known toxic effects [2, 6] are probably the main reasons for the differences observed in air pollution characteristics

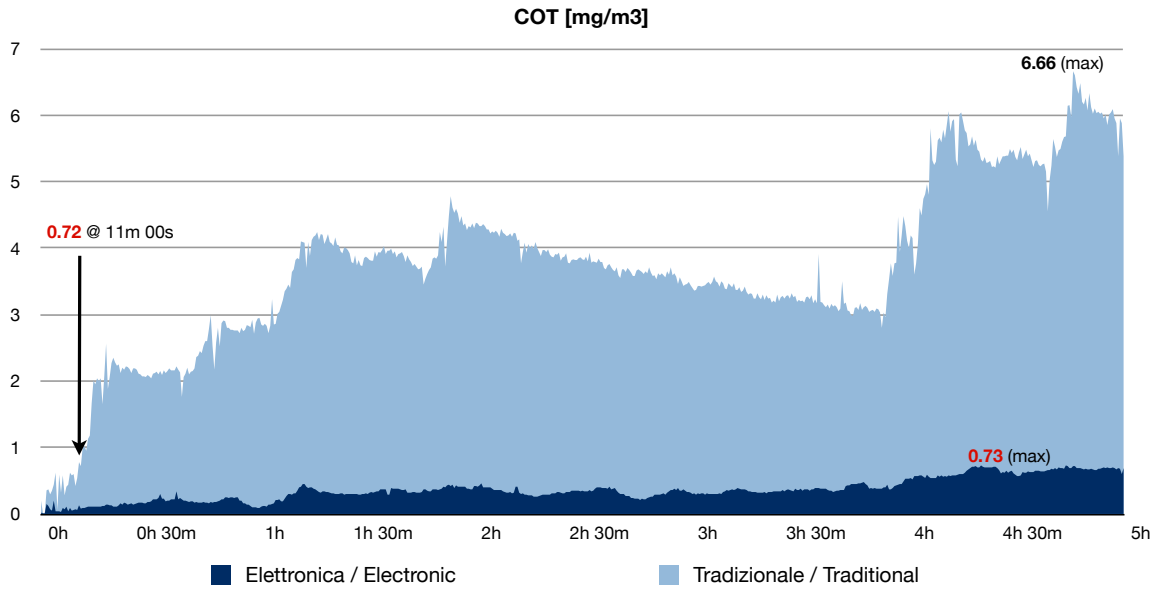

Fig. 8: Carbonio Organico Totale. / Total Organic Carbon.

te alla base delle differenze osservate, in termini di inquinamento dell'aria, tra fumo di tabacco e fumo elettronico.

Come considerazione finale, basandosi sui risultati ottenuti e sui dati dell'ARPA in materia di inquinamento urbano, potrebbe essere meno salutare, respirare l'aria di una grande città nell'ora di punta, piuttosto che sostare in una stanza con qualcuno che usa una sigaretta elettronica.

between e-cigarettes and tobacco smoking.

On the base of the obtained results and on ARPA data about urban pollution, we can conclude by saying that could be more unhealty to breath air in big cities compared to staying in the same room with someone who is vaping.

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Electronic cigarettes for smoking cessation: a randomised controlled trial

Christopher Bullen, Colin Howe, Murray Laugesen, Hayden McRobbie, Varsha Parag, Jonathan Williman, Natalie Walker

Summary

Background Electronic cigarettes (e-cigarettes) can deliver nicotine and mitigate tobacco withdrawal and are used by many smokers to assist quit attempts. We investigated whether e-cigarettes are more effective than nicotine patches at helping smokers to quit.

Methods We did this pragmatic randomised-controlled superiority trial in Auckland, New Zealand, between Sept 6, 2011, and July 5, 2013. Adult (≥18 years) smokers wanting to quit were randomised (with computerised block randomisation, block size nine, stratified by ethnicity [Māori; Pacific; or non-Māori, non-Pacific], sex [men or women], and level of nicotine dependence [>5 or ≤5 Fagerström test for nicotine dependence]) in a 4:4:1 ratio to 16 mg nicotine e-cigarettes, nicotine patches (21 mg patch, one daily), or placebo e-cigarettes (no nicotine), from 1 week before until 12 weeks after quit day, with low intensity behavioural support via voluntary telephone counselling. The primary outcome was biochemically verified continuous abstinence at 6 months (exhaled breath carbon monoxide measurement <10 ppm). Primary analysis was by intention to treat. This trial is registered with the Australian New Zealand Clinical Trials Registry, number ACTRN12610000866000.

Findings 657 people were randomised (289 to nicotine e-cigarettes, 295 to patches, and 73 to placebo e-cigarettes) and were included in the intention-to-treat analysis. At 6 months, verified abstinence was 7·3% (21 of 289) with nicotine e-cigarettes, 5·8% (17 of 295) with patches, and 4·1% (three of 73) with placebo e-cigarettes (risk difference for nicotine e-cigarette *vs* patches 1·51 [95% CI −2·49 to 5·51]; for nicotine e-cigarettes *vs* placebo e-cigarettes 3·16 [95% CI −2·29 to 8·61]). Achievement of abstinence was substantially lower than we anticipated for the power calculation, thus we had insufficient statistical power to conclude superiority of nicotine e-cigarettes to patches or to placebo e-cigarettes. We identified no significant differences in adverse events, with 137 events in the nicotine e-cigarettes group, 119 events in the patches group, and 36 events in the placebo e-cigarettes group. We noted no evidence of an association between adverse events and study product.

Interpretation E-cigarettes, with or without nicotine, were modestly effective at helping smokers to quit, with similar achievement of abstinence as with nicotine patches, and few adverse events. Uncertainty exists about the place of e-cigarettes in tobacco control, and more research is urgently needed to clearly establish their overall benefits and harms at both individual and population levels.

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Introduction

Since their launch in 2004, electronic cigarettes (e-cigarettes), a diverse range of battery operated devices that vaporise nicotine for inhalation, have been purchased by millions of people.[1] Many smokers use e-cigarettes to help them quit (27% of those making a quit attempt in the UK, in May, 2013[2]), and sales are increasing so rapidly that some analysts predict that they will surpass cigarette sales within a decade.[1]

The place of e-cigarettes in tobacco control is controversial,[3,4] and there is a paucity of reliable data to inform debate. Available research suggests that e-cigarettes have the potential to assist smokers to quit or reduce smoking: surveys show that many smokers try e-cigarettes for these reasons,[5,6] and studies show that e-cigarettes are capable of delivering nicotine into the bloodstream and attenuating tobacco withdrawal as effectively as nicotine replacement therapy (NRT).[7,8] Use of e-cigarettes also simulates behavioural and sensory dimensions of smoking. However, a trial in 300 smokers unwilling to quit showed low rates of cessation at 12 months for nicotine e-cigarettes and placebo e-cigarettes.[9] E-cigarettes also have potential to harm: researchers have detected toxins in e-cigarette fluid and vapour,[10] but at much the same concentrations as with NRT and lower than in cigarette smoke;[11] a review deemed e-cigarettes to be very unlikely to pose significant risks to smokers.[12]

In this trial we aimed to assess whether e-cigarettes with cartridges containing nicotine (nicotine e-cigarette) were more effective for smoking cessation than nicotine patches, and included a blind comparison with e-cigarettes containing no nicotine (placebo e-cigarette). We hypothesised that nicotine e-cigarettes would be more effective than patches and placebo e-cigarettes for smoking reduction, tobacco dependence, and relief of withdrawal symptoms, and that they would have no greater risk of adverse events than nicotine patches.

Methods

Study design and participants

We did this three parallel group, randomised controlled trial in Auckland, New Zealand. First randomisation was on Sept 6, 2011, and last follow-up was on July 5, 2013. The published protocol describes procedures in detail.[13] In brief, people were eligible if they were aged 18 years or older, had smoked ten or more cigarettes per day for the past year, wanted to stop smoking, and could provide consent. We recruited via community newspapers, inviting people to call the study centre for eligibility prescreening, done by research assistants, who also completed follow-up assessments. We excluded pregnant and breastfeeding women; people using cessation drugs or in an existing cessation programme; those reporting heart attack, stroke, or severe angina in the previous 2 weeks; and those with poorly controlled medical disorders, allergies, or other chemical dependence. Participants were mailed study information, and consent forms to sign and return. The Northern X Regional Ethics Committee approved the study (Number NTX/10/11/111); the Standing Committee on Therapeutic Trials approved the use of nicotine e-cigarettes because they were not permitted for sale in New Zealand, but could be imported for personal use or research.

Randomisation and masking

Callers who met the inclusion criteria and gave demographic details and information about nicotine dependence (Fagerström test for nicotine dependence [FTND][14]) were randomised by the study statistician (VP) in a 4:4:1 ratio to nicotine e-cigarettes, patches, or placebo

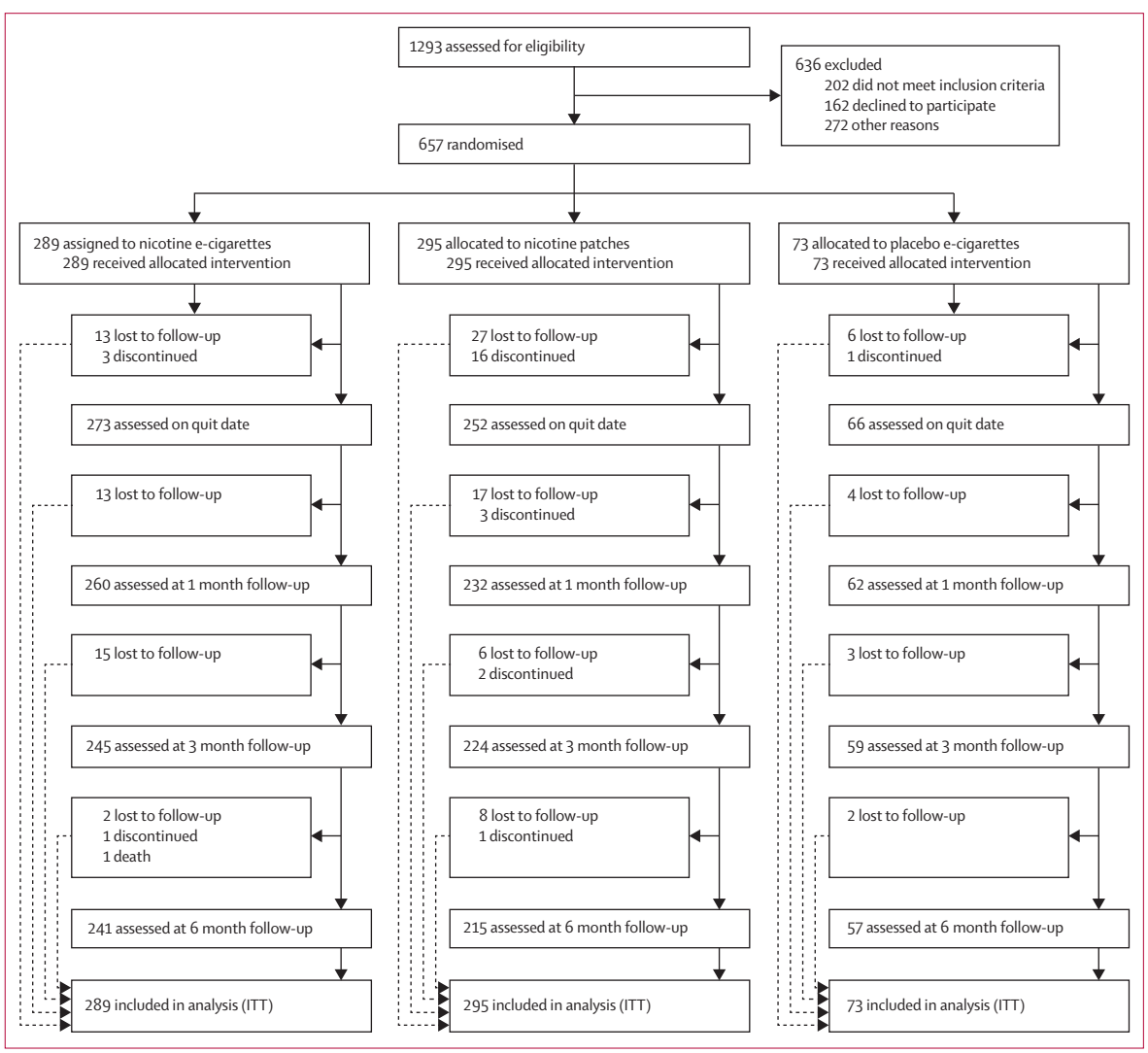

Figure 1: **Trial profile**

11 protocol violations occurred in the nicotine e-cigarettes group (three pregnancies, seven no biochemical validation, one undisclosed medication ineligibility). 11 protocol violations occurred in the patches group (four pregnancies, four no biochemical validation, three undisclosed medication ineligibility). Three protocol violations occurred in the placebo e-cigarettes group (one no biochemical validation, two undisclosed medication ineligibility). ITT=intention to treat.

e-cigarettes, with computerised block randomisation, block size nine, stratified by: ethnicity (Māori; Pacific; or non-Māori, non-Pacific), sex (men or women), and level of nicotine dependence (>5 or ≤5 FTND). It was not feasible to mask participants to allocation to patch or e-cigarettes. Research assistants undertaking outcome assessments used a list generated by the trial database giving no indication of product allocation.

Procedures

Elusion e-cigarettes are among the e-cigarette market leaders in Australasia; in New Zealand, nicotine e-cigarettes are not permitted to be sold, but nicotine-free e-cigarettes are widely available for sale and identical in appearance to nicotine versions. We commissioned analyses of these e-cigarettes: the liquid was free of diethylene glycol (a toxin detected in fluid in one brand of e-cigarettes[10]); nicotine cartridges (labelled 16 mg) contained 10–16 mg nicotine per mL; and placebo cartridges contained no nicotine. Vapour analyses done midway through the trial (using Goniewicz and colleagues' methodology[15]) showed that 300 puffs from one nicotine e-cigarette cartridge delivered 3–6 mg nicotine, equivalent to smoking between one and five tobacco cigarettes. The first 20 participants randomised to the nicotine e-cigarettes group were invited to take part in testing, and four completed the testing regimen. In these four participants, who had been using the nicotine e-cigarettes for at least 1 week, plasma nicotine concentrations were sampled every 10 min for 1 h, and peaked at 10 min after commencement of product use at 3·4 ng/mL, a median increase from baseline of 2·1 ng/mL. We chose nicotine patches (21 mg/24 h) for comparison with e-cigarettes because they are the most popular NRT product in New Zealand,[16] have proven effectiveness,[17] and few known adverse events.[17]

Participants allocated to patches were sent exchange cards in the mail redeemable for patches from community pharmacies, with instructions to use patches daily, from 1 week before until 12 weeks after their chosen quit day, consistent with smoking cessation guidelines.[18] We also supplied vouchers to these participants to cover dispensing costs. Participants in both e-cigarettes groups were couriered an e-cigarette, spare battery and charger, and cartridges (with labels masked to nicotine content), plus simple instructions to use them as desired from 1 week before until 12 weeks after their chosen quit day. All randomised participants were referred (by fax or by a scanned request) to Quitline, who called the participants to offer telephone-based behavioural support. Participants who declined or did not call back were still able to access other Quitline support, such as Txt2Quit (a free SMS support service). Quitline provided us with reports to monitor usage. After randomisation, additional baseline data were collected: education, smoking and quitting history, quitting self-efficacy, medication, withdrawal symptoms and stage of addiction (according to the autonomy over smoking scale, AUTOS),[19] and behavioural dependence (according to the Glover-Nilsson smoking behavioural questionnaire, GN-SBQ).[20]

The primary outcome was continuous smoking abstinence (self-reported abstinence over the whole follow-up period, allowing ≤5 cigarettes in total[21]), 6 months after quit day, verified at that point in time by exhaled breath carbon monoxide measurement (<10 ppm), using Bedfont Micro Smokerlyzers (Bedfont Scientific, Maidstone, UK). Carbon monoxide tests were administered by research assistants at the University of Aukland; participants were not paid for testing, but received transportation costs. Secondary outcomes assessed at 1, 3, and 6 months post quit day were: continuous abstinence, 7 day point prevalence abstinence (proportion reporting no smoking of tobacco cigarettes, not a puff, in the past 7 days), number of tobacco cigarettes smoked per day, proportion of participants reducing tobacco smoking, time to relapse to tobacco smoking, number of patches or cartridges used, use of other cessation treatments, withdrawal symptoms, stage of addiction,[19] smoking latency,[22] and adverse events. Data collection continued as scheduled if participants discontinued study treatments.

Statistical analysis

A sample size of 657 (292 in the nicotine e-cigarettes group, 292 in the patches group, 73 in the placebo

	Nicotine e-cigarettes (n=289)	Patches (n=295)	Placebo e-cigarettes (n=73)
Age (years)	43·6 (12·7)	40·4 (13·0)	43·2 (12·4)
Women	178 (62%)	182 (62%)	45 (62%)
Ethnicity*			
New Zealand Māori	95 (33%)	95 (32%)	23 (32%)
Non-Māori	194 (67%)	200 (68%)	50 (68%)
Education below year 12† or no qualification	150 (52%)	123 (42%)	38 (52%)
Average number of cigarettes (including RYO) smoked per day	18·4 (7·2)	17·6 (6·0)	17·7 (5·6)
Age started smoking (years)	15·6 (4·7)	15·2 (3·8)	15·7 (5·1)
Number of years smoking continuously	25·9 (13·1)	23·5 (12·9)	24·8 (13·7)
Type of tobacco usually smoked			
Factory made only	167 (58%)	167 (57%)	47 (64%)
RYO only	92 (32%)	92 (31%)	21 (29%)
Both	30 (10%)	35 (12%)	5 (7%)
Lives with other smokers	151 (52%)	149 (51%)	42 (58%)
At least 1 quit attempt in past 12 months	158 (55%)	169 (57%)	39 (53%)
FTND score	5·6 (2·0)	5·5 (2·0)	5·5 (2·0)
FTND >5 (high dependence)	157 (54%)	162 (55%)	40 (55%)
GN-SBQ score	20·1 (7·9)	20·1 (8·4)	21·4 (8·6)
Self-efficacy to quit‡	3·7 (1·0)	3·7 (0·9)	3·6 (1·0)
AUTOS total score	22·6 (7·2)	23·1 (7·6)	23·4 (7·3)

Data are mean (SD) or n (%). RYO=roll your own (loose tobacco) cigarettes. FTND=Fagerström test of nicotine dependence. GN-SBQ: Glover-Nilsson smoking behavioural questionnaire. AUTOS=autonomy over smoking scale; higher scores indicate greater dependence. *All non-Māori ethnicity categories aggregated as non-Māori.[25] †Age 16 or 17 years. ‡Self-efficacy to quit=belief in ability to quit this time, measured on scale of 1 to 5, 1=very low, 5=very high.

Table 1: **Baseline characteristics of participants**

	Nicotine e-cigarettes (n=289)	Patches (n=295)	Difference χ^2 p value	Relative risk (95% CI)	Risk difference (95% CI)
Continuous abstinence					
1 month	67 (23·2%)	47 (15·9%)	0·03	1·46 (1·04 to 2·04)	7·25 (0·84 to 13·66)
3 months	38 (13·1%)	27 (9·2%)	0·12	1·44 (0·90 to 2·33)	4·00 (–1·10 to 9·10)
6 months (primary outcome)	21 (7·3%)	17 (5·8%)	0·46	1·26 (0·68 to 2·34)	1·51 (–2·49 to 5·51)
Sensitivity analyses for 6 months continuous abstinence data					
Complete case analysis*	21/241 (8·7%)	17/215 (7·9%)	0·76	1·10 (0·60 to 2·03)	0·80 (–4·27 to 5·87)
Per-protocol analysis 1†	21/231 (9·1%)	15/207 (7·2%)	0·48	1·25 (0·66 to 2·37)	1·84 (–3·28 to 6·96)
Per-protocol analysis 2‡	20/211 (9·5%)	13/151 (8·6%)	0·78	1·10 (0·57 to 2·14)	0·87 (–5·10 to 6·84)
Per-protocol analysis 3§	12/147 (8·2%)	12/138 (8·7%)	0·87	0·94 (0·44 to 2·02)	–0·54 (–7·00 to 5·92)
Including not biochemically verified¶	30 (10·4%)	21 (7·1%)	0·16	1·46 (0·86 to 2·49)	3·26 (–1·32 to 7·84)
Repeated measures analysis‖					
Overall treatment effect	..	..	0·05	1·61 (1·00 to 2·57)	..
1 month effect	..	..	0·004	1·87 (1·23 to 2·85)	..
3 months effect	..	..	0·12	1·52 (0·89 to 2·58)	..
6 months effect	..	..	0·21	1·46 (0·81 to 2·62)	..
7 day point prevalence abstinence					
1 month	69 (23·9%)	51 (17·3%)	0·05	1·38 (1·00 to 1·91)	6·59 (0·05 to 13·13)
3 months	62 (21·5%)	50 (17·0%)	0·17	1·27 (0·91 to 1·77)	4·50 (–1·88 to 10·88)
6 months	61 (21·1%)	46 (15·6%)	0·09	1·35 (0·96 to 1·91)	5·52 (–0·75 to 11·79)

All analyses are intention to treat unless otherwise specified (assumes participants with missing smoking status were smoking). Data are n (%) or n/N (%) unless otherwise specified. *Complete case analysis: excludes 128 participants with missing 6 month visits (withdrawn or lost to follow-up; 48 in nicotine e-cigarettes group and 80 in patches group), and includes 456 participants (241 in nicotine e-cigarettes group and 215 in patches group). †Per-protocol analysis 1: excludes protocol violations: pregnancy, death, quitters who did not have biochemical verification, undisclosed medication ineligibility, withdrew, and lost to follow-up at 6 months. ‡Per-protocol analysis 2: excludes protocol violations from per-protocol analysis 1 plus: cross-overs, use of other or combined nicotine replacement therapy products, and use of non-nicotine replacement therapy (eg, varenicline). §Per-protocol analysis 3: excludes protocol violations from per-protocol analysis 2 plus: participants still using product to which they were randomised at 6 months. ¶Continuous abstinence including not biochemically verified: eight participants in nicotine e-cigarettes group: one moved, two refused, four did not attend appointment, one adverse event (birth) did not want to attend; four participants in patches group: one moved, three refused. ‖Output for repeated measures analysis is difference in least squares means, not relative risk.

Table 2: **Continuous smoking abstinence and 7 day point prevalence, nicotine e-cigarettes versus patches**

e-cigarettes group) conferred 80% power, with two-sided p=0·05, to detect an absolute difference of 10% in quit rates between the nicotine e-cigarettes group and patches group (1:1 ratio), and a 15% difference between the nicotine e-cigarettes group and placebo e-cigarettes group (4:1 ratio), with expected quit rates of 15% in the placebo e-cigarettes group and 20% in the patches group (based on meta-analyses of NRT trials).[23] We used SAS (version 9·3) for analyses. The primary analyses used the intention-to-treat approach (participants with unknown smoking status were assumed to be smoking). We calculated quit rates, relative risks (RR), and absolute risks for nicotine e-cigarettes versus patches, and for nicotine e-cigarettes versus placebo e-cigarettes. We compared treatment groups using χ^2 tests, with multivariate regression adjusting for other variables as appropriate. The proportions of participants with significantly reduced smoking consumption of at least 25% and 50% were calculated using the same methods. Change from baseline in each of the repeated AUTOS measures and cigarettes smoked per day (in non-abstainers) were analysed using mixed models with a compound symmetry covariance structure including baseline values. We also did per-protocol analyses for the primary outcome, in which participants with major protocol violations (eg, cross-over treatments, withdrawals, and loss to follow-up) were excluded. We assessed consistency of effects for pre-specified subgroups (men *vs* women, ethnicity [Māori *vs* non-Māori]) using tests for heterogeneity. Secondary analyses were done with overall cessation rates corrected for discordance between reported and verified cessation. We used Kaplan-Meier curves and the log-rank test for analyses of time to relapse. Adverse events were defined according to international guidelines, categorised by CB (masked to intervention product) as related or unrelated to the intervention, and analysed as serious or non-serious, by treatment group and association with study treatment, in line with recommended best practice.[24]

This trial is registered with the Australian New Zealand Clinical Trials Registry, number ACTRN12610000866000.

Role of the funding source

The sponsor of the study had no role in study design, data collection, data analysis, data interpretation, or

	Nicotine e-cigarettes (n=289)	Placebo e-cigarettes (n=73)	Difference Fisher's exact p value	Relative risk (95% CI)	Risk difference (95% CI)
Continuous abstinence					
1 month*	67 (23·2%)	12 (16·4%)	0·21	1·41 (0·81 to 2·46)	6·74 (–3·06 to 16·54)
3 months*	38 (13·1%)	5 (6·8%)	0·14	1·92 (0·78 to 4·70)	6·30 (–0·68 to 13·28)
6 months (primary outcome)	21 (7·3%)	3 (4·1%)	0·44	1·77 (0·54 to 5·77)	3·16 (–2·29 to 8·61)
Sensitivity analyses for 6 months continuous abstinence data					
Complete case analysis†	21/241 (8·7%)	3/57 (5·3%)	0·59	1·66 (0·51 to 5·36)	3·45 (–3·35 to 10·25)
Per-protocol analysis 1‡	21/231 (9·1%)	3/54 (5·6%)	0·59	1·64 (0·51 to 5·29)	3·53 (–3·62 to 10·68)
Per-protocol analysis 2§	20/211 (9·5%)	2/46 (4·3%)	0·36	2·18 (0·53 to 9·00)	5·13 (–1·97 to 12·23)
Per-protocol analysis 3¶	12/147 (8·2%)	1/30 (3·3%)	0·70	2·45 (0·33 to 18·13)	4·83 (–2·97 to 12·63)
Including not biochemically verified‖	30 (10·4%)	4 (5·5%)	0·26	1·89 (0·69 to 5·21)	4·90 (–1·39 to 11·20)
Repeated measures analysis**					
Overall treatment effect	..	..	0·13	1·91 (0·83 to 4·37)	..
1 month effect	..	..	0·09	1·80 (0·90 to 3·61)	..
3 months effect	..	..	0·16	2·00 (0·76 to 5·28)	..
6 months effect	..	..	0·23	1·92 (0·65 to 5·66)	..
7 day point prevalence abstinence					
1 month*	69 (23·9%)	12 (16·4%)	0·17	1·45 (0·83 to 2·53)	7·44 (–2·38 to 17·26)
3 months*	62 (21·5%)	12 (16·4%)	0·34	1·31 (0·74 to 2·29)	5·01 (–4·72 to 14·74)
6 months*	61 (21·1%)	16 (21·9%)	0·88	0·96 (0·59 to 1·57)	–0·81 (–11·40 to 9·78)

All analyses are intention to treat unless otherwise specified (assumes all participants with missing smoking status were smoking). Data are n (%) or n/N (%) unless otherwise specified. *Difference from χ^2 test. †Complete case analysis: excludes 64 participants with missing 6 month visits (withdrawn or lost to follow-up; 48 in nicotine e-cigarettes group and 16 in placebo e-cigarettes group) and includes 298 (241 in nicotine e-cigarettes group and 57 in placebo e-cigarettes group). ‡Per-protocol analysis 1: excludes protocol violations: pregnancy, death, quitters who did not have biochemical verification at 6 months, undisclosed medication ineligibility, withdrew, and lost to follow-up at 6 months. §Per-protocol analysis 2: excludes protocol violations from per-protocol analysis 1 plus: cross-overs, use of other or combined nicotine replacement therapy products, and use of non-nicotine replacement therapy (eg, varenicline). ¶Per-protocol analysis 3: excludes protocol violations from per-protocol analysis 2 plus: participants still using product to which they were randomised at 6 months. ‖Continuous abstinence including not biochemically verified: eight participants in nicotine e-cigarettes group who reported quitting did not attend for biochemical verification (one moved, two refused, four did not attend appointment, one adverse event [birth] did not want to attend); one participant in the placebo e-cigarettes group did not attend appointment. **Output for repeated measures analysis is difference in least squares means (not relative risk).

Table 3: **Continuous abstinence and 7 day point prevalence, nicotine e-cigarettes versus placebo e-cigarettes**

writing of the report. The corresponding author had full access to all the data in the study and had final responsibility for the decision to submit for publication.

Results

Of 1293 people who were assessed, 657 were eligible for inclusion in the study (figure 1). 289 people were assigned to nicotine e-cigarettes, 295 to patches, and 73 to placebo e-cigarettes. Participants' baseline characteristics were evenly balanced between treatment groups (table 1). Overall, loss to follow-up was 22%: 17% (48 of 289) in the nicotine e-cigarettes group, 27% (80 of 295) in the patches group, and 22% (16 of 73) in placebo e-cigarettes group.

Verified continuous abstinence at 6 months after quit day was highest in the nicotine e-cigarettes group (7·3%), followed by the patches group (5·8%), and placebo e-cigarettes group (4·1%; tables 2, 3). Achievement of abstinence was substantially lower than we anticipated, thus we had insufficient statistical power to conclude superiority of nicotine e-cigarettes to patches or to placebo e-cigarettes. 7 day point prevalence abstinence was closer to our estimate of 20%, and the RR suggested

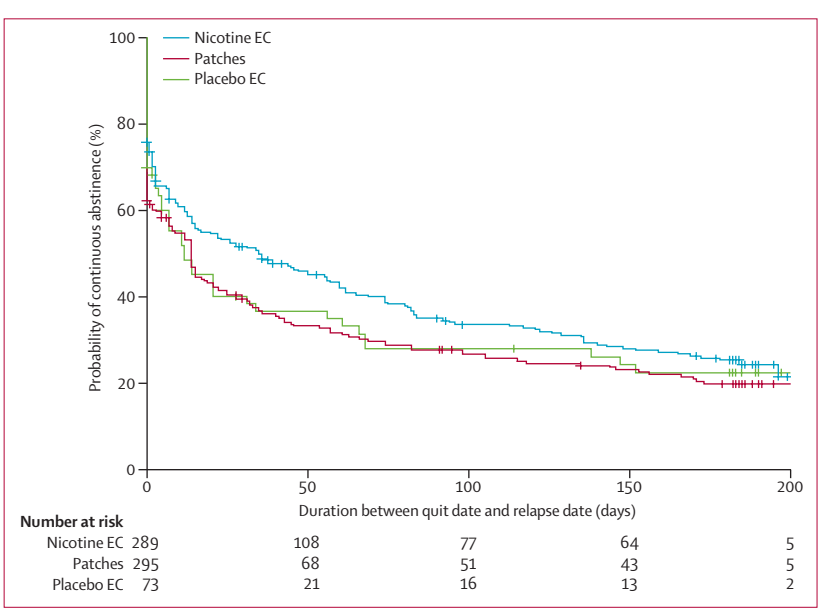

Figure 2: **Kaplan-Meier analysis of time to relapse**
EC=e-cigarettes.

a difference in favour of nicotine e-cigarettes, but was not significant at 6 months. Repeated measures analyses at 1 month and overall also showed a benefit of nicotine e-cigarettes compared with patches (table 2). However, both the point prevalence and repeated measures analyses used self-reported cessation. Subgroup analyses stratified by sex or ethnicity showed no significant differences in primary outcome (data not shown).

Quit rates were initially high then decreased in all groups (figure 2). Most participants relapsed within 50 days. Among those who relapsed, median time to relapse in the nicotine e-cigarettes group was 35 days (95% CI 15–56), more than twice as long as in the patches group (14 days, 95% CI 8–18, p<0·0001) or placebo e-cigarettes group (12 days, 5–34, p=0·09). Mean cigarette consumption decreased by two cigarettes per day more in the nicotine e-cigarettes group than the patches group (p=0·002; table 4). In the nicotine e-cigarettes group, 57% of participants reduced daily cigarettes by at least half at 6 months—a significantly greater proportion than in the patches group (41%; p=0·0002) and non-significantly higher than in the placebo e-cigarettes group (45%; p=0·08).

Over 6 months, AUTOS scores in the e-cigarettes groups halved from baseline compared with a decrease of a third in the patches group (data not shown). The difference between the nicotine e-cigarettes group and patches group in total AUTOS score reduction from baseline to 6 months was significant (1·56, p=0·02), but the difference between the nicotine e-cigarettes group and placebo e-cigarettes group was not significant (1·34, p=0·19). Behavioural dependence, as measured by GN-SBQ, was balanced at baseline, with 36% (105 of 289) of participants in the nicotine e-cigarettes group, 37% (109 of 295) in the patches group, and 42% (31 of 73) in the placebo group scoring "strong" or "very strong" dependence, but we identified no association between score and outcome (data not shown).

A higher number and proportion of adverse events occurred in the nicotine e-cigarettes group than in the patches group (table 5); however, we identified no evidence of an association with study product, and the event rate was not significantly different (incidence rate ratio for nicotine e-cigarettes *vs* patches 1·05, 95% CI 0·82–1·34, p=0·7).

Adherence to study treatments was significantly higher in the nicotine e-cigarettes group compared with the patches group (p<0·0001 at each follow-up assessment) and with the placebo e-cigarettes group (p<0·0001 at each follow-up assessment): at 1 month post quit day, 78% (203 of 260) of participants in the nicotine e-cigarettes group and 82% (51 of 62) of those in the placebo e-cigarettes group were using the allocated product, compared with 46% (107 of 232) of those allocated to patches. By 3 months, 51% (126 of 245) participants in the nicotine e-cigarettes group and 53% (31 of 59) of those in the placebo e-cigarettes group were still using allocated treatments, compared with only 18% (40 of 224) of those in the patches group; at 6 months, 29% (71 of 241) of the nicotine e-cigarettes group and 35% (20 of 57) of the placebo e-cigarettes group persisted with e-cigarette use, with only 8% (17 of 215) of those in the patches group still using patches. Among those in the nicotine e-cigarettes group verified as abstinent, 38% (eight of 21) still used e-cigarettes at 6 months; among non-quitters, 29% (63 of 220) still used e-cigarettes (whether nicotine e-cigarettes or placebo e-cigarettes is unclear). Since average daily use was low, some participants could have been using cartridges allocated at randomisation, others might have purchased cartridges online. Participants using nicotine e-cigarettes reported having used an average of 1·3 cartridges per day at 1 month, 1·1 per day at 3 months, and 0·7 per day at 6 months; in the placebo group participants reported using 1·1 cartridges per day at 1 month, 1·2 per day at 3 months, and 0·7 per day at 6 months. Nicotine patches were used as instructed (an average of one per day). Few participants used other cessation products: at 6 months, in both the nicotine

	Nicotine e-cigarettes		Patches		Difference (nicotine e-cigarettes–patches)		
	Mean	SE	Mean	SE	Mean	SE	p value
Overall	11·1	0·4	9·1	0·4	2·0	0·5	<0·0001
1 month	12·9	0·4	10·5	0·4	2·4	0·6	<0·0001
3 months	10·8	0·4	9·1	0·4	1·7	0·6	0·006
6 months	9·7	0·4	7·7	0·4	1·9	0·6	0·002

*For those reporting smoking at least one cigarette in past 7 days.

Table 4: **Change from baseline in cigarettes consumed per day during follow-up period, nicotine e-cigarettes and patches***

	Nicotine e-cigarettes		Patches		Placebo e-cigarettes	
	N	%	N	%	N	%
Total	137	100%	119	100%	36	100%
Event type						
Serious*	27	19·7%	14	11·8%	5	13·9%
Any non-serious event	110	80·3%	105	88·2%	31	86·1%
Relation to study treatment						
Definitely	0		1	0·8%	0	
Probably	1	0·7%	1	0·8%	1	2·8%
Possibly	5	3·6%	4	3·4%	1	2·8%
Unrelated	131	95·6%	113	95·0%	34	94·4%

107 participants in the nicotine e-cigarettes group had a total of 137 events. 96 participants in the patches group had a total of 119 events. 26 participants in the placebo group had a total of 36 events. Event rate was 0·8 events per person month in nicotine e-cigarettes group and patches group, and 0·9 in placebo e-cigarettes group. The difference between the rates in the nicotine e-cigarettes group and patches group were not significant (incidence rate ratio 1·05, 95% CI 0·82–1·34, p=0·7). *Serious adverse event by convention includes: death (n=1, in nicotine e-cigarettes group), life threatening illness (n=1, in nicotine e-cigarettes group), admission to hospital or prolongation of hospital stay (12% of all events in nicotine e-cigarettes group, 8% in patches group, and 11% in placebo e-cigarettes group), persistent or significant disability or incapacity, congenital abnormality, medically important (6% of all events in nicotine e-cigarettes group, 4% in patches group, and 3% placebo e-cigarettes group). No serious adverse events in any groups were related to product use.

Table 5: **Adverse events by type (serious or non-serious) and relation to study treatment**

e-cigarettes group and patches group, two participants had used bupropion and five had used varenicline in the past month; in the placebo e-cigarettes group, three participants reported using varenicline.

Quitline support was accessed by fewer than half of participants: 40% (115 of 289) in the nicotine e-cigarettes group, 36% (106 of 295) in the patches group, and 36% (26 of 73) in the placebo e-cigarettes groups, but a post-hoc analysis showed no benefit of use of support on the primary outcome for participants in the nicotine e-cigarettes group (p=0·67) or patches group (p=0·16).

There was sustained enthusiasm for e-cigarettes: at 1 month, 88% (230 of 260) of participants in the nicotine e-cigarettes group, and 92% (57 of 62) in the placebo e-cigarettes group stated that they would recommend their allocated product to a friend wanting to quit, compared with 56% (130 of 232) of those in the patches group; at 6 months the figures changed little, being 85% (205 of 241), 88% (50 of 57), and 50% (107 of 215), respectively. Among participants allocated to e-cigarettes, 40% (96 of 241) liked their tactile, cigarette-like qualities, sensory familiarity, perceived health benefits, taste, absence of cigarette odour, and ease of use.

Discussion

13 weeks of nicotine e-cigarette use resulted in increased smoking abstinence at 6 months compared with use of patches or placebo e-cigarettes, but these differences were not statistically significant. Nevertheless, the results were consistent across a range of analyses, and the 95% CIs do not exclude an advantage. In post-hoc analyses using a 5% non-inferiority limit for the risk difference (on the basis of a margin used in our non-inferiority smoking cessation trial of cytisine[26]), nicotine e-cigarettes were at least as effective as patches (the absolute risk difference for the primary outcome was 1·51 [95% CI –2·49 to 5·51]; –2·49 is within the margin of –5). Therefore, we conclude that among smokers wanting to quit, nicotine e-cigarettes might be as effective as patches for achieving cessation at 6 months. We identified no difference in adverse events with e-cigarettes compared with patches.

The strengths of our study include use of a conservative primary outcome measure, and rigorous trial conduct to mitigate risk of bias. We used a pragmatic design because we believe that an assessment of real-world effectiveness of e-cigarettes is a priority for policy development, although it could be argued a trial of a novel intervention should be more explanatory than pragmatic in design. Our study had several limitations. First, the effect size and estimates of abstinence on which the study sample size was calculated were optimistic; hence, statistical power to detect differences was reduced. Second, participants assigned to patches had a higher loss to follow-up and withdrawal rate than those assigned to e-cigarettes. Some of the participants might have agreed to take part in the study to try e-cigarettes, and then lost interest when randomised to patches. Those who reported previously trying to quit with patches or other forms of NRT (about 20% in the past year in each group) might have disadvantaged patches (by being more likely to give up on patches subsequently); however, at 6 months the difference between the results of the intention-to-treat analysis and per-protocol analysis was minimal, suggesting this bias was not a major issue.

Third, the modest abstinence rate for nicotine e-cigarettes is much the same as quit rates shown in studies of NRT products used without behavioural support.[27] Addition of more intensive support might have improved quit rates, but it would also have misrepresented the typically low support environment in which most e-cigarette users attempt to quit. The modest abstinence rates might have been compounded by inadequate nicotine replacement: as noted, the cartridges contained less nicotine than labelled, and delivery was inefficient (not uncommon in other early e-cigarette models[15,28]). Furthermore, users consumed on average just over one cartridge per day, delivering around only 20% of the nicotine obtained from cigarette smoking.[29] Although trials of the effects of early e-cigarettes on withdrawal relief showed that low levels of nicotine delivery attenuated withdrawal symptoms,[7,8] improved nicotine delivery by newer models of e-cigarettes provides greater withdrawal relief,

Panel: Research in context

Systematic review

We searched Medline, PsycINFO, CINAHL, Embase, and the Cochrane library using the terms "e-cig*" OR "elect* cigar*" OR "electronic nicotine", for reports published between Jan 1, 2005, and Aug 23, 2013. The strategy identified 186 articles, of which only one was a randomised, placebo-controlled trial with a cessation endpoint measured at 6 months or more.[9] This previous trial,[9] done between 2011 and 2012, recruited 300 adult Italian smokers unwilling to quit, with 100 randomised to each of three groups: 7·2 mg nicotine cartridges for 12 weeks, 6 weeks of 7·2 mg cartridges followed by 6 weeks of 5·4 mg cartridges, and 0 mg nicotine cartridges for 12 weeks. No behavioural support was provided but nine follow-up visits occurred, with carbon monoxide measures at each. The primary outcome was not clearly prespecified nor were calculations done to estimate power. Analysis was by intention to treat. At 12 months, 39% of participants had been lost to follow-up, a potential source of bias. Of those assessed, 9% had quit (13%, 9%, and 4% in the two nicotine e-cigarettes groups and placebo e-cigarettes groups, respectively) and reduction occurred in 10%, 9%, and 12%; none of the comparisons were statistically significant. The reliability of e-cigarettes was problematic. These results are much the same as those reported in previous trials of unsupported pharmacotherapy with patches[32] and are similar to our trial findings.

Interpretation

In our study, e-cigarettes, with or without nicotine, were modestly effective at helping smokers to quit. Nicotine e-cigarettes might be more effective or of similar effectiveness to patches, but so far studies have not had sufficient statistical power to draw more definitive conclusions. E-cigarette use was associated with few adverse events, similar to patches, but longer-term data are needed. Uncertainty exists about the place of e-cigarettes in tobacco control, and more research is urgently needed to clearly establish their overall benefits and harms at both individual and population levels.

potentially enhancing cessation effectiveness.[8] Trials of such second generation e-cigarettes are needed.

We included the placebo e-cigarettes group to explore the role of behavioural replacement by e-cigarettes, independent of nicotine delivery in cessation.[30] However, our study was underpowered to detect the small effect, and the GN-SBQ instrument, which purports to measure behavioural dependence but has not been widely used in this context, might have been inadequate for this purpose.

A third of the participants allocated to the e-cigarettes groups reported continued product use at 6 months, suggesting that they might have become long-term e-cigarette users. Those who had relapsed to smoking but continued to use e-cigarettes (so called dual use) at 6 months had reduced cigarette consumption. Research has shown higher cessation rates in people using NRT while still smoking;[31] if e-cigarettes act in the same way this would be a positive feature. Further research is needed to explore this area.

Finally, as far as we are aware, our trial provides for the first time adverse event information for 657 people randomly allocated to e-cigarettes or patches. The finding of no significant differences in occurrence of adverse events between groups over the duration of a standard NRT treatment course, and the further 3 months' monitoring, suggests such short-term e-cigarette use is of low risk. However, longer-term use requires more research (panel).

Our study has established benchmarks for performance of nicotine e-cigarettes relative to NRT and placebo e-cigarettes with which to design future, more adequately powered trials. Our findings point to potential for e-cigarettes in regard to cessation effectiveness beyond that noted in the present study. Furthermore, because they have far greater reach[1,2] and higher acceptability (as shown by the present study) among smokers than NRT, and seem to have no greater risk of adverse effects, e-cigarettes also have potential for improving population health.

Contributors

CB, NW, HM, and ML conceived the original idea for the trial, and sought and obtained funding. CB, NW, HM, ML, CH, VP, and JW wrote the study protocol. CH managed the day-to-day running of the trial, including all participant follow-up. VP did the data analyses. This Article was written by CB with input from all coauthors. CB is guarantor for this Article. All authors read and approved the final version.

Conflicts of interest

We declare that we have received no support from any companies for the submitted work and have no non-financial interests that might be relevant to the submitted work. ML, via his company Health New Zealand, previously did research funded by Ruyan (an e-cigarette manufacturer). CB and HM have done research on Ruyan e-cigarettes funded by Health New Zealand, independently of Ruyan. HM has received honoraria for speaking at research symposia, has received benefits in kind and travel support from, and has provided consultancy to, the manufacturers of smoking cessation drugs. NW has provided consultancy to the manufacturers of smoking cessation drugs, received honoraria for speaking at a research meeting and received benefits in kind and travel support from a manufacturer of smoking cessation drugs. JW has provided consultancy to the manufacturers of smoking cessation medications.

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[13] *UNI EN 1076:1999, Tubi di assorbimento mediante pompaggio per la determinazione di gas e vapori. Requisiti e metodi di prova / Absorbtion tubes by pumping for the determination of gas and vapors Requirements and test methods.*

[14] *UNI EN 1232:1999, Atmosfera nell'ambiente di lavoro. Pompe per il campionamento personale di agenti chimici. Requisiti e metodi di prova / Atmosphere in the workplace. Pumps for personal sampling of chemical agents Requirements and test methods.*

[15] *UNI EN 12619/135226, Determinazione carbonio organico totale (COT) (metodo continuo con rivelatore a ionizzazione di fiamma FID). L'utilizzo della norma UNI 12619/13526 é stato effettuato al semplice scopo di dare una valutazione sommaria dell'immissione di sostanze organiche totali in ambiente. / Determination of Total Organic Carbon (TOC) (continuous method with flame ionization detector FID). The standard UNI 12619/13526 has been used simply to give a rough estimate of the release of organic substances in the environment.*

[16] *UNI EN 13649:2002, Determinazione della concentrazione in massa di singoli composti organici in forma gassosa. Metodo mediante carboni attivi e desorbimento con solvente. / Determination of the mass concentration of each organic compound in gaseous form. Method by means of active carbons and desorption through the solvent.*

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From: mailinglist@capitol.hawaii.gov
To: HTHTestimony
Cc: vinkim@gmail.com
Subject: *Submitted testimony for SB2495 on Feb 7, 2014 09:00AM*
Date: Wednesday, February 05, 2014 12:10:45 AM

SB2495
Submitted on: 2/5/2014
Testimony for HTH/CPN on Feb 7, 2014 09:00AM in Conference Room 229

Submitted By	Organization	Testifier Position	Present at Hearing
Vin Kim	Business	Oppose	No

Comments:

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From: monkey0550
To: HTHTestimony
Subject: I oppose hb2079&sb2495, hb2321&sb2871
Date: Wednesday, February 05, 2014 1:01:45 PM

From my Android phone on T-Mobile. The first nationwide 4G network.

From: mailinglist@capitol.hawaii.gov
To: HTHTestimony
Cc: mendezj@hawaii.edu
Subject: *Submitted testimony for SB2495 on Feb 7, 2014 09:00AM*
Date: Tuesday, February 04, 2014 2:13:35 PM

SB2495
Submitted on: 2/4/2014
Testimony for HTH/CPN on Feb 7, 2014 09:00AM in Conference Room 229

Submitted By	Organization	Testifier Position	Present at Hearing
Javier Mendez-Alvarez	Individual	Support	No

Comments:

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From: mailinglist@capitol.hawaii.gov
To: HTHTestimony
Cc: josephsarabia18@yahoo.com
Subject: Submitted testimony for SB2495 on Feb 7, 2014 09:00AM
Date: Wednesday, February 05, 2014 11:27:01 AM

SB2495
Submitted on: 2/5/2014
Testimony for HTH/CPN on Feb 7, 2014 09:00AM in Conference Room 229

Submitted By	Organization	Testifier Position	Present at Hearing
Joseph Sarabia	Individual	Oppose	No

Comments: this bill contains no facts. electronic cigarettes are nowhere near categorized with tobacco products. i have been using electronic cigarettes for about 7 months now and im amazed and satisfied with the results. it helped me stop smoking cigarettes which in terms also helped prolong my health and life. the option of choosing different "nicotine" levels allows me as well as other elctronic cigarette users to taper off of nicotine in general. the fact stands that there is not 4,000 different chemicals entering my body, its just what the tobacco companies got me hooked on in the first place, the "nicotine."

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From: mailinglist@capitol.hawaii.gov
To: HTHTestimony
Cc: tmichel67@gmail.com
Subject: Submitted testimony for SB2495 on Feb 7, 2014 09:00AM
Date: Tuesday, February 04, 2014 11:19:07 PM

SB2495
Submitted on: 2/4/2014
Testimony for HTH/CPN on Feb 7, 2014 09:00AM in Conference Room 229

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

Comments: Members of the committee, Enacting Bill 2495 would effectively stunt the growth of new businesses in Hawaii along with forcing those who wish to use Personal Nicotine Delivery Devices "E-Cigarettes" to go to a Tobacco purveyor, a place most of us ex-smokers try to avoid, to get their products. I was a 2 PAD smoker for 35 plus years and have only succeeded in quitting smoking for more than a week one time. After ten days, at the first sign of major stress, I was right back on them. With my personal nicotine delivery device I have been smoke free for almost 6 months. A major achievement in my book and I feel better every day without them. But, if I would have had to visit a Tobacco store to get my supplies I am almost positive I would have stepped right back to Cigarettes in the beginning. It was having a place that didn't remind me of smoking, and people that were like minded in these shops, that gave me the support I needed to make it stick. This bill would shut down all of these businesses. In essence it would make it harder for most, impossible for some, to quit smoking. In the same vein it would make it easier to smoke. Therefore, you are assisting people in doing something that we all agree is detrimental to your health. On the other hand, there is absolutely no evidence that the use, or second hand inhalation, of the vapor these devices produce is a health risk at all. On the contrary, one of the main ingredients in this vapor is used in the majority of hospitals in the US for air quality, and has been for over fifty years. Until we have more evidence to go on I would urge you to be cautious when lumping these devices in the same category as Cigarettes. They are as much a cigarette as a bicycle is a car. Please educate yourselves on this issue and wait to pass judgement until some concrete information is available. If you need resources for your further research I would be happy to assist you with some links to reputable sources and documents. Thank you for your time

From: mailinglist@capitol.hawaii.gov
To: HTHTestimony
Cc: kmarushige@youngsmarket.com
Subject: *Submitted testimony for SB2495 on Feb 7, 2014 09:00AM*
Date: Tuesday, February 04, 2014 8:55:28 PM

SB2495
Submitted on: 2/4/2014
Testimony for HTH/CPN on Feb 7, 2014 09:00AM in Conference Room 229

Submitted By	Organization	Testifier Position	Present at Hearing
Kevin	Individual	Oppose	No

Comments:

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From: mailinglist@capitol.hawaii.gov
To: HTHTestimony
Cc: a.sunshiine@gmail.com
Subject: *Submitted testimony for SB2495 on Feb 7, 2014 09:00AM*
Date: Wednesday, February 05, 2014 12:25:11 AM

SB2495
Submitted on: 2/5/2014
Testimony for HTH/CPN on Feb 7, 2014 09:00AM in Conference Room 229

Submitted By	Organization	Testifier Position	Present at Hearing
Anya	Individual	Oppose	No

Comments:

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From: mailinglist@capitol.hawaii.gov
To: HTHTestimony
Cc: 1hawaii4me@gmail.com
Subject: *Submitted testimony for SB2495 on Feb 7, 2014 09:00AM*
Date: Tuesday, February 04, 2014 8:23:20 PM

SB2495
Submitted on: 2/4/2014
Testimony for HTH/CPN on Feb 7, 2014 09:00AM in Conference Room 229

Submitted By	Organization	Testifier Position	Present at Hearing
Mark Dietrich	Individual	Oppose	No

Comments:

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From: Chev
To: HTHTestimony
Subject: SB 2572 SB 2495
Date: Thursday, February 06, 2014 12:21:17 AM

Aloha,
My name is Chevys Ishikawa, this email is just to notify you folks that I would like to speak on behalf of our community at this Fridays hearing to oppose these two bills.

Any additional information is greatly appreciated!

-Chev

Sent from my iPhone

From: mailinglist@capitol.hawaii.gov
To: HTHTestimony
Cc: teresa.parsons@hawaii.edu
Subject: Submitted testimony for SB2495 on Feb 7, 2014 09:00AM
Date: Tuesday, February 04, 2014 11:02:23 PM

SB2495
Submitted on: 2/4/2014
Testimony for HTH/CPN on Feb 7, 2014 09:00AM in Conference Room 229

Submitted By	Organization	Testifier Position	Present at Hearing
Teresa Parsons	Individual	Support	No

Comments: Senators, Mahalo for launching this important slate of bills to address the growing misuse of the public through the sale, distribution, and marketing of e-cigarettes. These nicotine delivery devices contain similar toxic substances as cigarettes and other tobacco products. Using slick advertising to hide the dangers of this product must be countered by swift and effective legislation. I STRONGLY SUPPORT this measure to require those who sell electronic nicotine devices to conform to all the requirements of tobacco retailers and restrict the advertisement and display of these products to ensure children are not allowed to obtain these dangerous items. Mahalo for the opportunity to testify in SUPPORT of this measure.

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From: Kenneth Johnson
To: HTHTestimony; HLTtestimony; JUDtestimony
Subject: HB2079 & SB2495 & SB2212
Date: Thursday, February 06, 2014 4:46:02 AM

Good Morning,
I would like to spend the first part of my morning telling you about myself, my history, some factual studies as well as discuss the above Bills. Before I continue I would like to thank you in advance for allowing me to contact you on these matters.

I started smoking when I was 13 years old. I have tried many times and many approved methods to stop smoking. ALL have failed me and one even caused me a hospital stay and close to an assault charge. (Chantix). Jan 2nd 2014 I was given an e-cig called and Ego. I tried it and dropped my smoking habit that day. I went from 2 1/2 packs of cigs a day to not one in over a month. I am not alone in this as I am sure you will get other mails to support me on this. I am very active and passionate in my activism for e-cigs, due to the fact it has gotten me off the cancer causing tobacco products. I am not sure if you are familiar with the new peer study that has been done on e-cigs. This is the most current and up to date study there is out there. I have noticed that most Bills are being made up using the FDA study that was done in 1999. That is a 5 year old study that used products that were no longer on the shelves because the e-cig community does regulate itself and we watch closely what is being done to make this a safer comunity. Also if I am not mistaken the e-juices they tested were all from other countries. One of the biggest concern was propylene glycol, an ingredient IN Radiator Fluid. Just because it is an ingredient of one toxic substance does not make that ingredient toxic. Case in point.... there is water in radiator fluid as well. Should we ban water then? Here is a link to the peer study. Please take the time to read this is consider this peer study.

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

Here are my issues with the current bills that I have.

HB2079 & SB2495

(3) Specify that electronic smoking devices may only be sold where cigarettes and other tobacco products are sold by limiting the retail sale of electronic smoking devices to those retailers who also hold a retail tobacco permit;

Why? People who use the e-cigs are trying to change their life style by getting away from cigarettes. Why make them go to a place to be tempted to smoke again. Also why force someone who believes cigs are dangerous and need to be eliminated sell the product the oppose.

(4) Specify that the revenue from the electronic smoking device license fees shall be used to support smoking cessation programs in the State

The only method that most vapers have tried have failed us miserably. Most of us believe that vaping is the only method that has worked for us. Are you willing to put that on the approved

list?

(5) Amend Hawaii's anti-smoking statute to prohibit the use of electronic smoking devices in places open to the public and places of employment; and

Sampling is a big method used in getting people to switch over from cancer causing cigs to vaping. I know store owners who have allowed new customers come in and sample a product. Before they left they threw their packs of cigs away, right there in the store. I believe this should be amended to allow in Vape shops.

(6) Further clarify that the sale, distribution, or display of electronic smoking devices is restricted in the same manner as cigarettes and other tobacco products.

The majority of vapers believe age restrictions should be in place.

SB2212

Ok this one makes no sense to me. We are trying to break the habit of smoking tobacco, but you want us to only be able to buy tobacco flavored e juice, menthol or mint. I am sorry but that is like telling an alcoholic "Congrats on not drinking any more. But you can now only drink things that taste like beer, wine or alcohol." Please see the temptation factor you are putting on people who are attempting to break the chains that smoking has put on them. Please show the people that you support their decision to quit and not tempt them to return to cancer causing cigs.

Once again thank you so much for your time and consideration. If you have any questions for me I would be glad to answer them for you. If I do not have the answer I will sure look into it and come up with a well educated answer as well as state my sources for you to research as well.

Kenneth Johnson
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