

Tobacco tax

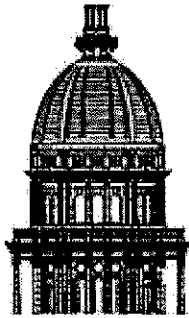
DEFINITION OF 'PIGOVIAN TAX'

A special tax that is often levied on companies that pollute the environment or create excess social costs, called negative externalities, through business practices. In a true market economy, a Pigovian tax is the most efficient and effective way to correct negative externalities. A type of a Pigovian tax is a "sin tax", which is a special tax on tobacco products and alcohol.

I Kimberly Sather am a registered and active voter in District 15. I dabbled in tobacco use as a youth but, didn't find it appealing. I started smoking at 38 years old due to the stress of a divorce. I found it at the time relaxing. I only planed to smoke until I got through the divorce which, took three years. I was still smoking 10 years later. I wanted to quit during that time. I tried nicotine gum, patches, Welbutrine, Chantix, and lozenges. They didn't work for me, in part because they didn't mimic the action of smoking (ie; the hand to mouth aspect of the habit). As I continued to smoke. I realized I had become a second class citizen. Because of my habit I smelled like an ashtray. My lung function was getting bad and I became fearful I would never quit. I was introduced to vaping over a year and a half ago. It took me a few months to actually quit 100% but, I have. I now feel better physically and better about myself. I no longer feel like a second class citizen. I am no longer a CIGARETTE SMOKER. A "sin tax" on this vaping products just puts former Oregon smokers back into being second class citizens. Had I quit using the other FDA approved methods, I would not be taxed on the use of such nicotine delivery systems. But, because I choose to vape instead, I am going to be penalized for using an alternative system. So, my question to you as the Representatives who we (Oregon Tax payers) elect into office. Is this tax you plan to impose a fair tax, will it really replace the money from the Tobacco Settlement or the revenue from tobacco sales tax. Will it cost more Oregonians their lives due to smoking related illness. How is not smoking tobacco a "sin"?

Thank you,

Kimberly Sather



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RESEARCH

E-Cigarettes Poised to Save Medicaid Billions

State Budget Solutions | by J. Scott Moody | March 31, 2015

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Electronic cigarettes (e-cigs) have only been around since 2006, yet their potential to dramatically reduce the damaging health impacts of traditional cigarettes has garnered significant attention and credibility. Numerous scientific studies show that e-cigs not only reduce the harm from smoking, but can also be a part of the successful path to smoking cessation.

The term "e-cig" is misleading because there is no tobacco in an e-cig, unlike a traditional, combustible cigarette. The e-cig uses a battery-powered vaporizer to deliver nicotine via a propylene-glycol solution-which is why "smoking" an e-cig is called "vaping." The vapor is inhaled like a smoke from a cigarette, but does not contain the carcinogens found in tobacco smoke.

Unlike traditional nicotine replacement therapy (NRT), such as gum or patches, e-cigs mimic the physical routine of smoking a cigarette. As such, e-cigs fulfill both the chemical need for nicotine and physical stimuli of smoking. This powerful combination has led to the increasing demand for e-cigs-8.2% use among nondaily smokers and 6.2% use among daily smokers in 2011.¹

The game-changing potential for dramatic harm reduction by current smokers using e-cigs will flow directly into lower healthcare costs dealing with the morbidity and mortality stemming from smoking combustible cigarettes. These benefits will particularly impact the Medicaid system where the prevalence of cigarette smoking is twice that of the general public (51% versus 21%, respectively).

Based on the findings of a rigorous and comprehensive study on the impact of cigarette smoking on Medicaid spending, the potential savings of e-cig adoption, and the resulting tobacco smoking cessation and harm reduction, could have been up to \$48 billion in Fiscal Year (FY) 2012.² This savings is 87% higher than all state cigarette tax collections and tobacco settlement collections (\$24.4 billion) collected in that same year.

Unfortunately, the tantalizing benefits stemming from e-cigs may not come to fruition if

artificial barriers slow their adoption among current smokers. These threats range from the Food and Drug Administration regulating e-cigs as a pharmaceutical to states extending their cigarette tax to e-cigs. To be sure, e-cigs are still a new product and should be closely monitored for long-term health effects. However, given the long-term fiscal challenges facing Medicaid, the prospect of large e-cigs cost savings is worth a non-interventionist approach until hard evidence proves otherwise.

**Table 1
Smokers Represent Significantly Larger Proportion of
Medicaid Recipients than General Population
2011**

State	Percent Smokers		Medicaid Enrollment	Number of Smokers on Medicaid
	Medicaid	General Population		
United States	51%	21.2% (median)	68,372,045	36,461,209
Alabama	52%	24.3%	938,313	487,923
Alaska	68%	22.9%	135,059	91,840
Arizona	49%	19.2%	1,989,470	974,840
Arkansas	54%	27.0%	777,833	420,030
California	45%	13.7%	11,500,593	5,175,262
Colorado	61%	18.3%	733,347	447,342
Connecticut	49%	17.1%	739,294	357,354
Delaware	58%	21.7%	223,225	129,471
Florida	46%	19.3%	3,529,173	1,761,420
Georgia	42%	21.2%	1,925,269	808,613
Hawaii	62%	16.8%	313,629	194,450
Idaho	62%	17.2%	409,456	253,863
Illinois	58%	20.9%	2,900,614	1,652,356
Indiana	68%	25.6%	1,208,207	821,581
Iowa	61%	20.4%	544,620	332,218
Kansas	54%	22.0%	363,755	196,425
Kentucky	65%	29.0%	1,065,840	692,796
Louisiana	43%	25.7%	1,293,869	556,364
Maine	63%	22.8%	327,524	206,340
Maryland	51%	19.1%	1,003,548	511,809
Massachusetts	53%	18.2%	1,504,611	797,444
Michigan	64%	23.3%	2,265,277	1,449,777
Minnesota	54%	19.1%	989,600	534,384
Mississippi	35%	26.0%	775,314	271,360
Missouri	66%	25.0%	1,126,505	743,493
Montana	70%	22.1%	136,442	95,009
Nebraska	64%	20.0%	254,000	181,760
Nevada	62%	22.9%	363,357	225,281
New Hampshire	80%	19.4%	152,182	121,746
New Jersey	36%	16.8%	1,304,257	469,533
New Mexico	50%	21.5%	571,621	285,811
New York	54%	18.1%	5,421,232	2,927,465
North Carolina	63%	21.8%	1,892,541	1,192,301
North Dakota	63%	21.9%	85,094	53,609
Ohio	65%	25.1%	2,526,533	1,642,246
Oklahoma	58%	26.1%	852,603	494,510
Oregon	67%	19.7%	690,864	462,544
Pennsylvania	70%	22.4%	2,443,909	1,710,736
Rhode Island	48%	20.0%	221,041	106,100
South Carolina	41%	23.1%	978,732	401,280
South Dakota	69%	23.0%	134,798	93,011
Tennessee	58%	23.0%	1,488,267	863,195
Texas	43%	19.2%	4,996,318	2,148,417
Utah	54%	11.8%	366,271	197,786
Vermont	67%	19.1%	184,088	123,339
Virginia	58%	20.9%	1,016,419	589,523
Washington	67%	17.5%	1,371,967	919,131
West Virginia	67%	28.6%	411,218	275,516
Wisconsin	63%	20.9%	1,292,799	814,463
Wyoming	62%	23.0%	76,372	47,351
District of Columbia	51%	20.5%	235,665	120,189

Source: Centers for Disease Control and Prevention, Centers for Medicare and Medicaid Services, and State Budget Solutions

Prevalence of Smoking in the Medicaid Population

According to the Centers for Disease Control and Prevention, in 2011, 21.2% of Americans smoked combustible cigarettes. However, as shown in Table 1, the smoking rate varies considerably across states with the top three states being Kentucky (29%), West Virginia (28.6%), and Arkansas (27%) and the three lowest states being Utah (11.8%), California (13.7%), and New Jersey (16.8%).³

Additionally, the smoking rate varies dramatically by income level. Nearly 28% of people living below the poverty line smoke while 17% of people living at or above the poverty line smoke.⁴

As a consequence, the level of smoking prevalence among Medicaid recipients is more than twice that of the general public, 51% versus 21%, respectively. However, this too varies considerably across states with the top three states being New Hampshire (80%), Montana (70%), and Pennsylvania (70%) and the three lowest states being Mississippi (35%), New Jersey (36%), and South Carolina (41%).⁵

In absolute terms, the U.S. Medicaid system includes 36 million smokers out of a total Medicaid enrollment of over 68 million. As such, this places much of the health burden and related financial cost of smoking on the Medicaid system which strains the system and takes away scarce resources from the truly needy.

Economic Benefit of Smoking Cessation and Harm Reduction

Smoking creates large negative externalities due to adverse health impacts. Table 2 shows the results of a

comprehensive study that quantified the two major costs of smoking in 2009—lost productivity and healthcare costs.⁶

Lost productivity occurs when a person dies prematurely due to smoking or misses time

from work due to smoking. This cost the economy \$185 billion in lost output in 2009.

Smokers incur higher healthcare costs when those individuals require medical services such as ambulatory care, hospital care, prescriptions, and neonatal care for conditions caused by smoking. This cost the economy \$116 billion in extra medical treatments.

Overall, in 2009 alone, the negative externalities of smoking cost the U.S. economy \$301 billion in lost productivity and higher healthcare costs. Not surprisingly, these costs were centered in high population states such as California (\$26.9 billion), New York (\$20.6 billion), and Texas (\$20.4 billion).

Literature Review On E-cig Impact On Harm Reduction Through Reduced Toxic Exposure and Smoking Cessation

E-cigs have only been around since 2006, yet their potential to dramatically reduce the damaging health impacts of traditional combustible cigarettes has garnered significant attention and credibility. Numerous scientific studies are showing that e-cigs not only reduce the harm from smoking, but is also a successful path to smoking cessation.

In perhaps the most comprehensive e-cig literature review to date, Neil Benowitz et al. (2014) identified eighty-one studies with original data and evidence from which to judge e-cig effectiveness for harm reduction.⁷ They concluded:

"Allowing EC (electronic cigarettes) to compete with cigarettes in the marketplace might decrease smoking-related morbidity and mortality. Regulating EC as strictly as cigarettes, or even more strictly as some regulators propose, is not warranted on current evidence. Health professionals may consider advising smokers unable or unwilling to quit through other routes to switch to EC as a safer alternative to smoking and a possible pathway to complete cessation of nicotine use."

There are two ways that e-cigs benefit current smokers. First, there is harm reduction for the smoker by removing exposure to the toxicity associated with the thousands of compounds, many carcinogenic, found in the burning of tobacco and the resulting smoke. Second, smoking cessation efforts by the smoker are enhanced by simultaneously fulfilling both the chemical need for nicotine and physical stimuli of smoking.

In the last few years the academic literature has exploded with articles on these two topics. The following is a selection of some of the most recent studies and their conclusions.

Reduced Toxic Exposure

Igor Burstyn (2014) concludes, "Current state of knowledge about chemistry of liquids and aerosols associated with electronic cigarettes indicates that there is no evidence that vaping produces

inhalable exposures to contaminants of the aerosol that would warrant health concerns by the standards that are used to ensure safety of workplaces . . . Exposures of bystanders are likely to be orders of magnitude less, and thus pose no apparent concern."⁸

State	Lost Productivity			Healthcare Costs	Total Smoking Costs
	Premature Death	Workplace	Total		
United States	117.1	67.5	184.6	116.4	301.0
Alabama	2.7	1.2	3.9	1.7	5.6
Alaska	0.2	0.2	0.4	0.3	0.7
Arizona	1.9	1.3	3.2	1.9	5.1
Arkansas	1.7	0.7	2.4	1.1	3.4
California	9.6	5.7	15.2	11.6	26.9
Colorado	1.3	1.2	2.5	1.6	4.1
Connecticut	1.2	0.7	1.8	1.7	3.6
Delaware	0.4	0.2	0.6	0.4	1.1
District of Columbia	0.3	0.1	0.4	0.5	0.9
Florida	7.9	4.4	12.3	7.3	19.6
Georgia	3.7	2.4	6.2	2.9	9.0
Hawaii	0.4	0.2	0.7	0.4	1.1
Idaho	0.4	0.3	0.7	0.4	1.1
Illinois	5.0	2.9	7.9	4.8	12.7
Indiana	3.0	2.1	5.1	2.6	7.7
Iowa	1.2	0.7	1.9	1.1	3.0
Kansas	1.0	0.6	1.6	1.0	2.6
Kentucky	2.6	1.3	3.9	1.8	5.7
Louisiana	2.4	0.9	3.3	1.8	5.1
Maine	0.6	0.3	0.9	0.7	1.6
Maryland	2.1	1.3	3.4	2.2	5.6
Massachusetts	2.2	1.3	3.4	3.7	7.1
Michigan	4.5	2.4	7.0	4.0	11.0
Minnesota	1.5	1.5	3.0	2.3	5.4
Mississippi	1.8	0.7	2.4	1.0	3.5
Missouri	3.0	1.5	4.5	2.7	7.2
Montana	0.3	0.2	0.6	0.4	0.9
Nebraska	0.6	0.5	1.1	0.7	1.8
Nevada	1.1	0.7	1.7	0.9	2.6
New Hampshire	0.5	0.3	0.8	0.6	1.4
New Jersey	2.9	1.8	4.7	3.6	8.3
New Mexico	0.5	0.4	0.9	0.6	1.5
New York	6.9	3.9	10.8	9.8	20.6
North Carolina	4.1	2.2	6.3	3.4	9.7
North Dakota	0.2	0.2	0.4	0.3	0.7
Ohio	5.7	2.9	8.6	5.2	13.9
Oklahoma	2.1	0.9	3.0	1.3	4.3
Oregon	1.3	0.8	2.1	1.3	3.4
Pennsylvania	5.4	3.2	8.5	5.7	14.2
Rhode Island	0.4	0.2	0.7	0.6	1.3
South Carolina	2.3	1.0	3.3	1.6	4.9
South Dakota	0.3	0.2	0.5	0.3	0.8
Tennessee	3.6	1.7	5.3	2.6	7.9
Texas	7.9	4.9	12.8	7.6	20.4
Utah	0.4	0.3	0.7	0.4	1.1
Vermont	0.2	0.1	0.4	0.3	0.7
Virginia	2.9	2.0	4.8	2.7	7.5
Washington	2.1	1.3	3.4	2.4	5.7
West Virginia	1.1	0.5	1.6	0.9	2.5
Wisconsin	2.0	1.4	3.4	2.4	5.8
Wyoming	0.2	0.2	0.4	0.2	0.6

Source: See Endnote 6 and State Budget Solutions

Neal Benowitz, et al. (2013) concludes, "The vapour generated from e-cigarettes contains potentially toxic compounds. However, the levels of potentially toxic compounds in e-cigarette vapour are 9-450-fold lower than those in the smoke from conventional cigarettes, and in many cases comparable with the trace amounts present in pharmaceutical preparation. Our findings support the idea that substituting tobacco cigarettes with electronic cigarettes may substantially reduce exposure to tobacco-specific toxicants. The use of e-cigarettes as a harm reduction strategy among cigarette smokers who are unable to quit, warrants further study."⁹

Kostantinos E Farsalinos et al. (2014) concludes, "Although acute smoking inhalation caused a delay in LV (Left Ventricular) myocardial relaxation in smokers, electronic cigarette use was found to have no such immediate effects in daily users of the device. This short-term beneficial profile of electronic cigarettes compared to smoking, although not conclusive about its overall health-effects as a tobacco harm reduction product, provides the first evidence about the cardiovascular effects of this device."¹⁰

Smoking Cessation

Emma Beard et al. (2014) concludes, "Among smokers who have attempted to stop without professional support, those who use e-cigarettes are more likely to report continued abstinence than those who used a licensed NRT [Nicotine Replacement Therapy] product bought over-the-counter or no aid to cessation. This difference persists after adjusting for a range of smoker characteristics such as nicotine dependence."¹¹

Christopher Bullen et al. (2013) concludes, "E-cigarettes, with or without nicotine, were modestly effective at helping smokers to quit, with similar achievement of abstinence as with nicotine patches, and few adverse events . . . Furthermore, because they have far greater reach and higher acceptability among smokers than NRT [Nicotine Replacement Therapy], and seem to have no greater risk of adverse effects, e-cigarettes also have potential for improving population health."¹²

Pasquale Caponnetto et al. (2013) concludes, "The results of this study demonstrate that e-cigarettes hold promise in serving as a means for reducing the number of cigarettes smoked, and can lead to enduring tobacco abstinence as has also been shown with the use of FDA-approved smoking cessation medication. In view of the fact that subjects in this study had no immediate intention of quitting, the reported overall abstinence rate of 8.7% at 52-weeks was remarkable."¹³

Konstantinos E. Farsalinos et al. (2013) concludes, "Participants in this study used liquids with high levels of nicotine in order to achieve complete smoking abstinence. They reported few side effects, which were mostly temporary; no subject reported any sustained adverse health implications or needed medical treatment. Several of the side effects may not be attributed to nicotine. In addition, almost every vaper reported significant benefits from switching to the EC [e-cigarette]. These observations are consistent with findings of Internet surveys and are supported by studies showing that nicotine is not cytotoxic, is not classified as a carcinogen, and has minimal effects on the initiation or propagation of atherosclerosis . . . Public health authorities should consider this and other studies that ECs are used as long-term substitutes to smoking by motivated exsmokers and should adjust their regulatory decisions in a way that would not restrict

the availability of nicotine-containing liquids for this population."¹⁴

Potential E-cig Medicaid Cost Savings

State	Medicaid Spending	Smoking Costs as Percent of Medicaid Spending	Smoking Costs on Medicaid
United States	415,154	11%	45,667
Alabama	5,027	9%	452
Alaska	1,348	15%	202
Arizona	7,905	18%	1,423
Arkansas	4,160	11%	458
California	50,165	11%	5,518
Colorado	4,724	17%	803
Connecticut	6,759	7%	473
Delaware	1,485	10%	148
District of Columbia	2,111	11%	232
Florida	17,907	11%	1,970
Georgia	8,526	10%	853
Hawaii	1,493	11%	164
Idaho	1,452	14%	203
Illinois	13,393	11%	1,473
Indiana	7,486	15%	1,123
Iowa	3,495	10%	350
Kansas	2,667	12%	320
Kentucky	5,702	12%	684
Louisiana	7,358	12%	883
Maine	2,413	14%	338
Maryland	7,657	12%	922
Massachusetts	12,926	11%	1,422
Michigan	12,460	13%	1,620
Minnesota	8,894	11%	978
Mississippi	4,466	9%	402
Missouri	8,727	14%	1,222
Montana	973	15%	146
Nebraska	1,722	15%	258
Nevada	1,739	11%	191
New Hampshire	1,187	15%	178
New Jersey	10,389	6%	623
New Mexico	3,430	12%	412
New York	53,306	11%	5,864
North Carolina	12,282	11%	1,351
North Dakota	744	12%	89
Ohio	16,352	13%	2,126
Oklahoma	4,642	12%	557
Oregon	4,587	15%	688
Pennsylvania	20,393	11%	2,243
Rhode Island	1,856	8%	148
South Carolina	4,848	11%	533
South Dakota	749	16%	120
Tennessee	8,798	11%	968
Texas	28,286	11%	3,111
Utah	1,903	14%	266
Vermont	1,353	15%	203
Virginia	6,906	11%	760
Washington	7,560	18%	1,361
West Virginia	2,790	11%	307
Wisconsin	7,096	13%	923
Wyoming	528	16%	85

Note: States do not sum to Total due to rounding.
Source: See Endnote 15 and State Budget Solutions

To date, the academic literature strongly suggests that e-cigs hold the promise of dramatic harm reduction for smokers simply by switching from combustible tobacco cigarettes to e-cigs. This harm reduction is due to both its positive impact on smoking cessation and reduced exposure to toxic compounds in cigarette smoke.

As a result, we can expect the healthcare costs of smoking to decline over time as the adoption of e-cigs by smokers continues to grow. Additionally, we can expect greater rates of adoption as e-cigs continue to evolve and improve based on market feedback—a dynamic that has never existed with other nicotine replacement therapies.

As discussed earlier, the potential savings to the economy are very large. In terms of healthcare alone, most of that cost is currently borne by the Medicaid system where the prevalence of cigarette smoking is twice that of the general public, 51% versus 21%, respectively. So what are the potential healthcare savings to Medicaid?

Brian S. Armour et al. (2009) created an impressive economic model to estimate how much smoking costs Medicaid based on data from the Medical Expenditure Panel Survey and the Behavioral Risk Factor Surveillance System.¹⁵

Overall, their model "... included 16,201 adults with weighting variables that allowed us to generate state representative estimates of the adult, noninstitutionalized Medicaid population."

The study concluded that 11% of all Medicaid expenditures can be attributed to smoking. Additionally, among the states these costs ranged from a high of 18%

(Arizona and Washington) to a low of 6% (New Jersey).

This study uses their percentage of Medicaid spending due to smoking and applies it to the latest year of available state-by-state Medicaid spending. As shown in Table 3, in FY 2012, smoking cost the Medicaid system \$45.7 billion. Of course, the largest states bear the brunt of these costs such as New York (\$5.9 billion), California (\$5.5 billion), and Texas (\$3.1 billion).

To put this potential savings to Medicaid into perspective, in FY 2012, state governments and the District of Columbia combined collected \$24.4 billion in cigarette excise taxes and tobacco settlement payments. As shown in Table 4, the potential Medicaid savings exceeds cigarette excise tax collections and tobacco settlement payments by 87%.

However, this varies greatly by state with high ratios in the South Carolina (435%), Missouri (409%), and New Mexico (260%), Arizona (238%), and California (238%) and low ratios in New Jersey (-39%), New Hampshire (-31%), Rhode Island (-17%), Connecticut (-13%), and Hawaii (-4%). Overall, 45 states and D.C. stand to gain more from potential Medicaid savings than through lost cigarette tax collections and tobacco settlement payments.

Note that many of the five states with negative ratios are distorted because excise tax collections are based on where the initial sale occurred and not where the cigarettes were ultimately consumed. This can vary greatly because of cigarette smuggling and cross-border shopping created by state-level differentials in cigarette excise taxes.¹⁶

For instance, New Hampshire has long been a source for out-of-state cigarette purchase from shoppers living in Massachusetts, Maine, and Vermont because of its lower cigarette excise tax. As such, the ratio is too high for Massachusetts, Maine, and Vermont and too low for New Hampshire. The same applies to New Jersey and Connecticut vis-à-vis New York and, more specifically, New York City, which levies its own cigarette tax on top of the state tax.

Hawaii is an exception due to its physical isolation which creates monopoly rents. Rhode Island levies a very high cigarette excise tax, but not relatively high enough compared to neighboring Connecticut and Massachusetts to drive a lot of cross-border shopping.

Other Potential E-cig Cost Savings

Another area of cost savings from greater e-cig adoption is the reduction in smoke and fire dangers in subsidized and public housing. According to a recent study, smoking imposes three major costs:

1. Increased healthcare costs from exposure to second hand smoke within and between housing units.
2. Increased renovation costs of smoking-permitted housing units.
3. Fires attributed to cigarettes.

As shown in Table 5, the study estimates that smoking imposes a nationwide cost of nearly \$500 million.¹⁷ The top three states facing the greatest expenses are New York (\$125 million), California (\$72 million), and Texas (\$24 million) while the top three states with the lowest expenses are Wyoming (\$0.6 million), Idaho (\$0.8 million), and Montana (\$1 million).

Applying Cigarette Taxes to E-cigs?

Many policymakers around the country have suggested applying the existing cigarette tax, wholly or in part, to e-cigs. This is bad public policy and is based on a fundamental misunderstanding of the cigarette tax.

The cigarette tax is what economists call a "Pigovian Tax" which is designed to mitigate negative externalities of certain actions. Cigarette smoking creates many negative externalities such as harmful health consequences to the user or to those in near proximity (second-hand smoke).

State	State Cigarette Tax Collections (a)	Tobacco Settlement Payments (b)	Smoking Costs on Medicaid	Smoking Costs on Medicaid as a Percent of State Cigarette Tax Collections and Tobacco Settlement Payments
United States	17,226	7,190	45,667	87%
Alabama	126	94	452	106%
Alaska	67	30	202	108%
Arizona	319	101	1,423	238%
Arkansas	247	51	458	54%
California	896	736	5,518	235%
Colorado	203	91	803	173%
Connecticut	418	124	473	13%
Delaware	121	27	148	1%
District of Columbia	36	38	232	214%
Florida	381	365	1,970	164%
Georgia	227	141	953	132%
Hawaii	122	49	164	4%
Idaho	48	25	203	177%
Illinois	606	274	1,473	67%
Indiana	465	130	1,123	89%
Iowa	225	66	350	20%
Kansas	104	55	320	95%
Kentucky	277	102	684	81%
Louisiana	133	141	853	222%
Maine	140	51	338	77%
Maryland	411	146	922	66%
Massachusetts	574	254	1,422	72%
Michigan	963	256	1,620	33%
Minnesota	422	167	978	66%
Mississippi	157	110	402	50%
Missouri	105	135	1,222	409%
Montana	87	30	146	24%
Nebraska	68	38	258	145%
Nevada	103	40	191	34%
New Hampshire	215	43	178	31%
New Jersey	792	231	623	39%
New Mexico	75	39	412	260%
New York	1,632	735	5,864	147%
North Carolina	295	141	1,351	210%
North Dakota	28	32	89	49%
Ohio	843	295	2,326	87%
Oklahoma	293	77	557	50%
Oregon	256	79	688	106%
Pennsylvania	1,119	337	2,243	54%
Rhode Island	132	47	148	17%
South Carolina	26	73	533	495%
South Dakota	60	24	120	42%
Tennessee	279	139	968	131%
Texas	1,470	475	3,111	60%
Utah	124	36	266	66%
Vermont	80	35	203	77%
Virginia	192	117	760	145%
Washington	471	151	1,361	119%
West Virginia	110	64	307	77%
Wisconsin	653	131	923	18%
Wyoming	26	19	85	90%

(a) Includes all forms of tobacco taxes.
(b) Includes Master Settlement Agreement and individual state payments.
Source: Department of Commerce; Census Bureau; Internal Revenue Service; and State Budget Solutions

**Table 5
Smoking Costs on Subsidized and Public Housing**

As detailed in this study, the negative externalities associated with traditional smoking are all but eliminated by e-cigs. Without evidence of actual negative externalities, applying the existing cigarette tax to e-cigs is simply bad public policy.

(Millions of Dollars) 2012	
State	Smoking Costs
United States	496.8
New York	124.7
California	72.4
Texas	28.3
Massachusetts	24.0
Florida	23.2
Ohio	21.7
Pennsylvania	17.7
New Jersey	15.8
Louisiana	14.4
North Carolina	13.9
Illinois	13.3
Tennessee	12.9
Michigan	12.8
Alabama	12.4
Georgia	11.6
Connecticut	10.7
Missouri	9.4
Indiana	8.3
Virginia	7.8
Mississippi	7.2
Kentucky	7.1
Minnesota	7.1
South Carolina	7.0
Maryland	7.0
Arkansas	6.8
Oklahoma	6.8
Wisconsin	6.5
Washington	5.0
Arizona	4.9
Colorado	4.5
West Virginia	4.3
Oregon	4.3
Maine	4.2
Rhode Island	4.0
Hawaii	3.8
Iowa	3.8
New Mexico	3.0
Kansas	2.9
Nebraska	2.1
Nevada	1.9
Vermont	1.9
New Hampshire	1.9
Utah	1.4
Delaware	1.3
North Dakota	1.2
South Dakota	1.1
Montana	1.0

Conclusion

Policymakers have long sought to reduce the economic damage due to the negative health impact of smoking. They have used tactics ranging from cigarette excise taxes to subsidizing nicotine replacement therapies. To be sure, smoking prevalence has fallen over time, but there is more that can be done, especially given the fact that so much of the healthcare burden of smoking falls on the already strained Medicaid system.

As with any innovation, no one could have predicted the sudden arrival into the marketplace of the e-cig in 2006. Since e-cigs fulfill both the chemical need for nicotine and physical stimuli of smoking the demand for e-cigs has grown dramatically. The promise of a relatively safe way to smoke has the potential to yield enormous healthcare savings. The most current academic research verifies the harm reduction potential of e-cigs.

As shown in this study, the potential savings to Medicaid significantly exceeds the state revenue raised from the cigarette excise tax and tobacco settlement payments by 87%. As such, the rational policy decision is to adopt a non-interventionist stance toward the evolution and adoption of the e-cig until hard evidence proves otherwise. While cigarette tax collections will fall as a result, Medicaid spending will fall even faster. This is a win-win for policymakers and taxpayers.

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State	Rate
Illinois	1.1
Iaho	0.8
Wyoming	0.6
Alaska	N.A.
District of Columbia	N.A.
Source: See Endnote 17 and State Budget Solutions	

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15. See Endnote 2 for reference.

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E-cigarettes, vaping and public health

A summary for policy-makers

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Counterfactual Consulting and Advocacy

February 2015

Version 3

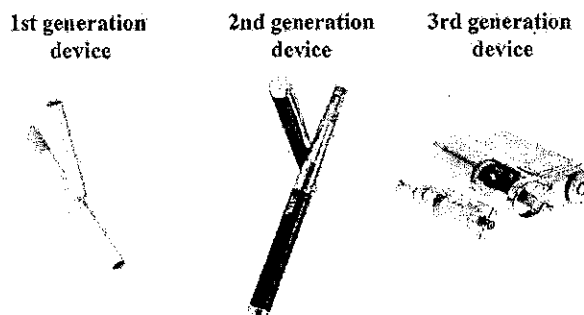
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1 Background

1.1 What are e-cigarettes?

E-cigarettes generally consist of a battery, a heating coil and a liquid containing nicotine. Drawing on the e-cigarette or pressing a switch activates the battery to heat the coil, which vaporises the liquid. This is then inhaled and the nicotine absorbed into the blood via mouth, throat and lungs. The liquids contain nicotine, water, a 'diluent' such as propylene glycol or glycerol, and a flavouring, such as tobacco, mint, vanilla or fruit. There are now hundreds of flavours and these are an intrinsic part of the appeal. The devices and the liquids can be sold as integrated units or with liquids sold separately. Some look like cigarettes (1st generation 'cig-a-likes'), some look like pens (2nd generation 'Ego' type), and the larger ones with tanks can look very distinctively different (3rd generation 'tanks' or 'mods').



Types of e-cigarette or vaping equipment

1.2 How have e-cigarettes come about?

The products have emerged only recently (since 2007) thanks to advances in battery technology, which can now provide sufficient power to vaporise an adequate flow of liquid and sufficient battery life to make devices practical. This has been the key enabling development – partly a spin-off from mobile phone technology. E-cigarettes first emerged in China, which is still the largest manufacturer by far, with increasingly sophisticated plant and designs.

1.3 How much are e-cigarettes used?

A survey conducted for Action on Smoking and Health estimated that there were 2.1 million adults in Great Britain using electronic cigarettes in March 2014. Of these, approximately 700,000 were ex-smokers while 1.3 million continued to use tobacco alongside their electronic cigarette use. Electronic cigarette use amongst never-smokers was negligible¹. For the US, CDC gives frequent use at 1.9% of adults and any e-cigarette use at 4.2% of adults², equating to around 4.6 and 10.1 million users respectively. A synthesis of 10 country surveys³ identified widespread use in many countries, including substantial use in those such as Australia where the products are, in practice, banned. According to this survey 7% of Australian smokers and former smokers were current users of e-cigarettes in 2013. This is likely to be a significant contributor to declines in smoking in Australia.

¹ ASH, Fact sheet: Use of electronic cigarettes in Great Britain, October 2014 [\[link\]](#)

² CDC, Tobacco Product Use Among Adults — United States, 2012–2013 [\[link\]](#)

³ Gravely S, Fong GT, Cummings KM, et al. Awareness, Trial, and Current Use of Electronic Cigarettes in 10 Countries: Findings from the ITC Project. *Int J Environ Res Public Health* 2014; 11: 11691–704. [\[link\]](#)

2 The public health case – tobacco harm reduction

2.1 Challenging the burden of smoking

In 2013, 19% of British adults aged 16 and older, roughly 9.9 million people, smoked⁴. Worldwide about 1 billion people smoke daily, about 6 trillion cigarettes are consumed annually (about 3 per adult person per day) and these numbers are *still rising*⁵. The current annual premature death tolls attributed to smoking are 100,000 in the UK and six million world-wide. WHO estimates smoking caused 100 million deaths in the 20th century. If current trends continue, it may cause one billion deaths in the 21st century⁶. The public health value of e-cigarettes could reduce this toll of death and disease by hundreds of millions if the promise is fulfilled.

The public health proposition is that:

- (1) E-cigarettes provide a satisfactory alternative to smoking (nicotine, sensory and ritual aspects) and will displace cigarette use in the consumer market for recreational nicotine.
- (2) E-cigarettes dramatically reduce risks to health, likely by 95-100%, among those who switch with negligible impacts on bystanders, at lower cost, and with lower social stigma. The vast majority of harm in smoking comes from tar and hot gases – products of combustion, rather than nicotine. These are almost entirely absent in e-cigarette vapour.
- (3) E-cigarettes are a market-based public health phenomenon that ‘meets people where they are’. The public health benefit does not rely on public spending, coercion, prohibition, punitive taxes, fear, stigma or treating smokers as though they are ill.
- (4) The risks of harmful unintended consequences, like gateways to smoking, are low, remain hypothetical and are so far unsupported by any evidence.

The alternative public health approach is to insist that smokers quit smoking and nicotine altogether, sometimes offering a variety of pharmaceutical aids and behavioural support. But this strategy simply does not work for many people because they cannot or do not want to quit smoking, or don't think the benefits justify the losses and efforts required. The public health case for e-cigarettes involves a major technological disruption of the continuing market for recreational nicotine. Global tobacco sales are variously estimated at \$700-800 billion (Bloomberg), mainly cigarettes, whereas sales of vapour products are no more than \$5 billion in 2014 (Euromonitor). There is scope for a major structural change in the market for recreational nicotine that could make substantial inroads into the billion deaths projected by WHO.

2.2 Benefits of vaping to a smoker

From the smoker's perspective, e-cigarettes create a new 'value proposition'. They offer many of the experiences of smoking (a nicotine hit, something to hold and gesture with, sensory experience etc) with few of the harms (long term risk is much lower, less social disapproval, minimal odour nuisance) and at a lower cost, with beneficial knock-on effects to the family budget – which can be especially important in poor families. Prior to the emergence of e-cigarettes, the alternatives were broadly

⁴ ONS, Opinions and Lifestyle Survey, Adult Smoking Habits in Great Britain, 2013, 25 November 2014 [\[link\]](#)

⁵ Ng M, Freeman MK, Fleming TD, et al. Smoking prevalence and cigarette consumption in 187 countries, 1980-2012. *JAMA* 2014; **311**: 183–92 [\[link\]](#). See full analysis at Counterfactual: *Are we in the endgame for smoking?* Jan 2015 [\[link\]](#)

⁶ WHO Factsheet *Tobacco*, May 2014 [\[link\]](#)

cast as 'quit or die' – this new value proposition fits between the two. It is likely to be successful, because it requires less effort to reduce the harm – i.e. it does not require complete nicotine cessation. **Expert views suggest a health risk of at least 95% or 20 times lower than smoking.**

In advice to a UK parliamentary hearing, leading UK smoking cessation experts; Professor Robert West of University College London, Professor Peter Hajek of Queen Mary University of London, Profesor Ann McNeill, of Kings College London, Dr Jamie Brown of University College London and Deborah Arnott, the Director of Action on Smoking and Health, put the relative risk in perspective⁷

From analysis of the constituents of e-cigarette vapour, e-cigarette use from popular brands can be expected to be at least 20 times safer (and probably considerably more so) than smoking tobacco cigarettes in terms of long-term health risks

Professor John Britton, Chair of the Royal College of Physicians Tobacco Group and Director of the UK Centre for Tobacco and Alcohol Studies, and his colleague Ilze Bogdanovica give a similar if unquantified message in an assessment for the government agency Public Health England⁸:

Overall however the hazards associated with use of products [e-cigarettes] currently on the market is likely to be extremely low, and certainly much lower than smoking.

Robert West & Jamie Brown, in an editorial for the British Journal of General Practice⁹, point out that we know enough to make reasonable judgements about e-cigarette risk relative to smoking.

Some reviews have bizarrely concluded that we do not know whether e-cigarette use is safer than smoking, ignoring the fact that the vapour contains nothing like the concentrations of carcinogens and toxins as cigarette smoke. In fact, toxin concentrations are almost all well below 1/20th that of cigarette smoke.

Professor Peter Hajek, reinforces the 95% reduction in risk, in an interview for News-Medical¹⁰

Electronic cigarettes are estimated to be at least 95% safer than cigarettes and they appeal to smokers who cannot or do not want to stop smoking, but who want to reduce the risks smoking poses to their health.

2.3 Do e-cigarettes help people to quit smoking?

An assessment of the trials undertaken at the end of 2014 for the Cochrane Library concludes¹¹

Combined results from two studies, involving over 600 people, showed that using an EC containing nicotine increased the chances of stopping smoking long-term compared to using an EC without nicotine. Using an EC with nicotine also helped more smokers reduce the amount they smoked by at least half compared to using an EC without nicotine.

The most comprehensive study so far of 'real world' use of e-cigarettes showed¹²

⁷ West R et al Briefing: Electronic cigarettes what we know so far. Presented to UK All-Party Parliamentary Group on Pharmacy: 10th June 2014 [\[link\]](#)

⁸ Britton J, Bogdanovica I. Electronic cigarettes: A report commissioned by Public Health England. May 2014 [\[link\]](#)

⁹ West R, Brown J. Electronic cigarettes: fact and fiction. Br J Gen Pract 2014; 64: 442–3. [\[link\]](#)

¹⁰ News-Medical, Electronic cigarettes and smoking cessation: an interview with Professor Peter Hajek, 5 Feb 2015 [\[link\]](#)

¹¹ McRobbie H, Bullen C, Hartmann-Boyce J, Hajek P. Electronic cigarettes for smoking cessation and reduction. Cochrane Database of Systematic Reviews 2014, Issue 12. Art. No.: CD010216. [\[link\]](#)

¹² Brown J, Beard E, Kotz D, Michie S, and West R (2014) Real-world effectiveness of e-cigarettes when used to aid

People attempting to quit smoking without professional help are approximately 60% more likely to report succeeding if they use e-cigarettes than if they use willpower alone or over-the-counter nicotine replacement therapies such as patches or gum

Survey data commissioned by Action on Smoking and Health in the UK¹³ also supports a good news story about people quitting smoking. 700,000 vapers are ex-smokers in Britain (~7% of smokers):

ASH estimates that there are currently 2.1 million adults in Great Britain using electronic cigarettes. Of these, approximately 700,000 are ex-smokers while 1.3 million continue to use tobacco alongside their electronic cigarette use. Electronic cigarette use amongst never smokers remains negligible

2.4 What is the potential?

The report by Britton and Bogdanovica for government agency Public Health England concluded¹⁴.

Smoking kills, and millions of smokers alive today will die prematurely from their smoking unless they quit. This burden falls predominantly on the most disadvantaged in society. Preventing this death and disability requires measures that help as many of today's smokers to quit as possible. The option of switching to electronic cigarettes as an alternative and much safer source of nicotine, as a personal lifestyle choice rather than medical service, has enormous potential to reach smokers currently refractory to existing approaches. The emergence of electronic cigarettes and the likely arrival of more effective nicotine-containing devices currently in development provides a radical alternative to tobacco, and evidence to date suggests that smokers are willing to use these products in substantial numbers.

Electronic cigarettes, and other nicotine devices, therefore offer vast potential health benefits, but maximising those benefits while minimising harms and risks to society requires appropriate regulation, careful monitoring, and risk management. However the opportunity to harness this potential into public health policy, complementing existing comprehensive tobacco control policies, should not be missed.

It is not only public health experts. One Wall Street analyst, Bonnie Herzog of Wells Fargo Securities, projects that vapour use will surpass smoking (in the US) within a decade (by which she means 2023)¹⁵. Much will depend on whether regulation encourages or suppresses innovation – and her forecast is contingent on an effective pro-innovation regulatory framework. In March 2014 she said:

Bottom line: if regulations don't stifle innovation, we continue to believe e-vapor consumption could surpass combustible cig consumption in the next decade, driving total profit pool growth and generating a roughly 7% CAGR.

If vaping came close to overtaking cigarette use, it would be one of the most remarkable disruptive public health technologies of modern times.

smoking cessation: A cross-sectional population study. *Addiction*109: [\[link\]](#)

¹³ ASH (UK) Fact sheet: Use of electronic cigarettes in Britain, July 2014 [\[link\]](#)

¹⁴ Britton J, Bogdanovica I. Electronic cigarettes: A report commissioned by Public Health England. May 2014 [\[link\]](#)

¹⁵ Cited in *The Economist*, Kodak moment, 23 September 2013. [\[link\]](#)

3 What are critics concerned about?

Opponents of e-cigarettes focus on two main arguments: risks to users and bystanders arising from exposure to vapour, population risks arising from changes in smoking or nicotine-using behaviour caused by e-cigarettes.

3.1 Risks arising from exposure to vapour

No-one should claim that vaping is entirely benign. It may prove to be, but that cannot be established without many years of data. However, vaping does not need to be *harmless* or *completely safe* to make deep inroads into the risks of disease if people switch from smoking.

Studies of liquids and vapour chemistry reveal traces of contaminants and thermal breakdown products that are potentially harmful, but at levels generally two orders of magnitude lower than in cigarette smoke and unlikely to pose a material threat. Critics of e-cigarettes routinely cite studies suggesting presence of harmful substances, but risk is determined by *exposure*, not merely by the presence of a hazardous substance – which are present in just about everything we consume at low levels. The most comprehensive literature review so far concluded¹⁶:

Current state of knowledge about chemistry of liquids and aerosols associated with electronic cigarettes indicates that there is no evidence that vaping produces inhalable exposures to contaminants of the aerosol that would warrant health concerns by the standards that are used to ensure safety of workplaces. ... Exposures of bystanders are likely to be orders of magnitude less, and thus pose no apparent concern.

Some commentators draw attention to the following to make the case that e-cigarettes are harmful.

3.1.1 Nicotine

The active drug in tobacco is not the primary cause of harm in smoking and would not be in vaping. It has been understood for four decades that: “people smoke for the nicotine but die from the tar”¹⁷. Nicotine is not a cause of cancer, cardiovascular disease or the respiratory conditions that dominate the ill health from smoking¹⁸. Pure nicotine is not completely benign, but it is widely sold in medicinal form and does not cause any serious illness¹⁹. The US Surgeon General has made a detailed assessment of nicotine risks²⁰, and though it is possible to measure many effects on the body, these are trivial compared to smoking: for health, it is *always* better to vape than to smoke.

3.1.2 Nicotine poisoning

There have been a small number of incidents of people or pets swallowing nicotine liquids and some have tried to characterise this risk by reference to the number of calls to poison centres. However,

¹⁶ Burstyn I. Peering through the mist: systematic review of what the chemistry of contaminants in electronic cigarettes tells us about health risks, *BMC Public Health* 2014;14:18. doi:10.1186/1471-2458-14-18 [Link]

¹⁷ Russell MJ. Low-tar medium nicotine cigarettes: a new approach to safer smoking. *BMJ* 1976;1:1430–3. [Link]

¹⁸ In England in 2013, smoking caused 79,700 deaths of which 37,200 were from cancer, 24,300 respiratory diseases, 17,300 circulatory diseases, 900 digestive diseases. Health and Social Care Information Centre, Statistics on Smoking in England, October 2014 [link]. No deaths have been attributed to pure nicotine use.

¹⁹ Farsalinos KE, Polosa R. Safety evaluation and risk assessment of electronic cigarettes as tobacco cigarette substitutes: a systematic review. *Ther Adv Drug Saf* 2014;5:67–86. [Link]

²⁰ US. Department of Health and Human Services. *The Health Consequences of Smoking: 50 Years of Progress*. A Report of the Surgeon General. 2014. P.116 [link]

recent analysis shows nicotine toxicity is perhaps 20 times lower than widely assumed²¹. Although calls to US poisons centres are rising in line with growth and public awareness of e-cigarettes and liquids, they represent a tiny fraction of the calls arising from medicines, cosmetics, domestic cleaning products etc^{22 23}. There is a simple protective measure available: to insist on child resistant packaging, for which there is an ISO standard²⁴.

3.1.3 Ultrafine particles

Some have claimed that the aerosol droplets in e-cigarette vapour have a similar effect on the body as the particles in tobacco smoke or diesel exhaust²⁵. This makes little sense as the chemistry of the vapour particle is completely different, and it is the toxicity of the particles that causes damage with tobacco smoke and environmental pollution – the entire argument is baseless²⁶.

3.1.4 Formaldehyde

A news story originating in Japan suggested that e-cigarette vapour could contain up to ten times as much formaldehyde as conventional cigarette smoke. This was in fact an anomalous single unpublished and unverifiable result, almost certainly arising from the device running hot and dry. Looking more carefully at the published results, the overall picture showed formaldehyde levels 6-50 times *lower* than for cigarettes²⁷. The mistake was repeated in a letter in the New England Journal of Medicine²⁸ claiming that formaldehyde-related cancer risks from e-cigarettes were 5-15 times higher than for cigarettes, but the experiment made the elementary error of running the vaporiser in 'dry puff' conditions that no human user would ever be exposed to²⁹. *Under normal operating conditions, no formaldehyde was detected*. Cigarettes contain thousands of chemicals not present in e-cigarettes and formaldehyde is widely present in the environment.

3.1.5 Carcinogens and toxicants

Carcinogens are found almost everywhere. For example writing in 1998, one of the leaders in the field said³⁰: "*Over 1000 chemicals have been described in coffee: 27 have been tested and 19 are rodent carcinogens. Plants that we eat contain thousands of natural pesticides, which protect plants from insects and other predators: 64 have been tested and 35 are rodent carcinogens*". The question is whether any carcinogens cause exposures at levels and via pathways that pose a material

²¹ Mayer B. How much nicotine kills a human? Tracing back the generally accepted lethal dose to dubious self-experiments in the nineteenth century. Arch Toxicol 2014; 88: 5–7. [\[link\]](#)

²² 2013 Annual Report of the American Association of Poison Control Centers' National Poison Data System (NPDS). Calls for e-cigarettes and nicotine liquids were 1,543 in 2013 and 3,957 in 2014, respectively just 0.06% and 0.15% of the total exposure calls. Table 17A shows calls for analgesics (298,633), cosmetics (199,838), cleaning substances (196,183) etc. [\[link\]](#)

²³ Full discussion of the evidence at Bates C. Keep calm it's only poison, The Counterfactual. 17 November 2014 [\[link\]](#)

²⁴ ISO 8317 Child resistant packaging [\[link\]](#)[\[guide\]](#)

²⁵ See for example, WHO paper for FCTC COP-6, Electronic nicotine Delivery Systems, 1 September 2014. Para 15-16 [\[link\]](#)

²⁶ Full discussion of the evidence at Bates C. Scientific sleight of hand: constructing concern about 'particulates' from e-cigarettes, The Counterfactual. 17 November 2014 [\[link\]](#)

²⁷ Farsalinos K. Electronic cigarette aerosol contains 6 times LESS formaldehyde than tobacco cigarette smoke. 27 November 2014. [\[Link\]](#)

²⁸ Jensen RP, Luo W, Pankow JF, Strongin RM, Peyton DH. Hidden formaldehyde in e-cigarette aerosols. N Engl J Med 2015; 372: 392–4. [\[link\]](#)

²⁹ See full detailed critique at Counterfactual, Spreading fear and confusion with misleading formaldehyde studies, 21 January 2015, with links to detailed assessments [\[link\]](#).

³⁰ Ames BN, Gold LS. The prevention of cancer. Drug Metab Rev 1998; 30: 201–23. [\[link\]](#)

risk. Where toxicants are found in e-cigarette vapour, they are found at much lower levels than tobacco smoke. The biggest study on toxicants in vapour³¹ concluded: *“The levels of the toxicants were 9-450 times lower than in cigarette smoke and were, in many cases, comparable with trace amounts found in the reference product”*. Many of the more important toxins in cigarette smoke are simply not present at all in measurable quantities in vapour. The data on toxicity and carcinogenicity are consistent with the claim that vaping is *at least* 95% safer than smoking.

3.1.6 Heavy metals

Traces of metals can be found in some e-cigarette vapour, but at very low levels that do not pose a material risk – equivalent to or lower than levels found and permitted in medicines³²; *“an average user would be exposed to 4-40 times lower amounts for most metals than the maximum daily dose allowance from impurities in medicinal products”*. Some regulations covering the materials used in device construction would reduce this still further.

3.1.7 Lung irritation

A February 2015 study exposed mice to e-cigarette vapour and concluded it demonstrates *“that e-cig exposure elicits impaired pulmonary anti-microbial defences”* (in mice)³³. In fact, the study greatly over-interpreted the applicability of a mouse study to humans³⁴, failed to measure impacts for tobacco smoke for comparative purposes and failed to note that free radical exposure was *150 times lower* than is typically found for smoking³⁵.

3.2 Risks to the population

As it becomes clearer that e-cigarettes offer smokers a 95-100% reduction in risk, the critics of e-cigarettes have moved their focus onto ‘population’ arguments. This is the idea that though vaping is very much less hazardous than smoking for an *individual*, at *population* level it could be more dangerous because it somehow causes changes in the way people smoke. For example:

- By visible displays of smoking-like behaviour or marketing it might ‘renormalise’ smoking.
- It might divert people from quitting smoking because they don’t feel discomfort of temporary withdrawal or under so much social pressure.
- It could be a ‘gateway’ to smoking for adolescents, and ‘kiddie flavours’ may be used to lure children into nicotine addiction and ultimately on to smoking.

There is no basis to believe any of these effects are real rather than tactical campaign arguments.

3.2.1 Renormalising smoking

The UK’s foremost experts in smoking cessation who also manage the surveillance of the market in

³¹ Goniewicz M., Knysak J., Gawron M., Kosmider L., Sobczak A., Kurek J., et al. . (2013) Levels of selected carcinogens and toxicants in vapour from electronic cigarettes. *Tob Control* 2014 Mar;23(2):133-9 [abstract][paper from March 2015]

³² Farsalinos KE, Polosa R. Safety evaluation and risk assessment of electronic cigarettes as tobacco cigarette substitutes: a systematic review. *Ther Adv Drug Saf* 2014;5:67-86. [link]

³³ Sussan TE, Gajghate S, Thimmulappa RK, et al. Exposure to electronic cigarettes impairs pulmonary anti-bacterial and anti-viral defenses in a mouse model. *PLoS One* 2015; [link]

³⁴ Explained by Mike Siegel, *New Study Reports Adverse Effects of E-Cigarette Aerosol on Mouse Respiratory Epithelial Cells*, The Rest of the Story, 5 February 2015. [link]

³⁵ Farsalinos K. A new study in mice provides no information for smokers but verifies e-cigarettes are less harmful, E-cigarette Research. 5 February 2015 [link]

nicotine products in England concluded³⁶:

Evidence conflicts with the view that electronic cigarettes are undermining tobacco control or 'renormalizing' smoking, and they may be contributing to a reduction in smoking prevalence through increased success at quitting smoking

The more plausible and obvious hypothesis is that e-cigarettes will function as an alternative to smoking; a gateway exit from smoking, and will normalise safer alternatives to smoking.

Marketing that looks like cigarette marketing. There have been some objections that some e-cigarette advertising looks like cigarette advertising³⁷. In fact it is not surprising or undesirable that some advertising looks this way: the advertisers are appealing to smokers to switch smoking behaviour to an alternative to smoking that very much less harmful. If the similar branding adds to the effectiveness of the appeal to smokers, then it is contributing to better health. Note that the use of tobacco brands in e-cigarette marketing ("brand stretching") is illegal in Europe and most jurisdictions where tobacco advertising is banned – so the only visible brands are *rivals to cigarettes*. A recent code published in the UK controls e-cigarette advertising in much the same way as alcohol advertising is controlled – this is a proportionate approach³⁸ and contrasts favourably with the near complete ban to be imposed by the European Union.

3.2.2 Reduced quitting

Where this has been studied properly and the results interpreted correctly, there is no sign of e-cigarettes reducing quitting, and nor would a neutral observer expect one³⁹. The most thorough survey in the world, the Smoking Toolkit Survey for England⁴⁰, concluded in January 2015, that: *Rates of quitting smoking are higher than in previous years. E-cigarettes may have helped approximately 20,000 smokers to stop last year who would not have stopped otherwise.*

3.2.3 Gateway effects

Many activists and some public officials have pointed to rising e-cigarette use among adolescents and suggested they pose a 'gateway' risk: that they will lead to more smoking. *There is no evidence supporting this hypothesis anywhere.* In fact e-cigarettes appeal primarily to existing smokers and the 'value proposition' they offer is strongest among existing smokers with mounting concern about the health and other costs. This expectation is confirmed by data. For example, the UK Office for National Statistics states⁴¹:

E-cigarettes are used almost exclusively by smokers and ex-smokers. Almost none of those who had never smoked cigarettes were e-cigarette users.

However, this has not stopped wild misinterpretations of data. For example in 2013, much media coverage was created in the United States over National Youth Tobacco Survey Data showing a rise

³⁶ West R. Brown J, Beard E. *Trends in electronic cigarette use in England*. Smoking Tool Kit Study. 13 June 2014 [\[link\]](#)

³⁷ See for example: Campaign for Tobacco Free Kids, 7 Ways E-Cigarette Companies Are Copying Big Tobacco's Playbook [\[link\]](#) and de Andrade M & Hastings G, The marketing of e-cigarettes: a UK snapshot, BMJ Blog 6 April 2013 [\[link\]](#)

³⁸ Committee on Advertising Practice, Advertising Code: Electronic Cigarettes, [\[non-broadcast\]](#)[\[broadcast\]](#)

³⁹ Letter to WHO Director General Margaret Chan: *The importance of dispassionate presentation and interpretation of evidence*. 26 June 2104. A letter from 50 scientists addresses some of these claims in more detail [\[link\]](#)

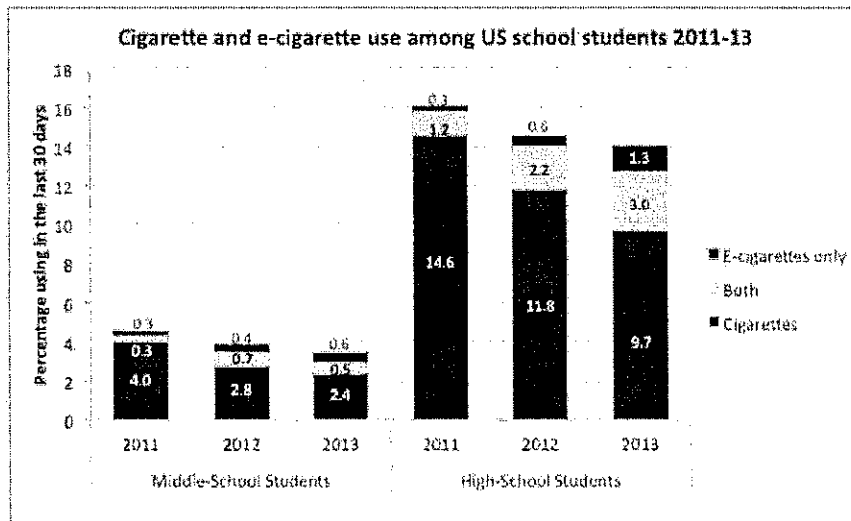
⁴⁰ West R. Brown J, Beard E. *Trends in electronic cigarette use in England*. Smoking Tool Kit Study. 15 January 2015 [\[link\]](#)

⁴¹ ONS, Opinions and Lifestyle Survey, Adult Smoking Habits in Great Britain, 2013, 25 November 2014 [\[link\]](#)

in e-cigarette use⁴². According to a top public health official:

This raises concern that there may be young people for whom e-cigarettes could be an entry point to use of conventional tobacco products, including cigarettes.

In fact the data do not support a gateway effect and a rise in e-cigarette use among adolescents would be expected to mirror the rise in use among adults. In reality, US teenage smoking prevalence fell sharply as e-cigarette use increased and e-cigarette use was highly concentrated among existing smokers⁴³. The relevant CDC data are shown in the chart below:



Source: raw data from CDC National Youth Tobacco Surveys (NYTS). Data analysis and graphic by Brad Rodu

Similar effects were found in France⁴⁴ and confirmed for the United States in the Monitoring the Future survey, which showed a rise in e-cigarette use, but also found record low rates and record annual declines for “daily” and “past 30 day” cigarette smoking by teens from 2013 to 2014⁴⁵. In essence we are seeing e-cigarette use rise in line with growth in adults, but cigarette smoking falling sharply. These are reasons to be positive, not to conclude that e-cigarettes a problem.

3.2.4 Understanding and defining gateway effects

It is difficult to find a proponent of the gateway effect who can rigorously define what they mean and how they would measure it. To establish a gateway effect is in practice difficult. It is necessary to show that a period of e-cigarette use is the *reason* why someone develops a consolidated smoking habit. It is not sufficient to show rising e-cigarette use coincided with rising smoking⁴⁶ –

⁴² CDC E-cigarette use more than doubles among U.S. middle and high school students from 2011-2012, 5 September 2013 [\[link\]](#)

⁴³ CDC MMWR Tobacco Product Use Among Middle and High School Students — United States, 2011 and 2012, 15 November 2013. [\[link\]](#) Higher resolution graphic [\[link\]](#)

⁴⁴ Survey reported in English on *Le blog de Jacques LeHouezec*, 16 May 2014. [\[link\]](#)

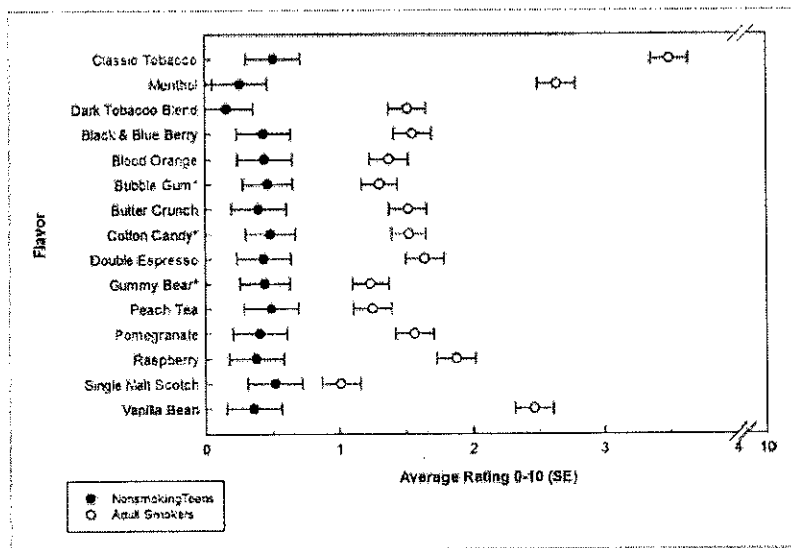
⁴⁵ L. D., O'Malley, P. M., Miech, R.A., Bachman, J. G., & Schulenberg, J. E. (2015). Monitoring the Future national results on adolescent drug use: Overview of key findings, 2014. Ann Arbor, Mich.: Institute for Social Research, the University of Michigan [\[link\]](#)

⁴⁶ Goniewicz ML, Gawron M, Nadolska J, Balwicki L, Sobczak A. Rise in Electronic Cigarette Use Among Adolescents in Poland. *J Adolesc Heal* 2014; 55: 713-5. [\[link\]](#)

there could be independent reasons for these trends, or a common factor driving them. Nor is it sufficient to show that a person used e-cigarettes first and then took up smoking – in the absence of e-cigarettes they may have simply started to smoke anyway. It is also possible that e-cigarette use in adolescents is *protective* – preventing or diverting the onset of a consolidated cigarette smoking habit. Some care is required in drawing causal conclusions from observational data on e-cigarette use but *every claim* for detecting a gateway effect fails to address these issues.

3.2.5 Kiddie flavours to appeal to children

It is often asserted, as if it is obvious, that flavours with childish characteristics will appeal to adolescents. There is no evidence for this, just assertion, and it is actually counter-intuitive: most adolescents are imitating adult behaviour, not reinforcing their status as children. The one study that has looked at the preferences of young people for e-cigarette flavours found extremely low interest. Teenagers were asked to rate their interest on a scale of 0-10 in using e-cigarettes and were offered a list of flavours. They reported minimal interest (average =0.41 out of 10), much less than adult smokers (1.73 out of 10) and interest did not vary much across flavours⁴⁷. To the extent that any preferences were revealed among teens, ‘Single Malt Scotch’ and ‘Classic Tobacco’ were top.



Other studies confirm that adults are attracted to supposedly juvenile flavours like cherry crush, or fruit loop. For example a survey of users of the world’s largest user forum found fruit to be the most popular flavour category⁴⁸. A similar survey of over 4,519 users found 44% used tobacco, 32% menthol/mint, 61% sweet, 15% nuts, 69% fruit, 37% drink, and 22% other⁴⁹. Non-users should understand that flavours are an important aspect of vaping and integral to the experience. They are also part of a migration away from tobacco. Initial switchers tend to favour tobacco flavours but gradually move on to non-tobacco flavours often as part of a permanent switch from smoking.

⁴⁷ Shiffman S, Sembower MA, Piliitteri JL, Gerlach KK, Gitchell JG. The impact of flavor descriptors on nonsmoking teens’ and adult smokers’ interest in electronic cigarettes. *Nicotine Tob Res* 2015; published online Jan 7 [\[link\]](#)[\[release\]](#).

⁴⁸ E-cigarette forum, Survey of users. *Big survey 2014 - initial findings eliquid*, 17 July 2014. [\[link\]](#)

⁴⁹ Farsalinos KE, Romagna G, Tsiapras D, Kyrzopoulos S, Spyrou A, Voudris V. Impact of flavour variability on electronic cigarette use experience: an internet survey. *Int J Environ Res Public Health* 2013; 10: 7272–82.[\[link\]](#)

3.3 Seeing through controversy

Many points are made against e-cigarettes but they almost all suffer from flaws and can mislead users about risks. Professor Robert West detailed six typical flaws (or 'tactics' if you believe this is deliberate) in an editorial in the journal *Addiction*⁵⁰.

It is worth highlighting the ways in which science is being misused so that readers can be better placed to evaluate the messages.

Failure to quantify: e.g., statement that e-cigarette vapour contains toxins so creating the impression that they are dangerous as cigarettes, without indicating that the concentrations are typically orders of magnitude less than tobacco smoke.

Failure to account for confounding and reverse causality: e.g., arguing that use of e-cigarettes reduces chances of stopping because in cross-sectional surveys the prevalence of e-cigarette use is higher in smokers than in recent ex-smokers.

Selective reporting: e.g., focusing on studies that appear to show harmful effects while ignoring those that do not.

Misrepresentation of outcome measures: e.g., claiming that e-cigarette use is prevalent among youth by using data on the proportion who have ever tried and creating the misleading impression that they are all current e-cigarette users.

Double standards in what is accepted as evidence: e.g., uncritically accepting conclusions from observational studies with major limitations when these claim that electronic cigarettes are causing harm, but discounting similar or better controlled studies when these appear to show the opposite.

Discrediting the source: e.g., arguing that researchers who have received financial support from e-cigarette manufacturers (and even companies that do not manufacture e-cigarettes) are necessarily biased and their results untrustworthy, and presenting themselves as having no conflicts of interest when their professional and moral stance represents a substantial vested interest.

3.4 The case of snus – a cautionary tale

Many of the same 'population' arguments were made on a precautionary basis in the case to ban 'oral tobacco' in 1992 throughout the EU, even though it is 95-100% less hazardous than smoking. On accession, Sweden was granted an exemption from the ban. In fact, this product is the reason why Sweden has by far the lowest rate of smoking in the EU: 13% Swedish adults vs 28% EU average⁵¹. Snus has three main effects in Sweden and Norway: it is used to quit smoking; it is used to substitute for smoking; it diverts young people from onset of smoking. It provides a compelling 'proof of concept' for tobacco harm reduction, and a warning about perverse impacts of regulation. It also showed that tobacco control activists were prepared to mount a campaign against a product that was achieving real reductions in disease and premature death.

3.5 Concern about the tobacco industry

A further source of critics' concern is the possible negative role of the tobacco industry, which is unsurprising given the history. In practice, and in the present, it is hard to see what this could be *if the e-cigarette industry remains competitive*. The tobacco industry's long-standing cigarette-based business model is threatened by e-cigarettes. To survive the disruption they will need to enter the market (as they are doing) and produce high quality attractive alternatives to smoking or risk losing share in the recreational nicotine market to other tobacco or non-tobacco e-cigarette companies. It is more likely that they will become important drivers of a wholesale switch from smoking to vaping

⁵⁰ West R, Electronic cigarettes: getting the science right and communicating it accurately, *Addiction*, virtual edition on e-cigarettes, December 2014. [[link](#)]

⁵¹ European Commission, [Special Eurobarometer 385](#), Attitudes of European Citizens to Tobacco, March 2012

through the mechanism of market-based competition. The real danger from tobacco companies arises from excessively burdensome regulation, eliminating competition from more agile or innovative competitors, leaving them with an oligopoly protected by regulatory barriers to entry, and endorsed paradoxically by health organisations. Unfortunately many public health establishment organisations and individuals are doing their utmost to cause this to happen, though not always realising that protection of tobacco companies from competition will be the effect, if not their aim⁵².

3.6 Disruptive technology also challenges public health

E-cigarettes have empowered smokers to take control of their risks and have greatly enhanced the welfare of hundreds of thousands of UK citizens. It has challenged the tobacco industry, but it has also challenged interests in the public sector and civil society who have played no role – or a hostile role – in its rise. For many smokers and vapers, the hostility of the public health establishment to vaping or tobacco harm reduction is highly perplexing. Here are several possible explanations:

- **Not invented here:** the products and harm reduction benefits have emerged through free play of producers and consumers in a lightly regulated market. No one in public health has given their approval or been asked for it, no public spending is required and public health organisations have no controlling influence.
- **Hostility to the private sector:** culturally, the public health establishment is inclined to paternalism, and state-based or not-for-profit interventions. It instinctively distrusts the private sector and capitalism, and is ill at ease with the idea of consumers as empowered agents.
- **Countercultural:** the toolkit of tobacco control is replete with coercive measures: restrictions penalties, (regressive) taxes, fear based campaigns, medicalisation of smoking and so on. Harm reduction approaches are non-judgemental, ‘meet people where they are’ and allow them to judge their own interests and preferences.
- **Undeclared motives:** some in tobacco control have a ‘non-smokers’ rights’ orientation, rather than ‘population health’ orientation, and these have different implicit objectives. As with any issue that involves a recreational drug, there are prohibitionist instincts at work, there may be affronted authority figures (‘doctor knows best’) and those with concerns about bodily purity⁵³.
- **Conflicts of interest:** public health academia, science, and advocacy is beset by ideological biases, prior positions to defend, funders’ interests to respect, charities’ declared policy positions, pharmaceutical funding, and highly prone to insularity and group-think.
- **Tobacco industry focus:** many activists and academics have defined their fight as with the tobacco industry and assume what is harmful to them is beneficial to health. This leads to lazy and muddled thinking in the area of tobacco harm reduction.

Not all individuals or organisations involved exhibit all or any of these characteristics, but they are drawn out here to emphasise that it is not safe to assume that anyone with a public health profession or remit to protect health is actually acting rationally in the interests of health.

⁵² See David Sweanor, *Big Tobacco’s Little Helpers*, The Counterfactual, 27 January 2015. [\[link\]](#) and Clive Bates, *Turning the tables on public health: let’s talk about the risks they create*, 3 July 2014 [\[link\]](#)

⁵³ See for example discussion by Alderman J, Dollar KM, Kozlowski LT. Commentary: Understanding the origins of anger, contempt, and disgust in public health policy disputes: applying moral psychology to harm reduction debates. *J Public Health Policy* 2010; 31: 1–16. [\[link\]](#)

4 Regulatory issues

4.1 Poor regulation is the primary risk to public health

The primary risk to the otherwise highly positive developments with e-cigarettes is poor and excessive regulation. At the heart of the regulatory challenge there is a 'double negative': being tough on e-cigarettes is being tough on the competitive alternative to cigarettes. There is a danger that loss-averse regulators and officials will place excessive focus on the residual risks associated with vapour products, but in doing so render them less effective and appealing as alternatives to smoking. In doing so, they will increase *total health risks* through the unintended consequence of additional continuing smoking. All regulatory proposals advanced so far suffer from this weakness.

4.2 Unintended consequences of regulation will dominate

The following table illustrates how it is possible for regulatory measures to have unintended harmful consequences – protecting the cigarette trade and leading to more smoking than there otherwise would be. These effects are likely to far outweigh the intended consequences of most regulatory proposals under development today.

Regulatory idea	Likely unintended consequence
Ban e-cigarette use in public places	Diminishes value proposition of e-cigarettes to users and 'denormalises' vaping, a much less risky option, diminishes the appeal of vaping relative to smoking, May promote relapse in existing vapers if they join smokers outside. Likely to lead to more smoking.
Restrictions on advertising, promotion and sponsorship	Reduces ability of e-cigarette brands to compete with cigarettes, and diminishes means to communicate value proposition to smokers. May reduce means to communicate innovation or build trusted brands. May turn ads into bland public information notices. Some restrictions are undoubtedly justified and a balance should be struck, but excessive restriction will protect the cigarette trade.
Product design restrictions and requirements – testing and paperwork	There are numerous subtle trade-offs in product design between safety and appeal and cost. For example, the perfectly safe product that no-one wants to buy may be worse for health if it means more people smoke. Excessive design regulation can impose high costs, burdens and restrictions, slow innovation and drive good products and firms out of the market through 'regulatory barriers' to entry. Very high spec regulations will tend to favour high volume, low diversity commoditised products made by tobacco or pharmaceutical companies. Regulation can adversely reshape the market and reduce the pace of innovation.
Ban flavours	All e-cigarettes and liquids are flavoured with something – and this forms a key part of the appeal. Many former smokers report switching to non-tobacco flavours as a way of moving permanently away from smoking. There is significant risk that loss of broad flavour categories will cause relapse among e-cigarette users, fewer smokers switching, and development of DIY and black market flavours – which may be more dangerous.
Ban flavours that appeal to kids	It is a common mistake in public health to believe that adolescents are attracted to things that adults regard as child-like, such candy-flavours. Adolescent experimentation is often about emulating adults or rejecting childhood. A ban on flavouring may have impacts on adults, but adolescents may simply switch to a different flavour – like tobacco.
Ban open systems because they may be used for other drugs	This might require 'closed systems' to be made mandatory (as proposed by tobacco company RJ Reynolds with this justification, but probably for anti-competitive reasons). But this has the effect of removing the 'open system' 2 nd and 3 rd generation products from the market. Many vapers report these are more effective alternatives to smoking. Note vaping may be a safer way to take other drugs than smoking – so there may be a harm reduction benefit to drug users.
Health warnings	Alarmist health warnings, even if technically correct, can be misleading and misunderstood by the public. This has always been the case with smokeless tobacco – warnings do not adequately communicate relative risk and therefore understate smoking risks or the advantage of switching. They may obscure much more important messages about relative risk compared to smoking that is not provided in official communications.

Regulatory idea	Likely unintended consequence
Ban sales to minors	There is near universal support for this. However it is worth noting that NRT is made available to people over 12 years in some jurisdictions – because young smokers also need to quit. It should not be assumed that ‘harm reduction’ should start at 18.
Prohibit health claims unless regulatory approval	This denies smokers real world truthful information about relative risk and may cause more smoking. It is uncontroversial that e-cigarettes are safer than smoking – the debate is over where in the range 95-100% less risky. This erects high and unnecessary regulatory barrier to truthful communication, and claim-making should be tested in the same way any consumer claim must be truthful and proportionate – not to the standard required for medicines.
Regulate as a medicine	E-cigarettes are not medicines – in common sense or in law. Using ill-fitting or excessive regulation designed for a different purpose would simply limit the development of competitive alternatives to cigarettes. The costs, burdens and restrictions of medicines regulation are excessive and serve little useful purpose (for example, ‘consistent dosing’ is important for medicines, but not for products where the user controls the dose).
Regulate as a tobacco product	Most tobacco regulation is designed to prevent, suppress and control tobacco use. With e-cigarettes the public health imperative is best served by these products growing and innovating to capture market share from cigarettes – many of the tools of tobacco control applied to e-cigarettes are therefore harm-inducing and protective of cigarette sales.

4.2.1 The risk of user countermeasures to overcome poor regulation

Regulators do not have a free hand. If regulation is excessive, or removes products from the market that users want, then users will revolt and legitimately subvert regulation that they perceive to be harmful to their health or welfare. It is better to avoid the development of unregulated black or grey markets and home producing by having proportionate regulation.

4.3 The current approach of key regulators is arbitrary and disproportionate

It is not possible to review all regulatory developments, especially in relation to marketing, age restrictions and banning vaping in public places. This section comments on the main initiatives with respect to regulating the product itself.

4.3.1 UK approach

The UK’s preferred approach was originally to regulate vapour products as medicines.⁵⁴ This onerous regime applies costs, burdens and restrictions that would dramatically contract the range of products and number of suppliers, whilst acting as a barrier to innovation⁵⁵ and unlawfully forcing a non-medical consumer product into a medical definition and regulatory regime⁵⁶. After this approach was rejected in the European Union, the UK has adopted the EU ‘twin track’ approach (see below). The UK government generally has a positive outlook towards tobacco harm reduction, but as long ago as 2009, its policy-makers incorrectly assumed such developments would come through pharmaceutical innovation. It has taken several years to adjust to a different reality – a process that is not yet complete. The separate jurisdictions on England, Scotland and Wales have adopted different stances on vaping in public and other policies.

4.3.2 European Union approach

The EU’s favoured approach is “twin track”: to regulate using measures designed for tobacco

⁵⁴ MHRA, Press Release: 13 June 2013, UK moves towards safe and effective electronic cigarettes and other nicotine-containing products [\[link\]](#). See overview page: Nicotine Containing Products [\[link\]](#).

⁵⁵ Bates C, Stimson S, Costs and consequences of regulating e-cigarettes as medicines, 20 September 2013 [\[link\]](#)

⁵⁶ Bates C, Are e-cigarettes medicines? Counterfactual March 2013. [\[link\]](#)

products or to allow medicine licensing. After the proposal of the Commission and Council to regulate e-cigarettes as medicines was thrown out by the European Parliament on 8 October 2013, a new directive was hastily contrived entirely behind closed doors, without any consultation and with minimal supporting analysis or scrutiny. The resulting directive (2012/40/EC – Article 20)⁵⁷ has numerous flaws of arbitrary and unscientific policy and poor policy-making process, and is likely to be found in breach of key treaty principles.

- **A ban on almost all advertising sponsorship and promotion.** The anti-competitive ban protects the incumbents from a disruptive challenger and is unjustified in a directive with a single market legal base, and disproportionate relative to tobacco. Most tobacco advertising is banned in the EU, but tobacco kills 700,000 per year. In contrast, vaping is likely to reduce premature deaths.
- **Limiting the strength of nicotine liquids to 20mg/ml.** Approximately 25-30% of consumers use liquids stronger than this. They may be more important for more heavily dependent smokers and those just switching. The threshold is arbitrary and pointless.
- **Limiting liquid container sizes.** We manage hazardous liquids (like bleach) by having packaging and labelling standards not by limiting the containers to tiny and inconvenient sizes.
- **Requiring large warnings.** The directive requires cigarette-like warnings that contain misleading and off-putting information covering 30% of the pack. The warnings are not proportionate.
- **Numerous technical measures** that would fail a reasonable risk-benefit assessment.
- **A continuing ban on snus** – despite it being the reason, beyond doubt, for the best tobacco-related health outcomes in Europe in Sweden, snus will remain banned throughout the rest of the EU. It is unscientific, unethical and probably unlawful to ban this product.

Legal challenge. A UK-based vendor, Totally Wicked, has challenged article 20 of the directive via the English Courts and a case will likely be heard in Court of Justice of the EU in 2016⁵⁸. The directive has entered into force and its provisions apply in stages from 2016/17.

4.3.3 United States approach

Following a legal challenge to its designation of e-cigarettes as medicines in 2010⁵⁹, the currently favoured approach of US Food and Drug Administration is to treat e-cigarettes as tobacco products on the basis that the pure nicotine used is originally extracted from tobacco. In April 2014, the FDA announced its intention to apply tobacco legislation to e-cigarettes⁶⁰ (the so-called 'deeming regulation'). This means the provisions of the Family Smoking Prevention and Tobacco Control Act will apply. This legislation was designed with the primary purpose of slowing innovation and creating burdens for the cigarette manufacturers, and it is wholly excessive and inappropriate to use this to regulate a disruptive low risk entrant to the cigarette market. It will mean almost all products are removed from the market and only the mass commodity products market by the largest companies will meet approval⁶¹.

⁵⁷ Directive 2014/40/EU 'Tobacco Products Directive' [\[link\]](#)

⁵⁸ See more details at: *Totally Wicked legal challenge to the Tobacco Products Directive e-cigarette measures*, Counterfactual, November 2014 [\[link\]](#)

⁵⁹ U.S. Court of Appeals for the D.C. Circuit, in *Sottera, Inc. v. Food & Drug Administration*, 627 F.3d 891 2010 [\[link\]](#)

⁶⁰ United States Food and Drug Administration. FDA proposes to extend its tobacco authority to additional tobacco products, including e-cigarettes (press release with links) 24 April 2014 [\[link\]](#). Also see SFATA (industry) [\[link\]](#) and CASSA (consumer) [\[link\]](#) resources

⁶¹ See CASAA assessment in: Fourth Call to Action for FDA Proposed Regulations Streamlined Version, 26 July 2014 [\[link\]](#)

4.3.4 Australia and Canada and other countries with *de facto* bans

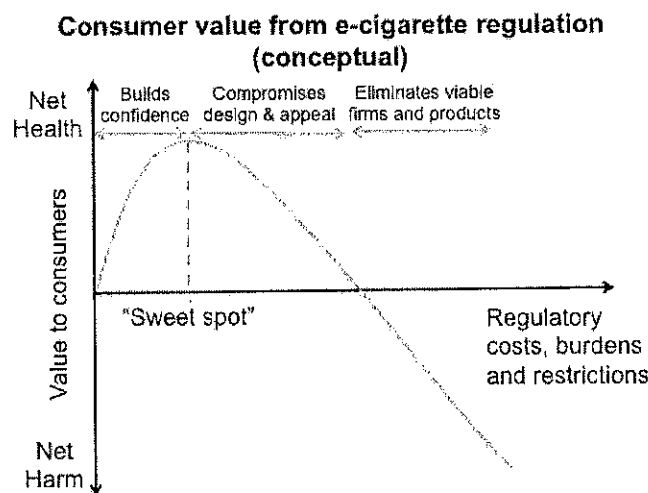
By defining these products as poisons or medicines, several jurisdictions have created an ostensible ban on e-cigarettes. As with all popular recreational drugs prohibition has led to a creative black market, which is likely to be reducing smoking and be beneficial to health. The force of the law has been used to ensure that cigarettes are widely available, while e-cigarettes are disadvantaged – a highly perverse approach to public health. It creates the appearance of toughness on the part of the regulator, but in practice it irresponsibly promotes an illegal and unregulated supply chain.

4.3.5 The World Health Organisation

WHO has taken on an activist advocacy role and strayed into misrepresentation and miscommunication of the science and policy issues⁶². The WHO's favoured approach is to classify these products as both medicines and tobacco and to apply the restrictive measure of the WHO's tobacco treaty (the Framework Convention on Tobacco Control)⁶³. The WHO would also like to include these products in UN targets to reduce tobacco consumption by 30% by 2025⁶⁴ – making it impossible to achieve this target by denying the most likely way of meeting it. Fifty-three of the world's top experts wrote to WHO in May 2014 to implore it to take a more constructive approach⁶⁵.

4.4 A better approach to regulation

The aim should be to achieve a 'sweet spot' of regulatory intervention that builds confidence among consumers and removes cowboys and rogue products from the market, but does not impose costs, burdens and restrictions that crush the smaller players, radically change the products available and obstruct innovation. This relationship is illustrated conceptually in the graphic below.



The optimum regulatory regime would strike a subtle balance between protecting users, non-users, bystanders and limiting the risks of harmful unintended consequences.

⁶² Bates C, WHO position on ENDS: A critique of the use of science and communication of risk, Oct 2014 [\[context\]](#)[\[report\]](#)

⁶³ See WHO position paper on ENDS, FCTC/COP/6/10 Rev.1 September 2014 [\[link\]](#) and Decision FCTC/COP6(9) from the Conference of the Parties to the FCTC, October 2014. [\[link\]](#)

⁶⁴ See Clive Bates review of WHO documents: WHO plans e-cigarette offensive, 17 April 2014 [\[link\]](#)

⁶⁵ Letter to Dr Margaret Chan, Director General WHO, Reducing the toll of death and disease from tobacco – tobacco harm reduction and the Framework Convention on Tobacco Control 26 May 2014 [\[context\]](#)[\[letter\]](#)

4.5 Elements of an appropriate regulatory regime

A reasonable proportionate regulatory regime (the 'sweet spot') may cover many of the following elements, and it may develop over time. This list is not intended to be a full discussion:

Liquids

- Requirement for use of pharmaceutical grade nicotine and diluents in liquids
- Requirement for flavours to be at least food grade
- A ban on ingredients known to be carcinogenic, mutagenic, repro-toxic or respiratory sensitisers.
- Purity standards or thresholds for contaminants in liquids
- Products should be as described – contain the stated content of nicotine and flavours
- Child resistant containers – this may adopt ISO8317 for example
- Use-by date

Devices

- Electrical safety specification: chargers and battery combinations should be safe
- Heat safety specification
- Materials used in devices should be approved for use with food
- Possible operating thresholds for devices, eg. for maximum temperature

Testing

- A testing regime should support the regulatory objectives and regulatory decisions
- Focus on quality of liquids and devices, rather than vapour measurements

Marketing

- Claims must be true, not misleading and supported by evidence
- Proportionate warnings related to toxicity and addictiveness
- Restrictions on themes and media attractive to under-25s
- Restriction of sales to adults
- Age-verification for sales – on internet or in shops – as with any age-sensitive product

Companies

- Registered address and 'responsible person' identified
- Quality management standard in place, eg. ISO9000
- Appropriate markings to give the means to identify and recall products

Vaping in public places

- There is no case for banning vaping by law or a blanket prohibition – the case for banning smoking by law rests on material harm to others
- There are many places, times, events, circumstances where vaping may be reasonable, desirable or commercially valuable and should not be ruled out by a blanket ban
- Owners and operators should decide their policy and make informed judgements [including the welfare value to vapers and smokers] and make clear whether vaping is permitted or not⁶⁶
- Vapers should approach vaping in public as a matter of etiquette with due regard for others

⁶⁶ See ASH structured questions: Will you permit or prohibit e-cigarette use on your premises? 2014 [\[link\]](#)

About the author

Clive Bates runs Counterfactual, a public interest consulting and advocacy organisation focussed on a broad approach to sustainability, policy-making for the long term and good governance. He was formerly a senior civil servant and Director of Action on Smoking and Health (London) as well as a founder of the NGO Framework Convention Alliance, set up to support the development of the WHO Framework Convention on Tobacco Control. He has been a long-term advocate of tobacco harm reduction^{67 68 69}, a critic of the public health establishment approach to harm reduction⁷⁰ and wrote about the policy challenge of products like e-cigarettes well before they were invented⁷¹.

Disclaimer. Views expressed in this brief do not necessarily reflect the views of former employers or affiliates. Clive Bates has no competing interests with respect to tobacco, pharmaceutical or e-cigarette industries.

⁶⁷ Bates C, Fagerström K, Jarvis MJ, *et al.* European Union policy on smokeless tobacco: a statement in favour of evidence based regulation for public health. *Tob Control* 2003;**12**:360–7. doi:[10.1136/tc.12.4.360](https://doi.org/10.1136/tc.12.4.360)

⁶⁸ McNeill A, Foulds J, Bates C. Regulation of nicotine replacement therapies (NRT): a critique of current practice. *Addiction* 2001;**96**:1757–68. doi:[10.1080/09652140120089508](https://doi.org/10.1080/09652140120089508)

⁶⁹ Bates C. Taking the nicotine out of cigarettes--why it is a bad idea. *Bull World Health Organ* 2000;**78**:944. [[link](#)]

⁷⁰ Bates C. Flaw in WHO Framework Convention on Tobacco Control: letter identified wrong problem with the framework convention. *BMJ* 2004;**328**:1320. doi:[10.1136/bmj.328.7451.1320](https://doi.org/10.1136/bmj.328.7451.1320)

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Article

Nicotine Levels and Presence of Selected Tobacco-Derived Toxins in Tobacco Flavoured Electronic Cigarette Refill Liquids

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Academic Editor: Paul B. Tchounwou

Received: 21 January 2015 / Accepted: 9 March 2015 / Published: 24 March 2015

Abstract: *Background.* Some electronic cigarette (EC) liquids of tobacco flavour contain extracts of cured tobacco leaves produced by a process of solvent extraction and steeping. These are commonly called Natural Extract of Tobacco (NET) liquids. The purpose of the study was to evaluate nicotine levels and the presence of tobacco-derived toxins in tobacco-flavoured conventional and NET liquids. *Methods.* Twenty-one samples (10 conventional and 11 NET liquids) were obtained from the US and Greek market. Nicotine levels were measured and compared with labelled values. The levels of tobacco-derived chemicals were compared with literature data on tobacco products. *Results.* Twelve samples had nicotine levels within 10% of the labelled value. Inconsistency ranged from –21% to 22.1%, with no difference observed between conventional and NET liquids. Tobacco-specific nitrosamines (TSNAs) were present in all samples at ng/mL levels. Nitrates were present almost exclusively in NET liquids. Acetaldehyde was present predominantly in conventional liquids while formaldehyde was detected in almost all EC liquids at trace

levels. Phenols were present in trace amounts, mostly in NET liquids. Total TSNAs and nitrate, which are derived from the tobacco plant, were present at levels 200–300 times lower in 1 mL of NET liquids compared to 1 gram of tobacco products. *Conclusions.* NET liquids contained higher levels of phenols and nitrates, but lower levels of acetaldehyde compared to conventional EC liquids. The lower levels of tobacco-derived toxins found in NET liquids compared to tobacco products indicate that the extraction process used to make these products did not transfer a significant amount of toxins to the NET. Overall, all EC liquids contained far lower (by 2–3 orders of magnitude) levels of the tobacco-derived toxins compared to tobacco products.

Keywords: electronic cigarette; tobacco; nitrosamines; aldehydes; nitrates; phenols; nicotine

1. Introduction

Electronic cigarettes (ECs) are becoming increasingly popular, with millions of users both in the US and in Europe [1–3]. These battery-powered devices deliver nicotine, although at a slower rate compared to tobacco cigarettes [4], and deal with the psycho-behavioural aspect of the addiction to smoking [5,6]. Due to these unique features they have the potential to serve as a valuable tobacco harm reduction product [7], by substituting tobacco cigarette consumption.

EC liquids consist mainly of propylene glycol, glycerol, nicotine and flavourings. Different flavour types are available, such as tobacco, sweets, fruits, beverages and nuts. Studies have shown that users frequently switch between flavours, while choices differ according to the duration of smoking substitution with EC use with tobacco flavours being more popular at EC use initiation [8]. In many cases, Generally Recognized As Safe (GRAS) flavour compounds for food are used [9], even for tobacco flavoured liquids. In other cases, industrially-produced tobacco absolute (used in the fragrance industry) is used, in an attempt to better simulate the tobacco flavour [10]. Additionally, there are cases of companies which produce their own (in-house) tobacco flavours by obtaining cured tobacco leaves from which an extract is produced, usually through solvent extraction and a steeping process [9]. These are commonly called Natural Extracts of Tobacco (NET). The main reason for their existence is anecdotal reports from EC consumer forums that they more accurately simulate the flavour of tobacco cigarettes and are used by consumers who prefer such flavour. A cytotoxicity study evaluated four NET samples and found that the aerosol of these liquids had cytotoxic properties on cultured cells, although at levels significantly lower compared to tobacco cigarette smoke [9]. It is unknown whether the use of NET leads to the delivery of toxic chemicals to the EC liquid, derived from the tobacco plant during the extraction process. Therefore, the purpose of this study was to evaluate the presence of selected chemicals derived from tobacco in NET EC liquids, and compare their levels with those present in liquids prepared with conventional (food GRAS or industrial tobacco absolute) flavourings. The focus of the study was to evaluate accuracy in nicotine labelling and content of tobacco-specific nitrosamines (TSNAs) and nitrates (which are present in the tobacco plant), phenols (which may be derived from heating cured tobacco leaves during flavour extraction) and aldehydes (which may be

both present in the tobacco plant and derived from heating). Finally, since ECs are potential tobacco harm reduction products, a relevant comparison with tobacco products was considered appropriate. Therefore, we compared the levels of TSNA and nitrate in EC liquids with literature data on tobacco products, and the levels of phenols with literature data on mainstream tobacco cigarette smoke.

2. Materials and Methods

2.1. Sample Selection

For the purpose of the study, EC liquids with tobacco flavour that were prepared using conventional flavour ingredients and NET-flavoured liquids were obtained from EC physical and internet shops. Information about the use of NET was obtained from the websites (internet shops) of the vendors. Unfortunately, no manufacturer (to the best of our knowledge) publicly reports the use of industrially produced tobacco absolute in their liquids, so, any liquid prepared without the use of NET was considered a conventional sample. Samples of conventional EC liquids were selected from the Greek market (manufactured in Greece and in Italy, all 10 samples). Samples using NET flavourings were obtained from the Greek (two samples, manufactured in the UK) and the US market (nine samples). In total, 21 samples were collected: 10 samples using conventional flavouring ingredients and 11 samples using NET. The samples were bought anonymously through e-shops or physical stores, and were immediately sent to the laboratory for analysis. All samples were refill (ready-to-use) liquids, and one bottle per liquid was tested.

2.2. Chemical Analysis

All methods used for this study were validated for linearity, recovery, precision and limits of detection in the EC sample matrix before use.

2.2.1. Nicotine

Nicotine calibration standards were prepared over a range of 100–2000 µg/mL in 2-propanol, with n-heptadecane as an internal standard. All EC samples were analysed at a 50-fold dilution in 2-propanol with n-heptadecane added. A Hewlett Packard Model 5890 Series II GC (Hewlett Packard, Santa Clara, CA, USA) was equipped with an FID and a Restek Stabilwax column 30 m × 0.32 mm × 1.0 µm. The temperature program was: 60 °C for 1 min, 20 °C/min to 240 °C for 2 min.

The materials used for the GC analysis were: 2-propanol (low water): Fisher Scientific (Waltham, MA, USA); n-heptadecane (99% CAS 629-78-7): Sigma-Aldrich (St. Louis, MO, USA); nicotine (≥99% CAS 54-11-05): Sigma-Aldrich.

2.2.2. TSNA

Calibration standards for N-nitrosornicotine (NNN) and 4-(methylnitrosamino)-1-(3-pyridyl)-1-butanone (NNK) were prepared over a range of 1–500 ng/mL in water, with NNN-d4 and NNK-d4 included as internal standards. The EC liquid samples were analysed at an 11-fold dilution in water and NNN-d4 and NNK-d4 added. Aliquots of the samples and standards were solvent-exchanged using SLE + cartridges (Biotage, Uppsala, Sweden) and eluted with methylene chloride. An Agilent 7890

GC coupled to an Agilent 7000 GC-MS Triple Quad mass spectrometer (Agilent, Santa Clara, CA, USA) was used for analysis. Separation was performed on an Agilent HP-5MS UI 30 m × 0.25 mm × 0.5 µm column, using helium as the carrier gas at 1.2 mL/min. A 5 µL injection was performed with the multimode inlet in PTV Solvent Vent mode. Initial inlet temperature was −10 °C, held for 2 minutes, then increased at 600 °C/min to 325 °C and held for the remainder of the run. The oven was operated at 35 °C for 2 min, then 50 °C/min to 230 °C for 5 min. The mass spectrometer was operated in positive chemical ionization (PCI) mode using ammonia as the reagent gas. Parent/daughter transitions were m/z 178→148 and m/z 178→120 for NNN, m/z 182.1→152.1 and m/z 182.1→124 for NNN-d4, m/z 208→122 and m/z 208→106 for NNK, and m/z 121→126 and m/z 212→152 for NNK-d4, with quantitation performed using the first transition listed for each compound. The limit of detection was 1ng/mL for both NNN and NNK. The materials used for the GC/MS/MS analysis were: deionized water, Millipore; methanol (Fisher OPTIMA®); methylene chloride (Fisher OPTIMA®); and ISOLUTE SLE + 1 mL supported liquid extraction cartridges (Biotage). Stock solutions of NNN (CAS 16543-55-8), NNN-d4 (CAS 66148-19-4), NNK (CAS 64091-91-4), and NNK-d4 (P/N 1707.10-K-AN) were purchased from Chiron (Trondheim, Norway).

2.2.3. Nitrate

Standards were prepared over a range of 0.5–50 µg/mL in water. The EC liquid samples were analysed at a 50-fold dilution in water. An Agilent Model 1100, High Performance Liquid Chromatograph was equipped with a Dionex ED40 detector functioning in conductivity mode with a Thermo Fisher AS14 column. The mobile phase was 8mm sodium carbonate and 1 mm sodium bicarbonate with a flow rate of 1.2 mL/min. The limit of detection was 2.5 µg/mL.

The materials used for the HPLC analysis were: deionized water—Millipore (Billerica, MA, USA); Sodium Carbonate, 99.0%, Sigma-Aldrich (P/N S7795); Sodium bicarbonate, Sigma-Aldrich (P/N S014); Anion Mix, Accustandard (New Haven, CT, USA, P/N IC-MAN-10-R1-1).

2.2.4. Phenols

The procedure followed was the HPLC phenol compound analysis method for mainstream cigarette smoke by the Cooperation Centre for Scientific Research Relative to Tobacco (CORESTA, Paris, France) [11], with the following modifications. Standards were prepared over a range of 0.05–10 µg/mL in mobile phase. All EC liquid samples were analysed at a 10-fold dilution in mobile phase. An Agilent Model 1100, High Performance Liquid Chromatograph was equipped with a fluorescence detector operating at an excitation of 280 nm and an emission at 310 nm and a Phenomenex Luna PFP, 4.6 × 150 mm, 3µ column. The limit of detection was 0.05 µg/mL for all phenols.

The materials used for the analysis were: deionized water, Millipore; methanol HPLC Grade, Sigma-Aldrich (P/N 34860); hydroquinone (CAS #123-31-9), Alfa Aesar (Ward Hill, MA, USA) P/N A11411; resorcinol (CAS #108-46-3), Sigma-Aldrich (P/N 398047); catechol (CAS #120-80-9), Alfa Aesar (P/N A10164); phenol (CAS #108-95-2), Alfa Aesar (P/N A15760); *m*-cresol (CAS #108-39-4), Sigma-Aldrich, (P/N C85727); *o*-cresol (CAS #95-48-7), Sigma-Aldrich (P/N C85700); *p*-cresol (CAS #106-44-5), Alfa Aesar (P/N A13531).

2.2.5. Formaldehyde and Acetaldehyde

The procedure followed was the HPLC carbonyl compound analysis method for mainstream cigarette smoke, by CORESTA [12], with the following modifications. Standards were prepared over a range of 0.1–20 µg/mL. All EC samples were analysed at 11.5-fold dilution. An aliquot of the sample was combined with the 2,4-dinitrophenylhydrazine (DNPH) trapping solution and allowed to derivatize for 20 min, then quenched with 0.050 mL of pyridine. An Agilent Model 1100, High Performance Liquid Chromatograph was equipped with an Ultraviolet (UV) Detector operating at 365 nm and a Supelco Ascentis Express C18, 3.0 × 75 mm column. The limit of detection was 0.05 µg/mL for all carbonyl compounds. The materials used for the HPLC analysis were: deionized water, Millipore; phosphoric acid (H₃PO₄), 85%, A.C.S Reagent, Sigma-Aldrich (P/N 438081) (CAS #7664-38-2); DNPH (50%), TCI America (Portland, OR, USA) P/N D0845; acetonitrile (CAS #75-05-8), HPLC grade, Fisher (P/N LS121); tetrahydrofuran (CAS #109-99-9), HPLC grade, Fisher (P/N T427); isopropanol (CAS #67-63-0), distilled-in-glass, Fisher (P/N A464); pyridine, (CAS #110-86-1), Sigma-Aldrich (P/N 270407); acetaldehyde-2,4-DNPH, (CAS #1019-57-4), Sigma Aldrich (P/N 442434); formaldehyde-2,4-DNPH, (CAS #1081-15-8), Sigma-Aldrich (P/N 442597).

2.3. Statistical Analysis

For chemicals that were below the limit of detection (LOD), a value of LOD/2 was used for statistical comparisons. Data distributions were examined by a Kolmogorov-Smirnov test, after substituting <LOD with LOD/2. Only nicotine data were normally distributed. Continuous variables were expressed as mean (SEM) or median (IQR). Differences in the measurements between the 2 groups were evaluated by independent-samples *t*-test or Mann-Whitney U test. Comparison between the labelled and the measured level of nicotine was performed by paired samples *t*-test, while the % deviation from labelled nicotine concentration was compared between conventional and NET liquids by using independent samples *t*-test. No statistical comparison between conventional and NET liquids was performed for chemicals which were detected >LOD in less than half of the samples in one of the groups. Comparison between EC liquids and literature data on tobacco products were performed by Mann-Whitney U tests; the median (IQR) was computed from the reported levels per sample in the studies used for the comparison. Additionally, all samples in our study with levels <LOD were considered as having levels of LOD/2. A two-tailed *p* value of <0.05 was considered significant, and analysis was performed by commercially available software (SPSS v. 18, Chicago, IL, USA).

3. Results

3.1. Liquid Sample Analysis

The results of the chemical analysis are displayed in Tables 1 and 2. On average, nicotine concentrations were similar to those labelled (paired *t*-test *p* = 0.092). Twelve samples were within 10% of the labelled value. Nine samples contained lower and 12 samples contained higher nicotine levels than labelled. Deviation from the labelled value ranged from −21% to 22.1%, with three samples exceeding 20% absolute deviation. No difference was found between groups in the deviation from labelled nicotine concentration.

Trace levels of TSNAs were found in all samples. In six samples, NNN was <LOD (three conventional and three NET samples), while NNK was detected in all samples. Higher levels of NNN and total TSNAs were observed in NET liquids, but the differences were not statistically significant ($p = 0.141$ for NNN, $p = 0.549$ for NNK and $p = 0.197$ for total TSNAs).

Nitrate was predominantly found in NET samples, with only two of them being nitrate-free. On the contrary, only two conventional samples contained detectable levels of nitrates.

Small amounts of phenols were detected in nine samples, seven of which were NET liquids. Catechol was detected in two NET samples. Two conventional and four NET samples contained *m*-cresol and *o*-cresol, with higher levels observed in NET liquids. *p*-Cresol was present in one conventional and three NET samples. Phenol was present in one conventional and four NET samples. Hydroquinone and resorcinol were not detected in any sample. Total phenols were higher in NET liquids (1.5 [0.2–4.1] $\mu\text{g/mL}$ vs. 0.2 [0.2–1.7] $\mu\text{g/mL}$), but the difference was not statistically significant ($p = 0.101$).

Acetaldehyde was detected in all but 3 conventional samples but only in three NET samples. Formaldehyde was present in all but one sample. The levels of formaldehyde were similar in the two groups ($p = 0.314$).

Table 1. Nicotine and tobacco-specific nitrosamines in electronic cigarette liquids produced with conventional flavours or natural extracts of tobacco (NET). Deviation from labelled nicotine level is also displayed.

	Labelled Nicotine (mg/mL)	Measured Nicotine (mg/mL)	Nicotine Deviation (%)	NNN (ng/mL)	NNK (ng/mL)	Total Nitrosamines (ng/mL)
Limits of detection		0.5		1.0	1.0	1.0
Conventional liquids						
AtmosLab Bal	18	21.6	20.1	<LOD	5.2	5.2
AtmosLab RY69	18	22	22.1	5.1	9.9	15.0
ElGreco Americano	18	17.6	-2.0	<LOD	1.7	1.7
ElGreco City	18	17.3	-3.9	<LOD	5.5	5.5
ElGreco Classic	18	18.2	0.9	<LOD	2.5	2.5
Flavourart MaxBlend	18	16.9	-6.2	2.0	5.8	7.7
Flavourart RY4	18	17.8	-1.0	17.3	22.4	39.7
Flavourart Virginia	18	19.9	10.7	4.1	4.1	8.2
Nobacco American Tobacco	18	21	16.4	1.6	3.4	5.0
Nobacco Golden Margy	12	12.2	1.6	<LOD	3.6	3.6
Average *	17.4 (0.6)	18.5 (0.9)	5.9 (3.3)	1.3 (0.5–4.4)	4.7 (3.2–6.8)	6.1 (3.8–9.9)

Table 1. Cont.

	Labelled Nicotine (mg/mL)	Measured Nicotine (mg/mL)	Nicotine Deviation (%)	NNN (ng/mL)	NNK (ng/mL)	Total Nitrosamines (ng/mL)
NET liquids						
Cravin Vapes BOMB	12	10.5	-12.8	6.4	3.7	10.1
Cravin Vapes Perique	12	10.8	-9.8	12.5	5.4	18.0
ElToro Cigarrillos	18	19.8	10.1	<LOD	2.6	2.6
ElToro Puros	24	25.8	7.6	<LOD	2.5	2.5
MOV FullVirginiaFlake	18	19	5.4	<LOD	3.2	3.2
MOV Pendragon	18	19.2	6.4	11.3	10.8	22.1
MOV Southern Gentleman	18	17.3	-3.9	16.7	9.2	25.9
Naturally Extracted Tobacco Big Spirit	12	11.6	-3.6	1.6	4.6	6.3
Naturally Extracted Tobacco NS Dark	12	9.5	-21.0	9.5	6.3	15.8
QuickNicJuice Grandpa's Night Cap	12	14.3	18.8	22.9	15.5	38.5
QuickNicJuice Hump Back	12	14.3	19.2	16.8	15.1	31.9
Average ^{a,b}	15.3 (1.2)	15.6 (1.5)	1.5 (12.9)	9.5 (0.5–16.7)	5.4 (3.2–10.8)	15.8 (3.7–25.9)

NNN, N-nitrosornicotine; NNK, 4-(methylnitrosamino)-1-(3-pyridyl)-1-butanone; LOD, limit of detection; NET, natural extract of tobacco. ^a Average presented as mean (SEM) or median (interquartile range). To obtain average values, samples with levels <LOD were considered as containing LOD/2. ^b No statistically significant differences between groups were observed.

Table 2. Level of nitrates, phenols and aldehydes in electronic cigarette liquids produced with conventional flavours or natural extracts of tobacco (NET). Hydroquinone and resorcinol were not detected in any of the samples.

	Nitrate (µg/mL)	Catechol (µg/mL)	<i>m</i> -Cresol (µg/mL)	<i>o</i> -Cresol (µg/mL)	<i>p</i> -Cresol (µg/mL)	Phenol (µg/mL)	Acetaldehyde (µg/mL)	Formaldehyde (µg/mL)
Limits of detection	2.5	0.05	0.05	0.05	0.05	0.05	0.12	0.12
Conventional liquids								
AtmosLab Bal	<LOD	<LOD	<LOD	<LOD	<LOD	<LOD	1.82	2.53
AtmosLab RY69	<LOD	<LOD	<LOD	<LOD	<LOD	<LOD	20.06	2.14
ElGreco Americano	7.5	<LOD	<LOD	<LOD	<LOD	<LOD	<LOD	2.91
ElGreco City	<LOD	<LOD	<LOD	<LOD	<LOD	<LOD	2.55	<LOD
ElGreco Classic	<LOD	<LOD	<LOD	<LOD	<LOD	<LOD	0.75	3.95
Flavourart MaxBle<LOD	<LOD	<LOD	0.32	4.40	<LOD	1.42	5.23	6.21
Flavourart RY4	<LOD	<LOD	<LOD	<LOD	<LOD	<LOD	3.61	0.73
Flavourart Virginia	<LOD	<LOD	<LOD	<LOD	<LOD	<LOD	<LOD	3.24
Nobacco American Tobacco	<LOD	<LOD	<LOD	<LOD	<LOD	<LOD	2.42	1.99
Nobacco Golden Margy	15.4	<LOD	0.45	5.46	0.69	<LOD	<LOD	1.94
Average ^a	-	-	-	-	-	-	2.1 (0.1–4.0)	2.3 (1.6–3.4)

Table 2. Cont.

	Nitrate (µg/mL)	Catechol (µg/mL)	<i>m</i> -Cresol (µg/mL)	<i>o</i> -Cresol (µg/mL)	<i>p</i> -Cresol (µg/mL)	Phenol (µg/mL)	Acetaldehyde (µg/mL)	Formaldehyde (µg/mL)
NET liquids								
Cravin Vapes BOMB	47.6	<LOD	<LOD	<LOD	<LOD	<LOD	<LOD	1.75
Cravin Vapes Perique	15.2	<LOD	<LOD	<LOD	<LOD	0.80	<LOD	2.31
ElToro Cigarrillos	<LOD	<LOD	<LOD	<LOD	<LOD	1.30	1.46	1.71
ElToro Puros	<LOD	<LOD	0.13	0.16	0.22	2.29	1.73	2.10
MOV Full Virginia Flake	15.2	<LOD	5.31	1.40	<LOD	<LOD	<LOD	27.95
MOV Pe< LODragon	145.2	<LOD	3.75	0.22	<LOD	<LOD	<LOD	4.77
MOV Southern Gentleman	163.8	1.71	0.83	0.35	0.87	3.65	<LOD	2.29
Naturally Extracted Tobacco Big Spirit	11.5	<LOD	<LOD	<LOD	<LOD	<LOD	0.45	4.96
Naturally Extracted Tobacco NS Dark	159.9	<LOD	<LOD	<LOD	<LOD	<LOD	<LOD	3.45
QuickNicJuice Gra< LODpa's Night Cap	317.9	1.71	<LOD	<LOD	1.03	<LOD	<LOD	4.28
QuickNicJuice Hump Back	32.6	<LOD	<LOD	<LOD	<LOD	<LOD	<LOD	3.17
Average^a	32.6 (11.5–159.9)	-	-	-	-	-	-	3.2 (2.1–4.8) ^b

LOD, limit of detection; NET, natural extract of tobacco. ^a Average presented as mean (SEM) or median (interquartile range). To obtain average values, samples with levels <LOD were considered as containing LOD/2. No average was calculated for chemicals which were detected in less than half of the samples.

^b No statistically significant difference between groups was observed.

3.2. Comparison with Tobacco Products

The results of this study concerning chemicals present in tobacco plant (TSNAs and nitrate) were compared with literature data on tobacco products. A study by Stepanov *et al.* measured NNN and NNK by Gas Chromatography in 16 samples of four brands of tobacco cigarettes and reported the results in amount per gram of tobacco [13], while CORESTA reported the results of nitrate levels per gram of tobacco in six cured tobacco samples [14]. The results of the comparison between levels per mL EC liquid and levels per gram of tobacco are displayed in Table 3. The average levels of NNN, NNK, total TSNAs and nitrate in all EC liquids were >1400, >100, >400 and >1300 times lower compared to tobacco respectively ($p < 0.001$ for all). For NET liquids alone, the respective levels were >250, >140, >200 and >300 times lower (Table 3). Phenols are present mostly in tobacco cigarette smoke, derived from heating of polyphenols present in the tobacco plant [15]. Therefore, a comparison between 1 mL of EC liquids and the smoke of one tobacco cigarette was performed, using the findings from analysis of seven commercial cigarette samples smoked under Health Canada Intense puffing regime by CORESTA using HPLC [11]. Total phenols were present at levels 1200 times lower in all EC liquids, and 160 times lower in NET liquids compared to tobacco cigarette smoke (Table 3).

Table 3. Difference between tobacco cigarette products and electronic cigarette liquids selected tobacco-derived toxins. Statistically significant differences were found for all analyses ($p < 0.001$).

	Tobacco Products (per g Weight)	EC Liquids (per mL) ^a	Ratio ^b	NET Liquids (per mL)	Ratio ^c
NNN (ng)	2750 (2125–2975)	1.9 (0.5–11.9)	1447	9.5 (0.5–16.7)	289
NNK (ng)	760 (552–1140)	5.2 (3.3–9.5)	146	5.4 (3.2–10.8)	141
Total nitrosamines (ng)	3440 (2833–3808)	7.7 (3.9–20.0)	447	15.8 (3.7–25.9)	218
Nitrate (µg)	10200 (1975–14700)	7.5 (1.3–40.1)	1360	32.6 (11.5–159.9)	313
Total phenols (µg) ^d	240 (127–252)	0.2 (0.2–3.5)	1200	1.5 (0.2–4.1)	160

EC, electronic cigarettes; NNN, N-nitrosornornicotine; NNK, 4-(methylnitrosamino)-1-(3-pyridyl)-1-butanone. Data presented as median (interquartile range) ^a Average of all EC liquids tested (both conventional and NET liquids). ^b Ratio of tobacco products divided by average from all EC liquids.

^c Ratio of tobacco products divided by average from NET liquids. ^d Phenols detected in the smoke of one tobacco cigarette.

4. Discussion

This is the first study to evaluate a specific group of EC liquids, using cured tobacco leaves to extract the flavouring (NET liquids), for the presence of selected tobacco-derived toxins. None of the liquid samples was free from potentially harmful chemicals. Compared to conventional liquids, levels of TSNAs and formaldehyde were similar in NET liquids, as was the deviation from labelled nicotine content of the samples. Phenols were more prevalent in NET liquids, while acetaldehyde was found predominantly in conventional liquids. A characteristic finding in NET liquids was the nearly universal presence of nitrate. Of note, the levels of TSNAs and nitrate in EC liquids were 1 to 2 orders of magnitude lower compared to tobacco products.

Differences between nicotine content and labelling have been detected in previous studies. Kischner *et al.* found discrepancies from –50% to 42% in labelling compared to true content of refill liquids [16]. Similar results were reported in another recent study [17]. Davis *et al.* found that 46 out of 50 liquids contained higher than labelled nicotine concentration [18]. Our results are in agreement with a study by Etter *et al.* who found that the deviation from the label ranged from –15% to 21% [19]. Moreover, almost half (43%) of the samples tested herein contained lower than labelled nicotine concentrations. Interestingly, we did not detect any difference between NET and conventional liquids in deviation of nicotine levels from the label, indicating either that the flavour extraction methods used do not extract nicotine from the tobacco leaves or that manufacturers of NET liquids may compensate for any nicotine being present in the flavouring extract in the formulation process.

TSNAs are probably the most important compounds associated with negative health effects in tobacco cigarettes, mostly due to a combination of abundance and strong carcinogenicity [20,21]. They are present in very high quantities in both tobacco cigarette and smokeless tobacco products (in µg/g of tobacco weight) [13]. Herein, the levels found were traces, in ng/mL range, verifying previous observations [7,22,23]. No statistically significant difference was observed between NET and conventional liquids in TSNAs levels; three of the five samples with the lowest levels of nitrosamines were in fact NET liquids. Although not studied until now, it is unlikely that nitrosamines are

additionally produced and emitted in EC aerosol during the evaporation process. Goniewicz *et al.* evaluated nitrosamine levels in the aerosol of 12 EC products, and found levels similar to our study [24].

Nitrate and aldehydes are compounds with significant toxic and carcinogenic potential. Nitrate is converted to nitrite in saliva [25] which can participate in the endogenous production of TSNAs [26]. A characteristic finding of this study was that nitrate was almost exclusively found in NET liquids, therefore, we can conclude that they are derived from the flavour extraction process. Still the levels were much lower compared to tobacco products. Acetaldehyde and formaldehyde were present in a substantial proportion of liquids, both conventional (both compounds) and NET samples (predominantly formaldehyde). These chemicals are also present in tobacco products but at much higher levels compared to EC liquids. It should be mentioned that acetaldehyde is a GRAS substance for use in food (FEMA Nr 2003), therefore, it is possible that the source of acetaldehyde is food flavourings used in conventional EC liquids. However, acetaldehyde is classified as a possible human carcinogen (Group 2B) by the International Agency of Research on Cancer [27], and every effort should be made to avoid the presence of acetaldehyde in EC liquids.

Phenols are compounds with significant genotoxic, cardiotoxic and carcinogenic properties. They are mostly present in tobacco cigarette smoke rather than tobacco leaves [28]. Phenols were detected in nine of the 21 samples tested (four conventional and five NET liquids), but none of them contained all the phenols tested. It is known that phenols may be produced from heating tobacco; therefore, it is possible that in some cases tobacco leaves are heated during the extraction process. Still, the levels present in the liquids tested were much lower compared to the levels found in tobacco smoke. It remains to be seen if phenols may be additionally produced from ECs during the evaporation process.

The results of the study indicate that a proportion of conventional liquids were also contaminated with tobacco-derived chemicals. Besides TSNAs, which may be derived at low levels from pharmaceutical grade nicotine and are also present in nicotine replacement therapy products [7], nitrate and phenols were found in a limited number of samples. Although compounds approved for food use are commonly used as flavourings in conventional liquids, several of them also use industrially-produced tobacco absolute (commonly used in fragrances) to imitate the tobacco flavour. Therefore, that could potentially be the source for the phenols and nitrate found in these liquids. To the best of our knowledge, companies do not usually mention if tobacco absolute is used in their flavours. We propose that this should be mentioned in the labelling, since tobacco absolute is not approved for food use and it may be the source of exposure to some additional toxic chemicals compared to liquids not using it.

Two of the NET samples evaluated in this study were previously examined in aerosol form to determine their cytotoxic properties on cultured cardiomyoblasts [8]. They were found to be cytotoxic, although at levels significantly lower compared to tobacco cigarette smoke. Interestingly, these samples showed a lower chemical constituent profile in the testing herein; in particular, they contained very low levels of TSNAs and no nitrate, while levels of aldehydes were similar to conventional liquids. They both contained phenols, although at very low levels. It is probable that some other chemicals, not evaluated in this study, may be responsible for the cytotoxic properties.

Certain limitations apply to this study. Firstly, only one sample per liquid was tested, therefore, we could not assess the inter-batch variability. Depending on the quality and consistency of the production process, it is possible that significant differences between batches may exist. This should be

further explored. Moreover, a larger selection of samples would increase the statistical power of the comparisons, especially in the cases of NNN, total TSNA and total phenols which were found at higher levels in NET compared to conventional liquids but the differences were not statistically significant. Still, the levels were very low in both groups compared to tobacco products. Formaldehyde and acetaldehyde are formed during the heating process of EC aerosol production [24]. Thus, the levels reported herein underestimate true exposure to the consumer. However, we have determined that another source of aldehydes is the liquid itself. This should be considered when assessing aldehyde emissions to the aerosol, and it is necessary to evaluate the presence of these compounds in the liquid used to produce the aerosol. Recent studies have detected aldehyde levels in the aerosol approximating [29] or exceeding [30] the levels found in tobacco smoke. Such levels are probably not affected by the presence of trace amounts of aldehydes in the liquid as found herein. However, a major pitfall in laboratory evaluation of aerosol chemistry is that overheating of the liquid, resulting in the dry puff phenomenon [31], cannot be detected; thus, the findings may not be associated with relevant exposure of user during normal daily use, and this should be addressed in future studies. Finally, the analysis focused on EC liquids and not on aerosol. Although unlikely, it is currently unknown whether TSNA and nitrate are produced during the heating and evaporation of the EC liquid; this should be explored through studies of aerosol chemistry.

5. Conclusions

In this study, EC liquids were evaluated for the presence of selected tobacco-derived chemicals. A specific category of liquids, produced by extracting flavour from cured tobacco leaves, was evaluated and compared with conventional liquids of tobacco flavour. Nicotine content did not deviate by more than 22% in any liquid, with more than half of them being within the 10% range which is accepted for pharmaceutical products. None of the liquids was free from potentially harmful chemicals. NET liquids could result in exposure to somewhat higher levels of toxins compared to conventional EC liquids, especially for nitrate and phenols. Major tobacco-derived toxins, such as TSNA and nitrates, were present at very low levels compared to tobacco products. Further studies should evaluate whether these chemicals are emitted to the aerosol, while clinical studies will determine whether the levels of toxins found in EC liquids and aerosol are associated with adverse health effects.

Author Contributions

Konstantinos E. Farsalinos and Gene Gillman had the original idea for the study. Konstantinos E. Farsalinos was responsible for sample collection. Gene Gillman, Matt S. Melvin, Amelia R. Paolantonio, Wendy J. Gardow, Kathy E. Humphries and Sherri E. Brown performed the chemical analysis. Konstantinos E. Farsalinos, Konstantinos Poulas and Vassilis Voudris were responsible for the data analysis and statistical comparisons. Konstantinos E. Farsalinos, Gene Gillman, Konstantinos Poulas and Vassilis Voudris drafted the manuscript. All authors read and approved the final manuscript.

Conflicts of Interest

No competing interests are reported in relation to the current study. A small number of KF's and VV's studies on electronic cigarettes were performed using unrestricted funds provided to the institution (Onassis Cardiac Surgery Center) by electronic cigarette companies. Enthalpy Analytical is a for-profit CRO and provides testing for the electronic cigarette industry but did not receive any compensation for this study.

Matt S. Melvin was working at Enthalpy Analytical at the time of the study but is currently employed by Lorillard Tobacco Company, Greensboro, NC 27401, USA.

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RESEARCH ARTICLE

Open Access

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

Igor Burstyn

Abstract

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

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

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

Conclusions: Current state of knowledge about chemistry of liquids and aerosols associated with electronic cigarettes indicates that there is no evidence that vaping produces inhalable exposures to *contaminants* of the aerosol that would warrant health concerns by the standards that are used to ensure safety of workplaces. However, the aerosol generated during vaping as a whole (*contaminants plus declared ingredients*) creates personal exposures that would justify surveillance of health among exposed persons in conjunction with investigation of means to keep any adverse health effects as low as reasonably achievable. Exposures of bystanders are likely to be orders of magnitude less, and thus pose no apparent concern.

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

Background

Electronic cigarettes (also known as e-cigarettes) are generally recognized as a safer alternative to combusted tobacco products (reviewed in [1]), but there are conflicting claims about the degree to which these products warrant concern for the health of the vapers (e-cigarette users). A vaper inhales aerosol generated during heating

of liquid contained in the e-cigarette. The technology and patterns of use are summarized by Etter [1], though there is doubt about how current, complete and accurate this information is. Rather conclusive evidence has been amassed to date on comparison of the chemistry of aerosol generated by electronic cigarettes to cigarette smoke [2-8]. However, it is meaningful to consider the question of whether aerosol generated by electronic cigarettes would warrant health concerns on its own, in part because vapers will include persons who would not have been smokers and for whom the question of harm reduction

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from smoking is therefore not relevant, and perhaps more importantly, simply because there is value in minimizing the harm of those practicing harm reduction.

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

The present work considers both the contaminants present in liquids and aerosols as well as the declared ingredients in the liquids. The distinction between exposure to declared ingredients and contaminants of a consumer product is important in the context of comparison to occupational or environmental exposure standards. Occupational exposure limits are developed for unintentional exposures that a person does not elect to experience. For example, being a bread baker is a choice that does not involve election to be exposed to substances that cause asthma that are part of the flour dust (most commonly, wheat antigens and fungal enzymes). Therefore, suitable occupational exposure limits are created to attempt to protect individuals from such risk on the job, with no presumption of "assumed risk" inherent in the occupation. Likewise, special regulations are in effect to protect persons from unintentional exposure to nicotine in workplaces (<http://www.cdc.gov/niosh/docs/81-123/pdfs/0446.pdf>; accessed July 12, 2013), because in environments where such exposures are possible, it is reasonable to protect individuals who do not wish to experience its effects. In other words, occupational exposure limits are based on protecting people from involuntary and unwanted exposures, and thus can be seen as more stringent than the

standards that might be used for hazards that people intentionally choose to accept.

By contrast, a person who elects to lawfully consume a substance is subject to different risk tolerance, as is demonstrated in the case of nicotine by the fact that legally sold cigarettes deliver doses of nicotine that exceed occupational exposure limits [9]: daily intake of 20 mg of nicotine, assuming nearly 100% absorption in the lungs and inhalation of 4 m³ of air, corresponds to roughly 10 times the occupational exposure limit of 0.5 mg/m³ atmosphere over 8 hours [10]. Thus, whereas there is a clear case for applicability of occupational exposure limits to contaminants in a consumer product (e.g. aerosol of electronic cigarettes), there is no corresponding case for applying occupational exposure limits to declared ingredients desired by the consumer in a lawful product (e.g. nicotine in the aerosol of an electronic cigarette). Clearly, some limits must be set for voluntary exposure to compounds that are known to be a danger at plausible doses (e.g. limits on blood alcohol level while driving), but the regulatory framework should reflect whether the dosage is intentionally determined and whether the risk is assumed by the consumer. In the case of nicotine in electronic cigarettes, if the main reason the products are consumed is as an alternative source of nicotine compared to smoking, then the only relevant question is whether undesirable exposures that accompany nicotine present health risks, and the analogy with occupational exposures holds. In such cases it appears permissible to allow at least as much exposure to nicotine as from smoking before admitting to existence of new risk. It is expected that nicotine dosage will not increase in switching from smoking to electronic cigarettes because there is good evidence that consumers adjust consumption to obtain their desired or usual dose of nicotine [11]. The situation is different for the vapers who want to use electronic cigarettes without nicotine and who would otherwise not have consumed nicotine. For these individuals, it is defensible to consider total exposure, including that from any nicotine contamination, in comparison to occupational exposure limits. In consideration of vapers who would never have smoked or would have quit entirely, it must be remembered that the exposure is still voluntary and intentional, and comparison to occupational exposure limits is legitimate only for those compounds that the consumer does not elect to inhale.

The specific aims of this review were to:

1. Synthesize evidence on the chemistry of liquids and aerosols of electronic cigarettes, with particular emphasis on the contaminants.
2. Evaluate the quality of research on the chemistry of liquids and aerosols produced by electronic cigarettes.

3. Estimate potential exposures from aerosols produced by electronic cigarettes and compare those potential exposures to occupational exposure standards.

Methods

Literature search

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

Comparison of observed concentrations in aerosol to occupational exposure limits

For articles that reported mass or concentration of specific compounds in the aerosol (generated by smoking machines or from volunteer vapers), measurements of compounds were converted to concentrations in the "personal breathing zone",^a which can be compared to occupational exposure limits (OELs). The 2013 Threshold Limit Values (TLVs) [10] were used as OELs because they are the most up to date and are most widely recognized internationally when local jurisdictions do not establish their own regulations (see <http://www.ilo.org/safework/info/publications/>

WCMS_113329/lang-en/index.htm; accessed July 3, 2013). TLVs are more protective than that of US Occupation Safety and Health Administration's Permissible Exposure Limits because TLVs are much more often updated with current knowledge. However, all OELs generally agree with each other because they are based on the same body of knowledge. TLVs (and all other OELs) aim to define environmental conditions to which nearly all persons can be exposed to all day over many years without experiencing adverse health effects. Whenever there was an uncertainty in how to perform the calculation, a "worst case" scenario was used, as is the standard practice in occupational hygiene, where the initial aim is to recognize potential for hazardous exposures and to err on the side of caution. The following assumptions were made to enable the calculations that approximate the worst-case personal exposure of a vaper (Equation 1):

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

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

The only exception to this methodology was when assessing a study of aerosol emitted by 5 vapers in a 60 m³ room over 5 hours that seemed to be a sufficient approximation of worst-case "bystander" exposure [6]. All calculated concentrations were expressed as the most stringent (lowest) TLV for a specific compound (i.e. assuming the most toxic form if analytical report is ambiguous) and

expressed as “percent of TLV”. Considering that all the above calculations are approximate and reflecting that exposures in occupational and general environment can easily vary by a factor of 10 around the mean, we added a 10-fold safety factor to the “percent of TLV” calculation. This safety factor accounts for considerable uncertainty about the actual number and volume of puffs since the number of puffs is hard to estimate accurately with reports as high as 700 puffs per day [14]. Details of all calculations are provided in an Excel spreadsheet (see Additional file 3).

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

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

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

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

Results and discussion

General comments on methods

In excess of 9,000 determinations of single chemicals (and rarely, mixtures) were reported in reviewed articles and reports, typically with multiple compounds per electronic cigarette tested [2-8,15-43]. Although the quality of reports is highly variable, if one assumes that each report contains some information, this asserts that quite a bit is known about composition of e-cigarette liquids and aerosols. The only report that was excluded from consideration was work of McAuley *et al.* [24] because of clear evidence of cross-contamination – admitted to by the authors – with cigarette smoke and, possibly, reagents. The results pertaining to non-detection of tobacco-specific nitrosamines (TSNAs) are potentially

trustworthy, but those related to polycyclic aromatic hydrocarbons (PAH) are not since it is incredible that cigarette smoke would contain fewer PAHs, which arise from incomplete combustion of organic matter, than aerosol of e-cigarettes that do not burn organic matter [24]. In fairness to the authors of that study, similar problems may have occurred in other studies but were simply not reported, but it is impossible to include a paper in a review once it is known for certain that its quantitative results are not trustworthy. When in doubt, we erred on the side of trusting that proper quality controls were in place, a practice that is likely to increase appearance of atypical or erroneous results in this review. From this perspective, assessment of concordance among independent reports gains higher importance than usual since it is unlikely that two experiments would be flawed in the same exact manner (though of course this cannot be assured).

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

It was also unclear from [38] what the volume of aerosol sampled was – a critical item for extrapolating to personal exposure and a common point of ambiguity in the published reports. However, in a personal exchange with the authors of [38] [July 11, 2013], it was clarified that the sampling pump drew air at 500 mL/min through e-cigarette for 10 min, allowing more appropriate calculations for estimation of health risk that are presented below. Such misleading reporting is common in the field that confuses concentration in the aerosol (typically measured

directly) with concentration in the air inhaled by the vaper (never determined directly and currently requiring additional assumptions and modeling). This is important because the volume of aerosol inhaled (maximum ~8 L/day) is small compared to the volume of air inhaled daily (8 L/min); this point is illustrated in the Figure 1.

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

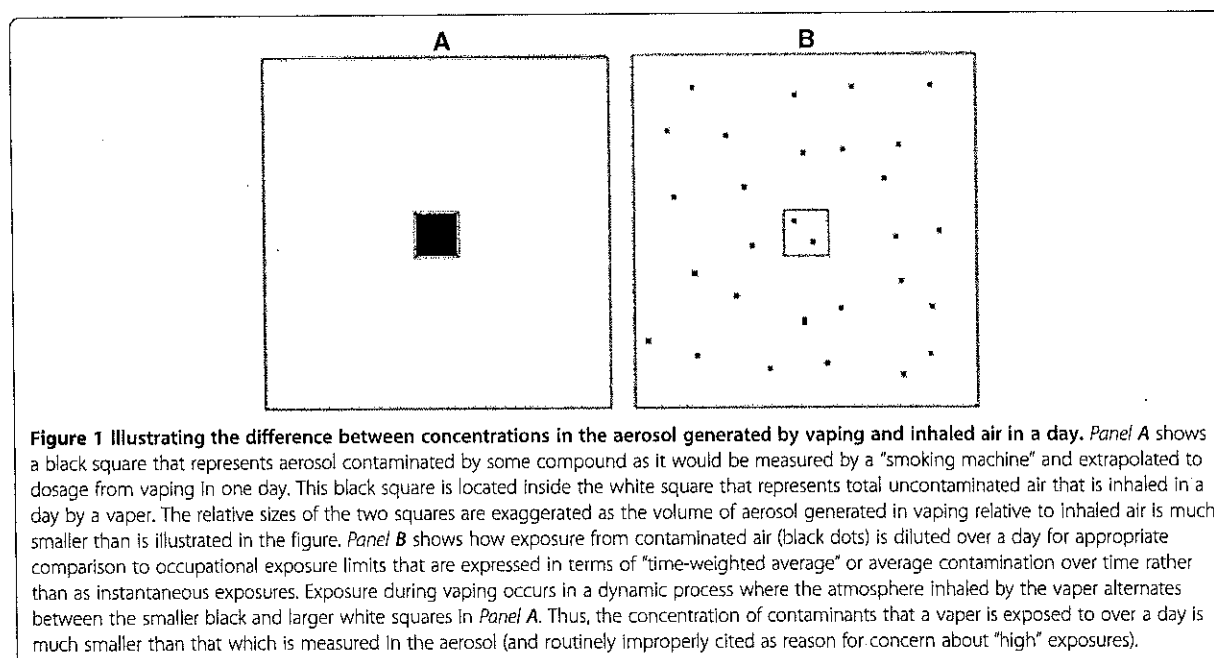
It is unhelpful to report the results in cigarette-equivalents in assessments that are not about cigarette exposure, as in [43], because this does not enable one to estimate exposures of vapers. To be useful for risk assessment, the results on the chemistry of the aerosols and liquids must be reported in a form that enables the calculations in Equations 1 and 2. It must be also be noted that typical investigations consisted of qualitative and quantitative phases such that quantitative data is available mostly on compounds that passed the qualitative screen. In the qualitative phase, presence of the

compounds above a certain limit of detection is determined. In the quantitative phase, the amount of only the compounds that are detected in the qualitative phase is estimated. This biased all reports on concentration of compounds towards both higher levels and chemicals which a particular lab was most adept at analyzing.

Declared Ingredients: comparison to occupational exposure limits

Propylene glycol and glycerin

Propylene glycol and glycerin have the default or precautionary 8-hour TLV of 10 mg/m³ set for all organic mists with no specific exposure limits or identified toxicity (http://www.osha.gov/dts/chemicalsampling/data/CH_243600.html; accessed July 5, 2013). These interim TLVs tend to err on the side of being too high and are typically lowered if evidence of harm to health accumulates. For example, in a study that related exposure of theatrical fogs (containing propylene glycol) to respiratory symptoms [46], "mean personal inhalable aerosol concentrations were 0.70 mg/m³ (range 0.02 to 4.1)" [47]. The only available estimate of propylene concentration of propylene glycol in the aerosol indicates personal exposure on the order of 3–4 mg/m³ in the personal breathing zone over 8 hours (under the assumptions we made for all other comparisons to TLVs) [2]. The latest (2006) review of risks of occupational exposure to propylene glycol performed by the Health Council of the Netherlands (known for OELs that are the most protective that evidence supports and based exclusively on scientific considerations rather than also accounting for feasibility as is the case for the



TLVs) recommended exposure limit of 50 mg/m³ over 8 hours; concern over short-term respiratory effects was noted [<http://www.gezondheidsraad.nl/sites/default/files/200702OSH.pdf>; accessed July 29, 2013]. Assuming extreme consumption of the liquid per day via vaping (5 to 25 ml/day and 50-95% propylene glycol in the liquid),^b levels of propylene glycol in inhaled air can reach 1–6 mg/m³. It has been suggested that propylene glycol is very rapidly absorbed during inhalation [4,6] making the calculation under worst case scenario of all propylene glycol becoming available for inhalation credible. It must also be noted that when consuming low-nicotine or nicotine-free liquids, the chance to consume larger volumes of liquid increases (large volumes are needed to reach the target dose or there is no nicotine feedback), leading to the upper end of propylene glycol and glycerin exposure. Thus, estimated levels of exposure to propylene glycol and glycerin are close enough to TLV to warrant concern. However, it is also important to consider that propylene glycol is certainly not all absorbed because visible aerosol is exhaled in typical vaping. Therefore, the current calculation is in the spirit of a worst case assumption that is adopted throughout the paper.

Nicotine

Nicotine is present in most e-cigarette liquids and has TLV of 0.5 mg/m³ for average exposure intensity over 8 hours. If approximately 4 m³ of air is inhaled in 8 hours, the consumption of 2 mg nicotine from e-cigarettes in 8 hours would place the vaper at the occupational exposure limit. For a liquid that contains 18 mg nicotine/ml, TLV would be reached upon vaping ~0.1-0.2 ml of liquid in a day, and so is achieved for most anyone vaping nicotine-containing e-cigarettes [1]. Results presented in [25] on 16 e-cigarettes also argue in favor of exceedance of TLV from most any nicotine-containing e-cigarette, as they predict >2 mg of nicotine released to aerosol in 150 puffs (daily consumption figure adopted in this report). But as noted above, since delivery of nicotine is the purpose of nicotine-containing e-cigarettes, the comparison to limits on unintended, unwanted exposures does not suggest a problem and serves merely to offer complete context. If nicotine is present but the liquid is labeled as zero-nicotine [25,44], it could be treated as a contaminant, with the vaper not intending to consume nicotine and the TLV, which would be most likely exceeded, is relevant. However, when nicotine content is disclosed, even if inaccurately, then comparison to TLV is not valid. Accuracy in nicotine content is a concern with respect to truth in advertising rather than unintentional exposure, due to presumed (though not yet tested) self-regulation of consumption by persons who use e-cigarettes as a source of nicotine.

Overall, the declared ingredients in the liquid would warrant a concern by standards used in occupational

hygiene, provided that comparison to occupational exposure limits is valid, as discussed in the introduction. However, this is not to say that the exposure is affirmatively believed to be harmful; as noted, the TLVs for propylene glycol and glycerin mists is based on uncertainty rather than knowledge. These TLVs are not derived from knowledge of toxicity of propylene glycol and glycerin mists, but merely apply to any compound of no known toxicity present in workplace atmosphere. This aspect of the exposure from e-cigarettes simply has little precedent (but see study of theatrical fogs below). Therefore, the exposure will provide the first substantial collection evidence about the effects, which calls for monitoring of both exposure levels and outcomes, even though there are currently no grounds to be concerned about the immediate or chronic health effects of the exposure. The argument about nicotine is presented here for the sake of completeness and consistency of comparison to TLVs, but in itself does not affect the conclusions of this analysis because it should not be modeled as if it were a contaminant when declared as an ingredient in the liquid.

Contaminants

Polycyclic aromatic hydrocarbons

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

Tobacco-specific nitrosamines

The same risk assessment considerations that exist for PAH also hold for carcinogenic tobacco-specific nitrosamines (TSNAs) [48] for which no occupational exposure limits exist because (a) these exposures do not appear to occur in occupational settings often enough to warrant development of TLVs, and (b) it is currently accepted in establishing TLVs that carcinogens do not have minimal thresholds of toxicity. As expected, because the TSNAs are contaminants of nicotine from tobacco leaf, there is also evidence of association between nicotine content of the liquid and TSNA concentrations, with reported concentrations <5 ng/cartridge tested [7]. Smaller studies of TSNA content in liquids are variable, with some not reporting any detectable levels [18,33,35] and others clearly identifying these compounds in the liquids when controlling for background contamination (n = 9) [23]. Analyses of aerosols indicate that TSNAs are present in amounts that can result in doses of < ng/day [5,33] to

$\mu\text{g}/\text{day}$ [8] (assuming 150 puffs/day) (see also [43]). The most comprehensive survey of TSNA content of 105 samples of liquids from 11 manufactures indicates that almost all tested liquids (>90%) contained TSNA in $\mu\text{g}/\text{L}$ quantities [36]. This is roughly equivalent to 1/1000 of the concentration of TSNA in modern smokeless tobacco products (like snus), which are in the ppm range [48]. For example, 10 $\mu\text{g}/\text{L}$ (0.01 ppm) of total TSNA in liquid [36] can translate to a daily dose of 0.025–0.05 μg from vaping (worst case assumption of 5 ml liquid/day); if 15 g of snus is consumed a day [49] with 1 ppm of TSNA [48] and half of it were absorbed, then the daily dose is estimated to be 7.5 μg , which is 150–300 times that due to the worst case of exposure from vaping. Various assumptions about absorption of TSNA alter the result of this calculation by a factor that is dwarfed in magnitude compared to that arising from differences considered above. This is reassuring because smokeless tobacco products, such as snus, pose negligible cancer risk [50], certainly orders of magnitude smaller than smoking (if one considers the chemistry of the products alone). In general, it appears that the cautious approach in face of variability and paucity of data is to seek better understanding of the predictors of presence of TSNA in liquids and aerosols so that measures for minimizing exposure to TSNA from aerosols can be devised. This can include considering better control by manufactures who extract the nicotine from tobacco leaf.

Volatile organic compounds

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

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

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

Levels of acrolein in exhaled aerosol reported in [6] were below 0.0016 mg/m^3 and correspond to predicted exposure of <1% of TLV (Table 2). It must be re-emphasized that all calculations based on one electronic cigarette analyzed in [38] are best treated as qualitative in nature (i.e. indicating presence of a compound without any particular meaning attached to the reported level with respect to typical levels) due to great uncertainty about whether the manner in which the e-cigarette was operated could have resulted in overheating that led to generation of acrolein in the aerosol. In fact, a presentation made by the author of [38] clearly stated that the “atomizer, generating high concentration carbonyls, had been burned black” [40,41]. In unpublished work, [40] there are individual values of formaldehyde, acrolein and glyoxal that approach TLV, but it is uncertain how typical these are because there is reason to believe the liquid was overheated; considerable variability among brands of electronic cigarettes was also noted. Formaldehyde and other aldehydes, but not acrolein, were detected in the analysis one e-cigarette [43]. The overwhelming majority of the exposure to specific VOC that are predicted to result from inhalation of the aerosols lie far below action level of 50% of TLV at which exposure has to be mitigated according to current code of best practice in occupational hygiene [51].

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

Diethylene glycol and ethylene glycol became a concern following the report of their detection by FDA [44], but these compounds are not detected in the majority of

Table 1 Exposure predictions based on analysis of aerosols generated by smoking machines: volatile organic compounds

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

[#]Average is presented when N > 1.

tests performed to date [3,15,17,19,23]. Ten batches of the liquid tested by their manufacture did not report any diethylene glycol above 0.05% of the liquid [42]. Methods used to detect diethylene glycol appear to be adequate to be informative and capable of detecting the compound in quantities < 1% of TLV [15,17,23]. Comparison to TLV is based on a worst case calculation analogous to the one performed for propylene glycol. For diethylene glycol, TLV of 10 mg/m³ is applicable (as in the case of all aerosols with no known toxicity by inhalation), and there is a recent review of regulations of this compound conducted for the Dutch government by the Health Council

of the Netherlands (jurisdiction with some of the most strict occupational exposure limits) that recommended OEL of 70 mg/m³ and noted lack of evidence for toxicity following inhalation [<http://www.gezondheidsraad.nl/sites/default/files/200703OSH.pdf>; accessed July 29; 2013]. In conclusion, even the quantities detected in the single FDA result were of little concern, amounting to less than 1% of TLV.

Inorganic compounds

Special attention has to be paid to the chemical form of compounds when there is detection of metals and other

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

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

[#]Average is presented when N > 1.

elements by inductively coupled plasma mass spectrometry (ICP-MS) [8,26]. Because the parent molecule that occurs in the aerosol is destroyed in such analysis, the results can be misleading and not interpretable for risk assessment. For example, the presence of sodium (4.18 µg/10 puffs) [26] does not mean that highly reactive and toxic sodium metal is in the aerosol, which would be impossible given its reactivity, but most likely means the presence of the ubiquitous compound that contains sodium, dissolved table salt (NaCl). If so, the corresponding daily dose of NaCl that arises from these concentrations from 150 puffs is about 10,000 times lower than allowable daily intake according to CDC (<http://www.cdc.gov/features/dssodium/>; accessed July 4, 2013). Likewise, a result for presence of silica is meaningless for health assessment unless the crystalline form of SiO₂ is known to be present. When such ambiguity exists, a TLV equivalence calculation was not performed. We compared concentrations to TLVs when it was even remotely plausible that parent molecules were present in the aqueous solution. However, even these are to be given credence only in an extremely pessimistic analyst, and further investigation by more appropriate analytical methods could clarify exactly what compounds are present, but is not a priority for risk assessment.

It should also be noted that one study that attempted to quantify metals in the liquid found none above 0.1-0.2 ppm levels [7] or above unspecified threshold [19]. Table 3 indicates that most metals that were detected were present at <1% of TLV even if we assume that the

analytical results imply the presence of the most hazardous molecules containing these elements that can occur in aqueous solution. For example, when elemental chromium was measured, it is compared to TLV for insoluble chromium IV that has the lowest TLV of all chromium compounds. Analyses of metals given in [43] are not summarized here because of difficulty with translating reported units into meaningful terms for comparison with the TLV, but only mercury (again with no information on parent organic compound) was detected in trace quantities, while arsenic, beryllium, chromium, cadmium, lead and nickel were not. Taken as the whole, it can be inferred that there is no evidence of contamination of the aerosol with metals that warrants a health concern.

Consideration of exposure to a mixture of contaminants

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

$$OEL_{\text{mixture}} = \sum_{i=1}^n (C_i / TLV_i), \quad (3)$$

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

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

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

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

^{##}Average is presented when N > 1.

OEL_{mixture} > 1, then there is evidence of the mixture exceeding TLV.

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

currently no reason to suspect that the trace amounts of the contaminants will react to create compounds that would be of concern.

Conclusions

By the standards of occupational hygiene, current data do not indicate that exposures to vapors from contaminants in electronic cigarettes warrant a concern. There are no known toxicological synergies among compounds in the aerosol, and mixture of the contaminants does not pose a risk to health. However, exposure of vapors to propylene glycol and glycerin reaches the levels at which, if one were considering the exposure in connection with a workplace setting, it would be prudent to scrutinize the health of exposed individuals and examine how exposures could be reduced. This is the basis for the recommendation to monitor levels and effects of prolonged exposure to propylene glycol and glycerin that comprise the bulk of emissions from electronic cigarettes other than nicotine and water vapor. From this perspective, and taking the analogy of work on theatrical fogs [46,47], it can be speculated that respiratory functions and symptoms (but not cancer of respiratory tract or non-malignant respiratory disease) of the vapor is of primary interest. Monitoring upper airway irritation of vapors and experiences of

unpleasant smell would also provide early warning of exposure to compounds like acrolein because of known immediate effects of elevated exposures (<http://www.atsdr.cdc.gov/toxprofiles/tp124-c3.pdf>; accessed July 11, 2013). However, it is questionable how much concern should be associated with observed concentrations of acrolein and formaldehyde in the aerosol. Given highly variable assessments, closer scrutiny is probably warranted to understand sources of this variability, although there is no need at present to be alarmed about exceeding even the occupational exposure limits, since occurrence of occasional high values is accounted for in established TLVs. An important clue towards a productive direction for such work is the results reported in [40,41] that convincingly demonstrate how heating the liquid to high temperatures generates compounds like acrolein and formaldehyde in the aerosol. A better understanding about the sources of TSNA in the aerosol may be of some interest as well, but all results to date consistently indicate quantities that are of no more concern than TSNA in smokeless tobacco or nicotine replacement therapy (NRT) products. Exposures to nicotine from electronic cigarettes is not expected to exceed that from smoking due to self-titration [11]; it is only a concern when a vaper does not intend to consume nicotine, a situation that can arise from incorrect labeling of liquids [25,44].

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

The key to making the best possible effort to ensure that hazardous exposures from contaminants do not occur is ongoing monitoring of actual exposures and estimation of potential ones. Direct measurement of personal exposures is not possible in vaping due to the fact the aerosol is inhaled directly, unless, of course, suitable biomarkers of exposure can be developed. The current review did not identify any suitable biomarkers, though cotinine is a useful proxy for exposure to nicotine-containing liquids. Monitoring of potential composition of exposures is perhaps best achieved through analysis of aerosol generated in a manner that approximates vaping, for which better insights are needed on how to modify "smoking machines" to mimic vaping given that there are documented differences in inhalation patterns [52] that depend

on features of e-cigarettes [14]. These smoking machines would have to be operated under a realistic mode of operation of the atomizer to ensure that the process for generation of contaminants is studied under realistic temperatures. To estimate dosage (or exposure in personal breathing zone), information on the chemistry of the aerosol has to be combined with models of the inhalation pattern of vapers, mode of operation of e-cigarettes and quantities of liquid consumed. Assessment of exhaled aerosol appears to be of little use in evaluating risk to vapers due to evidence of qualitative differences in the chemistry of exhaled and inhaled aerosol.

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

Future work in this area would greatly benefit from standardizing laboratory protocols (e.g. methods of extraction of compounds from aerosols and liquids, establishment of "core" compounds that have to be quantified in each analysis (as is done for PAH and metals), development of minimally informative detection limits that are needed for risk assessment, standardization of operation of "vaping machine", etc.), quality control experiments (e.g. suitable positive and negative controls without comparison to conventional cigarettes, internal standards, estimation of % recovery, etc.), and reporting practices (e.g. in units that can be used to estimate personal exposure, use of uniform definitions of limits of detection and quantification, etc.), all of which would improve on the currently disjointed literature. Detailed recommendations on standardization of such protocols lie outside of scope of this report.

All calculations conducted in this analysis are based on information about patterns of vaping and the content

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

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

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

quantities of organic compounds that may or may not be harmful at doses that occur during vaping.

Key conclusions:

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

across multiple studies, such that average exposure that can be calculated are higher than true value because they are “missing” all true zeros.

- Routine monitoring of liquid chemistry is easier and cheaper than assessment of aerosols. Combined with an understanding of how the chemistry of the liquid affects the chemistry of the aerosol and insights into behavior of vapors, this can serve as a useful tool to ensure the safety of e-cigarettes.
- The only unintentional exposures (i.e., not the nicotine) that seem to rise to the level that they are worth further research are the carrier chemicals themselves, propylene glycol and glycerin. This exposure is not known to cause health problems, but the magnitude of the exposure is novel and thus is at the levels for concern based on the lack of reassuring data.

Endnotes

^aAtmosphere that contains air inhaled by a person.

^bThis estimate of consumption was derived from informal reports from vaping community; 5 ml/day was identified as a high but not rare quantity of consumption and 25 ml/day was the high end of claimed use, though some skepticism was expressed about whether the latter quantity was truly possible. High-quality formal studies to verify these figures do not yet exist but they are consistent with report of Etter (2012).

^cThe term “VOC” loosely groups together all organic compounds present in aerosol and because the declared ingredients of aerosol are organic compounds, it follows that “VOC are present”.

Additional files

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

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

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

Competing interests

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

Authors' information

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

Acknowledgements

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

Received: 26 August 2013 Accepted: 2 January 2014

Published: 9 January 2014

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doi:10.1186/1471-2458-14-18

Cite this article as: Burstyn: Peering through the mist: systematic review of what the chemistry of contaminants in electronic cigarettes tells us about health risks. *BMC Public Health* 2014 **14**:18.

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