AMERICAN LUNG ASSOCIATION®
IN CALIFORNIA

E-Cigarettes

October 2014

POSITION:
The American Lung Association:

- Supports including e-cigarettes in smokefree laws and ordinances.
- Supports state laws that would prohibit the sale of any flavored e-cigarette product.
- Supports taxing e-cigarettes at a rate equivalent with all tobacco products, including cigarettes.
- Supports eliminating e-cigarette sales to youth, otherwise restricting youth access to e-cigarettes and requiring e-cigarette retailers to be licensed. E-cigarettes should be defined as tobacco products.
- Opposes creating new definitions for "vapor products" and/or "alternative nicotine products" in state laws. This tactic, which the tobacco industry is promoting in numerous states, has the potential to undermine existing tobacco control laws, including smokefree laws and tobacco taxes.

Background

- On April 24, 2014, the U.S. Food and Drug Administration (FDA) issued its proposal to begin oversight over e-cigarettes as tobacco products. Comments were due to FDA on August 8, 2014. The American Lung Association has urged FDA to finalize this regulation by the end of 2014.
- According to the FDA, electronic cigarettes, or e-cigarettes, are devices that allow users to inhale a vapor containing nicotine or other substances.[1]
- Unlike traditional cigarettes, e-cigarettes are generally battery-operated and use an atomizer to heat liquid from a cartridge until it becomes a chemical-filled aerosol.
- E-cigarettes are often available in flavors that may appeal to children and teens, including cotton candy, bubble gum, chocolate, strawberry and mint.[2]
- There are almost 470 different brands of e-cigarettes on the market today, and e-cigarettes come in 7,700 different flavors.[3]
- The class of e-cigarettes also includes e-hookahs, e-pens, e-cigars and other electronic products, all of which would be subject to FDA oversight.

Who Uses E-Cigarettes?

- An increasing number of youth: According to CDC, the number of students in grades 6-12 reporting having ever used an e-cigarette doubled from 3.3 percent to 6.8 percent from 2011 to 2012. Recent use of e-cigarettes among students grades 6-12 increased from 1.1 percent to 2.1 percent.[4]
- Adults: According to CDC, during 2010 to 2013, adults reporting that they have ever used an e-cigarette increased among every demographic group except those aged 18-24 years old, Hispanics, non-Hispanic Others, and those living in the Midwest.[5]
- Former and current smokers: In 2013, close to one in ten former and more than one in three current cigarette smokers had used an e-cigarette, which was an increase compared to 2011 for both groups. E-cigarette use among those who never had smoked cigarettes was a much lower 1-2 percent and did not increase over this period.[6]
- Current smokers: From 2010-2011, 72.0 percent of people who recently used e-cigarettes also currently smoked conventional cigarettes. That number rose to 76.8 percent during 2012-2013.[7]
- Additional and on-going research is needed to understand the full public health impact of e-cigarettes, including their impact on youth initiation, and whether current smokers are switching to these products instead of quitting or are using them in conjunction with regular cigarettes.

What are the Health Effects of E-Cigarettes?

- The health consequences of the use of e-cigarettes and exposure to secondhand e-cigarette emissions are unknown. There is currently no scientific evidence establishing the safety of e-cigarettes.
- In initial lab tests conducted in 2009, FDA found detectable levels of toxic cancer-causing chemicals, including an ingredient used in anti-freeze, in two leading brands of e-cigarettes and 18 various cartridges.[8] The lab tests also found that cartridges labeled as nicotine-free had traceable levels of nicotine.
- There is no evidence that shows the aerosol emitted by e-cigarettes is safe for non-users to inhale. In fact, two initial studies have found formaldehyde, benzene and tobacco-specific nitrosamines (a carcinogen) coming from the secondhand emissions from e-cigarettes. The use of e-cigarettes in public places and workplaces may also complicate efforts to enforce and comply with smokefree laws. The American Lung Association supports including the use of e-cigarettes in worksites and public places under smokefree laws.

Can E-Cigarettes Help Someone Quit Smoking?

- The FDA has not approved any e-cigarettes as a safe or effective method to help smokers quit. The U.S. Public Health Service has found that the seven therapies approved by the U.S. Food and Drug Administration in combination with individual, group or phone cessation counseling is the most effective way to help smokers quit. Until and unless the FDA approves a specific e-cigarette for use as a tobacco cessation aid, the American Lung Association does not support any direct or implied claims that e-cigarettes help smokers quit.
- A 2014 study published in the journal *Cancer* found that among cancer patients enrolled in a smoking cessation program, e-cigarette users were as likely or less likely as individuals who did not use e-cigarettes to still be smoking.[9]

Why Are E-cigarettes Tobacco Products?

- In 2010, the U.S. Court of Appeals for the District of Columbia determined that e-cigarettes should be regulated as tobacco products except when a product makes a therapeutic (quit smoking) claim. The American Lung Association has urged FDA to finalize its proposed regulation by the end of 2014 so that it can begin its oversight over e-cigarettes and other unregulated tobacco products.
- E-cigarette companies sued FDA to be regulated as tobacco products.
- The nicotine used in e-cigarettes is derived from tobacco.
- E-cigarette marketing mirrors strategies used by cigarette companies in the past, which they are no longer allowed to use because they appeal to youth.
- FDA has not found e-cigarettes safe and effective in helping smokers quit.

For More Information Please Contact:
Pam Granger at pam.granger@lung.org or 707-775-6045

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[1] U.S. Food and Drug Administration. "E-Cigarettes: Questions and Answers." September 9, 2010. Available at: http://www.fda.gov/ForConsumers/ConsumerUpdates/ucm225210.htm.

[2] U.S. Food and Drug Administration. "FDA Warns of Health Risks Posed by E-Cigarettes." July 23, 2009. Available at: http://www.fda.gov/ForConsumers/ConsumerUpdates/ucm173401.htm.

[3] Zhu SH et al. "Four hundred and sixty brands of e-cigarettes and counting: implications for product regulation." Tobacco Control. July 2014; 23 Suppl 3:ii3-ii9.

[4] Centers for Disease Control and Prevention. "Electronic Cigarette Use Among Middle and High School Students — United States, 2011–2012." *Morbidity and Mortality Weekly Report.* September 6, 2013; 62(35):729-30.

[5] King, BA, Patel R, Nguyen K, Dube S. "Trends in Awareness and Use of Electronic Cigarettes Among U.S. Adults, 2010-2013." *Nicotine & Tobacco Research*. September 2014; ntu191v3-ntu191.

[6] King, BA, Patel R, Nguyen K, Dube S. "Trends in Awareness and Use of Electronic Cigarettes Among U.S. Adults, 2010-2013." *Nicotine & Tobacco Research*. September 2014; ntu191v3-ntu191.

[7] King, BA, Patel R, Nguyen K, Dube S. "Trends in Awareness and Use of Electronic Cigarettes Among U.S. Adults, 2010-2013." *Nicotine & Tobacco Research*. September 2014; ntu191v3-ntu191.

[8] U.S. Food and Drug Administration. "Summary of Results: Laboratory Analysis of Electronic Cigarettes Conducted by FDA." July 22, 2009. Available at: http://www.fda.gov/NewsEvents/PublicHealthFocus/ucm173146.htm.

[9] Borderud, S. P., Li, Y., Burkhalter, J. E., Sheffer, C. E. and Ostroff, J. S. (2014), Electronic cigarette use among patients with cancer: Characteristics of electronic cigarette users and their smoking cessation outcomes. Cancer. doi: 10.1002/cncr.28811

Morris, Erin

From: johnzfitch@zoho.com on behalf of John@tbdliquids.com
Sent: Saturday, November 01, 2014 1:09 AM
To: Morris, Erin
Subject: Concerned About E-Cigarette Regulation

Dear Mr. Morris,

I am writing to you in regards to the pending legislation involving electronic cigarettes. I have attached to this email multiple scientific studies, and stories done on Vaping from credible news source's such as BBC.

I would love to sit down and talk to you about my concerns, or attend a public forum about the pending legislation. Please give me 15 minutes of your time and check these articles/studies I've sent you. Vaping truly is a medical advancement, and has also been proven to help smokers quit smoking much more effectively than patches/other smoking cessation products.

Thank You,
John Fitch

Video - "The Most Significant Advancement in health care since modern antibiotics" - https://www.youtube.com/watch?v=8rYSFiyZhwQ

Study - "Effectiveness of the Electronic Cigarette" - http://www.ncbi.nlm.nih.gov/pubmed/25358095

Video - "Are E-Cigarettes Safe?" BBC - https://www.youtube.com/watch?v=G5RzMPCnWbc

Study - "Does E-Cigarette Consumption Cause Passive Vaping - http://meetingdocs.alachuacounty.us/documents/bocc/agendas/2013-12-10/500347c5-b7d5-423c-b645-0860dc047067.pdf

Study Article - " E-Cigarette Regulations Hinder Public Health Goals" - http://humanevents.com/2014/09/29/studies-e-cigarette-regulations-hinder-public-health-goals/

Study - "Effectiveness of the Electronic Cigarette" - http://www.ncbi.nlm.nih.gov/pubmed/25358095

Video - "Are E-Cigarettes Safe?" BBC - https://www.youtube.com/watch?v=G5RzMPCnWbc

Study - "Does E-Cigarette Consumption Cause Passive Vaping - http://meetingdocs.alachuacounty.us/documents/bocc/agendas/2013-12-10/500347c5-b7d5-423c-b645-0860dc047067.pdf

Video - "The Most Significant Advancement in Health Care Since Modern Antibiotics" -

http://humanevents.com/2014/09/29/studies-e-cigarette-regulations-hinder-public-health-goals/

Study Article - " E-Cigarette Regulations Hinder Public Health Goals" - http://humanevents.com/2014/09/29/studies-e-cigarette-regulations-hinder-public-health-goals/

Morris, Erin

From: Arlie <ajhaig@sonic.net>
Sent: Tuesday, October 28, 2014 2:31 PM
To: Morris, Erin; jncombs
Subject: Additions to Smoking Regs
Attachments: FireAccessGardenGate.jpg

Hello Erin and Julie,

I'd like to suggest a situation where possible additions or clarifications to the proposed regulations might make sense.

I am the volunteer coordinator for Kawana Community Garden, located on the property belonging to Bellevue Union School District which also sites a school parking lot. It is across Moraga Drive from Kawana Elementary School (now Kawana Academy of Arts and Sciences, KAAS).

Our garden entrance gate leads to the fire access paved area between Moraga and the Burbank housing Cypress Ridge project. To its credit, that entity has banned smoking on its property. However, as a result, smokers now gravitate to the fire access pass-thru to congregate at the red fire gate. They now smoke within five or less feet from the entrance to our organically-run garden and smoke drifts to nearby garden plots where mothers and children tend their healthy vegetables.

It appears the current SR City Code (9-20.050 Prohibition of smoking in unenclosed places) says:
(B) Smoking shall be prohibited within a reasonable distance (minimum of 20 feet), as defined in this chapter, from any unenclosed area in which smoking is prohibited except while actively passing on the way to another destination and without entering or crossing any area in which smoking is prohibited.

The current school district code says:
The Board prohibits the use of tobacco products at any time in district-owned or leased buildings, on district property, and in district vehicles. (Health and Safety Code 104420; Labor Code 6404.5; 20 USC 6083)

I do not know if these two codes completely address our situation as there is no provision in Fire Department codes to prevent people from smoking in the fire access road area and I don't know if the City code applies to the School District code - i.e., 20 feet from edge of parking lot or garden fence.

I'd like to request that this be addressed in the new regulations. One partial solution is that Burbank management has promised to situate permanent ashtray stations further away from our fencing, however I cannot visualize where they would be considering the above.

See attached map clip.

Thank you,

Arlie Haig

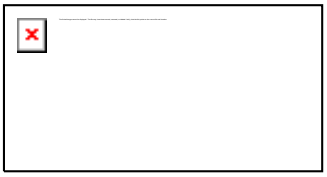
Morris, Erin

From: Regalia, Chuck
Sent: Thursday, October 16, 2014 8:24 AM
To: Morris, Erin
Cc: Kranz, Lisa
Subject: Fwd: Smoking Ordinance
Attachments: image001.jpg; image002.jpg

FYI

Chuck

Begin forwarded message:

> **From:** "Sheppard, Suzanne" <SSheppard@srcity.org>
> **Date:** October 16, 2014 at 8:15:25 AM PDT
> **To:** "McGlynn, Sean" <smcglynn@srcity.org>, "Regalia, Chuck" <CRegalia@srcity.org>
> **Subject: FW: Smoking Ordinance**
>
> Fyi…….this came in to Council
>
> **Suzanne Sheppard, Executive Assistant to the City Manager**
> City Manager's Office | 100 Santa Rosa Avenue, Room 10, Santa Rosa, CA 95404
> Tel. (707) 543-3013 | Fax (707) 543-3030 | ssheppard@srcity.org
>
> 
>
> 
>
> **From:** Debi Mumm [mailto:jnazmumm@gmail.com]
> **Sent:** Wednesday, October 15, 2014 4:06 PM
> **To:** _CityCouncilListPublic
> **Subject:** Smoking Ordinance
>
> As a landlord for a duplex, I have run into the problems of having a smoking tenant. I've scrubbed walls, thrown out carpet, replaced blinds and light fixtures all covered in smoke fueled grime. I have a no smoking clause in my contract now, but often have tenants ask to smoke in the yard. Having the city of Santa Rosa become smoke free will be a great asset to me, it will end many of the discussions I have to have repeatedly with tenants. I am pleased to see that all smoking substances are included in the ordinance. I am behind Santa Rosa becoming smoke free completely.

Thank you.

Debi B. Mumm

Morris, Erin

From: Dan <Harpoj@volcano.net>
Sent: Tuesday, October 14, 2014 7:02 AM
To: Morris, Erin
Subject: New Smoking Regs

I am just curious as to where you guys buy your dope…
if you actually believe section "a" will pass Constitutional Muster you get much better stuff than I do.

How do you get around the 4th, 5th, and 14th in even asking about what goes on in a person's home?

I am as anti-tobacco as is humanly possible but I think you will find that the constitution comes first for many of us and we will be right there with smokers
fighting your foolish effort to defecate on the Constitution for the United States.

I am embarrassed that you even pretend to be an American.
Gideon D. Asche

Morris, Erin

From: Niqueollette McGowan <niqueollettem@gmail.com>
Sent: Monday, October 13, 2014 2:32 PM
To: Morris, Erin
Subject: Re: City of Santa Rosa Smoking Regulations Update - Upcoming Public Meeting and Public Hearing

Good Afternoon, Ms. Erin Morris:

May I please have a status in regards to smoking in or around multi-unit dwellings? I would also like feedback from you in regards to the email I submitted to you. I would like this to be included in the newly drafted ordinance. I have included a copy below dated 10/02/14. :

Good Evening, Ms. Morris:

You may not remember me, but I attended the September Community Meeting. My name is Niqueollette and my son's name is Justice. We have breathing disabilities that are exacerbated by cigarette/cigar/marijuana smoke.

You had asked me for additional information in regards to our particular situation so that you may present it to your peers. Can you please specify which details you need so that I may pass it on to my attorney?

My 7 year old son and I are seeking additional changes to the existing ordinance as follows:

'Any landlord/owner of attached multifamily housing, including duplexes, apartments, townhouses, and condominiums and any building that contains two or more attached residential units that is engaged in or has ever engaged in retaliatory acts against a tenant with disabilities will be required to treat ALL units whether occupied or vacant as 'NEW'. Meaning, no transition time will be granted to bring 'smoking units' to a 'non-smoking unit' status.'

We would also like citations issued to tenants violating the no-smoking policy as well as the landlord/owner responsible for enforcing the policy. Holding the landlord/owner accountable is the only way to stop the retaliation.'

Unlawful retaliation occurs when someone in a position of authority (such as a government official, manager, or landlord) punishes an individual for making a legitimate complaint. By allowing a landlord/owner to partake in a transition period, you would in essence be allowing the opportunity for the landlord/owner to continue to retaliate against tenants with breathing disabilities.

On Mon, Oct 13, 2014 at 12:09 PM, Morris, Erin <EMorris@srcity.org> wrote:

Dear Community Members and Interested Parties:

Thank you for your interest in the City of Santa Rosa's Smoking Regulations Update. Two public meetings have been scheduled to present proposed changes to two separate aspects of Santa Rosa's smoking regulations. Both meetings are described in the attached notice, and public participation is invited. A draft of the revised smoking regulations will be posted on the City's web site in various locations, including on the project page, by this Thursday, October 16. The City Council is tentatively planned to consider the entire project at a public hearing in December 2014. A separate notice will be sent with the meeting details.

1. PUBLIC MEETING: REVISIONS TO CHAPTER 9-20 PROHIBITING SMOKING IN OR AROUND WORKPLACES, PUBLIC PLACES

On Wednesday, October 22, 2014, at or after 4:00 PM, in the Cypress Room at the Finley Community Center, 2060 West College Avenue, Santa Rosa, the Board of Community Services will hold a public meeting and will review the proposed changes to Chapter 9-20 of the City Code that would prohibit smoking on City-owned park and recreation lands. The proposed changes to Chapter 9-20 were initiated by the City Council. The purpose of this meeting is to provide an opportunity for the Board to review the proposal and to make a recommendation to the City Council.

2. PUBLIC HEARING: ZONING CODE TEXT AMENDMENT TO CHANGE THE DEFINITION OF "TOBACCO OR SMOKE SHOP" TO EXPLICITLY INCLUDE A RETAIL STORE THAT DEVOTES 30% OR MORE OF ITS DISPLAY FLOOR AREA TO ELECTRONIC SMOKING DEVICES AND RELATED ACCESSORIES

Notice is hereby given that a public hearing will be conducted by the Planning Commission on Thursday, October 23, 2014, at or after 4:00 PM, in the City Council Chamber, City Hall, 100 Santa Rosa Avenue, Santa Rosa. The purpose of the public hearing will be to receive public comment and recommendations prior to the Planning Commission acting on the requested Zoning Code text amendment to change the definition of "tobacco or smoke shop" to explicitly include a retail store that devotes 30% or more of its display floor area to electronic smoking devices and related accessories. This means that new electronic cigarette stores will need to obtain a Minor Conditional Use Permit prior to opening.

Any interested person is invited to appear and be heard on the proposed Zoning Code text amendment. The Planning Commission will make a recommendation to the City Council regarding the proposed changes. The proposed Zoning Code text amendment was initiated by the City Council and is exempt from the California Environmental Quality Act pursuant to 15061(3).

Additional Project Information

The proposal and additional information are on file in Community Development, Room 3, City Hall (100 Santa Rosa Avenue), and available for public inspection. The Department is open from 9:30 a.m. to 2:30 p.m. Monday through Thursday. You may also review the entire proposal on the City's web site at the following location: www.srcity.org/communitydev

If you cannot attend these meetings, you are encouraged to submit written comments and recommendations. Comments and questions may be directed to Erin Morris, Senior Planner, Community Development, City of Santa Rosa, 100 Santa Rosa Avenue, Room 3, Santa Rosa, CA 95404, telephone 707-543-3273 or e-mail: emorris@srcity.org.

Erin Morris | Senior Planner

Community Development |100 Santa Rosa Avenue, Room 3 | Santa Rosa, CA 95404

Tel. (707) 543-3273 | Fax (707) 543-3218 | emorris@srcity.org

City of Santa Rosa

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Thanks for all you are and do!

Niqueollette McGowan
(707) 304-6593 Bus. Phn.
Niqueollettem@gmail.com
Niqueollette.mcgowan@yahoo.com
www.facebook.com/niqueollette

"Nothing in the world can take the place of persistence. Talent will not; nothing is more common than unsuccessful men with talent. Genius will not; unrewarded genius is almost a proverb. Education will not; the world is full of educated derelicts. Persistence and determination alone are omnipotent."
Calvin Coolidge

Morris, Erin

From: Denise Hill <faire@sonic.net>
Sent: Monday, October 13, 2014 7:33 PM
To: Morris, Erin
Subject: RE: City of Santa Rosa Smoking Regulations - Sprengers Tap Room
Attachments: 2014-10-08 Sprengers 001.JPG

Hi, Erin,

Not sure who to send this to, but in regards to the current smoking regulations SR has in place, doesn't appear Sprengers Tap Room in the Brickyard on B Street is adhering to them. Hard to get a good shot, but the attached photo shows a common sight each morning of cig butts all around their outside tables. Hoping you can forward on to the appropriate person/dept.

Thanks

Denise Hill

From: Pacheco Gregg, Patti [mailto:PPachecoGregg@srcity.org]
Sent: Monday, October 13, 2014 1:21 PM
To: Pacheco Gregg, Patti
Cc: Morris, Erin
Subject: FW: City of Santa Rosa Smoking Regulations Update - Upcoming Public Meeting and Public Hearing

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Dear CAB Members:
Please see the email below from Senior Planner Erin Morris, and the attached public notice.
Patti

From: Morris, Erin
Sent: Monday, October 13, 2014 12:09 PM
Subject: City of Santa Rosa Smoking Regulations Update - Upcoming Public Meeting and Public Hearing

Dear Community Members and Interested Parties:

Thank you for your interest in the City of Santa Rosa's Smoking Regulations Update. Two public meetings have been scheduled to present proposed changes to two separate aspects of Santa Rosa's smoking regulations. Both meetings are described in the attached notice, and public participation is invited. A draft of the revised smoking regulations will be posted on the City's web site in various locations, including on the project page, by this Thursday, October 16. The City Council is tentatively planned to consider the entire project at a public hearing in December 2014. A separate notice will be sent with the meeting details.

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Erin Morris | Senior Planner
Community Development |100 Santa Rosa Avenue, Room 3 | Santa Rosa, CA 95404
Tel. (707) 543-3273 | Fax (707) 543-3218 | emorris@srcity.org

City of Santa Rosa


446
EVERY GAME.
EVERY SUNDAY.
$3 PINTS
$14 PITCHERS
WIN A BIKE

Morris, Erin

From: patricia steffensen <patriciasteffensen@yahoo.com>
Sent: Sunday, October 12, 2014 6:35 PM
To: Morris, Erin
Subject: Public Comment regarding Smoking Regulations Update

Comment to be shared with decision makers and placed in project file:

My name is Patricia Steffensen and I am a resident of the city of Santa Rosa.

I bring this before you because Pam Granger of the American Lung Association suggested smoking be flat-out be declared a nuisance so that even single-family residences where smoke can drift from one yard to another could be covered by the ban. I support what she asks and ask the council to include single family dwellings in the ban. I deserve equal protection from my city and should not be ignored because I do not live in a condominium or apartment.

My comments are specifically regarding marijuana smoke, which we all know is much more pungent and "stinky" than cigarette smoke. It is not a commentary on whether marijuana should be legalized or not.

I wish I could start my day with the windows open, peacefully enjoying the quiet morning, but I cannot - - my neighbor is smoking pot and the smoke is drifting into my kitchen and home.

I wish I could sit in the sunshine, or garden in my backyard, but I cannot - - my neighbor is smoking pot and the smoke is drifting into my backyard.

I wish my two grandsons could play in my backyard - - but wait a minute - - they do play in my back yard and inhale the pot smoke. They are ages 1 and 5. My neighbor who lives to the right of me has a 3 year old son. My neighbor to the left of me has a 1 year old granddaughter living with her.

I cannot sleep with my bedroom windows open because the pot smoke drifts into my bedroom at 2 a.m.

I get into my vehicle to drive and the interior of my vehicle smells like pot. My front yard smells like pot even though it is being smoked over 100 feet away.

By the way, he smokes it at least 6 times a day. He is very considerate and does not smoke it in HIS house – he smokes it in a shed next to the fence we share. I am sure his roommates tell his to take it outside because they do not want to smell it. We do not thank our pot smoker for being generous and sharing his smoke with us.

Morris, Erin

From: Regalia, Chuck
Sent: Tuesday, October 07, 2014 2:53 PM
To: Morris, Erin
Cc: Kranz, Lisa
Subject: FW: second hand smoke causing pneumonia relapse

FYI

Chuck Regalia | Assistant City Manager | Community Development Department |100 Santa Rosa Avenue | Santa Rosa, CA 95403 Tel. (707) 543-3189 | Fax (707) 543-3269 | cregalia@srcity.org

-----Original Message-----
From: Sheppard, Suzanne
Sent: Monday, October 06, 2014 7:35 AM
To: McGlynn, Sean; Regalia, Chuck
Subject: FW: second hand smoke causing pneumonia relapse

Fyi.....this came in to Council.

s

Suzanne Sheppard, Executive Assistant to the City Manager City Manager's Office | 100 Santa Rosa Avenue, Room 10, Santa Rosa, CA 95404 Tel. (707) 543-3013 | Fax (707) 543-3030 | ssheppard@srcity.org

-----Original Message-----
From: Kathleen Barry [mailto:barry.kathleen@att.net]
Sent: Thursday, October 02, 2014 11:41 PM
To: _CityCouncilListPublic
Subject: second hand smoke causing pneumonia relapse

I am am 73 years old, frail from my health being abused by second hand smoke from the resident who lives in a unit beneath the one I own. I am asking for your help and advice on what to do next. As I have tried everything. Here is my report to my primary care physician who has been treating me for two months for persistent pneumonia.

Dear Dr. Nichols,

I have been slowly recovering from the pneumonia which has lasted these two full months. My recovery has been slowed by smoking coming into my home the unit below mine. I have two heavy duty air purifiers on all the time. I was too weak to do anything about the smoking during the worst of the pneumonia. Two days ago on September 30, just as I was feeling I was really recovering, I retired to my bedroom to go to bed. It was filled with smoke from the unit below. I have been coughing unrelentingly since then and fearing a reversal of my progress out of pneumonia. I'll see you next week for my follow-up appointment with you. In the meantime, please make this a part of my medical records.

I have had an ongoing problem with a neighbor in a condo below mine who smokes excessively as does his roommate. Our condo association has adopted a rule in our CC&Rs prohibiting smoking in units where the second hand smoke reaches to another unit and provides cause for complaint. The owner of this unit has been fined up to $3,000 for violating these rules. At that point the police picked him up in Napa where he was telling people he was going to kill me. He was held for three days in a psych ward of the hospital there. I was notified by the Santa Rosa police and there is an open record of this with the police department. His had to go into arbitration with the Board of Directors and our lawyer, promised to stop smoking in his unit and indeed announced that he was stopping smoking altogether. He has never kept any part of that agreement. There are liens on his property as a result but he continues to smoke profusely.

Santa Rosa City Council: Please advise me on remedies. And please enact the legal changes on second hand smoke to cover multiple dwelling units as soon as possible. My life literally depends on your action.

Sincerely,

Kathleen Barry
1370 Townview Ave #306
Santa Rosa, Ca 95405
569-8435
barry.kathleen@att.net

Morris, Erin

From: johnzfitch@zoho.com on behalf of John@tbdliquids.com
Sent: Monday, October 06, 2014 11:21 AM
To: Morris, Erin
Subject: Re: RE: Changes to Vaping

Gotcha, so basically smoke shops in Santa Rosa can no longer offer testing of different liquids on-site in their store? If the testers contained no nicotine and were just the flavor vapor would that be allowed?

Thank you for getting back to me, I just want to stay on top of any legislation that may affect future plans of my business.

Regards,
John

---- On Mon, 06 Oct 2014 07:19:33 -0700 **Erin Morris <EMorris@srcity.org>** wrote ----

> Hi John:
>
> The current law pertaining to smoking in Santa Rosa includes e-cigarettes. Therefore vaping is not allowed where smoking is prohibited, such as in retail stores like electronic cigarette stores. The City Council directed my department (Community Development) to draft new regulations that would prohibit smoking/vaping in multifamily residential. I am still working on the draft law and am reviewing the similarities and differences between vapor and smoke to see how vapor ought to be regulated.
>
> Please let me know if you have any further questions or comments about this. The draft ordinance will be on our web site by next week, on the project page: http://ci.santa-rosa.ca.us/departments/communitydev/Pages/Smoking_Regulations_Update.aspx
>
> **Erin Morris** | **Senior Planner**
>
> Community Development |100 Santa Rosa Avenue, Room 3 | Santa Rosa, CA 95404
>
> Tel. (707) 543-3273 | Fax (707) 543-3218 | emorris@srcity.org
>
> City of Santa Rosa

From: johnzfitch@zoho.com [mailto:johnzfitch@zoho.com] **On Behalf Of** John@tbdliquids.com
Sent: Sunday, October 05, 2014 2:13 PM
To: Morris, Erin
Subject: Changes to Vaping

Hi Erin,

I'm a local resident of santa rosa who runs an online e-juice business for electronic cigarettes. I understand the council is changing the definition of smoking to include vaping. I need to know if that means I can no longer vape in smoke shops that allow it, or if I can even vape in my own home.

Please let me know the changes that have passed in regards to vaping.

Thanks,

John

Morris, Erin

From: Doug Van Deren <ljcsidekick@gmail.com>
Sent: Sunday, October 05, 2014 2:00 PM
To: Morris, Erin
Subject: City of Santa Rosa Smoking Regulations

Dear Ms. Morris:

Thank you for monitoring the Smoking Regulation Community Meeting on October 1st. I found the meeting very informative and appreciated the opportunity to participate in the meeting.

The issue of Smoking Regulations is a very serious matter since it involves quality of life and health issues; including, but not limited to, increasing the risk of heart disease and lung cancer and death from smoking.

As a nonsmoker my concerns primarily involve the ingestion of other people's smoke, commonly referred to as "secondhand" smoke. It has been proven that secondhand smoke has serious harmful effects; e.g., according to the Center for Disease Control website, "Since 1964, 2.5 million nonsmokers have died from exposure to secondhand smoke."

I appreciate that the City of Santa Rosa is expanding the smoking ordinances for public and private places and would like the City to also consider the following:

- Prohibit smoking on or near public sidewalks. Almost daily I walk 2 miles on a public sidewalk through a residential area and a business park. And almost daily I encounter people smoking, both tobacco and marijuana, either on the sidewalk or in close proximity to the sidewalk, such as in a door way or front yard; so that I have to breathe in secondhand smoke, which I can smell. Elimination of smoking is being proposed for walking and running on public trails and should be eliminated for walking and running on public sidewalks as well.

- Use the term "marijuana" along with "tobacco" when presenting smoking issues. Marijuana is now legal in certain situations and use of the term would help clarify smoking matters.

- Extend the smoking regulations to cover single family housing. No one in my household smokes but some of my neighbors do and occasionally I can smell tobacco and marijuana smoke in my yard and in my house.

The preceding would help in creating a safer and more enjoyable environment.

Please confirm your receipt of the email via return email. Thanks.

LJC Blessings,

Doug Van Deren

Morris, Erin

From: Jaime Russell <jaime.russell@sonoma.edu>
Sent: Monday, September 29, 2014 10:02 AM
To: Morris, Erin
Subject: Question about the Smoking Regulation Update

Good morning, I would like to attend the 2nd community meeting but am not sure if I can make that work with my family's previous commitments.

For clarification, would this update include prohibiting smoking on the deck or patio of attached multifamily housing? Point A in the proposed changes indicates that the update would "Prohibit smoking ***in*** attached multifamily housing…" which seems to significantly leave out an important piece to the definition. If decks and/or patios were included in the language, it would clearly prohibit smoking nearby open windows of neighbors which could be as close as 10 feet. This is a significant problem with our neighbors who rent the space and are prohibited from smoking inside their house. So, they smoke on the back deck all night long which quickly permeates our bedroom!

Thank you for your time,

Jaime Russell
707-799-8349

Morris, Erin

From: Richard Comfort <rcomfort8608@gmail.com>
Sent: Monday, September 29, 2014 5:52 PM
To: Morris, Erin
Subject: RE: meeting

My concerns are as follows:

1. Is the timing good?. As you are well aware, this legislation would primarily affect the less well-off elements in our city, which means that many Hispanic people would oppose it. The shooting of Andy Lopez is still a very active issue, and this would not be a good time to stir up the anti-government feelings in the community any further. Some could greet this as, "here they come again."
2. How would you propose to enforce this law? Get subpoenas to enter people's homes to catch them smoking? Having unenforceable laws on the books is not a good idea. It tends to breed disrespect for the law in general.
3. Do we really need this legislation? The law is clear that any owner of a multi-family dwelling has the right to declare it a non-smoking facility, so why not just appeal to building owners to do so? On the other hand, the City may not have the authority to control the specifics of leases among private parties. If people want smoke-free environments, they can appeal to their landlords to create them and/or hold building-wide elections on the issue. The City could support that solution in a variety of ways.
4. What costs will be associated with this legislation? No doubt considerable costs have already been incurred in preparing for the hearings. This comes at a time when citizens are unhappy about the condition of the roads, the failure to maintain public spaces adequately, and school issues. I would not like the job of explaining to them why we are spending money to stop people from smoking in their own homes and claiming that we don't have funds available to fix these pressing problems. What is City government for, after all? What little research there is on "second-hand smoke from the people next door" is poorly documented and very unevenly accepted. Some reliable sources believe there is no such evidence. It seems that lung cancer is not part of the equation. You should be absolutely certain that you have totally unimpeachable evidence before broaching this issue or you could be made out to look like prejudicial busybodies wanting to limit the life-style choices of certain citizens to solve problems that may not exist.

Richard Comfort, PhD
1320 North St., #3
Santa Rosa, CA
707-540-0094
mailto:rcomfort8608@gmail.com
For information concerning my services, please visit my website: comfortindexing.com

---

From: Morris, Erin [mailto:EMorris@srcity.org]
Sent: Monday, September 29, 2014 4:22 PM
To: Richard Comfort
Subject: RE: meeting

Yes, absolutely.

Erin

From: Richard Comfort [mailto:rcomfort8608@gmail.com]
Sent: Monday, September 29, 2014 4:21 PM
To: Morris, Erin
Subject: meeting

Hi Erin: I am unable to attend 10/1 meeting. May I email comments? RC

"*Intelligence is the ability to adapt to change."* Stephen Hawking

---

Richard Comfort, PhD
Intelligent Indexing
Santa Rosa, CA
707-540-0094
mailto:rcomfort8608@gmail.com
For information concerning my services, please visit my website: comfortindexing.com

Morris, Erin

From: Richard Comfort <rcomfort8608@gmail.com>
Sent: Friday, September 26, 2014 10:34 AM
To: Morris, Erin
Subject: smoking ordinance

Dear Ms. Morris: Upon reading the Report of the National Cancer Institute on second-hand smoke in *Forbes,* December 12, 2013, I tried to find reliable sources for the belief that smoke from next door can harm you. But I was unable to locate any scientific research on this subject. Would you be kind enough to point me to the best documented research?

_____

"*Intelligence is the ability to adapt to change."* Stephen Hawking

_____

Richard Comfort, PhD
Santa Rosa, CA
707-540-0094
mailto:rcomfort8608@gmail.com
For information concerning my services, please visit my website: comfortindexing.com

Morris, Erin

From: Richard Comfort <rcomfort8608@gmail.com>
Sent: Friday, September 26, 2014 4:22 PM
To: Morris, Erin
Subject: RE: smoking ordinance

Dear Erin Morris: Thank you for your reply and for the very interesting articles. I have read them with care. I tend to discount materials from ASHRAE a bit, given their obvious conflict of interest. But more important, I think, is that all of these articles pre-date the study by the National Cancer Institute (as reported in *Forbes*, 12/12/2013) which concluded that "A large-scale study found no clear link between secondhand smoke and lung cancer…." which seems to me to pretty well remove lung cancer from the list of potential harms caused by secondhand smoke. There are other less serious harms, of course, such as COPD, asthma, and so on, which, as far as I can determine, have never been carefully and scientifically measured apart from lung cancer. Also, it seems very difficult to separate the harm caused by smokers living in the same apartment from the harm that may arise from the people next door. So, yes, I would like to delve further into this topic and would appreciate it if you could provide a contact at the County Health Department. I'm sure you will agree that there is no such thing as too much study when the issue at hand could affect the lives of so many people.

_____
"*Intelligence is the ability to adapt to change.*" Stephen Hawking
_____

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---

From: Morris, Erin [mailto:EMorris@srcity.org]
Sent: Friday, September 26, 2014 3:12 PM
To: Richard Comfort
Subject: RE: smoking ordinance

Hi Dr. Comfort,

I have received a lot of research from a variety of sources, which I am reviewing as part of my work on the revised smoking regulations. I've selected a few articles that I believe are most related to your question about second hand smoke and how it affects people living in adjacent units . If you wish to delve further into this topic, you might contact the Sonoma County Health Department since they have access to additional scientific research and are professionals in the world of public health. I'd be happy to provide you with a contact person if that would be helpful.

Best regards,

Erin Morris | Senior Planner
Community Development |100 Santa Rosa Avenue, Room 3 | Santa Rosa, CA 95404
Tel. (707) 543-3273 | Fax (707) 543-3218 | emorris@srcity.org

City of Santa Rosa

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For information concerning my services, please visit my website: comfortindexing.com

Morris, Erin

From: Lin Kaplan <lkc@sonic.net>
Sent: Thursday, September 25, 2014 9:17 AM
To: Morris, Erin
Subject: RE: Proposed Changes to SR Smoking Regulations

Hi Erin,

Yes, it's impossible to separate airspace contamination from secondhand smoke on a single property with a shared wall between two units and contiguous outside living areas on the one lot.

Thanks,

Lin

From: Morris, Erin [mailto:EMorris@srcity.org]
Sent: Thursday, September 25, 2014 9:06 AM
To: Lin Kaplan
Subject: RE: Proposed Changes to SR Smoking Regulations

Hi Lin,

I will consider your comments but please keep in mind that single family homes with granny units are not considered multifamily. They are distinctly different than duplexes in that they are regulated and they function differently. When the State of California determined that all cities must allow second units in single family neighborhoods, it was found that adding the second unit is not considered density and the property remains a single family property. This is because in the case of a single family home with second unit, the property owner must live in either the primary or second unit; they are not allowed to rent out both. This makes the properties function quite different than multifamily rental properties, where the property owner is renting out two units to unrelated people, although I understand the point that of course smoke could be an issue for the owner-occupant or their tenant.

Erin Morris | Senior Planner
Community Development |100 Santa Rosa Avenue, Room 3 | Santa Rosa, CA 95404
Tel. (707) 543-3273 | Fax (707) 543-3218 | emorris@srcity.org

City of Santa Rosa

From: Lin Kaplan [mailto:lkc@sonic.net]
Sent: Thursday, September 25, 2014 8:58 AM
To: Morris, Erin
Subject: RE: Proposed Changes to SR Smoking Regulations

Hi Erin,

Thanks for your response. If I understand you correctly, you are considering exempting a second dwelling ("granny") unit that is attached to the main house on what was originally a single-family property but now shares a wall between the two units. If so, that is exactly the scenario that I suggest (and request) should also be included in the restrictions. It absolutely qualifies under the definition of "attached multifamily housing" since two units share a common wall. Please include this type of housing in the restrictions, so there can be no misunderstanding and also that the law extends protection to residents of that type of multifamily housing, too, from secondhand smoke.

I would suggest that a single-family property that has a granny unit, be it attached or detached but on that same property is a multi-unit and multi family living situation and should protect the residents of those dwellings as well and be included in the language of the law.

But strictly speaking, I submit that residents of what was a single family property that has been altered and is a multi-family dwelling with a shared wall should be protected (and spelled out as included) under a fair, equitable and non-contradictory revision of this law.

I appreciate your further consideration on this point.

Sincerely,

Lin Kaplan

From: Morris, Erin [mailto:EMorris@srcity.org]
Sent: Thursday, September 25, 2014 8:29 AM
To: Lin Kaplan
Subject: RE: Proposed Changes to SR Smoking Regulations

Hi Lin,

Thank you for sending written comments. I have begun work on drafting the changes to the law, which will be much more detailed than the summaries provided in the public meeting notice and on the web page. I will definitely take your comments into consideration. My intent at this point, based on City Council direction, is that smoking would not be allowed within any unit that shares a wall, with the possible exception of a second dwelling ("granny") unit on a single-family property. And there would be clear restrictions preventing smoking in private and shared yards adjoining units where smoking is not allowed. I have been looking at Petaluma's current ordinance as a model although theirs does not seem to cover units attached in twos. Nonetheless, they address outdoor smoking near units where smoking is not allowed and I may recommend similar language in Santa Rosa's ordinance.

Feel free to contact me if you would like to discuss further. My plan is to have a complete draft of the revised smoking ordinance ready for public review by the week of October 6. It will be placed on our web site to facilitate public access.

Best regards,

Erin Morris | Senior Planner
Community Development |100 Santa Rosa Avenue, Room 3 | Santa Rosa, CA 95404
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City of Santa Rosa

From: Lin Kaplan [mailto:lkc@sonic.net]
Sent: Wednesday, September 24, 2014 12:41 PM
To: Morris, Erin
Subject: Proposed Changes to SR Smoking Regulations

September 24, 2014

Hello Erin,

I am a Santa Rosa resident and have reviewed the Notice of Community Meeting and attachment dated September 11, 2014 regarding the proposed changes to the City of Santa Rosa's regulations pertaining to smoking in public and private places.

I have two comments that I wish to share:

1) In notation A of the changes proposed to Chapter 9-20, I strongly believe that it would add needed clarification (and effectiveness) if the wording would also specify "houses with attached one or more units." There are single family houses that have added an ATTACHED unit (where the two units share a wall). To aid home owners and renters who wish to prohibit smoking in compliance with the smoking ordinance, I suggest revising the wording with this inclusion to facilitate enforcement by the residents. I ask for you to include that wording in addition to "duplexes, apartments, townhouses and condominiums…"

2) The wording is vague when it states, "Prohibit smoking "IN" attached multifamily housing…" as to whether that means smoking would only be prohibited within the inside living space square footage but allowed in an outdoor perimeter space of the property, say on the attached deck or in the front or backyard. I strongly support a clear statement and that smoking should be explicitly prohibited on the interior AND outside area of a multifamily dwelling; that is, smoking would be prohibited on the entire property lot of a multifamily housing dwelling. Please stipulate fully and clearly by defining the precise property areas of multifamily housing where smoking is prohibited.

Thanks for the opportunity to contact you with my thoughts and concerns about the current draft of the proposal. With further editing and clarity in the wording and its intention, this ordinance has the potential to protect the citizens of Santa Rosa from smoking and its well-documented firsthand and secondhand health risks.

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Sincerely,

Lin Kaplan

Morris, Erin

From: Erick Beall <e.beal@digitalciggz.com>
Sent: Wednesday, September 24, 2014 3:36 PM
To: Morris, Erin
Subject: Research & Educational Materials for the Council's Review
Attachments: 1-s2.0-S0273230012001651-main.pdf; 1471-2458-14-18.pdf; ash.org_.uk_files_documents_ASH_715.pdf; DublinEcigBenchtopHandout.pdf; E-Cigarette Summit - Clive Bates Vaping.com.pdf; Ecigs-as-harm-reduction-article_Siegel.pdf; Electronic Cigarette FAQS.pdf; Electronic-Cigarettes_A-Survey-of-Users.pdf; Study_TSNAs_in_NJOY_Vapor.pdf; e_beal.vcf

Good Afternoon Ms. Morris -

Thank you for your prompt callback yesterday afternoon. I apologize I wasn't able to get back to you in time.

Attached are some important documents that could assist the council members in being brought up to speed with where the current medical and scientific data is regarding vapor products. We hope that you/they find them informative and we look forward to the meaningful discussions you have scheduled for us.

Very Truly Yours,

Erick C. Beall
Director of Sales / Store Manager
Digital Ciggz
2750 Mendocino Ave.
Santa Rosa, CA 95403
(707) 843-3047
e.beal@digitalciggz.com

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journal homepage: www.elsevier.com/locate/yrtph

Reduced exposure evaluation of an Electrically Heated Cigarette Smoking System. Part 1: Non-clinical and clinical insights

Matthias K. Schorp *, Anthony R. Tricker, Ruth Dempsey

Philip Morris International R&D, Philip Morris Products S.A., Quai Jeanrenaud 5, 2000 Neuchâtel, Switzerland

ARTICLE INFO

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Biomarkers of exposure
Cigarettes
Electrically Heated Cigarette Smoking System
EHCSS
Harmful and potentially harmful constituents
HPHC
Smoking

ABSTRACT

The following series of papers presents an extensive assessment of the Electrically Heated Cigarette Smoking System EHCSS series-K cigarette vs. conventional lit-end cigarettes (CC) as an example for an extended testing strategy for evaluation of reduced exposure. The EHCSS produces smoke through electrical heating of tobacco. The EHCSS series-K heater was designed for exclusive use with EHCSS cigarettes, and cannot be used to smoke (CC). Compared to the University of Kentucky Reference Research cigarette 2R4F and a series of commercial CC, mainstream cigarette smoke of both the non-menthol and menthol-flavored EHCSS cigarettes showed a reduced delivery of a series of selected harmful and potentially harmful constituents (HPHC), mutagenic activity determined using the *Salmonella typhimurium* Reverse Mutation (Ames) assay, and cytotoxicity in the Neutral Red Uptake Assay. Clinical evaluations confirmed reduced exposure to HPHC and excretion of mutagenic material under controlled clinical conditions. Reductions in HPHC exposure were confirmed in a real-world ambulatory clinical study. Potential biomarkers of cardiovascular risk were also reduced under real-world ambulatory conditions. A modeling approach, 'nicotine bridging', was developed based on the determination of nicotine exposure in clinical evaluations which indicated that exposure to HPHC for which biomarkers of exposure do not exist would also be reduced.

1. Introduction

There is an overwhelming medical and scientific consensus that cigarette smoking is causally related to lung cancer, heart disease, emphysema, and other serious diseases in smokers (US Department of Health and Human Services, 2010). There is no 'safe' cigarette and the best way for smokers to reduce the adverse health consequences of smoking is to quit.

For many years the public health communities' primary goal with respect to tobacco control has focused on reducing initiation, encouraging smoking cessation, and preventing relapse. There has been a growing interest in recent years, however, in alternative approaches including that of harm reduction (Gori, 1980; Institute of Medicine, 2001, 2012; Rodu and Godshall, 2006; Sweanor et al., 2007; Hatsukami et al., 2007; World Health Organization, 2007; Royal College of Physicians and Surgeons, 2007; Gilmore et al., 2009; Zeller et al., 2009; Family Smoking Prevention and Tobacco Control Act, 2009), stimulated perhaps by the observations that in spite of the significant efforts directed towards tobacco control and communication of the risks of smoking, many smokers still have little interest and/or success in quitting smoking. For example, according to the Surgeon General, although about 45% of smokers quit for a day, only approximately 5% succeed in obtaining long-term abstinence (US Department of Health and Human Services, 2010). The World Health Organization (WHO) Study Group on Tobacco Product Regulation has defined tobacco harm reduction as 'minimizing harms and decreasing total morbidity and mortality, without completely eliminating tobacco and nicotine use' (World Health Organization, 2007).

Amongst the literature surrounding the questions of harm-reduced products, much of the focus is on the requirements of an effective risk evaluation system. A significant development in tobacco control in the US has been the enactment of the Family Smoking Prevention and Tobacco Control Act (FSPTCA) (Family Smoking Prevention and Tobacco Control Act, 2009), which empowers the US Food and Drug Administration (FDA) to evaluate and regulate Modified Risk Tobacco Products (MRTPs) (Deyton et al., 2010). The FSPTCA defines a MRTP as 'any tobacco product that is sold or distributed for use to reduce harm or the risk of tobacco-related disease associated with commercially marketed tobacco products.' The FDA has also been charged to issue guidance or regulations on the scientific evidence required for the assessment and ongoing review of MRTPs in consultation with the US

* Corresponding author. Address: Philip Morris Products S.A., PMI Research & Development, Quai Jeanrenaud 5, 2000 Neuchâtel, Switzerland. Fax: +41 58 242 2811.

E-mail address: Matthias.Schorp@pmi.com (M.K. Schorp).

0273-2300
http://dx.doi.org/10.1016/j.yrtph.2012.08.008

Institute of Medicine (IOM), and published a Draft Guidance on "Modified risk Tobacco Product Applications" in March 2012 (Food and Drug Administration, 2012a).

The FSPTCA provides for the approval of an MRTP when reduced exposure or reduced risk has been demonstrated. Different levels of evidence are required for these respective approvals, with correspondingly greater ability for communicating product attributes. The FSPTCA requires applicants to demonstrate that the product, as actually used, will: (i) significantly reduce harm and the risk of tobacco-related disease to individual tobacco users; and (ii) benefit the health of the population as a whole, taking into account both users of tobacco products and persons who do not currently use tobacco products. The FSPTCA's recognition that harm reduction now has a statutory place alongside the regulations of food and medicine provides the platform for moving forward and a source of confidence that effective, appropriate MRTPs can be developed and commercialized.

The studies presented in this series of papers were performed prior to the enactment of the FSPTCA, and publication of the IOM Report (Institute of Medicine, 2012). At the time, we focused on evaluating exposure reduction at 'three levels': Firstly at the 'product level' (i.e., does the product have a reduced yield of a HPHC under a variety of laboratory conditions), secondly at the 'individual smoker level' (i.e., do smokers using these products experience reductions in their exposure to specific HPHC), and finally at the 'population level' (i.e., is this exposure reduction likely to be realized by both a significant proportion of the normal smoking population given that they are likely to represent a wide range of 'actual use' smoking behaviors). Three considerations appeared to be essential. Firstly, the product characterization, as determined in laboratory studies, should not be limited to comparisons under standardized smoking conditions but emulate anticipated conditions of actual use. Secondly, uptake of relevant HPHC should be determined in populations that are representative of those who are most likely to use the product (Hatsukami et al., 2007, 2012; World Health Organization, 2007). The latter requires valid biomarkers of exposure as well as selection of appropriate populations and reference products that can be considered as reasonably representative of those used by smokers who may switch to using the new products. Thirdly, consideration of the potential reduction in exposure by non-smokers to environmental aerosols produced by the MRTP vs. environmental tobacco smoke (ETS) from a CC must also be investigated. Tricker et al. (2009) has published a comparative indoor air quality assessment of EHCSS series-K vs. a CC.

Clearly, in consideration of both the Draft Guidance on "Modified Risk Tobacco Product Applications" (Food and Drug Administration, 2012a) and the IOM Report (Institute of Medicine, 2012), further work is needed in order to meet such a standards. We nevertheless consider that product testing is an iterative process and the data reported here should be considered as relevant, although not sufficient, for the evaluation of reduced exposure, reduced risk, and population harm.

Although the causal relationship between smoking and several diseases has been well established (Doll et al., 2004), there is still very little understanding of the underlying mechanisms. More than 5300 chemical compounds have been identified in cigarette tobacco smoke (Rodgman and Perfetti, 2009). Public health authorities and representatives now propose some 100 HPHC as possible causes of smoking-related diseases such as lung cancer, heart disease, and emphysema (Health Canada 2000; Food and Drug Administration, 2012b; Talhout et al., 2011). There is no consensus, however, that lowering or eliminating any single compound (or even a combination of compounds) in smoke would have a significant impact on risk. Partly in response to this dilemma, the IOM introduced the concept of a 'Potential Reduced-Exposure Product' (PREP) (Institute of Medicine, 2001), based on a first assumption that reduction of exposure is related to a reduction in harm.

We have focused on the development of products that substantially reduce or eliminate a wide spectrum of HPHC. Our current approach achieves this by eliminating direct tobacco combustion and limiting tobacco pyrolysis by heating at significantly lower temperatures than encountered in CC. However, the IOM and others conclude that simply reducing exposure does not necessarily equate to harm reduction (Institute of Medicine, 2001; World Health Organization, 2007; Zeller et al., 2009). Thus, a comprehensive assessment of reduced exposure is necessary, but is not sufficient for determining a modified tobacco product's potential to reduce risk. Novel testing strategies have been recently proposed by the IOM (Institute of Medicine, 2012).

The following series of papers presents an extensive assessment of the EHCSS series-K cigarette vs. CC as an example for an extended testing strategy for evaluation of reduced exposure. The concept of reduced exposure in this testing strategy considers a broad range of potential smoking behaviors, and characterizes the potential reductions in exposure to a range of HPHC in cigarette smoke which could be considered to be of importance in relation to smoking-related diseases.

2. The Electrically Heated Cigarette Smoking System (EHCSS)

Tobacco smoke from CC consists of an aerosol containing liquid droplets ('particulate phase') suspended in the gas–vapor phase. It is generated by complex and overlapping burning-, pyrolysis-, pyrosynthesis-, distillation-, sublimation-, and condensation processes (Borgerding and Klus, 2005). With minor exceptions, both pyrogenesis and pyrosynthesis of HPHC result from the thermal decomposition from organic tobacco compounds taking place at elevated temperatures (Baker, 2006; Borgerding et al., 1997; Torikai et al., 2005), thus, a reduction of these toxicants may be achieved by generating a simpler smoke aerosol, e.g., by heating rather than burning tobacco (e.g., ECLIPSE Expert Panel, 2000).

The first-generation of the EHCSS (series-E) has been subject to extensive analytical and toxicological evaluation (Patskan and Reininghaus, 2003) demonstrating simplified smoke chemistry compared to the University of Kentucky 1R4F reference research cigarette (Stabbert et al., 2003) and against a series of CC from the US (Roemer et al., 2004). The 1R4F cigarette is considered to be representative of the low 'tar' segment of the US cigarette market (Diana and Vaught, 1990). Notable was the significant reduction in carbon monoxide (CO) and increased yield of formaldehyde in EHCSS-E mainstream smoke, compared to the 1R4F cigarette. On a per milligram total particulate matter (TPM) basis the concentration of formaldehyde was increased approximately sevenfold (Stabbert et al., 2003). The *in vitro* genotoxicity and cytotoxicity of mainstream smoke (Tewes et al., 2003; Roemer et al., 2004; Schramke et al., 2006) and the biological activity of mainstream smoke was reduced in a 90-day sub-chronic rat inhalation study, compared to the 1R4F cigarette (Terpstra et al., 2003). A clinical evaluation performed in the US confirmed that exposure to selected mainstream cigarette smoke constituents was reduced (Roethig et al., 2005).

A second-generation EHCSS (series-JLI) was developed in which ammonium magnesium phosphate (AMP) was used in the cigarette paper to replace calcium carbonate (Fournier and Paine, 2001). It was anticipated that ammonia released during the pyrolysis of AMP would condense with formaldehyde to form hexamethylenetetramine (HMT). Chemical analysis of smoke from the EHCSS-JLI cigarettes containing AMP showed lower yields of formaldehyde and several reported HPHC, a further decrease in CO yield, and increased yields of ammonia and HMT (Roemer et al.,

2008). The impact of AMP on smoke composition, *in vitro* cytotoxicity and genotoxicity has been reported in detail (Roemer et al., 2008). Reduced toxicological activity of mainstream smoke was also determined in both a 90-day sub-chronic rat inhalation study and a 35-day study focusing on lung inflammation in rats (Moennikes et al., 2008). Clinical evaluations also confirmed reduced exposure to selected HPHC and reduced excretion of mutagenic material in urine (Roethig et al., 2007, 2008). Further clinical evaluations concluded that switching from CC to the second-generation EHCSS-JLI cigarette improved prognostic markers for cardiac disease assessed by symptom-limited spiroergometry (Unverdorben et al., 2007), heart rate and rate-pressure-product parameters (Unverdorben et al., 2008) after three days of product switching.

The third-generation EHCSS (series-K) electrical heater, which can be used with EHCSS menthol or non-menthol cigarettes provides up to 8 puffs per cigarette (Werley et al., 2008). The EHCSS uses controlled heating of tobacco at a temperature significantly less than encountered in the burning cone of a CC, and CC fail to activate the electronic system incorporated in the puff-activated heater. The EHCSS series-K cigarette contains a column of cigarette tobacco filler, wrapped in a tobacco mat with a cigarette paper overwrap. EHCSS-K3 and EHCSS-K6 cigarettes differ in the construction of the filter, with a more efficient filter being used in the EHCSS-K3 cigarette (Fig. 1).

The series-K cigarette is characterized by a reduced delivery of HPHC in mainstream smoke and reductions in several toxicological endpoints as observed in a battery of *in vitro* and *in vivo* assays (Werley et al., 2008). In addition, virtually eliminating the formation of sidestream smoke, which is normally formed by the smouldering of a CC, results in significantly lower concentrations of ETS when EHCSS cigarettes are smoked compared to a CC (Frost-Pineda et al., 2008a; Tricker et al., 2009). Selected biomarkers of exposure to HPHC have been shown to be reduced in clinical evaluations of CC smokers who switched to use the EHCSS-K6 cigarette (Frost-Pineda et al., 2008b,c). Favorable changes towards increased heart rate variability (Munjal et al., 2009) and pulmonary function (Unverdorben et al., 2010) have also been observed after switching from smoking CC to the EHCSS-K6 cigarette for three days.

3. Testing strategy

The current strategy is based on both non-clinical and clinical evaluations in which reduced exposure assessment is considered in a translational approach from 'product level – to smoker level – to population level'. The presented strategy is an extension of previous reduced exposure assessments of the 5 mg ISO tar EHCSS-K6 cigarette (Werley et al., 2008; Frost-Pineda et al., 2008b,c).

A key component of this strategy is the consideration of a range of machine smoking conditions for the laboratory assessments. It is known that smoking topography, e.g., puff volume, puff duration, inter-puff interval, varies greatly among smokers (Schorp, 2005), and this may explain, in part, the significant within- and between-smoker variability of nicotine uptake and toxicant exposure (Byrd et al., 1998; Jarvis et al., 2001; Ueda et al., 2002; Scherer et al., 2007a; Fidler et al., 2008; Mendes et al., 2009; Lindner et al., 2011). Consequently, we have investigated the performance of the products under 25 different machine smoking conditions reflective of multiple human smoking topographies. These laboratory studies include extensive smoke chemistry analysis in addition to *in vitro* assessments.

In addition, we have selected the CC used as comparator/reference products in the studies (Table 1) based on our understanding of the type of CC smoked by the populations considered most likely to switch to the EHCSS series-K cigarette in a number of different countries. It was considered essential, for example, to ensure that any reduction in exposure that may be achieved by switching to the EHCSS would remain valid when compared to exposure resulting from using a representative CC with low International Organization for Standardization (ISO) tar and nicotine yields. With these considerations in mind, six different CC were selected as benchmarks that either matched the ISO tar delivery of the EHCSS series-K cigarettes or represented the lowest ISO tar delivery of commercially available cigarettes in the countries in which clinical evaluations were performed (Table 1).

In selecting the sites for the clinical studies, we chose countries for which we had reason to believe smoking behavior patterns might be quite different. There is, for example, a general under-

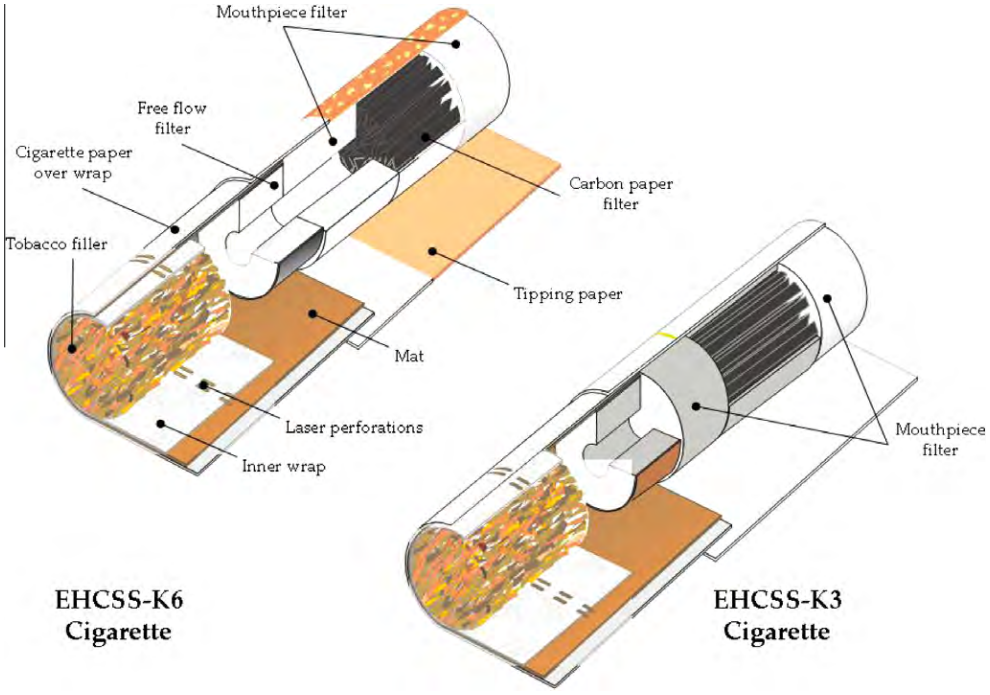

Fig. 1. Representation of the EHCSS-K6 and EHCSS-K3 Cigarettes.

Table 1
Mainstream smoke yields of tar, nicotine and carbon monoxide in EHCSS series-K cigarettes and comparator market cigarettes.

Cigarette	Brand name	Tar [mg/cig.]	Nicotine [mg/cig.]	CO [mg/cig.]
EHCSS-K3*	–	3	0.2	0.6
EHCSS-K6*	–	5	0.3	0.6
EHCSS-K6^{M}*	–	5	0.3	0.5
M6UK	*Marlboro*	6	0.5	7
M6J	*Marlboro*	6	0.5	7
M4J^{M}	*Marlboro Ultra Lights Menthol*	4	0.3	5
PM1	*Philip Morris One*	1	0.2	2
Lark1	*Lark One*	1	0.1	2
Lark1^{M}	*Lark One Menthol*	1	0.1	2

* Tar, nicotine and carbon monoxide were determined in conformity with International Organization for Standardization (ISO) methods. Puff count was set to 8 puffs based on lighter design, and data were obtained when the EHCSS-K was smoked on a linear smoking machine.

standing that smokers in Japan have different smoking behaviors and taste preferences for mentholated products compared to smokers in Western Europe (Ueda et al., 2002; Giovino et al., 2004) while Korea represents a cigarette market in which smokers have a preference for smoking cigarettes with very low smoking machine-measured ISO tar and nicotine yields.

4. *In vitro* toxicological assessment of test and marketed reference cigarettes

In Part 2 of this series of papers (Zenzen et al., 2012), 'product level' testing was performed to determine up to 49 HPHC in mainstream smoke of EHCSS-K3, EHCSS-K6, EHCSS-K6^{M} and four representative CC (M6UK, PM1, M6J, Lark1) according to ISO machine smoking conditions (International Organization for Standardization, 2000). The list of HPHC determined included compounds recommended by the US Consumer Product Safety Commission (US Consumer Products safety Commission in Consultation with the US Department of Health and Human Services, 1993) and evaluated for carcinogenicity (International Agency for Research on Cancer, 1987). The list of compounds analyzed included the determination of all nine HPHC recommended for mandated lowering of exposure levels (World Health Organization, 2008). In addition, smoke chemistry and *in vitro* toxicological assessment was performed using 25 different machine-smoking regimens delivering a range of nicotine yields between the 10th–90th percentiles of clinically determined nicotine uptake distributions ('Human Puffing Behavior' [HPB] regimens). The HPB protocols for each of the four CC were determined using a modeling approach (Urban et al., 2008), and a matrix approach was applied for the EHCSS series-K cigarettes (Zenzen et al., 2012). A subset of the data set (EHCSS-K6, M6UK, and PM1 cigarettes; ISO regimen and 15 additional experimental machine-smoking regimens reflecting HPB) was used to develop the 'nicotine bridging' method (Urban et al., 2012). The HPB regimens were used since standard machine-smoking protocols are not representative of human smoking behavior and cannot be used to predict the actual exposure of a smoker (Gori and Lynch, 1985).

In vitro toxicological assessment was performed to assess bacterial mutagenicity of the smoke particulate phase (condensate) towards three tester strains of *Salmonella typhimurium* (TA98, TA100, and TA1537 with S9 activation) in the *Salmonella* reverse mutation assay (Maron and Ames, 1983) according to recommendations by the Organization for Economic Co-operation and Development (Organization for Economic Co-operation and Development, 1997) and International Conference on Harmonization (International Conference on Harmonization, 1995). These strains were not used to determine excretion of mutagenic material in the urine of smokers in clinical studies (Tricker et al., 2012a,b,c,d). Instead, the strain YG1024, an *O*-acetyltransferase-overproducing derivative of TA98, was used which is more sensitive to the presence of mutagens in urine (Einistö et al., 1990; De Flora et al., 1995; Kuenemann-Migeot et al., 1997).

Cytotoxicity of both the particulate and the gas–vapor phase of mainstream smoke were determined by the Neutral Red Uptake (NRU) assay according to INVITTOX protocol No. 3a (INVITTOX, 1990). The test material was generated using both ISO and HPB machine-smoking regimens.

These non-clinical evaluations served to address four main objectives:

- To understand the new product's potential to reduce exposure based on reductions in smoke chemistry as compared to CC using multiple smoking regimen,
- To provide quantitative data to design clinical studies to test reductions in exposure to selected HPHC in the new product,
- To assess acceptability of the new product for use in human clinical studies, the minimum criteria of which was to ensure that the product would not present an increased or new hazard in comparison to CC, and
- To provide a broad range of measures to characterize the product which could not be directly determined in clinical evaluations.

5. Clinical evaluations

Controlled clinical studies are reported in Parts 3–7 of this series of papers (Martin Leroy et al., 2012; Tricker et al., 2012a,b,c,d). Studies were performed to determine the 'smoker level' exposure to selected HPHC when using test (i.e., EHCSS) and reference (i.e., CC) products. In order to substantiate the potential of a new tobacco product to reduce the exposure to HPHC, a reliable panel of biomarkers for assessing exposure in human smokers was used (World Health Organization, 2008). The panel of biomarkers of exposure to selected HPHC was selected based on (i) previously determined smoke chemistry (Part 2; Zenzen et al., 2012), (ii) ability of the biomarker of exposure to determine differences in exposure of the parent compound in cigarette smoke (Hecht, 2003; Feng et al., 2006; Carmella et al., 2009; Scherer et al., 2007b), and (iii) validation of the analytical methods for the determination of the biomarker in urine according to US FDA guidance (Food and Drug Administration, 2001). Individual tobacco smoke-specific and tobacco smoke-associated biomarkers of exposure were also selected depending on the individual study protocols resulting in a panel of biomarkers for the assessment of exposure to 12 selected HPHC and excretion of mutagenic material in urine (Table 2).

The panel of biomarkers of exposure included five of the nine toxicants (1,3-butadiene, acrolein, benzene, carbon monoxide, and 4-(methylnitrosamino)-1-(3-pyridyl)-1-butanone [NNK]) recommended for mandated lowering in cigarette mainstream smoke (World Health Organization, 2008). Of the remaining four smoke toxicants (acetaldehyde, benzo(a)pyrene, formaldehyde, and *N*′-nitrosonornicotine), suitable biomarkers of exposure and/or analytical methods were not available at the time of the studies. The panel of biomarkers of exposure included:

- Nicotine and its metabolites since these are well established tobacco-specific biomarkers for assessment of exposure to cigarette smoke (Society for Research on Nicotine and Tobacco Subcommittee on Biochemical Verification, 2002; Tricker, 2006). On a quantitative basis, the determination of the concentration of the molar sum of nicotine, cotinine, *trans*-3'-hydroxycotinine, and their respective glucuronide conjugates, expressed as nico-

Table 2
Summary of smoke constituent and biomarkers of exposure determined in the EHCSS clinical evaluations.

Smoke constituent	Biomarker of exposure	Country of evaluation				
		UK	Korea	Japan	Japan	Poland
		EHCSS-K3/K6	EHCSS-K3	EHCSS-K3/K6	EHCSS-K6[M]	EHCSS-K6
		Tricker et al. (2012a)	Tricker et al. (2012b)	Tricker et al. (2012c)	Tricker et al. (2012d)	Martin Leroy et al. (2012)
1,3-Butadiene	Monohydroxybutenyl mercapturic acid (MHBMA)	✓	✓	✓	✓	✓
2-Naphthylamine	2-Naphthylamine (2-NA)	–	✓	✓	✓	✓
4-Aminobiphenyl	4-Aminobiphenyl (4-ABP)	–	✓	✓	✓	✓
Acrolein	3-Hydroxypropyl mercapturic acid (3-HPMA)	✓	✓	✓	✓	✓
Acrylamide	Acrylamide mercapturic acid (AAMA)	–	✓	✓	✓	✓
	Glycidamide mercapturic acid (GAMA)	–	✓	✓	✓	✓
Benzene	*S*-Phenyl mercapturic acid (*S*-PMA)	✓	✓	✓	✓	✓
Carbon monoxide	Carbon monoxide (CO)	–	–	–	–	✓
	Carboxyhemoglobin (COHb)	✓	✓	✓	✓	✓
Crotonaldehyde	3-Hydroxy-1-methylpropyl mercapturic acid (3-HMPMA)	✓	✓	✓	✓	–
Nicotine	Cotinine (COT-P)	✓	✓	✓	✓	–
	Nicotine (NIC-P)		✓	✓	–	–
	Nicotine equivalents (NEq)[b]	✓	✓	✓	✓	✓
NNK[a]	Total 4-(methylnitrosamino)-1-(3-pyridyl)-1-butanol (NNAL)[c]	✓	✓	✓	✓	✓
Pyrene	Total 1-hydroxypyrene (1-OHP)[d]	✓	✓	✓	✓	✓
o-Toluidine	*o*-Toluidine (*o*-TOL)	–	✓	✓	✓	✓
Mutagens	*Salmonella* mutagenicity (YG1024 with S9)	✓	✓	✓	✓	–

[a] NNK, 4-(methylnitrosamino)-1-(3-pyridyl)-1-butanone.
[b] Nicotine equivalents (NEq) were determined as the molar sum of nicotine, cotinine, and *trans*-3'-hydroxycotinine plus their respective glucuronide conjugates.
[c] Total 4-(methylnitrosamino)-1-(3-pyridyl)-1-butanol (NNAL) was determined as the molar sum of 4-(methylnitrosamino)-1-(3-pyridyl)-1-butanol and its *O*-glucuronide conjugate.
[d] Total 1-hydroxypyrene (1-OHP) was determined as the molar sum of 1-hydroxypyrene and its glucuronide and sulfate conjugates.

tine equivalents (NEq), in 24-h urine provides an estimate of approximately 85% of the total nicotine uptake (Benowitz et al., 1994; Tricker, 2006). In addition, serum cotinine and plasma nicotine were also determined in some of the clinical evaluations (Benowitz, 1988).

- Carboxyhemoglobin (COHb) was selected as a biomarker of CO exposure based on its classical use for determination of tobacco smoke exposure (Rieben, 1992; Society for Research on Nicotine and Tobacco Subcommittee on Biochemical Verification, 2002; Scherer, 2006).
- Total 4-(methylnitrosamino)-1-(3-pyridyl)-1-butanol (NNAL) plus its *O*-glucuronide conjugate 4-[(methylnitrosamino)-1-(3-pyridyl)but-1-yl]-β-*O*-D-glucosiduronic acid (NNAL-Gluc) was determined as a tobacco-specific biomarker of exposure to NNK (Hecht and Tricker, 1999).
- Total 1-hydroxypyrene (1-OHP) plus its glucuronide and sulfate conjugates (Strickland et al., 1996) was determined as a surrogate marker for the total concentration of polycyclic aromatic hydrocarbons (PAHs) present in cigarette smoke (Brandt and Watson, 2003).
- 2-Naphthylamine (2-NA), 4-aminobiphenyl (4-ABP), and *o*-toluidine (*o*-TOL) were determined directly in urine (Riedel et al., 2006) as representative aromatic amines present in cigarette smoke (Matsuda and Hoffmann, 1969; Patrianakos and Hoffmann, 1979).
- *N*-Acetyl-*S*-(2-carbamoylethyl)-L-cysteine (AAMA) and *N*-(*R*,*S*)-acetyl-*S*-(2-carbamoyl-2-hydroxyethyl)-L-cysteine (GAMA) were determined in urine as biomarkers of exposure to acrylamide (Urban et al., 2006).
- 1-Hydroxy-2-(*N*-acetylcysteinyl)-3-butene and 1-(*N*-acetylcysteinyl)-2-hydroxy-3-butene (collectively called MHBMA for monohydroxybutenyl mercapturic acid) were determined in urine as a biomarker of exposure to 1,3-butadiene (van Sittert et al., 2000).
- 3-Hydroxy-1-methylpropylmercapturic acid (HMPMA) was determined as a biomarker of exposure to crotonaldehyde, an α,β-unsaturated aldehyde present in cigarette smoke (Scherer et al., 2007b).
- *S*-Phenyl mercapturic acid (*S*-PMA) was selected from several known metabolites of benzene as a biomarker of exposure to benzene in tobacco smoke (Melikian et al., 1993; Fustinoni et al., 2005).
- 3-Hydroxypropyl mercapturic acid (3-HPMA) was selected as a biomarker of exposure to acrolein (Mascher et al., 2001).

In addition, *Salmonella typhimurium* YG1024 was used to determine excretion of mutagenic material in urine (Einistö et al., 1990).

The clinical studies had one primary objective: To comparatively assess exposure reductions of EHCSS vs. CC smoke HPHC, when these products were used by different smoking populations. This testing strategy extends the observed differences in smoke chemistry reductions using standardized machine-smoking protocols ('product level'), to a measure of actual uptake in a controlled clinical environment ('smoker level'), minimizing biases such as dual use, or differential exposures from other sources. This approach partially addresses differences in smoking behavior and exposure to tobacco smoke HPHC, albeit with some limitations. For example, the circumstances of use within the clinical environment may be quite artificial and the maximum actual use level of the EHCSS (i.e., number of smoked cigarettes per day) was limited to the determined consumption of CC at Baseline. Thus, subjects could not increase their use of EHCSS above the number of CC they had originally smoked, i.e., one possible method for compensation was, in effect, prohibited by the study design (Scherer, 1999).

In Part 3 of this series of papers, an 8-day randomized, controlled, open-label, parallel-group, single-center study design was used to compare biomarkers of exposure to nine selected HPHC in cigarette smoke (Table 2) in 160 male and female Caucasian subjects smoking the M6UK cigarette at baseline who were randomized to continue smoking M6UK cigarettes, or switch to EHCSS-K3, EHCSS-K6, or PM1 cigarettes (for cigarette definitions see Table 1), or to no-smoking (Tricker et al., 2012a). The study was conducted in Belfast, Northern Ireland, The primary objectives of the study were to compare exposure to benzene and CO between the study groups on Day 8 vs. baseline (Day 0). The mean decreases from baseline to Day 8 were statistically significant ($p \leqslant 0.05$) for

all determined HPHC including CO and benzene, and excretion of mutagenic material in urine in the EHCSS-K3 (range: −41.2 ± 26.6% to −83.1 ± 9.2% [mean ± standard deviation]) and EHCSS-K6 (range: −35.5 ± 29.2% to −79.4 ± 14.6%) groups. The largest reductions in exposure occurred in the no-smoking group (range: −55.4 ± 45.0% to −100.0 ± 0.0%).

In Part 4 of this series of papers, an 8 day randomized, controlled, open-label, parallel-group, single-center study design was used to compare biomarkers of exposure to twelve selected HPHC (Table 2) in urine, in 72 male and female Korean subjects smoking the Lark1 cigarette at baseline who were randomized to continue smoking the Lark1 cigarette, or switch to using EHCSS-K3, or to no-smoking (Tricker et al., 2012b). The study was conducted in Seoul, South Korea. The primary objective of the study was to compare exposure to CO between the study groups on Day 8. CO exposure was significantly lower in the EHCSS-K3 group than in the Lark1 group at Day 8 ($p < 0.001$). The mean decreases from baseline (Day 0) to Day 8 were statistically significant (all $p < 0.05$) for 10 of 12 selected HPHC in mainstream cigarette smoke including CO, in the EHCSS-K3 group (range: −1.5 [−9.9, −0.1]% to −74.2 ± 10.1%). Exposure to acrolein (−1.3 ± 35.8%) was not significantly reduced, and exposure to crotonaldehyde was increased (28.1 ± 155.3%). The largest mean reductions in HPHC occurred in smokers who switched to no-smoking (−3.4 ± 41.8 to −98.9 ± 0.6%). Excretion of mutagenic material in urine was decreased significantly ($p < 0.05$) in the EHCSS-K3 and no-smoking groups (−31.8 ± 48.8% and −45.3 ± 29.7%, respectively).

In Part 5 of this series of papers, an 8-day randomized, controlled, open-label, parallel-group, single-center study design to compare biomarkers of exposure to twelve selected HPHC in cigarette smoke (Table 2) in 128 male and female Japanese subjects smoking M6J cigarettes at baseline who were randomized to continue smoking M6J cigarettes, or switch to EHCSS-K3, EHCSS-K6, or Lark1 cigarettes, or to no-smoking (Tricker et al., 2012c). The study was conducted in Osaka, Japan. The primary objective of the study was to compare exposure to CO between the study groups on Day 8. CO exposure was significantly lower in the EHCSS groups than in the Lark1 group at Day 8 ($p < 0.001$). The mean decreases from baseline (Day 0) to Day 8 were statistically significant ($p \leqslant 0.05$) for all biomarkers of exposure to the selected HPHC including CO, and mutagenic material in urine in the EHCSS-K3 (range: −9.8 ± 60.0 to −73.0 ± 13.0%) and EHCSS-K6 (range: −14.6 ± 51.8–−75.6 ± 11.4%) groups. The largest reductions in exposure to HPHC (all significant at the $p \leqslant 0.01$ level) occurred in the no-smoking group (range: −13.7 ± 90.9 to −97.6 ± 6.5%).

In Part 6 of this series of papers, a 6 day randomized, controlled, open-label, parallel-group, single-center study design was used to compare biomarkers of exposure to twelve selected HPHC in cigarette smoke (Table 2) and serum Clara cell 16-kDa protein, an indicator of lung epithelial injury, in 102 male and female Japanese subjects smoking the $M4J^M$ cigarette at baseline who were randomized to continue smoking $M4J^M$, or switch to smoking $EHCSS\text{-}K6^M$, or switch to $Lark1^M$, or to no-smoking (Tricker et al., 2012d). The study was also conducted in Osaka, Japan, and was designed to investigate the effect of menthol in the $EHCSS\text{-}K6^M$ cigarette. The primary objective of the study was to compare exposure to CO between the study groups on Day 5/6. Exposure to CO was significantly reduced on Days 5/6 for the $EHCSS\text{-}K6^M$ group than for both $M4J^M$ and $Lark1^M$ groups ($p < 0.001$). The mean decreases from baseline (Days −1/0) to Day 5/6 were statistically significant ($p \leqslant 0.05$) for exposure to CO, most biomarkers of exposure and excretion of mutagenic material in urine in the $EHCSS\text{-}K6^M$ group (−12.3 ± 34.9 to −83.4 ± 9.7%). The largest mean reductions ($p \leqslant 0.05$) in exposure to CO, most biomarkers of exposure to HPHC and excretion of mutagenic material in urine occurred in the no-smoking group (−1.4 ± 41.0 to −93.6 ± 9.0%). Serum concentrations of Clara cell 16-kDa protein were not significantly changed in all groups, compared to baseline.

In Part 7 of this series of papers, a one month randomized, open-label, ambulatory, controlled clinical study to compare biomarkers of exposure to ten selected HPHC in cigarette smoke (Table 2) in 316 male and female Polish subjects who smoked their usual brand of CC at baseline and were randomized to either continue smoking their own brand of cigarettes or switch to EHCSS-K6 (Martin Leroy et al., 2012). The study was conducted in Warsaw, Poland. The study was intended to assess whether changes in exposure to HPHC determined in the above short-term clinical confinement studies are representative of reductions in subjects switching to smoke the EHCSS-K6 cigarette under real-life conditions. Biomarker assessments were performed at baseline (Day 0) and at various time points until completion of the study (Day 35). The primary objective of the study was to compare high-sensitivity C-reactive protein (hs-CRP) and white blood cell (WBC) counts after one month (Day 35). Within-group comparisons showed reductions in median serum hs-CRP from baseline (1.37 mg/l) to the end of study (1.11 mg/l) for the EHCSS-K6 study group and from 1.18 to 0.85 mg/l in the CC group. Mean WBC counts decreased from 7.09 ± 1.73 G/l to 6.90 ± 1.64 G/l and 7.00 ± 1.63 G/l to 6.94 ± 1.60 G/l in the EHCSS-K6 and CC groups, respectively. All biomarkers of exposure to HPHC were decreased in the EHCSS-K6 group at Day 35, although increases in cigarette consumption were observed. However, none of the reductions in biomarkers of exposure between the EHCSS-K6 and CC groups was significant.

6. Nicotine bridging and population level modeling

In Part 8 of this series of papers (Urban et al., 2012), the concept of 'nicotine bridging' was used to model additional HPHC uptake distributions based on nicotine uptake distributions obtained for mainstream smoke chemistry analysis of 2 CC and the EHCSS-K6 using the ISO regimen and 15 additional experimental machine-smoking regimens reflecting HPB (Part 2; Zenzen et al., 2012) and a clinical evaluation (Part 3; Tricker et al., 2012a). Modeling HPHC uptake proportional to nicotine uptake distributions serves as a means to assess exposure to HPHC since biomarkers of exposure to nicotine can be directly measured in clinical/population-based studies and nicotine uptake distributions calculated (Urban et al., 2012). It is assumed that exposure distributions for other HPHC for which biomarkers of exposure are not available also show quantitative retention similar to the pulmonary deposition and retention of nicotine, which is almost (i.e., 90–100%) complete (Armitage et al., 2004; Baker and Dixon, 2006). Consequently, differences in exposure to HPHC from different cigarette designs, e.g., in smokers of CC and smokers switching to the EHCSS, can be estimated based on distribution analysis of clinically determined nicotine uptake and smoke chemistry data. Furthermore, reduced exposure assessment can be extended by evaluation of similarity of the CC ('test') nicotine uptake distribution in a clinical setting ('smoker level') with the population-based nicotine uptake distribution of similar ISO tar yield ('reference') cigarettes of the same geographical region ('population level'). A criterion for similarity (test population/reference population) used was the 90% confidence interval of the median nicotine uptake (ratio of medians of test/reference), which should lie within the interval of 0.8–1.25. This evaluation addresses some concerns related to the applicability of results obtained in a clinical study population to a larger population.

7. Learning's and further elaboration of reduced exposure evaluation

As described in the IOM Report (Institute of Medicine, 2001), population harm (morbidity and mortality associated with tobacco use) is a function of toxicity of the product (per use), the intensity of its use (per user), and the prevalence of use. These product testing components have been further extended by the FSPTCA to include that a MRTP will significantly reduce the risk of tobacco-related disease to individual users, and benefit the health of the population as a whole, taking into account both current and future users of tobacco products (Family Smoking Prevention and Tobacco Control Act, 2009; Institute of Medicine, 2012). It is clear that 'prevalence of use' and 'benefit the health of the population as a whole' are requirements at the 'population level' that require a product assessment strategy much beyond that described in this series of eight papers. Similarly, a recent review by Hatsukami et al. (2012) on 'Tobacco and nicotine product testing' suggests that further studies, in particular on population effects, may be needed to inform a decision on reduced substance exposure. Such evidence should include:

(i) Clinical evaluations using comparator products that are representative of a market sample of different CC. The HPHC yields of the MRTP should ideally, with the exception of nicotine, be below the HPHC yields in CC when expressed on a per mg nicotine basis. Special analytical techniques may be required to identify whether novel compounds are present in the smoke aerosol compared to CC (Knorr et al., 2011).
(ii) Short-term clinical trials that are representative of 'actual use', i.e., no limitations in smoking rate, and subjects should be allowed to smoke their preferred brand in the CC group.
(iii) Assessment of consumer acceptability and perceptions of the MRTP.
(iv) Determination of the population exposure of the MRTP as actually used by consumers.
(v) Determination of whether the reduction in exposure from a MRTP vs. CC is 'substantial' and supports a potential for reduced risk. A useful approach to this could be the risk and exposure reduction attained with the use of MRTP compared to smoking cessation (or cessation products) in clinical studies (Institute of Medicine, 2012), and
(vi) Estimation of the potential to reduce exposure to HPHC using modeling approaches such as HPHC-to-nicotine correlations (Zenzen et al., 2012) and 'nicotine bridging' (Urban et al. 2012).

8. Summary

Developing MRTPs has been one of PMI's top priorities for many years. The challenge posed to us, and others in this area, is to reduce consumer exposure to HPHC while assuring consumer acceptance of products that achieve those reductions. With the testing approach presented in this series of papers we present one of the most comprehensive evaluations of a potential reduced exposure product performed to date. The evaluation includes investigating the MRTP in the laboratory under an extensive range of conditions, controlled clinical studies in different populations, and an extended clinical evaluation of biomarkers of exposure and effect for a one month period under conditions of actual use. In addition, a modeling approach is used to estimate exposure HPHC for which biomarkers of exposure are not available, and by comparing nicotine uptake distributions on a population level. This provides a three-level heuristic exposure assessment of the MRTP at the 'product', 'smoker', and 'population level'.

On the product level, both an MRTP's aerosol and the conventional cigarette smoke yields to which it is compared was generated in a way that reflects human smoking behavior (taking into account, for example, data from nicotine uptake distributions from clinical or observational studies, in order to better anticipate the exposures that would result from actual product use). Smoking the same MRTP and representative CCs under multiple machine-smoking conditions to determine the HPHC/nicotine ratios over a range of nicotine yields is a novel concept to understand the impact on aerosol composition due to high intra- and inter-smoker variability of nicotine uptake.

We have also studied the performance of the MRTP in a series of clinical studies which compare the use of the product in several different populations. One of the concerns raised by tobacco and public health scientists (Hatsukami et al., 2012) has been that the subpopulation of individuals who may elect to use such products may have specific smoking characteristics which need to be represented in evaluation process. Consequently, populations from three different countries were evaluated using comparator cigarettes with similar ISO tar and nicotine deliveries to the MRTP. A series of clinical studies have been performed which were designed to measure exposure to selected HPHC in a highly controlled environment over a period of several days (Parts 3–6; Tricker et al., 2012a,b,c,d). Such studies are considered appropriate to examine human exposure occurring under natural conditions (Hatsukami et al., 2005). To investigate whether such studies represent real-world patterns of product use, we also investigated biomarkers of exposure and effect in smokers for a one month period under conditions of actual use (Part 7; Martin Leroy et al., 2012).

We have used a panel of biomarkers of exposure to selected HPHC based on the availability of validated analytical methods of determination; however, we realize that some limitations may apply to the selected panel of biomarkers of exposure. The specificity of AAMA and GAMA as biomarkers of exposure to acrylamide in cigarette smoke is limited due to widespread exposure to acrylamide in heat-treated carbohydrate rich foods (Bjellaas et al., 2007). Similarly, the ubiquitous occurrence of acrolein in the environment and endogenous formation during lipid peroxidation (Stevens and Meier, 2008) may limit the usefulness of 3-HPMA to assess changes in tobacco smoke-related exposure to acrolein. Similarly, the specificity of 1-OHP as a surrogate marker for exposure to polycyclic aromatic hydrocarbons (PAH) in cigarette smoke is limited due to multiple environmental sources of pyrene (Strickland et al., 1996). Nevertheless, 1-OHP has proved to be a suitable biomarker of exposure to PAH in studies investigating smoking of either EHCSS or conventional cigarettes, and non-smoking, under controlled conditions (Feng et al., 2006). Some doubt also exists as to the specificity of HMPMA as a biomarker of exposure to crotonaldehyde (Hecht et al., 2001). Several known metabolites which have been proposed as biomarkers of exposure to 1,3-butadiene lack sensitivity at low levels of exposure (van Sittert et al., 2000), while many known metabolites of benzene, e.g., *trans*,*trans*-muconic acid (*t*,*t*-MA), are either non-specific to benzene exposure (Medeiros et al., 1997) or are also present in the diet (Boogaard and van Sittert, 1996; Ruppert et al., 1997). The mainstream smoke constituents responsible for the excretion of mutagenic material in urine are also currently unknown. As a consequence, we have only used the *Salmonella* YG1024 tester strain which is known to be sensitive to the mutagenic activity of aromatic amino, hydroxylamino, and nitro compounds (Einistö et al., 1990), but is unable to detect the mutagenic activity of other classes of cigarette smoke mutagens excreted in urine.

Our current use of nicotine equivalent excretion in urine, the best available method to estimate total nicotine exposure, has also allowed the determination of effective HPHC-to-nicotine regressions for each of the HPHC determined using biomarkers of expo-

sure. The lowering of toxicants per unit dose of nicotine is considered to be critical by the public health community (Burns, 2006; Burns et al., 2008; World Health Organization, 2008) and has not been adequately addressed in previous studies. The presented series of papers provide clear evidence that this goal can be achieved for many smoke toxicants.

The final paper in this series (Part 8; Urban et al., 2012) offers an approach to bridge from laboratory and clinical studies performed under controlled conditions to estimate exposure at the population level.

Although regulatory guidance on the assessment of MRTPs should soon become available in the US (Family Smoking Prevention and Tobacco Control Act, 2009), we present our learnings from reduced exposure testing dating back to before the FSPTCA was enacted. We believe that the elements we present are a step towards a reasonable assessment strategy, but additional insight, in particular for the assessment of population level exposure, needs to be gained from future assessments.

9. Conflict of Interest statement

All authors are Philip Morris International (PMI) R&D employees. The work reported in all eight parts of this supplement was funded by PMI R&D.

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January 2013

ash briefing
action on smoking and health

Electronic cigarettes

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Summary

- E-cigarettes are evolving and there is increasing evidence to suggest that some if not all products provide effective nicotine delivery.
- There is little real-world evidence of harm from e-cigarettes to date, especially in comparison to smoking.
- E-cigarettes are used by both smokers and ex-smokers, but there is little evidence of use by those who have never smoked.
- ASH supports regulation to ensure the safety and reliability of e-cigarettes but, in the absence of harm to bystanders, does not consider it appropriate to include e-cigarettes under smokefree regulations.
- The Medicines and Healthcare products Regulatory Agency (MHRA) is currently reviewing options to regulate nicotine-containing products including e-cigarettes. Meanwhile, the National Institute for Health and Clinical Excellence (NICE) is developing guidance on harm reduction, which will include electronic cigarettes, for publication in May 2013.

Nicotine Substitution

Smoking is the largest, preventable cause of premature mortality in the UK. The goal of public health is to diminish the harm caused by tobacco products. While the ideal remains that people should stop using tobacco completely and permanently, consensus currently supports a properly regulated harm reduction approach[1,2,3]– a framework by which the harmful effects of smoking are reduced without requiring the elimination of a behaviour that is not necessarily condoned. Such strategies have proved successful in the past, for example within the contexts of needle exchange programmes for illicit drug use and the promotion of safer sex to prevent HIV infection.[4,5]

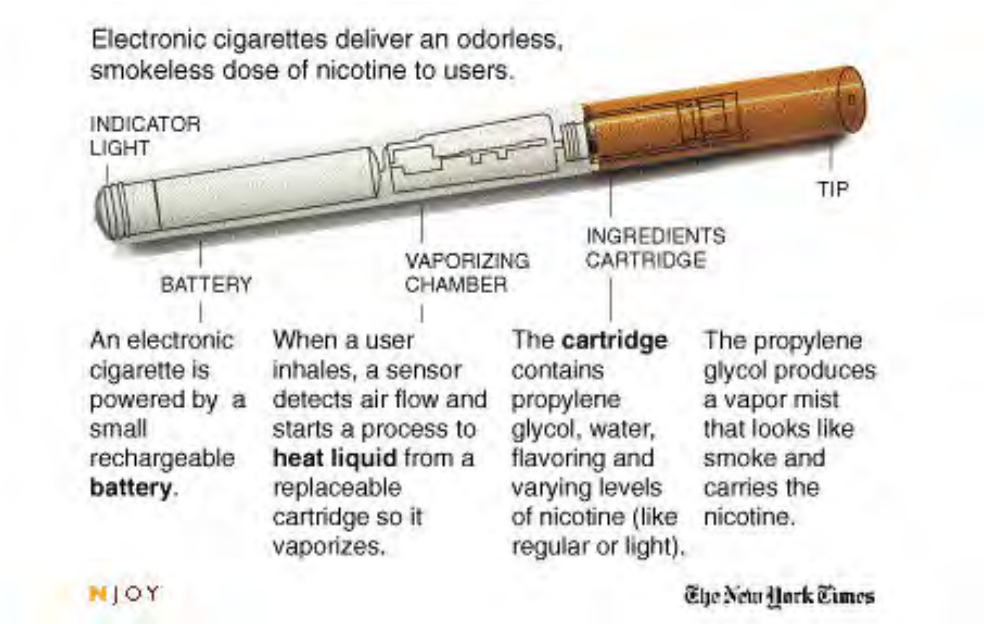
In 1976 Professor Michael Russell wrote: “People smoke for nicotine but they die from the tar.”[6] Indeed, the harm from smoking is caused almost exclusively by toxins present in tobacco released through combustion. By contrast, pure nicotine products, although addictive, are considerably less harmful. Electronic cigarettes consequently represent a safer alternative to cigarettes for smokers who are unable or unwilling to stop using nicotine.

The National Institute for Health and Clinical Excellence (NICE) is currently developing guidance on a harm reduction approach to smoking.[7] NICE’s recommendations, to be published in spring 2013, aim to inform on how best to reduce illness and deaths attributable to smoking through a harm reduction approach. As part of this guidance, NICE will include recommendations on electronic cigarettes.

What are e-cigarettes?

Electronic cigarettes, also known as electronic nicotine delivery systems (ENDS),[8] are designed to look and feel like cigarettes. They have been marketed as cheaper and healthier alternatives to cigarettes and for use in places where smoking is not permitted since they do not produce smoke.

A typical e-cigarette consists of three components: a battery, an atomiser and a cartridge containing nicotine. Most replaceable cartridges contain nicotine suspended in propylene glycol or glycerine and water. The level of nicotine in the cartridges may vary and some also contain flavourings.[9] Some e-cigarettes also have an indicator light at the end that glows when the user draws on the device to resemble a lit cigarette. When a user sucks on the device, a sensor detects air flow and heats the liquid in the cartridge so that it evaporates. The vapour delivers the nicotine to the user. There is no side-stream smoke but some nicotine vapour is released into the air as the smoker exhales.



Are e-cigarettes safe to use?

A draft review by the WHO's Tobacco Regulatory Group in 2009 notes that the extent of nicotine uptake and the safety of e-cigarettes have yet to be fully established.[8] Certainly, in the absence of thorough clinical evaluation and long term population level surveillance absolute safety of such products cannot be guaranteed. By comparison, the harm from tobacco smoking – the leading cause of preventable death in the UK – is well established.

Most of the safety concerns regarding electronic cigarettes relate to the absence of appropriate product regulation and inconsistencies in quality control. The current lack of any current authoritative oversight (although the MHRA is in the process of developing guidelines, see section on regulation) means that there is significant variability in device effectiveness, nicotine delivery and cartridge nicotine content both between and sometimes within product brands.[9] Furthermore, a recent study by the US Food and Drug Administration (FDA) has raised some safety concerns over the presence of toxins, released in low concentrations, from the vaporisation process of certain cartridges.[10] However, one study showed that after switching from tobacco to electronic cigarettes nicotine exposure was unchanged while exposure to selected toxicants was substantially reduced.[11]

There is little evidence of harmful effects from repeated exposure to propylene glycol, the chemical in which nicotine is suspended.[12,13] One study concludes that e-cigarettes have a low toxicity profile, are well tolerated, and are associated with only mild adverse effects.[14]

Is there a risk to non-users from e-cigarette vapour?

Although e-cigarettes do not produce smoke, users exhale a smoke-like vapour which consists largely of water. Any health risks of secondhand exposure to propylene glycol vapour

are likely to be limited to irritation of the throat. One study exposed animals to propylene glycol for 12 to 18 months at doses 50 to 700 times the level the animal could absorb through inhalation. Compared to animals living in normal room atmosphere, no localised or generalised irritation was found and kidney, liver, spleen and bone marrow were all found to be normal.[12]

The fact that e-cigarettes look similar to conventional cigarettes has been said to risk confusion as to their use in public places, such as on public transport.[15,16] However, given that the most distinctive feature of cigarette smoking is the smell of the smoke, which travels rapidly, and that this is absent from e-cigarette use, it is not clear how any such confusion would be sustained. Furthermore, the absence of risk from "secondhand" inhalation of vapour from e-cigarettes has been described as an "often unconsidered advantage" of e-cigarettes.[17] As an alternative to smoking, e-cigarettes are preferable in situations where secondhand smoke poses serious health risks to others, such as in vehicles or in the home.

Are e-cigarettes effective?

The degree of effectiveness depends on what effect is being measured. While public health professionals may be most concerned about their effectiveness in smoking cessation, the four benefits most widely perceived by smokers are the degree to which they satisfy the desire to smoke (60% of smokers), helping to cut down cigarettes (55%), help quit entirely (51%) and eradicating the smell of stale smoke (51%).[18,19] Effectiveness also varies between products and between users according to their experience in use.[20]

Currently in the UK, any nicotine-containing product which claims or implies that it can treat nicotine addiction is considered to be a medicinal product and is therefore subject to regulation by the MHRA. Consequently, e-cigarette manufacturers have avoided making such explicit claims. Furthermore, the WHO has stated that "the electronic cigarette is not a proven nicotine replacement therapy".[21]

Nevertheless, survey data suggests that about 4 in10[18] users do utilise them in an attempt to quit smoking and internet searches for the devices now exceed those for any other smoking cessation or nicotine replacement product.[22] There is some evidence to suggest that e-cigarette use leads to abstinence among some smokers who had not intended to quit.[23]

Empirical data on the effectiveness of e-cigarettes as a stop-smoking aid is limited and the risks and benefits are still being studied. Some reports from the published literature suggest that electronic cigarettes are inefficient nicotine delivery devices and result in only modest and unreliable increases in plasma nicotine levels.[24] Such findings appear to apply particularly to new users whereas studies using participants experienced in e-cigarette use have been found to derive more reliable nicotine intake levels.[14] Whether experienced users are able to use these devices in a way in which their nicotine intake is maximised, or the variability is down to such users preferring certain devices which might significantly differ from those used by inexperienced users, is yet to be determined.[25,26]

Nevertheless, growing evidence suggests that e-cigarettes are becoming more reliable in their nicotine delivery and that they have a beneficial impact in reducing subjective cravings and, in turn, number of cigarettes smoked.[14] Moreover, some studies have demonstrated an ability for certain brands of e-cigarettes to reduce subjective nicotine cravings despite delivering low plasma nicotine levels.[27]

Another feature of e-cigarettes that apparently lends to their effectiveness is an ability to satisfy the "hand to mouth" behavioural component that is not sufficiently addressed in more

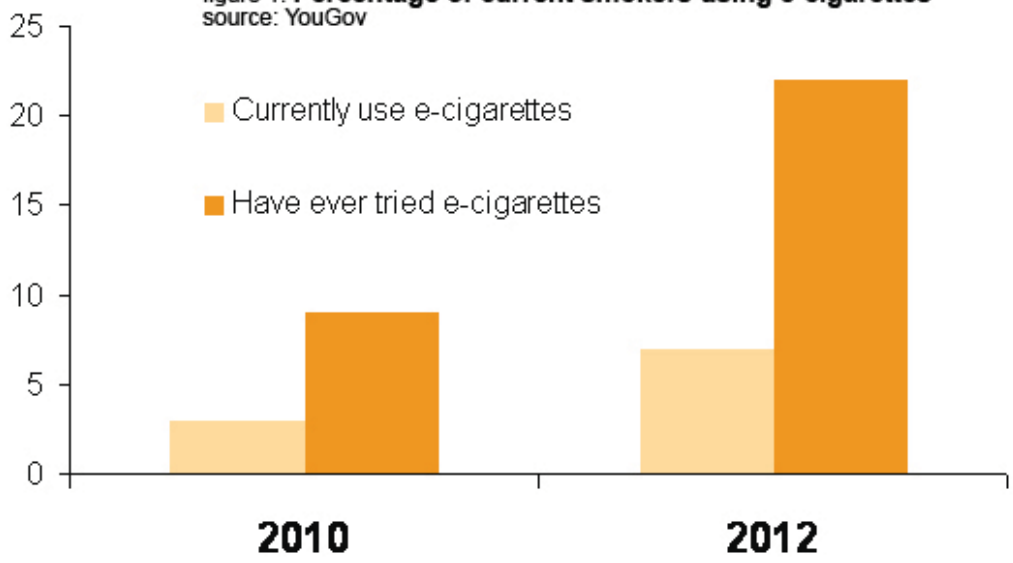
traditional nicotine replacement therapies. This has been demonstrated by users exhibiting reduced cravings, withdrawal symptoms and number of cigarettes smoked per day even when given a placebo e-cigarette.[14]

The potential value, and perceived effectiveness, of electronic cigarettes in aiding smoking cessation has been assessed in user surveys. Caution must be exercised with this data as the sample was recruited from e-cigarette users' websites. However, one such survey conducted internationally reported that 72% of users believed that e-cigarettes were beneficial in reducing cravings and withdrawal symptoms while 92% declared that the devices had reduced the number of conventional cigarettes they smoked. Indeed, in the same survey, 96% of former smokers claimed that e-cigarettes had helped them quit, and 79% reported a fear that if they stopped using them they would start smoking again.[9]

Who uses e-cigarettes in the UK?

Public awareness of e-cigarettes has grown substantially in recent years with online media playing an integral role in the growing popularity of the product. Between the years 2009 and 2011 searches via the search engine Google using the terms 'electronic cigarette' increased by fifty fold,[28] a fact the industry has attempted to capitalise on by funding various online adverts, web-pages and social networking site groups.[29] In addition to the influence of online media, there is also evidence to suggest that tighter tobacco control measures are also positively driving e-cigarette behaviour.[30]

figure 1: **Percentage of current smokers using e-cigarettes**
source: YouGov



According to an ASH YouGov survey awareness of electronic cigarettes has been increasing. For example, the percentage of smokers reporting in ASH YouGov surveys that they had never heard of e-cigarettes fell from 38% in 2010 to 21% in 2012.[31] Contemporaneous with this increased awareness has been an apparent doubling in the proportion of people reporting using the devices. According to a survey commissioned by ASH, 3% of smokers reported using e-cigarettes in 2010, a figure that increased to 7% in 2012. Similarly, the number of people reporting having tried e-cigarettes has increased significantly, more than doubling from 9% in 2010 to 22% in 2012 (see figure 1).

ASH estimates that there are 650,000 to 700,000 current users of e-cigarettes in the UK. This number is almost entirely made of current and ex-smokers; with perhaps as many as 125,000

people having replaced smoking with e-cigarette use. There is little evidence to suggest that anything more than a negligible number of non-smokers regularly use the product. [31,32]

Regulation

Currently, e-cigarettes are not regulated under smokefree law in the UK, and users are free to use them in public places such as bars, restaurants and on public transport.

An oft quoted advantage of smokefree legislation is that it de-normalises smoking, effectively distancing the behaviour from what is an accepted social norm. The ban on smoking in public places has reinforced in many people's minds that such behaviour has gone from a normal, widely accepted activity to one that is abnormal and unaccepted. There are concerns that e-cigarettes will undermine this process, threatening the now established practice of smokefree public places, such as at work or on public transport. However to date there is little evidence to suggest this is the case.

E-cigarettes are subject to general consumer protection law and it is the responsibility of trading standards officers to rule on their safety. In 2010, the Medicines and Healthcare Products Regulatory Agency (MHRA) held a public consultation on whether products containing nicotine such as e-cigarettes should be regulated.[33] Following this initial analysis a period of further research was commissioned, coordinated by the MHRA, and informed upon by an expert working group of the Commission on Human Medicines (CHM). This additional research will lead to a final decision being made in 2013. In the interim, the MHRA is working with e-cigarette manufacturers to develop a self-regulatory code of practice to foster high standards within the industry.

As well as the MHRA review, and following a referral from the Department of Health, NICE will publish its own guidance on e-cigarettes as part of a broader consultation on tobacco harm reduction, the results of which are expected to be published in May 2013. There is also a proposal to regulate nicotine- containing products as part of the revised EU Tobacco Products Directive.[34]

Conclusion

ASH believes that e-cigarettes, properly regulated to ensure safety and efficacy, should be made available as part of a harm reduction approach to tobacco. That is, we recognise that whilst efforts to help people stop smoking should remain a priority, many people either do not wish to stop smoking or find it very hard to do so. For this group, nicotine substitution products should be made available that deliver nicotine in a safe way, without the harmful components found in tobacco smoke. Most of the diseases associated with smoking are caused by inhaling smoke which contains thousands of toxic chemicals. By contrast, nicotine is relatively safe.

E-cigarettes, which deliver nicotine without the harmful toxins found in tobacco smoke, are likely to be a safer alternative to smoking. In addition, e-cigarettes reduce secondhand smoke exposure in places where smoking is allowed since they do not produce smoke. Nonetheless, nicotine is an addictive substance, e-cigarettes currently available are of highly variable safety and efficacy, and smokers are uncertain about the effectiveness of the product.

In the UK smokefree legislation exists to protect the public from the demonstrable harms of secondhand smoke. ASH does not consider it appropriate for electronic cigarettes to be subject to this legislation.

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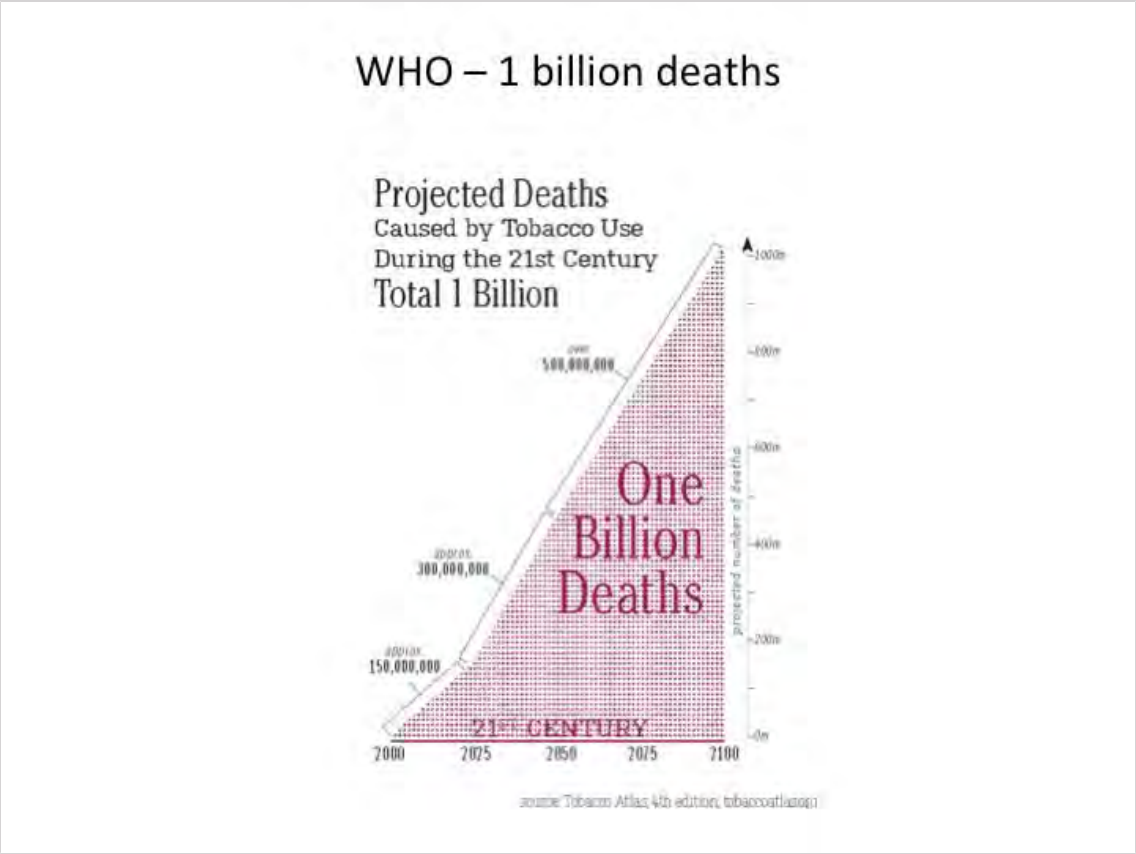
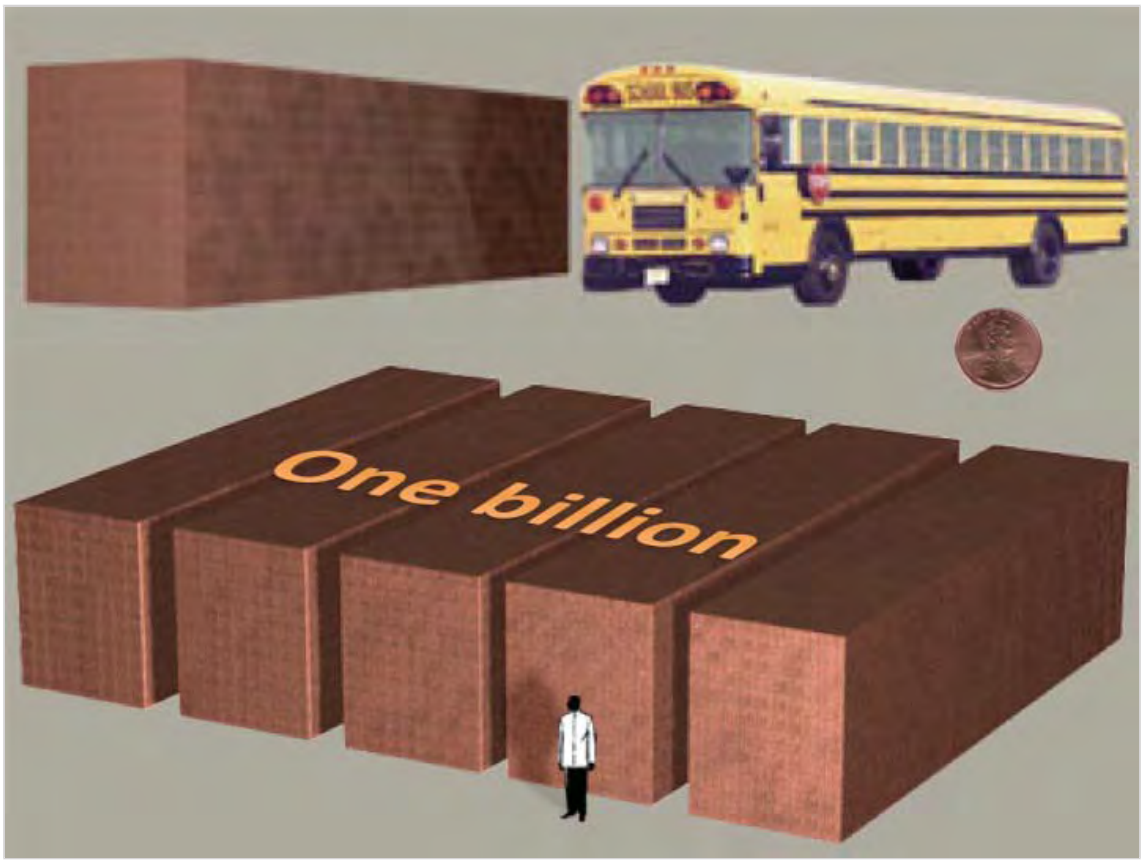
e-cigarette summit - clive bates

Clive Bates: Disclosure - no competing interests, and particularly important to say, I of course no longer speak for ASH or for the British Government, quite the contrary in fact. **(Laughter) Clive Bates:** Here we go. Right. Before I get stuck into the regulatory issues, let me just, a few words almost personally about why I think this is important.



I think everyone in public health, everyone involved in the smoking industry needs to keep an eye on the prize. And the prize relates to this one billion deaths that the WHO is estimating for the consequences of smoking in the 21st Century. Now, it's actually quite hard to find out where that number comes from but let's just keep it as an approximate sense of the impact of smoking in the 21st Century.



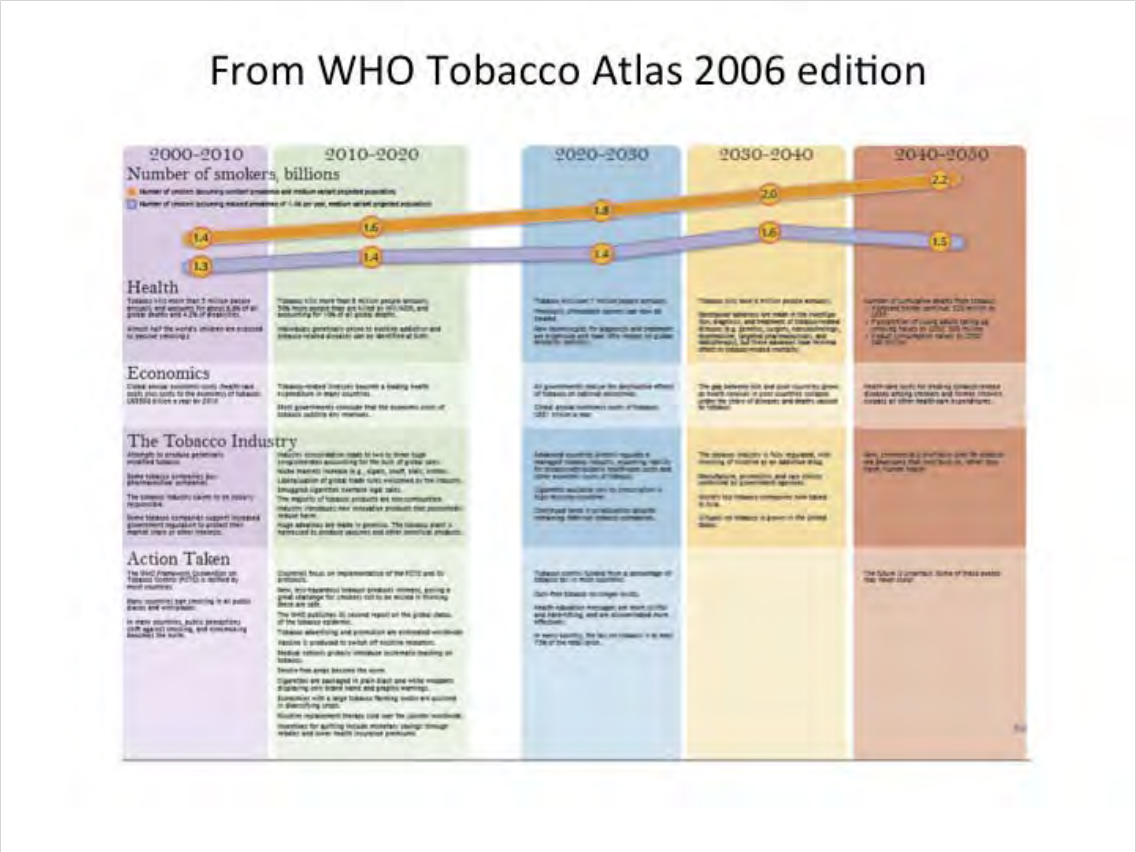
If you want to know what a billion looks like, it's five piles of pennies about the size of a bus, basically. It's a huge number of people, it's a huge number of personal storage, it's a huge amount of suffering is embodied in that number, a billion, that we toss around. And I want to go from the large-scale number just quickly to the sort of thing I get left on my blog and if you search the forums and the internet you can find these testimonies.

I smoked for 45 years and tried every NRT product available, none of them worked. I continued to smoke even though my health was getting worse, resulting in COPD and using oxygen daily.

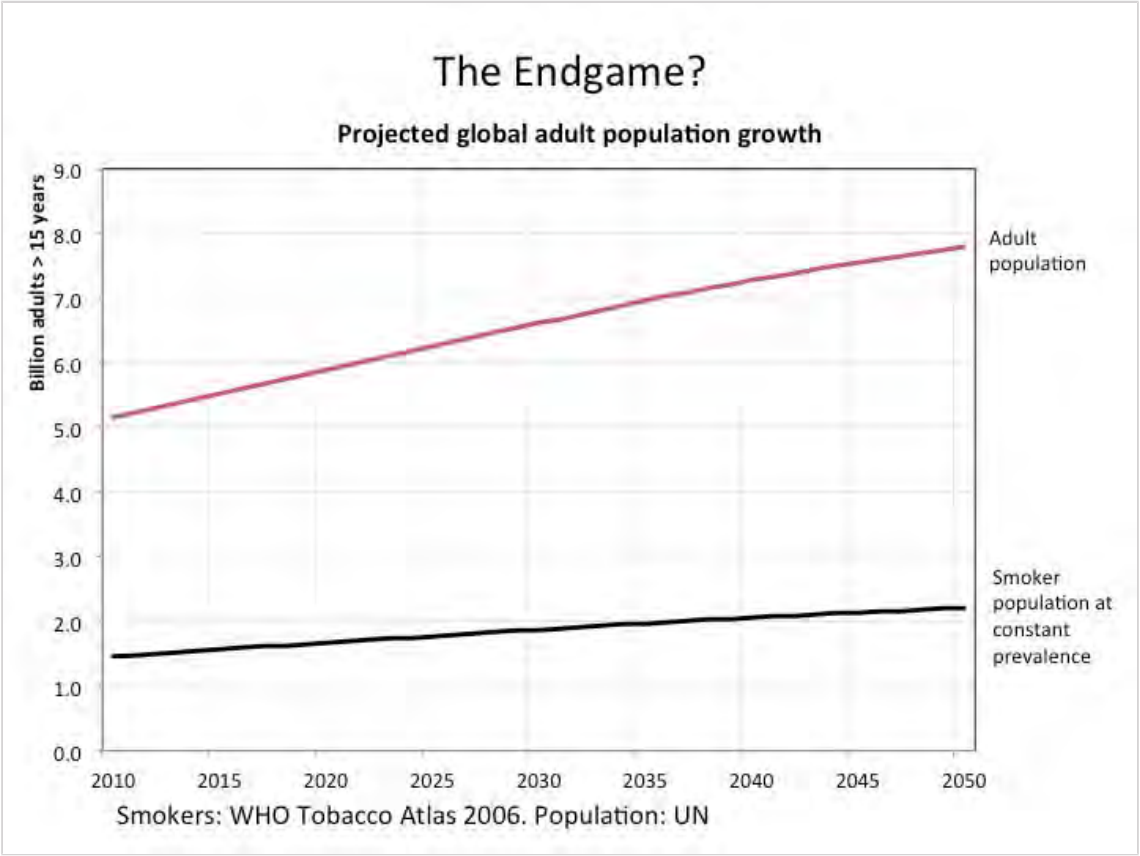
September 2011 I discovered e-cigarettes and they worked. It was like someone handed me a miracle. In less than a week I stopped using regular cigarettes. I haven't had a tobacco cigarette since.

Unsolicited comment left on www.clivebates.com

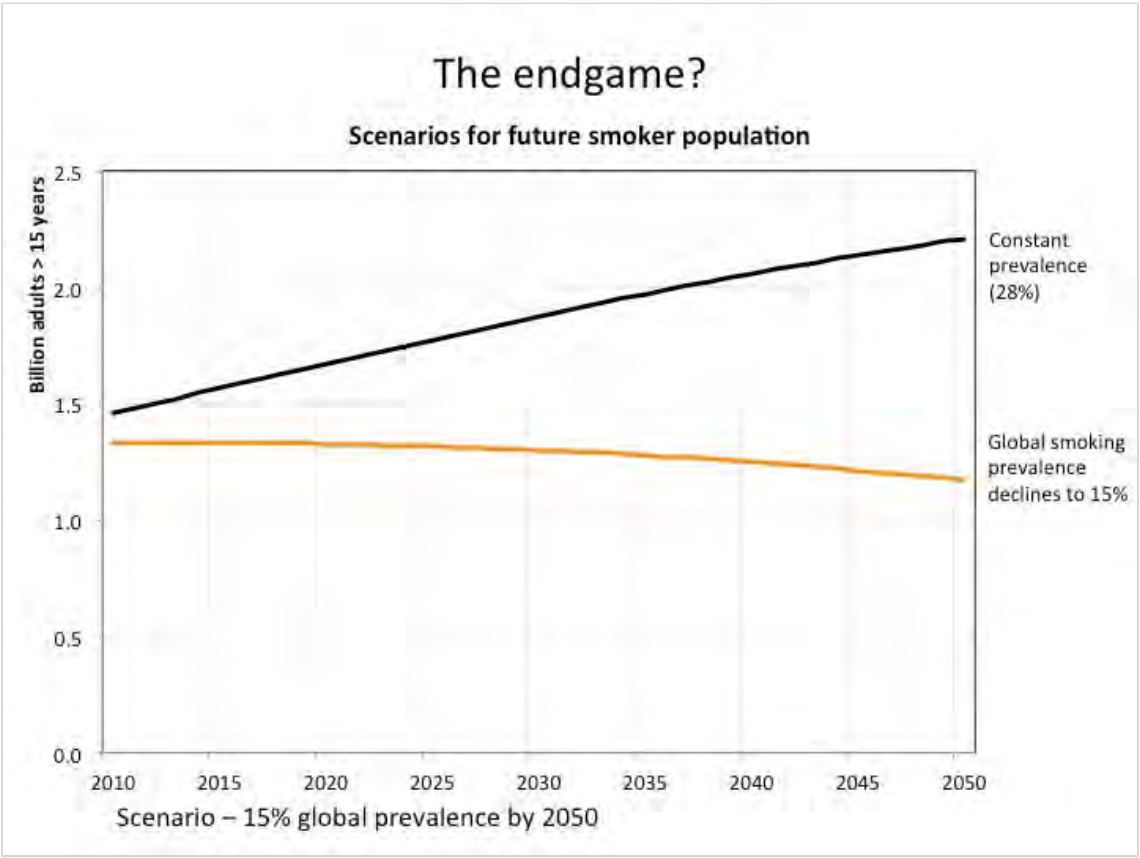
Just digest that for a minute. But basically, if you're in public health, this to me is the sort of thing that ought to get you out of bed every day. I find these sort of testimonies really moving. They're people whose lives have been changed and transformed by switching from smoking to a new technology. They're empowered, they feel much better about themselves, about their lives and everything, and there are literally thousands of these all over the internet. So the question we should be asking is: how do we get more of this? How do we get fewer of the billion and more of these great personal stories?



I just want to go back and investigate that billion a bit more. It's hard to find much information on this but the kind of last time anyone seems to have looked hard about what the future outlook for smoking in the world was was 2003 in a World Bank study which then got turned into these projections in the tobacco atlas which showed a number of smokers on current trends going to 2.2 billion by the middle of the decade, and then if some measures were taken dropping down to 1.5 billion in the world. Okay? And to be honest there isn't much more than that. So what I wanted to do, just to illustrate the start of this talk, was to take those numbers, use some actual data, recreate them slightly. So start with the growing adult population. This will all make sense in a minute, believe me.

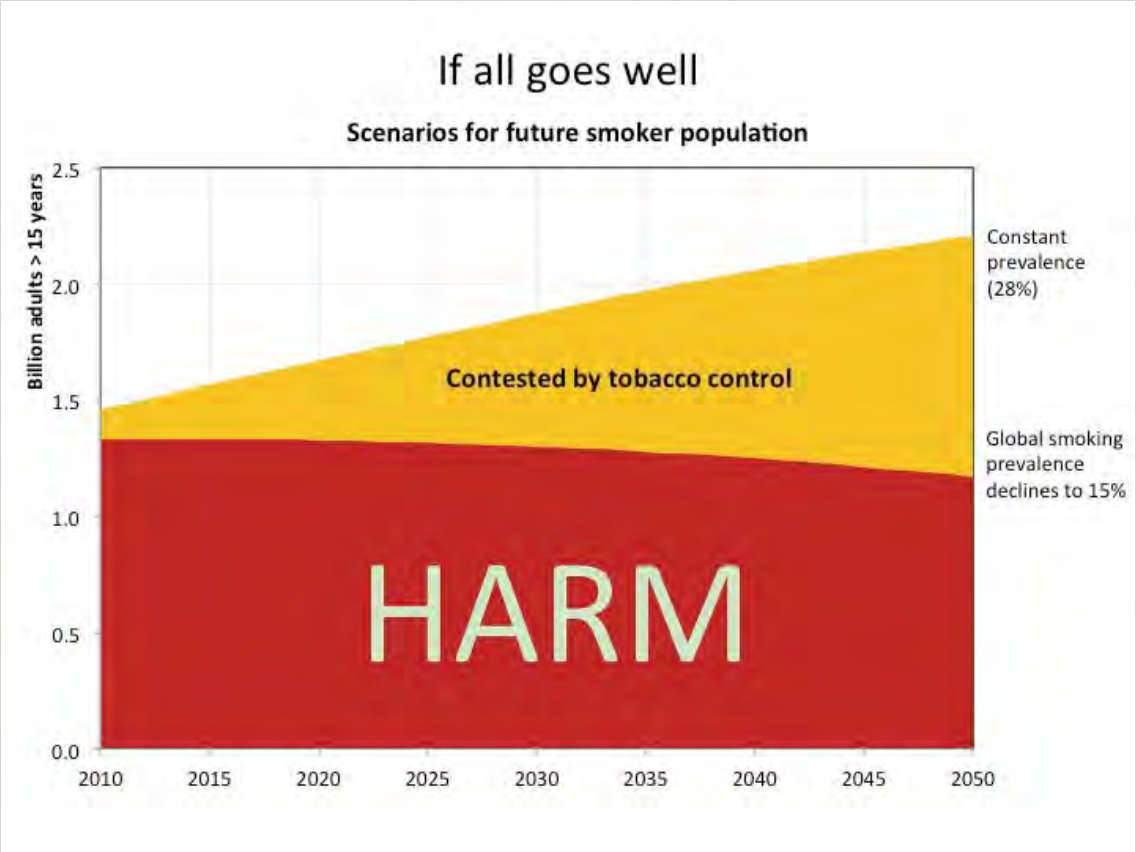


We start with the growing adult population, so these are the UN projections for people aged over 15, and it grows faster than the general population. There will be an extra 2.6 billion adults by 2050. If the current rate of smoking prevalence was to continue we'd have around 2.2 billion smokers by 2050 in the world and that's roughly the number that WHO was using.

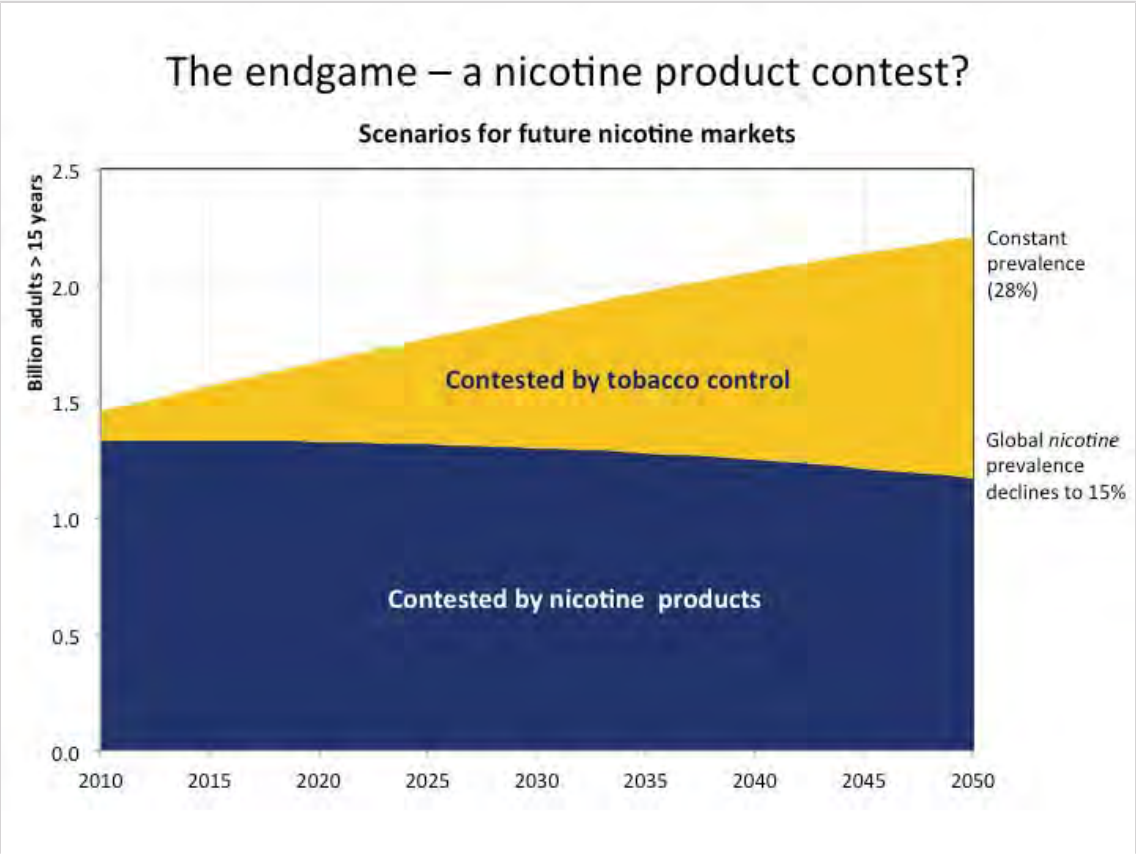


So let's re-plot that so we're just looking at smokers, so keep your eye on the black line. Re-plotted on a

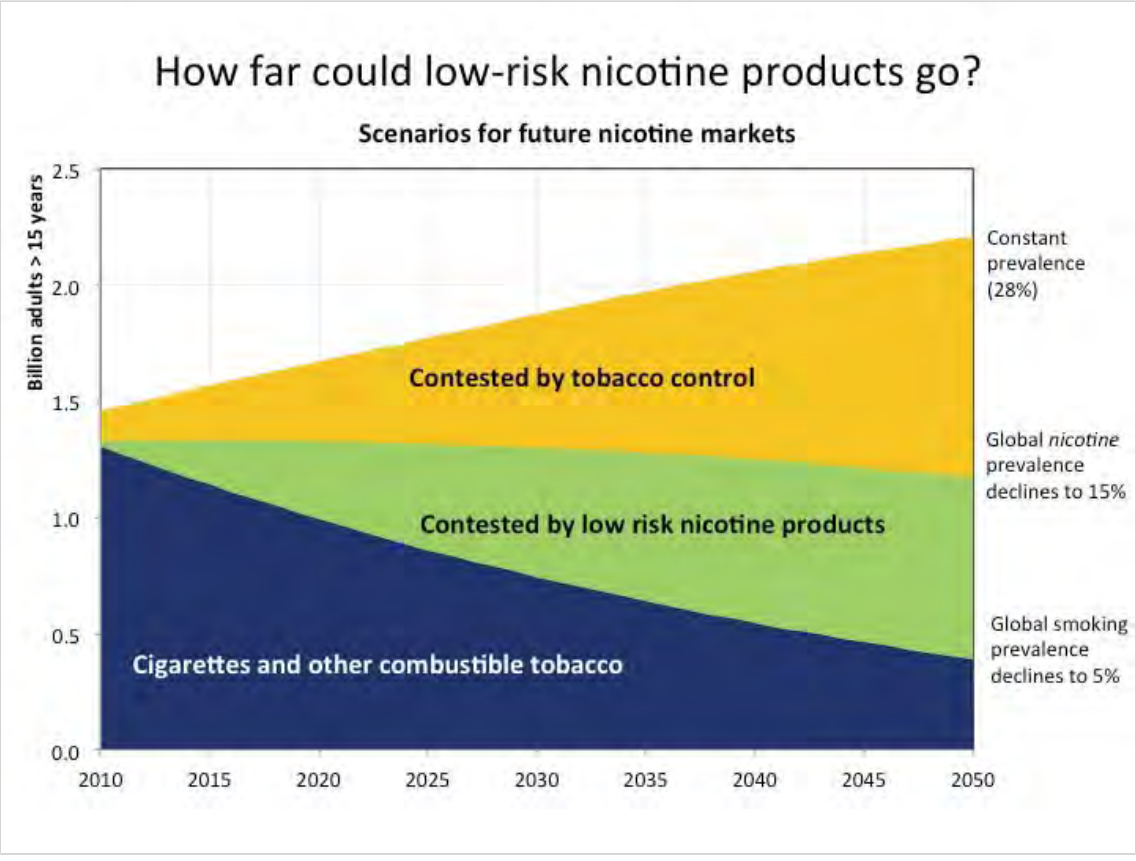
different axis. That's the number of smokers that there would be on current smoking prevalence worldwide taking account of population growth. Now the WHO's numbers in the tobacco atlas implied this trajectory which is actually consistent with achieving a 15% smoking prevalence worldwide by 2050, okay? And that's what they're sort of estimating might happen worldwide. Now let's look at this in a different way. What they're sort of saying here is that they think that's the kind of performance that can be achieved by tobacco control.



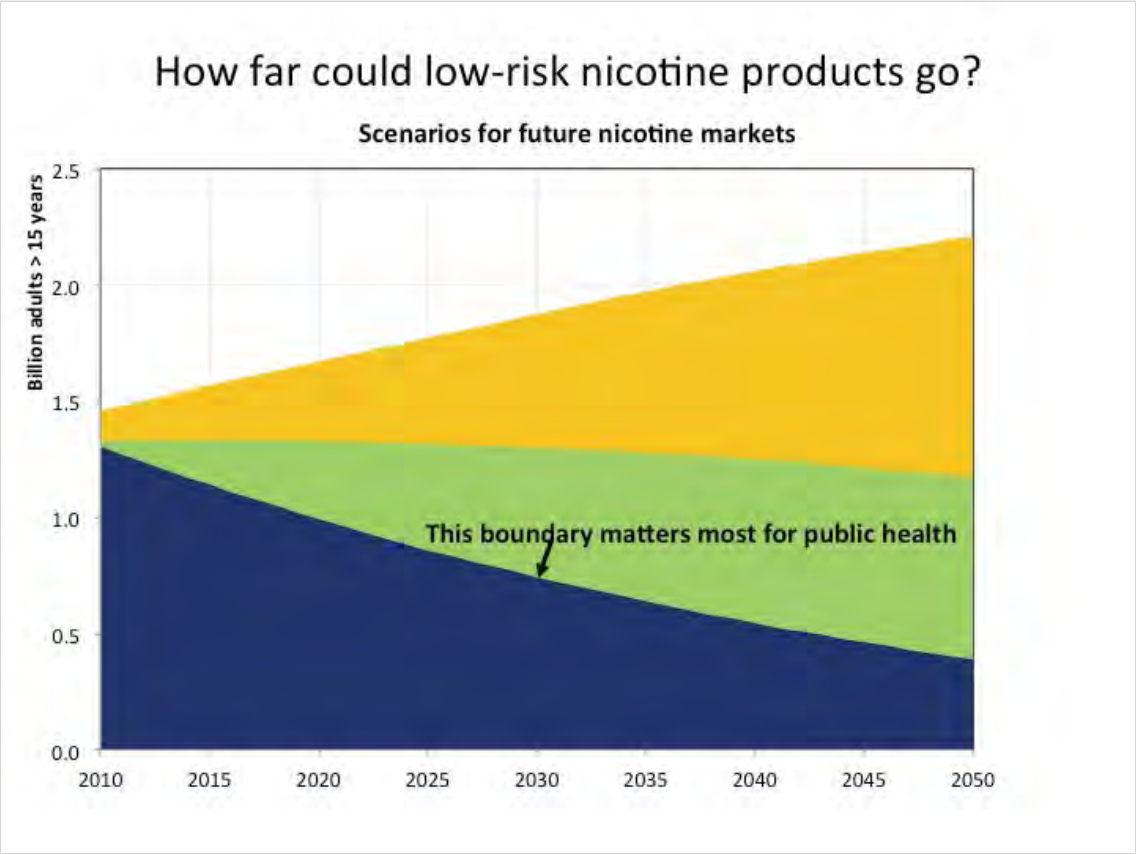
Might be more, might be less, who knows? But what they're kind of implying is that that wedge, the yellow wedge up at the top there is the sort of thing you could achieve with tobacco control, and under it is harm. This is person years of people continuing to smoke basically, billions of people continuing to smoke.



Now, the interesting thing about a supply-side response, different types of nicotine, is whether it can eat into that big, harmful area, and what I've drawn here is the idea that the top wedge is there kind of contested by tobacco control, and that's what you kind of get from the traditional package of measures which I very strongly support. And then you've got this big rump of continuing smoking that you might be able to address with a different strategy.

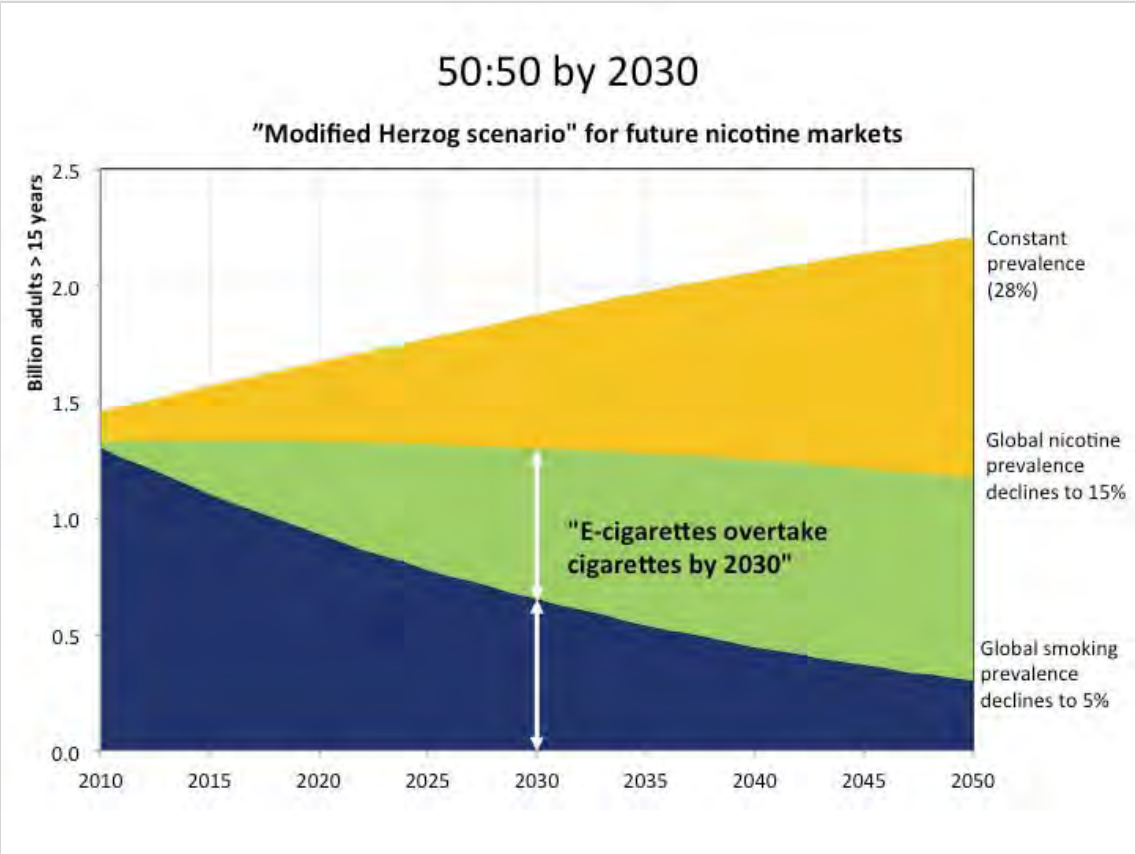


What I've done here is suggest that you might be able to get this green wedge in there, you might if you're really optimistic get a very large number of people to start to switch, and this additional strategy might reduce the area under this curve which is important for public health. Okay?

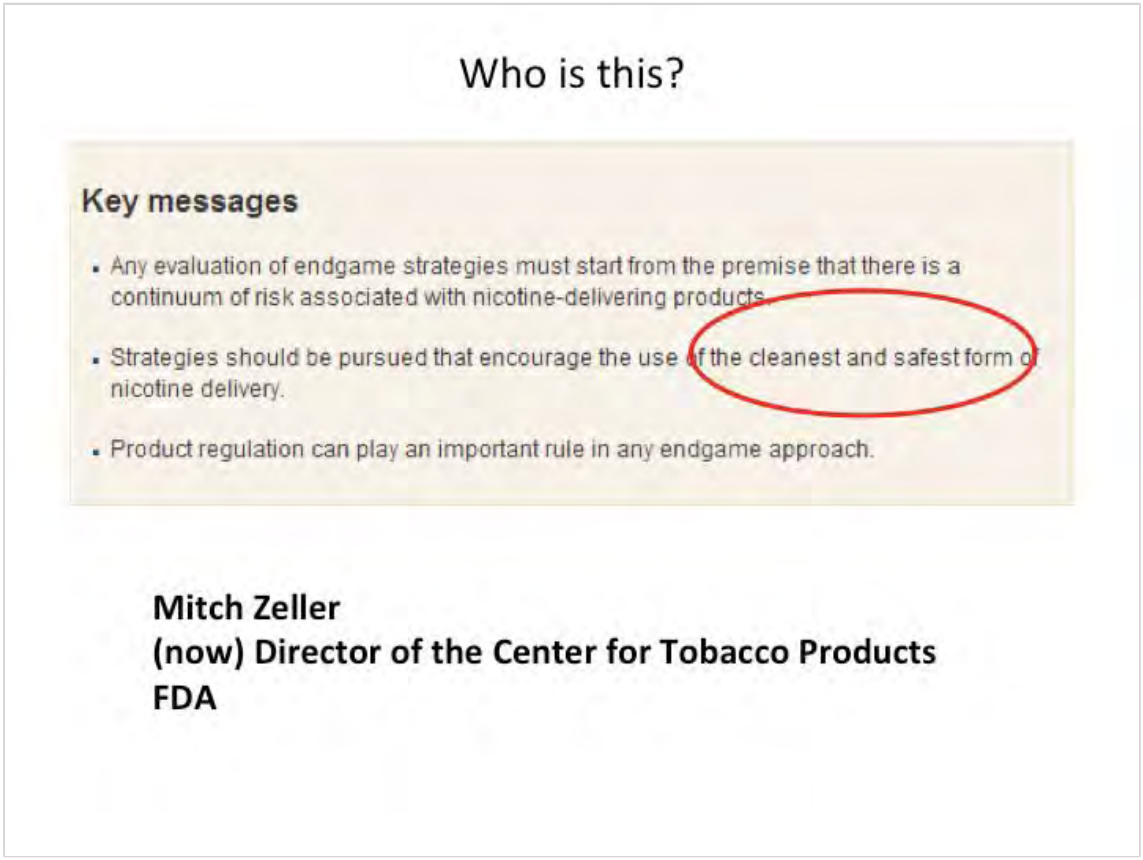


That's the boundary that matters most for public health. If you think e-cigarettes are not particularly dangerous then it's the number of people smoking, not the number of people that are using nicotine that really matters in terms of cancer, heart disease, respiratory illnesses and all the other nasties that come with smoking. Okay? Now, you might say, well these are just basically made up numbers, they're projections, they're in a model, but how realistic are they?

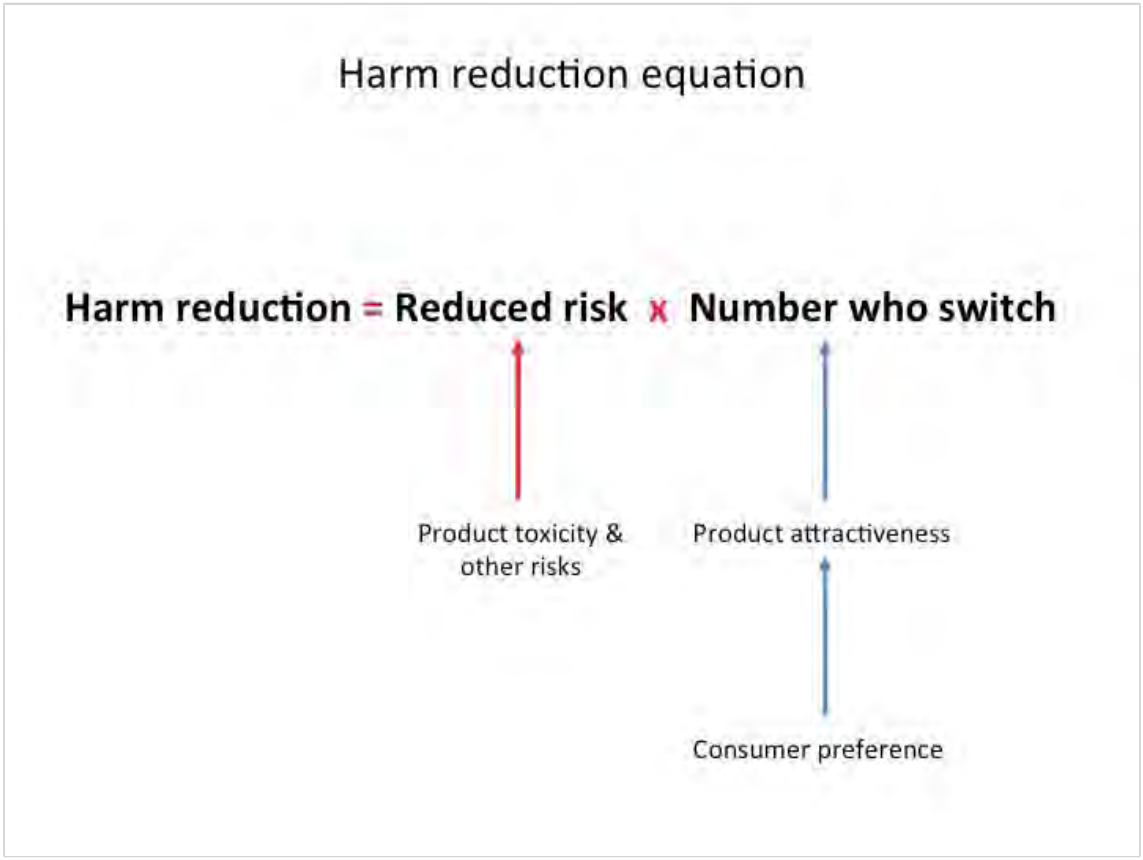
Well, I'm just drawing on this as quite a bullish commentator from one of the investment banks, and her view is that e-cigarettes might overtake traditional cigarettes in the next decade, and by that she means in the United States and by 2023. Okay? So there's people here in serious business who are looking at this industry think there is the possibility of a very disruptive revolution in these products, that would be an enormous impact on the cigarette market, on the tobacco industry if that did. I mean tobacco industry will be in the game, of course, but still extremely disruptive.



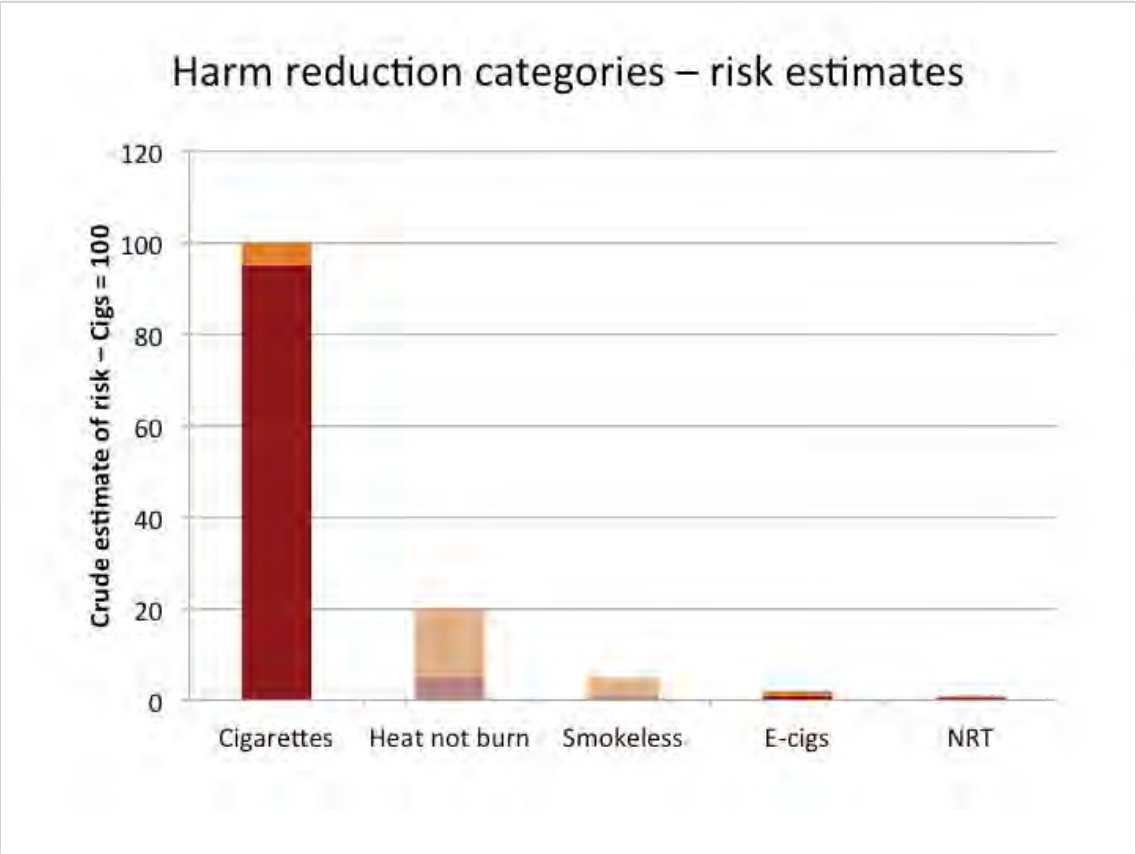
So if we just take that sort of thinking and let's say it's 2030 instead, that's the curve I showed before and that's the point at which e-cigarettes would overtake cigarette consumption, that would happen around 2030. So my whole point here is that we should be thinking really about how we get that green wedge. How do we get that green wedge to be as big and effective as possible and how do we minimise any of the unintended consequences that would come with it? And if I have a single message today it's focus on the opportunity, focus on the huge opportunity, don't become obsessed with the relatively minor risks, we'll come back to that.



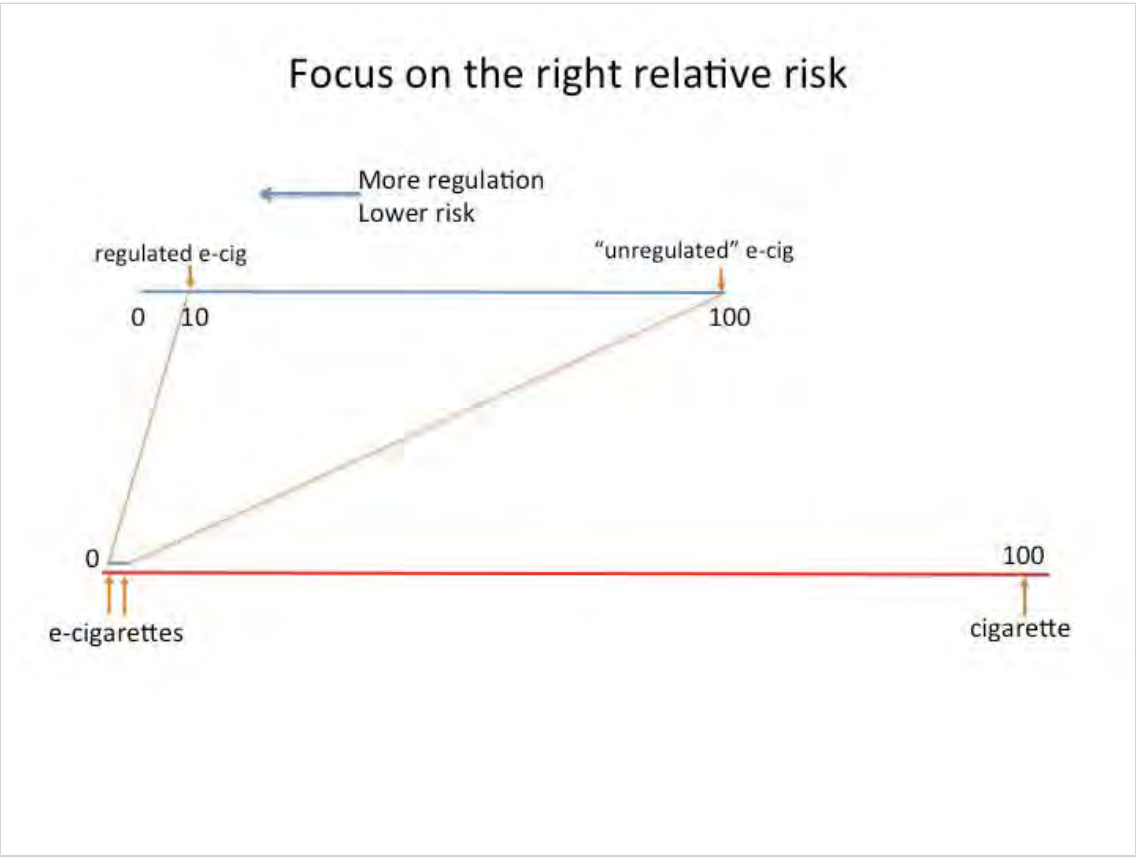
So here we go onto the regulatory piece of this. This is the sort of thing you hear people saying. “We need clean and safe nicotine delivery.” And this is Mitch Zeller now of the – he didn’t say this when he was there but he’s now of the FDA and in charge of the tobacco booth there. Okay? “Clean and safest as form of nicotine delivery.” Is that actually right? I don’t think it is right, actually, that we need the cleanest and safest form of nicotine delivery. Not if we’re concerned about that green wedge, the one billion, and getting as many people to switch.



So I have created this bespoke harm-reduction equation which I'm going to use. It's a very simple thing, don't worry, to try and illustrate what I think is a really simple idea behind this. Okay? We'll do a modification on this later to take account of population effects, but basically what you're trying to do is get reduced risk products. You want the reduction in risk to be as large as possible and you want the number to switch to be as large as possible. And the actual public health impact is the product of those two things. So if you have a really, really safe product that nobody wants to use, that's no good because nobody switches. If you have something that everyone switches to but doesn't do much to reduce harm that's no good either, and that might apply to some of the combustible harm-reduction strategies. Okay? Now the elements of this, let's start on this, really are a function of the product to some extent. The number who switch is a function of how attractive the product is and what consumers actually want to buy. Okay? So people aren't going to quitting centres or getting behavioural treatment for this. Buy them in shops instead of cigarettes. So it's not about an intervention, it's about what people choose to do, it's about consumer choice here. So let's just examine the first of those arms, the reduced risk side of it. Who knows what the reduced risks? I tried to get the panel earlier to say roughly what they thought the reduced risk was.



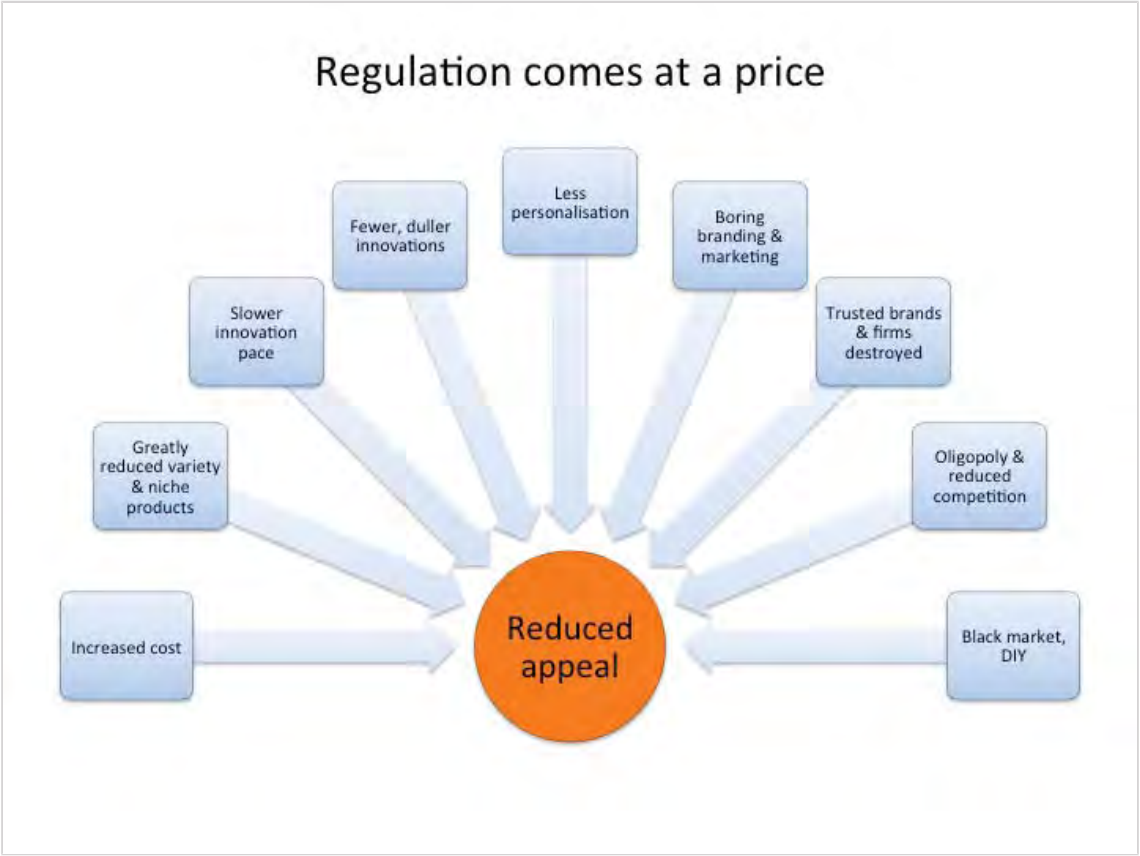
There's some work coming out from David Nutt fairly soon, but roughly speaking we're talking about one to two orders of magnitude reduction in risk compared to continued smoking, probably 95%+ reduction, whether it's for smokeless tobacco or for e-cigarettes; very hard to imagine these things just from the physics or chemistry being more risky than that.



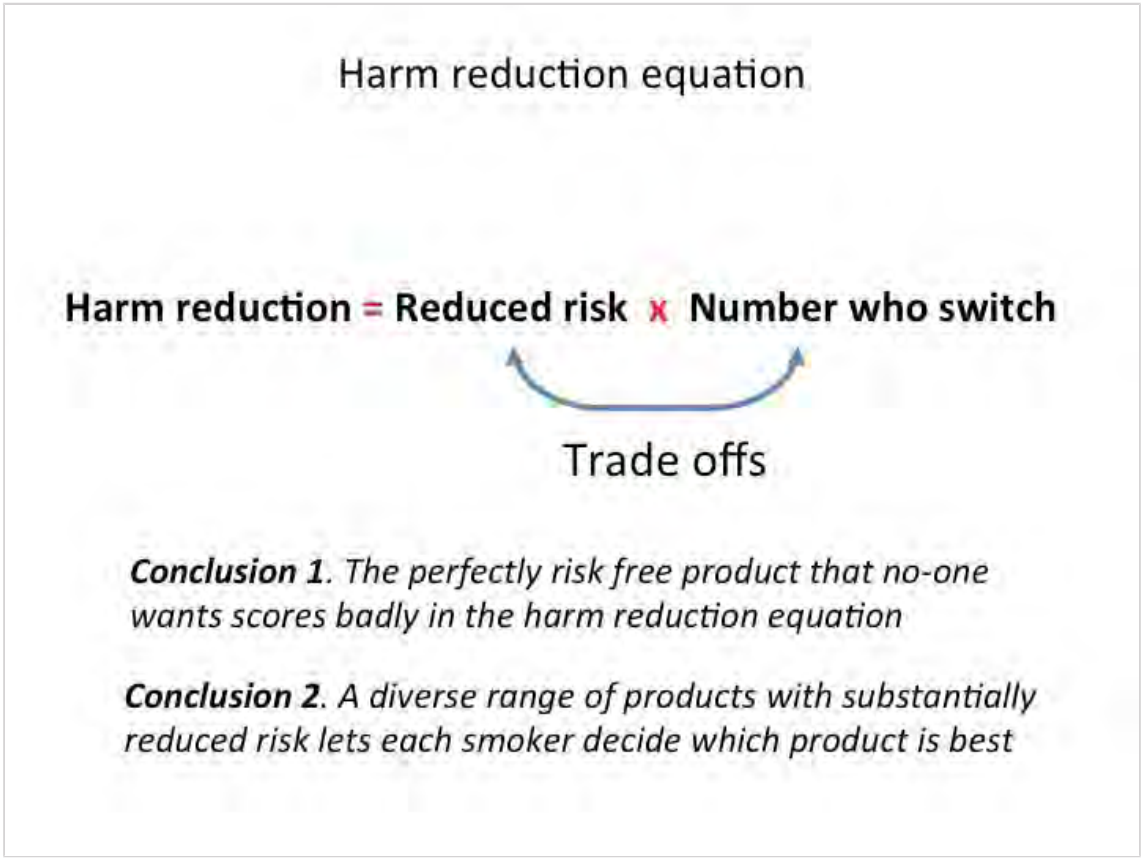
I'll try and illustrate this. Let's imagine this is a continuum of risk, and that should read 100 up there, for

ecigarettes, and a regulator comes along and says, “Look, I can make these products ten times safer by regulating them, by increasing the cost, make it more difficult, and so on, but I can make them ten times safer. Is that a good thing? Is that actually a good thing? Back to Mitch Seller’s comment. So an unregulated e-cigarette would be the risk of 100, and a regulated e-cigarette with a risk of ten. Sounds good, regulator’s really done the job well there, but actually I don’t really think it’s worth doing, and this is the reason why. Because when you plot them on a risk continuum with cigarettes, basically there’s almost no difference between something that’s 99% and something that’s 99.9% less dangerous than smoking. Okay? The whole thing here has to be about getting the risk in perspective and not spending a fortune, damaging the industry, restricting choice, making the products less attractive because you’ve tried to go from 99 to 99% less risky.

Okay, let’s go to the other column now, product attractiveness and consumer preference, and let us look at the unintended consequences of excessive regulation. And just remember what the analysts say about what’s driving the growth of these products, and the growth of these products is largely good, it’s largely an alternative to smoking and a good thing. They’re talking about the rapid pace of innovation, stepped-up advertising and a lot of internet buzz. Mostly these are things that regulators suppress, by the way. They don’t really do these sort of things that increase the interest and excitement around these products, and that’s a Wells Fargo thing.

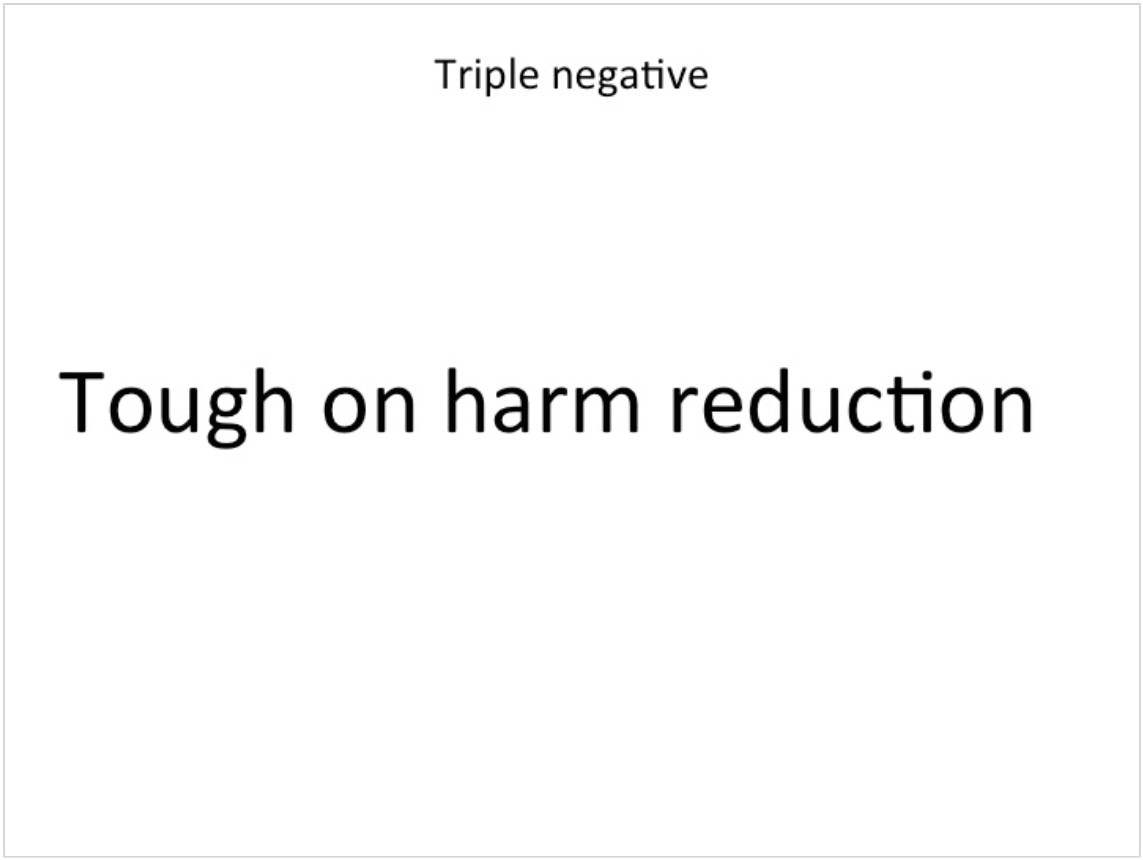


So regulation comes at a price and I just want to go through some of the unintended consequences of regulation that affect that second arm of my equation, the things that potentially reduce appeal. Greatly increased cost, huge investments needed in the supply chain, manufacturing regime and so on. Greatly reduced variety, it's expensive to get a product approved, niche products it won't be worth doing it, there will be only a certain number of things that will pass through a medicines regulation filter. So you would expect the cost to go up and the range of products to contract very dramatically, probably mostly towards those cigalike products that are produced by the larger companies. You would slow the pace of innovation, it isn't worth going to a regulator too often when it's expensive and very time-consuming to do it, and actually you get a bit of the censor in the head who says, "Actually it's not going to be worth it. I can't be bothered proving all this to the regulator." Fewer dollar innovations, so a lot of the buzz would go. I mean a lot of the excitement around e-cigarettes is around flavours, around mods and about special devices, again perhaps not really worth doing for the market. Less personalisation.



You might see one of the attractions of e-cigarettes as being able to configure it in a way that you seem really suits you. Now personalisation in medicine isn't actually a very common idea at all. So potentially thousands and thousands of different combinations of things making a product, how do you pass them all? The tendency to make the branding and marketing resemble the branding and marketing of haemorrhoid creams or NRT even is something that comes with the deadening hand of the regulator. A number of trusted brands and goodwill and choices would be destroyed by this, there's no question of that, and it's there in their impact assessment. We would tend to see dramatic concentration, so both at the product level and the firm level. A far smaller number of larger players who are able to clamber over the regulatory barriers to entry that they would create. And then finally, users are not stupid, they would take countervailing measures and there would be a growth and a thriving black market and DIY, all of which comes with more of the risks that you were trying to stop in the first place. So reduced appeal, the appeal is the key element in how we regulate e-cigarettes, we don't want to kill the product, we don't want to make it boring and bland. So there are trade-offs here. You could go a long way with the reduced risk, but you might reduce the number who switch, so the perfectly risk-free product that noone wants is very poor on the harm reduction equation. What you're really after is a diverse range of products, substantially reduced risk, let each smoker decide which is best.

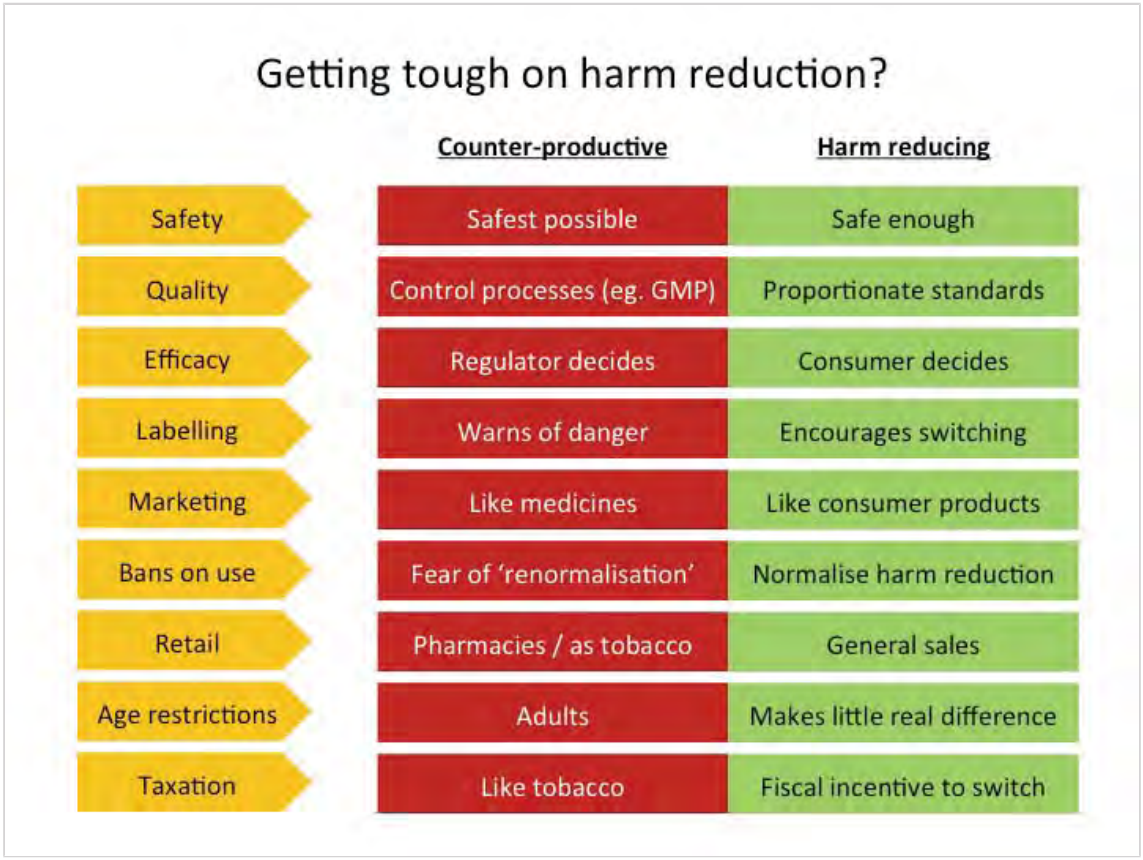
Did I mention that medicines regulation is probably illegal? It's a disproportionate, discriminatory, it's been struck down by five courts in the European Union, so even if you think it's going to bring certainty and everything it doesn't really because somebody will challenge it and it will fail in court later.



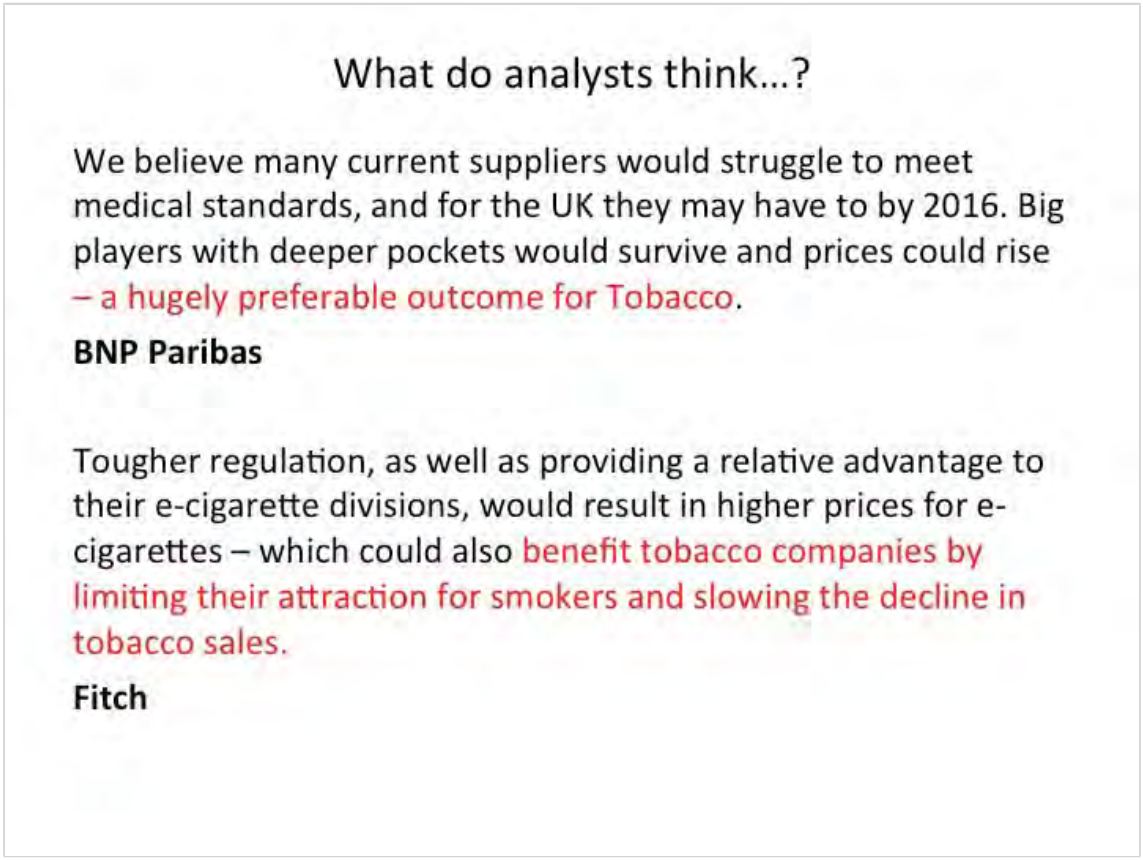
So what should you do from a regulatory point of view? Just this sentence is quite... I was toying with this this morning. Tough on harm reduction. It's a lovely triple negative involved in this and if you think that

tough regulation of harm-reduction ideas is a good idea you're basically being easy on harm, when you work through the triple negative that's behind this, and that's kind of the point that I really want to draw out in the next thing.

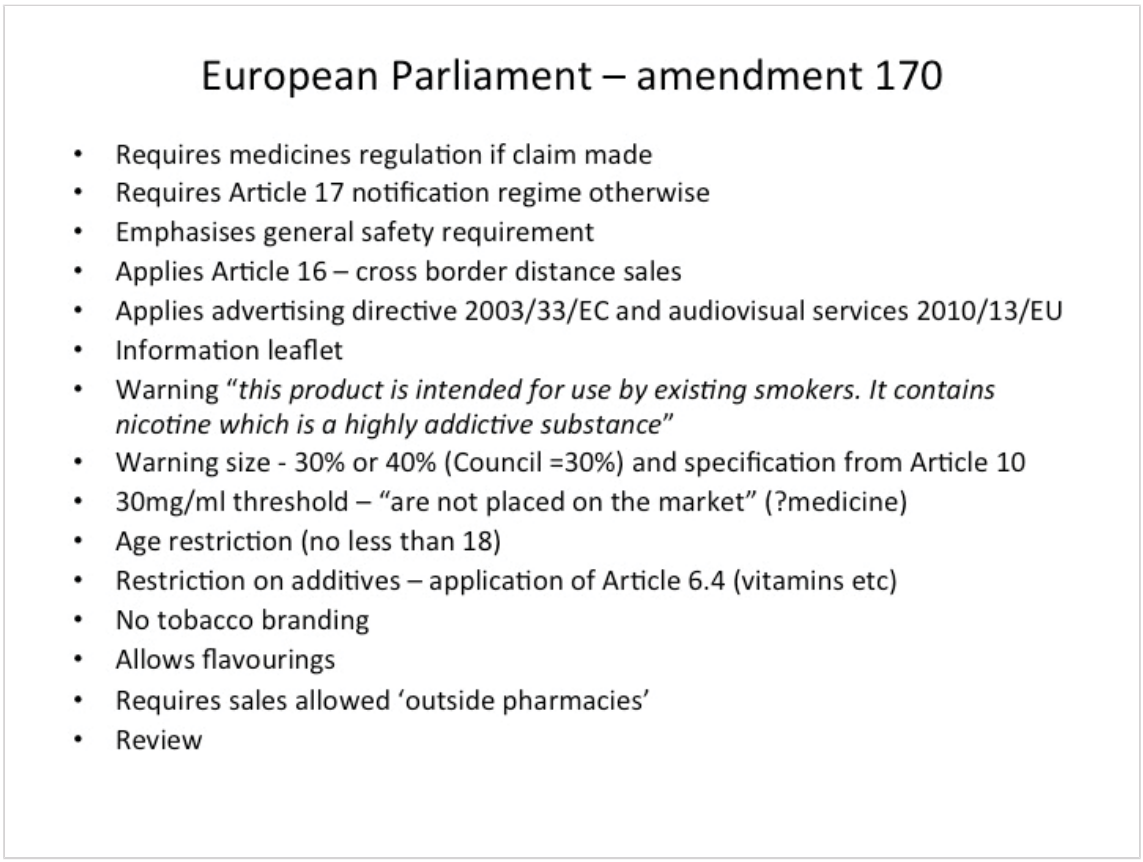
Before I do that, just people trip off the tongue, words like, you did it Linda, safety, efficacy, quality and everything. These have specialised meanings in medicines regulation, okay? They're not the way we mean it normally. So safety, is really primarily about adverse drug reactions, quality is about consistent drug dosing, and efficacy is about treating or preventing disease.



Okay? Now when we're talking about e-cigarettes we're really talking about something different. So what would getting tough on harm reduction mean? Here's a few of the dimensions of regulation. On the left, I've listed the counterproductive touch on harm reduction style of regulation, on the right the harm reducing. So you want it safe enough is right. You don't want huge, expensive process controls, you want proportionate standards that the companies can meet. You don't want the regulator deciding what a good product is for goodness sake, what do they know? They don't even use the product. So you want the consumer to decide that and the trusted mechanisms of creative destruction to work out what products are actually sold. Labelling, we've got a massive problem with excessive labelling. We want to encourage switching. We want to be marketing like consumer lifestyle products. People are fretting that ecigarettes look a bit like they're marketed as cigarettes. It's not surprising, they're trying to appeal to the same people doing roughly the same thing but with vastly reduce risk. Fear of normalisation. To be honest we want to normalise harm reduction, we want these products out in the world and people switching to them. We want cigarettes to look like old technology and these to look like the new thing. Retail, we want them available everywhere. Age restrictions? If you must, doesn't make much difference, and taxation you want a fiscal incentive to switch rather than big excise duties.

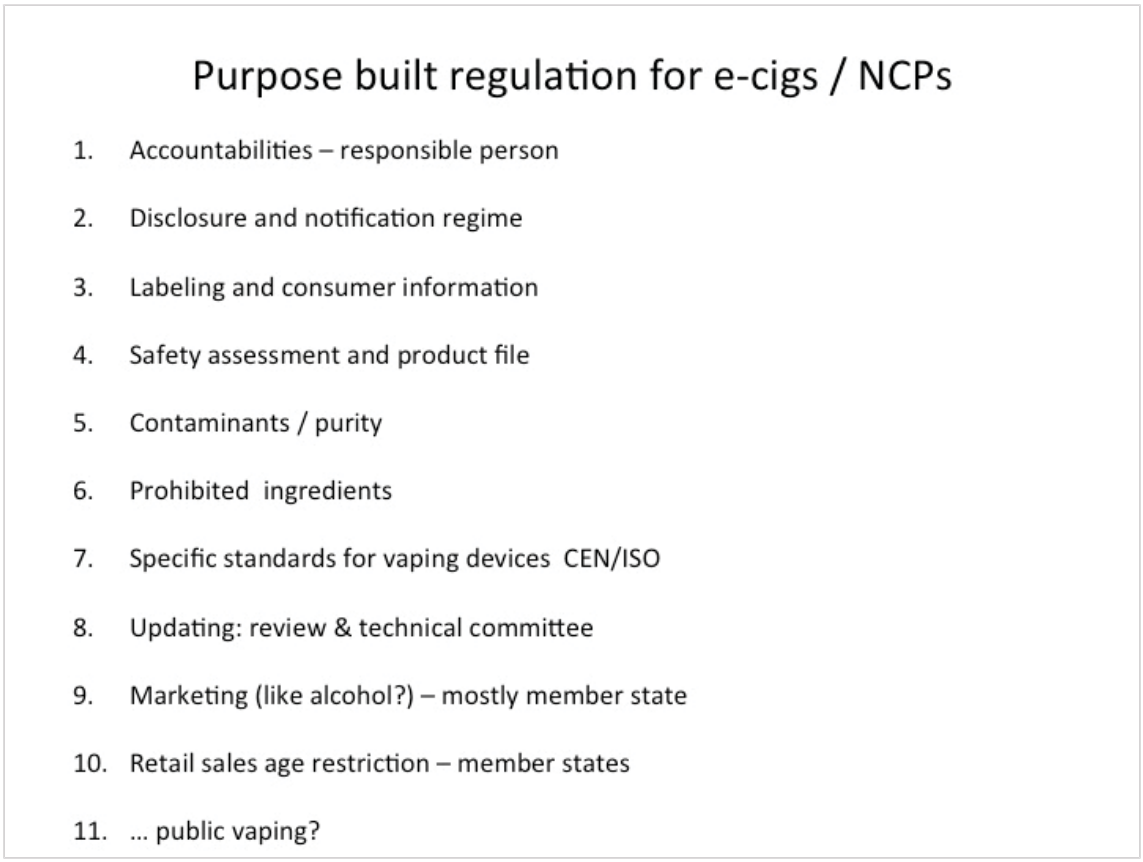


Heavy regulation, what do analysts think? They think it's a big win for the tobacco industry, and those who think it's clever to raise high regulatory barriers to entry in the cigarette industry need to reconcile themselves with these kind of statements. These things advantage the big players with deep pockets that will profit from a dramatic, violent consolidation of the industry.

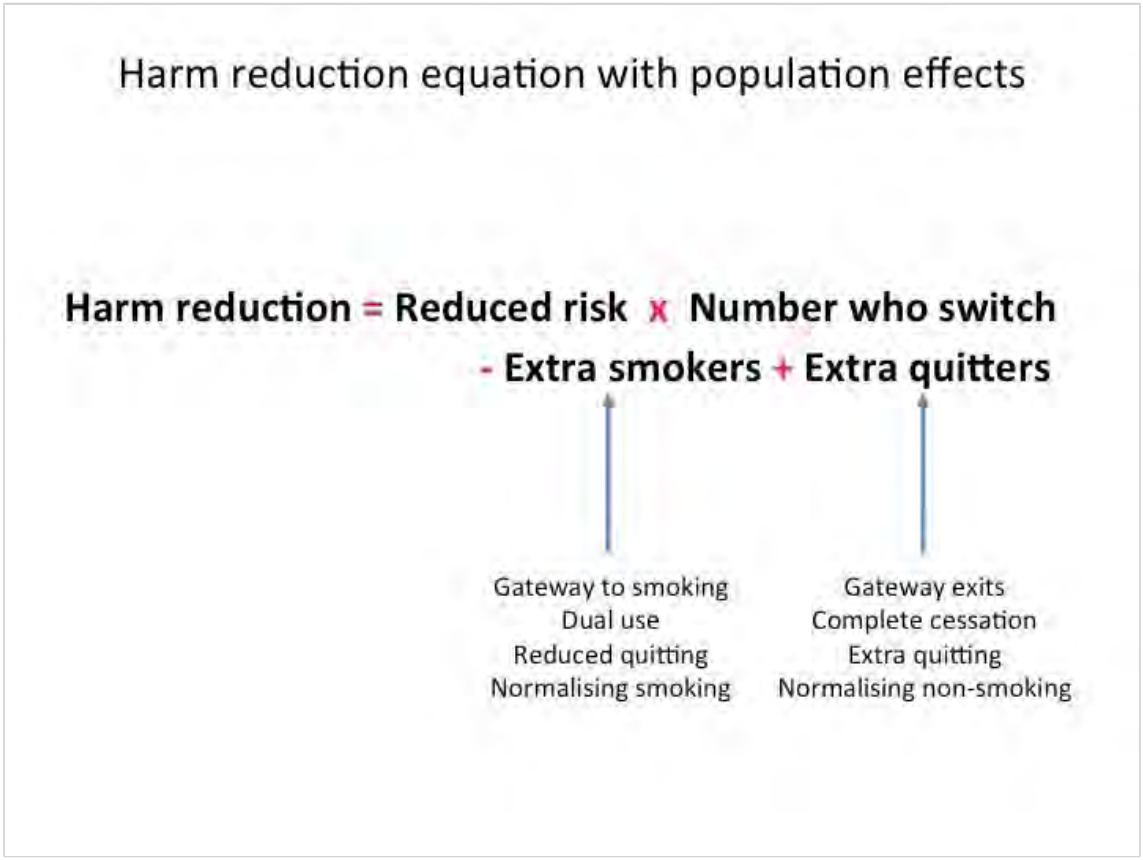


This is the thing that parliament's created instead. I won't go into it because it makes me feel a bit like

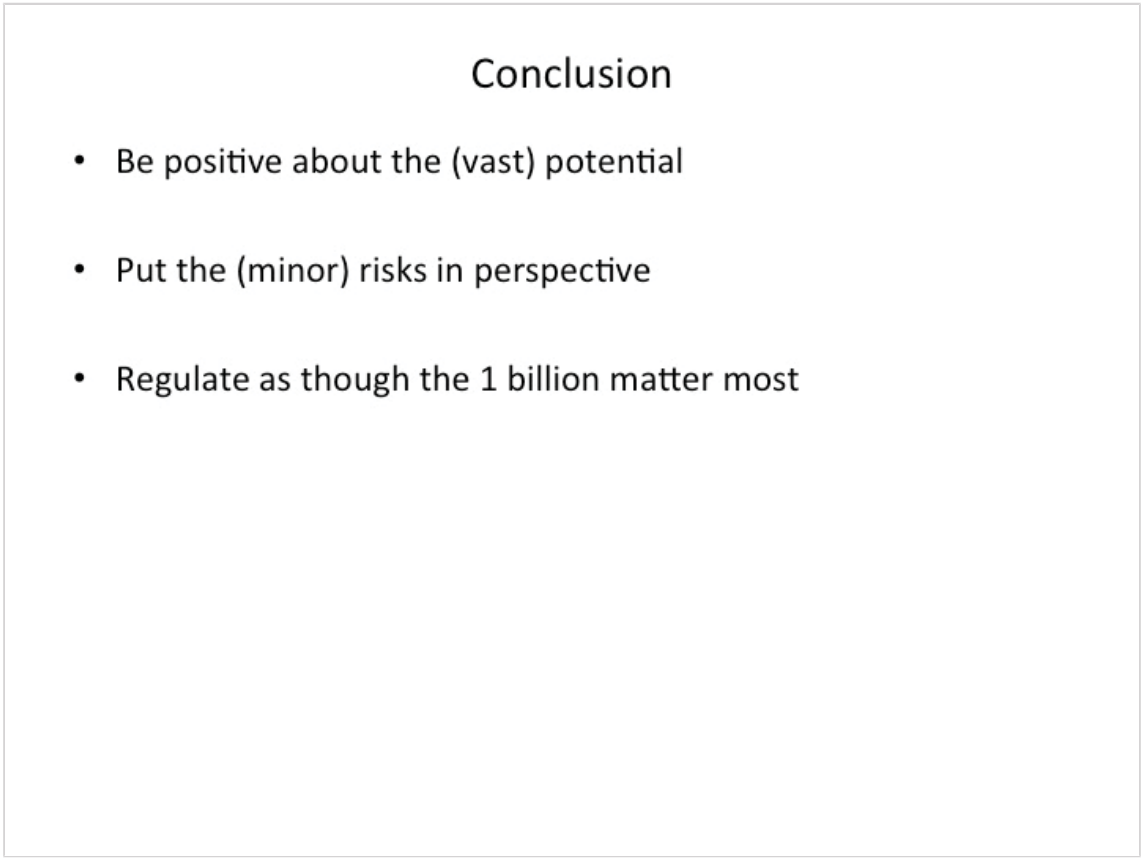
that. There's a lot of things wrong with it, it's ridiculous. It doesn't conform with my harm-reducing idea of regulation. Why would you want to prevent advertising of e-cigarettes? Ridiculous thing to do. Why would you introduce a 30mg/ml threshold? Absolutely no point to it and probably means that the products will be less attractive to heavy smokers. Why do you want to cover them with huge warnings when actually they're much better than cigarettes and so on. So I think you could learn from cosmetics regulation, and I've written a piece on this. There's a lot in common between cosmetics, they're fast-moving consumer goods, they pose risks to people, they can cause harm, they have to be high quality products and all the rest of it, and I think what we need to do now is move to purpose build regulation that is designed not to fit something that it isn't, not a medicine, not a tobacco product, not a cosmetic, not anything, but e-cigarettes and nicotine containing products.



For goodness sake, there's enough regulation produced in the world for them to do something that is specific to the actual product that they're trying to regulate. So these are the kind of elements that I think you need. Some of this is borrowed from cosmetics regulation. Down at the bottom, marketing, the idea that you have to ban advertising, you can put control on it, we have controls on alcohol advertising, nothing wrong with that. Retail sales restrictions matter for member states. Public vaping in my opinion absolutely no place for the law in this. This is a matter for the operators of spaces, etiquette to develop over time. Finally, very finally, the harm reduction equation extended for population effects, this is a big thing in the States. FDA, we're going to regulate these around population effects, which might mean you get some extra smokers or you get some extra quitters. They tend not to focus on the extra quitters by the way; they're more worried about these here.



And I can't go into this now, we'll probably come back to it in the discussion later, but basically there's a bunch of population effects that could derail this sort of idea. However, for every one of them there is another population effect which is beneficial and my contention is that the beneficial pathways through these population effects are much more likely, much, much more plausible and there are more of them, because you've introduced a much safer product into this kind of tobacco ecosystem, and we should stop the focus on them, and anyone who wants to raise those population effects shouldn't be raising it without thinking about what the consequences would be for the population effects that are actually highly desirable. And the last thing to say about this is this has all been worked through with Snus and the people who are worried about population effects say, "It's a gateway, it'll cause extra smoking." When none of those things actually happened they didn't change their mind about having a ban. So I think these things are often raised tactically rather than as a genuine concern.



Right, my final points. Be positive about the vast potential. The job of people in this room is to go after that green wedge, go after those testimonies. Keep the minor risks in perspective, don't over-regulate and therefore throw the baby out with the bathwater and make the products much less appealing and boring, and regulate really as if the one billion matter most. Thank you. **(Applause) Chair:** Okay. Thanks very much, Clive, for that very provocative talk. Those people who know Clive wouldn't be disappointed. I did you a bit of an injustice actually because you do have a few more minutes, so I can take a question of clarification from the floor. Deborah. **D Arnott:** Deborah Arnott, current chief executive of ASH. And I do wonder why you keep mentioning it, Clive, if you no longer speak on behalf of ASH, but that's another matter. **Clive Bates:** So people know who I am. **D Arnott:** But I do have a serious point which is that you talked about the costs of regulation and you came up with your alternative, but there's no attempt there to calculate what the costs would be of actually setting up a purpose-build regulatory system for e-cigarettes. Because actually it's not cost free, and I've never seen you do that calculation. **Clive Bates:** No, I mean the actual costs of the regulators themselves and the sort of regulatory interactions are really quite small in this. I mean the real costs of regulation comes from what the regulation requires the companies in the market to do. So it's costs of compliance basically, building pharmaceutical-grade factories to produce this stuff and having big IT systems, huge numbers of process controls and all the rest of it that goes with meeting the pharmaceutical, medical definitions of safety, quality and efficacy. So the way I'd look at it, Deborah, I mean these things aren't particularly... I haven't done a cost/benefit analysis on how much this would cost, but because I've been drawing on cosmetics regulation, which, it's not risk-free cosmetics by any means, I would say that we've got a very successful cosmetics industry, we've got a large number of brands, large, fast-moving consumer goods, a lot of innovation. Actually the Commission itself when it

proposed to include these in the directive back in 2010 said in its consultation that they would set standards for safety and quality, and that's what I'm advocating. It was a subsequent change where they decided that they would come back and classify these things as medicines which they plainly are not. So I think there will be costs of regulations and I think the costs should fall on the manufacturers, but the question is to keep those as low as possible consistent with the risks. I mean I don't really think that much regulation is really needed at all, but if we want regulatory red meat because that's what the European Parliament wants or the Council wants, then there are more proportionate and more modest forms of regulation than regulating these things as medicines. **Chair:** Okay. I suggest we move on. Thank you very much, Clive, thanks again for your talk.

Electronic Cigarette FAQS

What are electronic cigarettes?

Electronic cigarettes (also known as e-cigarettes or personal vaporizers) are an alternative to tobacco cigarettes. They are battery-operated devices that create a mist or vapor that is inhaled instead of smoke. The rechargeable battery powers a heating element called an "atomizer." The element uses low heat to turn liquid in the cartridge, which contains propylene glycol, glycerin, food flavoring and nicotine, into a fog-like mist.

There are many models of e-cigarettes available. Some look like traditional cigarettes, others look similar to a pen and some even look like small flashlights. Some have LED lights, some have built-in liquid reservoirs, others have combined atomizer cartridges, some are tubular and some are even rectangular boxes. They come in all shapes and sizes and have different features for former smokers who wish to distance themselves from anything resembling a traditional cigarette or want a longer battery life and/or better performance.

Are e-cigarettes safe?

While anything containing nicotine cannot be called 100% safe, evidence from numerous studies strongly suggests that they are magnitudes safer than tobacco cigarettes. Harm reduction experts can point to research supporting that switching from cigarettes to a smokefree product will reduce health risks to less than 1% of smoking traditional cigarettes - nearly the same as non-smokers. For tobacco harm reduction health professionals, it is misleading and irresponsible for public health officials to tell smokers that smokeless products, such as e-cigarettes, are "not a safe alternative to smoking" simply because they are "only" 99% safer and not 100% safe.

Do e-cigarettes contain anti-freeze?

No. This myth was created by a 2009 FDA press statement regarding electronic cigarettes. The FDA tested 18 cartridges from 2 companies. Of those 18 cartridges, 1 tested positive for a non-toxic amount of diethylene glycol (approximately 1%). While diethylene glycol is

occasionally used in anti-freeze, the chemical is not a standard ingredient in e-cigarette liquid and it has not been found in any other samples tested to date.

The base liquid for e-cigarette liquid is usually propylene glycol. Propylene glycol is considered GRAS (Generally Recognized As Safe) by the FDA and EPA. While it is also sometimes found in anti-freeze, it is actually added to make the anti-freeze less toxic and safer for small children and pets. Propylene glycol is a common ingredient found in many of the foods we eat, cosmetics we use and medications we take. It is also used in the fog machines used in theaters and night clubs.

Do e-cigarettes cause cancer just like tobacco cigarettes?

Though testing by the FDA and some researchers have discovered trace amounts of tobacco-specific nitrosamines, which are known to cause cancer with high exposure, the amounts found were extremely low and unlikely to cause cancer. To put it in perspective, an e-cigarette contains nearly the exact same trace levels of nitrosamines as the FDA-approved nicotine patch and about 1,300 times less nitrosamines than a Marlboro cigarette. This means that e-cigarettes would not be any more likely to cause cancer than FDA-approved nicotine gums, patches or lozenges.

What about all of the news reports that e-cigarettes contain toxic chemicals and metals?

The reports that there are studies that show potential health risks due to e-cigarette use are premature. In spite of what has been reported, the studies done to date have not only been largely inconclusive, but have actually found that the levels of contaminants detected in e-cigarette liquid and vapor are so low that it is highly doubtful they would even pose a health risk. Most certainly, they are thousands of times less of a risk than continuing to smoke. The fact is, the mere "detection" of a chemical does not mean that a product is hazardous. Every day we harmlessly consume and breathe in chemicals that would be toxic at much higher levels. It is disingenuous for public health organizations that disapprove of e-cigarettes to point to the trace levels found in e-cigarette studies as conclusive evidence of a potential health risk.

Dr. Igor Burstyn, of Drexel University, reviewed all of the available chemistry on e-cigarette vapor and liquid and found that the levels reported — even in those studies that were hyped as showing there is a danger — are well below the level that is of concern. His report was peer-reviewed and published January 2014 on Bio Med Central's Public Health Journal: "Peering through the mist: systematic review of what the chemistry of contaminants in electronic cigarettes tells us about health risks"

In 2011, The FDA issued a statement regarding the approved smoking cessation drug Chantix, which has been linked to over 500 deaths, suicidal tendencies and heart attacks. The FDA stated that "the drug's benefits outweigh the risks." E-cigarettes have been on the market nearly as long as Chantix, without reports of significant adverse reactions or deaths. Studies have shown that while chemicals have been detected, they are too low to pose any significant health risks and are certainly far less exposure than found in cigarette smoke. It is clear to anyone who reviews the more than 60 available studies on e-cigarette liquids and vapor that the benefits of e-cigarettes also "far outweigh the risks."

If there are over 60 studies of e-cigarette vapor and liquid, why do health experts say we don't know what is in them or that they may be more dangerous than traditional cigarettes?

Good question. Unfortunately, we don't have a clear answer. What we do know is that pharmaceutical companies do not like to see smokers switching to e-cigarettes instead of using pharmaceutical drugs and nicotine products. The pharmaceutical industry and its "foundations" fund a lot of anti-tobacco research and supports many of the anti-tobacco organizations and politicians that object to e-cigarettes and tobacco harm reduction policies.

We also know that there is a small, but very vocal, part of the public health community that is against anything that doesn't require 100% abstinence from all tobacco and nicotine. Their objection to e-cigarettes appear to be more ideological than science-based and it seems they would rather smokers remain uncertain enough about e-cigarette safety that they will choose to keep trying to quit smoking with traditional methods instead. Unfortunately, while this may be an option for those smokers who are actively trying to quit, it keeps smokers who aren't trying to quit - or who fail to quit using traditional methods - using the most hazardous product on the market, rather

than a far safer alternative.

Are e-cigarettes approved or regulated by the FDA?

The FDA currently considers e-cigarettes to be tobacco products. Originally, it claimed that e-cigarettes are being used as smoking cessation devices and therefore they needed to be regulated the same as pharmaceutical nicotine replacement therapy drugs (NRTs). In 2009, the FDA ordered customs officials to start seizing e-cigarette shipments coming into the country.

On April 25, 2011, FDA announced in a letter to stakeholders that it would not appeal the decision by the U.S. Court of Appeals for the D.C. Circuit in Sottera, Inc. v. Food & Drug Administration, stating that e-cigarettes and other products are not drugs/devices unless they are marketed for therapeutic purposes, but that products "made or derived from tobacco can be regulated as "tobacco products" under the FD&C Act. The FDA stated that it is aware that certain products made or derived from tobacco, such as electronic cigarettes, are not currently subject to pre-market review requirements of the Family Smoking Prevention and Tobacco Control Act. It is developing a strategy to regulate this "emerging class of products" as tobacco products under the Family Smoking Prevention and Tobacco Control Act. Products that are marketed for therapeutic purposes will continue to be regulated as drugs and/or devices. In late 2013, the FDA submitted its regulatory proposal to the OMB.

Contrary to some media reports and comments by legislators, regulation as a "tobacco product" under FSPTCA does not mean that e-cigarettes are automatically regulated in the exact same manner as tobacco cigarettes, ie., subject to PACT, flavoring prohibitions and indoor use bans nor subject to the same tax rates. However, it does mean sales of these products to minors are finally prohibited by law.

What e-cigarette brand most looks and tastes like a real cigarette?

This is the most common question on e-cigarette forums. The best answer to that question is "none" and "it doesn't matter."

Since those considering e-cigarettes are usually seeking to replace tobacco cigarettes, they are under the assumption that having the most realistic, tobacco-flavored e-cigarette will bring the most

satisfaction. The truth of it is that after switching to e-cigarettes for a few weeks, the vast majority of users discover that looks ultimately don't matter - performance does. And the best performing e-cigarettes don't necessarily look anything like traditional cigarettes because they require larger batteries. And the most popular flavors with experienced users are often as far from tobacco-tasting as one can get.

One problem is that none of the tobacco flavors really taste like burning tobacco - they taste more like fresh tobacco smells and slightly sweet. So, experienced e-cigarette users will tell you that nothing tastes exactly like a burning tobacco cigarette. But, we know you won't believe us and insist on buying something that looks and tastes like a tobacco cigarette. That's ok - we've all been there!

Read more: http://e-cigarette-forum.com

Can e-cigarettes help me quit smoking?

E-cigarettes are not approved to be marketed as nicotine cessation products like the nicotine gums and patches on the market. However, that doesn't mean that some smokers haven't found them an effective way to wean from nicotine. There is also a lot of real-world evidence and even some studies that strongly indicate that e-cigarettes are an effective alternative to smoking. Surveys show that up to 80% of e-cigarette users quit smoking traditional cigarettes while using e-cigarettes. One study showed e-cigarettes worked at least as well as the nicotine patch for nicotine replacement therapy.

However, while some users have gradually reduced the nicotine levels down to zero, the majority of e-cigarette users treat the devices as an alternate source of nicotine and not as a nicotine cessation program. So there is not as much scientific evidence yet that show how effective e-cigarettes are when used to treat or cure nicotine addiction. Yet, anecdotal reports by users who have used e-cigarettes as a way to wean from nicotine also indicates they seem to be very effective way to break smoking triggers and dramatically reduce nicotine levels. As with pharmaceutical NRTs, it depends upon the smoker and the strength of his or her addiction and resolve to quit. E-cigarettes also appear to be a much safer option for short-term use in the event of relapse.

The good news is, nicotine by itself has very low health risks, so switching to e-cigarettes can be nearly as good as quitting altogether.

The most important thing for those who cannot or will not quit nicotine to do is to stop the exposure to the harmful chemicals in cigarette smoke and e-cigarettes can help them do it.

What is CASAA's involvement in e-cigarette research?

In late 2010, CASAA's board of directors discussed CASAA's mission in relation to the current and future involvement in smokeless and e-cigarette research and studies and concluded that CASAA does not have the funding nor the staff to endorse, supervise and/or fund any ongoing research. At that time, the Board agreed to discontinue fundraising for research projects and instead continue to direct its efforts and funding toward the continued education of the public, media and legislators about tobacco harm reduction; provide public access to completed research and studies; and to continue the fight to keep smokeless alternatives available, effective and affordable.

To that end, CASAA forwarded any donations contributed by its members to the studies for which they were intended and voted not to do any more fundraising exclusively for research. Additionally, because CASAA has no first-hand involvement with any research or studies, we are unable to comment on the current progress, fundraising, validity or administration of any ongoing studies.

In 2013, CASAA raised funds from its members for a small grant of $15,000 to Dr. Igor Burstyn, who is an associate professor at Drexel University's Department of Environmental and Occupational Health and a researcher in the field of environmental and occupational health, with training in both epidemiology and occupational hygiene. Dr. Burstyn's paper, "Peering through the mist: systematic review of what the chemistry of contaminants in electronic cigarettes tells us about health risks" was peer-reviewed and published in Bio Med Central's Public Health Journal in January 2014. Dr. Burstyn reviewed all of the available chemistry on e-cigarette vapor and liquid and found that the levels reported — even in those studies that were hyped as showing there is a danger — are well below the level that is of concern. This is a definitive study that can be used to respond to claims that contaminants in e-cigarettes are dangerous and that there is a hazard to bystanders that calls for usage restrictions.

What scientific research on the safety and efficacy is available

for e-cigarettes?

In addition to Dr. Burstyn's paper, the CASAA web site provides links to all available e-cigarette research and tests. You can view this information in the CASAA E-cigarette section.

CASAA encourages the use of a link to the CASAA website as a means of providing accurate, unbiased information to consumers and the industry. Unless otherwise stated on casaa.org, CASAA does not have any affiliation with an organization, business, or individual that displays the CASAA logo or provides a link to the CASAA site.

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

Igor Burstyn

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

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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/safework/info/publications/WCMS_113329/lang–en/index.htm; 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 [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):

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

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.

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

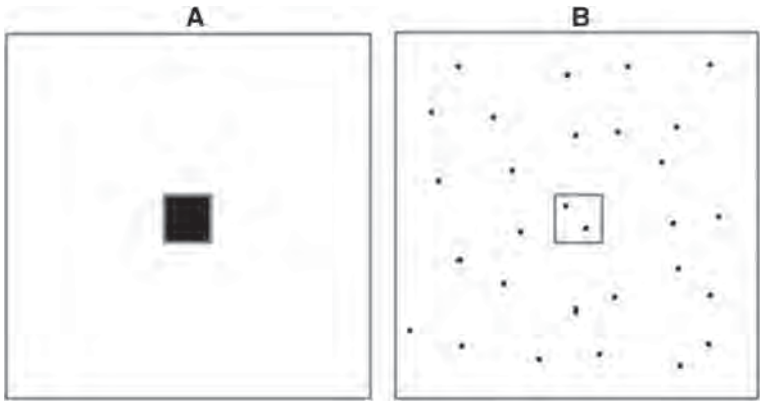

Figure 1 Illustrating the difference between concentrations in the aerosol generated by vaping and inhaled air in a day. *Panel* ***A*** shows a black square that represents aerosol contaminated by some compound as it would be measured by a "smoking machine" and extrapolated to dosage from vaping in 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).

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:

(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].

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

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.

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

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.

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.

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:

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

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

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.

$OEL_{mixture} > 1$, 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".

Additional files

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

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

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

Competing interests

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Authors' 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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NJOY®

Study to Determine Presence of TSNAs in NJOY Vapor

December 9, 2009

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Tobacco-Specific Nitrosamines (TSNAs) in NJOY Electronic Cigarettes

Report to:

Scottera, Inc. dba NJOY

December 9, 2009

NJOY, Inc. has requested Dr. Ben Thomas (President and Principal of Ben Thomas Group, LLC) to review the report issued by ANALYZE, Inc. concerning the levels of common tobacco-specific nitrosamines (TSNAs) that might be associated with the electronic cigarettes marketed by the NJOY company. NJOY also requested my assessment of the risk, if any, posed by the TSNAs to users of NJOY electronic cigarettes. This report summarizes my review and evaluation. Based on the findings of the ANALYZE chemists, little or no TSNAs are present in the aerosol ("smoke") to which a consumer would be exposed. Moreover, based on our review of the toxicology information relating to TSNA, we conclude that TSNAs do not raise health concerns from use of the NJOY product. The following comments are pertinent:

1. Professional Background

Appended for your information is a copy of my resume. I am an expert on health and environmental issues, with over 35 years of professional experience. I received my B.S. degree in biology from Tulane University, and my M.S. and Ph.D. degrees in pathology from the University of Texas Graduate School of Biomedical Sciences at Houston (at the M.D. Anderson Cancer Center). I was subsequently named a Rosalie B. Hite Postdoctoral Fellow in biochemistry at M.D. Anderson, where I investigated the mechanisms of toxicity and carcinogenicity.

Following my postdoctoral training, I accepted a position as a toxicologist with the Shell Oil Company, where I was responsible for the toxicological issues associated with oil products, aromatics, olefins, solvents, metals, radiation, synfuels, and other products and processes. I represented Shell in various industrial trade associations, and chaired the Toxicology Committee of the American Petroleum Institute (API), the API Benzene Toxicology Task Force; the API Neurotoxicity Task Force; the Butadiene Toxicology Research Task Group of the Chemical Manufacturers Association (now the American Chemical Council); among others.

In 1990, I joined the consulting industry, and have worked in that capacity since that time. I am appointed at the rank of Adjunct Professor to the faculty of the University of Texas Health Science Center at Houston, where I teach in the areas of toxicology, pathology, and health risk. In addition to my consulting and teaching activities, I am the Chief Operating Officer of CleanBlue Water LLC, a company dedicated to providing reliable and safe drinking water to small communities around the world.

2. Overview of Issue

NJOY Inc. is the distributor of a line of electronic cigarettes that use a microelectronic heating element to vaporize a small amount of nicotine dissolved in propylene glycol, glycerol and water. As these vapors cool, they condense to form a fine aerosol (tiny droplets of liquid suspended in the air) that visually resembles smoke and are inhaled by the user.

In July 2009, the US Food and Drug Administration (FDA) announced that an analysis of the ingredients of two leading brands of electronic cigarettes had detected known carcinogens and toxic chemicals to which users could potentially be exposed. The toxicants cited included four TSNAs – N-nitrosonornicotine (NNN); N-nitrosoanabasine (NAB); N-nitrosoanatabine (NAT); and 4-(methylnitrosamino)-1-(3-pyridyl)-1-butanone (NNK).

Because of the FDA findings, NJOY retained [redacted] to evaluate the TSNA content of the NJOY electronic cigarettes. [redacted] retained ANALYZE to collect the appropriate samples and conduct the analytical studies.

I have been asked by NJOY to evaluate the data from ANALYZE, and to consider the health implications of the TSNAs to the users of the NJOY products.

3. Technical Approach

This analysis is based on the information contained in the ANALYZE report, and on the available published scientific literature relating to the toxicity of TSNAs as identified through the PUBMED database of the U.S. National Library of Medicine.

In particular, I have critically evaluated the sampling and analytical methods developed and used by the ANALYZE chemists in order to confirm that the reported data are of a quality to allow me to draw valid and supportable conclusions. For purposes of health evaluation, only data related to TSNAs in generated aerosols (I.e., the material to which a user would be exposed) is considered here. It should be noted that no TSNAs were detected in the liquid cartridges by ANALYZE, although they suggested that propylene glycol or other constituent present in the liquid might be inhibiting their analysis

Similarly, I have also critically evaluated the relevant toxicological studies to assess what is known and reported about the health effects of TSNAs.

4. ANALYZE Report

Using a method based on that used by the FDA (Westenberger 2009), ANALYZE collected samples of the aerosols generated from four types of NJOY cartridges – Traditional Light; Traditional Ultra Light; Menthol Regular; and Menthol Light. In order to accurately measure air flow rates, ANALYZE forced breathing quality compressed air through the front end (battery end) of the electronic cigarette at a nominal flow of 3.5 SCFH. The aerosol was generated in 3-second "puffs" and was directed through a series of three capture flasks, each containing methylene chloride to dissolve any TSNAs from the aerosol into the solvent. Studies using reference TSNA standards indicated that recoveries using this sampling method were 75% or greater (note: these recoveries are acceptable for this method),

The TSNA content of the aerosol samples (collected in methylene chloride) was determined by drying the methylene chloride under nitrogen, then redissolving the residue into a small amount of ammonium acetate. The TSNAs in the ammonium acetate solution were then analyzed by a Liquid Chromatography – Mass Spectrometry/Mass Spectrometry (LC-MS/MS) method as described by Wu et al. (2008). Studies with reference TSNA standards determined the Limit of Detection (LOD) for each TSNA in the aerosol to be approximately 1.2 – 1.5 ng/L.

It should be emphasized that the LOD is determined empirically by the laboratory, and is defined as "the minimum concentration at which a compound can be detected reliably." The LOD is not the same as a Quantitation Limit (defined as "the minimum concentration at which a compound can be quantified reliably"). The Quantitation Limit is often ten-times the LOD or more – that is, in order to be reliably quantified, a TSNA would have to be present in the aerosol at a concentration of 12 – 15 ng/L or higher.

The studies conducted by ANALYZE were technically appropriate and appear to have been well done with regard to data quality and the conclusions that they reach. They sampled the aerosols generated by the NJOY electronic cigarettes, and tested for the presence of NNN, NAB, NAT, and NNK. Of the four TSNAs, only NAT was present in the collected aerosols. ANALYZE's best estimate was that the concentration of NAT in the aerosol samples were 2 – 5 ng/L (i.e., detectable, but not reliably quantifiable). NNN, NAB and NNK were not detected in the NJOY aerosols (i.e., technically, below the LOD; although the lack of demonstrable peaks in the chromatograms argues that these TSNAs are totally absent in the NJOY products).

5. Toxicology of NAT

A review was conducted of the published scientific literature relating to the toxicity of TSNAs, as identified through the PUBMED database of the U.S.

National Library of Medicine. The toxic and carcinogenic potential of NAT and other TSNAs was evaluated in the rat by Hoffman et al. (1984). This was the only relevant study identified in the published literature that evaluated the systemic toxicity and carcinogenicity of NAT following long-term exposure. In the study, 60 subcutaneous injections of NAT (total doses of 1, 3 and 9 mmol/kg) did not produce any change of body weight, nor any decreased survival in treated rats. In marked contrast to NNN and NNK, NAT did not produce tumors in any tissue (i.e., NAT was not toxic and not carcinogenic in this bioassay).

Comprehensive reviews of the toxicology of TSNAs have been compiled by Hecht (1998) and by the International Agency for Research on Cancer (IARC 2008).

6. Summary and Conclusion

In summary, of the four TSNAs evaluated by ANALYZE, only NAT was detected at low levels in the aerosol samples from the NJOY electronic cigarettes. NAT was tested by Hoffman et al. (1984) and was shown to be non-toxic and non-carcinogenic in rats receiving a combined subcutaneous dose of up to 9 mmol/kg. Based on the above, there is no evidence that carcinogenic TSNAs are present in the aerosol from NJOY electronic cigarettes. Thus, it is my conclusion that the TSNAs do not pose a health risk to the users of the electronic cigarettes distributed by NJOY.

Ben Thomas, Ph.D.
December 11, 2009

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Professional Profile

Dr. Ben Thomas brings more than 35 years of professional experience in the fields of toxicology, pathology, risk mitigation, regulatory negotiation, litigation support, strategic planning, program development, and program management. Ben received his bachelor degree in biology (chemistry minor) from Tulane University, and his master and doctoral degrees in pathology from the University of Texas Graduate School of Biomedical Sciences at Houston. He was named a Rosalie B. Hite Postdoctoral Fellow at the University of Texas M.D. Anderson Cancer Center, where he conducted research on the mechanisms of chemical toxicity and carcinogenicity. Dr. Thomas worked as a toxicologist for 12 ½ years with the Health, Safety & Environment department of Shell Oil Company. During that time, he was active in national and international health and environmental research programs, and at one point was overseeing more than $40 million in biomedical research. He chaired the Toxicology Committee of the American Petroleum Institute (API), the API Benzene Toxicology Task Force, the API Gasoline in Groundwater Task Force, the Toxicology Research Task Group on 1,3-Butadiene of the Chemical Manufacturers Association (now the American Chemical Council), and other industrial research panels. Ben joined the consulting industry in 1990, and is internationally recognized for his health and environmental expertise. He is well respected in the regulatory community, and was appointed as a member of the Science Advisory Panel of the National Urban Air Toxics Research Center (NUATRC), that was created by the Clean Air Act Amendments of 1990. In addition to his consulting and corporate work, Dr. Thomas holds an academic appointment as Professor (adjunct) at the University of Texas Health Science Center at Houston.

Credentials and Professional Honors

Ph.D., Pathology, University of Texas Health Science Center at Houston, 1973
M.S., Pathology, University of Texas Health Science Center at Houston, 1971
B.S., Biology, Tulane University, 1969

Rosalie B. Hite Postdoctoral Fellow, University of Texas M.D. Anderson Hospital & Tumor Institute, Houston (1974–1977); Sigma Xi

Employment History

President, Ben Thomas Group, LLC, 2009-Present
Senior Managing Scientist, [redacted], 2005-2009
Principal and Vice President, RAM Group, 2003–2005
Senior Scientist, Conestoga-Rovers & Associates/RAM Group, 2001–2003
Principal and Vice President, RAM Group, 1999–2001
Adjunct Professor (Toxicology/Risk Assessment), University of Texas Health Science Center, 1996–present
Principal and Executive Vice President; Compliance Solutions, Inc., 1995–1999
Principal/Senior Science Advisor; ENVIRON Corporation, 1993–1995
Regional Program Manager/Director of Toxicology and Risk Management, ENSR Consulting & Engineering, 1990–1993
Staff Toxicologist; Shell Oil Company; Health, Safety & Environment, 1977–1990

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Thomas B. A toxicologist's perspective of MTBE. Invited paper, presented at the Petroleum Marketing Attorneys Meeting, Washington, DC, April 4, 2000.

Thomas B. Toxicology of methyl tertiary-butyl ether (MTBE) – an update. Invited paper, presented at Mealey's UST and MTBE Litigation Conference, Amelia Island, FL, November 16, 1999.

Thomas B. Evaluation of health issues associated with E&P wastes. Invited paper, presented at the Louisiana Gulf Coast Oil Exposition, Lafayette, LA, October 29, 1999.

Thomas B. MTBE – toxicology and the use of animal data to prove causality. Invited paper, presented to the 2nd Annual Appellate Judges and Lawyers Symposium: Scientific Methodology and the Admissibility of Expert Testimony, The University of Kansas, Law and Organizational Economic Center, Lawrence, KS, May 13–15, 1999.

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Thomas B. Toxicological issues in the chemical processing industry. Invited paper; presented at the 1st Annual Symposium of the Mary Kay O'Connor Process Safety Center, George Bush Presidential Conference Center; College Station, TX, May 30–31, 1998.

Thomas B. The toxicology of methyl tertiary-butyl ether (MTBE). Invited paper, presented at Mealey's Underground Storage Tank Conference, Amelia Island, FL, June 9, 1998.

Thomas B. The toxicological significance of chemicals in water supplies (or what is clean water). Invited paper, presented at the ELA Seminar on New Ground-Water Supply Issues, Houston, TX, April 16, 1998.

Thomas B, Handley B. Offsite consequence analysis: the public connection. Invited paper, presented at the Hazard Assessment/Offsite Consequence Analysis Session, Petro-Safe 98, Houston, TX, January 28, 1998.

Thomas B, Handley B. Risk-based corrective action. Training course for the TNRCC certification of Corrective Action Project Managers. Texas Natural Resource Conservation Commission, contract through the Texas A&M Engineering Extension Service, 1997.

Thomas FB, Plunkett L, Libicki SB & Kappleman WB. The comprehensive assessment of risks due to emissions from hazardous waste incinerators. Training course for the Louisiana Department of Environmental Quality, Baton Rouge, LA, June 26–28, 1995.

Thomas B, Plunkett L, Wojciak J. Strategic approaches to implementing the Texas Water Commission's Risk Reduction Rules. Presented at the ENVIRON Workshop on the Risk Reduction Rules, Houston, TX, June 17,1993.

Thomas B. Risk characterization. Invited paper, presented to the Association for the Environmental Health of Soils, Houston, TX, May 12, 1993.

Thomas B, Thompson R, Lu C. The risk-based remediation of total petroleum hydrocarbon contamination of soils. Invited paper, presented at Petro-Safe '93, Houston, TX, January 27, 1993.

Cox LA, Jr., Thomas FB, Woodrow JO. Decisions with unknown consequences: a random valuation model. Presented at the Annual Meeting of the Society for Risk Analysis, San Diego, CA, December 9, 1992.

Thompson RA, Woodrow JO, Thomas FB. Risk based prioritization of remediation options. Presented at the Annual Meeting of the Society for Risk Analysis, San Diego, CA, December 7, 1992.

Thomas B, Brassow C. The TWC Risk Reduction Rules and remediation of soil contamination. Presented at How to Classify and Clean up or Dispose of Solid Waste, sponsored by Texas Environmental Education Services, Houston, TX, October 16, 1992.

Thomas FB. Multi-media risk assessment. Invited paper, presented to the Association for the Environmental Health of Soils, Houston, TX, July 1992.

Thomas FB. Risk assessment and the Clean Air Act Amendments. Presented at the ENSR Breakfast Seminar, Houston, TX, May 2, 1991.

Thomas FB. The evolving Material Safety Data Sheet. Invited paper, presented to the Dallas Bar Association, Environmental Law Section, Dallas, TX, March 28, 1991.

Thomas FB. Multi-media risk assessment. Invited paper, presented at the Bridgestone/Firestone Environmental Affairs Domestic Conference, May 8, Nashville, TN, 1991.

Thomas FB. Application of toxicology, epidemiology and industrial hygiene. Invited paper, presented at the "Toxic Tort Litigation" Course sponsored by the Continuing Legal Education Committee of the Houston Bar Association, October 11, Houston, TX, 1991.

Thomas FB. The science and art of risk assessment. Invited paper, presented at Marathon Oil Company's Health, Environment and Safety Conference, Houston, TX, October 10, 1990.

Thomas FB. Science vs. compliance: the argument for QA's involvement in science. Invited paper, presented at the Annual Meeting of the Society of Quality Assurance, Orlando, FL, October 3, 1990.

Thomas FB. The toxicology of 1,3-butadiene. Invited paper, presented to the American Petroleum Institute Toxicology Committee, Toronto, Ontario, September 2, 1990.

Thomas FB. Air toxics impacts on human health and the ecology. Presented at Air Toxic Compliance Conference, Executive Enterprises, Inc., Houston, TX, June 11–12, 1990.

Thomas FB. Toxicological overview of ethylene oxide, butadiene, gasoline, polyolefin manufacturing, and composites. Invited paper, presented at the American Occupational Health Association (AOHA) Conference, Houston, TX, May 3, 1990.

Von Burg R, Lakin M, Thomas B, Egan B. Public interest group use of your SARA 313 data. Invited paper, presented at the Annual Meeting of the National Petroleum Refiners Association, San Antonio, TX, March 25–27, 1990.

Thomas FB, Hulse M. Compounds in asphalt cement fumes and their health effects. Invited paper, presented to the International Society for Asphalt Pavements, Baltimore, MD, November 9, 1989.

Thomas FB. Neurotoxicology. Invited paper, presented to the Gulf Coast Section of the American Industrial Hygiene Association, Houston, TX, March 8, 1984.

Thomas FB. Neurotoxicology. Invited paper, presented to the Deep South Section of the American Industrial Hygiene Association, New Orleans, LA, October 31, 1983.

Thomas FB. Evaluation of the neurotoxic potential of hexacarbon solvent mixtures in the Sprague-Dawley rat. Invited paper, presented to the Mid-West Regional Chapter of the Society of Toxicology, Chicago, IL, May 12, 1983.

Lington AW, Lewis SC, Thomas FB, Granville GC, Cragg ST, Spencer PS. The neurotoxic activity of commercial hexane mixtures in the male rat (Part I). Presented to the Annual Meeting of the Society of Toxicology, 1983.

Lington AW, Lewis SC, Thomas FB, Granville GC, Cragg ST, Spencer PS. The neurotoxic activity of commercial hexane mixtures in the male rat (Part II). Presented to the Annual Meeting of the Society of Toxicology, 1983.

Thomas FB. Applications of Sephadex G-200 chromatography to the study of the copper binding components of human serum. Presented to the Southeastern Texas Section of the American Chemical Society, Houston, TX, 1974.

Mintz CG, Thomas FB, Furlong NB. Approaches to the in-vitro synthesis of ara-C apurinates. Presented to the Southwest Section of the American Association for Cancer Research, November 8-9, New Orleans, LA, 1974.

Thomas FB, Furlong NB. Biochemical studies on the role of DNA polymerase in benzo[a]pyrene carcinogenesis. Presented to the Southwest Section of the American Association for Cancer Research, November 8–9. New Orleans, LA, 1974.

Thomas FB. Atomic absorption spectrophotometry in the clinical laboratory. Presented to the Annual Convention of the Texas Society of Medical Technologists, Houston, TX, May 12, 1972.

Academic Appointments

- Professor (Adjunct Faculty), University of Texas Health Science Center at Houston, and The University of Texas M.D. Anderson Cancer Center at Houston (1996-Present)

Research Experience

- Chairman, Toxicology Work Group, Asphalt Institute (1989–1990)
- Chairman, Toxicology Committee, American Petroleum Institute (1987–1989)
- North American representative to the Butadiene Steering Committee, International Institute of Synthetic Rubber Producers (IISRP) (1986–1990)
- Chairman, 1,3-Butadiene Toxicology Research Task Group, Chemical Manufacturers Association (now American Chemical Council) (1985–1990)
- Chairman, Neurotoxicology Task Force (PS-29), American Petroleum Institute (1980–1985)
- Chairman, Benzene Toxicology Task Force (PS-7), American Petroleum Institute (1977–1990)

Science Advisory Boards/Panels

- Science Advisory Board, National Urban Air Toxics Research Center (1991–1993)

MATERIALS CHARACTERIZATION REPORT

Report No.: 0910.14 **Date:** October 21, 2009

Customer: [redacted]

Customer P.O.: 0900923.000 E0T0

Samples: Njoy Smokeless Cigarette Solution Cartridges:

- Traditional Light Mfg Date June 2009
- Traditional Ultra Light Mfg Date June 2009
- Menthol Regular Mfg Date June 2009
- Menthol Light Mfg Date June 2009

Nicotrol® Inhaler (Pharmacia & Upjohn Co)

- BDC 0009-5400-01 LB024A 01/2012

Objective: The objective of the proposed study is to detect and quantify any *Tobacco Specific Nitrosoamines* (TSNA's) in the liquid formulated product and vapor phase produced by Njoy e-cigarette units. The compounds of interest are those reported in the FDA study (Westenberger – May 4, 2009)[1]: N-nitrosonicotine (NNN), N-nitrosoanabasine (NAB), N-nitrosoanatabine (NAT) and 4-(methylnitrosoamino)-1-(3-pyridyl)-1-butanone (NNK). Using the same vapor phase capture technique, the TSNA content of the vapor produced by the Nicotrol® Inhaler was examined for comparison.

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ANALYZE

SUMMARY

1. The concentrations of the four target TSNA compounds (NNN, NAB, NAT and NNK) were measured in the liquid phase and the vapor phase generated from four Njoy cartridge products (Traditional Light, Traditional Ultra Light, Menthol Regular and Menthol Light). In addition, the TSNA concentration in the vapor phase from a Nicotrol® Inhaler was determined for comparison.

2. The LC-MS/MS analytical method to assay TSNAs employed for this study was adapted from that reported by J. Wu, P. Joza, M. Sharifi, W.S. Rickert and J.H. Lauterbach in Anal. Chem., **2008**, 80, 1341-1345.

3. The vapor capture method employed for this study was adapted from that reported by the FDA to trap nicotine and related compounds released from activation of e-cigarettes [B.J. Westenberger, CDER/OPS/OTR, Division of Pharmaceutical Analysis, FDA, May 4, 2009].

4. The limit of detection for the four TSNAs in the chromatography mobile phase is ca. 0.5 ppb.

5. No TSNAs were detected in the liquid extraction of one cartridge analyzed from each of the four Njoy sample types. The limits of detection were <55 ppb in solution. There is a significant matrix effect which affects the chromatography and mass spectroscopy. This matrix effect effectively limits the amount of propylene glycol and glycerol in the analysis solution and results in a further dilution of the TSNA concentration with concomitant rise in LOD.

6. All four target TSNA compounds (NNN, NAB, NAT and NNK) were observed to travel with vapor produced by a simulated Njoy matrix when placed in the filament assembly. It can be concluded from this result that any TSNAs present in Njoy solutions have the potential to be transferred to a second location through activation of the Njoy unit.

7. One of the four TSNA compounds, NAT, was observed in the vapor produced from each of the four Njoy products analyzed in this study. The concentrations of this compound in the vapor (expressed as nanograms per liter) are listed in Summary Table I.

Summary Table I – NAT Concentration in Sample Vapor

Sample ID	Concentration NAT in Vapor (ng/L)		
	Trial 1	Trial 2	Avg.
Traditional Light	2.7	2.3	2.5
Traditional Ultra Light	7.3	2.8	5
Menthol Regular	1.1	2.4	2
Menthol Light	4.0	2.4	3
Nicotrol® Inhaler	---	0.9	0.9*

*Further method development is required to validate the results from the Nicotrol® Inhaler listed here.

8. NNN, NAB and NNK were not detected in the vapor collected from the Njoy sample solutions. The limits of detection for these compounds are <2 ng/L in vapor, which translates to <30 ppb in the sample solution. It should be noted that these LOD values were obtained from a simulated sample matrix and not from an actual Njoy solution. While these values are likely similar to that of the Njoy products, compositional variations between the simulated matrix and the Njoy product may give rise to differences in these concentrations.

9. In addition to NAT, very low intensity signals associated with NAB and NNN (in one of two trials) were detected from the Nicotrol® Inhaler unit. The magnitudes of these signals were below the values required for reliable integration and quantitation. The capture method used to acquire all results from the Nicotrol® Inhaler vapor was optimized for the Njoy unit. Since there many differences between the two delivery systems, further method development is likely needed to optimize the capture system for the Nicotrol® Inhaler and validate the data obtained from this device.

10. A number of general considerations to this study are listed here:

- For the vapor capture from all Njoy samples, it was noted that the intensity of the signal from the deuterated internal standard compounds was considerably lower in capture flask 1 than in flasks 2 and 3. Likewise, several cases occurred when the NAT signal intensity was greater in flask 2 than in flask 1. These results strongly suggest that a suppression effect occurred in flask 1 which is likely due to the higher concentrations of other sample matrix components; e.g., propylene glycol. However, the comparison of analyte signal to internal standard signal, which was also suppressed, should compensate for this effect.

- For several of the sample trials, the NAT signal was detected in capture flask three. While the total intensity of this signal did not exceed 16% in all cases but one, there is a possibility that some NAT escaped from the vapor capture apparatus. This fact, combined with the 78% recovery of NAT in the evaporation study, necessitates the allowance of ca. 35% error for all NAT values.

- The ability to concentrate the capture solution volume by allowing the volatile methylene chloride solvent to evaporate results in the low levels of TSNAs that can be detected in the vapor phase experiments. However, due to the 75 – 83% recoveries in the evaporation study for the other three TSNA target compounds, an adjustment of +17-25% for the TSNA LODs may be warranted.

- At the conclusion of all sample analyses, the Njoy units were still able to generate visible vapor. Therefore, the sample cartridges were not exhausted. All TSNA concentrations were based on the initial five liters of vapor produced by the unit. It is unknown if the TSNA concentration in the vapor produced by the Njoy units is consistent over time or if the amount of TSNA entrained in the vapor changes as a function of usage.

- The volume of vapor collected and used in all calculations should be considered an estimate. Each 'puff' was performed manually with some variation (perhaps $\pm$ 10-20%) in total vapor volume inevitably exists between samplings.

INTRODUCTION

The Njoy units (battery and filament apparatus) and solution cartridges were received from M Neilson in August, 2009:

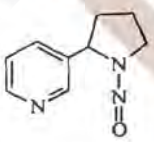
- Traditional Light Mfg Date June 2009
- Traditional Ultra Light Mfg Date June 2009
- Menthol Regular Mfg Date June 2009
- Menthol Light Mfg Date June 2009

One Nicotrol® Inhaler System containing 168 cartridges and 5 mouth pieces was also received:

- NDC 0009-5400-01 LB024A 01/2012

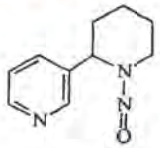
The objective of the proposed study is to detect and quantify any *Tobacco Specific Nitrosoamines* (TSNAs) in the vapor phase produced by Njoy ecigarette and Nicotrol® units. The compounds of interest are those reported in the FDA study (Westenberger – May 4, 2009)[1]: N-nitrosonicotine (NNN), N-nitrosoanabasine (NAB), N-nitrosoanatabine (NAT) and 4-(methylnitrosoamino)-1-(3-pyridyl)-1-butanone (NNK).

N-Nitrosonornicotine
(CAS 80508-23-2)



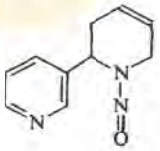
$C_9H_{11}N_3O$
177.20
177.090212
C 61.0% H 6.3% N 23.7% O 9.0%

N-Nitrosoanabasine
(CAS 1133-64-8)



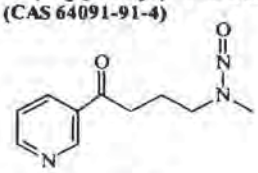
$C_{10}H_{13}N_3O$
191.23
191.105862
C 62.8% H 6.9% N 22.0% O 8.4%

N-Nitrosoanatabine
(CAS 71267-22-6)



$C_{10}H_{11}N_3O$
189.21
189.090212
C 63.5% H 5.9% N 22.2% O 8.5%

4-(Methylnitrosamino)-1-(3-pyridyl)-1-butanone
(CAS 64091-91-4)



$C_{10}H_{13}N_3O_2$
207.23
207.100776
C 58.0% H 6.3% N 20.3% O 15.4%

Standards used for analyte identification and quantitation were obtained from Toronto Research Chemicals, Inc. and Sigma Aldrich. All standards used are listed here:

Standard	Supplier
• N'-Nitrosonornicotine Cat# N535000 Lot# 7-MDB-87-1	Toronto Research Chemicals
• 4-(methylnitrosoamine)-1-(3-pyridinyl)1-1butanone Cat# 78013-10MG Lot# 0001435887	Sigma Aldrich
• N-Nitrosoanabasine Cat# N524250 Lot# 3-RSA-80-2	Toronto Research Chemicals
• N-Nitrosoanabasine (d4) Cat# N524252 Lot# 4-ELZ-86-2	Toronto Research Chemicals
• N-Nitrosoanatabine Cat# N524750 Lot# 8-MDB-106-1	Toronto Research Chemicals
• N'-Nitrosonornicotine (d4) Cat# N535002 Lot# 7-MDB-62-1	Toronto Research Chemicals

Method Development

Instrumental Method Development

The LC-MS/MS analytical method to assay TSNAs employed for this study was adapted from that reported by J. Wu, P. Joza, M. Sharifi, W.S. Rickert and J.H. Lauterbach in Anal. Chem., **2008**, 80, 1341-1345.

Analyte Detection. The capability of the Varian 1200 tandem quadrupole (with an intermediate collision cell) mass spectrometer to detect the four target TSNA compounds and the two deuterated TSNA internal standard compounds was verified by infusing standard solutions containing each analyte directly into the mass spectrometer. The standard solutions were made by diluting stock solutions (made in acetonitrile) with the intended capture solvent: 100 mM ammonium acetate. Resulting standard solution concentrations ranged between 500 – 250 ppb of target analyte.

Electrospray Ionization (ESI) was used for solvent introduction; the solutions were thusly monitored for signals with mass/ charge ratios (m/z) corresponding to the protonated target molecules. In all cases, signals with m/z values corresponding to the target analyte were detected, a positive result for instrument sensitivity to each compound. Full scan mass spectra from the direct infusion of the standard solutions are displayed in Figures 1a-c:

Figure 1a – ESI Direct Infusion Mass Spectra of NNN and NAB

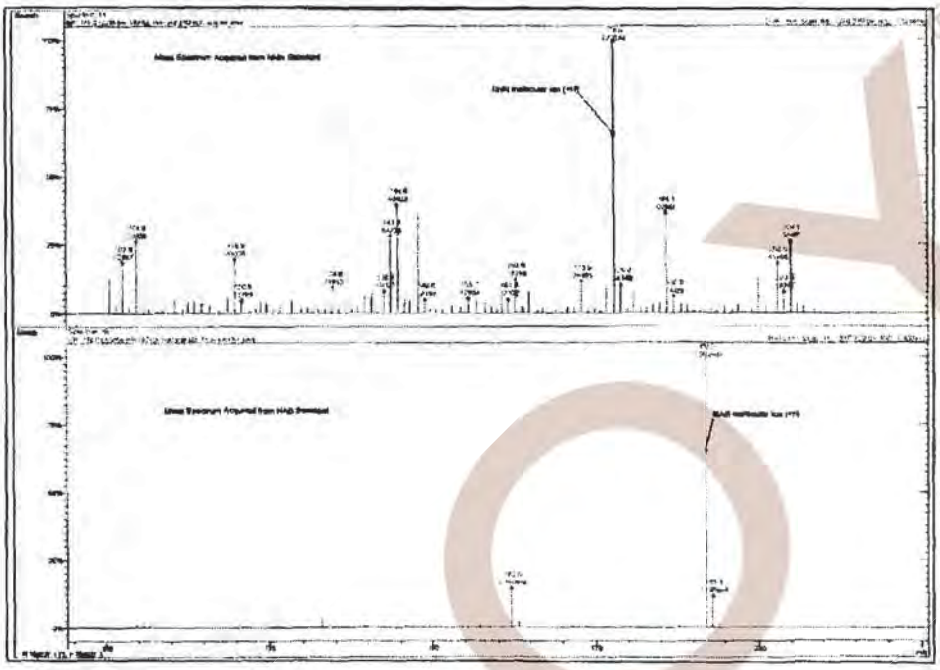


Figure 1b – ESI Direct Infusion Mass Spectra of NAT and NNK

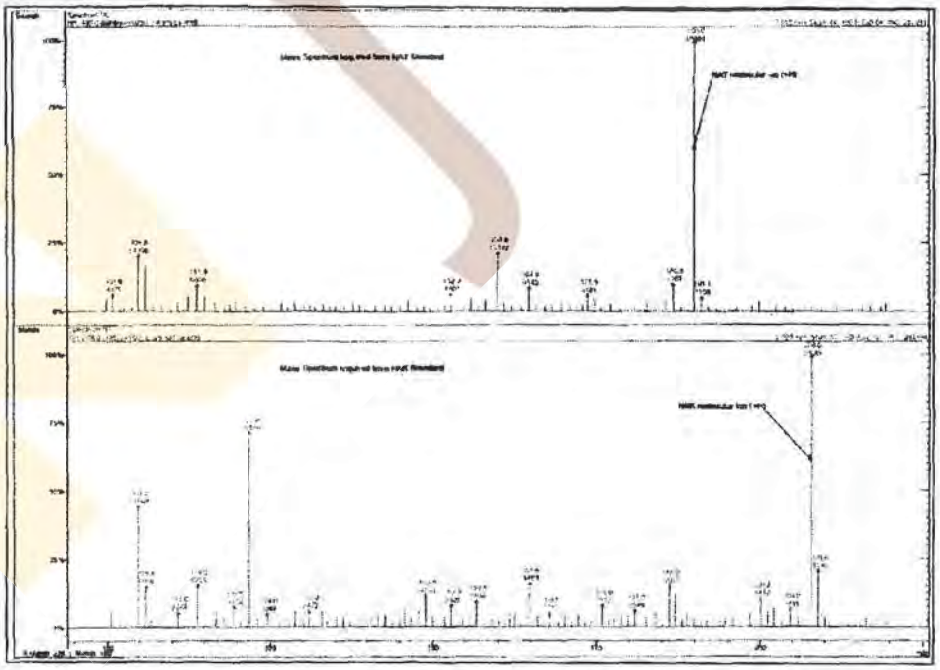
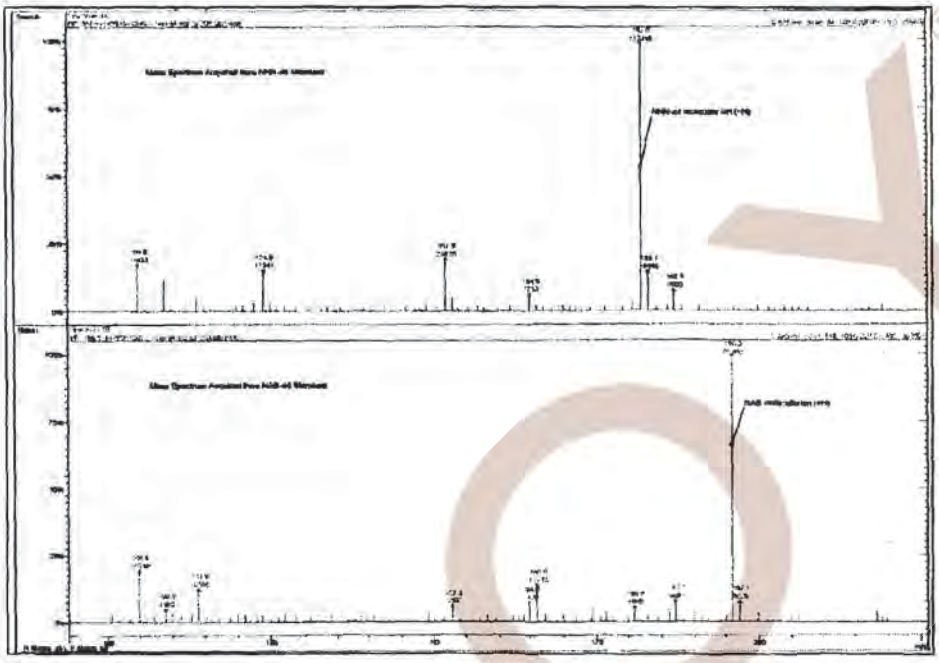


Figure 1c – ESI Direct Infusion Mass Spectra of NNN-d_4 and NAB-d_4



Further verification of target analyte identity was obtained by performing secondary fragmentation (e.g., MS/MS) from each target compound molecular ion. Detection of target fragments (described by Wu, Jingcun – *Analytical Chemistry*, February 15, 2008) in the resulting mass spectra verified the identity of the target compounds. All MSMS breakdown data are included in the Method Development Appendix.

Target Compound	Parent Ion (m/z)	Fragment Ions (collision energy)
NNN	178	148, 120
NAB	192	162, 133
NAT	190	160, 106
NNK	208	122, 106
NNN-d_4	182	152
NAB-d_4	196	166

Chromatographic Separation/ Detector Calibration. Solutions were constructed for response factor determination by the addition of deuterated internal standard to solutions of the target analytes. Stock solutions were then serially diluted to produce a series of standards with target analyte/ internal standard concentrations between ca. 400 – 2.5 ppb. Each solution was analyzed by the following chromatographic/ MS conditions to determine the relationship of target compound to internal standard signal intensities (e.g., response factor).

High Performance Liquid Chromatography-Mass Spectrometry (HPLC-MS/MS). HPLC is an analytical technique for the separation of organic compounds. Analytes separate according to their interaction with a stationary phase (column chromatography) and identified qualitatively based on their relative retention times within the column and quantitatively through integration of detector signal intensity, which is proportional to the analyte concentration. Detection is accomplished with a soft ionization mass spectrometer (MS) that is focused to the ion of interest based on a molecular formula or in full mass sweep if the ion need be selected since a reference standard is not available. Further structural information may be gathered by collision induced fragmentation generating an additional mass spectrum termed MS/MS; with chromatography termed HPLC-MS/MS. As previously described, infusion-MS (or MS/MS) data may be gathered for component verification if suitable chromatographic separation data is not available. A solution of the analyte is injected/infused directly into the MS bypassing the chromatographic separation.

Instrumental Conditions. All analyses were conducted using an Agilent 1100 HPLC system fitted with an auto-sampler, and Chemstation software. The solvent flow was plumbed into a Varian 1200 tandem quadrupole mass spectrometer equipped with a collision cell for secondary fragmentation. The analytical conditions by which all standard and sample chromatograms were acquired are listed below:

Column:	Waters Xterra MS C18 2.5 um (2.1X50mm)	
Eluent Phase A:	0.1% HOAc in Water	
Eluent Phase B:	0.1% HOAc in Methanol	
Mobile Phase:	Time (min)	%B
	0	25
	0.5	25
	2.5	5
	4.25	75
	5.0	5
	6.0	5
Solvent Flow Rate	0.15 ml/min	
Temperature:	60 °C	
Injection Volume	10 µL	
Run Time:	6 minutes	

Positive Polarity

Needle Voltage:	5000 V
Shield Voltage:	600 V
Nebulizing Gas:	51 psi (N_2)
Drying Gas:	150 °C, 21 psi
Housing:	50 °C
Capillary Voltage:	27 V
Detector:	Scan *m/z* 100- 220 (for direct infusion ESI)

SIM Conditions (for all HPLC-MS/MS)

Target Compound	Parent Ion (m/z)	Fragment Ions (collision energy)
NNN	178	148(-7.5V), 120(-16V)
NAB	192	162(-8.0V), 133(-18V)
NAT	190	160(-7.5V), 106(-14V)*
NNK	208	122(-10V), 106(-18.5V)*
NNN-d_4	182	152(-8.0V)
NAB-d_4	196	166(-9.0V)

* Ion fragment 106 was excluded from all analyses run on the second HPLC column used in this analytical study due to co-elution of NAT and NNK.

TSNA Standards in Mobile Phase. All chromatograms were acquired in MS/MS mode. The signals corresponding to all secondary fragments of each target compound were combined, producing individual chromatograms for each compound. The peaks were integrated and the resulting areas were used to calculate the response factor at various concentrations for each compound/ internal standard pair. Figures 2a-d are stacked plot comparison of SIM chromatograms produced by individual analyte solutions of various TSNA concentrations (ca. 2.2 – 0.3 ppb) diluted in mobile phase. These analyses were used to establish lower limits of detection for the target compounds individually *in the mobile phase* without the presence of sample matrix.

Figure 2a – Chromatograms of NNN Solutions for LOD in Mobile Phase

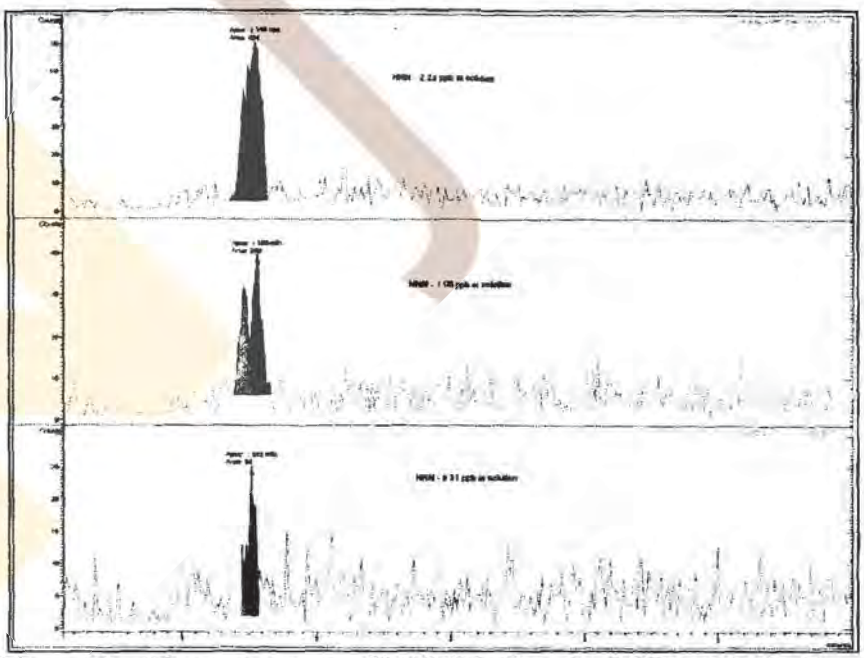


Figure 2b – Chromatograms of NAB Solutions for LOD in Mobile Phase

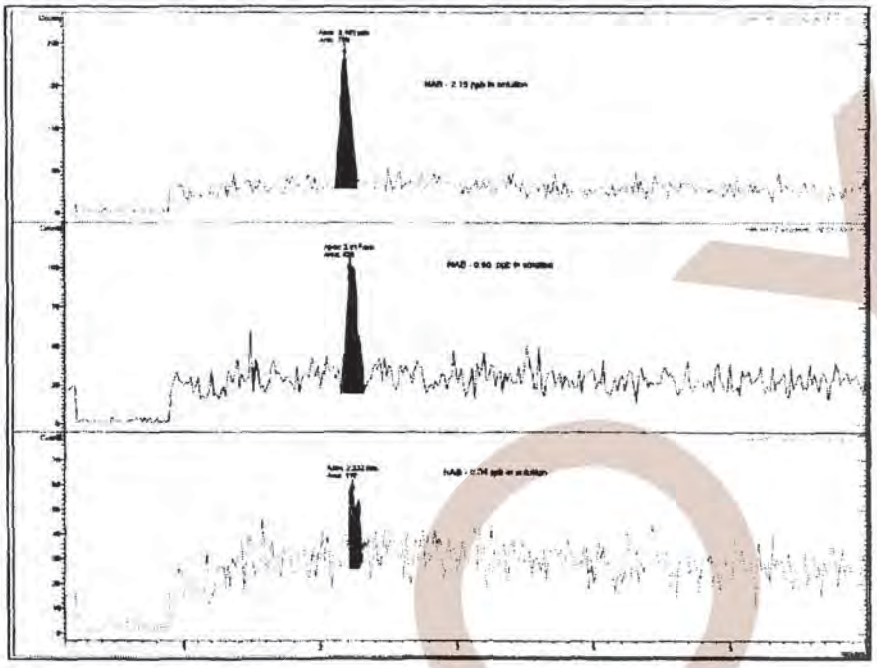


Figure 2c – Chromatograms of NAT Solutions for LOD in Mobile Phase

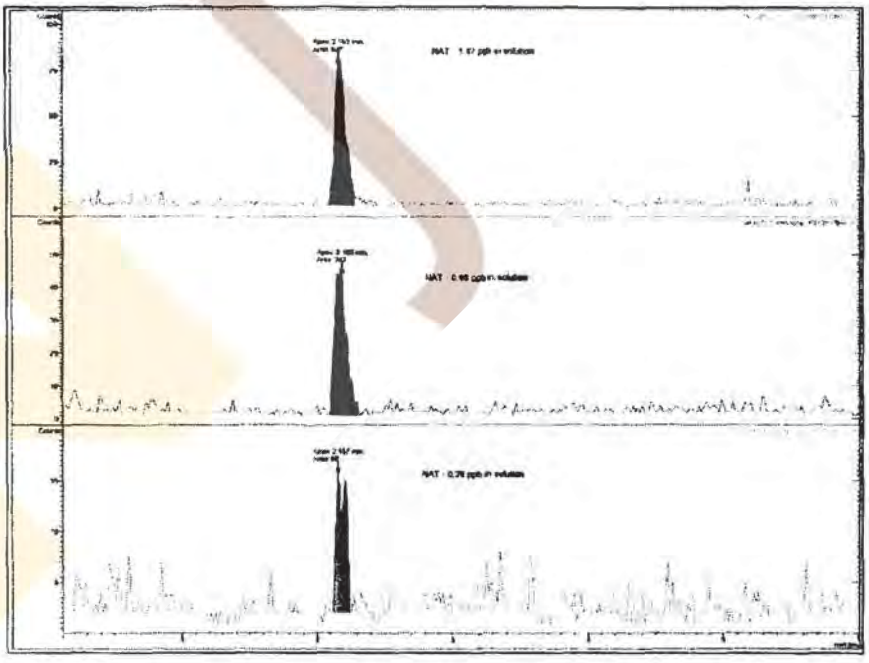
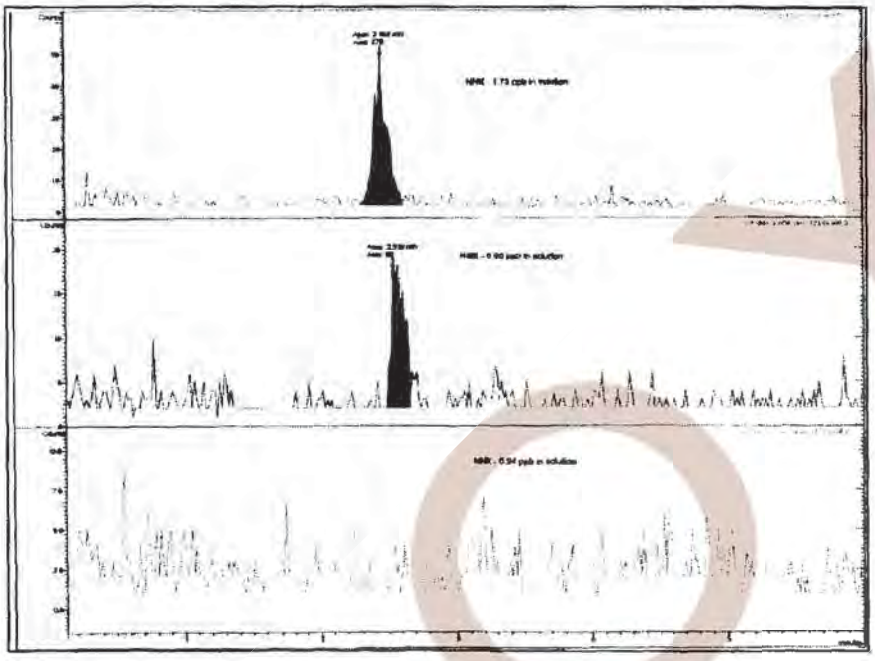


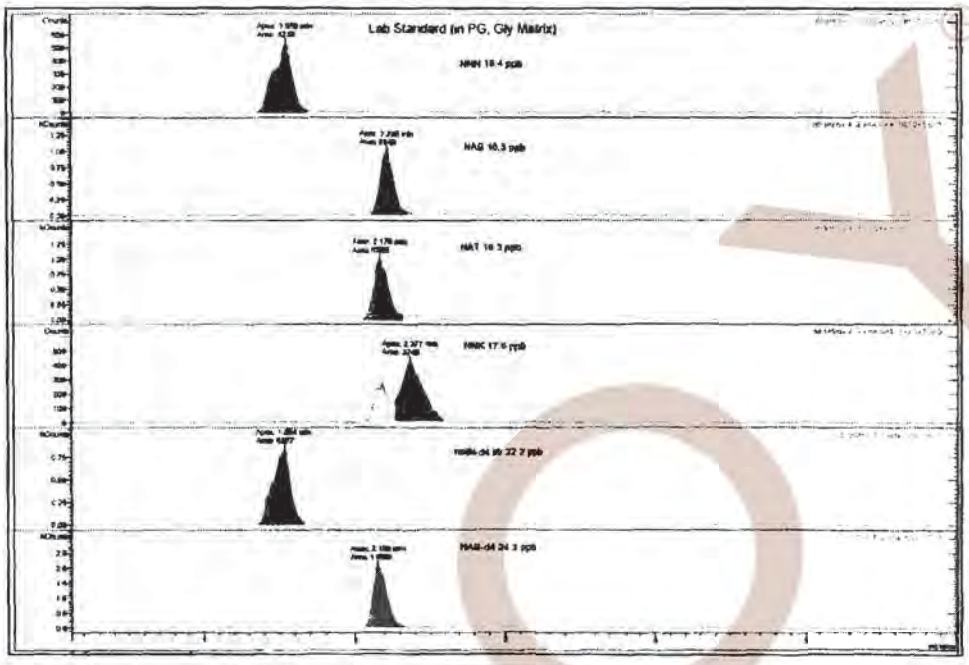
Figure 2d – Chromatograms of NNK Solutions for LOD in Mobile Phase



While the limits of detection (LOD) varied with specific TSNA, the average LOD is ca. 0.5 ppb.

TSNA Standards in Mobile Phase. In order to mimic the Njoy formulation, a lab matrix was made containing 60 wt-% water, 30 wt-% propylene glycol, 10 wt-% glycerol and 0.8 wt-% nicotine. The individual standards were added to this lab matrix to produce TSNA concentrations of ca. 10-25 ppb. A representative chromatogram is shown in Figure 3.

Figure 3 – Chromatograms Produced by Analysis of Standard Solution (Lab Matrix)



The retention times of each compound were influenced by the presence and concentration of other components of the sample matrix. Although retention time shifts were observed, identification of each compound was achieved by a) comparison with the elution time of deuterated standards and b) selective ion monitoring for secondary ion fragments exclusive to the target compounds. Table I lists all compounds and their approximate retention times.

Table I – Chromatography Results for Target Compounds

Compound ID	Retention Time (approx)	Chromatogram position in Displayed Stacks
NNN	1.4 – 1.6	top
NAB	2.1 – 2.3	second
NAT	2.1 – 2.3	third
NNK	2.2 – 2.5	fourth
NNN-d4	1.5	second to bottom
NAB-d4	2.2	bottom

A gradual increase of pressure within the liquid chromatograph was observed throughout the course of the study. This pressure exceeded usable limits just before the second set of sample analyses was performed; a second Waters Xterra MS C18 2.5 um (2.1X50mm) column was obtained and implemented into the system. Subtle differences in chromatographic separation were observed between columns; NAT and NNK were resolved by the first column used but co-

eluted on the second column. Due to this co-elution, the use of the common fragment ion m/z 106 for detection and quantitation was no longer viable and was excluded from all data from the second set of analyses on all samples. This exclusion altered the response factors; a different set of response factors were therefore applied to the first and second samplings of the Njoy and Nicotrol products. These response factors are listed in Tables IIa-b.

Due to structural similarity, NNN-d_4 is the chosen internal standard for NNN, NAB-d_4 is the chosen internal standard for NAB and NAT. The internal standard for NNK was NNN-d_4 based on retention time and similarity of response intensity.

Equation 1

$$\text{Response Factor} = \frac{\text{Area of Analyte X Concentration of Internal Standard}}{\text{Area of Internal Standard X Concentration of Analyte}}$$

Table IIa - Response Factors used for First Samplings

Compound ID	RF with NNN-d_4	RF with NAB-d_4
NNN	0.8210	---
NAB	---	1.0767
NAT	---	0.6274
NNK	0.7087	---

Three standard solutions (ca. 2, 5 and 20 ppb) were used to study the trend in response factors over various TSNA concentrations. For all analytes, the standard deviation of the response factors produced over this concentration range were <0.1. While good consistency was observed, the average value of the response factors acquired from the *least* concentrated solutions were eventually chosen for sample analysis due to the low levels of analyte detected in the sample extract solutions. All values are included in the Appendix Tables.

Table IIb - Response Factors used for Second Samplings

Compound ID	RF with NNN-d_4	RF with NAB-d_4
NNN	0.8654	---
NAB	---	1.0703
NAT	---	0.4913*
NNK	0.6189*	---

* The large variation between the RF values from the first and second column for NAT and NNK result in the modification of the ions included in the analyte signal (e.g., exclusion of m/z 106).

A solution of known concentration was run by the above listed conditions and used to verify the accuracy of the calculated response factors for each TSNA target compound. Table III lists all check standard recoveries:

Table III - Check Standard Recoveries

Compound ID	Check Standard Recovery (%)
NNN	112 ± 3
NAB	103 ± 4
NAT	108 ± 3
NNK	114 ± 7

A solution of only the two internal standards was run to insure that none of the four target analytes were contained in these standard solutions and would therefore contaminate sample extracts by addition. No signals corresponding to the target TSNAs were detected, a representative chromatogram from this study is included in the Calibration Appendix.

Liquid Solution Extraction Method Development

One cartridge from each of the following sets was extracted into a buffered aqueous solution (100 mM ammonium acetate) to determine the presence of TSNAs in the as received liquid:

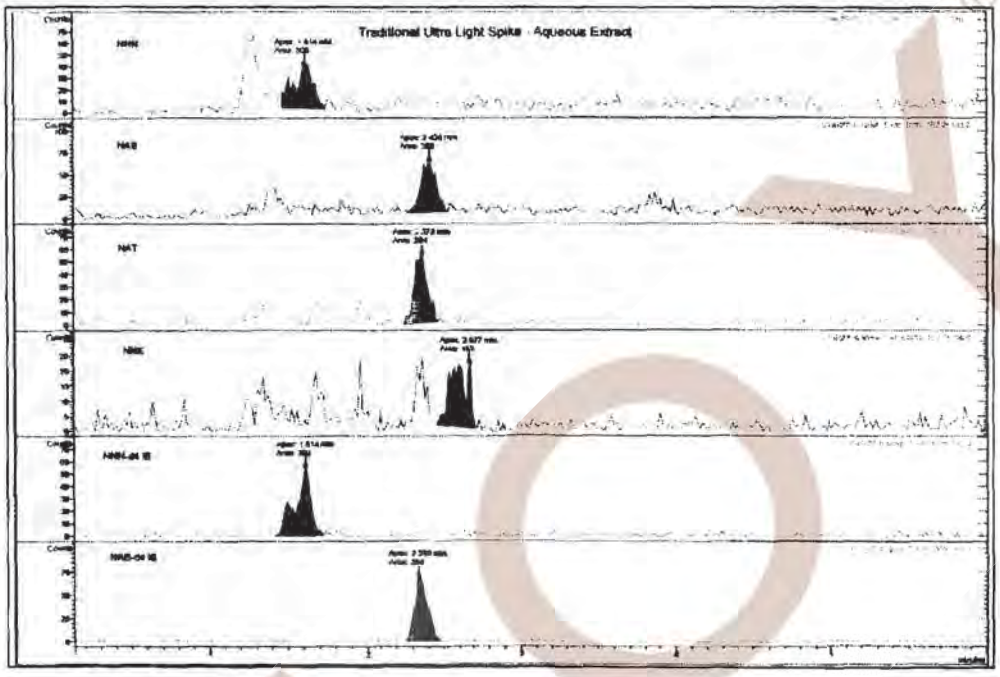
- Traditional Light Mfg Date June 2009
- Traditional Ultra Light Mfg Date June 2009
- Menthol Regular Mfg Date June 2009
- Menthol Light Mfg Date June 2009

The quantity of liquid solution in one 'Traditional Ultra Light' cartridge was determined by weighing the unit (after removed of outer casing, silicone plug and mouth piece) before and after removal of the liquid solution. The liquid was removed by pressing the saturated sponge onto a paper towel until no further moisture was observed. The inner casing was wiped dry with a Kimwipe. The cartridge component parts were then re-weighed and the difference was taken as the solution mass. The resulting mass (1.06 grams) was then used as a representative mass value for all extracted samples; determination of individual solution masses was not practical due to loss during handling.

Procedure. A 250 ml Erlenmeyer flask was silanized to deactivate the glass surface. A Njoy cartridge was then disassembled and all component parts in contact with the liquid solution were placed in the Erlenmeyer flask (sponge, inner casing and silicone plug). A volume of extraction solvent (10 ml of 100 mM ammonium acetate) was added to the flask and the solution was shaken on an automated wrist shaker for 30 minutes. A known quantity of internal standard solution was then added and the solution was analyzed for TSNA content by LC-MS/MS.

Determination of lower limit of detection in solution extract. A known amount the target TSNAs were spiked into a liquid extract of one Traditional Ultra Light cartridge. Figure 4 is the chromatogram produced by the analysis of this spiked sample solution. The peaks representing the elution of the target compounds are of low intensity. The limits of detection for the target compounds (LOD) by this extraction technique were determined from this analysis.

Figure 4 – Liquid Extract of Traditional Ultra Light Solution – Spiked with TSNA Target Compounds



While the target analytes were detected, the signal intensity of each was less than would be expected for the quantity of compound added. There is likely some matrix effect or loss during transfer/extraction of these compounds. The limit of detection for the four TSNA compounds in the presence of the Njoy solution matrix was determined by evaluating the strength of the signals produced in the spiked sample trial. These values were then used to calculate the LOD of each compound in the Njoy samples themselves. Table IV is a complete listing of all LOD levels:

Table IV - LOD of Liquid Extraction Method

Compound	LOD in solution with Njoy Matrix (ppb)	LOD in Sample – Calculated (ppb)
NNN	4.5	45 - 50
NAB	3.5	ca. 35
NAT	4.0	40 - 45
NNK	5.0	50 - 55

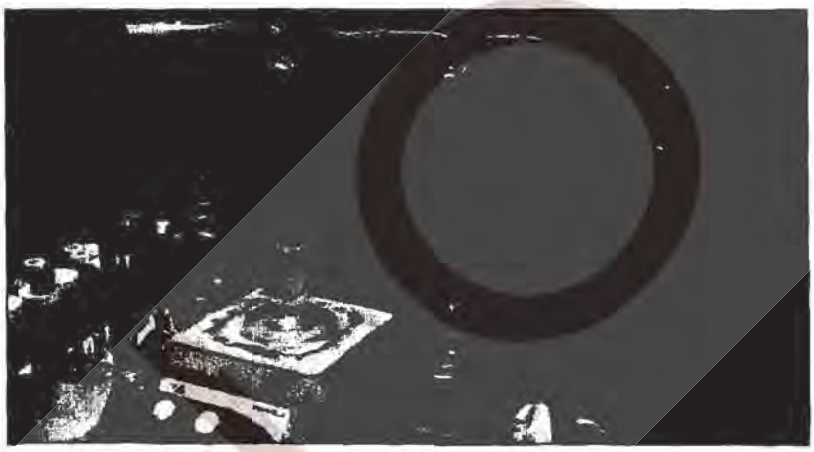
Vapor Capture Method Development

The sparging vapor capture method used by the FDA [B.J. Westenberger, CDER/OPS/OTR, Division of Pharmaceutical Analysis, FDA, May 4, 2009] for the capture of nicotine and related impurities was adapted with a number of modifications.

Procedure (Capture Method I, 'Pull')

1. All glassware was silanized to deactivate the glass surfaces.
2. The capture apparatus was set up, consisting of the e-cigarette, to in-line capture flasks, tubing and a 100 cc Drager hand pump, as displayed in Photo 1.

Photo 1 – Capture Apparatus Method I



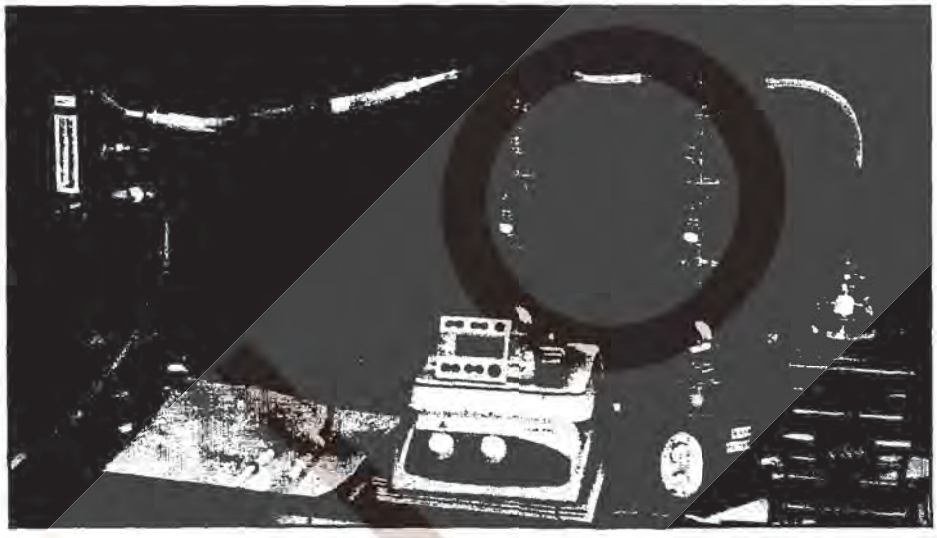
3. 75 ml of methylene chloride were placed in each capture flask. Multiple draws with the Drager hand pump were preformed such that the filament of the e-cigarette was observed to activate 100 times. The theoretical corresponding volume of vapor produced should be 10 liters.
4. All glass surfaces were rinsed down with methylene chloride, flowing nitrogen gas was used to reduce the capture solvent to a residue.
5. A minimal amount (ca. 4 ml) of 100 mM ammonium acetate was used to reconstitute the remaining residue. The resulting solution was analyzed by LC-MSMS.

Several problems were discovered with this initial capture method; most notably the ability of the Drager pump to activate the filament of the Njoy unit. While this was not observed to be a limitation in earlier trial when 100 mM ammonium acetate was used as the capture solution, the presence of methylene chloride vapor in the system likely depresses the actual pressure drop across the filament assembly due to the high vapor pressure of the solvent. It was therefore determined that a reliable volume could not be measured by drawing vapor through the capture apparatus. A second capture method in which positive pressure was applied to the front end of the capture apparatus (e.g., 'push' method) was developed.

Procedure (Capture Method II – 'Push')

1. All glassware was silanized to deactivate the glass surfaces.
2. The capture apparatus was configured such that a tank of breathing quality compressed air was connected to a flow regulator. This regulator was set to deliver 3.5 SCFH (standard cubic feet per hour) and connected by silicone tubing to a Njoy E-cigarette. The tubing was attached to the front portion of the E-cigarette (battery end) and the compressed air was used to push air through the device. Silicone tubing was attached to the mouth piece and the vapor was directed into the series of capture flasks. Photo 2 illustrates the capture apparatus in this second configuration.

Photo 2 – Capture Apparatus Method II



3. 150 ml of methylene chloride were added to each capture flask. Additionally, a third capture flask was added at the end of the apparatus. This addition was made due to some observed TSNA breakthrough into the second flask when lab matrix spiked trials were run.
4. Vapor from the Njoy unit was generated in 'puffs' lasting for 3 seconds. The unit was then allowed to recover between puffs for approximately 15 – 25 seconds. The required number of puffs (61) to produce a total of 5 liters of vapor was performed.
5. All glass surfaces were rinsed down with methylene chloride, flowing nitrogen gas was used to reduce the capture solvent to a residue.
6. A minimal amount (ca. 4 m*l*) of 100 mM ammonium acetate was used to reconstitute the remaining residue. Internal standard solution (ca. 0.05 grams) was added and the resulting solution was analyzed by LC-MS/MS.

Evaporation Validation. In order to determine whether any of the target TSNA compounds are lost upon evaporation of the capture solvent, 75 ml of methylene chloride was spiked with a known amount of TNSA standards. This solvent was then reduced to a residue with flowing nitrogen at room temperature. The residue was reconstituted in ca. 4 ml of 100 mM ammonium acetate and analyzed by LC-MS/MS. The detected TSNAs were quantified with the results shown in Table V.

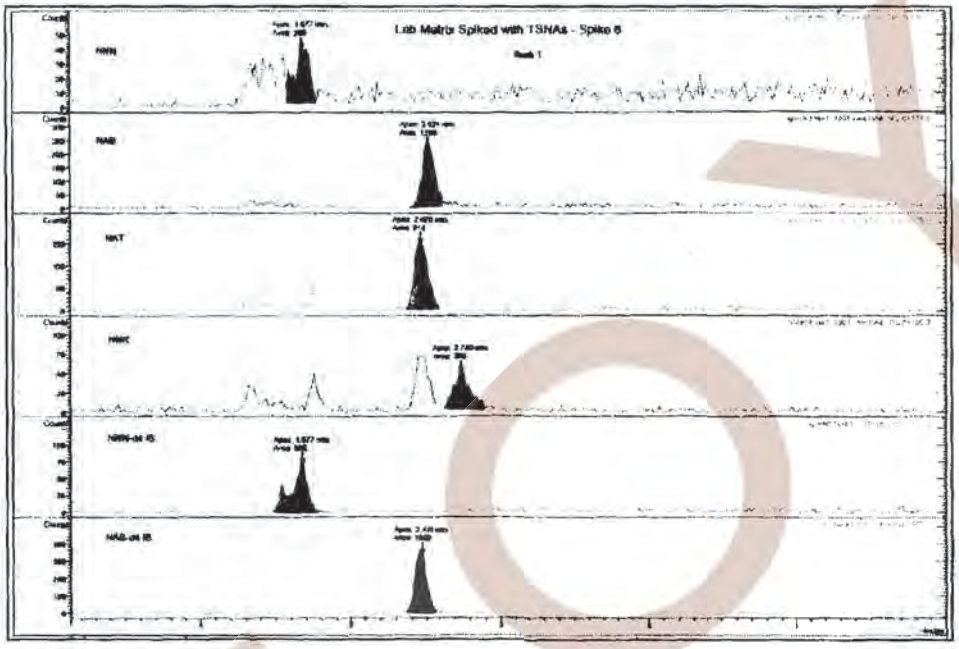
Table V – Evaporation Recoveries

Component ID	% Recovery
NNN	78
NAB	83
NAT	78
NNK	75

While some loss was observed, all recoveries were within 17-25% of the expected values. Losses may occur due to evaporation, but more likely occur during solvent transfer.

Lab Standard Control – Spiked with TSNA Compounds. Vapor from a lab standard solution was captured by the Capture Method II. A lab standard matrix was made up to simulate the Njoy solution matrix (30% PG, 10% Glycerol, 0.8 % nicotine and 60% water). This solution was then spiked with known amounts of each TSNA target compound. Figure 5a presents a stacked plot of the chromatograms produced by the analysis of the vapor solution from the lab standard solution spiked with TSNAs.

Figure 5a – Chromatograms from Lab Matrix Standard Spiked with Target TSNA Compounds



The detection of the target compounds in the residue from the capture flask confirms that these TSNA molecules can be transported from the liquid solution in the Njoy unit to a secondary location through the vapor.

A lower concentration spike solution was constructed to determine the LOD in solution by vapor capture method. Figure 5b is a stacked plot of all extracted ion chromatograms (EIC) for the target and internal standard compounds from this lower concentration lab matrix spike. Table VI contains the estimated lower concentration of the TSNA compounds in the sample solution that can be detected by the vapor capture method. The concentration of TSNA in the vapor (ng/ ml) from this solution is also listed:

Figure 5b – Chromatogram from Lower TSNA Concentration Spiked Lab Matrix

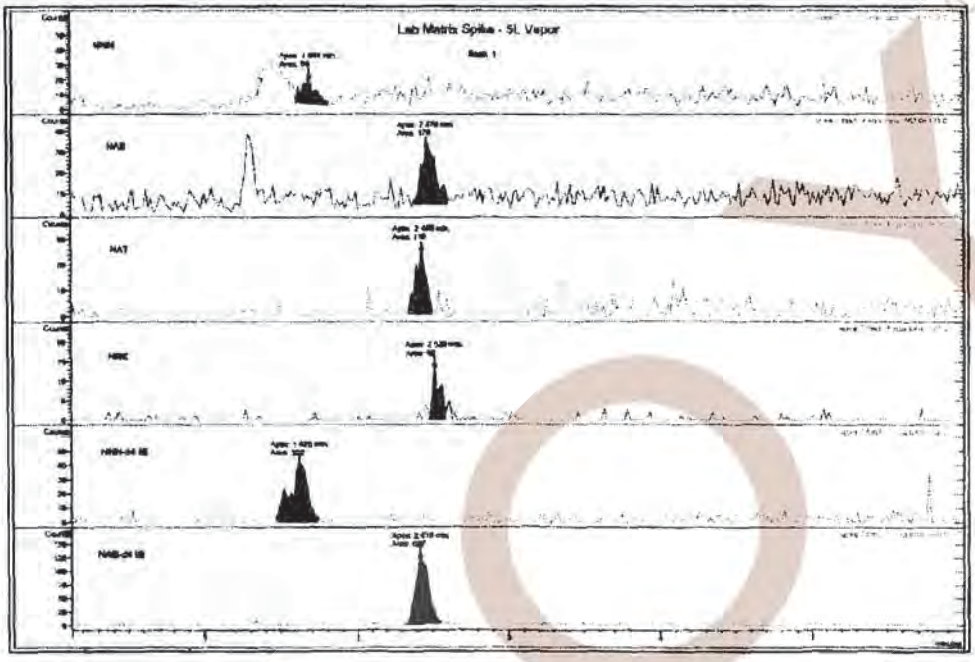


Table VI – LOD and TSNA Vapor Concentration Data
Vapor Capture Method II – Spiked Lab Matrix

Target Compound Identity	Limit of Detection (ppb in Solution)	Corresponding Concentration in Vapor (ng/L)
NNN	25 - 30	approx. 1.5
NAB	15 - 20	approx. 1.2
NAT	20 - 25	approx. 1.5
NNK	20 - 25	approx. 1.4

It should be noted that these results were obtained from a simulated sample matrix, not from an actual Njoy solution. While these values are likely similar to that of the Njoy products, compositional variations between the simulated matrix and the Njoy product may give rise to differences in these concentrations.

SAMPLE ANALYSIS

Njoy Liquid Extraction Results. The liquid from each cartridge was measured by weighing the saturated fibrous plug prior to extraction, and then removing, drying and weighing the plug after extraction. In addition to this plug, the plastic inner casing was included in the extraction vial; a small amount (likely only several micro liters) of liquid was observed on the inner surface of some of these devices. All masses associated with these extractions are included in Table VII.

Table VII – Extract Mass Data

Sample Identity	Sample Solution (grams)	NNN-d4 Standard Solution	NAB-d4 Standard Solution	Total Mass Extract (w/ 100 mM NH_4OAc)
Traditional Light	1.0271	0.0655	0.0786	10.8536
Traditional Ultra Light	1.0370	0.0746	0.0655	11.0036
Menthol Regular	1.0546	0.0774	0.0678	10.7202
Menthol Light	1.0220	0.0833	0.0641	10.6786

No target TSNA compounds were detected in any of the analyzed sample solutions by the liquid extraction method. No peaks were detected at the expected analyte retention times in the chromatograms produced by the sample liquid extracts; representative chromatograms are included in the Liquid Extraction Appendix. All limits of detection are listed in the Summary and in text Table IV.

Njoy Vapor Capture Results. The cleanliness of all glassware was verified prior to sample trials. Additionally, a Njoy unit was sampled without the addition of a solution cartridge to insure that none of the target TSNA compounds were produced by the unit itself. Propylene glycol was used to wet the filament for this trial to create vapor. EIC stacks of both glassware blanks and the Njoy unit blank (without cartridge) are included in the Vapor Sample Analysis Appendix.

The four Njoy sample types (listed on the Title Page) were sampled in duplicate. Each sampling consisted of 61 'puffs' introduced into the vapor capture apparatus. Each puff had a three second duration (stopwatch timed) with a flow rate of 3.5 SCFH. The volume of captured vapor was calculated in Equation II.

Equation II

1 SCFH = 7.86 ml/sec

3.5 SCFH X 3 seconds X 61 'puffs' = 5034 ml ≈ 5L

A steady stream of vapor was observed to flow from the Njoy unit into the first capture flask. This vapor was observed to 'break though' the capture solvent in flask 1, but was not observed above the solvent in flask 2. No vapor was visually observed to travel to flask 3.

Due to residual pressure in the vapor capture apparatus tubing, it was necessary to detach the tubing between the Njoy unit and capture flask 1 between each puff. This prevented additional vapor beyond the desired volume from being capture by this study. *The volume of vapor collected should be considered an estimate* as each puff was performed manually by simultaneously turning the knob of the gas cylinder regulator and activating the stopwatch. A slight delay then occurred between closing the pressure regulator value and disconnecting the tubing. Some variation in total vapor volume inevitably exists between samplings.

NAT was detected in the residue remaining from the vapor capture solutions in all four Njoy products. All sample EIC stacked chromatograms are included in the Vapor Sample Analysis Appendix. Table VIII contains the quantitative results achieved by LC-MSMS for the NAT concentration of the vapor produced by each of the four Njoy samples, calculated by Equation III.

Equation III

$$\text{Concentration of NAT in Solution} = \frac{\text{Area of Analyte X Concentration of Internal Standard}}{\text{Area of Internal Standard X NAT Response Factor}}$$

Total ng NAT from Sample = Concentration NAT in Solution X Total Mass Solution

Concentration NAT in Vapor (ng/L) = Total ng NAT from Sample/5 L

Table VIII – NAT Concentration of Sample Vapors

Sample ID	NAT Concentration in Residue Solution (ppb)			Total NAT from Sample (ng)			Concentration NAT in Vapor (ng/L)		
	Trial 1	Trial 2	AVG	Trial 1	Trial 2	AVG	Trial 1	Trial 2	AVG
Traditional Light	3.9	2.5	3	13.7	11.6	13	2.7	2.3	2.5
Traditional Ultra Light	8.4	3.1	6	36.4	13.8	25	7.3	2.8	5
Menthol Regular	1.6	2.8	2	5.7	11.9	9	1.1	2.4	2
Menthol Light	4.6	2.8	4	20.2	12.1	16	4.0	2.4	3

The limits of detection for the other three TSNA compounds are listed in the Summary section and in text Table VI.

Analytical and Vapor Capture Method Considerations for the Njoy Samples

General

1. For the vapor capture from all Njoy samples, it was noted that the intensity of the signal from the deuterated internal standard compounds was considerably lower in capture flask 1 than in flasks 2 and 3. Likewise, several cases occurred when the NAT signal intensity was greater in flask 2 than in flask 1. These results strongly suggest that a suppression effect occurred in flask 1 which is likely due to the higher concentrations of other sample matrix components; e.g., propylene glycol, glycerol. However, the comparison of analyte signal to internal standard signal, which was also suppressed, should compensate for this effect.

2. For several of the sample trials, the NAT signal was detected in capture flask three. While the total intensity of this signal did not exceed 16% in all cases but one, there is a possibility that some NAT escaped from the vapor capture apparatus. This fact, combined with the 78% recovery of NAT in the evaporation study, necessitates the allowance of ca. 35% error for all NAT values.

3. The ability to concentrate the capture solution volume by allowing the volatile methylene chloride solvent to evaporate results in the low levels of TSNAs that can be detected in the vapor phase experiments. However, due to the 75 – 83% recoveries in the evaporation study for the other three TSNA target compounds, an adjustment of +17-25% for the TSNA LODs may be warranted.

4. At the conclusion of all sample analyses, the Njoy units were still able to generate visible vapor. Therefore, the sample cartridges were not exhausted. All TSNA concentrations were based on the initial five liters of vapor produced by the unit. It is unknown if the TSNA concentration in the vapor produced by the Njoy units is consistent over time or if the amount of TSNA entrained in the vapor changes as a function of usage.

5. The volume of vapor collected and used in all calculations should be considered an estimate. Each 'puff' was performed manually with some variation (perhaps $\pm$ 10-20%) in total vapor volume inevitably exists between samplings.

Traditional Light

1. Only one of the triplicate LC-MS/MS analyses of the flask 1 solution (trial 2) produced an NAT signal with sufficient intensity for integration. The results of this run was used to represent the recovery of NAT from this flask with the two injections with lower signal intensities were not included. This omission may skew the results upward, making the NAT concentration results for this trial slightly elevated.

2. While NAT was detected in flask 2 of trial 1, the signal strength was not sufficient for integration. The NAT contribution from flask 2 was therefore not included and the trial 1 results may be slightly skewed downward.

3. Breakthrough of NAT to flask three was not observed in either trial of the Traditional Light product.

Traditional Ultra Light

1. Breakthrough of NAT signal to capture flask three was observed in both Traditional Ultra Light trials. The total NAT concentration from flask 3 was 16% and 12% of the total NAT assayed. It is therefore possible that some NAT was lost during the analysis of this product.

2. One of the triplicate analyses of the flask 1 solutions from trial 2 did not produce NAT signal of sufficient intensity for quantitation. This run was not included in the data calculation. The NAT may be slightly over represented from this flask.

Menthol Regular

1. Signals associated with the presence of NAT were *only* quantitated in the extract from flask 3 in trial 1. A very low intensity signal may indicate the presence of NAT in flask 1 as well, but the intensity of this signal is well below the limits of integration. This result is somewhat unexpected and has no explanation at present.

2. Signals associated with NAT were detected in all three flasks in trial 2. The signal strength was only sufficient for quantitation in flask 2.

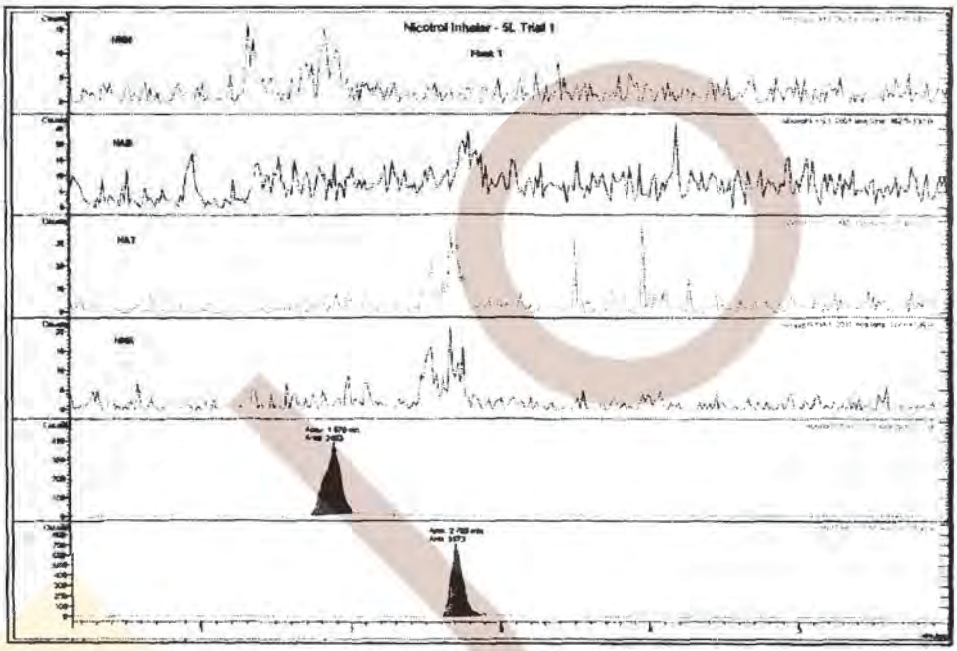
Menthol Light

NAT was detected in the extract from flasks 1 and 2 both analytical trials. No breakthrough was observed into flask 3 in trial 1. Two of the three flask 3 runs produced signal sufficient for integration in trial 2.

Nicotrol Inhaler. A Nicotrol® Inhaler unit with one cartridge insert was sampled by capture method II (e.g., push method). As was the case with the Njoy unit, approximately 5 L of air was passed through the Nicotrol® Inhaler unit. The air transported vapor bubbled through the three capture flasks containing methylene chloride.

Analysis of the residues produced by trial 1 sampling of the Nicotrol® Inhaler detected trace amounts of NNN, NAB and NAT. The signal strength from these analytes was extremely low, well below that required for integration. Figure 6a presents the stacked chromatograms from the residue in flask 1.

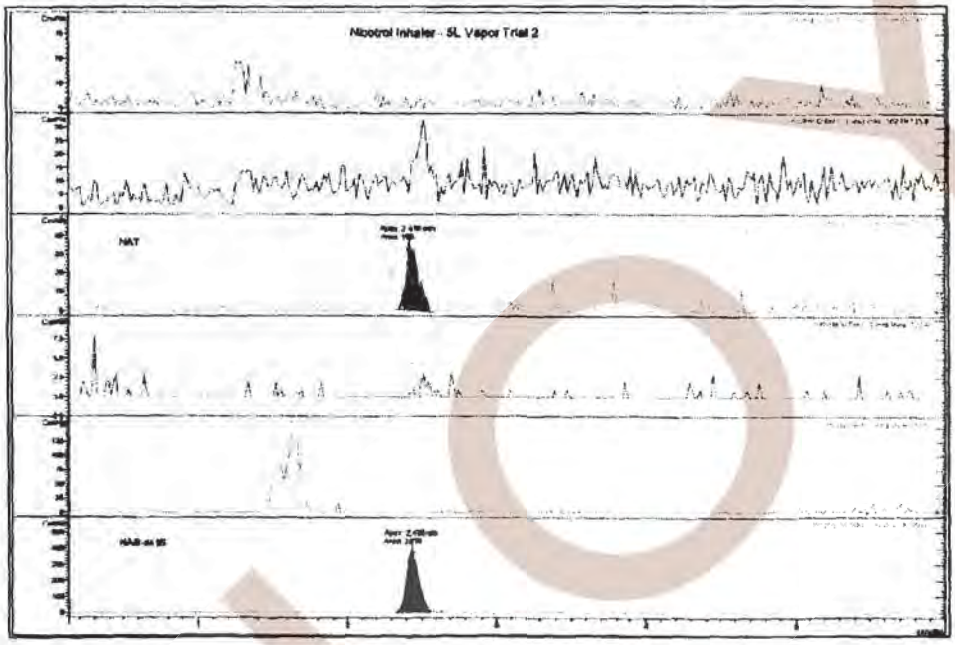
Figure 6a – Residue from Nicotrol® Inhaler – Trial 1 Flask 1



Note the very low intensity of peaks at ca. 1.8 min in the top EIC and 2.7 min in the second and third EIC. The peak at 2.7 min in the fourth EIC is likely associated with NAT and does not signify the presence of NNK (m/z 106 used for both analytes). No quantitation was possible from this trial.

A somewhat more intense signal associated with NAT was obtained in the second Nicotrol® Inhaler sampling trial from the residue in flask 1. NAB was again detected below the level of quantitation, NNN was not detected in this trial. Figure 6b is the stack EIC from flask 1, trial 2:

Figure 6b – Residue from Nicotrol® Inhaler – Trial 2 Flask 1



No TSNA signals were discernable from the background noise in residue from flasks 2 and 3 in either trial.

The peaks associated with NAT were integrated in the flask 1 chromatograms from trial 2 and used to calculate and estimated concentrations in the sample vapor are listed in Table IX.

Table IX - NAT Concentrations from Nicotrol® Inhaler Vapor

Sample ID	NAT Concentration in Residue Solution (ppb)			Total NAT from Sample (ng)			Concentration NAT in Vapor (ng/L)		
	Trial 1	Trial 2	AVG	Trial 1	Trial 2	AVG	Trial 1	Trial 2	AVG
Nicotrol® Inhaler	D	1.0	1	---	4.4	4	---	0.9	0.9

Due to differences in sample matrix, limits of detection for all TSNA compounds were not established from the Nicotrol® Inhaler unit vapor.

Considerations - Nicotrol® Inhaler

1. The Nicotrol® Inhaler unit does not produce a visible vapor as does the Njoy unit. It was therefore difficult to determine if the vapor capture apparatus was indeed activating the Nicotrol® Inhaler.

2. Due to the lack of visible vapor, it is unknown if the cartridge insert was exhausted prior to the completion of sampling.

3. No Nicotrol® Inhaler unit spike studies were performed to measure the efficiency of TSNA transfer by the sampling method. Further method development is required to validate the results from the Nicotrol® Inhaler.

As questions arise during your review of this report, please do not hesitate to call us.

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BMC Public Health

RESEARCH ARTICLE Open Access

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

Igor Burstyn

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

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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/safework/info/publications/WCMS_113329/lang–en/index.htm; 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 [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):

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

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.

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

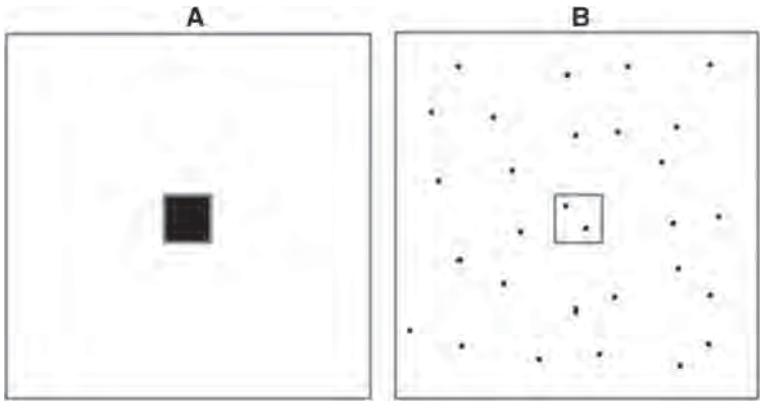

Figure 1 Illustrating the difference between concentrations in the aerosol generated by vaping and inhaled air in a day. *Panel* ***A*** shows a black square that represents aerosol contaminated by some compound as it would be measured by a "smoking machine" and extrapolated to dosage from vaping in 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).

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:

(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].

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

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.

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

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.

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.

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:

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

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

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.

$OEL_{mixture} > 1$, 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".

Additional files

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

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

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

Competing interests

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Authors' 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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Ruyan® E-cigarette Bench-top tests

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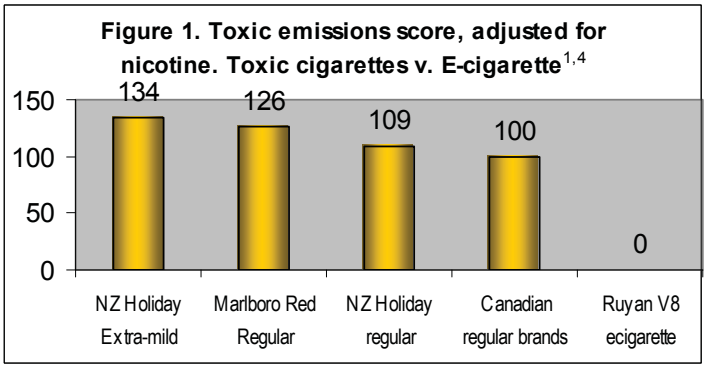
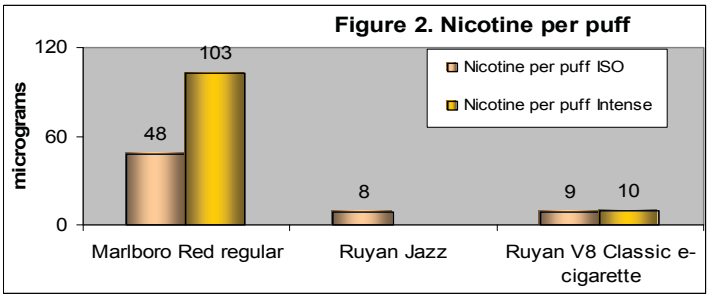


Background Electronic cigarettes, without tobacco, flame or smoke, claim to be cigarette substitutes and to deliver nicotine safely, without smoke toxicants. Are these claims justified?

Aim To assess the Ruyan® e-cigarette and its mist for safety, emissions, and nicotine dose.



Participating laboratories, methods, materials

1) Environmental Science and Research, Porirua NZ. *Cartridge liquid*: Monoamine oxidase inhibition (Kynur-amine substrate method); Nicotine (GCMS); Heavy metals (by ICP-MS)
2) Hill Laboratories, NZ. *Mist:* GCMS, Type II ATD, qualitative. 3) Hort Research, NZ. *Liquid* for 34 PAHs, by GCMS. 4) Labstat International ULC,Canada. *Liquid:* TSNAs, by LC-MS/MS. *Mist:* 14 PAHs and azarenes, Vinyl Chloride, acetamide, 7 volatile TSNAs. 5) Lincoln University, NZ. *Liquid:* HS-SPME & GCMS, qualitative. 6) National Radiation Lab. NZ For Pb210 gamma emitting nucleotides.
7) Syft Ltd NZ *Mist,Liquid* VOCs SIFT-MS
8) Duke University CNSCR Bioanalytical Lab. USA: *Mist:* Nicotine by GC MS.
9) British American Tobacco, Group R&D, (UK) *Liquid, mist:* Chemistry, smoke tests by ISO method. Nicotine in puffs, particle size (TSI 3090 MN USA), pressure drop.[1]

Test materials Ruyan in Beijing supplied V8 Classic e-cigarettes and 16 mg nicotine-labeled cartridges ex-factory to test laboratories, directly, or via distributors. Most were manufactured in 2008 and tested in 2008-9. Batteries were re-charged before testing, and fresh cartridges used. Shelf life at time of testing varied. An ISO machine smoked 1 mg tar cigarette provided smoke toxicants.[1]

Selection of toxicants for testing of e-cigarette mist. Selection was based on published priority lists of cigarette smoke toxicants:
9 recommended by WHO TobReg committee for mandatory lowering:[5]
37 prioritised by toxicological risk assessment by Fowles & Dybing[6] additional to the above 9;
13 additional to the above 46, priority tested on brands sold by British Columbia,[7] known loosely as the Hoffman analytes.
Not tested: acetaldehydes (delayed, due to world shortage of reagent); hydrazine, chlorinated dioxans, oxides of nitrogen, and urethane.

Results

Toxicology and safety In Ruyan V8 e-cigarette mist tested for over 50 priority-listed cigarette smoke toxicants so far, no such toxicant was found. A possible exception was mercury, detected in trace quantity of 0.17 ng per e-cigarette. However, this was barely above the reporting limit of 0.13 ng, and within the reported 38% coefficient of variation.

Chemistry The cartridge (labeled 16 mg), contained 13 mg[1] to 14 mg[3] nicotine and 1.1g propylene glycol (PG), and yielded >300 35 mL puffs of mist: 82% PG, 15% water, 1% free-based nicotine, 2% particulates and flavours.[1] Vaporisation occurred at 54˚**C**, powered by 0.1 mW per puff from lithium-ion battery.[1] Pressure drop was 152 mmWG, compared with 80-120 mmWG for a tobacco cigarette.[1] Particle size 0.04 micron (count median diameter), was about one-fifth of that for tobacco smoke.[1]

Nicotine delivery per puff A 35 mL puff from the Ruyan® V8 delivers only 10% of the nicotine obtained from a similar puff of a Marlboro regular cigarette. Deeper 50 mL puffs from the Ruyan V8 delivers only slightly more nicotine.

Site of nicotine absorption No deposition of aerosol nicotine occurred on pulling mist through a cascade impactor.[2]

Discussion

Main finding. Testing for over 50 cigarette key smoke toxicants found none in any but trace quantity, in Ruyan V8 mist.

Safety of e-cigarettes as a product class Safety results refer to the Ruyan® V8 Classic. However the low operating temperature (54˚**C**) of the atomiser - 5 to 10% of the temperature of a burning cigarette - suggests e-cigarettes as a class are unlikely to emit cigarette toxicants in their mist.

Nicotine dose (Figure 2) An e-cigarette user will need to take more puffs more often, and deeper puffs confer no advantage for V8 users. Six puffs every 5 minutes would deliver the same dose of nicotine delivered by shallow inhaling (10 puffs of 35 mL per puff) from one tobacco cigarette every hour, but would not achieve the high immediate nicotine boost which many smokers crave. Nicotine overdose is unlikely, even though nicotine delivery may vary between brands.

Nicotine absorption site The nicotine dose and particle size are too small to ensure deposition in the alveoli or bronchioles and rapid nicotine absorption as in cigarette smoking.

Limitations of study The results apply only for the products tested. Extrapolation to all product sold assumes production only from internationally-certified good manufacturing sites, and trademark enforcement.

Conclusion

Ruyan® V8 nicotine e-cigarette users do not inhale smoke or smoke toxicants. The modest reductions recommended in 2008 by WHO's Tobacco Regulation committee for 9 major toxicants in cigarette smoke, in line with Articles 9 and 10 of the FCTC (WHO Framework Convention Tobacco Control treaty), are already far exceeded by the Ruyan® e-cigarette, as it is free of all accompanying smoke toxicants.
Absolute safety does not exist for any drug, but relative to lethal tobacco smoke emissions, Ruyan e-cigarette emissions appear to be several magnitudes safer. E-cigarettes are akin to a medicinal nicotine inhalator in safety, dose, and addiction potential.
E-cigarettes are cigarette substitutes. If they can take nicotine market share from cigarettes, and that is the big question, they will improve smoker and population health. They may also have a secondary role as medicinal nicotine inhaler quitting aids. Further trials of acceptability, addiction potential, clinical safety, and quitting efficacy are needed.

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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

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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.

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Electronic cigarettes: a survey of users

Jean-François Etter

Abstract

Background: Little is known about users of electronic cigarettes, or their opinions, satisfaction or how and why they use such products.

Methods: An internet survey of 81 ever-users of ecigarettes in 2009. Participants answered open-ended questions on use of, and opinions about, ecigarettes.

Results: Respondents (73 current and 8 former users) lived in France, Canada, Belgium or Switzerland. Most respondents (77%) were men; 63% were former smokers and 37% were current smokers. They had used e-cigarettes for 100 days (median) and drew 175 puffs per day (median). Participants used the ecigarette either to quit smoking (53 comments), to reduce their cigarette consumption (14 comments), in order not to disturb other people with smoke (20 comments), or in smoke-free places (21 comments). Positive effects reported with ecigarettes included their usefulness to quit smoking, and the benefits of abstinence from smoking (less coughing, improved breathing, better physical fitness). Respondents also enjoyed the flavour of ecigarettes and the sensation of inhalation. Side effects included dryness of the mouth and throat. Respondents complained about the frequent technical failures of ecigarettes and had some concerns about the possible toxicity of the devices and about their future legal status.

Conclusions: Ecigarettes were used mainly to quit smoking, and may be helpful for this purpose, but several respondents were concerned about potential toxicity. There are very few published studies on ecigarettes and research is urgently required, particularly on the efficacy and toxicity of these devices.

Background

In recent years several manufacturers, mainly in China, have produced electronic cigarettes (ecigarettes) that are distributed in western countries, often by small, newly established companies [1-4]. Electronic cigarettes look and feel like cigarettes, but do not burn tobacco. The several existing brands vary but, in general, ecigarettes contain a battery and an electronic device that produces a warm vapour or 'mist'. The vapour usually contains nicotine and often - but not always - contains propylene glycol [5]. The vapour is inhaled and, as the user exhales, some visible vapour is released, but no tobacco smoke. Some ecigarettes also contain a light-emitting diode in the tip that glows when the user puffs, to resemble the burning end of a cigarette. The nicotine content of the cartridge varies, and the cartridges usually contain chemical additives and flavours (such as various brands of tobacco, chocolate, coffee, mint or fruit). The cartridges can usually be refilled, and refill bottles are provided with the device.

Electronic cigarettes are probably less harmful than tobacco smoking, but they are almost certainly more dangerous than medicinal nicotine inhalers [6,7]. However, to our knowledge, there is no published data on the safety of ecigarettes. Internationally, the legality of ecigarettes varies; they cannot be sold in Australia, Brazil, Canada, Denmark or Switzerland, but their sale is authorized in other countries (e.g. China, New Zealand) [5,8,9]. Analyses conducted by the United States Food and Drug Administration (FDA) showed that ecigarettes contain carcinogens, including nitrosamines, toxic chemicals such as diethylene glycol, and tobacco-specific components suspected of being harmful to humans (anabasine, myosmine, and beta-nicotyrine) [6]. The FDA also found that ecigarette cartridges labelled as containing no nicotine did in fact contain low levels of nicotine. Some manufacturers do not disclose the ingredients in their products. Furthermore, ecigarettes are not manufactured according to the high standards imposed on pharmaceutical companies. Consequently, the inhaled vapour may contain

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impurities that may be dangerous to consumers [6]. In particular, the origin of the nicotine itself is uncertain, as pesticide-grade nicotine rather than pharmacological-grade nicotine may be used in ecigarettes.

Little is known about ecigarettes, as few research reports have been published [10,11]. In addition to the FDA report mentioned above, reports from New Zealand, funded by Ruyan (a Chinese manufacturer of ecigarettes) concluded that the mist from the Ruyan ecigarette contains acetaldehyde and mercury [12,13]. A randomised trial in 40 smokers found that the Ruyan ecigarette delivered nicotine to the blood more rapidly than the nicotine inhaler, but less rapidly than cigarettes, and that the effect of the ecigarette on craving was similar to that of the nicotine inhaler, but less than that of cigarettes [14]. A recent U.S. study found that 10 puffs of an ecigarette delivered little or no nicotine [15].

The mist from ecigarettes is inhaled into the lung [13]. Although the particle size is apparently too small to ensure deposition in the lung alveoli [12], we are not aware of any study of lung absorption of ecigarette mist. Because lung inhalation may enable nicotine to pass rapidly into the blood, and thus rapidly relieve craving and tobacco withdrawal symptoms [14], ecigarettes have the potential to be at least as effective as currently approved nicotine replacement therapy (NRT) products, none of which deliver nicotine to the lung. In addition, the similarities in shape, actions and inhalation between ecigarettes and tobacco cigarettes could also help smokers quit. However, as there are no data to support the manufacturers' claims that ecigarettes help smokers quit, the World Health Organization asked the companies not to make any therapeutic claims [7,16]. If they claimed that ecigarettes help smokers quit, manufacturers would be subject to the legislation and regulation that applies to NRT products. In order to avoid this, some ecigarettes are now marketed for enjoyment, or as devices that enable smokers to "smoke" everywhere, including smoke-free places [3,4]. Nonetheless, some distributors present their products as an alternative to tobacco smoking, more or less implicitly suggesting that ecigarettes can be used to aid smoking cessation [1,2].

One may hypothesize that the positive effects of ecigarettes may include smoking cessation, smoking reduction or relapse prevention. The ecigarette could also be used as an aid during a preparation period before cessation, similar to the pre-cessation treatment or "cut down to quit" approach that is an approved indication for NRT [17]. On the other hand, ecigarettes may be dangerous because of the frequent and longterm lung inhalation of diethylene glycol, nicotine and other toxic components, and because of the sub-standard manufacturing process, relative to pharmaceutical products [7]. Because of its rapid nicotine delivery [14], the ecigarette also has the potential to be addictive. In addition, the refill bottles may be dangerous as they contain up to one gram of nicotine, whereas the fatal dose of nicotine is estimated to be 30 to 60 mg for adults and 10 mg for children [5]. The ecigarette may also enable smokers to continue to 'smoke' in smoke-free environments, thus delaying or preventing cessation in people who might otherwise quit. Finally, the fruit and chocolate flavours may appeal to young people, and this raises the concern that ecigarettes may facilitate initiation of nicotine dependence in young never-smokers [5]. However, none of these hypotheses has yet been tested.

Because of the huge burden of tobacco-related death and disease, and because ecigarettes have potential to help smokers quit, there is an urgent need for research into these products. First, there is a need to know why and how these products are used, and whether users are satisfied with them. The aim of this study was to assess usage patterns of ecigarettes, reasons for use, and users' opinions of these products.

Methods

As ecigarettes are mainly sold online, the internet is a logical way to reach users. We therefore posted a survey form, in French, on the smoking cessation website StopTabac.ch over a 34 day period between September and October 2009. This website receives approximately 120,000 visitors per month and is principally visited either by smokers who intend to quit or by recent quitters [18,19]. Links to the survey were posted on websites that either provide information about ecigarettes (ecigmag.com, forumecigarette.com) or sell them (econoclope.com, sedansa.be). After discussion with the head of the ethics committee of the Geneva University Hospitals (community medicine section, the committee to which our Institute is submitted), the study was exempted from approval.

Eligible participants were people who declared that they had ever used an ecigarette and who provided the brand name of the ecigarette that they had used most often. Subjects who did not name a brand were excluded, because this raised doubts about whether they had actually used an ecigarette. On the survey form, participants indicated whether they had ever used ecigarettes or were currently using them (subdivided into daily user, non-daily user, former user, never used). They also provided the total number of days that they had been using ecigarettes, the brand they used most often, the nicotine dose per unit, the flavour and the cost per package (using open-ended questions). In addition, subjects indicated whether ecigarettes had helped them to quit smoking, and current users indicated the number of puffs per day on ecigarettes.

In response to open-ended questions, participants wrote where they bought their ecigarettes, the reasons why they used them, what they considered to be the beneficial and undesirable effects of ecigarettes, and the most positive and negative points about the product. If they had stopped using ecigarettes, they explained why. Participants also listed which questions they had asked themselves about ecigarettes, and gave their opinion on the information leaflets or documents inserted in the ecigarette packages. Finally, they wrote general comments on the ecigarette.

Other questions also covered smoking status (daily, non-daily, former smoker, never smoker). Smokers stated the number of cigarettes they smoked per day, and former smokers stated when they had quit smoking. Participants were asked to supply their age, sex and country of residence.

Medians rather than means were used for continuous variables because medians are less sensitive to outliers, which can excessively influence means in small sample sizes.

Results

Answers were obtained from 214 people, but 123 of these had never used ecigarettes and ten did not name the brand of their ecigarette. These 133 subjects were excluded. All subsequent analyses included only the 81 respondents who declared that they had ever used ecigarettes and who indicated the brand that they had used most often. These 81 respondents included 72 daily users of ecigarettes, one non-daily user and eight former users (Table 1). They were relatively young (median age 37 years), and most (77%) were men. Respondents lived in France (81%), Belgium (8%), Canada (6%) and Switzerland (5%). Most (63%) were former smokers who had quit smoking relatively recently (median duration of abstinence: 100 days) (Table 1).

Table 1: Characteristics of ecigarette users, and usage patterns

Characteristic	
Number of respondents	81
Age, median (range), years	37 (19-65)
Men (%)	77
Smoking status (%)	
Former smokers	63
Daily smokers	23
Occasional (non-daily) smokers	13
Cigarettes per day, in smokers (median)	12
Days of abstinence, in former smokers, median (25th and 75th percentiles)	100 (30, 210)
Use of electronic cigarettes	
Days of use of the e-cigarette, median (25th and 75th percentiles)	100 (30, 210)
Number of puffs per day, median (25th and 75th percentiles)	175 (90, 275)
Number of puffs per day, range	10 to 600
Price per package, median, Euros (U.S. dollars)	40 (60)
Median dose of nicotine per unit, mg (25th and 75th percentiles)	14 (10, 16)
Does (did) the e-cigarette help you quit smoking? (%)	
Yes, a lot	79
Yes, somewhat	16
No, not at all	5

Use of the electronic cigarette

Most respondents had been using the ecigarette for slightly longer than three months, and current users took 175 puffs per day (median) from their device (Table 1). Sixteen different brands of ecigarettes were named, the most frequent being Janty (n = 17), Joye (n = 17), Sedansa (n = 14), Econoclope (n = 9), Liberty-cig (n = 8), Smoke51 and Edsylver (n = 2 each). All these brands of ecigarette deliver nicotine, and the median dose of nicotine per unit was 14 mg. The preferred flavour (open-ended field, 78 answers) was tobacco (n = 46, various flavours, e.g. "Turkish blend", "K-mel"), followed by mint (n = 6), fruit (n = 5, e.g. "apple"), vanilla (n = 4), coffee (n = 3) and tea (n = 2). Twelve respondents used several of these flavours.

Most respondents (n = 74; 94% of 79 answers) had bought their ecigarette on the internet, two had bought their device in China, two at a tobacco retail shop and one had bought it second hand. When asked whether the ecigarette helped them quit smoking, most respondents (79%) answered "a lot" (Table 1).

When asked why they chose to use ecigarettes (three open-ended fields, 225 comments), the most frequent answers were: that they used it to quit smoking; for their health (as ecigarettes were perceived to be less toxic than tobacco, e.g.: "it is better for health than tobacco"); because ecigarettes are less expensive than regular cigarettes; because ecigarettes can be smoked everywhere, including smoke-free places (e.g.: "I don't need to go outside to smoke anymore"); to avoid disturbing other people with second-hand smoke; for the pleasure of smoking it

(e.g.: "to continue to inhale, which is something I like"), and to reduce their cigarette consumption (Table 2).

The most frequently cited beneficial effects of ecigarettes (two open-ended fields, 134 comments) were: that it improved breathing and respiration (e.g.: "I have less breathlessness on exertion"); that it helps to quit smoking (e.g.: "I have quit smoking without problems"); that respondents coughed less, expectorated less and had fewer sore throats; that it improved their health and physical fitness; and that it did not cause unpleasant odours or bad breath (Table 3). Interestingly, one respondent suggested that the ecigarette device might be useful to administer other medications to the bronchia or lung. The two open-ended fields on the undesirable effects of ecigarettes elicited 61 comments (only half the number of comments received on the beneficial effects). The most frequent responses were that ecigarettes caused dry mouth and throat, vertigo, headache or nausea (Table 3).

The most frequently cited positive features of ecigarettes (three open-ended fields, 208 comments) were: that respondents liked the taste and variety of flavours; they appreciated the beneficial effects of the ecigarette on their health, breathing and cough; the absence of unpleasant odours or bad breath; they appreciated the pleasure of inhalation, and harsh sensation in the throat; they liked the act of using the ecigarette, which is similar to smoking; the ecigarette is less toxic than tobacco smoke; it facilitates smoking cessation; and that it can be used everywhere (Table 4).

Table 2: Reasons for using e-cigarettes: open-ended comments from e-cigarette users

	Number of comments
To quit smoking	53
For health, as e-cigarettes were perceived to be less toxic than tobacco	49
Less expensive than regular cigarettes	26
Can be smoked everywhere, including smoke-free places	21
To avoid disturbing other people, or producing environmental tobacco smoke or the smell of stale smoke	20
For the pleasure of smoking, including the pleasure of inhaling and smoking-related actions	19
To reduce cigarette consumption	14
Curious to test a new product	10
Ecigarettes taste and smell good	8
Previously failed to quit with either nicotine patch or bupropion	3
To get nicotine	2
Total (from three open-ended fields)	*225*

Table 3: Beneficial and undesirable effects of e-cigarettes: open-ended comments from ecigarette users

	Number of comments
Beneficial effects (total from two open-ended fields)	*134*
Improves breathing and respiration	31
Less cough, less expectoration, fewer sore throats	23
Helps to quit smoking	20
Improves health and physical fitness	17
Improves sense of taste and smell	11
Does not cause unpleasant odours or bad breath	10
Helps to reduce cigarette consumption	7
Sleeps better	4
Less craving for cigarettes	4
Cost	4
Pleasure of smoking the e-cigarette	2
Useful device to administer other medications to the bronchia or lung	1
Undesirable effects (total from two open-ended fields)	*61*
Dry mouth and throat	16
Vertigo, headache or nausea	7
Bad taste	4
Weight gain	3
Technical problems (batteries)	3
Difficult to accurately control dose of nicotine	3
Cost	3
No undesirable effects	13
Miscellaneous comments	9

When asked about the three most negative aspects of ecigarettes (three fields, 154 comments), respondents complained in particular about the poor quality of the devices. They also reported that that ecigarettes were difficult or impractical to use (e.g. "it is difficult to refill the liquid"), that the dosage was difficult to adjust (either too high or too low), that the liquid can leak out during use, and complained about the lack of information on the composition of the vapour and any health risks associated with ecigarettes (Table 4).

Respondents also stated which questions they had asked themselves about ecigarettes (three fields, 112 comments). This section showed that users wondered whether ecigarettes were safe, what the effects on health were, and whether ecigarettes are toxic (59 comments, including five that specifically mentioned propylene glycol). Respondents were also concerned that the e-cigarette might be banned, and about its future legal status (19 comments, e.g.: "let's hope it will not be prohibited"). They wanted to know about the composition of the liquid in the cartridge (10 comments, e.g.: "What exactly is the content of this liquid?", including four comments on the quality of the liquids), why no serious studies on ecigarettes have been published (5 comments), why ecigarettes are not sold in pharmacies (4 comments) and why the devices are not produced in western countries (3 comments).

When asked to comment on the documentation that accompanied their ecigarette (one field, 70 comments), most respondents answered that the inserts were good or satisfactory (31 comments), seven responded that they were only adequate, 15 responded that they contained too little information, four reported that there was no explanatory leaflet with their ecigarette, and two complained that there was no explanation of the health effects of ecigarettes. Three people responded that they used the internet and online discussion forums to obtain more information on ecigarettes (e.g.: "the insert was very brief, but fortunately, there are specialized internet discussion forums").

The section that asked participants to write general comments on the ecigarette (one field) elicited 64 comments. Twenty-one comments were very positive or enthusiastic (e.g. "brilliant" (6 times), "miracle product", "unbelievable", "very satisfied"), and 11 were positive but more neutral (e.g.: "good", "I recommend it"). Respondents also considered that the ecigarette helped them quit smoking (14 comments), that it was more effective than either nicotine patch or bupropion (5 comments), and that it enabled them to reduce their cigarette consumption (3 comments). Three people feared that the ecigarette would soon be banned. Four commented that ecigarettes need technical improvement, and six wrote negative comments (e.g.: "not helpful to quit", "avoid it").

Table 4: The most positive and negative aspects of ecigarettes: open-ended comments from e-cigarette users

	Number of comments
Positive points (total from three open-ended fields)	*208*
Taste and variety of flavours	38
Beneficial effects on health, breathing and cough	26
No unpleasant odours or bad breath	23
Inhalation, including harsh sensation in the throat and pleasure of inhaling	16
Less toxic than tobacco smoke	15
Facilitates smoking cessation	15
Can be used everywhere (the freedom)	15
The gestures or actions (similar to smoking)	13
Ease of use, design	10
Less expensive than cigarettes	9
No environmental tobacco smoke	8
Facilitates smoking reduction	5
No ash, dirt, or burned clothes	5
Can choose the dose of nicotine and number of puffs	5
Relieves craving for tobacco	3
Improves sense of smell and taste	2
Negative points (total from three open-ended fields)	*154*
Poor quality, lack of reliability and frequent failures	40
Batteries discharge too rapidly	27
Too expensive	14
Bad taste	14
Difficult or impractical to use; dosage is difficult to adjust	10
The liquid may leak during usage	10
Only sold on the internet	9

Table 4: The most positive and negative aspects of ecigarettes: open-ended comments from e-cigarette users (Continued)

No studies or information on the composition of the vapour and the health risks of the e-cigarette	8
Cartridges do not last long enough	6
Difficult to stop using the ecigarette without relapsing to smoking	4
Too big or too heavy	3
Too often asked by friends or colleagues to explain the device	2
Miscellaneous	7

Eight respondents had stopped using ecigarettes, and were asked to indicate why (two fields, 15 comments). Reasons included: it did not help me quit smoking (6 comments); it did not taste like cigarettes (3 comments); poor quality or not reliable (3 comments); because of concerns about risks and side-effects of ecigarettes (3 comments).

Interestingly, several respondents used a neologism (*vapoter*, in French) to describe the action of smoking an ecigarette; this term probably originated from "vapour" and spread in online discussion forums. The corresponding terms used on English-language forums (e.g. ecigarette-forum.com) are "vaping" and "vaper".

Discussion

Although, for legal reasons, ecigarettes are mainly marketed to current smokers either for enjoyment or for use in smoke-free places, our results suggest that most people who buy these products are current and former smokers who use ecigarettes to help quit smoking, just as they would use NRT. Our survey also showed that ecigarettes were liked by users, and were used quite intensively by this sample; almost all respondents were daily ecigarette users, and the number puffs per day (175) was substantial. However, as ecigarettes deliver about one-tenth of the nicotine per puff compared to cigarettes [12], this intensive puffing pattern may result in less exposure to nicotine than smoking. Interestingly, the median duration of ecigarette use corresponded to the median duration of abstinence in former smokers (100 days in both cases).

Respondents reported more positive than negative effects with ecigarettes: many reported positive effects on the respiratory system (breathing better, coughing less), which were probably associated with stopping smoking [20]. The fact that ecigarettes do not produce any unpleasant odours or environmental tobacco smoke was also appreciated. Most importantly, many respondents reported that the ecigarette helped them quit smoking, and several compared it favourably with either nicotine patch or bupropion. These preliminary findings, together with data showing that ecigarettes relieve craving and withdrawal [14], suggest that the ecigarette may be an effective aid to smoking cessation, and therefore merits serious investigation for this purpose. Ideally, future trials should compare the efficacy of ecigarettes versus NRT (particularly the nicotine inhaler), bupropion or varenicline. However, as ecigarettes are probably more toxic than NRT products [6], the former should probably only be recommended to smokers if they are substantially more effective than current NRTs, and if the toxic constituents of ecigarettes can be eliminated.

Interestingly, dry mouth and throat was a frequent adverse effect of the ecigarette. It may be useful to investigate why this occurs and how it might be minimised. It would also be interesting to investigate why ecigarettes appeal more to men than to women. Many respondents complained of the poor quality of ecigarettes, their frequent failures, the lack of durability of cartridges and batteries, and that the liquid sometimes leaks from the device during usage. Apparently competition between manufacturers has not yet resulted in products of sufficient technical quality.

Although users' comments were generally positive, many were concerned about the safety and toxicity of ecigarettes, and questioned why no study has yet investigated these aspects. Several respondents were also concerned about the future legal status of ecigarettes, and that they may possibly be banned. Indeed, health authorities in several countries have published warnings about, or have prohibited the sale of, ecigarettes [5-8]. From a public health perspective, however, the question is whether - at a population level - the potential benefits of the ecigarette outweigh its drawbacks. If ecigarettes are more effective than current NRTs, but are withdrawn from the market until approved as smoking cessation aids, ecigarette users might revert to smoking tobacco, which is more hazardous than ecigarettes. This could have a significant, negative impact on public health, because it can take several years to obtain legal approval for a new drug delivery system.

On the other hand, ecigarettes are not currently manufactured to the same rigorous standards as pharmaceutical products; they currently contain toxic components and are therefore almost certainly less safe than NRT products [6]. The legal status of the e-cigarette is unclear in many countries, and its regulation is complex; it is neither classed as a tobacco product, nor food, nor is it registered as a medicine. From the legal perspective, there is a difficult balance between the need to protect consumers

and the possibility now being offered to smokers to use a new, acceptable and potentially effective device to stop smoking. Given the enormous burden of disease and death caused by tobacco smoking, there is an urgent need for research into the toxicity, efficacy and public health impact of ecigarettes [10]. In addition, whether devices that resemble ecigarettes could be used to deliver medications other than nicotine to the lung and bronchia also warrants investigation. As the manufacturers and distributors of ecigarettes are relatively small companies that may be unable to afford the research costs, or possess the expertise or manpower to go through the regulatory approval process, support from governments, public health organizations or foundations may be needed to produce evidence on these novel devices.

One limitation of our study is that it was conducted in a self-selected sample of internet users. Whether this method over-sampled satisfied users, long-term users or heavy users of ecigarettes is unknown. Compared to population-based samples of smokers in Europe or the United States, visitors to the Stop-Tabac.ch website are more likely to have made a quit attempt in the previous year, are more motivated to quit smoking, are slightly less dependent on tobacco, and are more highly educated [18,19]. Thus, although our results provide useful and interesting preliminary information on ecigarette users, our findings may not be generalizable and should be interpreted with caution.

Conclusions

Our results suggest that ecigarettes are used mainly to quit smoking, and may be useful for this purpose. However, users were concerned about the potential toxicity of these devices. Very few studies have investigated ecigarettes and research is now urgently required, particularly to establish the efficacy and toxicity of these devices.

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Competing interests

The Institute of Social and Preventive Medicine of the University of Geneva received trial medications in 2005 from Pfizer, and the author consulted for Pfizer, a manufacturer of smoking cessation medications, in 2006-2007 (on the Swiss varenicline advisory board). No competing interest since then. No link to companies that either produce or distribute ecigarettes.

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Morris, Erin

From: Ellen Swedberg <Ellen.Swedberg@sonoma-county.org>
Sent: Thursday, September 18, 2014 10:48 AM
To: Jay Macedo; Morris, Erin; Terese Voge
Subject: FW: Smoking in City of Santa Rosa

Erin,

This woman was contacted about the community meeting, I believe she intended to send this email to the contact information on the bottom of the flier.

Ellen Swedberg

From: Ruth Uland
Sent: Thursday, September 18, 2014 9:39 AM
To: Ellen Swedberg; Jay Macedo
Cc: Terese Voge
Subject: FW: Smoking in City of Santa Rosa

FYI,

We received this email early this morning.

Ruth

707.565.6646

sonomacounty
DEPARTMENT OF HEALTH SERVICES

Please consider the environment before printing this e-mail, or opt to print on both sides of the paper.

From: Preventioninfo
Sent: Thursday, September 18, 2014 6:02 AM
To: Nicole Williams; Ruth Uland
Subject: FW: Smoking in City of Santa Rosa

From: Stephanie Bailey
Sent: Thursday, September 18, 2014 5:58:49 AM (UTC-08:00) Pacific Time (US & Canada)
To: Preventioninfo
Subject: Smoking in City of Santa Rosa

I live in a complex (moved here in 2006), and the smoking around here is getting out of hand; I see people smoking around babies and small kids. When I first moved here there was no smoking around/in pool area; now I see people holding babies in their laps puffing away. I am a disabled 64

year old and don't smoke, but I can't even open my windows or patio door without the smell of smoke coming into my apartment.

Spoke to Manager about it, he told me to deal with it. Plus when I use the landary room after he cleans it it smells so bad of smoke that I have to wait for about an hour or so to use it. Manager stated that even if they pass a law about smoking in the City of Santa Rosa he would do what he wants to because he is the BOSS of the complex.
The owner's of the complex is aware of this problem and knows that there are a lot of smokers who live in this complex; they stated that is was OK to smoke outside on their patio of common area but not inside the apartment they feel that people would move out if they enforced any ban on smoking; I feel it is a no win - win situation around here. Please help my health is not that good right now and I feel I don't have to live in a cave with doors and windows closed all the time because of the smell of others smoke coming from outside and through the heater vents of my apartments. Thank you for your time in reading my letter and hope it makes a difference for the better for all. Address of complex is 1620 Herbert St. Santa Rosa, CA 95401

Morris, Erin

From: Santa Rosa Community Acupuncture <srca888@gmail.com>
Sent: Wednesday, September 17, 2014 5:34 PM
To: Morris, Erin
Subject: re: SR City Smoking Ordinance

Hey Erin,

Ellen passed along your email address to me since I had inquired about city regulations pertaining to smoking a few months back. I won't be able to attend the community meeting because of my work schedule but I wanted to submit my comments to you.

Because of our location downtown, we frequently have people smoking in front of our door at distances closer than 20 feet. Certainly the shelter from the elements provided by the overhanging roof in the building we share with Outer Planes makes it an attractive spot. The alley between our building and the 7th Street Garage is also fairly popular but beyond the 20 foot mark where I might reasonably expect someone to refrain from smoking. As well, because of the age and draftiness of the building the smoke drifts in under the door and into the clinic. And so, much to my chagrin, I am put in the position of the fist-shaking fuddy-duddy yelling at the kids to "get off of my lawn."

On the one hand, it seems unfortunate that the city government would need to intervene into what amounts to bad manners. On the other hand, because of the nature of our business, it is important that our patients can access our clinic without having to inhale second hand smoke. Our patients often come to receive treatment for asthma, allergies and other respiratory ailments. If I worked in a bar, i think I would accept the fact that people may be smoking in front of my workplace. But since the health and welfare of our patients is an essential part of our business, more stringent regulations of public smoking might provide at least some additional protection against second hand smoke in our area.

Best,

Derek O. Doss, L.Ac.
--
Santa Rosa Community Acupuncture
535 7th St.
Santa Rosa, CA 95401
707-546-7722
www.santarosacommunityacupuncture.com

Morris, Erin

From: Brad Benson <bbenson@sonic.net>
Sent: Tuesday, September 16, 2014 1:35 PM
To: Morris, Erin
Subject: smoking ordinance

Erin,
We own a property in Santa Rosa that have tenants sensitive to smoking issues.
An adjacent property to ours used as a rehab center have tenants that smoke incessantly.
Is there anything that can be drawn up at the community meeting that will prohibit "care homes" like this from their residents smoking?

Thank you,

Brad Benson
Benson Corporate Offices
PO BOX 2246, SANTA ROSA, CA 95405
707-206-0262 office
707-206-0240 fax

Morris, Erin

From: Kathleen O'Connor <707kath@gmail.com>
Sent: Monday, September 15, 2014 11:38 AM
To: Morris, Erin
Cc: _PLANCOM - Planning Commission; _CityCouncilListPublic
Subject: Sept 25 2014 Mtg
Attachments: 2nd-hand-vaping.pdf; Electronic cigarettes_ review of use, content, safety, effects on smokers and potential for harm and benefit - Hajek - 2014 - Addiction.pdf; indoor-air-quality.docx; Levels of selected carcinogens and toxicants in vapour from electronic cigarettes.pdf; MargaretChan.pdf; SafetyEvalRiskAssessmentOfECFarsalinos.pdf; Successful smoking cessation with electronic cigarettes in smokers with a documented history of recurring relapses_ a case series - Springer.pdf; uses-as-a-cessation-device.pdf; VAPOR-Clean-Air-Study.pdf

Dear Ms Morris,

Santa Rosa is embarking on several long-term strategies to cultivate a high standard of quality of life both to residents and visitors.
to this end, here is information to help you make those plans.

After reading the minutes from the August 28, 2014 City Council meeting, I am providing information that addresses the concerns regarding smokless alternatives to tobacco products.

As an advocate, it is my mission to educate before municipalities legislate difficult to enforce policies.
Please note that I am self-financed and in no way compensated materially for my work.

To start from the beginning, here's a little presentation I put together:
http://www.slideshare.net/kathologist1/ecigvaping-fundamentals-and-ca-legislation-aug-slide-share1

Further reading:
(See attached vetted research for reference)

There is no question that regulation is necessary. Child proof caps, product labeling, and age restriction are very important. Product and ingredient standards are also very important. We know that there is a varying degree in quality control in the industry. Reasonable product standards would definitely benefit the end user.

As for health threats, there is no evidence that this product is in any way more dangerous than breathing the air near a city street. There are studies in air quality and side stream/secondhand emissions that prove that any harmful chemicals in vapor emissions is negligible and comparable to background levels.

There is no threat to public health with this product. There is no second hand danger. There is no reason to over regulate this industry. 50 prominent doctors and researchers recently authored a letter to the WHO asking for them to,

“resist the urge to control and suppress e-cigarettes”.

It goes on to state that electronic cigarettes could be a

“significant health innovation”.

Last week a scientific review of over 80 studies was published by the journal of “Addiction”, and funded in part by NIH stated that,

“Current evidence suggests that there is a potential for smokers to reduce their health risks if electronic cigarettes are used in place of tobacco cigarettes and are considered a step toward ending all tobacco and nicotine use.”

And,

“We need to think carefully about how these products are regulated. What we found is that there is no evidence that these products should be regulated as strictly as tobacco, or even more strictly than tobacco.”

And,

“Use of e-cigarettes by people who don’t smoke is very rare, there is no evidence to support arguments that e-cigarettes are a gateway to smoking tobacco.”

All evidence to date proves that this product is a benefit and not a threat to public health. Of course long term studies need to conducted. Conduct them. Do not regulate an industry that is potentially the greatest weapon against tobacco related illness and death, one that by all evidence is actually a public health benefit out of existence.

I thank you for your time. I know this is a lot to take in all in one go, but I hope you agree that long term strategies require us to go the extra step.

All the best,
--
Kathleen O'Connor
707.280.8570
http://LakeOfVape.com

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

Konstantinos E. Farsalinos and Riccardo Polosa

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

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

Introduction

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

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

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

Figure 1. Examples of electronic cigarette devices currently available on the market.

consisting of very large-capacity lithium batteries with integrated circuits that allow vapers to change the voltage or power (wattage) delivered to the atomizer. These devices can be combined with either second-generation atomizers or with rebuildable atomizers, where the consumers have the ability to prepare their own setup of resistance and wick.

Awareness and use (vaping) of ECs has increased exponentially in recent years. Data obtained from the HealthStyles survey showed that, in the US, awareness of ECs rose from 40.9–57.9% from 2010 to 2011, with EC use rising from 3.3–6.2% over the same time period [King *et al.* 2013]. In the United Kingdom, EC use in regular smokers increased from 2.7% in 2010 to 6.7% in 2012 [Dockrell *et al.* 2013]. Similar findings were obtained from the International Tobacco Control Four-Country Survey [Adkison *et al.* 2013]. A recent prospective study in Swiss army recruits showed that 12% of smokers who tried ECs progressed to daily use [Douptcheva *et al.* 2013]. It must be noted that this increase in EC use has occurred despite the concerns raised by public health authorities about the safety and appropriateness of using these products as alternatives to smoking [National Association of Attorneys General, 2013; Food and Drug Administration, 2009; Mayers, 2009].

The popularity of ECs may be due to their ability to deal both with the physical (i.e. nicotine) and the behavioral component of smoking addiction. In particular, sensory stimulation [Rose and Levin, 1991] and simulation of smoking behavior and cigarette manipulation [Hajek *et al.* 1989] are important determinants of a product's effectiveness in reducing or completely substituting smoking. These features are generally absent in nicotine replacement therapies (NRTs) and oral medications for nicotine dependence, whereas ECs are unique in that they provide rituals associated with smoking behavior (e.g. hand-to-mouth movement, visible 'smoke' exhaled) and sensory stimulation associated with it [Farsalinos *et al.* 2013b]. This explains why these products can be effective in reducing consumption of tobacco smoking [Bullen *et al.* 2013; Caponnetto *et al.* 2013b; Polosa *et al.* 2011] and are efficient as long-term substitutes of conventional cigarettes [Farsalinos *et al.* 2013b].

Methods

For this systematic review (Figure 2), we searched the PubMed electronic database by using keywords related to ECs and/or their combination (e-cigarette, electronic cigarette, electronic nicotine delivery systems). We obtained a total of 354 results, and selected 41 studies we judged relevant to research on EC safety/risk profile. Reference lists from these studies were also examined to identify relevant articles. We searched additional information in abstracts presented at scientific congresses (respiratory, cardiovascular, tobacco control, toxicology), and in reports of chemical analyses on EC samples that were available online. We also looked for selected studies on chemicals related to EC ingredients (e.g. nicotine, propylene glycol, glycerol, cinnamaldehyde, microparticles emission, etc.), but not specifically evaluated in EC research. In total, 97 publications were found, from which 15 chemical analyses of single or a limited number of EC samples were excluded because they were discussed in a review paper [Cahn and Siegel, 2011]. In total, 114 studies are cited in this paper.

Risk differences compared with conventional cigarettes and the issue of nicotine

Conventional cigarettes are the most common form of nicotine intake. Smoking-related diseases are pathophysiologically attributed to oxidative stress, activation of inflammatory pathways and the toxic effect of more than 4000 chemicals and carcinogens present in tobacco smoke [Environmental Protection Agency, 1992]. In addition, each puff contains $>1 \times 10^{15}$ free radicals [Pryor and Stone, 1993]. All of these chemicals are emitted mostly during the combustion process, which is absent in ECs. Although the addictive potential of nicotine and related compounds is largely documented [Guillem *et al.*

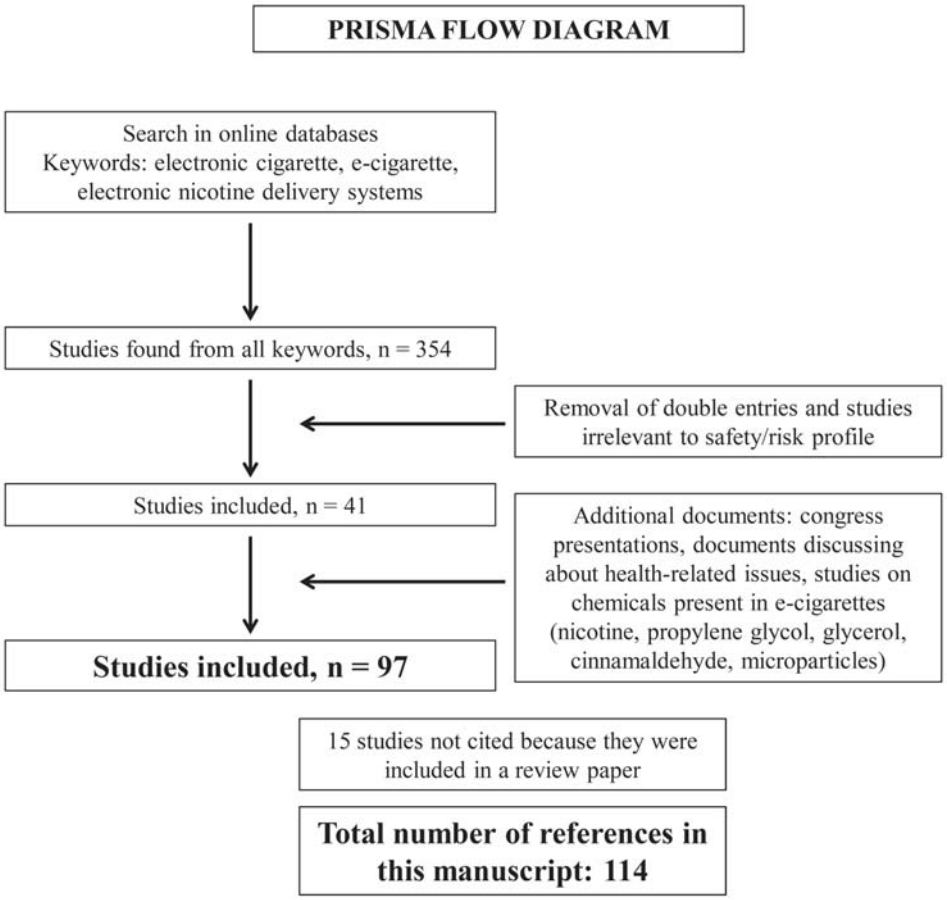

Figure 2. Methodology for literature research and selection of studies.

2005], much less dissemination has been given to the notion that nicotine does not contribute to smoking-related diseases. It is not classified as a carcinogen by the International Agency for Research on Cancer [WHO-IARC, 2004] and does not promote obstructive lung disease. A major misconception, commonly supported even by physicians, is that nicotine promotes cardiovascular disease. However, it has been established that nicotine itself has minimal effect in initiating and promoting atherosclerotic heart disease [Ambrose and Barua, 2004]. It does not promote platelet aggregation [Zevin *et al.* 1998], does not affect coronary circulation [Nitenberg and Antony, 1999] and does not adversely alter the lipid profile [Ludviksdottir *et al.* 1999]. An observational study of more than 33,000 smokers found no evidence of increased risk for myocardial infarction or acute stroke after NRT subscription, although follow up was only 56 days [Hubbard *et al.* 2005]. Up to 5 years of nicotine gum use in the Lung Health Study was unrelated to cardiovascular diseases or other serious side effects [Murray *et al.* 1996]. A meta-analysis of 35 clinical trials found no evidence of cardiovascular or other life-threatening adverse effects caused by nicotine intake [Greenland *et al.* 1998]. Even in patients with established cardiovascular disease, nicotine use in the form of NRTs does not increase cardiovascular risk [Woolf *et al.* 2012; Benowitz and Gourlay, 1997]. It is anticipated that any product delivering nicotine without involving combustion, such as the EC, would confer a significantly lower risk compared with conventional cigarettes and to other nicotine containing combustible products.

The importance of using nicotine in the long-term was recognized several years ago by Russell, indicating that the potential of nicotine delivery systems as long-term alternatives to tobacco should be explored in order to make the elimination of tobacco a realistic future target [Russell, 1991]. However, current regulations restrict the

long-term use of pharmaceutical or recreational nicotine products (such as snus) [Le Houezec *et al.* 2011]. In other words, nicotine intake has been demonized, although evidence suggests that, besides being useful in smoking cessation, it may even have beneficial effects in a variety of disorders such as Parkinson's disease [Nielsen *et al.* 2013], depression [McClernon *et al.* 2006], dementia [Sahakian *et al.* 1989] and ulcerative colitis [Guslandi, 1999]. Obviously, the addictive potential is an important factor in any decision to endorse nicotine administration; however, it should be considered as slight 'collateral damage' with minimal impact to vapers' health compared with the tremendous benefit of eliminating all disease-related substances coming from tobacco smoking. In fact, smokers are already addicted to nicotine; therefore the use of a 'cleaner' form of nicotine delivery would not represent any additional risk of addiction. Surveys have shown that ECs are used as long-term substitutes to smoking [Dawkins *et al.* 2013; Etter and Bullen, 2012]. Although consumers try to reduce nicotine use with ECs, many are unable to completely stop its intake, indicating an important role for nicotine in the ECs' effectiveness as a smoking substitute [Farsalinos *et al.* 2013b].

Nicotine overdose or intoxication is unlikely to occur with vaping, since the amount consumed [Farsalinos *et al.* 2013c] and absorbed [Nides *et al.* 2014; Dawkins and Corcoran, 2013] is quite low. Moreover, although not yet proven, it is expected that vapers will self-titrate their nicotine intake in a similar way to tobacco cigarettes [Benowitz *et al.* 1998]. Last, but not least, there is evidence suggesting that nicotine cannot be delivered as fast and effectively from ECs compared to tobacco cigarettes [Farsalinos *et al.* 2014]. Therefore, it seems that ECs have a huge theoretical advantage in terms of health risks compared with conventional cigarettes due to the absence of toxic chemicals that are generated in vast quantities by combustion. Furthermore, nicotine delivery by ECs is unlikely to represent a significant safety issue, particularly when considering they are intended to replace tobacco cigarettes, the most efficient nicotine delivery product.

Studies on the safety/risk profile of ECs

Findings on the safety/risk profile of ECs have just started to accumulate. However, this research must be considered work in progress given that the safety/risk of any product reflects an evolving body of knowledge and also because the product itself is undergoing constant development.

Existing studies about the safety/risk profile of ECs can be divided into chemical, toxicological and clinical studies (Table 1). Obviously, clinical studies are the most informative, but also the most demanding because of several methodological, logistical, ethical and financial challenges. In particular, exploring safety/risk profile in cohorts of well-characterized users in the long-term is required to address the potential of future disease development, but it would take hundreds of users to be followed for a substantial number of years before any conclusions are made. Therefore, most research is currently focused on *in vitro* effects, with clinical studies confined into evaluation of short-term use or pathophysiological mechanisms of smoking-related diseases.

Chemical studies

Chemical studies are relatively simple and cheap to perform and provide quick results. However, there are several disadvantages with this approach. Research is usually focused on the known specific chemicals (generally those known to be toxic from studies of cigarette smoke) and fails to address unknown, potentially toxic contaminants that could be detected in the liquid or the emitted aerosol. Problems may also arise from the detection of the chemicals in flavors. Such substances, although approved for use in the food industry, have largely unknown effects when heated and inhaled; thus, information on the presence of such substances is difficult to interpret in terms of *in vivo* effects. In fact, chemical studies do not provide any objective information about the effects of use; they can only be used to calculate the risk based on theoretical models and on already established safety levels determined by health authorities. An overview of the chemical studies performed on ECs is displayed in Table 2.

Laugesen performed the first studies evaluating the chemical composition of EC aerosols [Laugesen, 2008, 2009]. The temperature of the resistance of the tested EC was 54°C during activation, which is approximately 5–10% of the temperature of a burning tobacco cigarette. Toxic chemicals such as heavy metals, carcinogenic polycyclic aromatic hydrocarbons and phenols were not detected, with the exception of trivial amounts of mercury (0.17 ng per EC) and traces of formaldehyde and acetaldehyde. Laugesen

Table 1. Types of studies performed to determine safety and to estimate risk from EC use.

Type of studies	Research subject	Advantages	Disadvantages
Chemical studies	Evaluate the chemical composition of liquids and/or aerosol. Examine environmental exposure (passive 'vaping').	Easier and faster to perform. Less expensive. Could realistically be implemented for regulatory purposes.	Usually targeted on specific chemicals. Unknown effects of flavorings when inhaled. No validated protocols for vapor production. Provide no objective evidence about the end results (effects) of use (besides by applying theoretical models).
Toxicological studies	Evaluate the effects on cell cultures or experimental animals.	Provide some information about the effects from use.	Difficult to interpret the results in terms of human *in vivo* effects. More expensive than chemical studies. Need to test aerosol and not liquid. Standards for exposure protocols have not been clearly defined.
Clinical studies	Studies on human *in vivo* effects.	Provide definite and objective evidence about the effects of use.	Difficult and expensive to perform. Long-term follow up is needed due to the expected lag from initiation of use to possible development of any clinically evident disease. For now, limited to acute effects from use.

evaluated emissions based on a toxicant emissions score and reported a score of 0 in ECs compared with a score of 100–134 for tobacco cigarettes (Figure 3). The US Food and Drug Administration (FDA) also performed chemical analyses on 18 commercially available products in 2009 [Westenberger, 2009]. They detected the presence of tobacco-specific nitrosamines (TSNAs) but did not declare the levels found. Small amounts of diethylene glycol were also found in one sample, which was unlikely to cause any harm from normal use. Another study identified small amounts of amino-tandalafil and rimonambant in EC liquids [Hadwiger *et al.* 2010]. Subsequently, several laboratories performed similar tests, mostly on liquids, with Cahn and Siegel publishing a review on the chemical analyses of ECs and comparing the findings with tobacco cigarettes and other tobacco products [Cahn and Siegel, 2011]. They reported that TSNA levels were similar to those measured in pharmaceutical NRTs. The authors concluded that, based on chemical analysis, ECs are far less harmful compared with tobacco cigarettes. The most comprehensive study on TSNAs has been performed recently by a South Korean group, evaluating 105 liquids obtained from local retailers [Kim and Shin, 2013]. On average, they found 12.99 ηg TSNAs per ml of liquid, with the amount of daily exposure to the users estimated to be similar to users of NRTs [Farsalinos *et al.* 2013d]. The estimated daily exposure to nitrosamines from tobacco cigarettes (average consumption of 15 cigarettes per day) is estimated to be up to 1800 times higher compared with EC use (Table 3). Etter and colleagues evaluated the accuracy of nicotine labeling and the presence of nicotine impurities and degradation products in 20 EC liquid samples [Etter *et al.* 2013]. They found that nicotine levels were 85–121% of what was labeled, while nicotine degradation products were present at levels of 0–4.4%. Although in some samples the levels were higher than those specified in European Pharmacopoeia, they are not expected to cause any measurable harm to users.

Besides the evaluation for the presence of TSNAs, analyses have been performed for the detection of carbonyl compounds. It is known that the thermal degradation of propylene glycol and glycerol can lead to the emission of toxic compounds such as aldehydes [Antal *et al.* 1985; Stein *et al.* 1983]. Goniewicz and colleagues evaluated the emission of 15 carbonyls from 12 brands of ECs (mostly first-generation) [Goniewicz *et al.* 2013]. In order to produce vapor, researchers used a smoking machine and followed a regime of 1.8-second puffs with a very short 10-second interpuff interval, which does not represent realistic use [Farsalinos *et al.* 2013c]; although the puff duration was low, interpuff interval was remarkably short, which could potentially lead to overheating. In addition, the same puff number was used in all devices tested, although there was a significant difference in the design and liquid content between devices. Despite these limitations, out of 15 carbonyls, only 3 were detected (formaldehyde, acetaldehyde and acrolein); levels were

Table 2. Summary of chemical toxicity findings.

Study	What was investigated?	What were the key findings?	
		Liquid	Vapor
Laugesen [2009]	Evaluation of 62 toxicants in the EC vapour from Ruyan 16 mg and mainstream tobacco smoke using a standard smoking machine protocol.	N/A	No acrolein, but small quantities of acetaldehyde and formaldehyde found. Traces of TSNAs (NNN, NNK, and NAT) detected. CO, metals, carcinogenic PAHs and phenols not found in EC vapour. Acetaldehyde and formaldehyde from tobacco smoke were 55 and 5 times higher, respectively.
Westenberger [2009]	Evaluation of toxicants in EC cartridges from two popular US brands.	TSNAs and certain tobacco specific impurities were detected in both products at very low levels. Diethylene glycol was identified in one cartridge.	N/A
Hadwiger *et al.* [2010]	Evaluation of four refill solutions and six replacement cartridges advertised as containing Cialis or rimonambant.	Small amounts of amino-tandalafil and rimonambant present in all products tested.	N/A
Cahn and Siegel [2011]	Overview of 16 chemical toxicity studies of EC liquids/vapours.	TSNAs levels in ECs 500- to 1400-fold lower than those in conventional cigarettes and similar to those in NRTs. Other chemicals found very low levels, which are not expected to result in significant harm.	
Pellegrino *et al.* [2012]	Evaluation of PM fractions and PAHs in the vapour generated from cartomizers of an Italian EC brand.	N/A	PM fractions were found, but levels were 6–18 times lower compared with conventional cigarettes. Traces of PAHs detected.
Kim and Shin [2013]	TSNAs (NNN, NNK, NAT, and NAB) content in 105 refill liquids from 11 EC brands purchased in Korean shops.	Total TSNAs averaged 12.99 ng/ml EC liquid; daily total TSNA exposure from conventional cigarettes estimated to be up to 1800 times higher.	N/A
Etter *et al.* [2013]	Nicotine degradation products, ethylene glycol and diethylene glycol evaluation of 20 EC refill liquids from 10 popular brands	The levels of nicotine degradation products represented 0–4.4% of those for nicotine, but for most samples the level was 1–2%. Neither ethylene glycol nor diethylene glycol were detected.	N/A
Goniewicz *et al.* [2013]	Vapours generated from 12 brands of ECs and a medicinal nicotine inhaler using a modified smoking machine protocol	N/A	Carbonyl compounds (formaldehyde, acetaldehyde and acrolein), VOCs (toluene and trace levels of xylene), trace levels of TSNAs (NNN and NNK) and very low levels of metals (cadmium, nickel and lead) were found in almost all examined EC vapours. Trace amounts of formaldehyde, acetaldehyde, cadmium, nickel and lead were also detected from the Nicorette inhalator. Compared with conventional cigarette, formaldehyde, acetaldehyde and acrolein were 9–450 times lower; toluene levels 120 times lower; and NNN and NNK levels 380 and 40 times lower respectively.

(Continued)

Table 2. (Continued)

Study	What was investigated?	What were the key findings?	
		Liquid	Vapor
Williams *et al.* [2013]	Vapour generated from cartomizers of a popular EC brand using a standard smoking machine protocol	N/A	Trace levels of several metals (including tin, copper, silver, iron, nickel, aluminium, chromium, lead) were found, some of them at higher level compared with conventional cigarettes. Silica particles were also detected. Number of microparticles from 10 EC puffs were 880 times lower compared with one tobacco cigarette.
Burstyn [2014]	Systematic review of 35 chemical toxicity studies/ technical reports of EC liquids/vapours.	No evidence of levels of contaminants that may be associated with risk to health. These include acrolein, formaldehyde, TSNAs, and metals. Concern about contamination of the liquid by a nontrivial quantity of ethylene glycol or diethylene glycol remains confined to a single sample of an early technology product and has not been replicated.	

Abbreviations. CO, carbon monoxide; EC, electronic cigarette; NAT, N-Nitrosoanatabine; NNK, 4-(methylnitrosamino)-1-(3-pyridyl)-1-butanone; NNN, N-Nitrosonornicotine; PAHs, polycyclic aromatic hydrocarbons; PM, particulate matter; TSNAs, tobacco-specific nitrosamines; VOCs, volatile organic carbons.

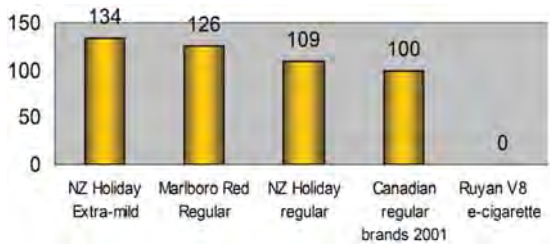

Figure 3. Toxic emissions score, adjusted for nicotine, for electronic cigarette and popular cigarette brands. (Reproduced with permission from Laugesen [2009]).

9–450 times lower compared with emissions from tobacco cigarettes (derived from existing literature but not tested in the same experiment). Formaldehyde and acetaldehyde were also emitted from the nicotine inhalator, although at lower levels. In addition, they examined for the presence of 11 volatile organic carbons and found only trace levels of toluene (at levels from 0.2–6.3 μg per 150 puffs) and xylene (from 0.1–0.2 μg per 150 puffs) in 10 of the samples; toluene levels were 120 times lower compared with tobacco cigarettes (again derived from existing literature but not tested in the same experiment).

Given that ECs have several metal parts in direct contact with the e-liquid, it is quite obvious to expect some contamination with metals in the vapor. Goniewicz and colleagues examined samples for the presence of 12 metals and found nickel, cadmium and lead emitted [Goniewicz *et al.* 2013]; the levels of nickel were similar to those present in a pharmaceutical nicotine inhalator, while lead and cadmium were present at 2–3 times higher levels compared with the inhalator. Still, the absolute levels were very low (few nanograms per 150 puffs). Williams *et al.* [2013] focused their research on the presence of heavy metals and silicate particles emitted from ECs. They tested poor quality first-generation cartomisers and found several metals emitted in the aerosol of the EC, specifying that in some cases the levels were higher compared with conventional cigarettes. As mentioned earlier, it is not unusual to find trace levels of metals in the vapor generated by these products under experimental conditions that bear little relevance to their normal use; however, it is unlikely that such small amounts pose a serious threat to users' health. Even if all the aerosol was absorbed by the consumer (which is not the case since most of the aerosol is visibly exhaled), an average user would be exposed to 4–40 times lower amounts for most metals than the maximum daily dose allowance from impurities in medicinal products [US Pharmacopeia, 2013]. Silicate particles were also found in the EC aerosol. Such particles come from the wick material, however the authors did not clarify whether crystalline silica oxide particles were found, which are responsible for respiratory disease. In total, the number of microparticles (< 1000 nm) estimated to be inhaled by EC users from 10 puffs were 880 times lower compared

Table 3. Levels of nitrosamines found in electronic and tobacco cigarettes. Prepared based on information from Laugesen [2009], Cahn and Siegel [2011] and Kim and Shin [2013].

Product	Total nitrosamines levels (ng)	Daily exposure (ng)	Ratio[4]
Electronic cigarette (per ml)	13	52[1]	1
Nicotine gum (per piece)	2	48[2]	0.92
Winston (per cigarette)	3365	50 475[3]	971
Newport (per cigarette)	3885	50 775[3]	976
Marlboro (per cigarette)	6260	93 900[3]	1806
Camel (per cigarette)	5191	77 865[3]	1497

[1]Based on average daily use of 4ml liquid
[2]Based on maximum recommended consumption of 24 pieces per day
[3]Based on consumption of 15 cigarettes per day
[4] Difference (number-fold) between electronic cigarette and all other products in daily exposure to nitrosamines

with one tobacco cigarette. Similar findings concerning microparticles were reported by Pellegrino and colleagues who found that, for each particulate matter fraction, conventional cigarettes released 6–18 times higher amounts compared with the EC tested [Pellegrino *et al.* 2012].

Burstyn has recently reviewed current data on the chemistry of aerosols and the liquids of ECs (including reports which were not peer-reviewed) and estimated the risk to consumers based on workplace exposure standards (i.e. Threshold Limit Values [TLVs]) [Burstyn, 2014]. After reviewing all available evidence, the author concluded that there was no evidence that vaping produced inhalable exposure to contaminants of aerosol that would warrant health concerns. He added that surveillance of use is recommended due to the high levels of propylene glycol and glycerol inhaled (which are not considered contaminants but ingredients of the EC liquid). There are limited data on the chronic inhalation of these chemicals by humans, although there is some evidence from toxicological studies (which are discussed later in this paper).

In conclusion, chemical studies have found that exposure to toxic chemicals from ECs is far lower compared with tobacco cigarettes. Besides comparing the levels of specific chemicals released from tobacco and ECs, it should be taken into consideration that the vast majority of the >4000 chemicals present in tobacco smoke are completely absent from ECs. Obviously, surveillance of use is warranted in order to objectively evaluate the *in vivo* effects and because the effects of inhaling flavoring substances approved for food use are largely unknown.

Toxicological studies

To date, only a handful of toxicological studies have been performed on ECs, mostly cytotoxicity studies on established cell lines. The cytotoxicity approach also has its flaws. Findings cannot be directly applied to the *in vivo* situation and there is always the risk of over- (as well as under-)estimating the interpretation of the toxic effects in these investigational models. An ample degree of results variability is to be expected from different cell lines and, sometimes, also within the same cell line. Comparing the potential cytotoxicity effects of EC vapor with those resulting from the exposure of cigarette smoke should be mandatory, but standards for vapor production and exposure protocols have not been clearly defined.

Bahl and colleagues [Bahl *et al.* 2012] performed cytotoxicity tests on 36 EC liquids, in human embryonic stem cells, mouse neural stem cells and human pulmonary fibroblasts and found that stem cells were more sensitive to the effects of the liquids, with 15 samples being moderately cytotoxic and 12 samples being highly cytotoxic. Propylene glycol and glycerol were not cytotoxic, but a correlation between cytotoxicity and the number and height of the flavoring peaks in high-performance liquid chromatography was noted. Investigations were just restricted to the effect of EC liquids and not to their vapors, thus limiting the importance of the study findings; this is not a trivial issue considering that the intended use of these products is by inhalation only and that it is unlikely that flavoring substances in the EC liquids will still be present in the aerosol in the same amount due to differences in evaporation temperature [Romagna *et al.* 2013]. Regrettably, a set of experiments with cigarette smoke extracts as

comparator was not included. Of note, the authors emphasized that the study could have underestimated the cytotoxicity by 100 times because when they added the EC liquids to the cell, medium final concentration was 1%. However, cells were cultured for 48 hours with continuous exposure to the liquid, while in real use the lungs come in contact with aerosol instead of liquid, the contact lasts for 1–2 seconds per puff and most of the aerosol is visibly exhaled. Finally, Cinnamon Ceylon, the liquid found to be mostly cytotoxic in this study, was not a refill liquid but a concentrated flavor which is not used in ECs unless it is diluted to 3–5%.

Romagna and colleagues [Romagna *et al.* 2013] performed the first cytotoxicity study of EC vapor on fibroblast cells. They used a standardized ISO 10993-5 protocol, which is used for regulatory purposes of medical devices and products. They tested the vapor of 21 liquid samples containing the same amount of nicotine (9 mg/ml), generated by a commercially available EC device. Cells were incubated for 24 hours with each of these vapors and with smoke from a conventional cigarette. Only one sample was found to be marginally cytotoxic, whereas cigarette smoke was highly cytotoxic (approximately 795% more cytotoxic), even when the extract was diluted up to 25% of the original concentration.

The same group also investigated the cytotoxic potential of 20 EC liquid samples in cardiomyoblasts [Farsalinos *et al.* 2013a]. Vapor was produced by using a commercially available EC device. Samples contained a wide range of nicotine concentrations. A base liquid mixture of propylene glycol and glycerol (no nicotine and no flavorings) was also included as an additional experimental control. Four of the samples examined were made by using cured tobacco leaves in a steeping process, allowing them to impregnate a mixture of propylene glycol and glycerol for several days before being filtered and bottled for use. Of note, this was the first study which evaluated a limited number of samples with an EC device delivering higher voltage and energy to the atomizer (third-generation device). In total, four samples were found to be cytotoxic; three of them were liquids made by using cured tobacco leaves, with cytotoxicity observed at both 100% and 50% extract concentration, while one sample (cinnamon flavor) was marginally cytotoxic at 100% extract concentration only. In comparison, smoke from three tobacco cigarettes was highly cytotoxic, with toxicity observed even when the extract was diluted to 12.5%. The samples made with tobacco leaves were three times less cytotoxic compared with cigarette smoke; this was probably due to the absence of combustion and the significantly lower temperature of evaporation in EC use. Concerning high-voltage EC use, the authors found slightly reduced cell viability without any of the samples being cytotoxic according to the ISO 10993-5 definition. Finally, no association between cell survival and the amount of nicotine present in the liquids was noted.

A recent study evaluated in more detail the cytotoxic potential of eight cinnamon-flavored EC liquids in human embryonic stem cells and human pulmonary fibroblasts [Behar *et al.* 2014]. The authors found that the flavoring substance predominantly present was cinnamaldehyde, which is approved for food use. They observed significant cytotoxic effects, mostly on stem cells but also on fibroblasts, with cytotoxicity associated with the amount of cinnamaldehyde present in the liquid. However, major methodological issues arose from this study. Once again, cytotoxicity was just restricted to EC liquids and not to their vapors. Moreover, the authors mentioned that the amount of cinnamaldehyde differed between liquids by up to 100 times, and this raises the suspicion of testing concentrated flavor rather than refills. By searching the internet and contacting manufacturers, based on the names of samples and suppliers mentioned in the manuscript, it was found that at least four of their samples were not refills but concentrated flavors. Surprisingly, the levels of cinnamaldehyde found to be cytotoxic were about 400 times lower than those currently approved for use [Environmental Protection Agency, 2000].

Few animal studies have been performed to evaluate the potential harm of humectants in EC liquids (i.e. propylene glycol and glycerol) when given by inhalation. Robertson and colleagues tested the effects on primates of inhaling propylene glycol vapor for several months and found no evidence of toxicity on any organ (including the lungs) after post-mortem examination of the animals [Robertson *et al.* 1947]. Similar observations were made in a recent study in rats and dogs [Werley *et al.* 2011]. Concerns have been raised in human use, based on studies of people exposed to theatrical fog [Varughese *et al.* 2005; American Chemistry Council, 2003] or propylene glycol used in the aviation industry [Wieslander *et al.* 2001]. Irritation of the respiratory tract was found, but no permanent lung injury or other

long-term health implications were detected. It should be reminded that, in these circumstances, nonpharmaceutical purity propylene glycol is used and in some cases oils are added, making it difficult to interpret the results in the context of EC use. Evidence for the potential harm of inhaled glycerol is sparse. A study using Sprague–Dawley rats found minimal to mild squamous metaplasia of the epiglottis epithelium in the high-dose group only, without any changes observed in lungs or other organs [Renne *et al.* 1992]. No comparative set of experiments with cigarette smoke was included, but it is well known that exposure to tobacco smoke in similar animal models leads to dramatic changes in the lungs, liver and kidneys [Czekaj *et al.* 2002].

In conclusion, toxicological studies have shown significantly lower adverse effects of EC vapor compared with cigarette smoke. Characteristically, the studies performed by using the liquids in their original liquid form have found less favorable results; however, no comparison with tobacco smoke was performed in any of these studies, and they cannot be considered relevant to EC use since the samples were not tested in the form consumed by vapers. More research is needed, including studies on different cell lines such as lung epithelial cells. In addition, it is probably necessary to evaluate a huge number of liquids with different flavors since a minority of them, in an unpredictable manner, appear to raise some concerns when tested in the aerosol form produced by using an EC device.

Clinical studies and research surveys

Clinical trials can be very informative, but they require monitoring of hundreds of users for many years to adequately explore the safety/risk profile of the products under investigation. Research surveys of EC users, on the other hand, can quickly provide information about the potential harm of these products and are much cheaper to run. However, self-reported data, highly self-selected study populations, and the cross-sectional design are some of the most common limitations of research surveys. Taken together, findings from surveys and follow-up studies of vapers have shown that EC use is relatively safe.

Polosa and colleagues followed up smokers for 24 months, after a 6-month period of intervention during which ECs were given [Polosa *et al.* 2013a]. Only mild symptoms such as mouth and throat irritation and dry cough were observed. Farsalinos and colleagues retrospectively evaluated a group of 111 EC users who had completely quit smoking and were daily EC users for a median period of 8 months [Farsalinos *et al.* 2013b]. Throat irritation and cough were the most commonly reported side effects. Similar findings have been observed in surveys [Dawkins *et al.* 2013; Etter *et al.* 2011]. However, it is expected that dedicated users who have more positive experiences and fewer side effects compared with the general population participate in such studies, therefore interpretation should be done with caution. The only two existing randomized controlled trials have also included detailed EC safety analysis. The ECLAT study [Caponnetto *et al.* 2013b], a three-arm, controlled, randomized, clinical trial designed to compare efficacy and safety of a first-generation device with 7.2, 5.4, or 0 mg nicotine cartridges, reported clinically significant progressive health improvements already by week two of continuous use of the device, and no serious adverse events (i.e. major depression, abnormal behavior or any event requiring an unscheduled visit to the family practitioner or hospitalization) occurred during the study. The ASCEND study [Bullen *et al.* 2013], a three-arm, controlled, randomized, clinical trial designed to compare the efficacy and safety of a first-generation device (with or without nicotine) with nicotine patches, reported no serious adverse events in any of the three study groups.

Few clinical studies have been performed to evaluate the short-term *in vivo* effects of EC use in current or former smokers. Vardavas and colleagues evaluated the acute effects of using an EC for 5 minutes on respiratory function [Vardavas *et al.* 2012]. Although they did not report the results of commonly-used spirometry parameters, they found that a sensitive measure of airways resistance and nitric oxide levels in exhaled breath were adversely affected. Similar elevations in respiratory resistance were reported by other research groups [Palamidas *et al.* 2013; Gennimata *et al.* 2012], who also documented some bizarre elevation in exhaled carbon monoxide levels after EC use; this finding has been challenged by several other studies [Farsalinos *et al.* 2013f; Nides *et al.* 2014; Van Staden *et al.* 2013]. Schober and colleagues found that EC use led to elevated exhaled nitric oxide [Schober *et al.* 2013], contradicting the findings from Vardavas and colleagues [Vardavas *et al.* 2012]. Characteristically, none of the above studies performed any comparative tests after smoking tobacco cigarettes. Flouris and colleagues found

that only smoking had an acute adverse effect on respiratory function [Flouris *et al.* 2013]; no difference was observed after the group of smokers was exposed to active or passive EC use.

Two studies have evaluated the short-term effects of ECs on the cardiovascular system. Farsalinos and colleagues evaluated the acute effects of using ECs with an 11 mg/ml nicotine-containing liquid on hemodynamics and left ventricular function, in comparison with the effects of cigarette smoking [Farsalinos *et al.* 2012]. They found that EC use resulted in a slight elevation in diastolic blood pressure while, after smoking, both systolic and diastolic blood pressure and heart rate were significantly elevated. Obviously, this was due to the relatively low nicotine content of the EC (which is considered medium strength). Diastolic dysfunction was observed in smokers after smoking, which was in line with findings from previous studies. However, no adverse effects were observed in EC users after using the device *ad lib* for 7 minutes. Another study by the same group [Farsalinos *et al.* 2013f], evaluated the acute effects of EC use on coronary flow. In particular, they measured the flow velocity reserve of the left anterior descending coronary artery by echocardiography after intravenous infusion of adenosine, representing the maximal ability of the artery to deliver blood to the myocardium. Smoking was associated with a decline in flow velocity reserve by 16% and an elevation in resistance to flow by 19%. On the contrary, no difference was observed in any of these parameters after using the EC. Blood carboxyhemoglobin levels were also measured in participants; baseline values were significantly higher in smokers compared with vapers and were further elevated after smoking but were not altered after EC use. Similar observations for carboxyhemoglobin levels were observed by Van Staden and colleagues [Van Staden *et al.* 2013].

A clinical case report of a smoker suffering from chronic idiopathic neutrophilia was published. According to that report [Farsalinos and Romagna, 2013], switching from smoking to EC use led to a reversal of the condition after 6 months. In addition, C-reactive protein levels, which were consistently elevated for more than 6 years, decreased to normal levels. Another case report of a patient with lipoid pneumonia was published, with the condition attributed to glycerin-based EC liquids used by the patient [McCauley *et al.* 2012]. However, glycerin is an alcohol (polyol) and thus it is impossible to cause lipoid pneumonia. Only oil-based liquids could be the cause for this condition; such liquids should not be used with ECs.

One study evaluated the acute effects of tobacco and EC use on white blood cell count [Flouris *et al.* 2012]. Smoking one tobacco cigarette caused an immediate elevation in white blood cells, neutrophils and lymphocytes, indicating acute inflammatory distress. On the contrary, no differences were observed after using ECs.

In conclusion, clinical studies evaluating the effects of short-term EC use on selected cardiovascular and respiratory functional outcomes have shown that even if some harmful effects of vaping are reported, these are considerably milder compared with smoking conventional cigarettes. However, it is difficult to assess the prognostic implications of these studies; longer-term data are needed before any definite conclusions are made.

Passive vaping

Passive smoking is an established risk factor for a variety of diseases [Barnoya and Navas-Acien, 2013]. Therefore, it is important from a public health perspective to examine the impact of EC use on bystanders. Indirect data can be derived from chemical studies in vapor mentioned above, which show that the potential of any significant adverse effects on bystanders is minimal. In fact, since sidestream exposure is nonexistent in EC (aerosol is produced only during activation of the device, while tobacco cigarettes emit smoke even when no puffs are taken), such studies are undoubtedly overestimating the risk of environmental exposure.

Few studies have focused on second-hand vaping. McAuley and colleagues [McAuley *et al.* 2012], although mentioning indoor air quality in the title of their study and finding minimal health-related impact, did not in fact evaluate second-hand vaping because aerosol was produced from an EC device and was evaluated without previously being inhaled by any user. Moreover, there were some problems with cross-contamination with tobacco cigarette smoke, which made the results somewhat questionable, at least for some of the parameters tested. Schripp and colleagues [Schripp *et al.* 2013] evaluated the emissions from an EC by asking a volunteer to use three different EC devices in a closed 8 m^3 chamber. From a selection of 20 chemicals analyzed, only formaldehyde, acrolein, isoprene, acetaldehyde and acetic acid were

detected. The levels were 5–40 times lower compared with emissions from a conventional cigarette. For formaldehyde, the authors specifically mentioned that the levels were continuously rising from the time the volunteer entered the room, even before he started using the EC. Moreover, no acute elevation was observed when the smoker used the three EC devices, contrary to the acute elevation and spiking of levels when a tobacco cigarette was lit. The authors concluded that formaldehyde was not emitted from the ECs but was due to human contamination, since low amounts of formaldehyde of endogenous origin can be found in exhaled breath [Riess *et al.* 2010]. Romagna and colleagues [Romagna *et al.* 2012] evaluated chemicals released in a realistic setting of a 60 m^3 room, by asking five smokers to smoke *ad lib* for 5 hours and five vapers to use ECs *ad lib* for a similar period of time on two separate days. Nicotine, acrolein, toluene, xylene and polycyclic aromatic hydrocarbons were detected in room air after the smoking session, with the amount of total organic carbon (TOC) reaching to 6.66 mg/m^3. In contrast, after the EC session, only glycerol was detected in minimal levels (72 $\mu g/m^3$), while TOC reached a maximum level of 0.73 mg/m^3. Characteristically, the amount of TOC accumulated after 5 hours of EC use was similar to the amount found after just 11 minutes of smoking. The study on heavy metals mentioned previously [Williams *et al.* 2013] could also be used to examine any potential risk of bystanders' exposure to toxic metals. The levels of heavy metals found in vapor were minimal, and considering the dispersion of these molecules in the whole room air, it is unlikely that any of these metals could be present in measurable quantities in the environment. Therefore, the risk for bystanders would be literally nonexistent. Contrary to that, Schober and colleagues [Schober *et al.* 2013] found that levels of aluminum were raised by 2.4 times in a 45 m^3 room where volunteers were asked to use ECs for 2 hours. This is a highly unexpected finding which cannot be supported by the findings of the study by Williams and colleagues [Williams *et al.* 2013]; because the levels found in the latter could not result in such elevation of the environmental levels of aluminum, unless nothing is retained in or absorbed from the lungs. Moreover, Schober and colleagues [Schober *et al.* 2013] found that levels of polycyclic aromatic hydrocarbons (PAHs) were raised by 20% after EC use. However, a major methodological problem of this study is that control environmental measurements were performed on a separate day and not on the same day of EC use. This is a major limitation, because the levels of environmental PAHs have significant diurnal and day-to-day variations [Ravindra *et al.* 2008]; therefore, it is highly likely that the differences in levels of PAHs (which are mainly products of combustion and are not expected to be emitted from EC use) represented changes due to environmental conditions and not due to EC use. Bertholon and colleagues [Bertholon *et al.* 2013] examined the EC aerosol exhaled from a user, in comparison with exhaled smoke from a smoker. The authors found that particle size diameters were 0.29–0.033μm. They observed that the half life of EC aerosol was 11 seconds compared with 20 minutes for cigarette smoke, indicating that risk of passive vaping exposure is significantly lower compared with passive smoking.

The recent findings by Czogala and colleagues [Czogala *et al.* 2013] led to similar conclusions. The authors compared the emissions of electronic and conventional cigarettes generated by experienced dual users in a ventilated full-sized room and found that ECs may emit detectable amounts of nicotine (depending on the specific EC brand tested), but no carbon monoxide and volatile organic carbons. However, the average ambient levels of nicotine of ECs were 10 times lower than those of conventional cigarettes (3.32 ± 2.49 *versus* 31.60 ± 6.91 $\mu g/m^3$).

In his review and comparison with TLVs, Burstyn found that emissions from ECs to the environment are not expected to pose any measurable risk for bystanders [Burstyn, 2014].

An issue that needs further clarification relates to the findings of microparticles emitted from ECs. In most studies, these findings are presented in a way implying that the risk is similar to environmental or smoking microparticles. In reality, it is not just the size but the composition of the microparticles that matters. Environmental microparticles are mainly carbon, metal, acid and organic microparticles, many of which result from combustion and are commonly called particulate matter. Particulate matter exposure is definitely associated with lung and cardiovascular disease [Peters, 2005; Seaton *et al.* 1995]. In the case of ECs, microparticles are expected to consist mostly of propylene glycol, glycerol, water and nicotine droplets. Metal and silica nanoparticles may also be present [Williams *et al.* 2013], but, in general, emissions from ECs are incomparable to environmental particulate matter or cigarette smoke microparticles.

Flouris and colleagues [Flouris *et al.* 2013] performed the only clinical study evaluating the respiratory effects of passive vaping compared with passive smoking. Researchers found significant adverse effects in spirometry parameters after being exposed to passive smoking for 1 hour, while no adverse effects were observed after exposure to passive vaping.

Although evaluating the effects of passive vaping requires further work, based on the existing evidence from environmental exposure and chemical analyses of vapor, it is safe to conclude that the effects of EC use on bystanders are minimal compared with conventional cigarettes.

Miscellaneous safety issues

Specific subpopulations: psychiatric and chronic obstructive pulmonary disorder patients

A challenging population subgroup with unique smoking patterns is that of psychiatric patients and in particular schizophrenic patients. This subpopulation is characterized by a very high smoking prevalence [De Leon and Diaz, 2005] with an excess of smoking-related mortality [Brown *et al.* 2000]. Currently, only NRTs are recommended to treat nicotine dependence in this specific subpopulation, but in general they are not particularly effective [Aubin *et al.* 2012]. ECs could be used as an alternative to smoking products in this group. Caponnetto and colleagues performed a prospective 12-month pilot study to evaluate the efficacy of EC use in smoking reduction and cessation in a group of 14 patients with schizophrenia [Caponnetto *et al.* 2013a]. In 50% of participants, smoking consumption went from 30 to 15 cigarettes per day at 52 weeks of follow up, while 14.3% managed to quit smoking. Importantly, no deterioration in their psychiatric condition was observed, and side effects were mild and temporary. The results were promising although an outdated EC device was used in this study.

There is also anecdotal evidence that successful smoking cessation could be attained by using an EC in smokers with other psychiatric conditions such as depression [Caponnetto *et al.* 2011a]. Both patients described in this case series stated that EC use was well tolerated and no adverse events were reported.

Considering that first-line oral medications for nicotine addiction are contraindicated in such patients (prescribing information for bupropion and varenicline carry a 'black-box' warning for certain psychiatric conditions), ECs may be a promising tool in these challenging patient groups.

Another subpopulation that may benefit from regular EC use is that of respiratory patients with chronic obstructive pulmonary disease (COPD), a progressive disease characterized by a persistent inflammatory response to tobacco smoke that generally leads to decline in lung function, respiratory failure, cor pulmonale and death. Consequently, smoking cessation plays a crucial part in the management of COPD patients. However, the available evidence in the medical literature indicates that COPD patients who smoke respond poorly to smoking cessation efforts [Schiller and Ni, 2006]. To date, no formal efficacy and safety assessment of EC use in COPD patients has been conducted. There is only evidence from a case report of inveterate smokers with COPD and a documented history of recurring relapses, who eventually quit tobacco smoking on their own by using an EC [Caponnetto *et al.* 2011b]. Significant improvement in quality of life and reduction in the number of disease exacerbations were noted. EC use was well tolerated with no reported adverse events.

Accidental nicotine exposure

Accidental ingestion of nicotine, especially by children, or skin contact with large amounts of liquid or highly concentrated nicotine solution can be an issue. However, the historically referenced lethal dose of 60 mg has recently been challenged in a review by Mayer [Mayer, 2013]; he found that the lethal levels currently reproduced in every document originated from dubious experiments performed in the 19th century. Based on post-mortem studies, he suggested that the acute dose associated with a lethal outcome would be 500–1000 mg. Taking into account that voluminous vomiting is the first and characteristic symptom of nicotine ingestion, it seems that far higher levels of nicotine need to be ingested in order to have lethal consequences.

A surveillance system of adverse events has been developed by the FDA, which identifies safety concerns in relation to tobacco products. Since 2008, 47 adverse events were reported for ECs

[Chen, 2013]. Eight of them were serious events such as hospitalizations for pneumonia, heart failure, seizures and hypotension and burns. A case of second-degree burns was caused by a battery explosion, which is generally a problem observed in lithium batteries and has occurred in other products (such as mobile phones). The author emphasized that the reported events were not necessarily associated with EC use but may have been related to pre-existing conditions or other causes. No condition was characteristically associated with EC use.

A recent review of the California Poison Control System database from 2010 to 2012 identified 35 cases (14 children) associated with EC exposure (accidental exposure in 25 cases) [Cantrell, 2013]. A total of five patients were evaluated in an emergency department and all were discharged within 4 hours. Nausea, vomiting, dizziness and oral irritation were most commonly reported. Taken together, data from surveillance systems of adverse events suggest that short-term adverse effects and accidental exposures to EC cartridges are unlikely to result in serious toxicity.

Notwithstanding, avoiding preventable contact with highly concentrated nicotine solution remains important; this can be achieved by specific labeling of the products, child-proof caps and proper education of consumers. There is no evidence that nicotine-containing EC liquids should be treated in any different way compared with other consumer products used every day in households (such as bleach, washing machine powder, etc.).

Electrical accidents and fires

The electronic equipment of ECs may be the cause for accidents. ECs are mainly composed of lithium batteries. There have been reports of explosions of batteries, caused either by prolonged charging and use of improper chargers or by design defects. Similar accidents have occurred with batteries of other popular devices, such as mobile phones. Therefore, this does not occur specifically with ECs, however, quality standards of production should be used in order to avoid such accidents.

Smoking is a major cause of residential fires. Between 2008 and 2010, an estimated annual average of 7600 smoking-related fires occurred in residential buildings in the US [US Fire Administration, 2012]. They account for only 2% of all residential building fires but for 14% of fire deaths. Since ECs are activated only when used by the person and there is no combustion involved, there is the potential to avoid the risk of smoking-related fires.

Use by youngsters and nonsmokers

Although beyond the scope of this review, it is important to briefly discuss the potential for addiction from EC use. It should be acknowledged that nicotine is addictive, although recent studies have shown that several other chemicals present in tobacco are associated with a significant enhancement of the addictiveness of nicotine [Lotfipour *et al.* 2011; Rose, 2006; Guillem *et al.* 2005]. Still, nicotine intake should not be recommended to nonsmokers. Smokers are already addicted to nicotine, thus ECs will be a cleaner form of nicotine intake, while at the same time they will maintain their sensory stimulation and motor simulation of smoking; these are important aspects of the addiction to smoking. Regulatory authorities have expressed concern about EC use by youngsters or by never-smokers, with ECs becoming a gateway to smoking or becoming a new form of addiction. However, such concerns are unsubstantiated; research has shown that EC use by youngsters is virtually nonexistent unless they are smokers. Camenga and colleagues [Camenga *et al.* 2013] examined the use of ECs and tobacco in a group of adolescents, in a survey conducted in three waves. In the first wave of the survey (February 2010), 1719 adolescents were surveyed from which only one nonsmoker was found to be using ECs. In the second and third wave of the surveys, only five nonsmoking adolescents were using ECs. In fact, these are adolescents who reported first ever use of ECs in the past 30 days; therefore they were not necessarily regular or daily EC consumers. The increased prevalence of EC use from 0.9% in 2010 to 2.3% in 2011 concerned smoking adolescents, therefore it should be considered a positive finding that smokers are experimenting with the significantly less harmful ECs. Similarly, the Medicines and Healthcare Products Regulatory Agency (MHRA) found that less than 1% of EC users are never-smokers [MHRA, 2013]. Data from the Centers for Disease Control [2013] National Youth Tobacco Survey reported doubling in EC experimentation by 13–18 year old students from 1.1% in 2011 to 2.1% in 2012; however, 90.6% of them were smokers. From the whole population, only 0.5% were nonsmokers experimenting with ECs.

Once again, participants were asked about ever experimenting with an EC in the past 30 days, not regular or daily EC use. Recently, a survey of more than 75,000 students in South Korea was published [Lee *et al.* 2013]. Although they found that 12.6% of them were daily smokers (8.6% were using only tobacco cigarettes and 3.6% were using both tobacco and ECs), only 0.6% of nonsmokers had used ECs in the past 30 days. Although the above mentioned data have been used as arguments to support the fact that a new epidemic of nicotine addiction through the use of ECs is appearing, in reality they are showing that any experimentation with ECs is done by smokers. This is in fact a positive finding, and could lead to reduced smoking prevalence through adoption of EC use. Therefore, ECs could serve as gateway from smoking; on the contrary, there is no evidence indicating that they could be a gateway to smoking. It is promising to see that penetration of EC use in youngsters is virtually nonexistent, especially when you take into consideration that there is currently no official regulation in most countries to prohibit the access to ECs by youngsters.

Conclusion

Existing evidence indicates that EC use is by far a less harmful alternative to smoking. There is no tobacco and no combustion involved in EC use; therefore, regular vapers may avoid several harmful toxic chemicals that are typically present in the smoke of tobacco cigarettes. Indeed, some toxic chemicals are released in the EC vapor as well, but their levels are substantially lower compared with tobacco smoke, and in some cases (such as nitrosamines) are comparable with the amounts found in pharmaceutical nicotine products. Surveys, clinical, chemistry and toxicology data have often been mispresented or misinterpreted by health authorities and tobacco regulators, in such a way that the potential for harmful consequences of EC use has been largely exaggerated [Polosa and Caponnetto, 2013]. It is obvious that some residual risk associated with EC use may be present, but this is probably trivial compared with the devastating consequences of smoking. Moreover, ECs are recommended to smokers or former smokers only, as a substitute for conventional cigarettes or to prevent smoking relapse; thus, any risk should be estimated relative to the risk of continuing or relapsing back to smoking and the low efficacy of currently approved medications for smoking cessation should be taken into consideration [Moore *et al.* 2009; Rigotti *et al.* 2010; Yudkin *et al.* 2003]. Nonetheless, more research is needed in several areas, such as atomizer design and materials to further reduce toxic emissions and improve nicotine delivery, and liquid ingredients to determine the relative risk of the variety of compounds (mostly flavorings) inhaled. Regulations need to be implemented in order to maintain the current situation of minimal penetration of EC use in nonsmokers and youngsters, while manufacturers should be forced to provide proof for the quality of the ingredients used and to perform tests on the efficiency and safety of their products. However, any regulatory decisions should not compromise the variability of choices for consumers and should make sure that ECs are more easily accessible compared with their main competitor, the tobacco cigarette. Consumers deserve, and should make, informed decisions and research will definitely promote this. In particular, current data on safety evaluation and risk assessment of ECs is sufficient enough to avert restrictive regulatory measures as a consequence of an irrational application of the precautionary principle [Saitta *et al.* 2014].

ECs are a revolutionary product in tobacco harm reduction. Although they emit vapor, which resembles smoke, there is literally no fire (combustion) and no 'fire' (suspicion or evidence that they may be the cause for disease in a similar way to tobacco cigarettes). Due to their unique characteristics, ECs represent a historical opportunity to save millions of lives and significantly reduce the burden of smoking-related diseases worldwide.

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Konstantinos Farsalinos is a researcher at Onassis Cardiac Surgery Center. He has never been funded by the pharmaceutical or the tobacco

industry. For some of his studies, the institution has received financial compensation from electronic cigarette companies for the studies' cost. His salary is currently being paid by a scholarship grant from the Hellenic Society of Cardiology.

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Effect of an electronic nicotine delivery device (*e*-Cigarette) on smoking reduction and cessation: a prospective 6-month pilot study

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Abstract

Background: Cigarette smoking is a tough addiction to break. Therefore, improved approaches to smoking cessation are necessary. The electronic-cigarette (e-Cigarette), a battery-powered electronic nicotine delivery device (ENDD) resembling a cigarette, may help smokers to remain abstinent during their quit attempt or to reduce cigarette consumption. Efficacy and safety of these devices in long-term smoking cessation and/or smoking reduction studies have never been investigated.

Methods: In this prospective proof-of-concept study we monitored possible modifications in smoking habits of 40 regular smokers (unwilling to quit) experimenting the 'Categoria' e-Cigarette with a focus on smoking reduction and smoking abstinence. Study participants were invited to attend a total of five study visits: at baseline, week-4, week-8, week-12 and week-24. Product use, number of cigarettes smoked, and exhaled carbon monoxide (eCO) levels were measured at each visit. Smoking reduction and abstinence rates were calculated. Adverse events and product preferences were also reviewed.

Results: Sustained 50% reduction in the number of cig/day at week-24 was shown in 13/40(32.5%) participants; their median of 25 cigs/day decreasing to 6 cigs/day ($p < 0.001$). Sustained 80% reduction was shown in 5/40 (12.5%) participants; their median of 30 cigs/day decreasing to 3 cigs/day ($p = 0.043$). Sustained smoking abstinence at week-24 was observed in 9/40(22.5%) participants, with 6/9 still using the e-Cigarette by the end of the study. Combined sustained 50% reduction and smoking abstinence was shown in 22/40 (55%) participants, with an overall 88% fall in cigs/day. Mouth (20.6%) and throat (32.4%) irritation, and dry cough (32.4%) were common, but diminished substantially by week-24. Overall, 2 to 3 cartridges/day were used throughout the study. Participants' perception and acceptance of the product was good.

Conclusion: The use of e-Cigarette substantially decreased cigarette consumption without causing significant side effects in smokers not intending to quit (http://ClinicalTrials.gov number NCT01195597).

Background

With well over one billion smokers' worldwide, cigarette smoking is a global epidemic that poses a substantial health burden and costs [1]. This is because cigarette smoke harms several organ systems of the human body, thus causing a broad range of diseases, many of which are fatal [2,3]. The risk of serious disease diminishes rapidly after quitting and life-long abstinence is known to reduce the risk of lung cancer, heart disease, strokes, chronic lung disease and other cancers [4,5].

Although evidence-based recommendations indicate that smoking cessation programs are useful in helping smokers to quit [6], smoking is a very difficult addiction to break. It has been shown that approximately 80% of smokers who attempt to quit on their own, relapse within the first month of abstinence and only about 3-5% remain abstinent at 6 months [7]. Although there is little doubt that currently-marketed smoking cessation

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products increase the chance of committed smokers to stop smoking, they reportedly lack high levels of efficacy, especially in the real life setting [8]. Although this is known to reflect the chronic relapsing nature of tobacco dependence, the need for novel and effective approaches to smoking cessation interventions is beyond doubt.

The electronic-cigarette (e-Cigarette) is a battery-powered electronic nicotine delivery device (ENDD) resembling a cigarette designed for the purpose of nicotine delivery,where no tobacco or combustion is necessary for its operation [9] (Figure 1). Consequently, this product may be considered as a lower risk substitute for factory-made cigarettes. In addition, people report buying them to help quit smoking, to reduce cigarette consumption and to relieve tobacco withdrawal symptoms due to workplace smoking restrictions [10]. Besides delivering nicotine, e-Cigarettes may also provide a coping mechanism for conditioned smoking cues by replacing some of the rituals associated with smoking gestures (e. g. hand-to-mouth action of smoking). For this reason, e-Cigarettes may help smokers to remain abstinent during their quit attempt or to reduce cigarette consumption. A recent internet survey on the satisfaction of e-Cigarette use has reported that the device helped in smoking abstinence and improved smoking-related symptoms [11]. Under acute experimental conditions, two marketed electronic cigarette brands suppressed tobacco abstinence symptom ratings without leading to measurable levels of nicotine or CO in the exhaled breath [12]. The e-Cigarette is a very hot topic that has generated considerable global debate with authorities wanting to ban it or at least regulate it. Consequently, a formal demonstration supporting the efficacy and safety of these devices in smoking cessation and/or smoking reduction studies would be of utmost importance.

With this in mind, we designed a prospective proof-of-concept study to monitor possible modifications in the smoking habits of a group of well characterized regular smokers experimenting the most popular marketed e-Cigarette in Italy ('Categoria'; Arbi Group Srl, Milano, Italy) focusing on smoking reduction and smoking abstinence. We also monitored adverse events and measured participants' perception and acceptance of the product.

Methods

Participants

Healthy smokers 18-60 years old, smoking ≥ 15 factory-made cigarettes per day (cig/day) for at least the past 10 years and not currently attempting to quit smoking or wishing to do so in the next 30 days were recruited from the local Hospital staff in Catania, Italy. None of the participants reported a history of alcohol and illicit drug use, major depression or other psychiatric conditions. We also excluded subjects who reported recent myocardial infarction, angina pectoris, high blood pressure (BP > 140 mmHg systolic and/or 90 mmHg diastolic), diabetes mellitus, severe allergies, poorly controlled asthma or other airways diseases. The study protocol was discussed with the Chair of the local institutional ERB (Comitato Etico Azienda Vittorio Emanuele) in February 2010. In consideration of the fact that e-cigarette use is a widespread phenomenon in Italy, that many e-cigarette users are enjoying them as consumer goods, that this type of product is not regulated as a drug or a drug device in Italy (end users can buy e-cig almost

Figure 1 Structure of the 'Categoria' electronic-cigarette (e-Cigarette). The e-Cigarette is a battery-powered electronic nicotine delivery device (ENDD) resembling a cigarette designed for the purpose of providing inhaled doses of nicotine by way of a vaporized solution to the respiratory system. This device provides a flavor and physical sensation similar to that of inhaled tobacco smoke, while no smoke or combustion is actually involved in its operation. It is composed of the following key components: (1) the inhaler - also known as 'cartridge' (a disposable non-refillable plastic mouthpiece - resembling a tobacco cigarette's filter - which contains an absorbent material that is saturated with a liquid solution containing nicotine); (2) the atomizing device (the heating element that vaporizes the liquid in the mouthpiece and generates the mist with each puff); (3) the battery component (the body of the device - resembling a tobacco cigarette - which houses a lithium-ion re-chargeable battery to power the atomizer). The body of the device also houses an electronic airflow sensor to automatically activate the heating element upon inhalation and to light up a red LED indicator to signal activation of the device with each puff. Each pre-filled 'Original' cartridges used in this study contains nicotine (7.25 mg/cartridge) dissolved in propylene glycol (233.7 mg/cartridge) and vegetable glycerin (64.0 mg/cartridge) [details can be found at: http://www.liaf-onlus.org/public/allegati/categoria1b.pdf].

anywhere - internet, tobacconists, pharmacies, restaurants, and shops), and that only healthy smokers not willing to quit smoking would participate, it was felt that the study fulfilled the criteria of an observational naturalistic investigation and was exempt from the requirement from ethical approval. Participants gave written informed consent prior to participation in the study.

Study Design and Baseline Measures

Eligible participants were invited to use an ENDD ('Categoria' e-Cigarette, Arbi Group Srl, Milano, Italy) and were followed up prospectively for 6 months. They attended a total of five study visits at our smoking cessation clinic (Centro per la Prevenzione e Cura del Tabagismo (CPCT), Università di Catania, Italy): a baseline visit and four follow-up visits, (at week-4, week-8, week-12 and week-24) (Figure 2).

At baseline (study visit 1), basic demographic and a detailed smoking history were taken and individual pack-years (pack/yrs) calculated together with scoring of their level of nicotine dependence by means of Fagerstrom Test of Nicotine Dependence (FTND) questionnaire [13]. Subjective ratings of depression were assessed with the Beck Depression Inventory (BDI) [14]. Additionally, levels of carbon monoxide in exhaled breath (eCO) were measured using a portable device (Micro CO, Micro Medical Ltd, UK). Participants were given a free e-Cigarette kit containing two rechargeable batteries, a charger, and two atomizers and instructed on how to charge, activate and use the e-Cigarette. Key troubleshooting were addressed and phone numbers were supplied for both technical and medical assistance. A full 4-weeks supply of 7.4 mg nicotine cartridges ("Original" cartridges; Arbi Group Srl, Milano, Italy) was also provided and participants were trained on how to load them onto the e-Cigarette's atomizer. Random checks confirmed that the nicotine content per cartridge was 7,25 mg. Detailed toxicology and nicotine content analyses of "Original" cartridges had been carried in a laboratory certified by the Italian Institute of Health and can be found at: http://www.liaf-onlus.org/public/allegati/categoria1b.pdf

Participants were permitted to use the study product *ad libitum* throughout the day (up to a maximum of 4 cartridges per day, as recommended by the manufacturer) in the anticipation of reducing the number of cig/day smoked, and to fill a 4-weeks' study diary recording product use, number of any tobacco cigarettes smoked, and adverse events.

Participants were invited to came back at week-4 (study visit 2), week-8 (study visit 3), and week-12 (visit 4), a) to receive further free supply of nicotine cartridges together with the study diaries for the residual study periods, b) to record their eCO levels, and c) to give back completed study diaries and unused study products.

Study participants attended a final follow-up visit at week-24 (study visit 5) to report product use (cartridges/day) and the number of any tobacco cigarettes smoked (from which smoking reduction and smoking abstinence could be calculated), to re-check eCO levels and to rate the degree of usefulness of the study product. In particular, participants were asked to rate their level of satisfaction with the products compared to their usual cigarettes using a visual analogue scale (VAS) from 0 to 10 points (0 = being 'completely unsatisfied', 10 being = 'fully satisfied'); on the same scale, they also rated helpfulness (in keeping them from smoking) and whether they would recommend it to a friend who wanted to stop/reduce smoking. Adverse events were obtained from their study diaries.

Given the observational nature of this study, no emphasis on encouragement, motivation and reward for the smoking cessation effort were provided since this study was intended to monitor the case of a smoker (unwilling to quit) trying out an unconventional nicotine delivery device in a real world setting. Although participants were allowed to smoke their own brand of cigarette as they wished, smoking cessation services were provided to those who would spontaneously ask for assistance with quitting. These subjects were excluded from the study protocol.

Study outcome measures

The primary efficacy measure was sustained 50% reduction in the number of cig/day at week-24 from baseline (***reducers***) [15]; defined as sustained self-reported 50% reduction in the number of cig/day compared to baseline for the 30 days period prior to week-24 study visit (eCO levels were measured to verify smoking status and confirm a reduction compared to baseline).

A secondary efficacy measure of the study was sustained 80% reduction in the number of cig/day at week-24 from baseline (***heavy reducers***); defined as sustained self-reported 80% reduction in the number of cig/day compared to baseline for the 30 days period prior to week-24 study visit (eCO levels were measured to verify smoking status and confirm a reduction compared to baseline).

An additional secondary efficacy measure of the study was sustained smoking abstinence at week-24 (***quitters***); defined as complete self-reported abstinence from tobacco smoking (not even a puff) for the 30 days period prior to week-24 study visit (eCO levels were measured to objectively verify smoking status with an eCO concentration of ≤10 ppm).

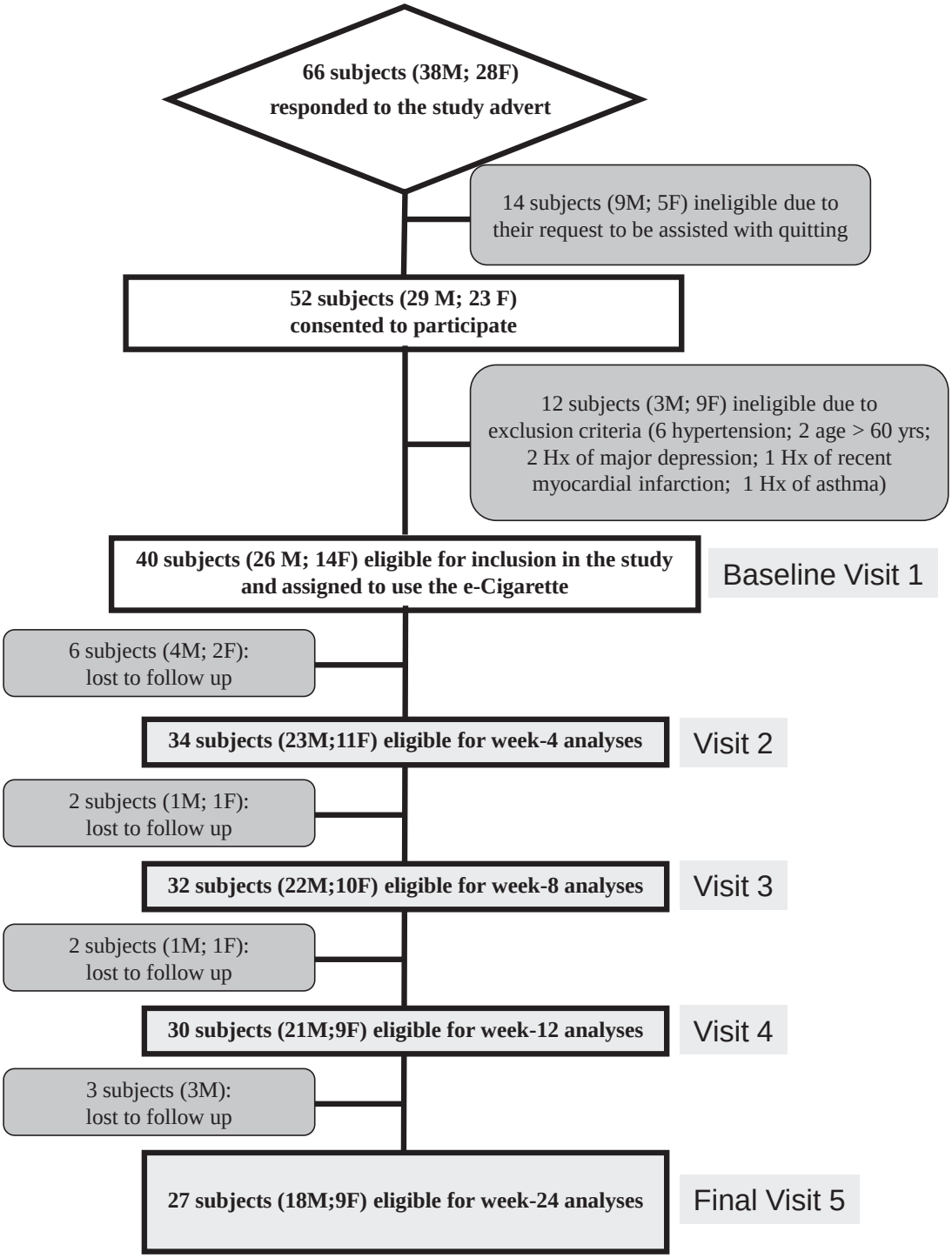

Figure 2 Number of patients recruited and flow of patients within the study. A total of 66 subjects with specifically predefined smoking criteria (smoking ≥ 15 cig/day for at least the past 10 years) responded to the advert; of these, 14 subjects were not included in the study because they spontaneously seek assistance with quitting (these were then invited to attend the local smoking cessation clinic, which offers standard support with cessation counselling and pharmacotherapy for nicotine dependence). The remaining 52 subjects consented to participate into the study; of these, 12 were not considered eligible because of the exclusion criteria (6 had a high blood pressure, 2 were older than 60; 2 had a diagnosis of major depression; 1 suffered from recent myocardial infarction; 1 had uncontrolled allergic asthma). In the end, 40 volunteers were included in the study and were issued with e-Cigarette kits loaded with nicotine cartridges. By the end of the study, a total of 13 subjects were lost to follow-up due to failure of attending their control visits. Overall 27 participants were available for analyses at the 24-week follow-up visit.

Those smokers who failed to meet the above criteria at the final week-24 follow-up visit (study visit 5) were categorized as reduction/cessation failures (***failures***).

Statistical Analyses

This was a proof-of-concept pilot study, the first of its kind, hence no previous data could be used for power calculation. However, using our previous experience in smoking cessation studies, we estimated that a sample of 40 subjects would have been adequate to acquire quit/reduction rates from 70-75% of the subjects enrolled [16]. Primary and secondary outcome measures were computed by including all enrolled participants - assuming that all those individuals who were lost to follow-up are classified as failures (intention-to-treat analysis). The changes from baseline (study visit 1) in number of cig/day and in eCO levels were compared with data recorded at subsequent follow-up visits using Wilcoxon Signed rank test as these data were non-parametric. Parametric and non-parametric data were expressed as mean (± SD) and median (interquartile range (IQR)) respectively. Correlations were calculated using Spearman's Rho Correlation. Statistical methods were 2-tailed, and P values of < 0.05 were considered significant.

Results

Participant characteristics

After excluding for the study exclusion criteria, a total of 40 (M 26; F 14; mean (± SD) age of 42.9 (± 8.8) years) regular smokers (mean (± SD) pack/yrs of 34.9 (± 14.7)) consented to participate and were included in the study (Table 1; Figure 2). Twenty-seven (67.5%) completed all study visits and returned for their final follow-up visit at week-24. Baseline characteristics of those who were lost to follow-up were not significantly different from participants who completed the study.

Outcome measures

Participants' smoking status at baseline and at 24-week is shown on Table 2. Taking the whole cohort of participants (n = 40), an overall 80% reduction in median cig/day use from 25 to 5 was observed by the end of the study ($p < 0.001$). Sustained 50% reduction in the number of cig/day at week-24 was shown in 13/40 (32.5%) participants, with a median of 25 cig/day (IQR 20, 30) decreasing significantly to 6 cig/day (IQR 5, 6)($p < 0.001$). Of these tobacco smoke reducers, five (12.5%) could be classified as sustained heavy reducers (at least 80% reduction in the number of cig/day) at week-24. They had a median consumption of 30 cig/day (IQR 25, 35) at baseline, decreasing significantly to 3 cig/day (IQR 3, 6) ($p = 0.043$). There were 9/40 (22.5%) quitters, with 6/9 still using the e-Cigarette by the end of the study. Overall, combined sustained 50% reduction and smoking abstinence was shown in 22/40 (55%) participants, with a median of 25 cig/day (IQR 20, 30) decreasing significantly to 3 cig/day (IQR 0, 6)($p < 0.001$), which is equivalent to an overall 88% reduction. Details of mean cigarette use and eCO levels throughout the study is shown in Figure 3 and 4.

Table 1 Patient Demographics

	Parameter	Mean (± SD)*
Subjects eligible for inclusion(n = 40)		
	Age	42.9 (± 8.8)
	Sex	26M; 14F
	Smoking Years	26.9 (± 8.8)
	FTND	6.0 (6, 8)*
	Beck Depression Inventory	9 (5, 12.3)*
	Cigarettes/day	25 (20, 30)*
	eCO	23.5 (15.8, 36)*
†Subjects available for week-24 analyses(n = 27)		
	Age	42.6 (± 8.4)
	Sex	18M; 9F
	Smoking Years	27.2 (± 8.9)
	FTND	7 (6, 7)*
	Beck Depression Inventory	9 (5, 12.5)*
	Cigarettes/day	25 (20, 30)*
	eCO	24 (15.5, 37)*

*Non-parametric data expressed as median (IQR).

† Subjects excluding those lost-to-follow-up.

Abbreviations: SD - Standard Deviation; M - Male; F - Female; FTND - Fagerstrom Test of Nicotine Dependence; eCO - exhaled carbon monoxide; IQR - interquartile range.

Table 2 Subject Parameter Outcomes Following 24 Weeks of Electronic Cigarette Use

Parameter	AT BASELINE	AT 24-Weeks Post E-Cigarette	*p value‡*
Sustained 50% (excluding quitters) reduction in cigarette smoking (n = 13)			
Age	40.1 (± 7.7)†	6 (5, 6)*	< 0.001
Sex	8M; 5F	8 (6, 11)*	0.001
Smoking Years	24.5 (± 8.7)†		
Cigarettes/day	25 (20, 30)*		
eCO	18 (14, 33)*		
Sustained 80% (excluding quitters) reduction in cigarette smoking (n = 5)			
Age	40.6 (± 10.4)†	3 (3, 6)*	0.043
Sex	4M; 1F	6 (4, 10)*	0.042
Smoking Years	25.4 (± 11.8)†		
Cigarettes/day	30(25, 35)*		
eCO	15 (14, 44)*		
Sustained 100% (quitters) reduction in cigarette smoking (n = 9)			
Age	44.7 (± 9.3)†	0 (0, 0)*	0.008
Sex	8M; 1F	3 (2, 3)*	0.008
Smoking Years	29 (± 9.6)†		
Cigarettes/day	25 (23, 30)*		
eCO	31 (23, 41)*		
Sustained > 50% (including quitters) reduction in cigarette smoking (n = 22)			
Age	42 (± 8.5)†	3 (0, 6)*	< 0.001
Sex	16M; 6F	5.5 (3, 9.5)*	< 0.001
Smoking Years	26.3 (± 9.1)†		
Cigarettes/day	25 (20, 30)*		
eCO	27 (15.5, 37.5)*		
Smoking Failure (< 50% smoking reduction) (n = 5)			
Age	45.6 (± 7.9)†	20 (20, 20)*	0.157
Sex	2M; 3F	28 (17, 31)*	0.892
Smoking Years	31.2 (± 7)†		
Cigarettes/day	25 (20, 25)*		
eCO	18 (16, 32)*		

Abbreviations: SD - Standard Deviation; M - Male; F - Female; eCO - exhaled carbon monoxide.

‡p value - within group Wilcoxon Signed Rank Test.

† Parametric data expressed as mean (± SD).

*Non-parametric data expressed as median (interquartile range(IQR)).

Product Use

Details of mean cartridge use throughout the study is shown in Figure 5. The reported number of cartridges/day used by our study participants was dissimilar, ranging from a maximum of 4 cartridges/day (as per manufacturer's recommendation) to a minimum of 0 cartridges/day ('zero' was recorded in the study diary, when the same cartridge was used for more than 24 hours). For the whole group (n = 27), a mean (± SD) 2.0 (± 1.4) cartridges/day was used throughout the study. The number of cartridges/day used was slightly higher when these summary statistics were computed with the exclusion of the eight study failures; the value increasing to a mean (± SD) of 2.2 (± 1.3) cartridges/day. Correlation between the number of cartridges/day and smoking reduction in those participants with sustained 50% reduction in smoking was not significant (Rho -0.003; p = 0.988). Likewise, the correlation between the number of cartridges/day, and combined sustained 50% reduction and smoking abstinence was also non-significant (Rho -0.185; p = 0.546).

Adverse Events

The most frequently reported adverse events were mouth irritation (20,6%), throat irritation (32,4%), and dry cough (32,4%) (Table 3). These events were most commonly reported at the beginning of the study and appeared to wane spontaneously by study visit 5. Remarkably, side effects commonly recorded during smoking cessation trials with drugs for nicotine dependence were absent (i.e. depression, anxiety, insomnia, irritability, hunger, constipation were not reported).

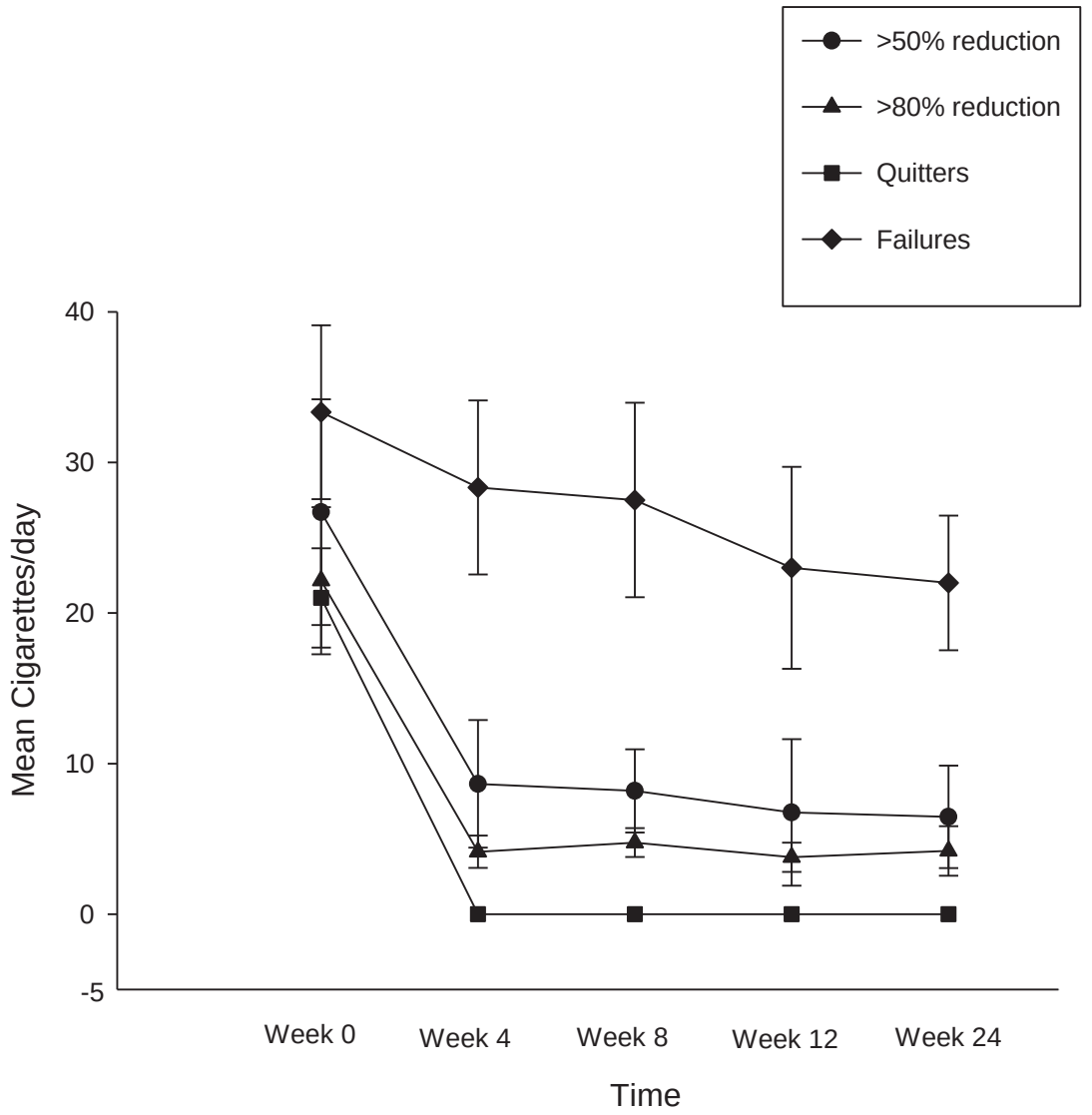

Figure 3 Changes in the mean (± SD) cigarette use for each study subgroups throughout the study.

Moreover, no serious adverse events (i.e. events requiring unscheduled visit to the family practitioner or hospitalisation) occurred during the study.

Product Preferences

The 'Categoria' e-Cigarette rated scores well above the mean for satisfaction and for helpfulness (enabling them to refrain from smoking), their mean (± SD) VAS values being 6.3 (± 2.5) and 7.5 (± 2.7) respectively. Moreover, it was observed that participants would enthusiastically recommend the e-Cigarette to friends or relatives who wanted to stop/reduce smoking, the mean (± SD) VAS value being 8.0 (± 3.4). Predictably, the e-Cigarette rated even higher scores when these summary statistics were computed with the exclusion of the study failures (n = 8). On the contrary, the perception and acceptance of the product by those who failed to remain abstinent or to reduce smoking (n = 5) was poor; the mean (± SD) VAS values for satisfaction and for helpfulness being 2.2 (± 0.8) and 2.5 (± 1.0), respectively. As expected, these individuals were unlikely to recommend the 'Categoria' e-Cigarette to friends or relatives; the mean (± SD) VAS value being 2.3 (± 1.2).

Among the most positive features of e-Cigarettes were the pleasure of inhalation and exhalation of the vapour. Other positive features mentioned included cleaner and fresher breath, absence of odours in clothing and hair. Although the overall participants' perception and acceptance of the product was good, its ease of use could be improved and technical defects reduced. During the course of the study, five study participants could not use the product as recommended and had to be retrained

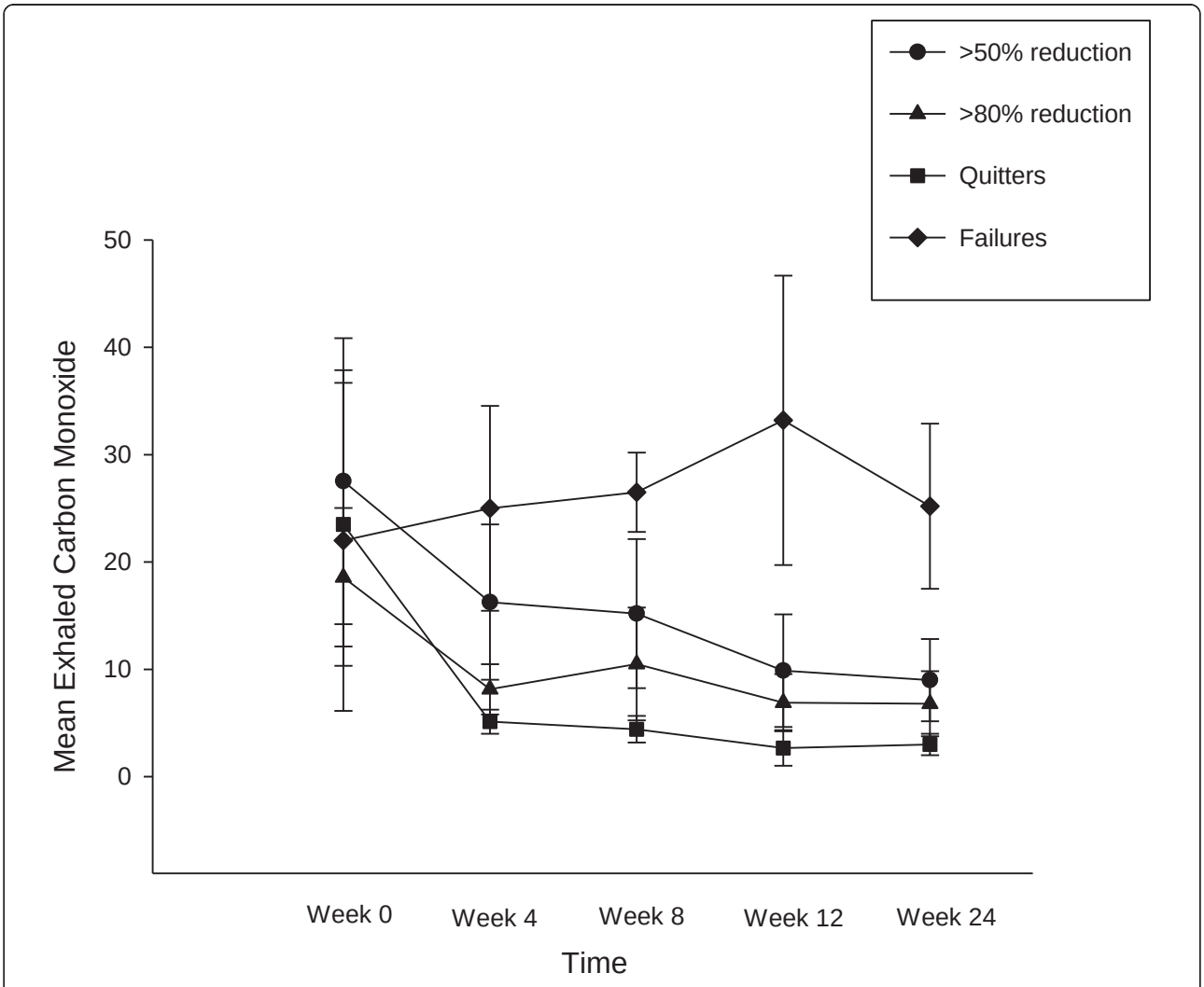

Figure 4 Changes in the mean (± SD) eCO levels for each study subgroups throughout the study.

within 72 hours. Three participants reported that the device often failed to produce mist when puffed (three atomizers had to be substituted). Another two were given a faulty charger (chargers were immediately replaced). According to study participants, perception and acceptance of the product could be improved by increasing manufacturing standards, by providing a recharge lasting at least 24 hours, by reducing the weight of the device and by substituting the hard plastic mouthpiece.

Discussion

In this pilot study, we have shown for the first time that substantial and objective modifications in the smoking habits may occur in smokers using e-Cigarettes, with significant smoking reduction and smoking abstinence and no apparent increase in withdrawal symptoms. Participants were not only enthusiastic about using the e-Cigarette, but the majority (67.5%) were also able to adhere to the program and to return for the final follow-up visit at week-24 with an overall quit rate of 22.5%. Moreover, at least 50% reduction in cigarette smoking was observed in 32.5% of participants. Overall, combined reduction and smoking abstinence was shown in 55% of participants. These preliminary findings are of great significance in view of the fact that all smokers in the study were, by inclusion criteria, not interested in quitting. Although not directly comparable with classic cessation and/or reduction studies with other pharmaceutical products because of its design (the present study is not an ordinary cessation study), the results of our study are in general accordance with the findings published in the medical literature [17].

The large magnitude of this effect suggests the e-Cigarette strongly suppressed cigarette use. However, no correlations were observed between the number of

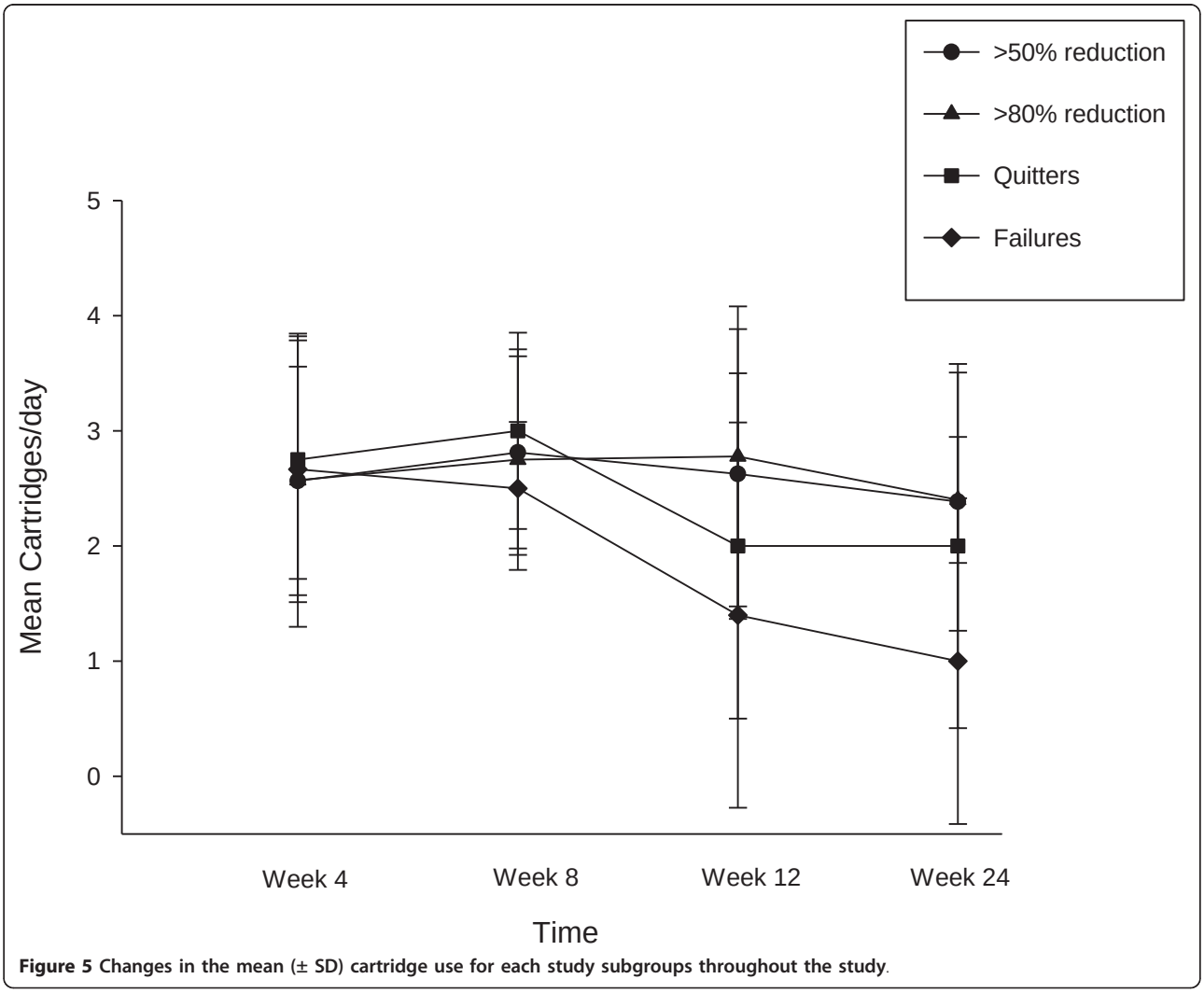

Figure 5 Changes in the mean (± SD) cartridge use for each study subgroups throughout the study.

Table 3 Adverse events reported by participants who completed all study visits

Adverse Event	Study Visits			
	4-week n/n (%)	8-week n/n (%)	12-week n/n (%)	24-week n/n (%)
Throat irritation*	11/34 (32,4%)	5/32 (15,6%)	5/30 (16,7%)	4/27 (14,8%)
Mouth Irritation*	7/34 (20,6%)	4/32 (12,5%)	3/30 (10,0%)	2/27 (7,4%)
Sore Throat	4/34 (11,8%)	1/32 (3,1%)	1/30 (3,3%)	0/27 (0,0%)
Dry cough	11/34 (32,4%)	6/32 (18,8%)	3/30 (10,0%)	3/27 (11,1%)
Dry mouth	3/34 (8,8%)	1/32 (3,1%)	1/30 (3,3%)	1/27 (3,7%)
Mouth ulcers	1/34 (2,9%)	1/32 (3,1%)	1/30 (3,3%)	0/27 (0,0%)
Dizziness§	5/34 (14,7%)	2/32 (6,3%)	2/30 (6,7%)	1/27 (3,7%)
Headache	4/34 (11,8%)	2/32 (6,3%)	2/30 (6,7%)	1/27 (3,7%)
Nausea	5/34 (14,7%)	2/32 (6,3%)	1/30 (3,3%)	1/27 (3,7%)

* Throat and mouth irritation were described either as tickling, itching, or burning sensation

§ Dizziness, was also used to mean vertigo and light-headedness.

nicotine cartridges/day used and the level of smoking reduction. This is not unexpected, in view of the powerful interaction between physical and behavioural dependence of smoking [18,19] and the modest increases in blood nicotine levels measured after the use of this type of devices [20]. Therefore, it is unlikely that the observed positive effect of the e-Cigarette is due to nicotine delivery. Rather, the strong suppression of smoking in association with the absence of correlation between cartridges use and level of smoking reduction, suggests that the positive effect of the e-Cigarette may be also due to its capacity to provide a coping mechanism for conditioned smoking cues by replacing some of the rituals associated with smoking gestures (e.g. hand-to-mouth action of smoking). In agreement with this, we have recently demonstrated that nicotine free inhalators can only improve quit rates in those smokers for whom handling and manipulation of their cigarette played an important role in their ritual of smoking [21].

Although dry cough and mouth ulcers can be associated with withdrawal effects, typical withdrawal symptoms of smoking cessation trials with drugs for nicotine dependence were not reported during the course of the study. It is possible that the e-Cigarette by providing a coping mechanism for conditioned smoking cues could mitigate withdrawal symptoms associated with smoking reduction and smoking abstinence. In contrast from other ENDDs such as Eclipse (which is known to generate substantial level of eCO) [22], e-Cigarettes use does not lead to increased eCO levels [12]. In the present study, the smoking reduction with 'Categoria' e-Cigarette use was associated to a substantial decrease in the level of eCO. The most frequent adverse events were mouth irritation, throat irritation and dry cough, but all appeared to wane spontaneously with time. These are likely to be secondary to exposure to propylene glycol mist generated by the e-Cigarette's atomizer. Propylene glycol is a low toxicity compound widely used as a food additive and in pharmaceutical preparations. Exposure to propylene glycol mist may occur from smoke generators in discotheques, theatres, and aviation emergency training and is known to cause ocular, mouth, throat, upper airway irritation and cough [23,24]. Dizziness was often reported by participants at the beginning of the study and can be brought about by the hyperventilation associated to the greater puffing time with the e-Cigarette. Alternatively, the dizziness as well as other reported adverse events such as nausea and headaches may be due to nicotine overuse. The substantial reduction in the frequency of dizziness observed by the end of the study may be due to the improved familiarisation with the puffing technique and/or to the overall reduction in nicotine use. Therefore, the 'Categoria'" e-Cigarette can be seen as a safe way to smoke although larger and longer studies will be required for a full assessment of its adverse events.

The 'Categoria' e-Cigarette rated high scores for a range of subjective ratings of user preferences suggesting that the product was functioning as an adequate cigarette substitute. Hence, participants were more likely to recommend the e-Cigarette to friends or relatives. Conversely, as would be expected the perception and acceptance of the product by those who failed to remain abstinent or to reduce smoking was poor and these individuals were unlikely to recommend the e-Cigarette. We cannot exclude that technical problems (particularly those who went unreported) and difficulty of use (it takes time to familiarize with the puffing technique) could have affected the number of lost to follow-up and failures. Although the overall participants' perception and acceptance of the product was good, its ease of use could be improved. Technical defects could be reduced by increasing manufacturing standards, providing a recharge lasting at least 24 hours, reducing the weight of the device and substituting the hard plastic mouthpiece. These latter two suggestions would improve device acceptability for certain common rituals of cigarette smoking, e.g. keeping the cigarette between lips.

Harm-reduction strategies are aimed at reducing the adverse health effects of tobacco use in individuals unable or unwilling to quit. Reducing the number of cig/day is one of several kinds of harm reduction strategies [25]. It is uncertain whether substantial smoking reduction in smokers using the e-Cigarette will translate in health benefits, but a number of studies have analyzed the ability of smoking reduction to lower health risks and have reported some reductions in cardiovascular risk factors and lung cancer mortality [26-28]. Moreover, reduction in cigarette smoking by e-Cigarette may well increase motivation to quit as indicated by a substantial body of evidence showing that gradually cutting down smoking can increase subsequent smoking cessation among smokers [15,29-32]. While not the treatment of choice, reduced smoking strategies might be considered for recalcitrant smokers unwilling to quit, as in the case of our study population.

There are some limitations in our study. Firstly, this was a small uncontrolled study, hence the results observed may be due to a chance finding and not to a true effect; consequently the results should be interpreted with caution. However, it would have been quite problematic to have a placebo arm in such a study. Secondly, 32.5% of the participants failed to attend their final follow-up visit, but this is not unexpected in a smoking cessation study. Thirdly, because of its unusual design (smokers not willing to quit, e-Cigarettes were used throughout the entire study period) this is not an ordinary cessation study and therefore direct comparison with other smoking cessation products cannot be made. Fourthly, failure to complete the study and smoking cessation failures could be due to occurrence of technical defects for the e-Cigarette. However, this could not be assessed with confidence in the present study. Lastly, assessment of withdrawal symptoms in our study was not rigorous. Withdrawal was assessed at each visit by simply asking about the presence/absence of irritability, restlessness, difficulty concentrating, increased appetite/weight gain, depression or insomnia. It is likely that this way of collecting information is liable to recall bias. Therefore, the reported lack of withdrawal symptoms in the study participants should be considered with caution.

Conclusions

Current smoking cessation interventions can increase the chance of quitting in committed smokers who are already motivated and prepared to stop smoking [33],

but a broader range of interventions are needed in order to bring more smokers into treatment and increase the numbers who are motivated to make quit attempts. Although not formally regulated as a pharmaceutical product, the e-Cigarette can help smokers to remain abstinent or reduce their cigarette consumption. By replacing tobacco cigarettes, the e-cigarette can only save lives.

Here we show for the first time that e-Cigarettes can substantially decrease cigarette consumption without causing significant side effects in smokers not intending to quit. However, large and carefully conducted RCTs will be required before a definite answer about the efficacy and safety of these devices can be formulated. Some of these trials are now in progress in Italy [34-36] and New Zealand [37] and hopefully they will be able to confirm and expand the preliminary observations reported in the present article.

Abbreviations

e-Cigarette: Electronic-Cigarette; ENDD: Electronic Nicotine Delivery Device; Cig/day: Cigarettes smoked per day; BP: Blood pressure; mmHg: millimetres of mercury; FTND: Fagerstrom Test of Nicotine Dependence; BDI: Beck's Depression Inventory; eCO: exhaled carbon monoxide; mg: milligrams; Cartridges/day: cartridges used per day; VAS: Visual Analogue Score; ppm: parts per million; Pack/yrs: pack-years; SD: standard deviation; IQR: interquartile range

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Authors' contributions

RP: Principal investigator, protocol design, interpretation of the data, writing of the ms; PC: conduction of the study, interpretation of the data, writing of the ms; JBM: statistical analyses, interpretation of the data, writing of the ms; GP: recruiting of patients, conduction of the study, writing of the ms; DC: recruiting of patients, conduction of the study; CR: protocol design, interpretation of the data, writing of the ms. All authors have read and approved the final manuscript.

Competing interests

None of the authors have any competing interests to declare, but RP has received lecture fees from Pfizer and, from Feb 2011, he has been serving as a consultant for Arbi Group Srl.Arbi Group Srl (Milano, Italy), the manufacturer of the e-Cigarette supplied the product, and unrestricted technical and customer support. They were not involved in the study design, running of the study or analysis and presentation of the data.

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Wednesday, December 11, 2013

First Study to Examine Passive Vaping Under Real-Life Conditions Finds No Chemicals of Concern in Room Air

In the first study of human exposure produced by passive vaping under real-life conditions, researchers from Italy and Greece found no chemicals of concern in room air while five electronic cigarette users vaped for a five-hour session in a 60 cubic meter closed room.

The researchers compared the constituents of room air during passive vaping to those present during passive smoking. During passive smoking, levels of chemicals were as follows (all in micrograms per cubic meter):

Nicotine: 34
Acrolein: 20
Polycyclic aromatic hydrocarbons: 9.4
Carbon monoxide: 11
Xylene: 0.2
Toluene: 1.7

The detected levels of these same chemicals during the passive vaping session were as follows:

Nicotine:0
Acrolein: 0
Polycyclic aromatic hydrocarbons: 0
Carbon monoxide: 0
Xylene: 0
Toluene: 0

(Romagna G, Zabarini L, Barbiero L, Bocchietto E, Todeschi S, Caravati E, Voster D, Farsalinos K. Characterization of chemicals released to the environment by electronic cigarettes use (ClearStream-AIR project): Is passive vaping a reality? Presented at the 14th Annual Meeting of the Society for Research on Nicotine and Tobacco, 2012, Helsinki, Finland.)

The Rest of the Story

These results should be viewed as preliminary, especially because only one brand of electronic cigarettes was tested. There could be variability between various brands, so no firm conclusions should be drawn until many brands of electronic cigarettes are tested under realistic exposure conditions.

Nevertheless, these results seem to suggest that electronic cigarettes at least have the potential to present little risk to bystanders. Not only can we say that there is currently no evidence that passive vaping is harmful, but we can now say that the first study to examine passive vaping under realistic conditions found no chemicals of concern in the ambient air.

One previous study (Flouris et al., 2013) did find an increase in serum cotinine levels in nonsmokers exposed to passive vaping; however, that study involved blowing air using an air pump into an experimental chamber. It did not involve the actual, real-life use of electronic cigarettes by humans. Also, that study measured only serum cotinine; it did not measure the levels of contaminants in the ambient air.

Stan Glantz and others have been using that study to argue that passive vaping is hazardous to bystanders. Of course, they ignore the results of the present study - the only one to be conducted under realistic conditions and to actually measure potentially hazardous chemical exposures. The finding that there were no detectable levels of nicotine, acrolein, polycyclic aromatic hydrocarbons, carbon monoxide, xylene, and toluene is inconvenient to Glantz's argument that electronic cigarettes are a significant health hazard to non-vaping bystanders.

Glantz and others also fail to inform the public that the Flouris et al. study -- which they tout as demonstrating the significant hazards of passive vaping - actually showed that exposure to electronic cigarette vapor in the experimental chamber for one hour had no effect on acute lung function of nonsmokers. This was in contrast to secondhand smoke, which adversely affects acute lung function.

The rest of the story is that there is no current evidence that passive vaping poses any significant threat to the health of bystanders. Thus, I do not see any public health justification for banning vaping in public places at the present time.

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Case report

Successful smoking cessation with electronic cigarettes in smokers with a documented history of recurring relapses: a case series

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Abstract

Introduction

Smoking cessation programs are useful in helping smokers to quit, but smoking is a very difficult addiction to break and the need for novel and effective approaches to smoking cessation interventions is unquestionable. The E-cigarette is a battery-powered electronic nicotine delivery device that may help smokers to remain abstinent during their quit attempt. We report for the first time objective measures of smoking cessation in smokers who experimented with the E-cigarette.

Case presentation

Three Caucasian smokers (two men aged 47 and 65 years and one woman aged 38 years) with a documented history of recurring relapses were able to quit and to remain abstinent for at least six months after taking up an E-cigarette.

Conclusions

This is the first time that objective measures of smoking cessation are reported for smokers who quit successfully after using an E-cigarette. This was accomplished in smokers who repeatedly failed in previous attempts with professional smoking cessation assistance using the usual nicotine dependence treatments and smoking cessation counselling.

Introduction

Cigarette smoke harms nearly every system of the human body, thus causing a broad range of diseases, many of which are fatal [1, 2]. The risk of serious disease diminishes rapidly after quitting and life-long abstinence is known to reduce the risk of lung cancer, heart disease, strokes, chronic lung disease and other cancers [3, 4]. Although evidence-based recommendations indicate that smoking cessation programs are useful in helping smokers to quit [5], smoking is a very difficult addiction to break. It has been shown that approximately 80% of smokers who attempt to quit on their own relapse within the first month of abstinence and only about 3% to 5% remain abstinent at six months [6]. Although there is little doubt that currently-marketed smoking cessation products increase the chance of committed smokers stopping smoking, they reportedly lack high levels of efficacy - particularly in the real life setting [7]. Although this is known to reflect the chronic relapsing nature of tobacco dependence, the

need for novel and effective approaches to smoking cessation interventions is unquestionable.

The E-cigarette is a battery-powered electronic nicotine delivery device (ENDD), often resembling a cigarette. It is designed to deliver nicotine to the respiratory system, where neither tobacco nor combustion are necessary for its operation [8] (Figure 1). Consequently, it is likely that this product may be considered as a lower risk substitute for factory-made cigarettes. In addition, people report buying them to help quit smoking, to reduce cigarette consumption, and to relieve tobacco withdrawal symptoms due to workplace smoking restrictions [9]. Besides delivering nicotine to the lung, E-cigarettes may also provide a coping mechanism for conditioned smoking cues by replacing some of the rituals associated with smoking gestures (for example the hand-to-mouth action of smoking). For this reason, E-cigarettes may help smokers to remain abstinent during their quit attempt. To date there has been no formal demonstration supporting the efficacy of these devices in smoking cessation studies.

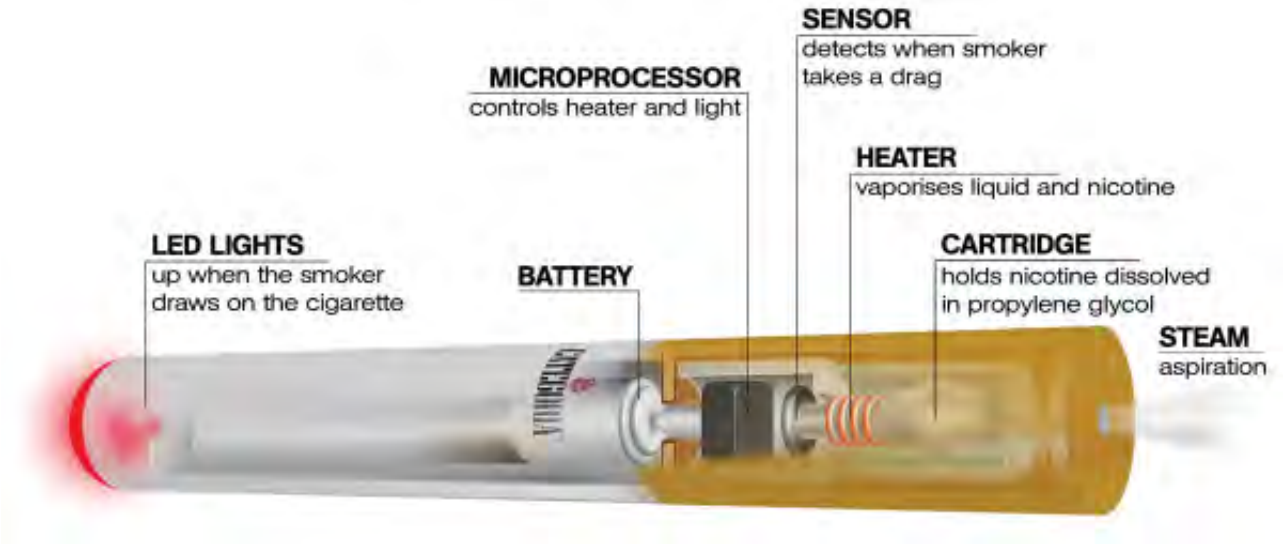

Figure 1

The E-cigarette is a battery-powered electronic nicotine delivery device (ENDD) designed for the purpose of providing inhaled doses of nicotine by way of a vaporized solution to the respiratory system. This device provides a flavor and physical sensation similar to that of inhaled tobacco smoke, while no smoke or combustion is actually involved in its operation. It is composed of the following key components: **(1)** the inhaler - also known as 'cartridge' (a disposable plastic mouthpiece - resembling a tobacco cigarette's filter - which contains an absorbent material that is saturated with a liquid solution containing nicotine); **(2)** the atomizing device (the heating element that vaporizes the liquid in the mouthpiece and generates the mist with each puff); **(3)** the battery component (the body of the device - resembling a tobacco cigarette - which houses a lithium-ion re-chargeable battery to power the atomizer). The body of the device also houses an electronic airflow sensor to automatically activate the heating element upon inhalation and to light up a LED (Light Emitting Diode) indicator to signal activation of the device with each puff.

To the best of our knowledge, we report for the first time objective measures of smoking cessation in three heavy smokers who experimented with the E-cigarette.

Case presentations

In this case series we describe three heavy smokers with an established history of relapses who have been repetitively managed for nicotine dependence at our university clinic for smoking cessation (Centro per la Prevenzione e Cura del Tabagismo - CPCT; Università di Catania; Italy). Our patients (two men aged 47 and 65 years and one woman aged 38 years), were of Caucasian ethnicity. At CPCT, smoking cessation programs are based on an adaptation of the Clinical Practice Guideline on Smoking Cessation of the U.S. Department of Health and Human Services [5] and have been described previously in detail [10]. The staff at CPCT includes a dedicated team of clinical psychologists, physicians, and nurses with at least three years of experience.

Patient 1

A 47-year-old Caucasian male lawyer with a diagnosis of severe nicotine dependence attended our smoking cessation clinic four years ago. He smoked 32 cigarettes per day (45 pack/years) with a significant level of nicotine dependence (Fagerstrom Test of Nicotine Dependence - FTND = 8). His concentration of exhaled breath carbon monoxide (eCO) reading at baseline was 31 ppm. No history of alcohol abuse, major depression or other psychiatric conditions was reported. He was subjected to intensive treatment for nicotine dependence four years ago and subsequently after seven months. He participated in other intensive treatments for nicotine dependence three years ago and two years ago. On each occasion, he was prescribed a combination of nicotine patches and bupropion and was offered smoking cessation counselling throughout the program. His last relapse occurred one month after treatment'. During a routine telephone follow-up two years ago, he reported having quit smoking on his own after taking up an E-cigarette. He was then invited to visit our clinic to allow us to collect more informations and conduct further investigations. He told us that he started experimenting with an E-cigarette (loaded with a high nicotine concentration: 7.2 mg nicotine per cartridge) two years ago. A few weeks later, he was able to discontinue tobacco smoking completely. He kept using his E-cigarette for another few months before stopping use of the E-cigarette as well. Abstinence from tobacco smoking was then objectively assessed by measuring the concentration of exhaled breath carbon monoxide concentration (eCO); the measured eCO value was within the normal range (eCO = 4 ppm). He has been abstinent from tobacco smoking for approximately six months with no reported lapse or relapse during this period of time. The E-cigarette was well tolerated with no reported adverse effects.

Patient 2

A 38-year-old Caucasian female social worker with a diagnosis of severe nicotine dependence

attended our smoking cessation clinic four years ago. She smoked 28 cigarettes per day (28 pack/years) with a significant level of nicotine dependence (FTND = 8). Her eCO reading at baseline was 29 ppm. Some mild depression assessed by the Self-rating Depression Scale (SDS) was also documented in her case notes. She was treated for nicotine dependence at our clinic four years ago and again two years ago. On each occasion, she was prescribed nicotine patches and bupropion. She was offered smoking cessation counselling throughout the program. Her last relapse occurred two years ago.

During a routine telephone follow-up one year ago, she reported having quit smoking on her own after taking up an E-cigarette. She was then invited for a follow-up visit at our clinic, during which abstinence was reviewed objectively by measuring the concentration of eCO. She told us that she had started experimenting with an E-cigarette (loaded with high nicotine concentration: 7.2 mg nicotine per cartridge) two years ago. Three months later, she was able to discontinue tobacco smoking completely. She kept using the E-cigarette with a high nicotine concentration for another month before switching to mentholated cartridges, which she now uses frequently during social events.

Abstinence from tobacco smoking was confirmed objectively by very low levels of eCO (eCO = 2 ppm). She has been abstinent from tobacco smoking for approximately seven months with no reported lapse or relapse during this period of time. Overall, the E-cigarette was well tolerated with occasional dry cough being reported.

Patient 3

A 65-year-old Caucasian male pharmacist with a known diagnosis of chronic obstructive pulmonary disease (COPD) was seen for a routine follow up in our chest clinic two years ago. He had been a heavy smoker for nearly 50 years (89 pack/years) and had a past history of alcohol abuse. He was treated for nicotine dependence twice by the local services for addiction on two occasions seven years ago and four years ago. On both occasions he was prescribed nicotine patches and attended group counselling sessions. Four years ago, he came to our smoking cessation clinic. He smoked 30 to 40 cigarettes per day with a significant level of nicotine dependence (FTND = 10). His eCO baseline reading was 34.9 ppm. He was started on varenicline (a partial agonist of the α4β2 nicotinic acetylcholine receptor approved specifically for smoking cessation therapy) in association with smoking cessation counselling, but he was lost to follow-up by one month after his quit date.

When he came for his routine follow-up appointment at the chest clinic two years ago, he announced that he had quit tobacco smoking on his own after taking up an E-cigarette loaded with nicotine cartridges. Two months after taking up an E-cigarette loaded with nicotine cartridges, he was able to discontinue tobacco smoking completely. He continued using his E-cigarette on a regular basis. Predictably, this patient noted a significant improvement in quality of life, manifested by increased

energy levels and exercise tolerance. Moreover, he has reported no significant exacerbations of his symptoms during the past two years.

Abstinence from tobacco smoking was confirmed objectively by measuring the concentration of exhaled breath carbon monoxide concentration (eCO); the measured eCO value being within the normal range (eCO = 5 ppm). The E-cigarette was well tolerated with no reported adverse events.

Discussion

This is the first time that objective measures of smoking cessation are reported in smokers with a documented history of recurring relapses, who quit smoking after taking up an E-cigarette with the intention of quitting tobacco smoking. This was accomplished by heavy smokers who repeatedly failed in previous attempts with professional smoking cessation assistance based on the usual nicotine dependence treatments and smoking cessation counselling. Some studies have found that multiple failed attempts have a negative effect on a smoker's confidence in being able to quit smoking cigarettes [11].

The COPD patient was a particularly difficult case with an FTND of 10 (maximum score) and a documented history of recurring relapses. The available evidence in the medical literature indicates that, in contrast with smokers in the general population, COPD patients who smoke typically respond poorly to smoking cessation efforts; they have a greater degree of physical nicotine dependence [12] and appear to be less motivated to quit smoking [13].

We cannot discount that the success observed in our patients may be simply due to the repeated number of quit attempts and not necessarily to E-cigarette use. However, we later contacted these patients and asked if they took up the E-cigarette with the intention to quit and if they believed that they would not have quit if it weren't for the E-cigarettes. Answers to both questions were positive for all three patients. Thus, these patients felt that they would not have quit tobacco smoking without the help of E-cigarettes.

The remarkable success stories of these three smokers require consideration. The widely acknowledged beneficial role of pharmacotherapy in smoking cessation is likely to be due to its ability to address the physical component of tobacco dependence. However, taking pills or patches for nicotine addiction is unlikely to resolve the psychological components associated with tobacco dependence. As a matter of fact smoking is much more than the addicting effect of nicotine; the smoking habit also includes the rituals that each smoker associates with his or her habit [14]. Smoking cessation products cannot replace the rituals associated with the act of smoking.

Counselling for smoking cessation is intended to help smokers in coping with this important aspect of

their life by implementing personalized replacement rituals, but even counselling for smoking cessation lacks high levels of efficacy. Therefore, it is likely that the smokers described in our case series coped successfully with the psychological components associated with their tobacco dependence by using a device resembling a cigarette, which - although being mainly designed for the purpose of nicotine delivery to the respiratory system - has the additional advantage of being a valid substitute for the tactile sensations of the cigarette and other sensations associated with smoking gestures.

An important aspect that needs to be highlighted in relation to the findings of the present case series is the putative risk of E-cigarettes. In June 2009, the US Food and Drug Administration (FDA) announced in a press conference that 'a laboratory analysis of electronic cigarette samples has found that they contain carcinogens and toxic chemicals such as diethylene glycol (DEG), an ingredient used in antifreeze' [15]. The actual lab report revealed that the 'carcinogens' referred to in the FDA's press conference were tobacco specific nitrosamines (TSNAs), but failed to specify the quantity detected. The FDA's report did state that the quantity of DEG detected in the liquid in one of the 18 samples was 1% (0.01 ml), but did not point out that this is a non-toxic quantity. The FDA did not report finding DEG, or any other harmful chemical, in the vapor [16]. A number of reports available over the Internet have subsequently characterized, quite extensively, the components contained in E-cigarette liquid and vapor using gas chromatography mass spectrometry (GC-MS). They demonstrate that the primary components of E-cigarette cartridges are propylene glycol (PG), glycerin, and nicotine [17]. Laugesen tested E-cigarette mist for more than 50 priority-listed cigarette smoke toxicants and found none [18]. This report only revealed traces (8.2 ng/g) of TSNAs in the 'high' nicotine cartridge of an E-cigarette.

It must be noted that this amount is equal to the quantity reported to be present in a nicotine medicinal patch.

Recently, Cahn and Siegel have reviewed the results of 16 laboratory analyses of E-cigarette liquid, including the FDA's 'Final Report'. TSNAs were reported in two studies, but at trace levels, which are similar to those found in a nicotine patch, and, most importantly, about 500-fold to 1400-fold lower than TSNA levels measured in regular cigarettes. The presence of DEG was reported in the FDA's report in one of the 18 cartridges, yet none of the other 15 studies found any DEG. The authors stated, 'Other than TSNAs and DEG, few, if any, chemicals at levels detected in E-cigs raise serious health concerns. Although the current data are insufficient to conclude that E-cigarettes are safe in absolute terms and that further studies are needed to comprehensively assess their safety, these products appear to be much safer than tobacco cigarettes and comparable in toxicity to conventional nicotine replacement products' [19].

In a recent prospective proof-of-concept study, we monitored possible modifications in the smoking habits of 40 smokers not willing to quit who were experimenting with a 7.4 mg nicotine/cartridge E-cigarette [20]. Combined sustained smoking reduction and smoking abstinence was shown in 55% of

the participants, with an overall 88% fall in the number of cigarettes smoked per day. Mouth and throat irritation, and dry cough were common, but diminished substantially by the end of the study. Retailers all over the world have already sold hundreds of thousands of E-cigarettes, yet there is no evidence that these products have endangered anyone.

Lastly, there may be some concern that non-smokers might take up use of an E-cigarette, become addicted to nicotine, and eventually start to smoke tobacco cigarettes. The fear of this 'gateway effect' has been mentioned in connection with the European Union ban on the sale of snus, a type of smokeless tobacco that is neither chewed nor smoked. The available evidence would indicate that snus provides a gateway out of smoking rather than into it. Snus is a type of finely ground moist snuff that delivers significant levels of nicotine. Snus does not produce any of the toxic combustion products and it is manufactured in a way that produces low levels of tobacco-specific nitrosamines, the main carcinogens responsible for oral cancers in users of other smokeless tobacco products [21].

Sweden now has one of the lowest smoking prevalence rates in the world [22]. Ranstrom and Foulds found the odds of initiating daily smoking were significantly lower for men who had started using snus than for those who had not (odds ratio (OR) = 0.28, 95% confidence interval (CI) 0.22 to 0.36) [23]. Another study found that the quit ratio for smoking was significantly higher for daily snus users in six of seven data sets collected during 2003 to 2008 in Norway [24]. In the United States of America (USA) 73% of the most recent quit attempts using smokeless tobacco resulted in smokers achieving smoking abstinence [25].

In a survey that included 3037 ever-users of E-cigarettes, only one of the 2850 respondents who used nicotine-containing E-cigarettes was a never-smoker [26]. The authors of the study did not report the reason. Given the fact that 70% of the ever-users succeeded in quitting smoking, the E-cigarette would also appear to be a gateway away from smoking. In previous quit attempts, 70.5% had tried nicotine therapy, 29.1% used bupropion, and 19.4% used varenicline. Users of both snus and E-cigarettes might be less likely to later switch to smoking if governments and health organizations made it clear that smoking carries enormously greater health risks than nicotine that comes from non-smoked sources.

Obviously, these products need to be adequately regulated, but thus far, there have been heterogeneous regulatory responses. Some countries have completely banned the sale and marketing of E-cigarettes whereas others allow marketing within their regulatory frameworks. Internet marketing of E-cigarettes and the inadequacy and misapplication of import product codes, however, impede systematic regulation [27]. More research on E-cigarettes must be conducted in order to ensure that the decisions of regulators, healthcare providers and consumers are evidence-based.

Conclusions

The most important message from this case series is that these smokers, with a documented history of recurring relapses, were able to quit smoking and to remain abstinent for at least six months after taking up an electronic cigarette. Although the present findings cannot be generalized, high quit rates would be desirable in a population that generally responds poorly to smoking cessation efforts. Larger controlled studies are needed to confirm this interesting finding, particularly for those smokers for whom the handling and manipulation of their cigarettes play an important part of the ritual of smoking.

Consent

Written informed consent was obtained from the patients for publication of this case report and any accompanying images. A copy of the written consent is available for review by the Editor-in-Chief of this journal.

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Competing interests

The authors declare that they have no competing interests.

Authors' contributions

RP, PC, CR, CL and DC were responsible for the study conception, data retrieval and draft of the manuscript. All authors read and approved the final manuscript.

Addiction

REVIEW

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Electronic cigarettes: review of use, content, safety, effects on smokers and potential for harm and benefit

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ABSTRACT

Aims We reviewed available research on the use, content and safety of electronic cigarettes (EC), and on their effects on users, to assess their potential for harm or benefit and to extract evidence that can guide future policy. **Methods** Studies were identified by systematic database searches and screening references to February 2014. **Results** EC aerosol can contain some of the toxicants present in tobacco smoke, but at levels which are much lower. Long-term health effects of EC use are unknown but compared with cigarettes, EC are likely to be much less, if at all, harmful to users or bystanders. EC are increasingly popular among smokers, but to date there is no evidence of regular use by never-smokers or by non-smoking children. EC enable some users to reduce or quit smoking. **Conclusions** Allowing EC to compete with cigarettes in the market-place might decrease smoking-related morbidity and mortality. Regulating EC as strictly as cigarettes, or even more strictly as some regulators propose, is not warranted on current evidence. Health professionals may consider advising smokers unable or unwilling to quit through other routes to switch to EC as a safer alternative to smoking and a possible pathway to complete cessation of nicotine use.

Keywords Electronic cigarettes, harm reduction, prevalence, product safety, regulation, smoking cessation.

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INTRODUCTION

Electronic cigarettes (EC) are devices designed to deliver nicotine without tobacco smoke by heating a solution of nicotine, flavouring, additives and propylene glycol and/or vegetable glycerine. Invented by Lik Hon in Hong Kong in 2003 [1], they became available in Europe and the United States in 2006 [2]. EC are undergoing a rapid evolution driven by competition. There are dozens of manufacturers and hundreds of EC models. Tobacco manufacturers joined this market in 2012, when Lorillard bought Blu e-cigs (http://investors.lorillard.com/investor-relations/news/2012/default.aspx).

During the past few years EC have been gaining popularity, primarily among smokers who want to reduce the risks of smoking [3,4]. The growing sales of EC, driven initially by word of mouth and user enthusiasm, are now seen by financial analysts to threaten sales of cigarettes [5,6]. The reaction by the public health community to this unfolding phenomenon has ranged from enthusiastic support to vigorous opposition. Regulatory bodies around the world are deciding whether to allow EC to compete with cigarettes freely, submit them to a more restrictive regulation than cigarettes, e.g. as medicinal devices, or ban them. Their verdicts will probably feature among the key public health decisions of our time.

Commentators in favour of EC restrictions believe that the product has a potential to increase cigarette use by re-normalizing smoking, i.e. reducing motivation of smokers to quit completely, providing a gateway to smoking for non-smokers or facilitating an increase in smoking prevalence indirectly. They argue that EC should be banned or submitted to much stricter controls than smoked tobacco. They emphasize evidence that nicotine can be addictive and warn that health risks from long-term EC use may yet emerge (e.g. [7–10]).

EC advocates believe that, on the contrary, the product has a potential to reduce and, if it continues to develop, eventually end cigarette use by allowing smokers to switch to a safer product. They argue that achieving this potential requires little government expenditure and involvement and that it is in the public health interest to allow EC to compete with cigarettes in the market-place. They emphasize evidence that use of nicotine without tobacco toxicants poses minimal risks, except in the case of well-defined subpopulations such as pregnant smokers (e.g. [11–15]).

Both sides of the debate agree that any policy and regulatory decisions affecting EC should be guided by evidence. This review summarizes the literature on patterns of EC use, content, safety and effects on users and considers the implications of the evidence.

Search strategy and selection criteria

We searched Medline, PsycINFO, EBM reviews (including Cochrane Methodology Register, Health Technology Assessment and NHS economic evaluation database), Google Scholar, EMBASE and CINAHL (to February 2014). We combined the following search terms 'e-cig*' OR 'elect* cigar*' OR 'electronic nicotine'. We also searched the reference lists of articles identified by this search strategy and selected those that addressed the key themes of the review. After removing duplicates, this search identified 286 records that were screened independently by two reviewers (P.H. and H.M.). Most papers were opinion-pieces. Ninety-nine full-text papers were reviewed. Papers were deemed relevant ($n = 81$) to this review if they presented original data and provided evidence that could guide regulatory decisions.

Note that we use the words 'EC' for electronic cigarettes and 'cigarettes' for conventional cigarettes. EC use is increasingly labelled as 'vaping' and EC users as 'vapers', but we are using EC use/EC user throughout.

SURVEYS OF EC USERS

Prevalence of EC use and characteristics of users

EC use was negligible in 2008–09, but increased steadily over the following years: in the United States in the general population it increased from 0.6% in 2009 to 2.7% in 2010 [16] and to 6.2% in 2011 [17]. In the United Kingdom, use in smokers increased from 2.7% in 2010 to 6.7% in 2012 [2] and to 11% in 2013 [18]. About one-third (30% to 38%) of ever users used EC within the past 30 days [2,16,17,19–23]. Some 12–14% of smokers who tried EC progressed to daily use [23,24].

EC users tend to be younger, more educated and have higher income than non-users [17,25,26]. There is no clear association between e-cigarette use and gender [20,26–28]. Most of these surveys are from Europe and the United States, and the results may not apply to other countries.

EC experimentation and regular use by never-smokers

Studies conducted to date have found that the prevalence of EC experimentation (ever use) in never-smokers ranged from 0.1 to 3.8% (median 0.5%), and use in the past 30 days ranged from 0 to 2.2% (median 0.3%) [2,16,17,20,22,23,25,27–29]. A recent report on EC use among US children was interpreted as showing worryingly high levels of use [30], but extrapolated data show that among middle school students in 2012, 0.5% of never smokers tried EC. The figure for high school students was 0.7%. Among children, current use was confined to those who have already tried smoking [18]. 'Current use' in non-smokers (any use over the past 30 days, not daily use) was reported in only 0.04% [31]. A study assessing daily use in non-smokers found none [23]. For comparison, 39.5% of twelfth-graders (17–18-year-olds) tried cigarettes in the United States in 2011 [32], and about half of children who try conventional cigarettes progress to regular use.

Surveys of regular EC users

A number of studies recruited EC users over the internet. These results need to be interpreted with caution, because internet surveys attract primarily EC enthusiasts [3].

The most popular e-liquids had a nicotine content of 18 mg/ml [3,33–37], and the most popular flavours were tobacco, mint and fruit [3,4,36,38].

Users reported consistently that EC helped them either to quit smoking (42–99%) [3,4,34–37,39] or to reduce it (60–86%) [3,24,36,39]. EC were perceived as less addictive than cigarettes [35,37], and time from waking up to use was longer for EC than for cigarettes [36,37]. Only 18% reported that they craved EC as much as tobacco [36].

Summary

EC use is on the increase. Experimentation by children is a small fraction of experimentation with cigarettes, and daily use in never-smokers has not been documented so far. It appears that some 12–14% of smokers who try EC become daily users, suggesting that EC in their current form are less satisfactory than cigarettes to most users. In surveys, regular EC users report that these devices helped them to limit or stop smoking and they perceive EC as less addictive than cigarettes.

EC CONTENT

The interpretation of studies of the chemical composition of the e-liquids and aerosols is complicated by the fact that there exist many brands and models with different e-liquids, batteries, heating elements, nicotine concentrations and flavourings, although most of them use e-liquids from a small number of manufacturers in China, the United States and Europe [40]. It is also important to differentiate between the chemical compositions of e-liquid and aerosols that users inhale.

Propylene glycol (PG) and glycerol

The results of extensive studies on animals, reviewed elsewhere [40,41], suggest that PG should be safe for inhalation in humans, although in children, chronic exposure to PG in indoor air may exacerbate or induce rhinitis, asthma, eczema and allergic symptoms [42]. Acute and chronic respiratory effects, including reduced lung function, were reported in people chronically exposed to theatre fogs containing PG [43]. PG has a desiccation effect, which is why EC users sometimes report dry throat and mouth [3,4,36,37].

Glycerol (purified vegetable glycerine) is non-toxic, but can produce toxic acrolein when heated to higher temperatures. Acrolein was detected in the aerosol of some EC brands, but at levels much lower than in cigarette smoke [44]. Acrolein intake by smokers given glycerol-based EC was reduced by 60% in those who continued to smoke (EC use was accompanied by a reduction in smoking) and by 80% in those who stopped smoking [45].

Impurities and toxicants in e-liquids

Nicotine in e-liquids, like nicotine in nicotine replacement treatment (NRT), is extracted from tobacco and thus includes impurities such as cotinine, anabasine, anatabine, myosmine and beta-nicotyrine [46,47]. An early study found nitrosamines and tobacco-specific impurities 'at very low levels' and diethylene glycol in one of the cartridges [48]. Later studies of other products found no evidence of diethylene glycol [46]. No tobacco-specific nitrosamines or polycyclic aromatic hydrocarbons were found in 20 EC products [49], while an analysis of samples from 11 manufacturers [50] found nitrosamine concentrations approximately 1000 times lower than those in smokeless tobacco products [51]. Analysis of EC aerosol (as opposed to e-liquid) identified low levels of some toxicants [44]. In some cases these were comparable to levels found in NRT, which are considered safe, and overall at levels 9–450 times lower than in cigarette smoke [44].

Metal particles were found in the liquid and aerosol from an EC model [52], but the report did not assess the clinical significance of the levels detected. These levels are 10–50 times below the levels allowed in inhalation medicines [53].

EC liquid can be cytotoxic in *in-vitro* studies (e.g. [54]) but users inhale aerosol, not liquid. Aerosol from one of 21 e-liquids was cytotoxic, due to the flavouring containing substances from roasted coffee beans, but this was 800 times less cytotoxic than tobacco smoke [55].

PG and glycerol inhalation is likely to pose a low risk, although their long-term effects as well as the effects of long-term inhalation of EC flavourings and additives need to be studied.

Passive exposure

Most second-hand smoke from cigarettes is generated as sidestream smoke from the tip. EC do not generate sidestream aerosol. It is only what is exhaled by the users that enters the ambient air. EC aerosol does not include most of the chemicals found in tobacco smoke or the 'sidestream' smoke, but users exhale nicotine and some other particles, primarily consisting of flavours, aroma transporters, glycerol and PG [56–59].

No long-term study has been conducted so far, but pollutant levels are much lower than from cigarettes and are likely to pose a much lower risk (if any) compared to cigarettes [41,56].

Labelling of nicotine content of e-liquid

Nicotine is the addictive chemical in tobacco smoke, but its involvement in smoking-related harm (outside pregnancy) is very small, if any, compared to cigarette smoking [60,61].

In several reports, nicotine was detected in products labelled as zero nicotine. In one study, a manufacturer included similar nicotine levels in differently labelled cartridges, including zero nicotine [47]. In all other cases, nicotine detected in zero-nicotine cartridges was only at trace levels and unlikely to have any psychoactive effects [47–49].

For the major e-liquid brands tested thus far, the labelling of nicotine content is accurate [46] and the nicotine content across cartridges and across batches has good consistency [62,63], although labelling for some brands can be vague, inaccurate or absent. However, beyond the general rule that EC users cannot obtain high nicotine levels if there is too little nicotine in the e-liquid, there is little relationship between nicotine in cartridges and nicotine in aerosol [63]. This is because the mechanical features of EC, such as the size of the battery, the nature of the heating element and the ventilation holes, etc. play a major role. In addition, individual inhalation characteristics have further substantial influence on nicotine levels delivered to the user (see below).

Summary

E-liquids and aerosols tested so far contain some toxicants in concentrations much lower than in tobacco smoke and negligible concentrations of carcinogens. Passive exposure to EC aerosol can expose non-users to nicotine, but at concentrations unlikely to have any pharmacological significance. Humectants in EC appear to be safe for inhalation, but the effects on EC users with asthma and other respiratory diseases are not known. Nicotine intake from EC is determined by a host of factors in addition to nicotine content of the e-liquid.

EC SAFETY

Adverse events

None of the experimental [37,59,64–73] or prospective follow-up studies [74,75] reported serious adverse events (SAEs). Adverse events (AEs) were mild to moderate and included symptoms such as mouth and throat irritation and dry cough, similar to those reported in surveys of EC users [3,4,35–37]. There were no significant differences in AEs between EC and control groups in two randomized trials [76,77]. There were no SAEs in one trial [77], and in the other SAEs were considered to be unrelated to the products under study [76].

Among reports from 481 EC users on online forums that had sections dedicated specifically to the reporting of adverse health effects of EC use, the most common AEs were effects on the mouth and throat (around 50% of events) [78]. An increase in blood pressure, a potentially more concerning effect, was reported by 2% of correspondents.

The US Food and Drug Administration Center for Tobacco Products (CTP) collects data regarding AEs from a variety of sources. Between 2008 and the first quarter of 2012, the CTP received 47 reports of AEs related to EC, eight of which were deemed serious. With the exception of two, no causality was attributed to the EC. The two were infant death caused by choking on an EC cartridge and facial burns caused by EC exploding [79]. We are aware of two further media reports of exploding EC [80,81].

Regarding AEs reported in the medical literature, an EC user developed lipoid pneumonia, which resolved when EC use ceased [82]. An elderly heavy smoker experienced three episodes of acute asymptomatic atrial fibrillation, each preceded by EC use. She stopped EC use and had no further episodes [83].

Regarding the cardiovascular effects of EC, nicotine in EC increases heart rate after overnight abstinence [72,73]. Short-term EC use does not adversely affect haematological or blood chemistry parameters, or cardiovascular function in smokers or ex-smokers [84–87].

Regarding effects on respiratory function, 5 minutes of EC use generated an increase in airways resistance, associated with a 16% decrease in fractional exhaled nitric oxide (FeNO), a marker of bronchial inflammation, with no change in the control group. These effects were not considered clinically significant [59].

In another study, smoking a cigarette led to a significant reduction in forced expiratory volume in 1 second/forced vital capacity (FEV_1/FVC), while EC use generated no acute change in lung function. There were no significant changes in FeNO in either group [69].

Risks of nicotine poisoning

A claim is often repeated that an ingestion of 30–60 mg of nicotine is fatal [88], but this assertion is based on dubious self-experiments in the 1890s [89]. Tobacco and NRT have been available to hundreds of millions of people, but fatal poisoning by nicotine is extremely rare. We are aware of one newspaper report of a fatal poisoning of a 2-year-old child who drank e-liquid [90] and of one case study on an 18-month-old child who drank e-liquid, was admitted to hospital with vomiting, ataxia and lethargy, and was discharged after 24 hours of observation [91]. With the increase in EC use, there has been an increase in calls to poison centres following accidental exposures, but these remain lower than calls following such exposure from tobacco and none resulted in any serious harm [92]. Several suicide attempts were recorded where adults drank up to 1500 mg of nicotine in e-liquid, which resulted in vomiting but recovery within a few hours [93].

Summary

Although surveys of users, prospective clinical studies and randomized controlled trials to date have not found any SAEs, several such events have been reported as case studies and in the media. Given the high media interest in EC, the number of such reports is remarkably low. Data to date show that EC pose a minimal risk of nicotine poisoning from the device as intended to be used, but e-liquid can be dangerous or lethal if ingested, particularly by small children.

EFFECTS ON SMOKERS

Nicotine levels in EC users

Early studies using brief fixed puffing schedules and smokers naive to EC use found low or no nicotine delivery [64,68,71]. With greater familiarity with the device and less restricted use, plasma nicotine delivery was comparable to that from oral NRT products (4–5 ng/ml) [3,70,73]. Some experienced EC users achieve nicotine

levels which are close to those obtained from smoking, but only after extended EC use (up to 14 ng/ml after 60 minutes of *ad libitum* use [33,65,72,94] compared with 10–20 ng/ml after smoking a cigarette) [95,96]. Importantly, users experienced in using the same model differed in how much nicotine they extracted from it [65]. As with cigarettes, user behaviour is an important factor in nicotine delivery.

Effects of EC use on withdrawal symptoms and on smoking behaviour

Using EC after overnight abstinence from smoking significantly reduces urges to smoke within 5–30 minutes [64,66–68,71,73]. Non-nicotine EC can also have this effect [64,66,67].

Three small studies evaluated the effects of EC in smokers not intending to reduce or quit smoking. They reported a ≥50% reduction in smoking at the end of 1 week in 32% of participants, including 14% who stopped smoking altogether [70]; sustained ≥50% reduction in 28% of participants and additional 13% abstinence rate at 2 years [75,97]; and ≥50% reduction in 50% of participants and additional 14% abstinence rate at 1 year in smokers with schizophrenia [74].

Data from representative surveys [19], surveys of EC users [3,4,24,34–37,39] and from clinical trials [45,74–77,97,98] show consistently that smokers who use EC and smoke at the same time (so called dual users) reduce their cigarette consumption.

Effects of EC on smoking cessation

Several case studies reported the benefits of EC in helping people who have failed to quit with other methods [99–101].

Several studies evaluated relationships between EC use and smoking reduction and cessation. Among the general population, EC users and non-users had the same quit rate, but EC use was associated with a significant reduction in cigarette consumption [19]. Among callers to a quitline, those who ever used EC compared with other callers had more previous failed quit attempts, were more likely to live with smokers and were less likely to quit at the current quit attempt [102]. The finding is due probably to bias by intention—more dependent smokers who choose to use EC and are also less likely to quit smoking. Similar findings have been observed with NRT [103]. One other study was interpreted as showing that EC use inhibits cessation, but another interpretation is that it showed that EC use is related to smoking history [104]. Adolescents who tried cigarettes at least once but are not smoking now were less likely to ever try EC than adolescents who smoke. In two cohorts, smokers who have tried EC had a similar likelihood of quitting as other smokers [19,21], but in a large population sample, smokers attempting to stop smoking with the help of EC were more likely to succeed than those using NRT bought from a store (without any professional supervision) or trying to quit unaided [105].

Among 'dual users', 46% quit smoking altogether after 1 year [106].

A randomized trial of 300 smokers not intending to quit compared the effects of two nicotine-containing and a nicotine-free EC provided for 12 weeks. The study used an EC with poor nicotine delivery that often malfunctioned and was subsequently discontinued [77]. At 1 year, smoking abstinence rates were 13, 9 and 4% in the three groups, respectively. There were no differences in smoking reduction in those who continued to smoke. The two nicotine EC groups merged had a higher quit rate than the non-nicotine group (11 versus 4%, $P = 0.04$).

A randomized trial in 657 treatment-seeking smokers compared EC with nicotine patches (21 mg) and with non-nicotine EC. The study used EC with low nicotine delivery [76]. Participants received a referral to a telephone quitline but no face-to-face contact. In this minimal support context, biochemically validated continuous abstinence rates at 6 months were 7.3, 5.8 and 4.1% in the three groups, respectively [not significant (NS)]. While the results were suggestive of a benefit for EC users, the study did not have adequate power to detect what would be a realistic margin of difference from the two active comparators. EC generated significantly higher self-reported smoking reduction and higher user endorsements than patches.

In the United Kingdom, where the use of EC to assist smoking cessation has now overtaken use of NRT, and detailed figures are available on month-to-month changes in smoking behaviour, the rise in EC use has been accompanied by an increase in successful quit attempts [107] and a continuing decrease in smoking prevalence [108].

Summary

EC reduce urges to smoke and there is preliminary evidence that EC use facilitates both quitting and reduction in cigarette consumption in smokers interested in quitting smoking. In England, which has the most detailed data on EC and cigarette use, the growth in EC use has been accompanied by an increase in smoking cessation rates, a continued reduction in prevalence and no increase in smoking uptake [107,108]. Whether EC are contributing to these favourable tobacco control trends is as yet unclear.

CONCLUSIONS

Important regulatory verdicts are being currently made and science-based decisions are needed to maximize

benefits and minimize risks to public health. The key issue to consider is whether EC use is likely to increase or decrease smoking-related morbidity and mortality. There are several hypothetical routes to a negative outcome and one route to a positive outcome. The reviewed evidence can contribute to their assessment. EC would generate negative outcomes if:

- Chemicals in EC cause excess morbidity and mortality. *Evidence*: health effects of long-term EC use are currently not known and a degree of risk may yet emerge. However, based on the data available regarding the toxicant content of EC liquid and aerosol, long-term use of EC, compared to smoking, is likely to be much less, if at all, harmful to users or bystanders. This is because unlike cigarettes, EC do not deliver combustion-generated toxicants that are linked to cancer, chronic lung disease and cardiovascular disease (CVD).
- Smokers who would otherwise quit combine EC and cigarettes instead of quitting and maintain a similar smoking rate. *Evidence*: EC use is associated with smoking reduction and there is little evidence that it deters smokers interested in stopping smoking tobacco cigarettes from doing so.
- Young people who would not try cigarettes otherwise start using EC and then move on to become smokers. *Evidence*: although there have been claims that EC is acting as a 'gateway' to smoking in young people, the evidence does not support this assertion. Regular use of EC by non-smokers is rare and no migration from EC to smoking has been documented (let alone whether this occurred in individuals not predisposed to smoking in the first place). The advent of EC has been accompanied by a decrease rather than increase in smoking uptake by children [109]. Ongoing surveillance is needed to address this important point.
- EC use will increase smoking prevalence indirectly, e.g. by making smoking acceptable again in the eyes of people who cannot tell the difference between EC and cigarettes, via machinations of the tobacco industry, or by weakening tobacco control activism. *Evidence*: there are no signs that the advance of EC is increasing the popularity of smoking or sales of cigarettes.

There is one hypothetical route to the positive outcome, i.e.:

- That EC reduce harm at the individual and population level by reducing cigarette use. In the most optimistic scenario, EC would continue to improve in providing smokers with what they want from their cigarettes, until the use of conventional cigarettes virtually disappears. *Evidence*: EC reduces cigarette use by facilitating smoking reduction and cessation on individual level, but the prevalence of EC use has been low until recently and the effect of EC use on cigarette consumption on the population level has not been established so far.

Implications for policy makers

The European Parliament has recently rejected a proposal to licence EC as medicines. There is a concern that medicinal regulation would disadvantage EC compared to cigarettes, make them more expensive, stifle their development and may drive them fully into the arms of the tobacco industry as the only player able to afford the large entry barriers [12,110]. In Europe, EC are subject to consumer protection legislation, and most countries are likely to ban sales to people under 18, as has recently been introduced in the United Kingdom. Advertising restrictions are also forthcoming [111,112]. Some regulators, however, believe these actions are not sufficient because of the hypothetical routes to negative outcomes discussed above. Regulatory decisions will provide the greatest public health benefit when they are proportional, based on evidence and incorporate a rational appraisal of likely risks and benefits.

Implications for researchers

Our review points to two key research priorities. One is ongoing surveillance of the temporal relationship between country-specific markers of EC use and smoking behaviour. Close monitoring, for which some instruments already exist [113–115], is needed to track changes in EC use and smoking prevalence. Sales data will also be informative; if increased EC sales are accompanied by an increase in cigarette sales, EC could be re-normalizing smoking and further regulatory steps would be required, while if they are associated with a decrease in cigarette sales, this would indicate a public health benefit of liberal regulation. The second priority concerns EC safety. Epidemiological studies are required that compare health outcomes in cohorts of regular EC users (who either use only EC or both EC and cigarettes) with matched cohorts of smokers and non-smokers. These need to be supplemented by laboratory and clinical studies of EC contents and effects on smoking behaviour.

Implications for health professionals

While there is not yet conclusive evidence about the effectiveness of e-cigarettes to generate smoking cessation or reduction, health-care professionals (HCP) should support smokers unable or unwilling to stop tobacco use who wish to switch to EC to reduce harm from smoking. HCP should emphasize the importance of stopping using cigarettes and nicotine altogether.

Declaration of interests

P.H., N.B. and T.E. have no links with any e-cigarette manufacturer. J.F.E. was reimbursed by a manufacturer of e-liquids for travelling to London and to China. H.M. was

an investigator in a public-good funded ASCEND e-cigarette trial for which PGM International provided products at no cost, and has undertaken research on Ruyan e-cigarettes, for which the University of Auckland was funded by Health New Zealand, independently of Ruyan.

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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]

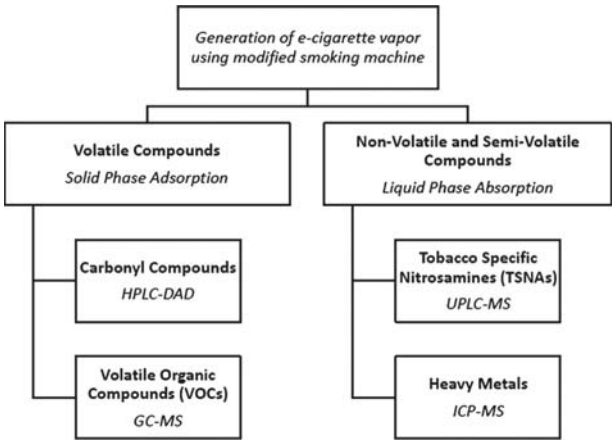

Figure 1 Analytical procedures applied in the study to test carcinogens and selected toxicants in vapour from e-cigarettes. GC-MS, gas chromatography-mass spectrometry; HPLC-DAD, high-performance liquid chromatography with diode array detector; ICP-MS, inductively coupled plasma-mass spectrometry; TSNA,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

Abstract Electronic cigarette consumption ('vaping') is marketed as an alternative to conventional tobacco smoking. Technically, a mixture of chemicals containing carrier liquids, flavors, and optionally nicotine is vaporized and inhaled. The present study aims at the determination of the release of volatile organic compounds (VOC) and (ultra)fine particles (FP/UFP) from an e-cigarette under near-to-real-use conditions in an 8-m^3 emission test chamber. Furthermore, the inhaled mixture is analyzed in small chambers. An increase in FP/UFP and VOC could be determined after the use of the e-cigarette. Prominent components in the gas-phase are 1,2-propanediol, 1,2,3-propanetriol, diacetin, flavorings, and traces of nicotine. As a consequence, 'passive vaping' must be expected from the consumption of e-cigarettes. Furthermore, the inhaled aerosol undergoes changes in the human lung that is assumed to be attributed to deposition and evaporation.

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Key words: Electronic cigarette; Indoor air quality; Formaldehyde; Ultrafine particles; Propylene glycol; Third-hand smoke.

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Practical Implications
The consumption of e-cigarettes marks a new source for chemical and aerosol exposure in the indoor environment. To evaluate the impact of e-cigarettes on indoor air quality and to estimate the possible effect of passive vaping, information about the chemical characteristics of the released vapor is needed.

Introduction

Electronic cigarettes show a rapidly growing market share and are advertised as a healthier alternative to conventional smoking. These 'e-cigarettes' contain a small battery-driven heating unit that vaporizes a mixture of chemicals, the so-called 'liquids'. They usually contain flavors and carrier substances and may be purchased with and without nicotine. The nicotine content roughly differs between 0 and 20 mg/ml depending on the brand (Trehy et al., 2011). A common carrier of the 'liquids' is 1,2-propanediol (propylene glycol, PG) that leads to a visible fume during exhalation. This compound is also frequently used as a solvent in dosage formulations of aerosolized drug delivery systems such as pressurized metered-dose inhalers and nebulizers for the clinical practice (Montharu et al., 2010). However, the frequency of use is expected to be higher in case of e-cigarette vaping, leading to a different exposure pattern. Propylene glycol is also a common humectant for tobacco cigarettes (Paschke et al., 2002). In contrast to conventional cigarettes, the released compounds are not generated from a combustion process (as a smoke) but by direct evaporation (as a vapor). For this reason, the term 'vaping' has been established among e-cigarette users as an analog to the conventional cigarette 'smoking' (Etter, 2010).

A recent study reports adverse physiological effects after the short-term use of e-cigarettes (Vardavas et al., 2011). This effect may be attributed to propylene glycol that is known to cause upper airway irritations (Wieslander et al., 2001). However, a comprehensive exposure assessment that compares the nicotine intake from e-cigarettes and conventional cigarettes – which also considers the impact of the carrier substances – is not available at the present state. Furthermore, the release of the organic compounds from the 'liquids' and

the release of particles into the indoor environment are still mostly unknown. In contrast, the impact of environmental tobacco smoke from conventional smoking on the indoor air quality has been intensively researched in the past decade. Numerous studies report the release of particulate matter (Nazaroff and Klepeis, 2003) and organic compounds such as formaldehyde, from the combustion of tobacco products (Baek and Jenkins, 2004; Baker, 2006; Paschke et al., 2002). These scientific findings led to a ban on smoking in public buildings and restaurants in many countries. This ban had a positive influence on the indoor air quality in these buildings (Bohac et al., 2010; Gleich et al., 2011).

Beyond indoor climate, airflow conditions, room size, and number of e-cigarette users, many other parameters have the potential to affect 'passive vaping'. The concentrations of the exhaled compounds during e-cigarette consumption can be expected to differ with the composition of the applied 'liquids', the type of e-cigarette in use, the age of the e-cigarette (e.g., owing to remains of previous 'liquids'), length of the puff, and interval between the puffs. Moreover, the composition of the exhaled air will be affected by age, sex, activity, health status, and diet of the user (Riess et al., 2010).

Another important aspect in the future discussion about e-cigarettes will be the effect of 'third-hand smoke' that mainly describes human exposure against residues of smoking on clothes, furniture, and other indoor surfaces (Matt et al., 2011). In case of e-cigarettes, the solvent of the 'liquids' may remain on available surfaces and be a source for the contamination of residents. Even more important might be the accidental spilling of 'liquids' that can lead to unintended uptake of nicotine by skin permeation – an effect that is intentionally used for nicotine patches (Hammer et al., 2011). It can be assumed that the health impact of e-cigarette use is mainly influenced by the safety and quality of the applied 'liquids'.

The present study provides first indications about the entry of volatile organic compounds (VOCs) and ultrafine particles into the indoor environment connected with the use of electronic cigarettes. One measurement was performed in a full-scale emission test chamber with one e-cigarette and different 'liquids'. Additional small-scale chamber measurements were performed to identify the effect of aerosol aging and the impact of different e-cigarette types. The experiments aim at the identification of the released compounds under near-to-real-use conditions to estimate the effect of 'passive vaping'.

Material and methods

Large-scale vaping/smoking experiment

The experiment was performed in an 8-m^3 stainless-steel emission test chamber. This chamber was operated at 23°C and 50% relative humidity at an air exchange rate of 0.3/h. The formaldehyde concentration in the chamber was continuously recorded every 30 s by an AL4021 formaldehyde auto analyzer (AeroLaser). A fast mobility particle sizer (FMPS; TSI Inc., Shoreview, MN, USA) recorded the particle number concentration of fine and ultrafine particles (FP/UFP) in the size range between 5.6 and 560 nm at 1 Hz in 32 channels.

Before the experiment and after each smoking event, 3 l of chamber air was pumped (200 ml/min) through stainless-steel tubes filled with 300 mg Tenax TA. The tubes were analyzed via thermal desorption (Ultra/Unity 2; Markes Int., Llantrisant, UK) and gas chromatography (6890 Series GC System; Agilent, Santa Clara, CA, USA; HP5MS 60 m × 250 μm × 0.3 μm column) coupled with mass spectrometry (5973N MSD; Agilent) according to ISO 16000-6. In parallel, lower aldehydes (formaldehyde, acetaldehyde, etc.) were collected using silica gel cartridges containing 2,4-dinitrophenylhydrazine (DNPH). The cartridges were analyzed according to ISO 16000-3 using high-performance liquid chromatography coupled with a variable wavelength detector (HPLC 1200 Infinity; Agilent).

A volunteering smoker took a seat in the chamber, and the chamber blank was measured after 20 min of conditioning. The e-cigarette was then filled with an apple-flavored nicotine-free 'liquid' (Liquid 1) outside of the chamber and given to the test person through a sampling port. The person took six deep-lung puffs (puff length ~ 3 s) with a delay of 60 s between each puff. The air sampling on Tenax TA tubes started at puff 4 and lasted 15 min. This procedure was performed for another two 'liquids', Liquid 2 and Liquid 3 (see Table 1).

After the e-cigarette was removed from the chamber, a conventional tobacco cigarette was lit outside the chamber and given to the test person. The sampling procedure was identical to the e-cigarette measurement.

For the determination of the feasible puff length, the mouthpiece and the wick (see Figure 1) were removed from the e-cigarette and the temperature of the heating coil was measured via thermography (ThermaCAM B20; FLIR Systems, Wilsonville, OR, USA) during

Table 1 Characteristics of the 'liquids'

Sample	Flavor	Main aroma compound	Nicotine content[a]
Liquid 1	Apple	3-Methylbutyl-3-methylbutanoate	0 mg/ml
Liquid 2	Apple	3-Methylbutyl-3-methylbutanoate	18 mg/ml
Liquid 3	Tobacco	Ethyl maltol	18 mg/ml
Conventional cigarette	–	–	0.8 mg/cigarette

[a]As stated by the manufacturer. [Correction added on 6 August 2012, after first online publication: Nicotine content for Liquid 2 and Liquid 3 changed from 1.8 mg/ml to 18 mg/ml.]

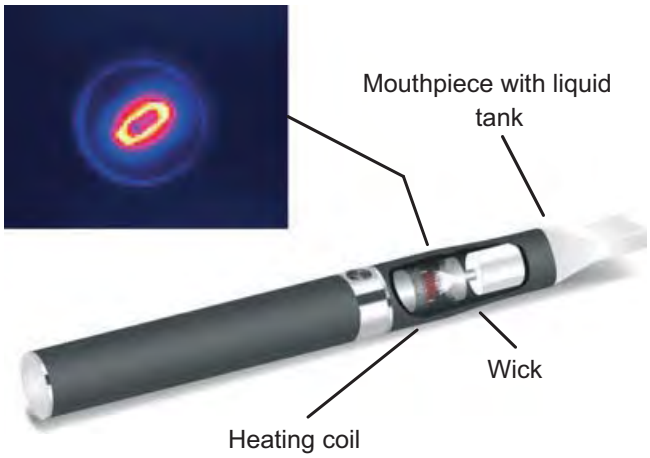

Fig. 1 Scheme of the tested e-cigarette A. The thermographic image shows the temperature distribution of the heating unit without 'liquid' (>350°C in the center)

heat-up. The time-resolved analysis showed an interval of 3 s between start of the cigarette and reaching stable temperature conditions. The puff length was equally increased for e-cigarette and tobacco cigarette, even though the length of the puff was approximately 1 s longer than specified in ISO 3308 (2000). The puff interval (60 s) was selected according to ISO 3308. The number of puffs (10 in ISO 3308) had to be adapted to the new smoking conditions because the tobacco cigarette was depleted after six puffs.

Vapor analysis

An aerosol aging experiment was performed in a 10-l glass emission test chamber. The chamber is double walled and is temperature controlled by water. The air in the chamber is mixed by a small fan. The e-cigarette was connected to the inlet, and a pump was used to produce a slight underpressure that transfers the aerosol directly into the chamber. The e-cigarette was operated for 3 s. The aerosol was aged in the chamber for 1, 3, 5, 7, and 10 min at 37°C. Additionally, the aerosol was aged 5 min at 23, 37, and 50°C. Then, the FMPS (sample flow rate of 8 l/min) was connected to the chamber, and the chamber inlet was equipped with a HEPA filter.

Analysis of VOCs in exhaled breath

After measuring the VOC chamber blank, an e-cigarette consumer was asked to exhale one e-cigarette puff into the 10-l glass chamber. The VOCs within the chamber were then determined by GC/MS after sampling on Tenax TA tubes (6L, 150 ml/min).

Table 2 Characteristics of the tested e-cigarettes

Sample	Casing	Delivery system	Comparative price
e-Cigarette A	Stainless steel/rubber	Tank	High (>35 Euro)
e-Cigarette B	Stainless steel	Cotton	Medium
e-Cigarette C	Stainless steel	Tank	Low (<25 Euro)

Measurement with three different e-cigarettes

Three different types of e-cigarettes (see Table 2) were filled with 'liquid' from the same stock (Liquid 1). The cigarette was operated for 3 s. The vapor from the e-cigarettes was transferred into the 10-l glass chamber using a pump. The chamber was set to 37°C and an air exchange rate of 3/h. Directly after injection of the vapor, sampling on Tenax TA was performed for 60 min (100 ml/min) and sampling on DNPH was performed for 200 min (120 ml/min). Between each measurement, the chamber was heated to 60°C for 24 h at maximum air exchange rate (6/h). The measured concentration c_S ($\mu g/m^3$) is converted into the released mass per puff MPP (μg/puff) according to Equation 1 using the sample volume V_S (m^3), the number of puffs n (puff), and the ratio between sample flow $\dot{V}_S$ (m^3/h) and chamber exhaust flow $\dot{V}_C$ (m^3/h). Additionally, the value is corrected for the expected exponential decay of the concentration because of the air exchange rate k (/h).

$$\mathrm{MPP}=\frac{c_S}{n}\cdot V_S\cdot\frac{\dot{V}_C}{\dot{V}_S}\cdot\frac{\int_0^\infty e^{-k\cdot t}\,dt}{\int_0^t e^{-k\cdot t}\,dt}=\frac{c_S}{n}\cdot V_S\cdot\frac{\dot{V}_C}{\dot{V}_S}\cdot\frac{1}{1-e^{-k\cdot t}} \quad (1)$$

Descriptions of the performed experiments as well as the measured climatic conditions during measurement are summarized in Table 3.

Results and discussion

Emission of volatile organic compounds

Electronic cigarettes use a completely different principle of operation compared to tobacco cigarettes. The 'liquid' is vaporized and because of the thermodynamic properties of 1,2-propanediol (K_p = 188°C, ΔH_v = 64.5 kJ/mol at 298.15 K) (Verevkin, 2004), the heat from the coil (see Figure 1) is led off, which avoids pyrolysis. In contrast, conventional cigarettes release numerous compounds into the indoor environment. Paschke et al. (2002) listed hundreds of ingredients in tobacco cigarettes that form volatile combustion products. In Table 4, the 20 compounds with the highest concentrations in the 8-m^3 chamber air are summarized. During operation of the e-cigarette, the carrier substance of the 'liquids', 1,2-propanediol, was detected in the chamber atmosphere but the concentration was below the limit of determination. In contrast, a high concentration of 1,2-propanediol was observed for smoking of the conventional cigarette. The compound is known to be pyro-

Table 3 Description of the performed experiments

Experiment	Chamber	T (°C)[a]	RH (%)[a]	e-Cig.	'Liquid'	Smoker	Analytics
Large-scale experiment	8-m^3 stainless steel	24.1 ± 1.1	44.5 ± 8.2	A	1–3	Yes	Fast mobility particle sizer (FMPS), AeroLaser, Tenax, DNPH
Vapor analysis/aging	10-l glass	22.7 ± 0.1	36.9 ± 0.5	A	1	No	FMPS
		37.1 ± 0.2	18.9 ± 0.6				
		49.9 ± 0.1	11.0 ± 0.6				
Exhaled breath	10-l glass	37.0 ± 0.2	27.2 ± 4.3	A	1	Yes	Tenax
Three e-cigarettes	10-l glass	36.8 ± 0.2	20.2 ± 0.6	A	1	No	Tenax, DNPH
		37.1 ± 0.2	18.2 ± 0.6	B			
		37.1 ± 0.2	17.7 ± 0.6	C			

[a]These values provide the measured mean climatic conditions (measuring interval: 1 min) and the standard deviations during performing the experiments.

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

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

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

lyzed to acetaldehyde and acetone during smoking (Paschke, 2002).

Ohta et al. (2011) proposed the formation of formaldehyde, acetaldehyde, and methylglyoxal in the e-cigarette because of the oxidation of propylene glycol during contact with the active heating coil. However, continuous monitoring only showed a slight increase in the formaldehyde concentration in the 8-m^3 emission test chamber before and during the consumption of the three 'liquids' (see Table 4 and Figure 2). This might be caused by the person in the chamber itself, because people are known to exhale formaldehyde in low amounts (Riess et al., 2010) and the increase was already observed during the conditioning phase (Figure 2). Furthermore, the release of formaldehyde was also below the limit of detection in the small-scale experiments. The expected rise of the formaldehyde concentration in the chamber from smoking a conventional cigarette with a peak value of 114 ppb is shown in Figure 2. Other indoor pollutants of special interest, such as benzene, were only detected during the tobacco smoking experiment. The rising concentrations of acetic acid and acetone during e-cigarette operation may also be attributed to the metabolism of the consumer.

Although 1,2-propanediol was detected in traces only in the 8-m^3 chamber during the consumption of e-cigarettes, this compound must be released owing to the visible fume in the exhaled breath. To determine the VOC composition in the breath gas directly, an e-cigarette smoker exhaled into a 10-l glass chamber. The identified chemical species are shown in Figure 3. The experiment revealed a high amount of 1,2-propanediol in the exhaled air. Other main components were the

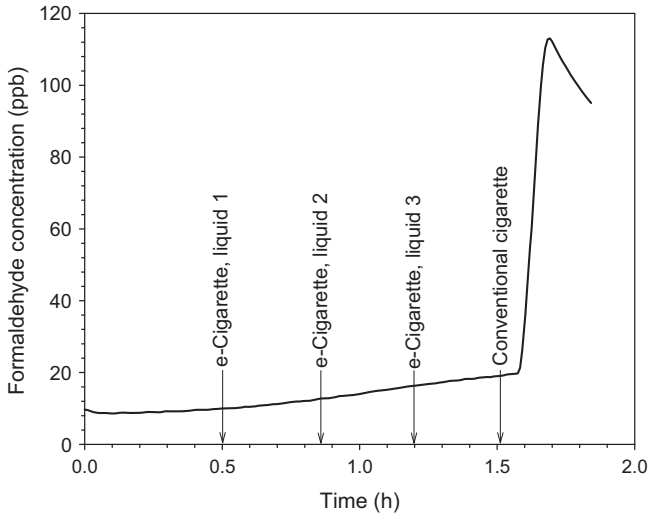

Fig. 2 Formaldehyde concentration in the 8-m^3 test chamber during consumption of e-cigarettes (Liquids 1–3) and one conventional cigarette

carrier substance 1,2,3-propanetriol, the flavoring source diacetin as well as traces of apple oil (3-methylbutyl-3-methylbutanoate) and nicotine. The fact that these compounds were not detectable during the 8-m^3 emission test chamber measurement is assumed to be caused by the short usage (6 min per 'liquid') and sink effects of the chamber for the very polar 1,2-propanediol.

Regarding the variability of e-cigarettes, the VOC emission strength seems to differ with different types of e-cigarettes (Table 5). While the e-cigarettes A and C have similar emission patterns, the emission from e-cigarette B is significantly higher. Formaldehyde was not detected during any measurement. With e-cigarette C, almost three times more propylene glycol is released per puff. This deviation is assumed to be caused by the 'liquid' supply technique. In case of e-cigarettes A and C, the 'liquid' is stored in a tank, while e-cigarette B features a cotton unit that is drenched with the 'liquid'. However, a general correlation between emission strength and 'liquid' supply technique (tank or cotton) is not possible from this limited data set. The effect of other systems, such as underpressure-activated e-cigarettes, was not determined in this study and is an important topic for further research.

Aerosol release from the e-cigarette

The airborne particles being related to the e-cigarette experiment are assumed to be formed from supersaturated 1,2-propanediol vapor. In contrast to the conventional cigarette, which continuously emits particles from the combustion process itself, the e-cigarette aerosol is solely released during exhalation. The e-cigarette aerosol measured in the 8-m^3 chamber is bimodal: one maximum is found in the range of 30 nm and one in the range of 100 nm (see Figure 4a). During the ongoing experiment, the ultrafine particle mode increased. The particles in the higher mode are assumed to be evaporated or deposited in the human lung. Because of the high vapor pressure of 1,2-propanediol (p_s = 17.36 Pa at 298.15 K) (Verevkin, 2004), the dynamics of the aerosol is expected to be fast. For comparison, the particle size distribution of the conventional cigarette provides a single mode with a maximum at 100 nm and a higher total number concentration (see Figure 4b).

For characterization of the e-cigarette aerosol, it was passed directly from the mouthpiece into a 10-l glass emission test chamber. Then, it was aged for 5 min at 23, 37, and 50°C, respectively. From Figure 5a, it is obvious

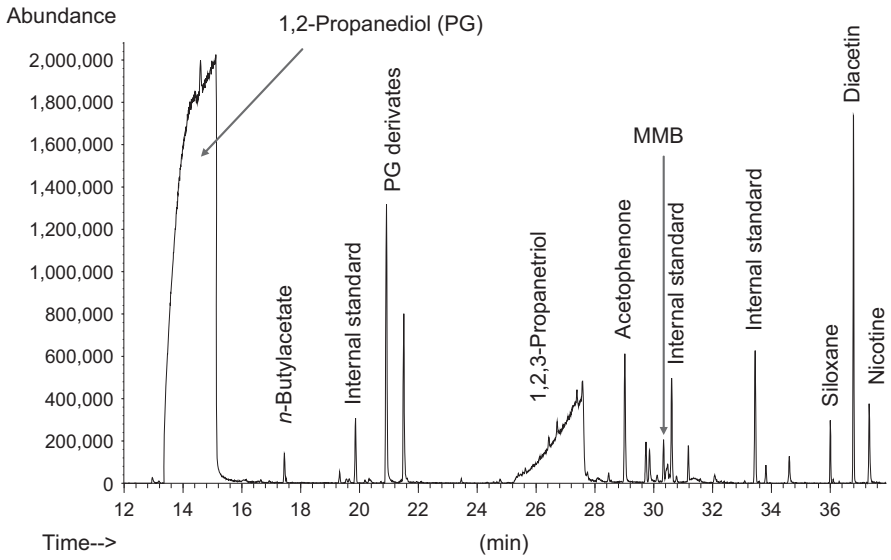

Fig. 3 Gas chromatogram of one exhaled e-cigarette puff (Liquid 2) in a 10-l glass chamber (sampled on Tenax TA, 3 l sampling volume) (MMB = 3-methylbutyl-3-methylbutanoate; PG = propylene glycol)

Table 5 Comparison of the release of volatile organic compound for a number of selected compounds from three types of e-cigarettes A-C (one puff, 3 s) in a 10-l glass chamber using Tenax TA and DNPH

	Concentration (μg/m^3)			Estimated mass per puff (μg/puff)[a]		
Compound	A	B	C	A	B	C
1,2-Propanediol	53 000	175 000	64 000	1673	5525	2021
1,2,3-Propanetriol	326	477	161	10	15	5
3-Methylbutyl-3-methylbutanoate	3	35	10	0.1	1.1	0.3
Diacetin	2	1	1	0.06	0.03	0.03
Triacetin	<1	<1	<1	<0.03	<0.03	<0.03
Nicotine	7	7	4	0.2	0.2	0.1
Formaldehyde[b]	<2	<2	<2	<0.25	<0.25	<0.25
Acetaldehyde[b]	<1	<1	<1	<0.13	<0.13	<0.13
Propanal[b]	<1	<1	<1	<0.13	<0.13	<0.13

[a]The conversion factors based on the sample volume, the sample flow, and the exponential decay of the concentration (see Equation 1).
[b]DNPH method.

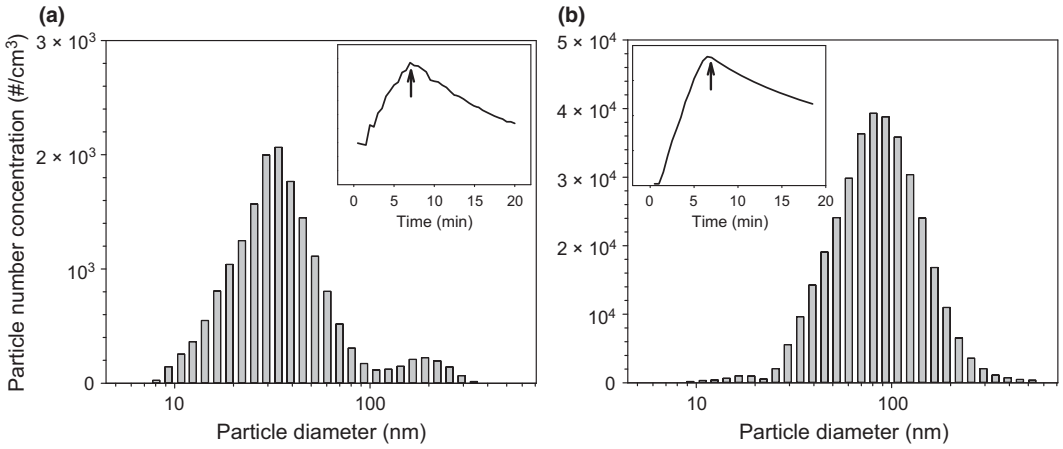

Fig. 4 (a) Aerosol size distribution during consumption of an e-cigarette in the 8-m^3 chamber. (b) Aerosol size distribution during consumption of a conventional cigarette in the 8-m^3 chamber. The arrows in the insets of (a) and (b) indicate the actual time in concentration development

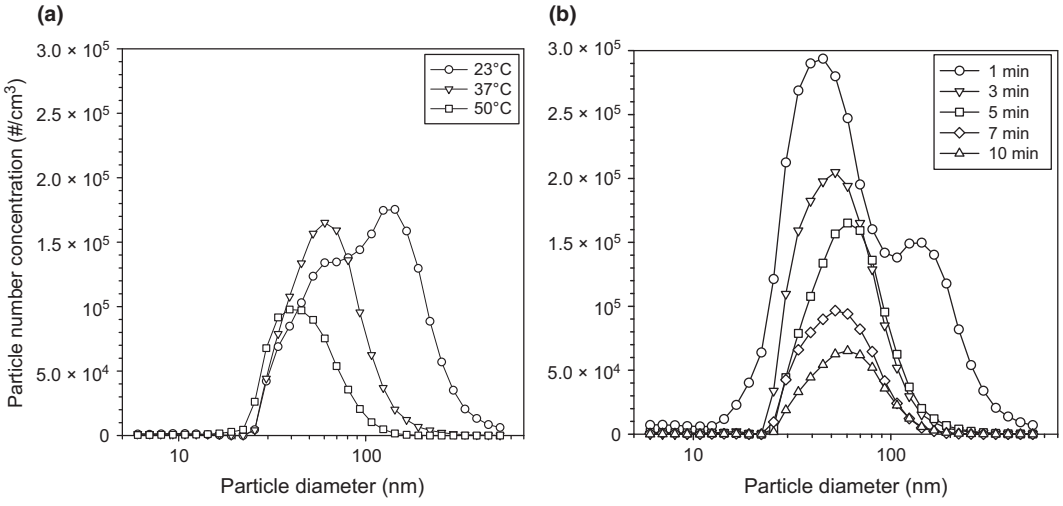

Fig. 5 Aerosol size distributions of aged e-cigarette aerosols in a 10-l glass chamber. The aerosol was aged for 5 min at different temperatures (a) and for different times at 37°C (b)

that because of increasing temperature, the aerosol shifts from a bimodal size distribution with maxima at 60 and 100 nm into a single-mode distribution with a maximum at 45 nm. Figure 5b demonstrates the effect of aging at 37°C. Between 1 and 3 min, the higher mode at 100 nm disappeared and a single-mode aerosol with a maximum

at 45 nm is left. This 'shrinking' of the particles can be attributed to the evaporation of the particles under ideal conditions. However, in the real indoor environment, the present airborne particles might affect aging, for example, owing to coagulation. The inlet air of the large-chamber experiment was free of particles, and thus, the experimental results in both chambers are conclusive. In total, these findings prove that the influence of the e-cigarette on the indoor air particle concentration cannot be determined solely from direct aerosol sampling at the source. The dynamics and changes of the aerosol size distribution resulting from the dwell time in the human lung must be considered.

Conclusions

The consumption of e-cigarettes causes emissions of aerosols and VOCs, such as 1,2-propanediol, flavoring substances, and nicotine, into indoor air. During inhalation of e-cigarette vapor, the aerosol size distribution alters in the human lung and leads to an exhalation of smaller particles. This effect is caused by the evaporation of the liquid particles in the lung and also in the environment after exhalation. The quantity of the inhaled vapor could be observed to depend on the 'liquid' delivery system of the e-cigarette in use.

Overall, the e-cigarette is a new source of VOCs and ultrafine/fine particles in the indoor environment. Therefore, the question of 'passive vaping' can be answered in the affirmative. However, with regard to a health-related evaluation of e-cigarette consumption, the impact of vapor inhalation into the human lung should be of primary concern.

Acknowledgements

The authors are grateful to Manuela Lingnau for preparing the e-cigarette scheme and Friedrich Schlüter for providing the thermographic image. The authors especially like to thank Frank Fuhrmann for stimulating the interest in the e-cigarette topic. This work was financially supported by internal Fraunhofer WKI research funds.

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Dr Margaret Chan
Director General
World Health Organisation
Geneva

CC: FCTC Secretariat, Parties to the FCTC, WHO Regional Offices

26 May 2014

Dear Dr Chan

Reducing the toll of death and disease from tobacco – tobacco harm reduction and the Framework Convention on Tobacco Control (FCTC)

We are writing in advance of important negotiations on tobacco policy later in the year at the FCTC Sixth Conference of the Parties. The work of WHO and the FCTC remains vital in reducing the intolerable toll of cancer, cardiovascular disease and respiratory illnesses caused by tobacco use. As WHO has stated, up to one billion preventable tobacco-related premature deaths are possible in the 21st Century. Such a toll of death, disease and misery demands that we are relentless in our search for all possible practical, ethical and lawful ways to reduce this burden.

It is with concern therefore that a critical strategy appears to have been overlooked or even purposefully marginalised in preparations for FCTC COP-6. We refer to 'tobacco harm reduction' - the idea that the 1.3 billion people who currently smoke could do much less harm to their health if they consumed nicotine in low-risk, non-combustible form.

We have known for years that people 'smoke for the nicotine, but die from the smoke': the vast majority of the death and disease attributable to tobacco arises from inhalation of tar particles and toxic gases drawn into the lungs. There are now rapid developments in nicotine-based products that can effectively substitute for cigarettes but with very low risks. These include for example, e-cigarettes and other vapour products, low-nitrosamine smokeless tobacco such as snus, and other low-risk non-combustible nicotine or tobacco products that may become viable alternatives to smoking in the future. Taken together, these tobacco harm reduction products could play a significant role in meeting the 2025 UN non-communicable disease (NCD) objectives by driving down smoking prevalence and cigarette consumption. Indeed, it is hard to imagine major reductions in tobacco-related NCDs without the contribution of tobacco harm reduction. Even though most of us would prefer people to quit smoking and using nicotine altogether, experience suggests that many smokers cannot or choose not to give up nicotine and will continue to smoke if there is no safer alternative available that is acceptable to them.

We respectfully suggest that the following principles should underpin the public health approach to tobacco harm reduction, with global leadership from WHO:

1. *Tobacco harm reduction is part of the solution, not part of the problem.* It could make a significant contribution to reducing the global burden of non-communicable diseases caused by smoking, and do so much faster than conventional strategies. If regulators treat low-risk nicotine products as traditional tobacco products and seek to reduce their use without recognising their potential as low-risk alternatives to smoking, they are improperly defining them as part of the problem.

2. *Tobacco harm reduction policies should be evidence-based and proportionate to risk, and give due weight to the significant reductions in risk that are achieved when a smoker switches to a low risk nicotine product*. Regulation should be proportionate and balanced to exploit the considerable health opportunities, while managing residual risks. The architecture of the FCTC is not currently well suited to this purpose.

3. *On a precautionary basis, regulators should avoid support for measures that could have the perverse effect of prolonging cigarette consumption.* Policies that are excessively restrictive or burdensome on lower risk products can have the unintended consequence of protecting cigarettes from competition from less hazardous alternatives, and cause harm as a result. Every policy related to low risk, non-combustible nicotine products should be assessed for this risk.

4. *Targets and indicators for reduction of tobacco consumption should be aligned with the ultimate goal of reducing disease and premature death, not nicotine use* per se*, and therefore focus primarily on reducing smoking*. In designing targets for the non-communicable disease (NCD) framework or emerging Sustainable Development Goals it would be counterproductive and potentially harmful to include reduction of low-risk nicotine products, such as e-cigarettes, *within these targets*: instead these products should have an important role in *meeting the targets*.

5. *Tobacco harm reduction is strongly consistent with good public health policy and practice and it would be unethical and harmful to inhibit the option to switch to tobacco harm reduction products*. As the WHO's Ottawa Charter states: "*Health promotion is the process of enabling people to increase control over, and to improve, their health"*. Tobacco harm reduction allows people to control the risk associated with taking nicotine and to reduce it down to very low or negligible levels.

6. *It is counterproductive to ban the advertising of e-cigarettes and other low risk alternatives to smoking*. The case for banning tobacco advertising rests on the great harm that smoking causes, but no such argument applies to e-cigarettes, for example, which are far more likely to reduce harm by reducing smoking. Controls on advertising to non-smokers, and particularly to young people are certainly justified, but a total ban would have many negative effects, including protection of the cigarette market and implicit support for tobacco companies. It is possible to target advertising at existing smokers where the benefits are potentially huge and the risks minimal. It is inappropriate to apply Article 13 of the FCTC (Tobacco advertising, promotion and sponsorship) to these products.

7. *It is inappropriate to apply legislation designed to protect bystanders or workers from tobacco smoke to vapour products.* There is no evidence at present of material risk to health from vapour emitted from e-cigarettes. Decisions on whether it is permitted or banned in a particular space should rest with the owners or operators of public spaces, who can take a wide range of factors into account. Article 8 of the FCTC (Protection from exposure to tobacco smoke) should not be applied to these products at this time.
8. *The tax regime for nicotine products should reflect risk and be organised to create incentives for users to switch from smoking to low risk harm reduction products.* Excessive taxation of low risk products relative to combustible tobacco deters smokers from switching and will cause more smoking and harm than there otherwise would be.
9. *WHO and national governments should take a dispassionate view of scientific arguments, and not accept or promote flawed media or activist misinterpretations of data*. For example, much has been made of 'gateway effects', in which use of low-risk products would, it is claimed, lead to use of high-risk smoked products. We are unaware of any credible evidence that supports this conjecture. Indeed, similar arguments have been made about the use of smokeless tobacco in Scandinavia but the evidence is now clear that this product has made a significant contribution to reducing both smoking rates and tobacco-related disease, particularly among males.
10. *WHO and parties to the FCTC need credible objective scientific and policy assessments with an international perspective.* The WHO Study Group on Tobacco Product Regulation (TobReg) produced a series of high quality expert reports between 2005 and 2010. This committee should be constituted with world-class experts and tasked to provide further high-grade independent advice to the WHO and Parties on the issues raised above.

The potential for tobacco harm reduction products to reduce the burden of smoking related disease is very large, and these products could be among the most significant health innovations of the 21st Century – perhaps saving hundreds of millions of lives. The urge to control and suppress them as tobacco products should be resisted and instead regulation that is fit for purpose and designed to realise the potential should be championed by WHO. We are deeply concerned that the classification of these products as tobacco and their inclusion in the FCTC will do more harm than good, and obstruct efforts to meet the targets to reduce non-communicable disease we are all committed to. We hope that under your leadership, the WHO and FCTC will be in the vanguard of science-based, effective and ethical tobacco policy, embracing tobacco harm reduction.

We would be grateful for your considered reaction to these proposals, and we would like to request a meeting with you and relevant staff and a small delegation of signatories to this letter. This statement and any related information will be available on the Nicotine Science and Policy web site (http://nicotinepolicy.net) from 29 May 2014.

Yours sincerely,

Signatories this statement at 26 May 2014

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Morris, Erin

From: Barbara Stafford <barbara@barbarastafford.com>
Sent: Saturday, August 30, 2014 8:22 AM
To: Morris, Erin
Subject: Smoke free ordinance and Vista del Lago

Hi Erin

Thanks so much for your efforts on making Santa Rosa more smoke free!

I was the person at the Council Meeting from Vista del Lago. Jay Macedo said that you are planning to visit VDL to get more information and I think that's wonderful. I hope you talk with our HOA Board of Directors which is made up of residents and actually makes the decisions -- not just the Property Management Company.

I don't know that smoking is a huge issue in VDL as fewer people smoke these days, but for homeowners like me who have the misfortune of having renters next door who are heavy smokers the only remedy is to not use my back patio and keep most of my windows closed.

I do know that when I ask my neighbors who live in the same type of unit I do how they feel about smoking in general, they're say they're not affected. When I ask them how they would feel if a smoker or smokers moved in next door, they all say "I would hate it!"

I think you will see if you visit just how close many of the units are... and how it is impossible to escape from a neighbor's smoke -- especially if they are renters who are prohibited by their lease from smoking inside and are doing 100% of their smoking outside.

I'd love to help you out in any way I can. I'll be out of town for the next week on the mountains but will check my email when I get back.

Best,

Barbara

:: :: :: ::

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Morris, Erin

From: Pam Granger <Pam.Granger@lung.org>
Sent: Tuesday, August 26, 2014 2:09 AM
To: _CityCouncilListPublic
Cc: Morris, Erin
Subject: ALA supports Community Development Department tobacco control recommendations with 3 suggestions
Attachments: 14-08-25 ALA supports CDD recommendations to SR CC.docx

AMERICAN LUNG ASSOCIATION®
IN CALIFORNIA

August 25, 2014

Mayor Scott Bartley and members of the City Council of Santa Rosa
100 Santa Rosa Avenue
Santa Rosa, CA 95401

Dear Mayor Bartley and Council members,

The American Lung Association in California is enthusiastic about the City of Santa Rosa updating their tobacco control policy to strengthen protections from secondhand smoke exposure. The growing body of evidence about the harmful effects of exposure to secondhand smoke has grown exponentially in the eight years that have passed since the council last made changes to the city's tobacco ordinance in 2006 and Santa Rosa is positioned to benefit from lessons learned during that time.

In reviewing the August 26 Council Agenda Item 12.4 Smoking Regulation Update the Lung Association strongly supports 5 of the 6 recommendations being brought forth to council by the Community Development Department:

1) Prohibit smoking in attached multifamily housing, including duplexes, apartments, and condominiums and any building that contain two or more attached residential units;
2) Eliminate any allowance for smoking in "recreational areas" and on City-owned recreational properties including parks;
3) Prohibit smoking at all City-owned properties including (but not limited to) office buildings, recreation centers, public safety facilities, parking garages, and parking lots;
5) Revise the definition of "smoking" in Chapter 9-20 to explicitly include use of electronic cigarettes, and evaluate the Zoning Code to determine if revisions are needed related to electronic cigarettes; and
6) Evaluate increasing the percentage of guest rooms within hotels and motels that must be smoke-free from 50% to 75%.

We make three recommendations:

1. It would be our suggestion to broaden item *4) Prohibit smoking at bus stops and within bus shelters* to regulating smoking in "**service areas**." This would capture bus stops and within bus shelters in addition to other places where the public must line up to wait for services. This broader term would better align with a category in the State of Tobacco Control Report. Example below from Sonoma County ordinance:

   "Service Area" means any area, Enclosed or Unenclosed, designed to be regularly used by one or more persons to receive or wait to receive a service or make a transaction whether or not such service

includes the exchange of money, including, for example, ATMS, bank teller windows, public telephones, ticket lines, bus stops and cab stands.

2. It would also be our suggestion to **declare secondhand smoke a public nuisance on residential property**. California law affirms that anything which is injurious to health or obstructs the free use of property, so as to interfere with the comfortable enjoyment of life or property, is a nuisance. Local governments have broad latitude to declare nuisances and are not constrained by prior definitions of nuisance. Declaring secondhand smoke a nuisance would provide some help for residents with zero lot lines or living in mobile homes without shared walls which would not be covered in recommendation 1), but who have toxic drifting secondhand smoke problems. If loud music is considered a nuisance, shouldn't secondhand smoke be? Example below from Union City:

   For all purposes within the jurisdiction of the City of Union City, nonconsensual exposure to smoke occurring on or drifting into residential property is a nuisance, and the uninvited presence of smoke on residential property is a nuisance and a trespass. Any person bringing a civil action to enforce the nuisance provision contained in this section need not prove an injury different in kind or in degree from injury to others to prove a violation of this chapter. (Ord. 740-10 § 2, 2010)

3. We also suggest increasing "reasonable distance" from twenty (20) feet in the current policy to **twenty-five (25) feet** for consistency with the updated Sonoma County Unincorporated policy as so much of Santa Rosa borders with the County.
   Example below from Sonoma County:

   "Reasonable Distance" means a distance that ensures that occupants of an area in which Smoking is prohibited are not exposed to Smoke created by smokers outside the area. This distance shall be a minimum of twenty-five (25) feet.

The American Lung Association thanks all the councilmembers in advance for moving forward with a strong ordinance to protect the health of our residents by providing equal access to clean and healthy air where they live, work and play.

FYI - The 2015 State of Tobacco Control Report Card would result in an overall grade of "B" based upon Community Development Department and ALA recommendation #1- "Service Area"

Santa Rosa "State of Tobacco Control" Report Card - before and after ordinance update		Possible Points	**Santa Rosa - Current Grade 8/1/14**	**Post ordinance update**
Overall Tobacco Control Grade			**D**	**B**
Total Points		12	**4**	**8**
Smokefree Outdoor Air			**A**	**A**
Dining		4	4	4
Entryways		4	4	4
Public Events		4	4	4
Recreation Areas		4	4	4
Service Areas -	with ALA suggestion	4	2	4
Sidewalks		1	1	1
Worksites		1	0	1

Total Points	22	**19**	**22**
Smokefree Housing		**F**	**A**
Nonsmoking Apartments	4	0	4
Nonsmoking Condominiums	4	0	4
Nonsmoking Common Areas	4	0	4
Nonsmoking Housing Authority	1	n/a	n/a
Total Points	13	**0**	**12**
Reducing Sales of Tobacco Products		**F**	**F**
Tobacco Retailer Licensing	4	0	0
Total Points	4	**0**	**0**
Emerging Issues Bonus Points			
Emerging Products Definition - Secondhand Smoke	1	0	1
Emerging Products Definition - Licensing	1	0	0
Retailer Location Restrictions	1	0	0
Sampling of Tobacco Products	1	1	1
Sale of Tobacco Products in Pharmacies	1	0	0
Flavored Tobacco Products	1	0	0
Minimum Pack Size of Cigars	1	0	0
Total Points	7	**1**	**2**

Best regards,

Pam Granger | Advocacy Manager - North Coast
American Lung Association in California
(707) 775-6045 office
(866) 515-4625 e-fax
(707) 775-8185 cell
pam.granger @lung.org | http://www.lung.org/california

Join the American Lung Association in California LUNG FORCE Walk - San Francisco on November 8, 2014 at Crissy Field, Golden Gate National Recreation Area.
Sign up now at LUNGFORCE.ORG/Walk

Morris, Erin

From: Michelle McGarry <MMcGarry@nccwb.org>
Sent: Tuesday, August 26, 2014 1:40 PM
To: Morris, Erin
Cc: Jay.Macedo@sonoma-county.org
Subject: Letter of Support for Smoke-free Ordinance Updates

August 26, 2014

Mayor Scott Bartley and members of the City Council of Santa Rosa
100 Santa Rosa Avenue
Santa Rosa, CA 95401

Dear Mayor Bartley and Council members,

As Chairperson of the Coalition for a Tobacco-free Sonoma County, I commend you for taking the next steps to ensure the residents' of multi-unit housing in Santa Rosa are given the right to breathe clean air in their own homes. In addition, I congratulate you for moving forward to update the City of Santa Rosa's outdoor tobacco control policies as well. In eight years, the harmful effects of secondhand smoke exposure are incredibly tangible. Strengthening smoke-free ordinances are truly the only remedy to ensure that thousands of the city's citizens, especially children, may enjoy the freedom of exposure to unhealthy air.

In reviewing the August 26 Council Agenda Item 12.4 Smoking Regulation Update the Coalition for a Tobacco-free Sonoma County strongly supports 5 of the 6 recommendations being brought forth to council by the Community Development Department:

1) Prohibit smoking in attached multifamily housing, including duplexes, apartments, and condominiums and any building that contain two or more attached residential units;
2) Eliminate any allowance for smoking in "recreational areas" and on City-owned recreational properties including parks;
3) Prohibit smoking at all City-owned properties including (but not limited to) office buildings, recreation centers, public safety facilities, parking garages, and parking lots;
5) Revise the definition of "smoking" in Chapter 9-20 to explicitly include use of electronic cigarettes, and evaluate the Zoning Code to determine if revisions are needed related to electronic cigarettes; and
6) Evaluate increasing the percentage of guest rooms within hotels and motels that must be smoke-free from 50% to 75%.

We make three recommendations:

1. It would be our suggestion to broaden item 4) Prohibit smoking at bus stops and within bus shelters to regulating smoking in "service areas." This would capture bus stops and within bus shelters in addition to other places where the public must line up to wait for services. This broader term would better align with a category in the State of Tobacco Control Report. Example below from Sonoma County ordinance:

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2. It would also be our suggestion to declare secondhand smoke a public nuisance on residential property. California law affirms that anything which is injurious to health or obstructs the free use of property, so as to interfere with the

comfortable enjoyment of life or property, is a nuisance. Local governments have broad latitude to declare nuisances and are not constrained by prior definitions of nuisance. Declaring secondhand smoke a nuisance would provide some help for residents with zero lot lines or living in mobile homes without shared walls which would not be covered in recommendation 1), but who have toxic drifting secondhand smoke problems. If loud music is considered a nuisance, shouldn't secondhand smoke be?
Example below from Union City:

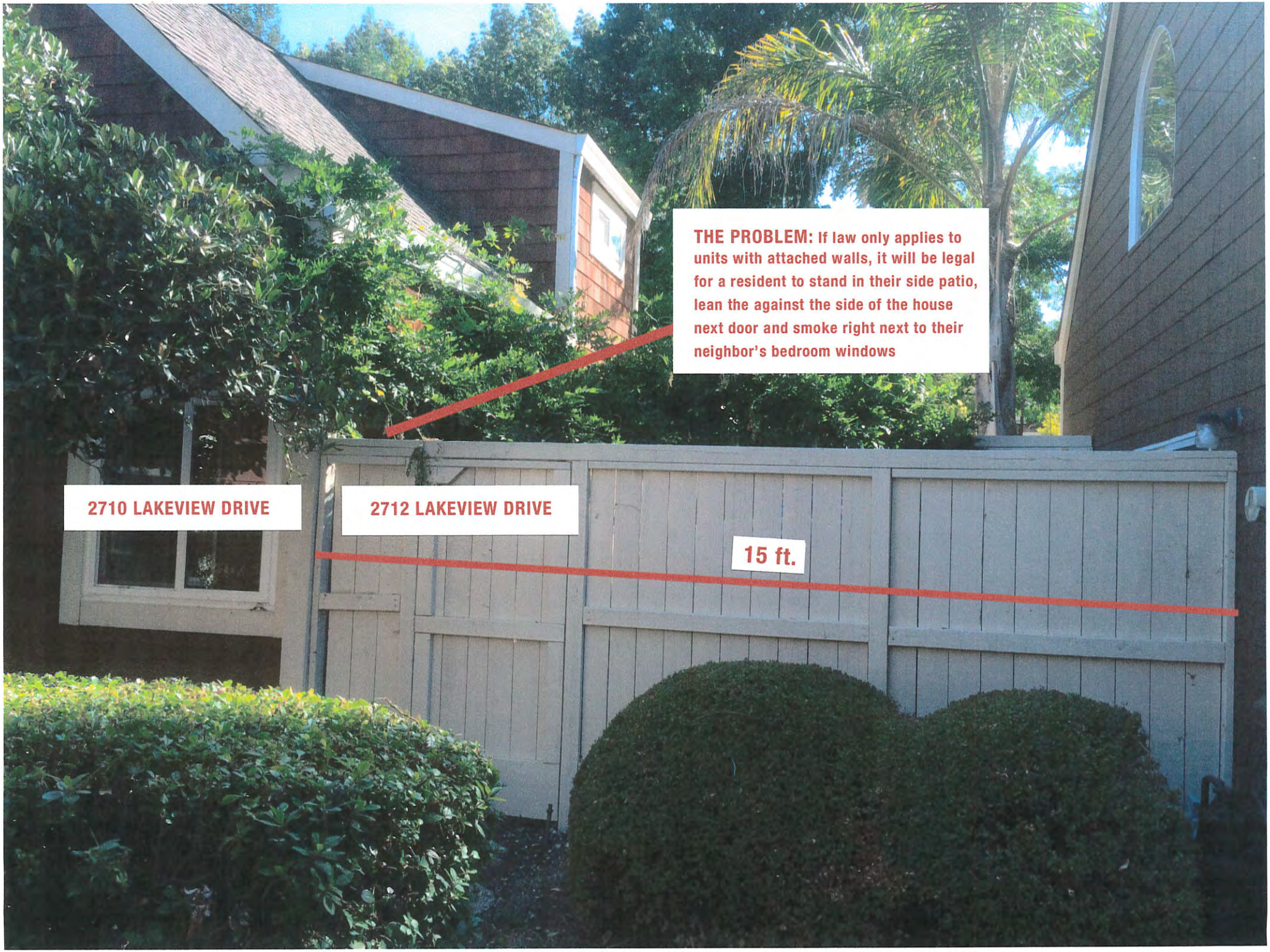
For all purposes within the jurisdiction of the City of Union City, nonconsensual exposure to smoke occurring on or drifting into residential property is a nuisance, and the uninvited presence of smoke on residential property is a nuisance and a trespass. Any person bringing a civil action to enforce the nuisance provision contained in this section need not prove an injury different in kind or in degree from injury to others to prove a violation of this chapter. (Ord. 740-10 § 2, 2010)

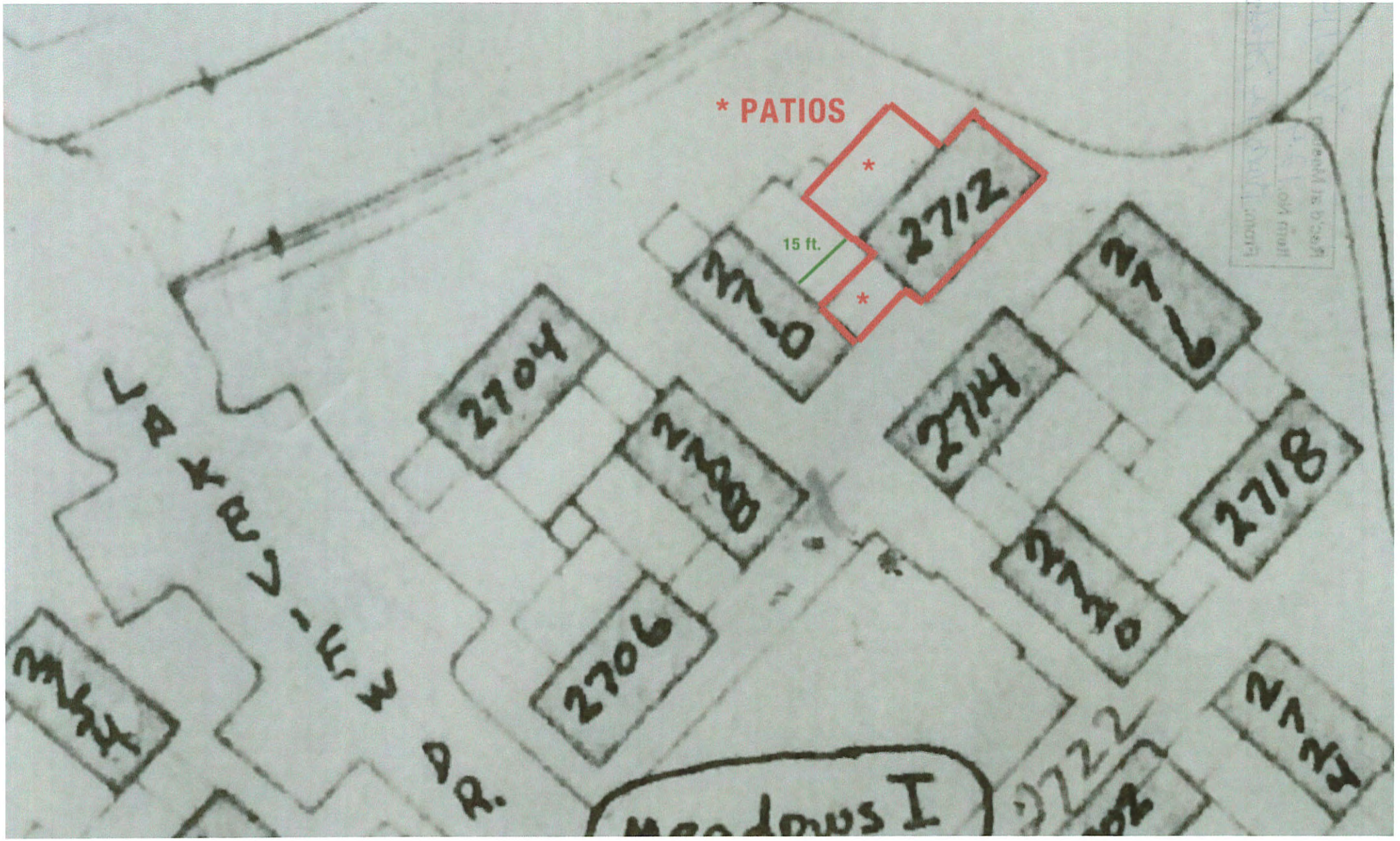
3. We also suggest increasing "reasonable distance" from twenty (20) feet in the current policy to twenty-five (25) feet for consistency with the updated Sonoma County Unincorporated policy as so much of Santa Rosa borders with the County.
Example below from Sonoma County:

"Reasonable Distance" means a distance that ensures that occupants of an area in which Smoking is prohibited are not exposed to Smoke created by smokers outside the area. This distance shall be a minimum of twenty-five (25) feet.

The Coalition for a Tobacco-free Sonoma County thanks all the councilmembers in advance for moving forward with a strong ordinance to protect the health of our residents by providing equal access to clean and healthy air where they live, work and play.

Michelle Escobar-McGarry, Chairperson of the Coalition for a Tobacco-free Sonoma County
Northern California Center for Well-Being
365 Tesconi Circle Ste. B
Santa Rosa, Ca 95401
(707) 575-6043 x 19
mmcgarry@nccwb.org


THE PROBLEM: If law only applies to units with attached walls, it will be legal for a resident to stand in their side patio, lean the against the side of the house next door and smoke right next to their neighbor's bedroom windows
2710 LAKEVIEW DRIVE
2712 LAKEVIEW DRIVE
15 ft.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LAKEVIEW DR.
Meadows I

ALLIANCE
PROPERTY MANAGEMENT
Professional Real Estate Management Lic. #01317582

Rec'd at Meeting 8/26/14
Item No. 12.4
From: Michelle Escobar-McGarry

August 26, 2014

To whom it may concern:

I am writing to express my support in concept for a non-smoking ordinance in multi-family housing. Our firm manages over 800 residential rental units in Sonoma County, with over 80% of those units in Santa Rosa. We care about the health and wellbeing of our residents, as well as maintaining the value of our client's properties.

The modification to current city ordinance should be crafted carefully so a landlord is not unjustly held liable for a tenant's failure to comply. We will actively engage tenants and make sure they are aware of the changes, but it will help to have the ordinance in place.

Additionally, the ordinance should include e-cigarettes and "all combustible material" as suggested in the staff report.

I encourage you to contact me if you have any questions. I am happy to be more involved in the discussion as this moves through the process of creating a permanent change.

Sincerely,

Jock McNeill, RMP
President/Broker
2014 Chapter President, North Coast Rental Housing Association
Past President, Marin and Sonoma Chapter, National Association of Residential Property Managers

SONOMA COUNTY
Asthma Coalition

August 25, 2014

Mayor Scott Bartley and members of the City Council
City of Santa Rosa
100 Santa Rosa Avenue
Santa Rosa, CA 95401

Dear Mayor Bartley and Council members,

The Sonoma County Asthma Coalition applauds the City of Santa Rosa for embarking on updating the city's anti-smoking ordinance to reduce harmful exposures of secondhand smoke. The Asthma Coalition has been a strong advocate for many years of stronger regulations to protect the health of Santa Rosa residents from harmful smoke exposures. We strongly support all of the six recommendations included in staff report, with particular emphasis on the importance of prohibiting smoking in multiunit housing and expanding outdoor areas where smoking is prohibited. We are very appreciative that the recommendations include electronic cigarettes, whose health impacts are unknown, and whose use among youth has doubled in one year, according to the CDC.

The Asthma Coalition supports all of the recommendations as follows:

1) Prohibit smoking in attached multifamily housing, including duplexes, apartments, and condominiums and any building that contain two or more attached residential units;
2) Eliminate any allowance for smoking in "recreational areas" and on City-owned recreational properties including parks;
3) Prohibit smoking at all City-owned properties including (but not limited to) office buildings, recreation centers, public safety facilities, parking garages, and parking lots; 4) Prohibit smoking at bus stops and within bus shelters;
5) Revise the definition of "smoking" in Chapter 9-20 to explicitly include use of electronic cigarettes, and evaluate the Zoning Code to determine if revisions are needed related to electronic cigarettes; and
6) Evaluate increasing the percentage of guest rooms within hotels and motels that must be smoke-free from 50% to 75%.

The Sonoma County Asthma Coalition thanks all the councilmembers in advance for moving forward with a strong ordinance to protect the health of our residents, especially those who are most vulnerable because they suffer from asthma or other lung diseases, or because they are low income and must live in multiunit housing.

In appreciation,

Shan Magnuson, Chair
Sonoma County Asthma Coalition

AMERICAN LUNG ASSOCIATION®
IN CALIFORNIA

August 25, 2014

Mayor Scott Bartley and members of the City Council of Santa Rosa
100 Santa Rosa Avenue
Santa Rosa, CA 95401

Dear Mayor Bartley and Council members,

The American Lung Association in California is enthusiastic about the City of Santa Rosa updating their tobacco control policy to strengthen protections from secondhand smoke exposure. The growing body of evidence about the harmful effects of exposure to secondhand smoke has grown exponentially in the eight years that have passed since the council last made changes to the city's tobacco ordinance in 2006 and Santa Rosa is positioned to benefit from lessons learned during that time.

In reviewing the August 26 Council Agenda Item 12.4 Smoking Regulation Update the Lung Association strongly supports 5 of the 6 recommendations being brought forth to council by the Community Development Department:

1) Prohibit smoking in attached multifamily housing, including duplexes, apartments, and condominiums and any building that contain two or more attached residential units;
2) Eliminate any allowance for smoking in "recreational areas" and on City-owned recreational properties including parks;
3) Prohibit smoking at all City-owned properties including (but not limited to) office buildings, recreation centers, public safety facilities, parking garages, and parking lots;
5) Revise the definition of "smoking" in Chapter 9-20 to explicitly include use of electronic cigarettes, and evaluate the Zoning Code to determine if revisions are needed related to electronic cigarettes; and
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We make three recommendations:

1. It would be our suggestion to broaden item *4) Prohibit smoking at bus stops and within bus shelters* to regulating smoking in "**service areas**." This would capture bus stops and within bus shelters in addition to other places where the public must line up to wait for services. This broader term would better align with a category in the State of Tobacco Control Report. Example below from Sonoma County ordinance:

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> "Reasonable Distance" means a distance that ensures that occupants of an area in which Smoking is prohibited are not exposed to Smoke created by smokers outside the area. This distance shall be a minimum of twenty-five (25) feet.

The American Lung Association thanks all the councilmembers in advance for moving forward with a strong ordinance to protect the health of our residents by providing equal access to clean and healthy air where they live, work and play.

Best regards,

Pam Granger
Advocacy Manager
American Lung Association in California
(707) 775-6045
Pam.granger@lung.org

Morris, Erin

From: Pam Granger <Pam.Granger@lung.org>
Sent: Friday, July 18, 2014 11:22 AM
To: _CityCouncilListPublic; Bartley, Scott
Cc: Regalia, Chuck; CMOffice
Subject: Coalition for a Tobacco-free Sonoma County, the Sonoma County Asthma Coalition and American Lung Association oppose a new e-cigarette store downtown
Attachments: 14-07-12 ALA opposes E-Cig 101 Digital Cigarettes application.docx

Dear Mayor Bartley and Council Members – Below is your copy of a letter sent Monday to the Community Development Department in opposition to a new retail, wholesale and online sale electronic cigarette shop. I know we sound like a broken record, however the Coalition for a Tobacco-free Sonoma County, the Sonoma County Asthma Coalition and our community partners are concerned that, in addition to traditional smoke/drug paraphernalia shops, electronic cigarette and hookah shops are slipping unnoticed into prime downtown and youth sensitive locations. The longer you wait to discuss this growth of locations for sales of addicting products, the harder it will be to shape the city in a more healthy direction both physically and economically. It doesn't matter how the nicotine is delivered, the end result is addiction-something we know you don't support. Check out the new Tobacco Free Kids report on how the tobacco industry has made cigarettes more additive and more attractive – they are in the electronic nicotine product business using their unregulated marketing
expertise. http://www.tobaccofreekids.org/content/what_we_do/industry_watch/product_manipulation/2014_06_19_DesignedforAddiction_web.pdf If you have time, go to section on nicotine starting on page 11. "The tobacco industry's own documents show that the tobacco companies have spent billions of dollars studying the effects of nicotine and precisely how to control the delivery and amount of nicotine to ensure that smokers become addicted and stay addicted. The documents demonstrate that they have known for decades that the key to their business is creating and sustaining dependence on nicotine, and they have purposely designed their products to do this effectively and efficiently." You don't have to wait to take action – you can create a moratorium on new outlets giving you time to investigate these issues. Thanks for thinking about it. Pam

AMERICAN LUNG ASSOCIATION®
IN CALIFORNIA

July 12, 2014

Eric Gage, City Planner
Community Development Department
City of Santa Rosa
100 Santa Rosa Avenue, Room 3
Santa Rosa, CA 95402

Re: E-Cig 101 Digital Cigarettes, 555 Mendocino Ave. Santa Rosa
Notice of Application: File Number: CUP 14-048

Dear Mr. Gage,

The American Lung Association in California is writing to recommend that the City of Santa Rosa reject the application for an electronic cigarette store at 555 Mendocino Avenue planning to offer **retail, wholesale and online sale** of electronic cigarettes and vaporizers for liquid nicotine for three reasons.

1. There currently exists an overconcentration of smoke/head/ e-cig shops, including **Citrus Smoke Shop** at 608 Mendocino and the **X Toxic Vapor Lounge** a mere four blocks away at 730 Third Street. There is no public convenience or necessity warranting the applicant's business.
2. This location proximity to youth sensitive locations such as the **Santa Rosa Plaza** and **Courthouse Square** and in a "prime corner location", according to the realtor's ad.
3. Adding one more store selling incredibly addicting nicotine is counter to the Council's interest in their **Goal 6: Commit to Making Santa Rosa a Healthy Community.**

Once again we call on the Santa Rosa City Council to declare a moratorium on approving any additional tobacco/smoke/e-cigarette shops until there is further discussion as to setting parameters for regulating their concentration and location. Right now, there are no zoning restrictions to limit the number of tobacco retailers or their location. Unfortunately, this means that a new tobacco/e-cigarette retail outlet can be located near schools, playgrounds, youth centers, or anywhere that youth gather for activities.

Why should you care?

- As was stated in the recent staff report to the Sonoma County Board of Supervisors, the use of e-cigarettes and other electronic nicotine delivery devices is a rising public health concern.
- The addictive nature of nicotine, its health effects (a neurotoxin listed in the Proposition 65 *Chemicals Known to the State to Cause Cancer and Reproductive Toxicity*), and its growing use among youth through electronic smoking devices is especially concerning.
- An increasing number of youth: A 2013 report by the Centers for Disease Control and Prevention (CDC) found that the percentage of high school students who had ever used e-cigarettes more than doubled in one year's time, going from 4.7 percent in 2011 to 10 percent in 2012.
- A factor that is contributing to increased use among youth is that these products are sold in an assortment of flavors that are attractive and targeted to youth. These include such flavors as bubble gum, chocolate, grape, and strawberry.
- A prime corner location downtown is the wrong place for this business.

The American Lung Association supports restricting youth access to tobacco and other nicotine delivery devices as a way to prevent underage use. Not only is there currently a high concentration of outlets in the downtown core, but studies and common sense dictate that these retail stores should not be located in close proximity to where children frequent such as malls, schools or parks.
We provide free technical assistance to cities and counties and look forward to working with Santa Rosa again.
Sincerely,

Pamela Granger| Advocacy Manager - North Coast
American Lung Association in California
(707) 775-6045 office
(866) 515-4625 e-fax
(707) 775-8185 cell
pam.granger @lung.org | http://www.lung.org/california

CC: Santa Rosa City Council
Sonoma County Department of Health Services