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March 5, 2014

To: Members of the Senate Committee on Judiciary and Labor
From: Senator Glenn Grothman
Re: Senate Bill 440

Electronic smoking devices are smoking cessation tools that allow the smoker to relieve his or her cravings by emulating the act of smoking while breathing vapor, which may or may not contain nicotine (depending on the product). This gives them the illusion of smoking without the extra health risks, and in fact has helped many people quit smoking entirely.

Current state law forbids smoking in most enclosed public areas. Because the definition of "smoking" includes cigarettes, cigars, pipes, and "any other lighted smoking instrument," smokeless products like electronic smoking devices are not mentioned and therefore not specifically exempted.

This legislation clearly exempts "inhaling or exhaling vapor or a vaporized solution" from electronic devices that do not contain tobacco from the definition of "smoking" so that smokers can be free to use this successful cessation tool wherever they would like.

I have heard from many consumers that would like the freedom to use these products in all spaces. I have also spoken to bar and restaurant owners that would like to allow individuals to use these products in their establishments. Many of these establishments currently allow individuals to use vaping products and the owners and employees do not receive complaints from any of their other customers.

Please join me in supporting this legislation that will help individuals stop smoking and allow them to use electronic smoking devices freely without worrying about violating state law.

My name is Kristin Noll-Marsh. I am 46 years old, a Wisconsin resident and a former smoker. I have also served as the volunteer vice president of CASAA, the Consumer Advocates for Smoke-free Alternatives Association, for the past 4 ½ years.

CASAA is a non-profit 501(c)(4), all-volunteer organization with a grassroots membership of thousands of individuals from all walks of life. We are a consumer-focused organization, not a trade association.

I strongly urge this committee to vote "yes" on SB 440. This is a landmark bill that will set Wisconsin apart from the knee-jerk legislation currently occurring across the country. I truly believe that the day will come when those attempting to restrict access to and use of e-cigarettes will be forced to explain why they treated a powerful tool, made to reduce the health risks of smoking, as though it was a public health risk - without any science to back it up. You have the opportunity to make Wisconsin the leader in supporting tobacco harm reduction policies, by protecting an important incentive for smokers to switch to products that can reduce their health risks by 99%. Banning public use of these products only reduces their appeal to adult smokers.

This is a photo of my family. Four of the six people pictured were smokers, who now no longer smoke because of e-cigarettes. My youngest daughter, born when I was 39 years old, is the reason why I didn't want to die early from smoking-related diseases. Unfortunately, that still didn't get me to actually quit. Although I had quit while pregnant and nursing, I still started smoking again. I thought I would smoke until I died, but then I saw an e-cigarette. I bought it on a whim - and that is very important for you to hear – I wasn't trying to quit smoking. Gums and patches only work if you are trying to quit and if you want to quit. I bought that e-cigarette because it was less expensive than smoking, I could still use it when the smoking ban took effect and I could eliminate my exposure to harmful cigarette smoke. The effectiveness and safety of FDA-approved gums and patches was meaningless to me, because I wasn't planning to quit smoking. Yet here I am today, smoke-free for nearly five years.

in-law even quit using the e-cigarette. Ironically, my adult sons didn't start using an e-cigarette until their smoking friends started using them. Sadly, it seems smoking is still considered to be more "cool" than e-cigarettes in this 18 to 25 year old group.

My story may be anecdotal and not scientific, but I can tell you that surveys of thousands of CASAA members tell the same story. Thousands of people who didn't intend to quit smoking, yet did when they tried an e-cigarette. It may not be the results of a controlled study in a lab, but it is happening in the real world, every day. This is not something that should be easily dismissed.

I was never a political person. I didn't get involved in activism until I started using an e-cigarette and saw all of the misinformation being presented to lawmakers by organizations such as the American Lung Association and American Cancer Society. Frankly, I was shocked that these organizations were coming out against e-cigarettes rather than encouraging their use. That is how I came to be involved with CASAA. I wanted people to know the truth.

Today you may hear a lot of statistical and scientific claims being made, but I can guarantee that you will not hear the whole truth from many of those public health organizations. I've told you of my personal experience, but as a CASAA representative, I ask for just a few more minutes of your time to tell you important facts that you won't hear from public health organizations today. Otherwise, please refer to my written testimony provided.

Since CASAA's founding in 2009, we have educated the public and increased awareness about the benefits of reduced harm alternatives to smoking, including e-cigarettes. We also encourage responsible legislative policy designed to improve public health by recognizing that smoke-free nicotine-containing products are inherently far less dangerous than smoking. That is why we support this bill.

You may have heard that we don't know what is in e-cigarettes or conversely, that harmful chemicals and carcinogens have been found in e-cigarettes, including a chemical found in anti freeze. However, the carcinogens detected were at the same harmless levels as found in FDA-approved nicotine gums and patches. The so-called anti freeze chemical had been detected in only one of the samples tested by the FDA and that it was at a level so low that an adult would have to drink over half a gallon of the liquid for it to be toxic.

Over 60 chemical studies have been done and those studies were reviewed by Dr. Igor Burstyn, of Drexel University's School of Public Health, who concluded in a peer-reviewed and published study that *"there is no evidence that [e-cigarette use] produces inhalable exposures to contaminants of the aerosol that would warrant health concerns by the standards that are used to ensure safety of workplaces....Exposures of bystanders are likely to be orders of magnitude less, and thus pose no apparent concern."*

There are unsubstantiated and vague concerns that e-cigarettes used in public may cause confusion and complicate enforcement of smoking bans, but there is no evidence of this happening. I have been using my device in public since 2009 and have never had anyone confuse it with smoking. No one has ever been bothered by the vapor either. Any time I've been approached, I'm asked "Is that one of those e-

cigarettes?" and "Where can I get one?" At a 2013 hearing in New York City, regarding an ordinance to include e-cigarette use in the Smoke-free Air Act, the New York City Hospitality Alliance testified that e-cigarettes have not become an issue of concern among association members. Using e-cigarettes inside has also reduced noise and cluttering on sidewalks caused by traditional cigarette smokers in front of some bars and clubs.

It sometimes seems that what e-cigarettes look like, rather than their actual health effects, are more of a concern to some. That e-cigarettes will send the wrong message to youth and somehow "renormalize" or even glamorize smoking. But that is the exact opposite of what we think will happen. Seeing e-cigarettes in use in public is not sending a message that smoking is OK, but instead sends the message that someone is choosing to not smoke. My 12 year old step-daughter's mother smokes and my daughter tells her all of the time that she should get an e-cigarette instead. If my 12 year old child can make that distinction, so can any child. The more our youth see e-cigarettes in use, the less they will see people actually smoking.

Although youth e-cigarette use (which includes even trying an e-cigarette only once) doubled from 1.1% to 2.1% nationally between 2011 and 2012, youth smoking and tobacco use actually declined during that same period. Youth tobacco use is at a historical low.

There is no evidence that e-cigarettes are leading youth to smoke conventional cigarettes, because the youth surveys reported by the CDC didn't ask smoking youth which they used first. However, we do know that the survey showed that less than 1% (0.63%) of the students surveyed had tried e-cigarettes without having smoked previously.

Then there are the flavors. Obviously, e-cigarette companies are targeting youth with sweet flavors, because adult smokers wouldn't want them. Of course, FDA-approved nicotine gums and lozenges, which are clearly marketed to adult smokers, don't come in sweet flavors such as cherry, orange, fruit chill, cinnamon and mint.

As a 46 year old former smoker, I am here to tell you that if there weren't e-cigarette flavors like peach and chocolate available, I'd still be smoking today. Incidentally, tobacco companies only started selling e-cigarettes in 2012 and none of the tobacco company e-cigarettes are available in bubblegum or other candy flavors.

There may be things you hear today that I haven't mentioned and I welcome you to call on me if you would like to know all of the facts. For the health of the nearly 900,000 adult smokers in Wisconsin, most of who will not try to quit smoking anytime soon, I urge you to vote yes on SB 440.

Thank you.

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UW-CTRI
UNIVERSITY OF WISCONSIN
Center for Tobacco Research & Intervention

A Summary of the Science Regarding Electronic Cigarettes

University of Wisconsin Center for Tobacco Research and Intervention (UW-CTRI)
March 4, 2014

Background: Electronic cigarette ("e-cigarette") use ("vaping") has increased dramatically in recent years, and use among American youth doubled between 2011 and 2012[1]. While there is limited scientific evidence regarding the health effects of e-cigarettes for individuals, most people agree that an *individual who totally switches* from combustible (burnt) cigarettes to e-cigarettes probably reduces his/her health risks. But, most people using these products *don't totally switch* – in fact, the way most people use e-cigarettes is *in addition* to combustible cigarettes[2].

There is much we don't know about e-cigarettes, including:

1) **E-Cigarettes have not been proven as a safe product for the user or those around the user:**
   - They quickly affect the respiratory system – even after 5 minutes, some adverse effects on the lungs have been reported[3].
   - It is unclear whether e-cigarette use results in environmental exposure to nicotine and other chemicals.

2) **The content of e-cigarette vapor is unknown:**
   - They are markedly heterogeneous products, with over 250 brands on the market, many of them manufactured in China and other foreign sites with no regulation.
   - Ingredients, flavors, and amount of nicotine delivered vary widely across brands.

3) **The FDA has not yet reviewed the safety of e-cigarette use:**
   - Such an FDA review will provide detailed data on e-cigarettes.

4) **E-cigarettes have not been proven as effective as a smoking cessation device:**
   - There is insufficient evidence regarding both the long- and short-term effects of e-cigarettes on quitting. Findings thus far have been mixed and modest.
   - E-cigarettes have not been approved by the FDA for smoking cessation.
   - There is rampant dual use of e-cigarettes with combustible cigarettes[4].
     - About 75% of e-cigarette users ("vapers") report they are also smokers (daily + non-daily smokers).
     - About 12% are former smokers.
     - About 3% are never smokers.

5) **The combination of cessation counseling ("coaching") and FDA-approved medications has been endorsed by the United States Public Health Service[5] as both safe and effective in helping smokers quit:**
   - Coaching + medication = quit rates that are 4 to 5 times higher than quitting on your own. If tobacco users want to quit, they should talk to their doctor or call

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1-800-QUIT NOW for free help and FDA-approved medications from the Wisconsin Tobacco Quit Line.

6) **One of the most effective ways to reduce tobacco use is to stop young people from ever starting:**
   - The added sweet flavoring and aggressive marketing of e-cigarettes could entice children to use them. The adolescent brain is exquisitely sensitive to the addictive properties of nicotine – a product delivered by e-cigarettes. As a result, there is a concern that e-cigarettes may serve as a "gateway drug" for youth to lifelong nicotine addiction and the use of deadly combusted cigarettes. The United States Centers for Disease Control recently published data showing rapid growth in e-cigarette use among young people within the last two years[1].
   - The United States Surgeon General has concluded that nicotine can be as difficult to quit as heroin or cocaine[6].

7) **Allowing e-cigarette use indoors runs counter to the overwhelming trend nationwide:**
   - 9 states and 108 municipalities, including Chicago, do not allow e-cigarette use where tobacco is banned[7].
   - Only one state, Utah, allows e-cigarette use despite a smoking ban, and that has a sunset date in 3 years.

Conclusion: Given these substantial concerns, the lack of data, and ongoing research that should clarify these issues over time, a March 2014 scientific review by the UW-CTRI concludes that there are substantial public health concerns regarding indoor e-cigarette use. As a result, the UW-CTRI concludes there is not sufficient scientific evidence to support or recommend e-cigarette use indoors.

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The New York Times | http://nyti.ms/1kVMEOm

BUSINESS DAY | THE NEW SMOKE

E-Cigarettes, by Other Names, Lure Young and Worry Experts

By MATT RICHTEL MARCH 4, 2014

SAN FRANCISCO — Olivia Zacks, 17, recently took a drag of peach-flavored vapor from a device that most people would call an e-cigarette.

But Ms. Zacks, a high school senior, does not call it that. In fact, she insists she has never even tried an e-cigarette. Like many teenagers, Ms. Zacks calls such products "hookah pens" or "e-hookahs" or "vape pipes."

These devices are part of a subgenre of the fast-growing e-cigarette market and are being shrewdly marketed to avoid the stigma associated with cigarettes of any kind. The products, which are exploding in popularity, come in a rainbow of colors and candy-sweet flavors but, beneath the surface, they are often virtually identical to e-cigarettes, right down to their addictive nicotine and unregulated swirl of other chemicals.

The emergence of e-hookahs and their ilk is frustrating public health officials who are already struggling to measure the spread of e-cigarettes, particularly among young people. The new products and new names have health authorities wondering if they are significantly underestimating use because they are asking the wrong questions when they survey people about e-cigarettes.

Marketers of e-hookahs and hookah pens say they are not trying to reach young people. But they do say that they want to reach an audience

head of sales and marketing for Romman Inc. of Austin, Tex., which operates several websites that sell hookahs as well as e-cigarettes and e-hookahs. "A lot of the difference is branding."

Sales of e-hookahs have grown "exponentially" in the last 18 months, Mr. Querbach said.

Public health authorities worry that people are being drawn to products that intentionally avoid the term "e-cigarette." Of particular concern is use among teenagers, many of whom appear to view e-cigarettes and e-hookahs as entirely different products when, for all practical purposes, they are often indistinguishable.

Indeed, public health officials warn that they may be misjudging the use of such products — whatever they are called — partly because of semantics. A survey by the Centers for Disease Control and Prevention found that 10 percent of high school students nationwide said that they had tried e-cigarettes in 2012, double the year before. But the C.D.C. conceded it might have asked the wrong question: Many young people say they have not and will not use an e-cigarette but do say they have tried hookah pens, e-hookahs or vaping pens.

The C.D.C. is sending a tobacco-use survey to 20,000 students nationwide that asks about e-cigarette experimentation but does not identify the devices by other names. The state of California, through a nonprofit partner called WestEd, is asking virtually the same question of 400,000 students.

Brian King, senior adviser to the Office on Smoking and Health at the C.D.C., said the agency was aware of the language problem. "The use of hookah pens could lead us to underestimate overall use of nicotine-delivery devices," he said. A similar problem occurred when certain smokeless tobacco products were marketed as snus.

Other health officials are more blunt.

"Asking about e-cigarettes is a waste of time. Twelve months ago, that was the question to be asking," said Janine Saunders, head of tobacco use prevention education in Alameda County in Northern California.

"Asking about e-cigarettes is a waste of time. Twelve months ago, that was the question to be asking," said Janine Saunders, head of tobacco use prevention education in Alameda County in Northern California.

In October, Ms. Saunders convened a student advisory board to discuss how to approach "e-cigs." "They said: 'What's an e-cig?' " Ms. Saunders recalled, and she showed what she meant. "They said: 'That's a vape pen.' "

Health officials worry that such views will lead to increased nicotine use and, possibly, prompt some people to graduate to cigarettes. The Food and Drug Administration is preparing to issue regulations that would give the agency control over e-cigarettes, which have grown explosively virtually free of any federal oversight. Sales of e-cigarettes more than doubled last year from 2012, to $1.7 billion, according to Wells Fargo Securities, and in the next decade, consumption of e-cigarettes could outstrip that of conventional cigarettes. The number of stores that sell them has quadrupled in just the last year, according to the Smoke Free Alternatives Trade Association, an e-cigarette industry trade group.

The emergence of hookah pens and other products and nicknames seems to suggest the market is growing well beyond smokers. Ms. Zacks was among more than 300 Bay Area high school students who attended a conference focused on health issues last month on the campus of the University of California, Berkeley. Many students talked about wide use of e-hookahs or vaping pens — saying as many as half of their classmates had tried one — but said that there was little use of e-cigarettes.

Ms. Zacks said the devices were popular at her high school here. "E-cigarettes are for people trying to quit smoking," she said, explaining her understanding of the distinction. "Hookah pens are for people doing tricks, like blowing smoke rings."

James Hennessey, a sophomore at Drake High School in San Anselmo, Calif., who has tried a hookah pen several times, said e-hookahs were less dangerous than e-cigarettes. He and several Drake students estimated that 60 percent of their classmates had tried the devices, that

and flavor," said Andrew Hamilton, a senior from Drake.

Actually, it is possible for e-cigarettes or e-hookah devices to vary in nicotine content, and even to have no nicotine. Mr. Querbach at Romman said that 75 percent of the demand initially was for liquids with no nicotine, but that makers of the liquids were expanding their nicotine offerings. Often, nicotine is precisely the point, along with flavor.

Take, for example, the offerings of a store in San Francisco called King Kush Clothing Plus, where high school students say they sometimes buy their electronic inhalers. On a counter near the back, where tobacco products are sold, are several racks of flavored liquids that can be used to refill e-cigarettes or hookah pens. The flavors include cinnamon apple, banana nut bread, vanilla cupcake, chocolate candy bar and coconut bomb. They range in nicotine concentration from zero to 24 milligrams — about as much as a pack of 20 ordinary cigarettes — but most of the products have some nicotine. To use the refills, it is necessary to buy a hookah pen, which vary widely in price — around $20 and upward.

It is also possible to buy disposable versions, whether e-cigarettes or hookah pens, that vary in nicotine content and flavor. At King Kush, the Atmos ice lemonade-flavored disposable electronic portable hookah promises 0.6 percent nicotine and 600 puffs before it expires.

Emily Anne McDonald, an anthropologist at the University of California, San Francisco who is studying e-cigarette use among young people, said the lack of public education about the breadth of nicotine-vapor products was creating a vacuum "so that young adults are getting information from marketing and from each other."

"We need to understand what people are calling these before we send out large surveys," Dr. McDonald said. Otherwise the responses do not reflect reality, "and then you're back to the beginning."

A version of this article appears in print on March 5, 2014, on page A1 of the New York edition with the headline: E-Cigarettes, by Other Names, Lure Young and Worry Experts.

Hello, my name is Don Muehlbauer, I am here to speak for the passage of SB440. As background, I am not and have never been a smoker, nor a vaper, and don't plan to ever become one. I hold both Engineering and Business degrees from the University of Wisconsin – Milwaukee, and I am the founder of the second largest US-Based manufacturer of flavored nicotine solutions, or eliquid, used in electronic cigarettes. We are based in Wauwatosa, WI, were the first ISO9001:2008 quality certified eliquid laboratory in the USA and manufacture for Durasmoke and several other national and international brands.

SB440 is not about whether electronic cigarettes are effective for smoking cessation (attached referenced medical studies say they work better than any other alternative for cessation) or whether they are perfectly safe (nothing is perfectly safe, not the caffeine in your coffee or the metals in your antiperspirant).

SB440 is about whether users of electronic cigarettes should be "quarantined" from indoor areas where smoking is banned, so it's about whether electronic cigarettes are as dangerous for innocent bystanders as regular cigarettes are.

We fully support upcoming FDA regulations about ecig safety and look forward to meeting the future requirements. In the meantime, we believe that enough scientific data has been collected to answer the appropriate question for SB440... not are electronic cigarettes completely safe, but how do they compare to tobacco cigarettes for bystanders... the "2nd hand vapor" issue.

Before looking at the scientific data, it's important to understand the basic difference between smoke from a tobacco cigarette and vapor from an electronic cigarette. The first thing to note is that smoke is a product of combustion (fire), and the related chemical reactions that occur due to that fire. One of the major bad things in tobacco smoke is carbon monoxide... a result of burning most anything. The carbon monoxide doesn't come from the tobacco, it's a result of a chemical reaction caused by combustion/fire. According to the American Cancer Society website at: http://www.cancer.org/cancer/cancercauses/tobaccocancer/questionsaboutsmokingtobaccoandhealth/questions-about-smoking-tobacco-and-health-cancer-and-health :

> *The smoke from these products is a complex mixture of chemicals produced by the burning of tobacco and its additives. The smoke is made up of more than 7,000 chemicals, including over 60 known to cause cancer (carcinogens).*

The GREAT news about electronic cigarettes is a familiar saying... but backwards, "where there is no fire, there is no smoke". In an electronic cigarette, a flavored nicotine solution is heated until it vaporizes, so what appears to be smoke is actually a condensing liquid vapor. More GREAT news about electronic cigarettes is that just heating a liquid until it's a vapor is not combustion, so the liquid becomes a vapor, but it's chemical composition doesn't change. There is no chemical reaction.

So what's in a typical eliquid... Well, we manufacture the stuff, so let me tell you one of our actual recipes, for mint flavored eliquid:

- First, there are only 3 or 4 ingredients
- Ingredient one/two is used to make the vapor, either Propylene Glycol or Vegetable Glycerin or a mixture of the two. These are GRAS, or Generally Recognized As Safe, by the FDA. In fact, the scary sounding Propylene Glycol is used in many, many foods, flavorings, and is the chemical used in Fog Machines on stage to make stage "smoke"
- Ingredient three is Flavoring. We use natural flavorings wherever possible, our mint flavor uses natural Spearmint Oil.
- Ingredient 4 is nicotine. We sell 5 nicotine levels, from 0% nicotine to 2.4% nicotine (about the same as a standard cigarette). There is no USA standard, but in the UK, nicotine is not considered a toxin unless it's over 7.5%. Medical studies show the effects of just nicotine, without all the other stuff in smoke, is fairly comparable to caffeine.

I know some of the medical folks say more studies are necessary, that we are inhaling more of the "generally safe" ingredients in ecig vapor than we are in normal daily life... I don't believe that's true. As a person with allergies myself, I'd say that anyone who works 8 hours a day at Bed Bath and Beyond or at a Yankee Candle shop is inhaling much more of these same ingredients/day than any ecig user... and I don't believe there's any legislation pending related to inhalation of these same ingredients from other sources.

Next, let's look at actual scientific data on the topic.

First, we've received feedback from MANY, MANY customers, that their medical professionals, including dentists, GP docs, oncologists, surgeons, and even pediatricians, ALL prefer they use electronic cigarettes, if the other option is to use a tobacco cigarette. Details are an attachment to my speech for brevity, please review if you are interested. In short, I have NEVER heard of any medical professional telling a patient... You know, until we know more about these ecig things, I really think you'd be better off smoking tobacco cigarettes...

Now let's look at just a few of the medical studies that have been done, that show the use of electronic cigarettes and the resulting 2nd hand vapor, are MUCH safer than smoking.

STUDY #1

Publisher: European Society of Cardiology

Date: 8/25/2012

Topic: Cardiovascular Disease Prevention - Risk Assessment and Management

Findings:

- Smoking is the most preventable risk factor for cardiac and lung disease and is expected to cause 1 billion deaths during the 21st century.

- Since heart disease is the main cause of morbidity and mortality in smokers, with 40% of deaths in smokers due to coronary artery disease alone, the research team decided to perform the first clinical study of the acute effects of electronic cigarettes on cardiac function.
- The researchers found that smoking one tobacco cigarette led to significant acute myocardial dysfunction but electronic cigarettes had no acute adverse effects on cardiac function. Smoking a tobacco cigarette had important hemodynamic consequences, with significant increases in systolic and diastolic blood pressure and in heart rate. In contrast, electronic cigarettes produced only a slight elevation in diastolic blood pressure.

HOW THIS RELATES TO SB440 – For both the vaper and the 2nd hand vaper – minimal cardiac effect (the major problem with tobacco)

STUDY #2

PUBLISHER: Tobacco Control

Date: published Online first 3/6/2013

Topic: Levels of selected carcinogens and toxicants in vapour from electronic cigarettes

Findings:

- The aim of this study was to screen e-cigarette vapours for content from four groups of potentially toxic and carcinogenic compounds, Cabonyls, volatile organic compounds, nitrosamines and heavy metals
- We found that e-cigarette vapours contained some toxic substances. The levels of the toxicants were 9 to 450 times lower than in cigarette smoke, and were, in many cases, comparable with trace amounts found in the reference products.

HOW THIS RELATES TO SB440 = the vapor from an electronic cigarette is between 10x safer to 450x safer than tobacco smoke, but certainly much safer than tobacco smoke

STUDY #3

Publisher: American Journal of Preventative Medicine

Date: April, 2011

Topic: Electronic Cigarettes as a Smoking Cessation Tool

Findings:

- The primary finding was that the 6-month point prevalence of smoking abstinence among the e-cigarette users in the sample was 31.0% (95% CI=24.8%, 37.2%). A large percentage of respondents reported a reduction in the number of cigarettes they smoked (66.8%) and almost half reported abstinence from smoking for a period of time (48.8%). Those respondents using e-cigarettes more than 20 times per day had

a quit rate of 70.0%. Of respondents who were not smoking at 6 months, 34.3% were not using e-cigarettes or any nicotine-containing products at the time.

HOW THIS RELATES TO SB440 – Use of electronic cigarettes is the best smoking cessation tool available today, their use directly relates to lower total nicotine use for everyone, and should be encouraged.

Last, An opinion piece by one pediatrician, but I think very interesting...

Publisher: BMJ, formerly known as the British Medical Journal

Date: 10/7/2013

Topics: E-cigarettes: good for children?

Findings:

- 'The main untapped potential of e-cigarettes, however, might not be in treatment of the minority of smokers seeking help with quitting, but rather as a safer consumer product for use by smokers in general.' One could add that they may also be a safer product for those who share the same space as smokers. From a pediatrician's perspective, e-cigarettes would appear to be an undeniably good thing: virtually no harmful substances are released into the environment, and it may be that parents who cannot shake off their nicotine addiction could improve their children's health by switching. Interestingly, in this study, a third of those who failed to give up tobacco completely continued to use e-cigarettes alongside the real thing. As so many parents are unable to quit completely, perhaps we could persuade some to use only e-cigarettes when around their children.

Finally, I would like to thank the sponsors of both bills AB762 and SB440 – Representative John Jagler, Representative David Murphy, Representative Craig, Representative Kleefisch, and especially Senator Glen Grothman, for sponsoring bills that use the currently available science and common sense to help their constituents.

Thank you.

ATTACHMENT - Customer and Medical Professional Stories

My first story is about Mike, a 24 year old co-worker, who came into my office in 2009 to show off "the new toy he just bought". It was an electronic cigarette. Mike had been using it for about 2 weeks, and had noticed that he was breathing better and wasn't as winded at work as he had been. Mike was the reason we got into the electronic cigarette business.

Next, I'd like to tell you about Tom, a piano player in Florida. Tom went to his dentist for a normal cleaning/checkup. Wiithout prompting, his dentist told him he could see he quit smoking. He hadn't, he had switched to vaping.

My next story is about Jacquiline from California. Jacquiline's doctor told her he'd prefer she not smoke, but if she must, to use an electronic cigarette, and to buy her eLiquid from us, an American eLiquid manufacturer. (I don't personally know Jacquiline's doctor, but I assume he is also a customer of ours.)

Next, I'd like to tell you about a personal friend of mine, Tony from West Allis, Wisconsin. Tony is an elderly gentleman, a very heavy smoker and has some other very serious issues. I met Tony in person in 2010, as he doesn't have access to the internet, and I personally delivered his first electronic cigarette and eliquid. We get together at least on the phone every month or so. I can't say this is absolute medical truth, but I know if Tony were here, he'd tell you, and he would believe, that his electronic cigarette saved his life, that he wouldn't be here without it.

Next, I'd like to tell you an anonymous story, as it's about the father of one of our employees, who was a very heavy smoker. His son convinced him to try an electronic cigarette, and he started out with a very high level of nicotine, higher than traditional cigarettes. Over time, his son moved him down from our highest, to regular, to light, nicotine levels, without every telling the father that anything was changing. The father didn't notice, and his nicotine usage was reduced by 2/3.

Last story, an email from Julie in Florida, I will paraphrase, but you can to see her entire email in print:

> *You want to hear motivating? Here's our story... My entire family smokes... well smoked. From my grandparents, down to my parents and siblings and all of my aunts and uncles... most of my cousings. As of 2004, for the previous 38 years, every single person that passed away in my family had been diagnosed with cancer. My father died from lung cancer at the age of 64. No cancer death has been from the same type of cancer either. Only one person survived longer than 3 months after diagnosis (18 months to be exact). Not one heart attack, stroke, accident or any natural cause of death. They were all cancer related. Apparently my gene pool is riddled with cancer receptors.*
>
> *In 2004, at the age of 36, I was diagnosed with cancer. Stage 3, very aggressive. With the knowledge of all of the cancer deaths in my family, and the short time between diagnosis and death, I still couldn't quit smoking (although I did cut back quite a bit). No one in my family could*

quit either. As shocked as we all were with my diagnosis, the cigarettes seemed to be stronger than our will to live a long life. Two years after I beat my battle with cancer, I lost my mom to a very rare form of cancer. Can you guess if any of us quit then? Nope, not a one of us. You wouldn't know it by our idiotic actions, but we are not an uneducated bunch of people.

Fast forward to this year. We all continued to smoke like chimneys. I have my ritual follow up with my oncologist. We have a problem. Seems to be that a new cancer is trying to pry it's way into my life and I need to have surgery to get rid of it. My oncologist starts with the finger wagging again and tells me that I HAVE TO QUIT SMOKING. Uh huh, ok, will do. I schedule my surgery to take place in three weeks and I leave the office... and have a cigarette. Stupid is as stupid does.

Two days later I am at my sisters when her step daughter introduces us to an ecig. Novel I think. It's a Gen Y thing. But we all tried it anyway and were kind of impressed. My brother gets there and he actually had bought one already. Now I'm REALLY impressed. Remember, he is the 2 – 3 pack a day, 30 year, never gonna quit and you can't make me. He was the first to order from you. He got his order within a couple of days and came over to see us. We tried his Ego with MegaCartomizer and it was a done deal. We all ordered from you and as soon as we got our kit, we quit smoking----immediately----without even trying. To be honest, everybody did this because regular cigarettes were just too expensive anymore. Nobody, except for me (just a little) did this with the intention of completely quitting. Just trying to supplement our expensive habit with something less expensive intermittently. Anyway....

Three week pass and I go in for surgery. It was to take an hour, but after 15 minutes I was done. Surgeon comes out and tells my husband that most of the cancerous cells were gone prior to the actual surgery. He said if what he saw that day was what he had seen the first day, there wouldn't have been a surgery, just a wait and see approach. My husband tell s him I quit smoking three weeks prior, except for the ecig. He was happy to hear it and said that smoking the ecig was fine with him and probably has saved my life in the long run. Oh, and he happens to be my sister in laws oncologit too. Not only does this garbage run IN my family, it runs OUT of my family and into others as well! When we told the oncologist that my sister in law had also quit he said "I'll believe it when I see it." And sure enough, she had an appointment with him the next day. He could hardly believe it, but he could tell she quit. His interested in hearing more about it from us. So far, all three of my oncologsts, my allergist and my regular MD are in full support of my "smoking" the ecig.

As far as "How do we feel?" We can breathe! I mean really breathe. Deep inhales without coughing up a lung. We can smell things better, which is good and bad, because not all things smell good! WE SMELL GOOD though! Gonna save money on hand lotion, perfume, gum and mints too. We walk without getting out of breath. We seem to have more energy, but maybe that's because we aren't always out of breath. The bottom line to my very long story for your very to the point question.....

1. *No intention of quitting smoking, but we all quit the very day we got our order from you. We still get on the phone and say "I can't believe you quid" to each other.*
2. *We have never, ever, felt so good in our ENTIRE adult lives. Inside and out.*
3. *Oncologist approved, at least around here.*
4. *In my situation, probably a life saving move. I am one of those lives being saved as quoted in your email. I really am living proof, as we found out through my oncologist and the outcome of my surgery.*

Sorry to have written such a long letter, but I thought you might be interested in how your product has positively affected an entire family, and probably saved their lives as well.

Thanks again for your help. As you can see, I really needed it.

Julie

These stories are just a very few from the 10's of thousands of customers we deal with. It's very common to hear people say that after about 2 weeks of only using an electronic cigarette, and not also smoking regular cigarettes, their smoker's cough is reduced, or gone. They tell us they breathe better. Some even comment that they now use less sugar in their coffee, because their taste buds came back.

Health First
WISCONSIN

TO: Members, Senate Judiciary and Labor Committee
FROM: Melissa Horn, Government Relations Director at Health First Wisconsin
RE: Senate Bill 440
DATE: March 5, 2014

Thank you for the opportunity to submit testimony on Senate Bill 440, legislation that would endorse an exemption of electronic smoking devices (e cigarettes) from our state's smoke-free law. Health First Wisconsin urges the committee to oppose this legislation as it would unnecessarily create a special exemption for e cigarettes and send a misleading message that these products are safe to consume.

Wisconsin's smoke-free law is widely popular among the public. In fact, since the law was enacted, polling has shown that 75% of Wisconsinites support the law, with 89% viewing it as a law that protects the health of employees and customers, and 86% saying it has made establishments nicer and more enjoyable to patronize.[i] There is no need to open up a law that is clearly working and well-liked to promote a product that, if anything, potentially poses a risk to the public.

On their own websites, manufacturers of e cigarettes like *Johnson Creek Smoke Juice & Electronic Cigarettes* even say "products and accessories are only intended for committed smokers of legal smoking age and not by non-smokers, children, women who are pregnant or may become pregnant or any person with an elevated risk of, or preexisting condition of, any medical condition which includes, but is not limited to, heart disease, diabetes, high blood pressure or asthma".[ii] Furthermore, they state their products "may be poisonous if orally ingested" and add "for their own protection, please keep out of reach from children". Product websites like *V2 Cigs* explicitly warn about the nicotine in the inhalants of their products that they "can be toxic if inhaled or ingested and may cause irritation if it comes into contact with your eyes or skin".[iii] So, again, why would we want to create a special exemption for these products when the companies that make them even recognize how dangerous they are to inhale for an individual much less those around them?

There is no reason Wisconsin needs to call out exceptions to the law when the public made clear and continues to strongly support safe, healthy work environments and establishments to patronize.

Lastly, many other rule-making authorities are prudently restricting exposure to e cigarettes rather than endangering the public to their potential health problems. The U.S. Department of Transportation recently proposed a rule to ban e cigarettes from airlines[iv], Amtrak has banned the use of electronic smoking devices on trains and in any area where smoking is prohibited[v] and the Air Force Surgeon General issued a memorandum highlighting the safety concerns regarding electronic cigarettes[vi] and placed them in the same category as tobacco products. In addition, the National Attorney Generals Association[vii] and countless other leading health organizations have actively been urging the Food and Drug Administration to regulate these devices as tobacco products due to the hazards they could pose to the public. Does Wisconsin really want to be the state that instead endorses these products when it's clear everyone else is urging further study of their risk and are taking steps to limit the exposure of these inhalants to the public?

There is no reason to go backward on our smoke-free law by opening it up to promote a product that poses an unknown amount of threat towards the health and safety of the public. Please oppose this exemption and protect our popular and effective statewide smoke-free air law as is. Alternatively, we urge the committee to instead look to pass legislation that improves environments where Wisconsinites and visitors live, work and play.

[i] Survey, Public Opinion Strategies, June 15-16, 2011. Surveying "500 likely voters in Wisconsin."
[ii] *Johnson Creek Smoke Juice & Electronic Cigarettes*. Retrieved March 3, 2014 from https://www.johnsoncreeksmokejuice.com
[iii] *V2 Cigs. Retrieved March 3, 2014 from* http://www.v2cigs.com
[iv] *U.S. Department of Transportation*. U.S. Department of Transportation Proposes to Ban the Use of Electronic Cigarettes on Aircraft. Retrieved on March 3, 2014 from http://www.dot.gov/briefing-room/us-department-transportation-proposes-ban-use-electronic-cigarettes-aircraft
[v] *Amtrak*. Smoking Policy. Retrieved on March 3, 2014 from http://www.amtrak.com/smoking-policy
[vi] *U.S. Air Force*. AF surgeon general issues warning about safety of electronic cigarettes. http://www.af.mil/News/ArticleDisplay/tabid/223/Article/115820/af-surgeon-general-issues-warning-about-safety-of-electronic-cigarettes.aspx
[vii] *National Association of Attorney Generals*. Re: Regulation of E Cigarettes. Retrieved on March 3, 2014 from http://www.naag.org/assets/files/pdf/E%20Cigarette%20Final%20Letter%20(5)(1).pdf

To: Members of the Wisconsin State Senate, Committee on Judiciary and Labor,
From: Allison Miller, Wisconsin government relations director, American Cancer Society Cancer Action Network
RE: Testimony in opposition to Senate Bill 440
Date: March 5, 2014

Dear Chairman Grothman and members of the committee:

The American Cancer Society Cancer Action Network (ACS CAN), the nonprofit, nonpartisan, advocacy affiliate of the American Cancer Society, is opposed to Senate Bill 440, which will allow the use of electronic cigarettes in public places and workplaces where smoking is otherwise prohibited.

Wisconsin is on the cusp of celebrating the fourth anniversary of the state's smoke-free air law in July. The law is incredibly popular. Allowing the use of electronic cigarettes or e-cigarettes in public spaces undermines this popular and effective law and creates confusion for business owners, the public and in enforcement efforts.

More research is needed on electronic cigarettes.
ACS CAN has significant concerns about the potential public health effects of electronic cigarettes. Over the last several years, there has been a dramatic growth in the marketing and sale of e-cigarettes and in the claims being made by e-cigarette manufacturers, as well as a proliferation in the various types of e-cigarettes being sold. Despite the dramatic rise in the use of e-cigarettes, very little is known about their ingredients, their health risks to users and bystanders, their impact on youth tobacco use or whether they are effective in helping smokers quit.

There are more than 250 types of e-cigarettes on the market today and the products vary considerably by ingredients and quality control. E-cigarette makers claim their ingredients are "safe" but without any standards there is no sure way for e-cigarette users to know what they are consuming and the extent of potential risk.

Only a limited number of studies have so far examined the contents of e-cigarette vapor. Some of the studies have found them to contain heavy metals, volatile organic compounds and tobacco-specific nitrosamines, among other ingredients. A 2009 study done by the Food and Drug Administration (FDA) found cancer-causing substances in several of the e-cigarette samples tested.

The health effects of e-cigarettes are scientifically uncertain, especially their long-term effects. Additionally, the effects of secondhand vapor from e-cigarettes require further study, especially to determine differences among the many brands and types of e-cigarettes.

Until more research is conducted and the FDA determines if they're safe, we strongly recommend that states treat e-cigarettes like all other tobacco products.

Electronic cigarettes should not be exempt from Wisconsin's smoke-free air law.
Because electronic cigarette use simulates the behavior of smoking, use of these products complicates enforcement of the smoke-free air law and weakens its effectiveness. Use of an e-cigarette in public places normalizes the action of smoking which can result in higher youth smoking rates and a slower decline in cessation rates.

Additionally, the use of these products, which often resemble traditional cigarettes, and produce a visible cloud when exhaled, are causing confusion for the public and enforcement officials alike. Explicitly exempting e-cigarettes from the restrictions imposed by smoke-free would add to this confusion and could lead to false reports of violations of the smoke-free law.

Moreover, business operators, striving to follow existing law shouldn't have to become experts at differentiating between cigarettes and e-cigarettes. If it looks like someone is smoking in a public space where it is prohibited, it should be treated as such.

Growing evidence shows electronic cigarettes are an increasing problem among youth.
The use of e-cigarettes is increasing, including among youth. A recent Centers for Disease Control and Prevention (CDC) report shows that in the United States from 2011 to 2012—just one year—the percentage of youth (middle and high school students) using e-cigarettes more than doubled. Furthermore, more than 75% of the youth surveyed who used e-cigarettes also smoked conventional cigarettes. As well, 1 in 5 who used e-cigarettes had never tried traditional cigarettes. This could indicate that e-cigarettes are a gateway to traditional tobacco products.

Overall, the need for more research is absolutely essential to guard against possible public health risks and prevent e-cigarettes from creating a new generation of youth tobacco users, increasing the overall number of people addicted to nicotine, convincing current tobacco users not to quit or re-glamorizing the act of smoking. The committee can ensure that history does not repeat itself with a new generation of products by opposing SB 440 and maintaining the integrity of Wisconsin's smoke-free air law.

Wisconsin Medical Society

Your Doctor. Your Health.

TO: Senate Committee on Judiciary and Labor
Senator Glenn Grothman, Chair

FROM: Mark Grapentine, JD
Senior Vice President - Government Relations

DATE: March 5, ~~2013~~ 2014

RE: Opposition to Senate Bill 440

On behalf of more than 12,000 members statewide, the Wisconsin Medical Society thanks the committee for this opportunity to share our concerns with Senate Bill 440, which would exempt electronic cigarettes (e-cigarettes) and other electronic smoking devices from the state's successful smoke-free law. The Society opposes the bill, as little independent research has been conducted into the devices' ingredients and either primary or second-hand health impacts.[1] Rather than exempting the devices from the state's smoke-free law, the Society believes sales of the devices should be restricted until gaining approval and continuing regulation from the U.S. Food and Drug Administration (FDA).

Electronic cigarette manufacturing

Electronic cigarettes and other electronic smoking devices are currently produced without any regulatory oversight on the manufacturing, marketing, and quality control processes. A laboratory analysis conducted in 2009 by the FDA's Center for Drug Evaluation Office of Compliance tested 18 electronic cigarette samples from leading brands.[2] The analysis found several cartridges contained detectable levels of nitrosamines, a known carcinogen, and one cartridge to contain an antifreeze ingredient. Additionally, cartridges labeled as containing no nicotine tested positive for nicotine and the amount of nicotine consumed varied and differed from their labeling across the samples.[3]

Secondhand exposure risk

The secondhand exposure risk from e-cigarettes is unclear; current research should be further developed before deciding whether e-cigarettes should be exempt from the state's smoke-free law. One study specifically examining the secondhand exposure risk found the air concentrations of nicotine emitted by the devices ranged from 0.82 to 6.23 $\mu g/m^3$. The study calls for more research to determine the possible health consequences of secondhand exposure to nicotine, especially among vulnerable populations such as children and pregnant women.[4]

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[1] http://www.fda.gov/newsevents/publichealthfocus/ucm172906.htm
[2] http://www.fda.gov/downloads/drugs/scienceresearch/ucm173250.pdf
[3] http://www.fda.gov/newsevents/publichealthfocus/ucm173146.htm
[4] http://ntr.oxfordjournals.org/content/early/2013/12/10/ntr.ntt203.short?rss=1

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Smoking-cessation tool
No studies have directly measured the effectiveness of e-cigarettes in helping smokers quit tobacco cigarettes. Studies exist on short-term use and suggest electronic smoking devices may be as effective as nicotine patches and inhalers for quit rates and have minimal adverse side effects.[5] E-cigarette manufacturers have conducted their own studies regarding e-cigarettes serving as a potential smoking cessation tool, but have not applied to the FDA to have the devices approved and regulated for that purpose. More independent research is needed.

Impact on youth
A number of organizations, including the Centers for Disease Control and Prevention, the American Academy of Pediatrics, the International Union Against Tuberculosis and Lung Diseases, and the FDA have expressed their concern that e-cigarettes may increase the use and addiction to nicotine and tobacco products in children. A report released by the CDC in 2013[6] found electronic cigarette use among middle and high school students almost doubled from 2011 to 2012. Additionally, some believe that vapor flavors like "bubble gum" and "cotton candy" are marketed with youth in mind. Some groups are concerned that an attraction to e-cigarettes could increase youth/teen addiction to nicotine.

American Medical Association stance
The American Medical Association conducted research into the safety and effectiveness of electronic cigarette use.[7] This study led to adoption of new policy in this area, which the Society's Council on Legislation recently endorsed:

> **H-490.909 Use of Electronic Cigarettes in Smoking Cessation Programs**
> Our AMA urges that: (1) e-cigarettes be classified as (nicotine) drug delivery devices and should be subject to FDA regulation with appropriate standards for identity, strength, purity, packaging, and labeling with instructions and contraindications for use, including age of the user; (2) state legislatures prohibit the sales of e-cigarettes and all other nicotine devices that are not FDA-approved; and (3) as currently marketed, e-cigarettes be included in smokefree laws but separately defined from tobacco products. (CSAPH Rep. 6, A-10; Reaffirmation: I-12)

In exempting e-cigarettes from the state's smoke-free law, Senate Bill 440 is essentially the state's endorsement for the devices' greater use. The Society believes more evidence is needed before making such an endorsement, and therefore we oppose the legislation.

Thank you for this opportunity to share the Society's stance on this bill. If you have further questions, please feel free to contact us at any time.

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[5] http://www.biomedcentral.com/1471-2458/11/786 and
http://www.plosone.org/article/info%3Adoi%2F10.1371%2Fjournal.pone.0066317
[6] http://www.cdc.gov/mmwr/preview/mmwrhtml/mm6245a2.htm
[7] http://www.ama-assn.org/resources/doc/csaph/a10csaph6ft.pdf

Johnson Creek™
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Support for Senate Bill 440

Thank you for allowing all of us to present our opinions to you in regards to Senate Bill 440.

As a leader in this industry, we have a vested interest in its success. But it is bigger than just our interest. It's about one of America's most coveted values, the freedom to choose. We see using e-cigarettes as a choice for smokers of legal age and this bill helps ensure the freedom to use these devices in public places.

In 2008, our founder and CEO, Christian Berkey, was a heavy smoker, and working as a manager in an Apple store near Milwaukee. An avid fan of technology and by trade and personal choice, he was an early adopter of electronic devices. He found an ad on the Internet for something called an electronic cigarette. Intrigued, he ordered one. When it arrived from China, he marveled at the mechanics of it – but choked on the horrible, chemical tasting e-liquid inside. Mr. Berkey set out to build a better mousetrap. Many months and many recipes later, he came up with an e-liquid he liked. To test his theory, he asked people on an online e-cigarette forum if they'd like to try it and give him feedback. When the dozen or so volunteers he'd hoped for turned into 400 people, he quit his job, cashed in his 401K plan, created a website, and founded Johnson Creek Enterprises (named after the small town in which he lived). That was July 25, 2008. It was the beginning of the Great Recession.

Fast forward to 2013, a mere five years after its formation. Inc. Magazine named us as one of the fastest growing privately held companies in America. Specifically, # 9 in Wisconsin, #56 in consumer goods and #873 in America. Johnson Creek has joined the ranks of Intuit, Zappos, Under Armour, and Microsoft who all earned similar awards in past years. In 2013, we shared that honor with LivingSocial and Otterbox, among others.

In this same 5 year period, we went from the original 3 employees to the 60 we have today. In 2011, we moved our headquarters to a 42,500 square foot campus in Hartland and have expanded within that space three times. We hire the best candidates and offer 75% employer paid medical, dental, & vision insurance as well as 100% employer paid STD, LTD and term life insurance. All of these benefits (including spouse and dependent benefits at the same rates) are available after just 30 days + first of the month after hire.

What this means is that we are as passionate about our employees as we are about creating a new option for smokers of legal age. We work hard to provide this option and do so in a thoughtful and responsible manner. Johnson Creek cares about its

customers, its employees and its community. Offering a new product like electronic cigarettes and e-liquid brings with it a responsibility to provide smokers with the highest quality product possible. We have been ISO 9001:2008 certified since 2012 and follow current Good Manufacturing Practices. Julianne will speak further about this in her testimony.

As pioneers in the industry, we were the first company to introduce shrink banding of our bottles, child-resistant caps, and the listing of all ingredients on our labels as well as nicotine warnings. These things are adopted by many companies now and it's thanks, in part, to the innovation and commitment to quality that we foster at Johnson Creek. We enjoy and respect the trust our customers give us and look forward to FDA regulation to help standardize benchmarks and best practices for the entire industry.

Johnson Creek is a strong and willing partner. By enacting this legislation into law, you are not only choosing to protect the livelihood of many people in our state, but more importantly, you are also choosing to protect the rights of adults to make new choices. We'd like to see all legislators take the same thoughtful and responsible path as all of you are doing, by taking the time to rationally learn about e-liquid, the hardware, the industry and the risks and benefits of this new frontier. Unfortunately, we are seeing a patchwork of diverse legislation around the country.

I would like to close by personally inviting you out to our offices in Hartland for a tour of our facility. Recently we produced a video on what it means to be "Made in America." You can find that video on the home page of our website at www.smokejuice.com. Thank you in advance for your consideration.

Susan Geiger
Director of Communications
Johnson Creek Enterprises
(920) 545-2020
susan@smokejuice.com
www.smokejuice.com

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Quick facts about Johnson Creek

Our facility:

- we occupy 42,500 SF and 51% of the building we rent
- we are ISO 9001:2008 certified
- we adhere to strict good manufacturing processes (GMP's)
- our lab is 4,200 SF

Our products:

- we manufacture 27 unique flavors, in 4 different nicotine strengths, across 3 different product lines
- we manufacture 7 unique flavors, in 3 different nicotine strengths for bluCigs, the market leader in the e-cig industry. blu is owned by Lorillard Tobacco
- our bottled product comes packaged with a shrink band, child resistant cap, nicotine warning, ingredient listing

Our team:

- we've been in business for 5+ years
- we currently employ 55 full time employees, 1 part time employee and 3 temp-to-hire full time employees
- we offer 75% employer paid medical, dental & vision insurance to all employees after 30 days of hire + 1st of the month
- not only do we cover the employee at 75%, but we also cover their spouse and child(ren) at 75%
- we offer 100% employer paid STD, LTD and term life insurance to all employees after 30 days of hire + 1st of the month
- we hired 26 employees in 2013, almost doubling our head count
- we were named to Inc. Magazine's 5000/500 fastest growing, privately held companies in the US. #873 overall, #56 for consumer products and #9 in the state of WI
- we've already hired 4 full time employees and 3 temp-to-hire full time employees in 2014

Our revenue:

- 2010 $1.6M
- 2011 $2.7M
- 2012 $7.6M
- 2013 $8.5M

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Support for Senate Bill 440

I am Director of Product Development for Johnson Creek Enterprises, the largest manufacturer of smoke juice, or e-Liquid, in the United States. We also sell our own electronic cigarette, Vea. I strongly support Senate Bill 440.

My background as an engineer is integral to improving the manufacturing processes we use, as well as improving the products themselves. My job has a direct impact on the experience of our customers AND my fellow employees. While working for Johnson Creek over the last 18 months I've gravitated toward the company's belief that valuing one's employees creates a better value for one's customers. This priority has allowed our company to nearly double in size year after year, and it will help to create even more jobs and more positive experiences for our customers. Personally, I look forward to advancing the technology of our industry to create more valuable solutions for customers and coworkers alike.

As someone who works with electronic cigarette technology on a daily basis I am obliged to discuss the fundamental differences between traditional cigarettes and electronic cigarettes. The traditional cigarette functions on the principle of burning tobacco to produce smoke, while the electronic cigarette functions by heating a liquid solution to evaporate it into a vapor or aerosol. The combustion of a traditional cigarette undergoes a chemical reaction that releases even more chemicals than are already present. On the other hand an electronic cigarette merely vaporizes the ingredients from the liquid to the aerosol form without the existence of a combustion reaction.

Moreover, the physical differences between the two are hard to miss. Electronic cigarettes are composed of a battery (used as an energy source), which is connected to a cartridge that contains a heating element (known as an atomizer) and a liquid solution that may or may not contain nicotine. Many consumers call these cartridges "cartomizers," which is a portmanteau of cartridge and atomizer. Cartomizers are available in countless form factors and styles, but they almost all function on the same principle. This principle uses the power of electricity to vaporize liquid without combustion or its byproducts.

With that said I would like to offer an invitation to all of you to visit our facility where we can provide you with more information about our company and our technology. Thank you for your time.

Joe Dralle
Director of Product Development

X

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As the Quality Assurance Manager at Johnson Creek Enterprises and I am strongly in support of Senate Bill 440.

I have been a member of the Johnson Creek Enterprises family since August 2013 and was introduced into the world of electronic cigarettes and vaping about the same time. In this relatively short period of time, I have witnessed and will give testimony to the benefits of vaping and JCE.

We are the largest manufacturer of smoke juice in the United States and because of this, it is our responsibility to set the standard in regulating our industry. Our most important core value is "Be Aware, Accurate and Honest". As the Quality Assurance Manager this value is rudimentary to the manufacturing of smoke juice, and we have excelled in this by:

- Being ISO 9001:2008 certified since 2012
- Following strict cGMP's
- Being OSHA Certified yearly
- Having 15 employees certified in First Aid, CPR & AED
- Implementing and maintaining our Hazard Analysis and Critical Control Point Program and our Quality Management System
- Having a Vendor Certification program
- Routinely auditing our vendors
- Batch testing by Gas Chromatography Mass Spectrometer Flame Ionization
- Random 3rd party verification testing of our batch testing

What these programs & initiatives bring to our company and our smoke juice is, in short, quality. Each of our vendors is certified by Johnson Creek Enterprises before we order from them through our vendor surveys, which goes to the extent of auditing our vendors at their manufacturing site. Our shipping and receiving program demands that each good received is not only in optimal quality, but each shipping truck, out going product, and internal inventory is maintained to the highest degree possible. Being ISO 9001:2008 certified brings extreme validation to the quality practices we perform, this standard validates that what we do at Johnson Creek Enterprises adheres to the International Standards Organization.

Not only does our company provide validated quality in smoke juice, it is an outstanding company to have in the State of Wisconsin. I am honored to be one of the few people who can say, without a doubt, I love my job.

It isn't just the respect and support I have for Johnson Creek Enterprises but also the respect and support I have for the e-cigarette industry that has caused me to speak today. A family friend of mine is a true American in every sense of the word. He is an amazing man who served his country for 8 year, 2 tours in Iraq, as a Marine Corporal, and continues to serve his country today by being a career firefighter in the State of New York. He used to smoke two packs a day for 10 years. For a Christmas gift, I gave him our e-cigarette and smoke juice to try. He is so delighted with an alternative to cigarette that he has switched to vaping and smoking just 3 cigarettes a day. I am proud to be able to provide him an alternative to the cigarette with the quality smoke juice that Johnson Creek Enterprises creates.

Please let me express, that if anyone has questions regarding quality in e-cigarettes or Johnson Creek Enterprises, that I would be happy to answer them.

Julianne Endres
Quality Assurance Manager
Johnson Creek Enterprises

WISCONSIN NURSES ASSOCIATION

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TO: Senator Glenn Grothman, Chair
Members of the Senate Committee on Judiciary and Labor

FROM: Gina Dennik-Champion, RN, MSN
Executive Director, Wisconsin Nurses Association

DATE: Wednesday, March 5, 2014

RE: Opposition to SB 440 - Exempting electronic smoking devices from the types of smoking devices that may not be used in certain locations.

On behalf of the Wisconsin Nurses Association, I would like to thank you Chairperson Grothman and members of the Senate Committee on Judiciary and Labor for holding a public hearing on Senate Bill 440, legislation that seeks to exempt for the purposes of "smoking" in public indoor locations the latest in nicotine-delivery paraphernalia.

My name is Gina Dennik-Champion. I am a registered nurse and serve as the Executive Director of the Wisconsin Nurses Association (WNA). WNA advocates on behalf of Wisconsin's 76,000 Registered Nurses on issues pertaining to health policies impacting nursing care and practice. Part of nursing practice includes educating the public on health promotion and prevention strategies that support quality of life.

The WNA appreciates the opportunity for a public hearing on a product and paraphernalia that allows the user to deliver an addictive drug like nicotine directly into the human body by smoking or inhaling vaporized chemicals. The common term for this type of delivery system is "vaping."

Policymakers and the general public need to better understand the health effects and addiction outcomes of electronic cigarettes.

During the public hearing yesterday on the assembly companion bill (AB-762) the attorney for the legislative council informed the members that the smoking ban in Wisconsin already does not include electronic cigarettes. According to the attorney, the state smoking ban defines "smoking" as smoking tobacco products and while electronic cigarettes do not use tobacco they are currently not part of the smoking ban.

The health care profession have serious concerns about the lack of research and evidence regarding the impact of electronic cigarettes has on the health and addiction of the individual using the device and the health of individuals surrounding the smoker.

WNA would like to see public protection at the state and federal level regarding this product before usage increases. We believe and support that regulation and oversight needs to be developed by the U.S. Food and Drug Administration (FDA). The regulatory standards for these devices must address the identity, strength, purity, packaging and labeling with instructions and contraindications for use, including age of the user.

It is for these reasons Senator Grothman and members of the Committee that WNA requests that you oppose Senate Bill 440.

Thank you.

WPHCA
Wisconsin Primary Health Care Association

Lisa Davidson, Director of Government Relations and Advocacy
Testimony in opposition to Senate Bill 440

March 5, 2014

Dear Chairman Grothman and Committee Members,

Thank you for the opportunity to speak with you today regarding our concerns with Senate Bill 440. WPHCA is the member association for the Community Health Centers serving Wisconsin. In 2012 we provided comprehensive medical, dental and behavioral health services to over 300,000 patients in our state. As health care providers to your constituents, we cannot support Senate Bill 440 and ask you to oppose this legislation.

WPHCA is proud to have supported the smoke-free workplace law in our state. The law is working; not only is the air cleaner for workers and patrons to enjoy, but we also now know the law is very popular. We are concerned that the actual and perceived implications of this bill weaken Wisconsin's smoke-free laws and believe that there is little evidence to support such a change in definition.

Allowing electronic smoking devices to be used inside our workplaces will not only confuse consumers, but puts at risk those who work in and patronize these establishments. Vapor emitted from these devices contain nicotine, which is a sticky substance that remains on surfaces for days and weeks, so the hazardous carcinogens continue to be created over time, which are then inhaled, absorbed or ingested. Allowing an unknown substance to circulate in the air affecting workers and patrons is contrary to the intent of the law.

To date there is no conclusive evidence that electronic smoking devices are safe. These products are currently unregulated, which leaves a great deal of unknowns not only about the health risks, but also about product manufacturing and safety. In addition, there is no scientific evidence that electronic smoking devices are an effective cessation tool. It is irresponsible to make unproven exceptions which allow for and encourage Wisconsin residents to inhale an unknown and unregulated substance either directly or through second hand contact.

Please oppose Senate Bill 440. Thank you for your consideration.

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March 6, 2014

To: Members of the Committee on Judiciary and Labor
Dona Wininsky, Director of Public Policy and Communications
American Lung Association in WI
Re: SB440

Dear members of the committee,

The American Lung Association in Wisconsin respectfully urges you to vote no on the recommendation for passage of SB440, which would exempt e-cigarettes from the state's smoke-free law.

First, the long-term impact of e-cigarettes on the health of our state's residents remains unknown. Some of the studies that have been conducted, like a 2009 study by the U.S. Food and Drug Administration found that some of these devices contained toxic carcinogenic chemicals in addition to nicotine. Yet even those limited studies don't even begin to scratch the surface of investigating the 250 plus brands currently offered. Without federal oversite, each of these brands is free to include any combination and assortment of ingredients – including toxins – in their products.

Secondly, there's no reason to change Wisconsin's very successful and strongly supported smoke-free air law that protects owners, workers and customers from the dangers of second hand smoke. Granting e-cigarette smokers an exemption will also cause enforcement problems throughout the state by creating confusion and inconsistency in the application of the law.

That is why we oppose SB440 and its companion bill AB762. If you have any questions regarding our position, please call us at 1-800-586-4872. Thank you for your time and consideration.

American Heart Association | American Stroke Association

To: Members of the Senate Committee on Judiciary & Labor

From: Chris Klein, Government Relations Director, American Heart Association

Re: Testimony is opposition to SB 440

Date: March 5, 2014

Dear Chairman Grothman and members of the committee:

I appreciate the opportunity to submit testimony in opposition to Senate Bill 440, which would allow the use of electronic cigarettes in public places and workplaces where smoking is otherwise prohibited.

This proposed legislation would create a special exemption for electronic cigarettes. There is no reason e-cigarettes should be treated differently than other tobacco products. Creating a separate classification for e-cigarettes will send the message that that these new products are safe and kids may believe they then must be safe to consume.

The Center for Disease Control and Prevention (CDC) recently released a report that showed the use of electronic cigarettes among middle and high school students more than doubled from 2011 to 2012. The CDC's disturbing data on the increased use of electronic cigarettes reinforces the need for the U.S. Food and Drug Administration (FDA) to take immediate action to oversee these products.

The evidence is increasingly clear that e-cigarettes are appealing to children and youth, likely because they are available in a wide variety of appealing candy and fruit flavors, including chocolate, cotton candy, gummy bear, bubble gum, Atomic Fireball, orange soda, as well as grape, apple and strawberry. This report raises the concern that e-cigarettes may be an entry point for youths to begin using more traditional tobacco products, including cigarettes.

Every day, each of the 1,200 Americans who die from tobacco-related diseases is replaced by two smokers under the age of 26. If e-cigarettes are luring high school and middle school students into a lifetime of addiction, it represents a public health tragedy.

Attorneys General of 40 U.S. states have urged the FDA to regulate e-cigarettes like tobacco as there has been a drastic increase in use of the product by children and youth who want to experience the effects of nicotine. The 40 attorneys general noted that nicotine is highly addictive and has an immediate bio-chemical effect on the brain and body.

The Family Smoking Prevention and Tobacco Control Act (Tobacco Control Act), which passed the Congress with overwhelming bipartisan majorities and was signed into law on June 22, 2009, gave the FDA immediate authority over cigarettes, smokeless and roll-your-own tobacco. It also gave the authority to the Secretary of Health and Human Services to deem other tobacco products subject to FDA's jurisdiction. Under this provision, the FDA has stated it plans to regulate e-cigarettes. Until this occurs, there is no federal oversight of these products or restrictions in place to protect the public health against potential risks posed by these products, particularly to the health of our children.

The American Heart Association has serious concerns about the potential public health effects of e-cigarettes and significant additional research is needed on these products and how they are used. Until more research is conducted and the FDA issues regulations, we strongly recommend that states treat e-cigarettes like all other tobacco products.

Thank you and please contact me at 608-320-9026 or chris.klein@heart.org with any questions.

International Journal of Hygiene and Environmental Health xxx (2013) xxx–xxx

Contents lists available at ScienceDirect

International Journal of Hygiene and Environmental Health

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

Use of electronic cigarettes (e-cigarettes) impairs indoor air quality and increases FeNO levels of e-cigarette consumers

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ARTICLE INFO

Article history:
Received 12 September 2013
Received in revised form
28 November 2013
Accepted 29 November 2013

Keywords:
Electronic cigarette
e-Cigarette
Vaping
Indoor air quality
Nicotine
Volatile organic compounds
Polycyclic aromatic hydrocarbons
FeNO
Health effects
Secondhand smoking

ABSTRACT

Despite the recent popularity of e-cigarettes, to date only limited data is available on their safety for both users and secondhand smokers. The present study reports a comprehensive inner and outer exposure assessment of e-cigarette emissions in terms of particulate matter (PM), particle number concentrations (PNC), volatile organic compounds (VOC), polycyclic aromatic hydrocarbons (PAH), carbonyls, and metals. In six vaping sessions nine volunteers consumed e-cigarettes with and without nicotine in a thoroughly ventilated room for two hours. We analyzed the levels of e-cigarette pollutants in indoor air and monitored effects on FeNO release and urinary metabolite profile of the subjects. For comparison, the components of the e-cigarette solutions (liquids) were additionally analyzed.

During the vaping sessions substantial amounts of 1,2-propanediol, glycerine and nicotine were found in the gas-phase, as well as high concentrations of $PM_{2.5}$ (mean 197 $\mu g/m^3$). The concentration of putative carcinogenic PAH in indoor air increased by 20% to 147 ng/m^3, and aluminum showed a 2.4-fold increase. PNC ranged from 48,620 to 88,386 $particles/cm^3$ (median), with peaks at diameters 24–36 nm. FeNO increased in 7 of 9 individuals. The nicotine content of the liquids varied and was 1.2-fold higher than claimed by the manufacturer.

Our data confirm that e-cigarettes are not emission-free and their pollutants could be of health concern for users and secondhand smokers. In particular, ultrafine particles formed from supersaturated 1,2-propanediol vapor can be deposited in the lung, and aerosolized nicotine seems capable of increasing the release of the inflammatory signaling molecule NO upon inhalation. In view of consumer safety, e-cigarettes and nicotine liquids should be officially regulated and labeled with appropriate warnings of potential health effects, particularly of toxicity risk in children.

Introduction

Environmental tobacco smoke (ETS) is by far the most significant indoor air quality issue, bearing a health risk by inducing lung cancer and cardiovascular disorders in non-smokers (IARC, 2004; US, 2006). It is also considered as important risk factor for asthma, respiratory infections and sudden infant death syndrome in children (EPA, 1992, 1997; Raupach et al., 2008). National regulators in USA and Europe have progressively banned tobacco smoking from public buildings, bars, cafés and restaurants which led to improved indoor air quality in these buildings (Bohac et al., 2010; Gleich et al., 2011). The smoke-free policies and constantly surging tobacco prices prompted consumers to look for alternatives to conventional smoking. New products, especially electronic nicotine delivery systems also known as electronic cigarettes or e-cigarettes, have become popular in spite of insufficient data on their safety for both users and secondhand smokers (Etter et al., 2011).

E-cigarettes do not burn tobacco but produce a respirable aerosol without smoke or flame from a battery-powered heater and liquid-containing cartridges (Trtchounian et al., 2010).

Abbreviations: DNPH, 2,4-dinitrophenylhydrazine; e-cigarette, electronic cigarette; eCO, exhaled carbon monoxide; FeNO, exhaled nitric monoxide; GC, gas chromatography; HPLC, high-performance liquid chromatography;-3-OH-cotinine, trans-3′-hydroxycotinine; 3-HPMA, 3-hydroxypropylmercapturic acid; LOD, limit of detection; MS, mass spectrometry; PAH, polycyclic aromatic hydrocarbons; PM, particulate matter; PNC, particle number concentrations; VOC, volatile organic compounds.

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http://dx.doi.org/10.1016/j.ijheh.2013.11.003

Depending on the brand, the liquids usually contain nicotine in different concentrations (8.5–22.2 mg/ml) (Cameron et al., 2013), humectants to produce the vapor (especially 1,2-propanediol) and flavors (e.g. tobacco, vanilla, cherry). Despite the growing popularity of e-cigarettes, consumers do not have valid information on the chemical content of liquids or on their safety. In particular, liquids labeled as nicotine-free may contain low levels of nicotine (FDA, 2009), and the risk of impurities (e.g. nitrosamines) is of major concern to health care authorities (FDA, 2009). There is not only a lack of internationally certified manufacturing sites, and liquids freely available via the Internet are not subject to official quality control.

Because e-cigarettes are marketed for delivering nicotine and sometimes other substances, there is a need for regulation, as for other drug delivery devices. Thus far there has been a wide range of responses across countries and states, ranging from no regulation to complete bans (Etter et al., 2011). The empirical basis for these decisions is uncertain, and more research on the health effects of and risks from e-cigarettes must be conducted to ensure that the decisions of regulators, health care providers and consumers are based on scientific evidence.

The aim of our study was to perform a comprehensive exposure assessment by analyzing the indoor air concentration of e-cigarette emissions in terms of particulate matter (PM), particle number concentrations (PNC), volatile organic compounds (VOC), polycyclic aromatic hydrocarbons (PAH), carbonyls, and metals. For this purpose, we simulated a real-world scenario (café-like setting) in an environmentally controlled room with predetermined occupancy density and air exchange rate. Before and after the vaping sessions, the concentrations of exhaled carbon monoxide (eCO) and nitric oxide (FeNO) were measured to reveal acute effects of e-cigarette use on physiological parameters. FeNO has already been used in a previous study on e-cigarettes (Vardavas et al., 2012) and is sensitive to a number of factors including eosinophilic inflammation, airway caliber, mucus production, oxidative stress, and enzyme activity, all of which might be affected by e-cigarettes. Additionally, the uptake of nicotine and other VOC was investigated by analysis of urinary nicotine metabolites and mercapturic acids. To support consumer protection, we furthermore analyzed the chemical composition of the e-cigarette liquids and checked for the presence of impurities (nitrosamines).

Materials and methods

Study design

The study was carried out in a room in the office building of the Bavarian Health and Food Safety Authority in Munich, Germany. Room size was 18 m^2 and its volume 45 m^3. The room contained three tables and a wardrobe (café-like setting), and was operated at an average air exchange rate of 0.56 h^{-1}. The measurements were taken on seven days in July 2012 at the same time of the day. On the first day (control day) the air was monitored without vaping activities and on the following six days with e-cigarette consumption. Before the measurements, the room was thoroughly ventilated, and the window was kept tilted during the measurement periods. Subjects were asked to give spot urine before each exposure, and eCO and FeNO were measured using established monitoring devices (BreathCO, Vitalograph, Hamburg, Germany; NIOX MINO, Aerocrine, Bad Homburg, Germany); FeNO was assessed at the standard expiratory flow rate of 50 ml/s. During each vaping session three study subjects took a seat around a table and consumed an e-cigarette filled with a tobacco-flavored nicotine-free liquid (Liquid 1) from 10 am to 12 pm, while recording their individual number of puffs. This procedure was repeated on five consecutive days for the nicotinic variant of Liquid 1 and for another two other tobacco-flavored liquids (Liquid 2 and 3), each of these with and without nicotine (overall six experiments with three volunteers at each session). The equipment for sampling and monitoring was placed on 2 tables at the side of the room about 1 m above floor level and 1 m away from the e-cigarette consumers. After exposure eCO and FeNO were measured again to determine acute effects of e-cigarette use on these measures. For metabolite analysis subjects were asked to collect urine for another 24 h.

Liquids (with and without nicotine, all with tobacco flavor) and e-cigarettes were commercially available (Red Kiwi, Seevetal, Germany). The nicotine content of the liquids was 18 mg/ml according to the manufacturers' declarations. The e-cigarette contained a rechargeable lithium-ion battery, an electronic circuit, a vaporizer, and a mouthpiece with a refillable tank. Batteries were charged before the study and between study days to ensure their correct operation.

Subjects

Nine adult volunteers (all males, 20–30 years old, mean age 24.7 ± 4.2 years, size 173–198 cm, weight 63–85 kg) were recruited for participation in the study. In each vaping session three of them consumed first a nicotine-free and on the day after a nicotinic e-cigarette for two hours. All subjects judged themselves as healthy and were not under medication for at least 15 days before biomonitoring. In particular there was no evidence for pulmonary disease or other chronic conditions (e.g. renal or liver disease) that might influence FeNO and nicotine metabolism. All subjects were occasional smokers with a cigarette consumption of <10 cigarettes per week (no e-cigarettes) and capable of nicotine abstinence 48 h prior to each vaping session. Before taking part in the study, the subjects were familiarized with the device by vaping one e-cigarette under the instruction of the laboratory staff. Thereafter, each subject was given a test set including an e-cigarette and a non-nicotinic liquid to freely practice vaping for one week at home. Participants were asked to refrain from cigarette smoking for at least 48 h prior to their scheduled session. The ethical committee of the Bavarian Medical Association approved the study, and volunteers were enrolled in the study after giving written informed consent. The investigation was conducted according to the Declaration of Helsinki.

Chemical characterization of liquids

1,2-Propanediol, glycerine

To 0.3 g of each liquid 0.1 g internal standard (1,3-propanediol) were added. This mixture was dissolved in 5 ml isopropanol and diluted 1:5 with isopropanol. The GC analysis was carried out on an Agilent 6890 gas chromatograph with flame ionization detector (GC-FID). Separation was performed on an Agilent DB-WAXetr (polyethylene glycol) capillary column with following dimensions: 30 m length, 0.32 mm inner diameter and 1 μm film thickness. The GC oven temperature was programmed from an initial temperature of 150 °C for 2 min, followed by a ramp to 220 C at 5 °C/min with a hold time of 20 min. 1-μl-samples were injected into the GC inlet at a 40:1 split ratio with helium carrier gas flow rate of 1 ml/min. Temperatures of injector and detector were 240 °C. The analytes were positively identified by comparison of their retention times with those of standards. Quantification followed the internal standard quantification method. The limit of detection (LOD) for 1,2-propanediol was 0.5%. The results were confirmed by analysis via a second GC-column (Agilent HP 5 capillary column) and in the case of glycerine by enzymatic analysis.

Please cite this article in press as: Schober, W., et al., Use of electronic cigarettes (e-cigarettes) impairs indoor air quality and increases FeNO levels of e-cigarette consumers. Int. J. Hyg. Environ. Health (2013), http://dx.doi.org/10.1016/j.ijheh.2013.11.003

Nicotine

Samples were prepared by adding 100 μl internal standard solution (heptadecane, 25 mg/ml isopropanol) to 0.3 g of each liquid. This mixture was diluted with 2 ml isopropanol. The gas chromatograph instrument was an Agilent 6890 equipped with a flame ionization detector (GC-FID). Separation was carried out on an Agilent HP 5 (5% phenylmethyl polysiloxane) capillary column with following dimensions: 30 m length, 0.32 mm inner diameter and 0.25 μm film thickness. The GC oven temperature was programmed from 140 °C (held 5 min) to 210 °C at 20 °C/min with a hold time of 25 min. 1-μl-samples were injected into the GC inlet at a 20:1 split ratio with helium carrier gas flow rate of 1 ml/min. Temperatures of injector and detector were 250 °C and 280 °C, respectively. Nicotine was positively identified by comparison of retention time with that of the standard. Quantification again followed the internal standard quantification method. The LOD for nicotine was 0.1%. The results were confirmed by analysis on a second GC-column (Agilent DB-WAXetr capillary column).

Other organic compounds

Gas chromatography–mass spectrometry (GC/MS) was carried out with a Shimadzu QP2010 instrument equipped with an AOC-20i injector and a mass selective detector operated in the single-ion monitoring mode. A 1-ml-aliquot of each liquid was diluted with 10 ml chloroform and subjected to GC/MS analysis. Analyte separation was performed using helium as carrier gas with constant flow at 35 cm/sec and a 20 min temperature program composed as follows: 95 °C for 2 min, then 12 °C per min to 250 °C, then 10 °C per min to 280 C, then held for 2 min at 280 °C. The MS transfer line temperature was 275 °C. A three-point calibration curve was prepared for both the respective analyte and its internal standard, and quantification was performed using the ratio of peak areas under a single ion chromatogram.

Nitrosamines

For analysis of tobacco-specific nitrosamines, a 1-ml-aliquot of each liquid was spiked with 10 μl internal standard (NNK-d_4) in preparation for LC/MS/MS analysis. N′-nitrosonornicotine (NNN), N′-nitrosoanatabine (NAT), N-nitrosoanabasine (NAB), and 4-(methylnitrosamino)-1-(3-pyridyl)-1-butanone (NNK) were analyzed by tandem mass spectrometry using selected reaction monitoring (SRM) detection. The LOD ranged from 0.22 ng/ml (NAB) to 0.38 ng/ml (NNK).

Analysis of indoor air parameters

Particle mass, particle number concentration

Continuous measurements of particle mass (PM_{10}, $PM_{2.5}$, $PM_{1.0}$) were made using an optical laser aerosol spectrometer (LAS) (Dust monitor 1.108 operated with factory default settings, Grimm Technologies, Ainring, Germany). This spectrometer works by constantly drawing air via a volume-controlled pump (1.2 l/min) through a flat beam of laser light. The scattered signals generated while particles cross the beam are detected with a high-speed photo diode, analyzed by an integrated pulse height analyzer and counted. The LAS measures particle concentrations in 15 size ranges from 0.300 to 20 μm. For our purposes the continuous measurements were stored minute-by-minute on a data logger. PNC were measured using a Wide Range Aerosol Spectrometer (WRAS, Grimm Technologies, Ainring, Germany). The WRAS comprises two particle counters and sizers: GRIMM 5.403 SMPS+C and GRIMM 1.108 LAS (described above), combined via software to one unit. The GRIMM 5.403 consists out of a high-resolution particle counter (CPC) attached to a "Vienna Type" electrostatic classifier (M-DMA). The complete WRAS covers the size range from 0.005 to >20 μm.

Volatile organic compounds

Indoor air samples were collected with a constant flow of 0.2 l/min with Tenax GR as adsorbent and analyzed using a thermodesorption unit (Gerstel, Mülheim, Germany) coupled to GC/MS (gas chromatograph 6890A coupled to MSD 5973N, Agilent, Waldbronn, Germany). The desorption temperature was 230 °C. The LOD for a single compound was 0.04 μg/m^3 using a sample volume of 24 l.

Aldehydes/ketones

Airborne concentrations of aldehydes and ketones were determined by DNPH method according to NIOSH Method 2018 (DNPH, 2,4-dinitrophenylhydrazine). Air was sampled on LpDNPH H10 Cartridges (Supelco, Bellefont, USA) with a constant flow rate of 0.1 l/min for 120 min. Elution of aldehyde derivatives was performed by 5 ml acetonitrile (LiChrosolv, Merck, Germany). A Dionex HPLC system UltiMate 3000 containing of sampler, degaser, gradient pump, column oven, and UV detector was used to carry out the measurements. Aldehyde derivatives were separated by a binary gradient (water/acetonitrile) on a reversed-phase column SUPELCOSIL LC-18 (250 mm × 4.6 mm, particle size 5 μm). UV detection wavelength was 360 nm. The LOD was 0.033 mg aldehyde per sample, resulting in 0.03 mg/m^3 aldehyde in air sample. Formaldehyde, acetaldehyde, butyraldehyde, acrolein, and acetone were analyzed.

Polycyclic aromatic hydrocarbons

Gaseous and particle-bound PAH were determined by collecting indoor air with a medium volume sampler equipped with a sampling unit consisting of a $PM_{2.5}$-inlet, a quartz fiber filter and a polyurethane foam. Filter and PU foam were extracted with toluene after addition of deuterated PAH standards, purified on a silica column and analyzed by GC/MS. Naphthalene, acenaphthylene, acenaphthene, phenanthrene, fluorene, anthracene, fluoranthene, pyrene, benzo[*a*]anthracene, chrysene, benzo[*b*]-+benzo[*k*]fluoranthene, benzo[*a*]pyrene, dibenzo[*a,h*]anthracene, indeno[1,2,3-*cd*]-pyrene, and benzo[*ghi*]perylene were determined as single PAH compounds. Additionally, the sum of these 16 PAH according to US-EPA was calculated. The LOD was 0.1 ng/m^3 using a sample volume of 10 m^3.

Metals/elements

Samples were collected on 47 mm quartz fiber filters (Pieper, Bad Zwischenahn, Germany) using a medium volume sampler equipped with a $PM_{2.5}$ sampler as sample inlet which operated at a constant flow of 2.3 m^3/h over a 2-h sampling period parallel to e-cigarette vaping. Before use, the filters (coming from the same production lot) were analyzed for their heavy metal blank values. After a closed-vessel microwave decomposition of the filter samples using nitric acid and hydrogen peroxide as oxidizing agents, the target analytes were measured using inductively coupled plasma-mass spectrometry (ICP-MS).

Indoor climate

Indoor carbon dioxide (CO_2) was measured using a continuously monitoring infrared sensor (Testo 435) (Testo, Vienna, Austria). The instrument was programmed for a 1-min data logging interval and values were averaged over the 2-h period of each vaping session. Indoor humidity, temperature and air pressure were measured simultaneously with a separate sensor connected to the Testo instrument. Indoor carbon monoxide (CO) was measured using a Fourier transform infrared (FTIR) spectrometer (Ansyco, Karlsruhe, Germany).

Determination of urinary nicotine metabolites by LC/MS/MS

Internal exposure to nicotine was determined by the quantification of urinary nicotine and its metabolites cotinine and

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trans-3′-hydroxycotinine using a slightly modification of a LC/MS/MS-method (Xu et al., 2004). Shortly, 400 μl of urine was buffered to pH 4.5 using 400 μl of 0.1 M ammonium acetate buffer, 10 μl of the isotopically labeled internal standards (d_3-nicotine, d_3-cotinine and d_3-trans-3′-hydroxycotinine, 10 mg/l) were added and 10 μl of this solution were directly injected in the LC/MS/MS-system. The analytical column was a Phenomenex Fusion RP (150 mm × 4.6 mm) with 2 mM ammonium acetate (pH 4.5) in water and 2 mM ammonium acetate (pH 4.5) in acetonitrile as eluents at a flow rate of 0.4 ml/min. Between-series precision was determined using a native smokers' urine sample that was analyzed with every batch ($n = 12$); it was 4.4% for urinary nicotine ($c = 886$ μg/l), 4.2% for urinary cotinine ($c = 1464$ μg/l) and 3.3% for urinary trans-3′-hydroxycotinine ($c = 1614$ μg/l). The accuracy of this method is assured by regular successful participation of our laboratory in round robins for the determination of nicotine and cotinine in urine (www.g-equas.de). Urinary creatinine concentrations were determined photometrically using a 96-well-plate photometer (Larsen, 1972).

Determination of urinary mercapturic acids by LC/MS/MS

Urinary mercapturic acids were determined as described previously (Schettgen et al., 2008). The mercapturic acids of benzene (S-PMA), benzylalcohol/toluene (S-BMA), styrene (PHEMA), 1,3-butadiene (DHBMA and MHBMA) and acrylonitrile (CEMA and CHEMA) were determined using specific automated column-switching LC/MS/MS-methods. Sample preparation and clean-up was carried out automatically by online-enrichment of the analytes on a Restricted-Access-Material column (RAM). After transfer of the analytes to the analytical column, they were further separated from matrix compounds and finally quantified by tandem mass-spectrometry using isotopically labeled analogs of the analytes as internal standards. The LOD of the methods was determined to be 0.05 μg/l urine for S-PMA, 0.5 μg/l urine for S-BMA, 0.3 μg/l urine for PHEMA, 10 μg/l and 2 μg/l urine for DHBMA and MHBMA, as well as 1 μg/l urine for both CEMA and CHEMA; this is sufficient to determine a background excretion of these mercapturic acids in urine within the general population. The mercapturic acid of acrolein (3-HPMA) was enriched and cleaned up from urinary matrix using an offline solid phase extraction on a SPE-column (ENV+, 100 mg from Separtis GmbH, Grenzach-Wyhlen, Germany). The acid was subsequently separated and quantified by LC/MS/MS using isotopically labeled 3-HPMA as internal standard. Accuracy of the determination of S-PMA in human urine is assured by regular successful participation of our laboratory in round robins (www.g-equas.de). For the other analytes, round robins were not available during the study period.

Statistical analysis

Data are described by mean values and standard deviations or by median values and percentiles, depending on the purpose and distribution. Wilcoxon matched-pairs signed-ranks test was employed to compare values of eCO, FeNO and urinary metabolites before versus after e-cigarette consumption. A p value < 0.05 was considered statistically significant.

Results

Table 1 gives the results of the liquid analysis in terms of humectants, nicotine, and other (volatile) organic compounds. All liquids consisted to >90% of the humectants 1,2-propanediol (mean ± SD, 559.2 ± 51.5 g/l) and glycerine (480.3 ± 41.0 g/l). Nicotine levels (22 ± 0.8 mg/ml) were on average 22% above the manufacturers' declaration of 18 mg/ml, but liquids labeled as nicotine-free had no nicotine present. All e-cigarette solutions contained small amounts of sensitizing chemicals including benzylalcohol, menthol, vanillin, and L-limonene, which were mainly present in Liquid 1. None of the liquids comprised the tobacco-specific nitrosamines NNN, NAT, NAB, and NNK (data not shown).

The results of particle measurements and major climate parameters during the six vaping sessions and on the control day are presented in Table 2. Overall, the amount of PM was markedly higher on the vaping days than on the control day, with generally the highest values on the vaping days without nicotine. Overall, mass concentrations showed a mean value of 197 μg/m³ (control 6 μg/m³) for $PM_{2.5}$ (90th percentile: 373 μg/m³ vs. 8 μg/m³), with the maximum during the 5th vaping session (Liquid 3 without nicotine: 514 μg/m³). PNC also reached high median values ranging from 48,620 to 88,386 particles/cm³, with peaks at diameters 24–36 nm. Indoor concentrations of CO and CO_2 showed no difference between control and vaping periods.

Table 3 summarizes the results for VOC and aldehydes/ketones. A distinct increase versus control was found for 1,2-propanediol (mean ± SD, 199.2 ± 93.2 μg/m³ vs. <0.04 μg/m³), glycerine (72.7 ± 6.9 μg/m³ vs. <0.04 μg/m³) and nicotine (2.2 ± 1.7 μg/m³ vs. <0.04 μg/m³). Formaldehyde, benzene and the pyrolysis products acrolein and acetone did not exceed background concentrations. Only during vaping session 4 (Liquid 2 with nicotine) the level of formaldehyde was higher than on the control day (55 μg/m³ vs. 25 μg/m³). Indoor concentrations of the sensitizing chemicals vanillin and benzylalcohol were only slightly increased in comparison to control values (0.3 ± 0.2 μg/m³ vs. <0.04 μg/m³; 5 ± 3 μg/m³ vs. 4 μg/m³).

The sum of all measured 16 PAH was approximately 30–90% higher during the vaping sessions (Table 4) compared to the control day. The total concentration of PAH was dominated by the more volatile substances naphthalene, acenaphthene, fluorene and phenanthrene. With regard to the seven PAH classified as probable carcinogens by the IARC (IARC, 2002, 2010), the concentration increased on average by 20% from 122.8 ng/m³ (control) to 147.3 ± 26.2 ng/m³ (vaping sessions). The concentrations of elements and metals found in indoor air (Table 5) showed a 2.4-fold increase for aluminum (482.5 ± 158.6 ng/m³ vs. 203.0 ng/m³). The rare-earth elements lanthanum and cerium, the concentrations of which are usually elevated by conventional tobacco smoking (Böhlandt et al., 2012), exhibited no increase and were in the range of outdoor air levels of below 0.5 ng/m³ and 1 ng/m³, respectively. Moreover, no significant increase was observed for the toxic and potentially carcinogenic elements cadmium, arsenic and thallium.

The mean ± SD puff rate over all subjects and sessions was 1.1 ± 0.4 puffs per minute. Before and after e-cigarette consumption eCO and FeNO in the subjects' exhaled air were measured. As illustrated in Fig. 1, 7 of 9 individuals showed a slight but statistically significant ($p = 0.030$) rise of FeNO after vaping a nicotinic e-cigarette. The effect was not statistically significant ($p = 0.554$; increase in 3 of 9 subjects), when nicotine-free liquids were used. eCO levels which are known to be strongly elevated by conventional cigarette smoking were not significantly influenced by e-cigarette consumption (data not shown).

The results of metabolite analysis of urine samples are depicted in Fig. 2. On average, vaping e-cigarettes with nicotine resulted in a significant increase of urinary nicotine and cotinine, but not 3-OH-cotinine levels. Interestingly, 3-HPMA, the mercapturic acid metabolite of the pyrolysis product acrolein, was also elevated after nicotinic vaping, while the other analyzed mercapturic acids showed no increase in the urine of the subjects (data not shown). Nicotine-free vaping had no statistically significant impact on all

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Table 1
Component analysis (mg/l) of liquids[a] vaporized during the vaping sessions.

Compounds	CAS	Liquid 1		Liquid 2		Liquid 3	
		− nicotine	+ nicotine	− nicotine	+ nicotine	− nicotine	+ nicotine
1,2-Propanediol	57-55-6	547,000	529,000	546,000	529,000	673,000	531,000
Glycerine	56-81-5	497,000	507,000	485,000	498,000	390,000	505,000
Nicotine	54-11-5	0.0	23,000	0.0	22,000	0.0	21,000
Sabinene	3387-41-5	0.0	1.5	0.0	0.0	0.0	0.0
Trimethylpyrazine	14667-55-1	12.1	12.4	0.3	0.3	0.5	0.5
Benzylalcohol[b]	100-51-6	59.4	60.5	0.5	3.1	0.9	2.7
Phenylethylalcohol	60-12-8	3.1	3.3	0.8	0.8	2.6	3.0
p-Dimethoxybenzene	150-78-7	14.7	15.6	0.9	1.1	0.7	0.9
Menthol[b]	1490-04-6	1.3	1.1	4.1	4.2	2.9	8.8
Ethylmaltol	4940-11-8	47.0	46.0	0.0	0.0	253.2	0.5
2-(2-Butoxyethoxy)ethanol	112-34-5	3.2	3.9	3.3	5.5	1.8	117.0
Anisaldehyde	123-11-5	9.6	9.4	0.8	1.0	0.6	0.7
p-Propenylansiole	104-46-1	11.4	13.4	0.0	0.0	0.0	0.0
γ-Dodecalactone	2305-05-7	0.0	0.5	0.6	0.6	0.0	0.0
Furaneol	3658-77-3	323.9	522.2	2207.1	7622.7	0.0	0.0
β-Pinene	127-91-3	1.6	2.5	0.0	0.0	0.0	0.3
Corylon	80-71-7	774.4	691.2	0.0	0.0	234.2	4.2
Ethylvanillin	121-32-4	59.2	54.8	0.0	0.0	0.0	0.0
Dihydrocoumarin	119-84-6	72.3	60.8	1.3	1.7	0.9	1.1
Vanillin[b]	121-33-5	135.3	140.4	0.0	3.1	22.8	167.1
Acetophenone	98-86-2	5.5	5.7	3.2	2.5	0.7	0.7
Ethylphenylacetate	101-97-3	7.5	4.1	0.5	0.0	0.0	0.0
Camphor	76-22-2	3.8	4.9	0.0	0.0	0.0	0.0
δ-Undecalactone	710-04-3	0.0	0.0	1.0	0.7	7.0	5.9
L-Limonene[b]	5989-27-5	2.4	2.2	1.6	1.9	1.8	2.2

[a] All liquids were labeled as tobacco-flavored.
[b] Known contact allergens. CAS: Chemical Abstracts Service number.

urinary metabolite levels measured in this study. Only nicotine was found slightly but significantly elevated possibly due to passive exposure to cigarette smoke prior to the nicotine-free vaping session (Benowitz et al., 2009).

Discussion

Since tobacco smoking is being progressively banned from public places worldwide, electronic cigarettes (e-cigarettes) show a

Table 2
Statistical characteristics of the distributions of particulate matter[a] and room climate parameters in indoor air during the 2-h vaping sessions and the control period.

	No vaping[b]	Liquid 1		Liquid 2		Liquid 3	
		− nicotine	+ nicotine	− nicotine	+ nicotine	− nicotine	+ nicotine
10th percentile							
$PM_{1.0}$ (μg/m³)	2	105	9	11	11	127	9
$PM_{2.5}$ (μg/m³)	3	126	13	17	16	169	16
PM_{10} (μg/m³)	34	158	31	41	31	198	46
PNC (N/cm³)[c]	4140	68,867	46,444	29,733	44,287	65,805	33,485
90th percentile							
$PM_{1.0}$ (μg/m³)	3	521	64	244	72	577	244
$PM_{2.5}$ (μg/m³)	8	636	79	290	90	819	324
PM_{10} (μg/m³)	61	683	115	304	116	866	363
PNC (N/cm³)[c]	4943	92,673	58,490	66,124	57,886	100,656	55,307
Median							
$PM_{1.0}$ (μg/m³)	2	242	13	62	22	421	31
$PM_{2.5}$ (μg/m³)	6	296	18	74	30	561	49
PM_{10} (μg/m³)	45	332	40	93	57	604	85
PNC (N/cm³)[c]	4365	85,724	53,552	56,441	53,068	88,386	48,620
Mean							
$PM_{1.0}$ (μg/m³)	2	293	28	98	40	376	80
$PM_{2.5}$ (μg/m³)	6	353	35	121	51	514	110
PM_{10} (μg/m³)	47	398	63	141	74	555	145
PNC (N/cm³)[c]	4466	82,800	52,568	51,385	51,321	85,446	46,572
Geometric diameter (nm)	43	31	27	24	28	36	33
Air exchange rate (1 h^{-1})	0.76	0.39	0.56	0.37	0.40	0.74	0.74
Temperature (°C)	24	25	26	26	27	27	27
Relative humidity (%)	48	48	53	57	56	48	44
Air pressure (hPa)	964	956	954	957	955	958	958
CO (ppm)	0.00	0.02	0.04	0.00	0.00	0.00	0.00
CO_2 (ppm)	1380	1710	1486	1665	1606	1239	1216

[a] Calculated PM in accordance to VDI 4300-11.
[b] Determined without e-cigarette the day before first vaping session.
[c] PNC, particle number concentrations; size range 5 nm to > 20 μm.

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Table 3
Indoor air concentrations (μg/m³) of volatile organic compounds and aldehydes/ketones measured during a 2-hour use of e-cigarettes containing different liquids[a] with (+) or without (–) nicotine, or at the control day.

Compounds	CAS	No vaping[b]	Liquid 1		Liquid 2		Liquid 3	
			– nicotine	+ nicotine	– nicotine	+ nicotine	– nicotine	+ nicotine
Formaldehyde	50-00-0	25.0	24.0	28.0	27.0	55.0	28.0	21.0
Acetaldehyde	75-07-0	20.0	19.0	22.0	19.0	25.0	162.0	16.0
Butyraldehyde	123-72-8	<10	<10	<10	<10	<10	<10	<10
Acetone	67-64-1	<10	<10	<10	<10	<10	<10	<10
Acrolein	107-02-8	<10	<10	<10	<10	<10	<10	<10
Benzene	71-43-2	0.2	0.2	0.3	0.2	0.3	0.2	0.3
Benzaldehyde	100-52-7	3.7	1.7	2.2	2.9	5.0	3.1	2.3
Benzylalcohol[c]	100-51-6	4.0	4.4	1.9	4.9	11.0	2.5	2.9
Benzylbenzoate	120-51-4	<0.04	<0.04	<0.04	<0.04	<0.04	0.3	<0.04
2,5-Dimethylfuran	625-86-5	<0.04	<0.04	<0.04	<0.04	<0.04	<0.04	<0.04
3-Ethenylpyridine	1121-55-7	<0.04	<0.04	<0.04	<0.04	<0.04	<0.04	<0.04
Glycerine	56-81-5	<0.04	72.0	77.0	71.0	81.0	76.0	59.0
L-Limonene[c]	5989-27-5	2.2	0.8	0.9	2.4	3.1	0.5	1.4
Menthol[c]	1490-04-6	0.4	0.4	0.7	1.1	1.3	0.6	0.7
Nicotine	54-11-5	<0.04	<0.04	0.6	0.9	1.3	–[d]	4.6
1,2-Propanediol	57-55-6	<0.04	160.0	140.0	110.0	175.0	395.0	215.0
Vanillin[c]	121-33-5	<0.04	0.2	0.1	0.2	0.4	0.6	0.3

[a] Each of the six liquids was vaporized by three e-cigarette consumers during an individual vaping session.
[b] VOC background concentrations were determined without any e-cigarette exposure the day before first vaping session.
[c] Known contact allergens.
[d] Not determinable.

rapidly growing market share, although data on their safety for users and secondhand smokers are limited. The present study offers a comprehensive exposure assessment by analysis of the effects of e-cigarettes on indoor air quality in terms of PM, PNC, VOC, PAH, carbonyls, and metals. FeNO levels of the subjects were measured to determine acute effects of e-cigarette consumption on a physiological read-out. The uptake of nicotine and other VOC by the e-cigarette consumers was investigated via urinary nicotine metabolites and mercapturic acids. We also analyzed the chemical composition of the liquids and checked for the presence of nitrosamines.

The nicotine content of e-cigarette solutions varies by manufacturer (Cameron et al., 2013; Goniewicz et al., 2013b) and can sometimes be markedly higher than declared (FDA, 2009). Such differences were also observed in our study, as the nicotine content of liquids was 1.2-fold higher than claimed by the manufacturer. Still, liquids labeled as nicotine-free had no nicotine present, in contrast to previous findings (FDA, 2009). Nicotine is a potent parasympathomimetic alkaloid and psychoactive drug that acts on the nicotinic acetylcholine receptors in the central nervous system to induce the release of several neurotransmitters (Tweed et al., 2012). Increased levels of dopamine in the reward circuits of the brain

Table 4
PAH concentrations (ng/m³) measured during the 2-h e-cigarette vaping sessions and at the control day.

PAH (IARC group)[a]	No vaping[b]	Liquid 1		Liquid 2		Liquid 3	
		– nicotine	+ nicotine	– nicotine	+ nicotine	– nicotine	+ nicotine
Acenaphthene (3)	51.0	41.0	100.0	83.0	120.0	70.0	63.0
Acenaphthylene (n.c.)	1.0	1.4	3.0	2.1	2.8	3.3	9.5
Anthracene (3)	2.0	<0.2	<0.2	3.6	7.8	3.7	8.3
Benzo[*a*]anthracene (2B)	<0.2	<0.2	<0.2	<0.2	<0.2	<0.2	<0.2
Benzofluoranthenes[c] (2B)	2.3	2.5	2.7	2.6	3.2	3.7	4.1
Benzo[*a*]pyrene (1)	<0.2	<0.2	<0.2	<0.2	<0.2	<0.2	0.4
Benzo[*ghi*]perylene (3)	0.5	<0.2	0.4	0.3	0.4	0.4	0.5
Chrysene (2B)	0.5	<0.2	0.5	0.4	0.5	0.5	0.4
Dibenzo[*a,h*]anthracene (2A)	<0.2	<0.2	<0.2	<0.2	<0.2	<0.2	<0.2
Fluoranthene (3)	12.0	6.0	11.0	13.0	17.0	17.0	16.0
Fluorene (3)	32.0	28.0	69.0	60.0	100.0	70.0	91.0
Indeno[1,2,3-*cd*]pyrene (2B)	<0.2	<0.2	0.4	0.3	0.3	0.5	0.6
Naphthalene (2B)	120.0	120.0	170.0	110.0	150.0	130.0	180.0
Pyrene (3)	8.6	4.6	8.3	7.8	11.0	9.6	8.9
Phenanthrene (3)	120.0	73.0	180.0	170.0	250.0	220.0	240.0
Sum of all PAH	349.9	276.5	545.2	453.1	663.0	528.8	622.6
Sum of 1/2A/2B-PAH	122.8	122.5	173.6	113.4	154.0	134.7	185.4

[a] Assessment of the PAH carcinogenicity by the International Agency for Research on Cancer (IARC):

- carcinogenic to humans (IARC group 1)
- probably carcinogenic to humans (IARC group 2A)
- possibly carcinogenic to humans (IARC group 2B)
- no evidence to their carcinogenicity in humans (IARC group 3)
- n.c., not classified

[b] PAH background concentrations were determined without any e-cigarette exposure the day before first vaping session.
[c] Sum of benzo[*b*]fluoranthene and benzo[*k*]fluoranthene.

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Table 5
Concentrations of metals/elements (ng/m³) measured during the 2-h e-cigarette vaping sessions and at the control day.

	No vaping[a]	Liquid 1		Liquid 2		Liquid 3	
		− nicotine	+ nicotine	− nicotine	+ nicotine	− nicotine	+ nicotine
Al	203.0	709.0	667.0	269.0	434.0	351.0	465.0
As	0.8	1.5	1.7	<0.2	1.3	0.4	<0.2
Bi	0.1	1.1	1.2	0.1	0.3	0.2	0.2
Ca	<2000.0	3142.0	2161.0	<2000.0	<2000.0	<2000.0	<2000.0
Cd	<0.1	1.2	0.2	<0.1	0.2	<0.1	<0.1
Ce	<0.2	0.5	0.5	2.4	0.7	0.2	0.3
Co	4.4	1.7	1.9	0.6	2.7	<0.5	<0.5
Cr	1376.0	476.0	475.0	236.0	655.0	65.3	113.0
Cu	31.9	16.2	27.2	127.0	21.0	13.1	12.3
Fe	6669.0	2402.0	3771.0	1666.0	3149.0	1131.0	585.0
K	<1000.0	<1000.0	<1000.0	<1000.0	<1000.0	<1000.0	<1000.0
La	<0.1	0.3	0.3	1.9	0.5	0.2	0.2
Mg	112.0	356.0	299.0	130.0	189.0	105.0	<100.0
Mn	149.0	84.0	57.7	24.8	66.5	<5.0	<5.0
Mo	15.5	<10.0	<10.0	<10.0	<10.0	<10.0	<10.0
Na	<1000.0	3492.0	2610.0	<1000.0	<1000.0	<1000.0	<1000.0
Ni	668.0	216.0	213.0	151.0	356.0	8.1	19.8
Pb	10.1	5.7	5.8	6.8	3.2	10.9	<3.0
Sb	<2.0	<2.0	<2.0	<2.0	<2.0	<2.0	<2.0
Sn	<5.0	7.1	8.6	<5.0	<5.0	<5.0	<5.0
Ti	24.7	52.2	42.8	40.5	33.1	30.6	<20.0
Tl	<1.0	<1.0	<1.0	<1.0	<1.0	<1.0	<1.0
V	<10.0	<10.0	<10.0	<10.0	<10.0	<10.0	<10.0
Zn	<500.0	<500.0	<500.0	<500.0	<500.0	<500.0	<500.0

[a] Metal background concentrations determined without e-cigarette the day before first vaping session.

are responsible for the apparent euphoria and relaxation, but also for addiction to nicotine consumption (Benowitz, 2010). Nicotine has a higher affinity for acetylcholine receptors in the brain than those in skeletal muscle; at toxic doses (adults: 30–60 mg, children: 6–10 mg) it causes death by respiratory paralysis (Katzung, 2006). Our results confirm that liquids contain amounts of nicotine that are potentially lethal for adults and children. As nicotine readily passes into the bloodstream following dermal contact, spilling of 5 ml of e-cigarette liquid (equivalent to 110 mg nicotine) onto the skin can cause severe intoxications or even death. There is a considerable health risk, if young children accidentally touch or swallow nicotine solutions, especially when liquids are not sold in child-safe containers. Moreover, the tested e-cigarette solutions contained several sensitizing chemicals including benzylalcohol and L-limonene. Clinical data show that these substances can produce allergic contact dermatitis and immediate contact reactions, characterized by itching and the appearance of wheals, erythema, and pruritus (Chow et al., 2013; Nardelli et al., 2011). Recent studies also reported the presence of carcinogenic nitrosamines in e-cigarette solutions (Goniewicz et al., 2013a; Trehy et al., 2011).

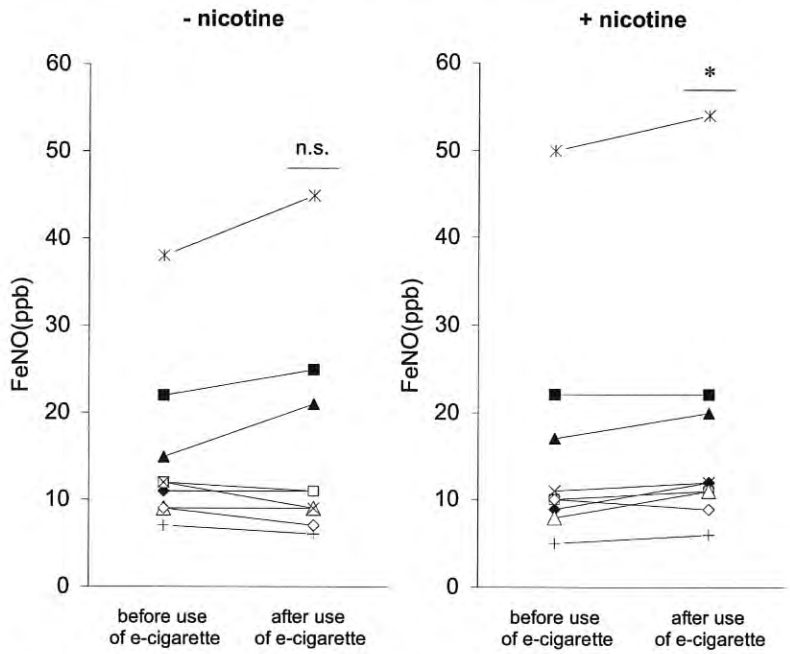

Fig. 1. Seven out of nine volunteers showed increased FeNO levels after vaping an e-cigarette with nicotinic liquid (right panel) but only three with nicotine-free liquid (left panel). Each symbol represents NO (ppb) in the exhaled air of each of the subjects before and after vaping an e-cigarette with (+, right panel) or without (−, left panel) nicotine for 2 h. *$p = 0.030$; n.s., not significant in pre-post comparison.

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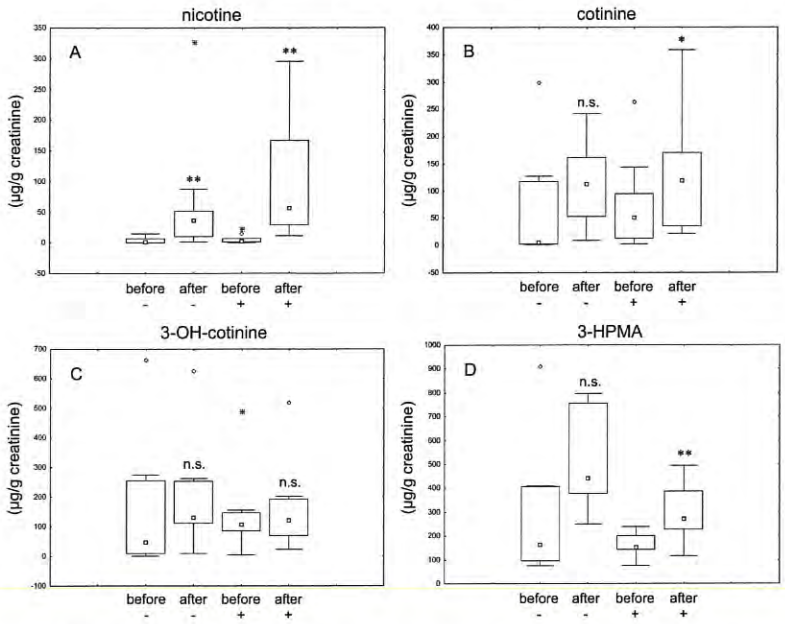

Fig. 2. Box plots show the concentrations of (A) nicotine, (B) cotinine, (C) trans-3′-hydroxycotinine (3-OH-cotinine), and (D) 3-hydroxypropylmercapturic acid (3-HPMA) measured in urine samples of nine subjects collected before and after vaping an e-cigarette with (+) or without (−) nicotine. $^{*}p < 0.05$; $^{**}p < 0.01$; n.s., not significant in pre-post comparison.

Our analyses, however, did not confirm this observation in the liquids used by us. These considerations indicate that e-cigarette solutions should be labeled with appropriate warnings of potential health effects, particularly regarding children.

Analysis of indoor air quality during vaping sessions showed that e-cigarettes are not emission-free. We found substantial amounts of 1,2-propanediol, glycerine and nicotine in the gas-phase as well as high concentrations of $PM_{2.5}$ (mean 197 $\mu g/m^3$), which is consistent with previous findings in indoor air (McAuley et al., 2012; Pellegrino et al., 2012). With regard to the seven PAH classified as probable carcinogens by the IARC (IARC, 2002, 2010), their concentration increased by 20% to 147.3 ng/m^3 during the vaping sessions. Similarly, aluminum showed a 2.4-fold increase in indoor air, which has also been reported by Williams and co-workers (Williams et al., 2013). PNC ranged from 48,620 to 88,386 particles/cm^3 (median) with peaks between 24 and 36 nm. For comparison, the particle size distribution of a conventional filter cigarette peaks at 100 nm and shows a higher total number concentration (Schripp et al., 2013). The fine and ultrafine particles related to the use of e-cigarettes are probably formed from supersaturated 1,2-propanediol vapor and should be partially deposited in the human lung.

There are few data on adverse physiologic effects after short-term use of e-cigarettes (Vardavas et al., 2012). Using an e-cigarette and liquids containing < 10% nicotine for only 5 minutes led to an immediate decrease in FeNO and an increase in airway resistance. This effect may be attributed to nicotine (see below) and/or 1,2-propanediol that is capable of causing acute ocular and upper airway irritations in healthy individuals (Wieslander et al., 2001). Recently, a case report even described the occurrence of exogenous lipoid pneumonia due to inhalation of glycerine present in e-cigarette solutions (McCauley et al., 2012). In our study, seven out of nine subjects showed a rise of FeNO after nicotinic but not non-nicotinic e-cigarette consumption.

FeNO is commonly considered as a marker of eosinophilic airway inflammation but also depends on other factors. As it is well known, a reduction of the bronchial area due to smooth muscle action or an impairment of NO transfer from the mucosa into the lumen due to mucosal fluid imbalance, or an interaction with inhaled oxidants can lead to a decrease of FeNO. Such factors might have been active in the acute response observed after 5-min e-cigarette vaping (Vardavas et al., 2012), and the increase in airway resistance would be consistent with the decrease in FeNO, without invoking inflammatory mechanisms, as the increase could be associated with a reduction in bronchial area. In contrast, subjects consumed e-cigarettes for as much as two hours in our study, and this could well have led to different or even opposite responses. Literature findings on bronchial effects of nicotine are not consistent but there are some data on acute bronchoconstrictor effects, with subsequent time-dependent bronchodilator action in cats (Thompson et al., 1990). These data seem of interest as cats are sometimes considered to be better suited for the physiological comparison with humans than rats or mice.

For the interpretation of our results is seems of interest that nicotine has been shown to enhance NO production by activation of the endothelium nitric oxide synthase (eNOS) and the inducible NO synthase (iNOS) (Chen et al., 2004). NO from eNOS is known to act as neurotransmitter in the central nervous system or as potent vasorelaxant though modulation of muscular tone (Moncada et al., 1989). It could be possible that vasodilation increases the total amount of NO transported into the lumen of the respiratory tract. In contrast, NO from iNOS is generally defined as a deleterious molecule within the processes of inflammation (Southan and Szabo, 1996) and seems to predominantly transcriptionally activated. It is not clear from the literature at which time scale these different mechanisms work, however direct physiologic effects, e.g. by vasodilation or changes in bronchial area, after a 2-h exposure would be more plausible than direct effects on iNOS via common transcription factors (Ahn and Aggarwal, 2005). Comparing with the results by Vardavas et al. (2012), the issue of FeNO in response to e-cigarette vaping seems interesting and worth of further study.

In contrast to FeNO, there were no changes in eCO. We measured eCO not because we expected a significant CO load from e-cigarettes, in contrast to conventional cigarettes or Shisha, but because CO is considered as a potential marker of oxidative stress (Babusikova et al., 2008). Exhaled CO is, however, notoriously

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difficult to attribute to pathophysiological alterations due to disturbances arising from the CO contained in inhaled air.

The data on urinary metabolites confirm the uptake of nicotine and acrolein through e-cigarette consumption. Nicotine is metabolized in the liver by cytochrome P450 (CYP) enzymes, primarily CYP2A6 (Benowitz et al., 2006). The major metabolite is cotinine. Other primary metabolites include nicotine N′-oxide, nornicotine or trans-3′-hydroxycotinine, which is formed from cotinine by hydroxylation (Hukkanen et al., 2005). We observed a significant increase of nicotine and cotinine levels in urine samples of subjects who consumed e-cigarettes with nicotinic liquids. Interestingly, 3-HPMA, the mercapturic acid metabolite of acrolein, was also elevated, although in indoor air no acrolein could be observed. Acrolein is a strong irritant for the skin, eyes, and nasal passages and is commonly associated with the risk of lung cancer (Feng et al., 2006).

Overall, our data underline that e-cigarettes are not emission-free and impair indoor air quality. Exposure to e-cigarette pollutants might be a health concern, as fine and ultrafine particles formed from supersaturated 1,2-propanediol vapor can be deposited in the lung. Physiologic effects in consumers, though difficult to interpret, are suggested by the slight increase of FeNO after vaping nicotine-containing liquids. Whether effects also occur in passive smokers, is uncertain. Recent data on leukocyte populations in the blood and parameters of conventional spirometry did not indicate alterations induced by passive or even active vaping of e-cigarettes (Flouris et al., 2013, 2012) but these measures are not likely to be the most sensitive markers. Further research is needed to address particularly the issue of potential long-term effects of e-cigarette use. This is relevant because e-cigarettes are used by many consumers in order to facilitate withdrawal from cigarette smoking. It is currently not clear whether and in which specific circumstances this strategy works (Odum et al., 2012) and, more importantly, whether subjects stop the e-cigarette use after some time or continue with it instead of conventional cigarettes. In view of consumer protection, e-cigarettes and especially nicotine-containing liquids, as extremely toxic substances, should be officially regulated and labeled with appropriate warnings on health risks, particularly toxicity in children. Recently, a corresponding draft law regarding better regulation of e-cigarettes was also passed by the European Parliament.

Conflict of interest statement

The authors declare that there are no conflicts of interest.

Acknowledgments

The authors thank all volunteers for participation in the study. The excellent technical assistance of Beate Emmelot and Ludwig Fembacher is greatly appreciated. The study was funded by the Bavarian State Ministry of Health and Cure.

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Please cite this article in press as: Schober, W., et al., Use of electronic cigarettes (e-cigarettes) impairs indoor air quality and increases FeNO levels of e-cigarette consumers. Int. J. Hyg. Environ. Health (2013), http://dx.doi.org/10.1016/j.ijheh.2013.11.003

Inhalation Toxicology

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

Inhal Toxicol, 2013; 25(2): 91–101
© 2013 Informa Healthcare USA, Inc. DOI: 10.3109/08958378.2012.758197

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RESEARCH ARTICLE

Acute impact of active and passive electronic cigarette smoking on serum cotinine and lung function

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Abstract

Context: Electronic cigarettes (e-cigarettes) are becoming increasingly popular yet their effects on health remain unknown.

Objective: To conduct the first comprehensive and standardized assessment of the acute impact of active and passive e-cigarette smoking on serum cotinine and lung function, as compared to active and passive tobacco cigarette smoking.

Materials and methods: Fifteen smokers (≥15 cigarettes/day; seven females; eight males) and 15 never-smokers (seven females; eight males) completed this repeated-measures controlled study. Smokers underwent a control session, an active tobacco cigarette (their favorite brand) smoking session and an active e-cigarette smoking session. Never-smokers underwent a control session, a passive tobacco cigarette smoking session and a passive e-cigarette smoking session. Serum cotinine, lung function, exhaled carbon monoxide and nitric oxide were assessed. The level of significance was set at $p \leq 0.001$ to adjust for multiple comparisons.

Results: e-Cigarettes and tobacco cigarettes generated similar ($p > 0.001$) effects on serum cotinine levels after active (60.6 ± 34.3 versus 61.3 ± 36.6 ng/ml) and passive (2.4 ± 0.9 versus 2.6 ± 0.6 ng/ml) smoking. Neither a brief session of active e-cigarette smoking (indicative: 3% reduction in FEV1/FVC) nor a 1 h passive e-cigarette smoking (indicative: 2.3% reduction in FEV1/FVC) significantly affected the lung function ($p > 0.001$). In contrast, active (indicative: 7.2% reduction in FEV1/FVC; $p < 0.001$) but not passive (indicative: 3.4% reduction in FEV1/FVC; $p = 0.005$) tobacco cigarette smoking undermined lung function.

Conclusion: Regarding short-term usage, the studied e-cigarettes generate smaller changes in lung function but similar nicotinergic impact to tobacco cigarettes. Future research should target the health effects of long-term e-cigarette usage, including the effects of nicotine dosage.

Keywords

e-Cigarette, health, lung inflammation, respiratory system, tobacco cigarette

History

Received 10 October 2012
Revised 29 November 2012
Accepted 10 December 2012
Published online 30 January 2013

Introduction

Tobacco smoking is responsible for the largest amount of deaths and disability-adjusted life years in high-income countries (Lopez et al., 2006). In low- and middle-income countries which were infiltrated by the tobacco industry more recently, smoking has not had enough time to top the list and, thus, represents the third leading cause of death and disability (Lopez et al., 2006). In recent years, as the number of smokers worldwide is reaching record highs and anti-smoking policies are proliferating (Flouris et al., 2010b; Flouris & Oikonomou, 2010), several new products are being launched by the industry of alternative smoking products with hopes for increasing market shares and revenues. One of the most popular products in the market is the electronic cigarette (e-cigarette), a battery-powered device that simulates tobacco cigarettes by vaporizing nicotine and other chemicals into an inhalable vapor. The available data suggest that sales of e-cigarettes are increasing (Pauly et al., 2007), while Google searches for "electronic cigarettes" have increased by 5000% over the past 2 years (Yamin et al., 2010). This technology became popular despite the concerns expressed by the World Health Organization, the US Food and Drug Administration and a number of Health Ministries worldwide (World Health Organisation, 2010) about the lack of research on their safety and efficacy (Etter et al., 2011; Flouris & Oikonomou, 2010). Indeed, among many e-cigarette users, this product has come to epitomize the more mature (i.e. informed and health-concerned) generation of smokers, yet there is no evidence suggesting that e-cigarettes may be less harmful than tobacco burning cigarettes.

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Inhal Toxicol, 2013; 25(2): 91–101

A recent study (Vardavas et al., 2012) aiming to assess the acute pulmonary effects of active e-cigarette smoking had experimental design and methodological limitations that constrained the clinical significance of its findings. Some of the limitations included the lack of a proper control group and subject randomization, lack of comparisons of the effect of e-cigarette smoking against that of tobacco cigarette smoking, not controlling for the influence of recent (i.e. previous ≥ 5 hours) smoking on the obtained results and adopting an uncontrolled 5 min e-cigarette smoking protocol. As recently showed (Flouris et al., 2009), controlled human exposure studies can provide key information about the health effects of pollutants such as smoke. However, such studies must appropriately randomize human subjects and expose them to a carefully controlled stimulant/environment in order to eliminate confounding factors and be easily extrapolated to the effects of more chronic or recurrent exposures (Eisner, 2009). To this effect, we present the first comprehensive and standardized assessment regarding the short-term impact of active and passive e-cigarette smoking on lung function and serum cotinine, as compared to active and passive tobacco cigarette smoking in controlled sessions.

Materials

Ethics statement

This non-randomized repeated-measures controlled study was conducted according to the principles expressed in the Declaration of Helsinki and was approved by the University of Thessaly Ethics Review Board. All volunteers provided written informed consent.

Participants

Two groups of adult volunteers participated: 15 smokers ($\geq$15 cigarettes/day; eight males; seven females; 23.5–54 years; 155–197 cm; 52–112 kg; 10–68 pack years) and 15 never-smokers (eight males; seven females; 18–57 years; 150–189 cm; 46–89 kg). Exclusion criteria included pregnancy, signs of acute illness, abnormal spirometry (conducted prior to each session) and/or other evidence of pulmonary disease or other chronic conditions that might influence spirometry results (including heart conditions, malignancies, chronic renal or liver disease, autoimmune and immunodeficiency conditions). Individuals using medication known to influence the lung function including bronchodilators, corticosteroids and all kinds of medication used for airways disease (e.g. antileukotrienes, theophylline etc.) were also excluded. Smokers reporting previous use of e-cigarettes were also excluded for ethical reasons (i.e. possible relapse into tobacco cigarette smoking; Eissenberg, 2010; Vansickel et al., 2010). All women participants were premenopausal with regular menstruation and were tested during the late luteal phase of their menstrual cycle. A flowchart of the participant recruitment and assessment process is provided in Figure 1.

Experimental design

Each group attended three sessions administered in a random order and separated by a minimum of 7 d wash-out period (Figure 2). All subjects participated in each experimental session once. The group of smokers underwent a control session ($ACTIVE_{CON}$), an active tobacco cigarette smoking session ($ACTIVE_{TOB}$) and an active e-cigarette smoking session ($ACTIVE_{E\text{-}CIG}$), each lasting 30 min. In $ACTIVE_{CON}$, smokers were asked to pseudo-smoke an unlit-cigarette from a brand of their choice. In $ACTIVE_{TOB}$, smokers were asked to smoke two tobacco cigarettes from a brand of their choice. In $ACTIVE_{E\text{-}CIG}$, smokers were asked to puff an e-cigarette in order to absorb enough nicotine to match two of their favorite tobacco cigarettes as described below. Measurements were conducted before, immediately after, and 1 h after active smoking (Figure 2).

The group of never smokers underwent a control session ($PASSIVE_{CON}$), a passive tobacco cigarette smoking session ($PASSIVE_{TOB}$) and a passive e-cigarette smoking session ($PASSIVE_{E\text{-}CIG}$), each lasting 1 h. In $PASSIVE_{CON}$, participants were exposed to normal room air. In $PASSIVE_{TOB}$ and $PASSIVE_{E\text{-}CIG}$, participants were exposed to air polluted with tobacco cigarette smoke and e-cigarette vapor, respectively, adjusted to simulate bar/restaurant levels (Flouris et al., 2009). Measurements were conducted before, immediately after and 1 h after each exposure (Figure 2).

Prior to each session, participants' exhaled carbon monoxide (CO) was measured. As previously reported (Bullen et al., 2010), the assigned session was allocated if CO was $\leq$15 ppm in smokers and $\leq$1 ppm in never smokers. If CO was >15 ppm in smokers, >1 ppm in never-smokers or the participants reported active smoking or excessive passive smoking in the previous 10 h, the session was rescheduled. Based on these criteria, a total of three sessions were rescheduled.

Active smoking protocols

In the $ACTIVE_{CON}$ session, smokers were asked to pseudo-smoke an unlit-cigarette from a brand of their choice for 30 min. In the $ACTIVE_{TOB}$ session, smokers were asked to smoke two tobacco cigarettes from a brand of their choice within 30 min. Finally, in the $ACTIVE_{E\text{-}CIG}$ session, smokers were asked to take a specific number of puffs from an e-cigarette device (model: Giant, Nobacco G.P., Greece) within 30 min. In the latter session, a new cartridge (within its expiration date) and a fully charged battery were used for each session. Based on its label, the e-cigarette liquid used (Nobacco USA Mix, Nobacco G.P., Greece) had a "tobacco taste" and contained 11 mg/ml of nicotine, which is an average concentration since the range of nicotine content in e-cigarette liquids normally range between 0 to 36 mg/ml. Information regarding the e-cigarette device and the liquid used is available at the manufacturer's website (Nobacco G.P., 2012). They were selected for this study because the specific liquid is the only one available in the Greek market that has been analyzed by an independent publicly funded research institute (Leondiadis, 2009). This analysis, reviewed in detail elsewhere (Flouris & Oikonomou, 2010), demonstrated that the liquid used incorporates >60% propylene glycol, <10% nicotine, <5% linalool, <5% tobacco essence and <1% methyl vanilyn (Leondiadis, 2009).

Previous research have shown that a given number of puffs on an e-cigarette result in significantly less nicotine absorption

DOI: 10.3109/08958378.2012.758197

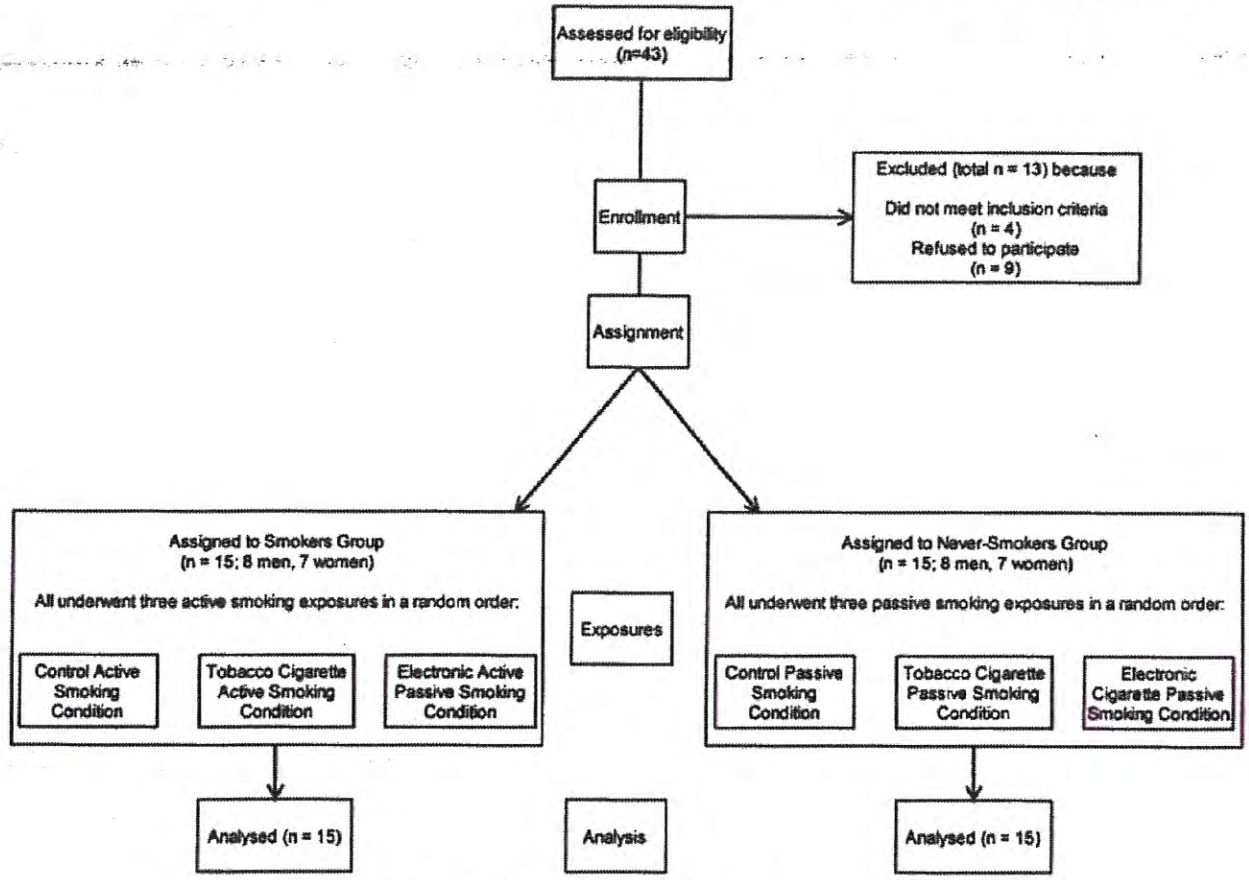

Figure 1. Flowchart of the participant recruitment and assessment process.

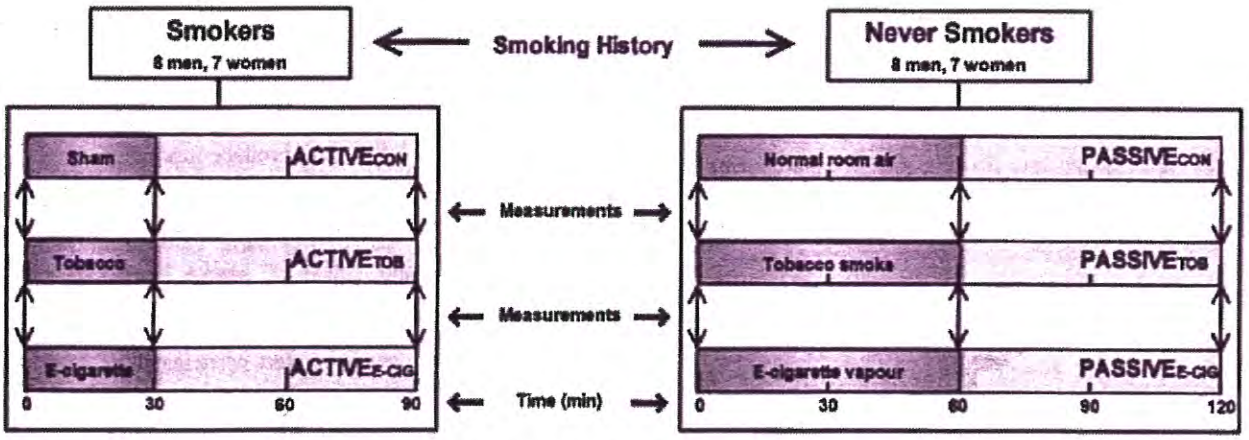

Figure 2. Outline of the experimental design used in this non-randomized repeated-measures controlled study. ACTIVE and PASSIVE indicate active and passive smoking, respectively. CON, TOB and E-CIG indicate the control, tobacco cigarette and electronic cigarette sessions, respectively.

compared to that generated by the same number of puffs from a tobacco cigarette (Eissenberg, 2010; Vansickel et al., 2010). Thus, results from studies that used similar puffs across products may reflect a lower nicotine dose instead of reduced particulates, Tar and CO. Therefore, in order to create a relatively similar stimulus (from a nicotine standpoint), it was deemed appropriate to calculate the number of puffs for each participant in the $ACTIVE_{E\text{-}CIG}$ session based on (i) the nicotine content of the participant's tobacco cigarette, (ii) the tobacco cigarette to e-cigarette nicotine absorption ratio, (iii) the nicotine concentration in the e-cigarette liquid, as well as (iv) the number of puffs required to consume 1 ml of liquid in an e-cigarette. The information required to derive (ii), (iii) and (iv) was obtained through a pilot study using an independent sample of 178 e-cigarette smokers who were previously tobacco cigarette smokers.

Given that the vast majority of e-cigarettes are sold online (Etter et al., 2011), the internet is the most appropriate means to reach users. We therefore posted two survey forms, in English and Greek, on the survey website www.surveymonkey.com over a 3-month period between 14 September 2011 and 13 December 2011. Links to the survey were posted on international (e-cigarette-forum.com, minicigarette.net, vaporboards.com, electroniccigaretteforum.net, new-smoke.com, vaportalk.com, vaporgossip.com) and Greek (e-kapnisma.gr) websites that provide information about e-cigarettes and/or sell them. Eligible participants were people who declared that they were previous tobacco cigarette users and were currently using e-cigarettes and who could also provide the brand names of both the tobacco cigarette and the e-cigarette that they used most often. Participants were asked to respond to five survey questions: "1. On average, how many tobacco cigarettes did you use to smoke per day?" (response from 1 to >120 with increments of 1); "2. What brand of tobacco cigarettes did you use to smoke?"; "3. What is the quantity (in mg) of nicotine in the liquid you use for your e-cigarettes?" (response from 1 to >36 with increments of 1); "4. On average, how many ml of e-cigarette liquid do you use per day?" (response from 0.5 to >10 with increments of 0.5); "5. On average, how many times do you puff your e-cigarette in order to smoke 1 ml of liquid?" (response from 1 to >200 with increments of 1).

A total of 178 e-cigarette users completed the entire survey and were considered for the analysis. Of those, 141 completed the English survey, while 37 completed the Greek survey. Responses from both surveys were analyzed simultaneously. Results from questions 1 through 4 revealed that nicotine consumption via e-cigarettes was 1.5 times higher than nicotine consumption via tobacco cigarettes. Assuming that the users aimed for the same effect, this means that the average tobacco cigarette/e-cigarette nicotine absorption ratio is 1.5. Results from the 5th question demonstrated that the median number of puffs required to consume 1 ml of e-cigarette liquid was 50. Thus, e-cigarette puffs can be corrected to match a tobacco cigarette in terms of nicotine absorption after taking into account the nicotine content of the e-cigarette liquid. Based on the above, the e-cigarette puffs equivalent to that of 1 tobacco cigarette, while controlling for nicotine absorption, was calculated as:

$$\text{e-cigarette puffs} = (\text{TOB}_{\text{NIC}} \cdot 1.5 \cdot 50)/\text{eCIG}_{\text{NIC}}$$

where TOB_{NIC} is the tobacco cigarette nicotine content (in mg), 1.5 is the average tobacco cigarette/e-cigarette nicotine absorption ratio, 50 is the average number of puffs required to consume 1 ml of liquid and eCIG_{NIC} is the e-cigarette liquid nicotine content (in mg) per ml. Since two tobacco cigarettes were smoked in the $\text{ACTIVE}_{\text{TOB}}$ session, the result of the above equation was multiplied by 2 to derive the total number of puffs during the $\text{ACTIVE}_{\text{E-CIG}}$ session. Based on this method, the total number of puffs during the $\text{ACTIVE}_{\text{E-CIG}}$ session ranged from 3 [for a subject who smoked "extra light" cigarettes (0.2 mg of nicotine per cigarette)] to 14 (for two subjects who smoked cigarettes containing 1 mg of nicotine per cigarette). The median puff number was 11, and the mean ± SD puff number was 10.4 ± 2.7.

Passive smoking protocols

In the $\text{PASSIVE}_{\text{CON}}$ session, never-smokers were exposed to normal room air for 1 h inside a 60 m^3 environmentally controlled chamber (air temperature: 21 °C; air velocity: 0.05 $m\,s^{-1}$; humidity: 45%). In the $\text{PASSIVE}_{\text{TOB}}$ session, participants were exposed to air polluted with tobacco cigarette smoke at a stable CO concentration to simulate bar/restaurant levels (23 ± 1 ppm; CO90 CO–CO_2 analyzer, Martindale Electric Ltd., Watford, UK), for 1 h inside the same chamber, as previously described (Flouris et al., 2008, 2009, 2010a; Metsios et al., 2007). The desired CO concentration of the gas mixture was achieved by combustion of cigarettes from various popular brands [i.e. equal number of Camel (Tar: 16 mg; Nicotine: 1.1 mg), Davidoff Classic (Tar: 12 mg; Nicotine: 0.9 mg), Gauloises Filter (Tar: 12 mg; Nicotine: 0.9 mg), Original Red Lucky Strike (Tar: 26 mg; Nicotine: 1.6 mg), Marlboro Reds (Tar: 16 mg; Nicotine: 1.2 mg), Prince Classic (Tar: 21 mg; Nicotine: 1.1 mg) and Silk Cut Purple King Size (Tar: 5 mg; Nicotine: 0.5 mg) tobacco cigarettes]. Mainstream smoke was generated from cigarettes by using an air pump (DYN, Volos, Greece) set at an air flow rate of 4 l min^{-1}. Cigarettes were half smoked using the air pump and then were left lit for 2 min to generate sidestream smoke, and then the rest of the cigarettes were smoked. An average of 29.2 ± 0.9 cigarettes were smoked in order to achieve the required level of CO in the exposure chamber. In the $\text{PASSIVE}_{\text{E-CIG}}$ session, participants were exposed to air polluted with e-cigarette vapour for 1 h in the same chamber. In this case, a simulated a bar/restaurant e-cigarette smoking environment was achieved by smoking e-cigarettes (device and liquid similar to those used during the $\text{ACTIVE}_{\text{E-CIG}}$ session) via the same air pump set at an air flow rate of 4 l min^{-1} for the same time as in the $\text{PASSIVE}_{\text{TOB}}$ session.

In previous experiments (Flouris et al., 2008, 2009, 2010a; Metsios et al., 2007) we simulated a passive smoking environment by placing lit cigarettes in ashtrays and using nearby fans to circulate the air in the room (i.e. 100% sidestream smoke). In the current study, we were forced to use an air pump given that e-cigarettes produce vapor only when a vacuum is generated. However, the increased oxygen and burn temperature produced by applying air current within the cigarettes via the air pump may have resulted in more efficient combustion and "cleaner" smoke. Therefore, we conducted a pilot study to assess lung function prior to and following the current protocol and the one used in our previous studies. Seven never-smokers participated in the two sessions that were conducted using identical pre-calibrated equipment and in a random order at the same time of the day on two separate days scheduled 7 d apart.

Cotinine biochemical analysis

Veins of the antecubital fossa were accessed for the collection of 5 ml of whole blood. Blood was centrifuged and serum samples were frozen without delay to −20 °C until analyzed. Two milliliters of each sample were placed in test tubes. Ketamine (10 µl from a 10 ppm solution) was added into each sample as an internal standard. Further, 1.5 ml ammonium formate (5 mM, pH = 3.1) was added to each sample that was followed by a solid phase extraction step. Column (Varian,

bond Elut–C18, 100 mg, 1 ml; Varian, Inc, Walnut Creek, CA) activation was executed by adding 1 ml of methanol and 1 ml of ammonium formate. Thereafter, the sample solution was passed through the column and washed with 1 ml of water. Elution was performed by 1 ml of methanol containing 5% ammonium hydroxide (v/v). The collected solution was acidified by 100 µl HCl (1% in methanol) and evaporated under a gentle nitrogen steam at 25 °C (Miller et al., 2010). Samples were reconstituted in 100 µl of methanol and analyzed by liquid chromatography mass spectrometry (LCMS).

A LCMS system (Shimadzu LCMS-2010 EV, Shimadzu Co., Kyoto, Japan) equipped with an electrospray ionization interface, an autosampler, solvent degasser, binary pump and a heated/cooled column compartment was used for cotinine extraction from serum samples and analysis. The column was a Discovery C18 Column (25 cm × 4.6 mm, 5 µm; SupelCo, Bellefonte,PA). Both mass spectrometer and HPLC inlet were controlled by Shimadzu LCMS solution software (LCMS Solution version 3) that was also used for data acquisition and processing. The instrument was tuned and calibrated using autotune procedures recommended by the manufacturer. Curved desolvation line and heat block temperatures were 250 °C and 200 °C, respectively. The detector voltage was 1.5 kV and the nebulizing gas flow was 1.5 l/min.

Twenty microliters from each extracted sample were placed into the chromatograph column at a temperature of 45 °C. A gradient of 10 mM ammonium acetate, pH = 5.2, (solvent A) and an acetonitrile (solvent B) were selected for routine use: starting at 10% of solvent B, 90% B (15 min linear ramp), 10% B (5 min). The total mobile phase flow rate was 0.6 ml/min. The detection was done in selected ion monitoring positive mode using ion fragments with *m/z* 163, 204 for nicotine, *m/z* 177, 218 for cotinine and *m/z* 238, 279 for ketamine. The fragments used for quantification were *m/z* 163, *m/z* 177 and *m/z* 238 for nicotine, cotinine and ketamine, respectively.

Lung function

Spirometry was performed according to the American Thoracic Society recommendation (American Thoracic Society, 1995) using a spirometer (Spirobank II; MIR, Rome, Italy) and always by the same technician to ensure reliability. Values measured included forced vital capacity (FVC), forced expiratory volume in 1 s (FEV_1), FEV_1/FVC ratio, peak expiratory flow (PEF) and forced expiratory flow in the middle 50% of FVC (FEF_{25-75}). Moreover, exhaled CO was assessed using a breath CO monitor (Breath CO Monitor; Clement Clarke International, Essex, UK) and the fraction of exhaled nitric oxide (FeNO) was measured using a breath NO analyser (NObreath, Bedfont, Rochester, UK) at 50 ml s^{-1} exhalation flow.

Sample size estimation

Given the two distinct sub-populations (i.e. smokers and never-smokers) investigated in this study, *a priori* sample size calculations were conducted separately and the larger sample size required was used. For active smoking in smokers, the minimum required sample size was determined using a recent e-cigarette study (Eissenberg, 2010), where plasma nicotine was measured prior to and immediately following tobacco cigarette (2.0 versus 16.8 ng ml^{-1}) and e-cigarette (2.0 versus 2.5 ng ml^{-1}) active smoking. Given the lack of previous passive e-cigarette smoking studies, the minimum required sample size for passive smoking in never-smokers was determined using a tobacco cigarette passive smoking study (Metsios et al., 2007), where serum cotinine was measured prior to and immediately following a similar 1 h tobacco cigarette passive smoking exposure (8 versus 23.17 ng ml^{-1}) and a control exposure (8.27 versus 9.17 ng ml^{-1}).

Sample size calculations were conducted using G*Power 3.0 [Institut der Universität Bonn, Bonn, Germany (Faul et al., 2007)]. The A.R.E. method of the "Wilcoxon signed-rank test" incorporated in the "*t* tests" family with "*a priori*" as the type of power analysis was used to calculate the power of the within effect. A two-tailed test was selected. Statistical power and α error probability were set to 0.95 and 0.05, respectively. The minimum required sample size was determined by calculating the effect size *d*. Using the aforementioned published data (Eissenberg, 2010; Metsios et al., 2007), the resulting minimum required sample sizes for smokers and never-smokers were 11 and 6 participants, respectively. The protocols of power analyses and the corresponding central and non-central distributions are provided in Figure 3. In order to confidently detect a reasonable departure from the null hypothesis, the total sample size studied in each sub-population was 15 participants.

Statistical analysis

Four analyses were conducted in order to examine the purpose of the present study. The first analysis assessed the validity of the adopted model for the calculation of e-cigarette puffs in the $ACTIVE_{E\text{-}CIG}$ session (see the "Active smoking protocols" section). For this purpose, Kendall's tau-b and the Wilcoxon signed-rank test were applied on the serum cotinine data obtained immediately after and 1 h after the $ACTIVE_{TOB}$ and the $ACTIVE_{E\text{-}CIG}$ sessions. The second analysis aimed to detect potential differences between our previously used ($PASSIVE_{TOB1}$) and the currently used ($PASSIVE_{TOB2}$) passive smoking protocol (see the "Passive smoking protocols" section). This was achieved by comparing the lung function data within each individual data collection time point (baseline, immediately post and 1 h post-exposure) using the Mann–Whitney *U* test. In the third analysis, Friedman tests followed by *post hoc* Wilcoxon signed-rank tests were used to assess changes over time (prior to, immediately after and 1 h after active or passive smoking) within the same session ($ACTIVE_{CON}$, $ACTIVE_{TOB}$, $ACTIVE_{E\text{-}CIG}$, $PASSIVE_{CON}$, $PASSIVE_{TOB}$ and $PASSIVE_{E\text{-}CIG}$) on all examined variables (FVC, FEV_1, FEV_1/FVC ratio, PEF, FEF_{25-75}, CO, FeNO and cotinine). In the fourth analysis, Friedman tests followed by *post hoc* Wilcoxon signed-rank tests were used to detect changes across sessions (CON, TOB and E-CIG) within each time point (prior to, immediately after and 1 h after smoking) for both active and passive smoking. The accepted level of significance was $p \leq 0.05$ and, where applicable, it was adjusted for multiple comparisons using the Bonferroni correction. As such, the level of significance for analyses three and four was set at $p \leq 0.001$.

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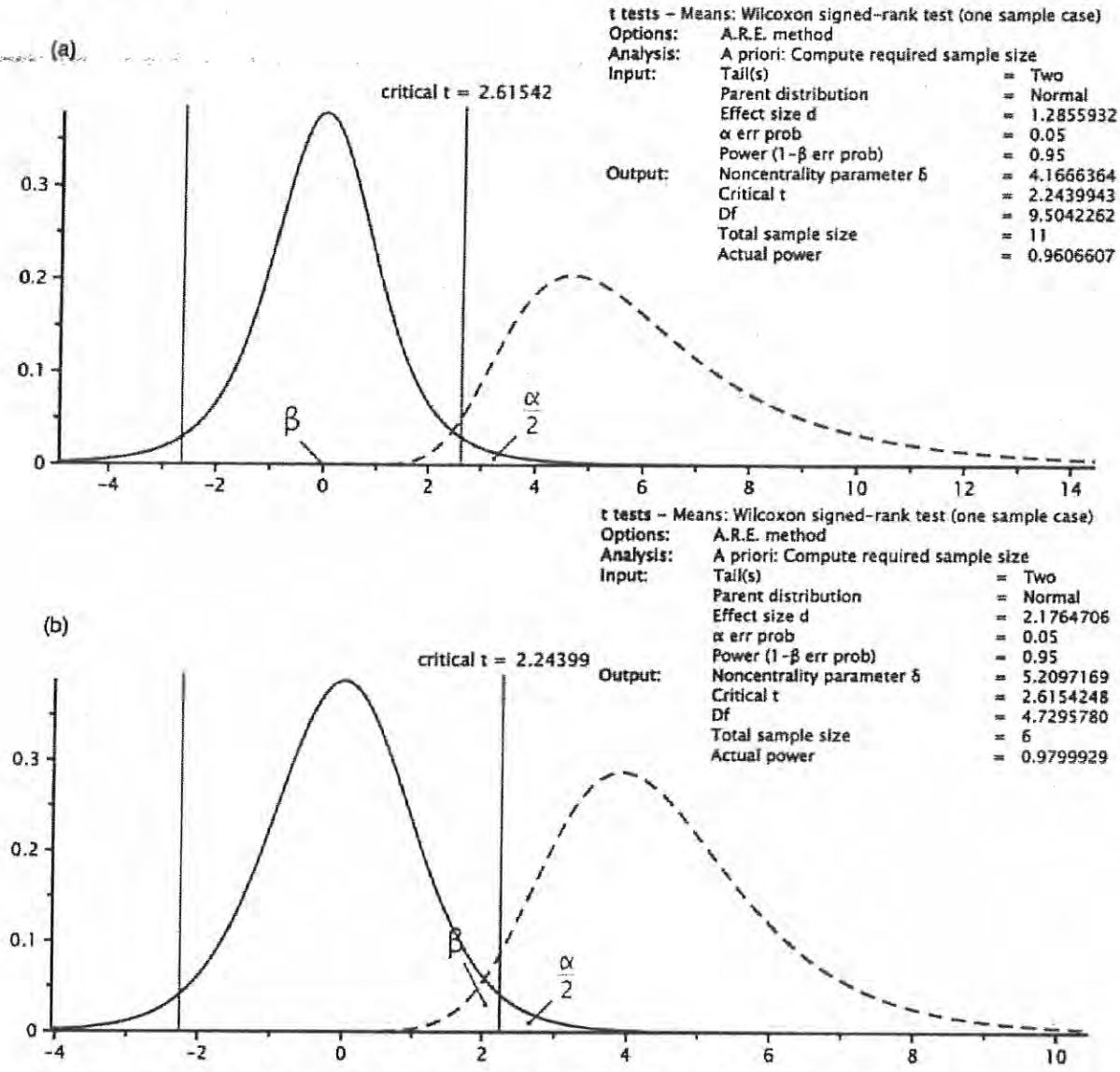

Figure 3. Protocols of power analyses and the corresponding central and non-central distributions for each sub-population for the calculation of the minimum required sample size: smokers (a); never-smokers (b).

Results

For the first analysis, the levels of serum cotinine detected immediately after and 1 h after the $ACTIVE_{TOB}$ and the $ACTIVE_{E\text{-}CIG}$ are illustrated in Figure 4. A statistically significant linear association was detected (tau-b = 0.585, $p < 0.001$) as well as no mean difference ($z = -1.29$, $p = 0.199$) between the serum cotinine levels observed immediately after and 1 h after the $ACTIVE_{TOB}$ and the $ACTIVE_{E\text{-}CIG}$ sessions. For the second analysis, the lung function results from the previously used ($PASSIVE_{TOB1}$) and the currently used ($PASSIVE_{TOB2}$) passive smoking protocol are provided in Table I. Mann–Whitney U tests comparing the lung function data within each individual data collection time point (i.e. baseline, immediately post and 1 h post-exposure) detected no statistically significant differences between the two protocols ($p > 0.05$).

Results for both active and passive smoking are illustrated in Figures 5 and 6, respectively. In the third analysis aiming to detect changes across time, Friedman's tests demonstrated no statistically significant fluctuations during the $ACTIVE_{CON}$ session ($p > 0.001$). In contrast, FEV_1/FVC ($\chi^2 = 17.71$, $p < 0.001$), $FEF_{25\text{-}75}$ ($\chi^2 = 17.29$, $p < 0.001$) and CO ($\chi^2 = 20.32$, $p < 0.001$) changed significantly across time during the $ACTIVE_{TOB}$ session, while the change observed in cotinine levels was slightly above the significance level ($\chi^2 = 12.13$, $p = 0.002$). During the $ACTIVE_{E\text{-}CIG}$ session, cotinine was the only parameter that fluctuated significantly ($\chi^2 = 14.93$, $p = 0.001$). Post-hoc Wilcoxon signed-rank tests revealed that cotinine and CO increased, while FEV_1/FVC decreased significantly immediately after smoking in the $ACTIVE_{TOB}$ session ($p \leq 0.001$). One hour following smoking, CO returned to baseline levels ($p > 0.001$). Similar tests

DOI: 10.3109/08958378.2012.758197

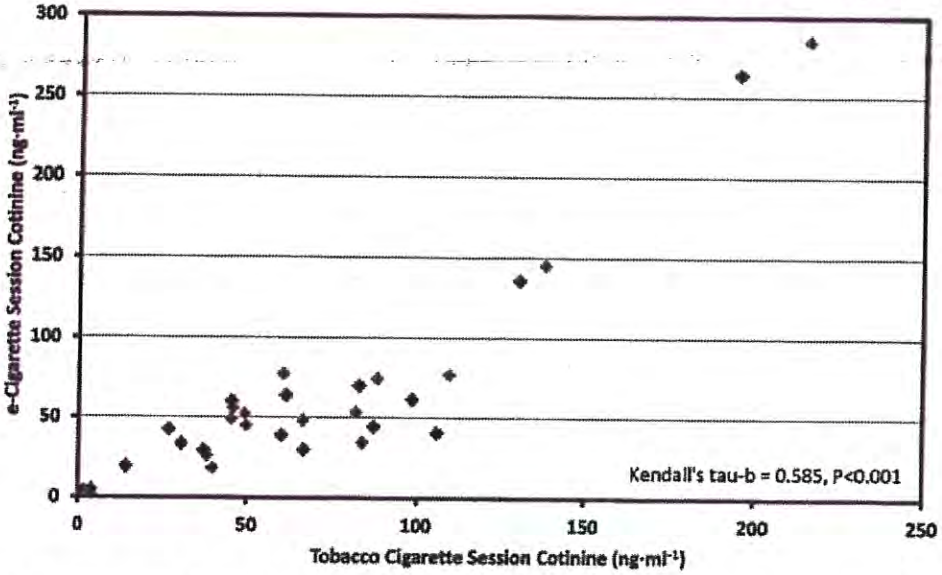

Figure 4. Scatter plot of serum cotinine levels detected immediately after (black symbols) and 1 h after (gray symbols) the $ACTIVE_{TOB}$ and the $ACTIVE_{E\text{-}CIG}$ sessions.

Table 1. Lung function results (mean ± sd) across time during the two tobacco cigarette passive smoking protocols.

Protocol	Time	FeNO	CO	FVC	FEV_1	FEV_1/FVC	PEF	FEF_{25-75}
$PASSIVE_{TOB1}$	Baseline	14.4 ± 7.6	1.0 ± 0.0	5.3 ± 1.1	4.4 ± 0.8	0.8 ± 0.1	9.3 ± 2.2	4.4 ± 1.0
	Post	13.1 ± 7.8	2.9 ± 0.7	5.2 ± 1.0	4.2 ± 0.7	0.8 ± 0.1	8.9 ± 1.8	4.3 ± 1.0
	1 h Post	11.6 ± 8.3	3.7 ± 0.8	5.2 ± 1.1	4.3 ± 0.8	0.8 ± 0.1	9.0 ± 2.0	4.4 ± 1.1
$PASSIVE_{TOB2}$	Baseline	15.3 ± 8.9	1.0 ± 0.0	5.3 ± 1.1	4.4 ± 0.8	0.8 ± 0.1	9.3 ± 1.9	4.4 ± 1.0
	Post	11.4 ± 8.2	2.7 ± 1.4	5.2 ± 1.0	4.3 ± 0.9	0.8 ± 0.1	9.1 ± 2.0	4.3 ± 1.2
	1 h Post	10.7 ± 9.0	4.0 ± 1.3	5.2 ± 1.1	4.3 ± 0.8	0.8 ± 0.1	9.2 ± 2.2	4.3 ± 1.2

FeNO = exhaled nitric oxide; CO = exhaled carbon dioxide; FVC = forced vital capacity; FEV_1 = forced expiratory volume in 1 s; PEF = peak expiratory flow; FEF_{25-75} = forced expiratory flow in the middle 50% of FVC; $PASSIVE_{TOB1}$ = previously used tobacco cigarette passive smoking protocol; $PASSIVE_{TOB2}$ = currently used tobacco cigarette passive smoking protocol.

on the $ACTIVE_{E\text{-}CIG}$ data revealed a significant increase in cotinine immediately after smoking ($p = 0.001$).

In never-smokers, Friedman's tests demonstrated no statistically significant fluctuations during the $PASSIVE_{CON}$ and the $PASSIVE_{E\text{-}CIG}$ sessions ($p > 0.001$). In contrast CO ($\chi^2 = 26.18$, $p < 0.001$) changed significantly across time during the $PASSIVE_{TOB}$ session, while the observed changes in cotinine ($\chi^2 = 11.83$, $p = 0.003$) and FEV_1/FVC ($\chi^2 = 10.80$, $p = 0.005$) were just above the significance level. Post-hoc Wilcoxon signed-rank tests revealed that cotinine and CO increased significantly immediately after passive smoking in the $PASSIVE_{TOB}$ session ($p \leq 0.001$). One hour following passive smoking, CO returned to baseline levels ($p > 0.001$).

In the fourth analysis, which aimed to detect changes across trials within each individual data collection time point, Friedman tests demonstrated no statistically significant differences at baseline ($p > 0.001$). In contrast, cotinine ($\chi^2 = 20.13$, $p < 0.001$), FEV_1/FVC ($\chi^2 = 25.66$, $p < 0.001$), FEF_{25-75} ($\chi^2 = 15.70$, $p < 0.001$) and CO ($\chi^2 = 26.07$, $p < 0.001$) were significantly different across trials immediately following active smoking. Cotinine levels ($\chi^2 = 25.20$, $p < 0.001$) remained significantly different among trials 1 h after active smoking. Post-hoc Wilcoxon signed-rank tests revealed that cotinine levels were higher immediately after as well as 1 h after active smoking in the $ACTIVE_{TOB}$ and the $ACTIVE_{E\text{-}CIG}$ sessions compared to those observed in the $ACTIVE_{CON}$ session ($p < 0.001$). Moreover, immediately after active smoking FEV_1/FVC was decreased and CO was increased in the $ACTIVE_{TOB}$ session compared to both the $ACTIVE_{CON}$ and the $ACTIVE_{E\text{-}CIG}$ sessions ($p < 0.001$).

In never-smokers, Friedman's tests demonstrated no statistically significant differences across trials at baseline as well as at 1 h after passive smoking ($p > 0.001$). Immediately after passive smoking CO ($\chi^2 = 25.40$, $p < 0.001$) was different across trials, while the difference detected in cotinine was just above the significance value ($\chi^2 = 12.04$, $p = 0.002$). Post-hoc Wilcoxon signed-rank tests revealed that cotinine levels were higher immediately after as well as 1 h after passive smoking in the $PASSIVE_{TOB}$ and the $PASSIVE_{E\text{-}CIG}$ sessions compared to those observed in the $PASSIVE_{CON}$ session ($p < 0.001$). Also, the CO was increased in the $PASSIVE_{TOB}$ session compared to both the $PASSIVE_{CON}$ and the $PASSIVE_{E\text{-}CIG}$ sessions immediately after passive smoking ($p < 0.001$), while no changes were observed 1 h thereafter ($p > 0.001$).

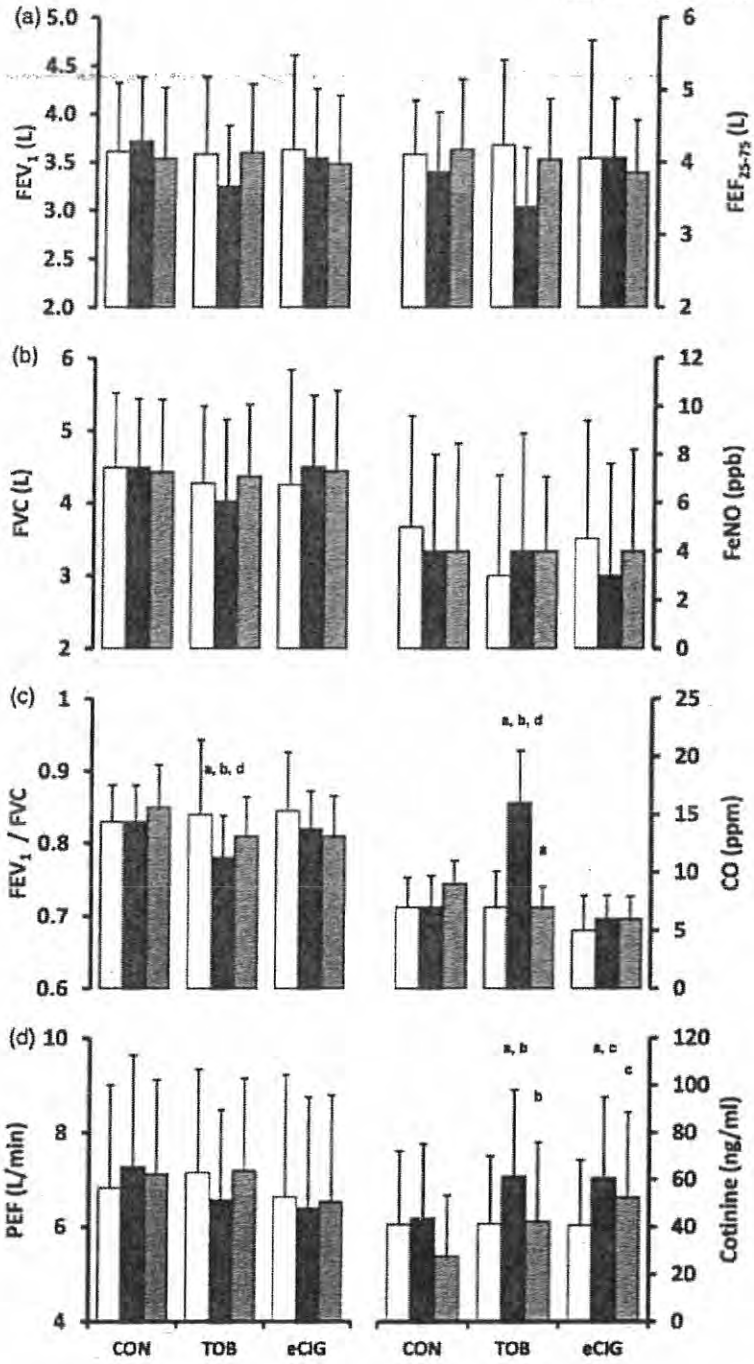

Figure 5. Results (median ± mean absolute deviation) of all the examined parameters prior to, immediately following and 1 h following active smoking. White bars represent baseline, black bars represent immediately after smoking, while gray bars represent 1 h post-smoking. a = significant ($p \leq 0.001$) difference from preceding time point within the same session; b = tobacco cigarette trial (TOB) found significantly ($p \leq 0.001$) different from control trial (CON) within the same time point; c = electronic cigarette trial (E-CIG) found significantly ($p \leq 0.001$) different from CON within the same time point; d = TOB found significantly ($p \leq 0.001$) different from E-CIG within the same time point. No statistically significant differences were observed between baseline and 1 h after smoking within the same session.

Discussion

In this study, we present the first comprehensive and standardized assessment regarding the impact of short term active and passive e-cigarette smoking on cotinine concentration and lung function compared to active and passive tobacco cigarette smoking. The results suggest that the effect of e-cigarettes on serum cotinine levels is similar to that generated by tobacco cigarettes during both active and passive smoking. Indeed, after taking into account that e-cigarette users adjust the concentration of nicotine in the liquid that they use in order to produce an effect similar to that of tobacco cigarettes, active e-cigarette and tobacco cigarette smoking resulted in similar increases in serum cotinine concentration levels. Furthermore, we found that e-cigarettes generated smaller changes in lung function compared to tobacco cigarettes.

Previous research has shown that, for a given number of puffs, nicotine absorption is significantly lower in e-cigarettes compared to tobacco cigarettes (Eissenberg, 2010; Vansickel et al., 2010). Our results confirm these findings demonstrating that nicotine consumption via e-cigarettes is 1.5 times higher than nicotine consumption via tobacco cigarettes. Thus, results from studies that used similar puffs across products

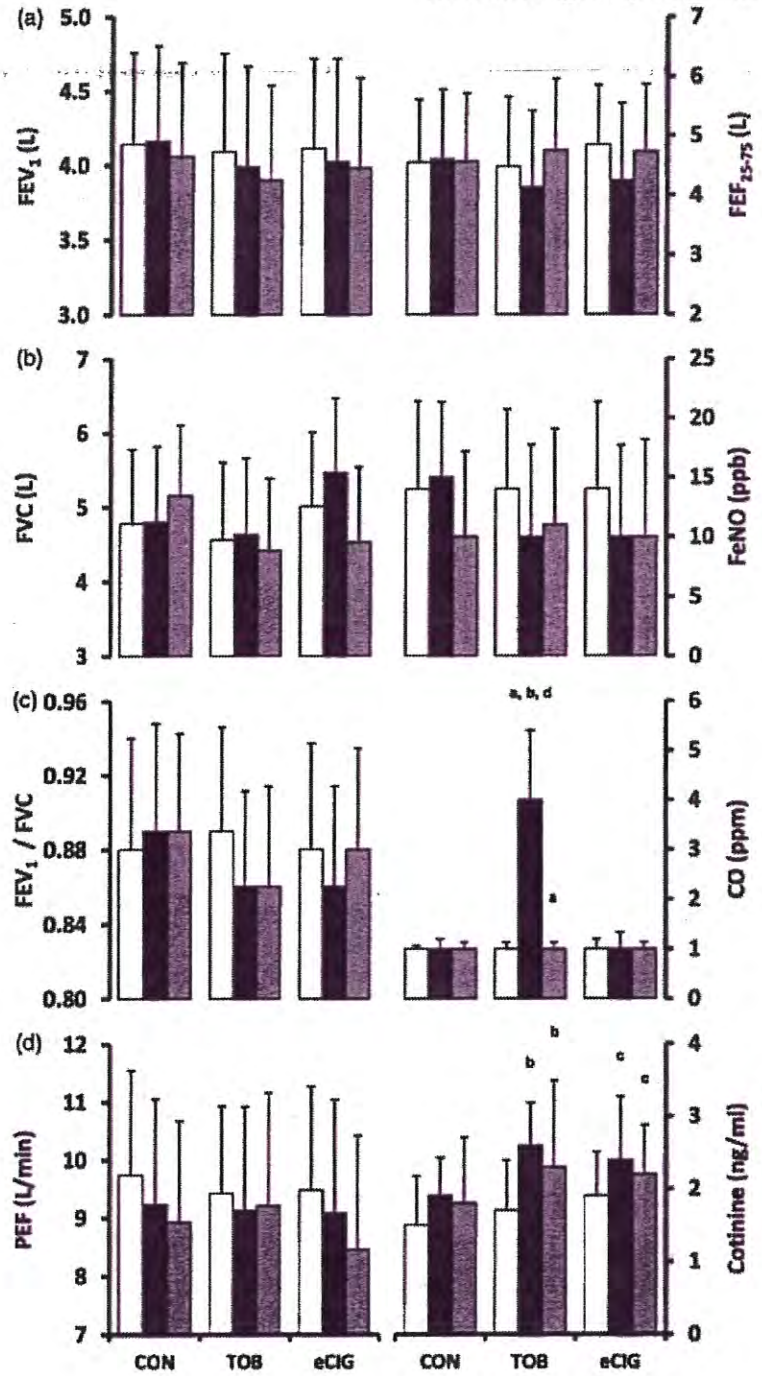

Figure 6. Results (median ± mean absolute deviation) of all the examined parameters prior to, immediately following and 1 h following passive smoking. White bars represent baseline, black bars represent immediately after smoking, while gray bars represent 1 h post-smoking. a = significant ($p \leq 0.001$) difference from preceding time point within the same session; b = tobacco cigarette trial (TOB) found significantly ($p \leq 0.001$) different from control trial (CON) within the same time point; c = electronic cigarette trial (E-CIG) found significantly ($p \leq 0.001$) different from CON within the same time point; d = TOB found significantly ($p \leq 0.001$) different from E-CIG within the same time point. No statistically significant differences were observed between baseline and 1 h after smoking within the same session.

may reflect a lower nicotine dose instead of reduced exposure to toxicants. In the present study, in order to create a relatively similar stimulus (from a nicotine standpoint), we used a survey method to calculate the number of puffs in the $ACTIVE_{E\text{-}CIG}$ session needed to deliver equivalent nicotine to each participant's preferred tobacco cigarette brand. To our knowledge, this is the first study in the peer reviewed literature to use this method. The present serum cotinine results demonstrate similar increases (compared to baseline) in the $ACTIVE_{TOB}$ and the $ACTIVE_{E\text{-}CIG}$ sessions, and no statistically significant differences between them. Moreover, we observed a statistically significant association and no mean difference between the serum cotinine levels observed immediately after and 1 h after smoking in the $ACTIVE_{TOB}$ and the $ACTIVE_{E\text{-}CIG}$ sessions. These results support the validity of this model, confirming that our results are not influenced by changes in nicotine dose.

The assessment of lung function demonstrated that neither a brief session of active e-cigarette smoking nor a 1 h passive e-cigarette smoking session significantly interfered with normal lung function. On the other hand, acute active and passive tobacco cigarette smoking undermined lung function, as repeatedly shown in previous studies (Eisner et al., 2007;

Flouris et al., 2008, 2009, 2010a; Metsios et al., 2007; Yates et al., 2001). It should be noted, however, that while some indices (e.g. FEV_1 in smokers) were not affected following active or passive e-cigarette smoking, their levels were not significantly different from those observed following active or passive tobacco cigarette smoking, respectively. While this is probably due to large response variability, the present results do not suggest that the acute effects of e-cigarettes on lung function are completely different than those of tobacco cigarettes.

The spirometry results regarding active e-cigarette smoking are in line with the only other published study (Vardavas et al., 2012) that assessed the acute pulmonary effects of active e-cigarette smoking. Both studies report no effects of active e-cigarette smoking on spirometry indicators. However, Vardavas and colleagues (2012) reported a significant reduction in FeNO following active e-cigarette smoking, which is contrary to our finding of no effect of active e-cigarette smoking on FeNO. Moreover, Vardavas and colleagues (2012) extended their lung function assessment by measuring total respiratory resistances, reporting significant adverse effects of active e-cigarette smoking. It is important to note, however, that the experimental design of that study incorporated methodological limitations that constrain the clinical significance of its findings. Some of these limitations include the lack of proper control group and subject randomization, lack of comparisons on the effects of e-cigarette smoking compared to that of tobacco cigarette smoking, not controlling for the influence of recent (i.e. previous $\geq$5 hours) smoking on the obtained results, and adopting a random and uncontrolled 5 min e-cigarette smoking protocol. Controlled human exposure studies must appropriately randomize human subjects and expose them to a carefully controlled stimulant/environment in order to eliminate confounding factors and be easily extrapolated to the effects of more chronic or recurrent exposures. To our knowledge, the present study represents the first comprehensive and standardized assessment regarding the acute and short-term impact of active and passive e-cigarette smoking on the function and inflammation of the lungs, as compared to active and passive tobacco cigarette smoking.

Chronic lung disease is normally a long-term process. However, even brief exposures to air pollution can stimulate mechanisms that contribute to its development (Flouris, 2009; Flouris et al., 2009). Indeed, production of growth factors and type 1 procollagen in the small airways is rapidly increased within the first few minutes of smoke inhalation (Churg et al., 2006). Leucocytes start bonding to endothelial cells within 5 min (Lehr et al., 1991), while lung inflammation (as seen through FeNO) is increased within the first 15 min (Yates et al., 2001). By 20 min, platelet activation is increased (Davis et al., 1989), while within 1 h nearly all body systems are affected (Flouris et al., 2008, 2009, 2010b; Metsios et al., 2007). All these mechanisms are linked with the development and/or exacerbation of chronic lung disease. While it is essential to study the effects of long-term e-cigarette vapor inhalation (both active and passive), investigating its acute phase represents an essential first step in the germane research agenda (Etter et al., 2011).

The tobacco cigarette and e-cigarette smoking used in the present study were neither extreme nor prolonged. The protocols used for active and passive smoking have been standardized by our group (Flouris et al., 2008, 2009, 2010a, 2012; Metsios et al., 2007) and others (Bullen et al., 2010; Vansickel et al., 2010). For passive smoking, concentrations of CO as high as 33 ppm have been recently reported at bars (Goniewicz et al., 2009), while CO concentrations of up to 29 ppm have been previously reported in workplace environments (White & Froeb, 1980). In addition, a number of studies on the acute health effects of passive smoking have used CO concentrations between 30 and 40 ppm (Giannini et al., 2007; Kato et al., 1999; Leone and Balbarini, 2008), while exposures at 24 ppm are considered moderate (Scherer et al., 1990). Yet, it is important to note that the present results apply to the e-cigarette device and liquid tested and may not describe appropriately the acute and short-term usage of other devices and/or liquids. Also, the current lung function results are limited by the impossibility of blinding our participants to active and passive smoking. However, suggestibility does not appear to underlie acute physiological responses to smoke inhalation (Urch et al., 1988).

It is concluded that, for the e-cigarettes tested, the effect of active and passive e-cigarette smoking on serum cotinine levels is similar to that generated by tobacco cigarette smoking. Moreover, neither a brief session of active e-cigarette smoking nor a 1 h passive e-cigarette smoking significantly interfere with normal lung function. In contrast, acute active and passive tobacco cigarette smoking significantly undermine lung function. Future research should target the health effects of long-term e-cigarette usage, including the effects of nicotine dosage. In addition, research and validation via independent organizations must be incorporated within the design and implementation of the e-cigarette technology in order to protect public health.

Acknowledgements

ADF, MSC, AZJ, AMT and YK were involved in the study conception and design; ADF, MSC, KPP, AZJ, KK and YK were involved in the recruitment of subjects, measurements and handling of samples; MNT, AWH and AMT performed the cotinine analysis; ADF and MSC performed the analysis of data and drafted the manuscript; all authors revised the manuscript and read and approved its final version.

Declaration of interest

This study did not receive funding from external sources. The salary of ADF is paid by the Centre for Research and Technology Thessaly. He has served as an expert consultant for the World Health Organization regarding electronic nicotine delivery systems. All authors, except AWH, report no financial or personal relationships with other people or organizations that could influence (bias) their actions. AWH is a member of the Scientific Advisory Board of PMI.

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Indoor Air 2013; 23: 25–31
wileyonlinelibrary.com/journal/ina

INDOOR AIR
doi:10.1111/j.1600-0668.2012.00792.x

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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Received for review 20 February 2012. Accepted for publication 28 May 2012.

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.]

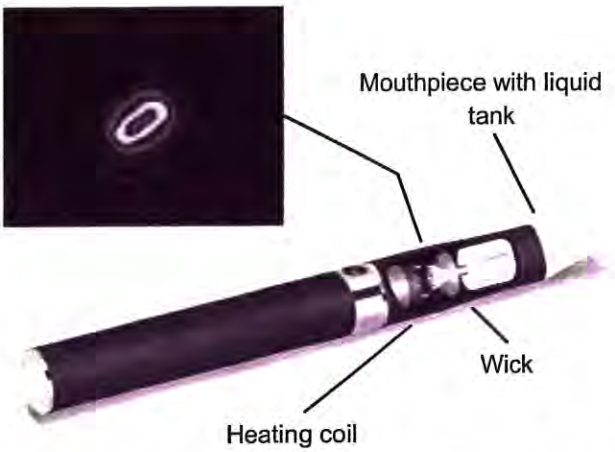

Fig. 1 Scheme of the tested e-cigarette A. The thermographic image shows the temperature distribution of the heating unit without 'liquid' (> 350°C in the center)

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).

$$\mathrm{MPP}=\frac{c_S}{n}\cdot V_S\cdot\frac{\dot{V}_C}{\dot{V}_S}\cdot\frac{\int_0^\infty e^{-k\cdot t}\,dt}{\int_0^t e^{-k\cdot t}\,dt}=\frac{c_S}{n}\cdot V_S\cdot\frac{\dot{V}_C}{\dot{V}_S}\cdot\frac{1}{1-e^{-k\cdot t}} \qquad (1)$$

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-m³ 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 (μg/m³) of selected compounds during the 8-m³ 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-m³ 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-m³ 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

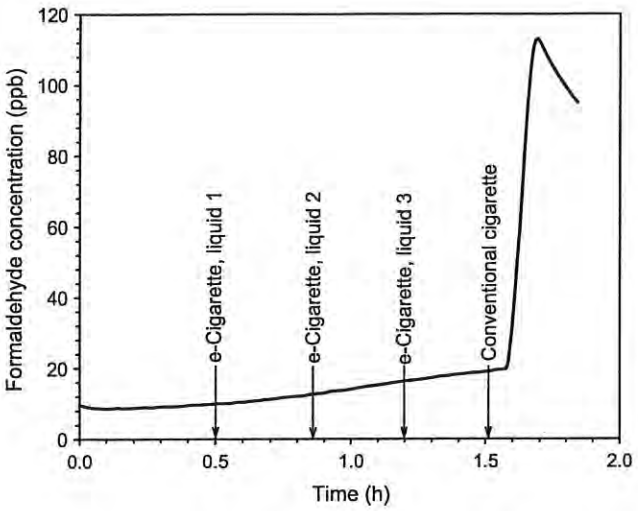

Fig. 2 Formaldehyde concentration in the 8-m^3 test chamber during consumption of e-cigarettes (Liquids 1–3) and one conventional cigarette

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

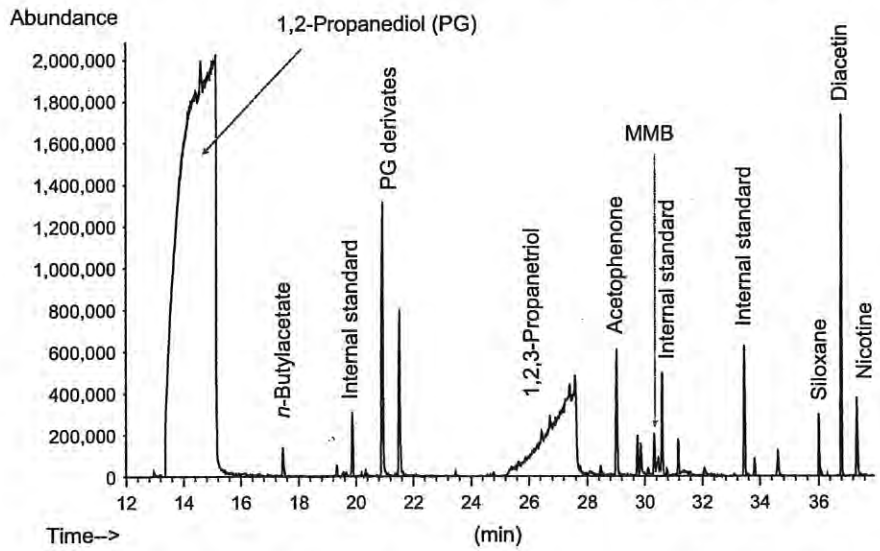

Fig. 3 Gas chromatogram of one exhaled e-cigarette puff (Liquid 2) in a 10-l glass chamber (sampled on Tenax TA, 3 l sampling volume) (MMB = 3-methylbutyl-3-methylbutanoate; PG = propylene glycol)

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

Compound	Concentration ($\mu g/m^3$)			Estimated mass per puff (μg/puff)[a]		
	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.

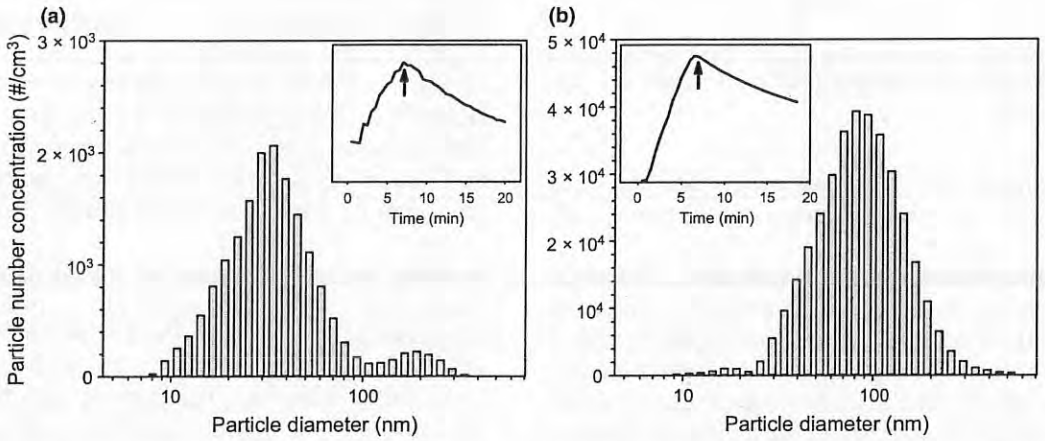

Fig. 4 (a) Aerosol size distribution during consumption of an e-cigarette in the 8-m^3 chamber. (b) Aerosol size distribution during consumption of a conventional cigarette in the 8-m^3 chamber. The arrows in the insets of (a) and (b) indicate the actual time in concentration development

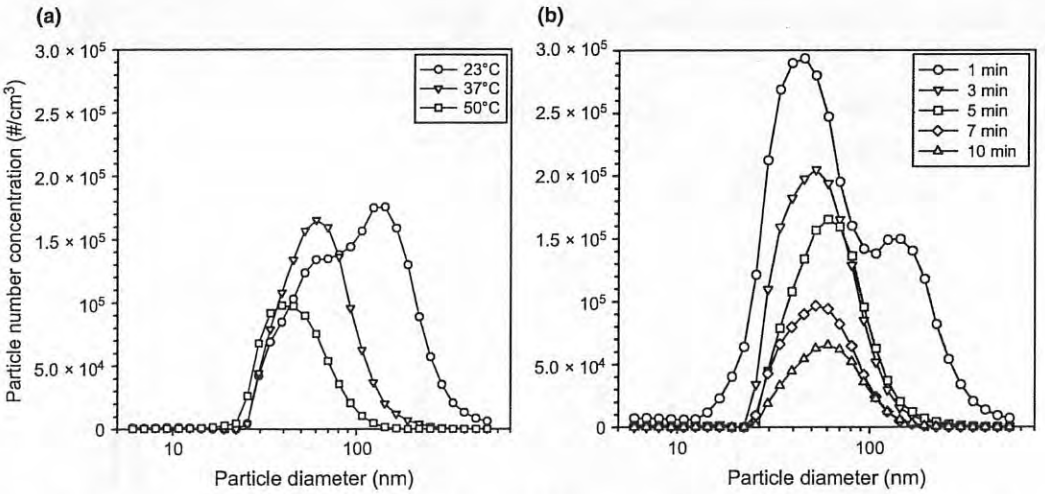

Fig. 5 Aerosol size distributions of aged e-cigarette aerosols in a 10-l glass chamber. The aerosol was aged for 5 min at different temperatures (a) and for different times at 37°C (b)

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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Testimony Opposing SB440
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5 March 2014

To the members of the Senate Committee on Judiciary and Labor, thank you for this opportunity to share with you my thoughts on SB440. I am a practicing primary care pediatrician with public health training. I spend a lot of time in my clinical work as well as population health work and medical education looking at population- and policy-based approaches to improving the health of Wisconsin's citizens.

SB440 is a bill which allows for a commercial product with unknown health implications to be used widely. "E-cigarettes" have no clear unbiased research indicating their safety to both users and those in the environments around them. I strongly support calls for FDA regulation with appropriate standards for identity, strength, purity, packaging and labeling with instructions and contraindications for use — including age of the user.

Additionally, from a pediatric perspective, broadening the number of locations at which children could observe behaviours that may lower their own resistance to eventual nicotine addiction is poor policy. I have many parents who are addicted to nicotine tell me that they don't smoke around their young children and "always go outside" (even in the deeply frigid Wisconsin winter, interestingly enough). That is certainly preferable to smoking in their immediate vicinity, but not only is second-hand smoke a direct health threat, the fact is that even very young children know what their parents are going outside to do – and this can translate into an acceptance of such behavior. While many parents are surprised to hear this, the single greatest influence on children's decisions around actions is generally what their own parents may do or think.

This is not theoretical: Centers for Disease Control and Prevention data indicates that the number of middle and high school students who reported using e-cigarettes doubled from 2011 to 2012. In 2012, 1.78 million middle and high school students had tried "vaping". While there is much talk about (but no evidence supporting) whether electronic cigarettes may offer a "safer" solution to nicotine addiction, let's be very clear: the best route is to avoid starting a nicotine addiction in the first place.

Finally, I would be remiss if I didn't point to the long history the tobacco industry has of marketing in both overtly and inherently deceptive ways. Many claims were made for the health benefits of tobacco until overwhelming scientific evidence revealed those claims to be false. Additionally, marketing to children has been accomplished through a number of routes, not the least of which is via the use of flavors. Electronic cigarettes have gone this route already, and I fear that the twin appeals of flavoring and the unproven perception of safety through broader visibility will effectively create the next generation of nicotine addicts.

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