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May 30, 2107

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To whom it may concern:

I am a health researcher with a special interest in public policy and substance use who has been following developments in Australian policy regarding Electronic Nicotine Delivery Systems (ENDS or electronic cigarettes) with concern. Based on the available evidence, I strongly support policy to make it easy for smokers to switch to far less harmful forms of nicotine delivery such as ENDS. As an Australian citizen and someone who cares about health outcomes, I am deeply troubled that present policies create practical, financial and even legal obstacles to smokers who may wish to gain these benefits.

I was the director of Australia's National Drug Research Institute at Curtin University in Western Australia for 8 years before moving to Canada in 2004 as Professor and Director at the Centre for Addictions Research of British Columbia (CARBC) at the University of Victoria. [link] A copy of this report is provided as part of this submission.

'Clearing the Air' report

Earlier this year, my colleagues and I published 'Clearing the Air', a comprehensive review of the evidence on the harms and benefits of electronic cigarettes, funded by the Canadian Institutes of Health Research.

The main findings of the review were that

1. There is encouraging evidence that vapour devices can be at least as effective as other nicotine replacements as aids to help tobacco smokers quit.
2. There is no evidence that vaping is a gateway to tobacco smoking. On the contrary, it appears to be replacing – rather than encouraging – tobacco smoking among young people.
3. Second hand exposure to vapour has been shown to create measurable but small exposure to nicotine (which in itself is virtually harm free) and no significant exposure to carcinogens such as found in tobacco smoke.
4. There is strong evidence that vapour from ENDS is less toxic than tobacco smoke.

Our conclusion was that 'policy should not be driven by ungrounded fears of a 'gateway effect' but, rather, be geared towards helping tobacco smokers quit'. The evidence suggests that ENDS could play a valuable role as a tobacco harm reduction tool for smokers who are unable or unwilling to quit and are likely to have an overall positive effect on public health.

Canadian legislation on ENDS

In line with this evidence, the Canadian Government has recently introduced the Tobacco and Vaping Products Act, which regulates vaping products as a separate class of products to tobacco [media release]. The legislation follows a Report of the Standing Committee on Health, 'Vaping: Toward a regulatory framework for e-cigarettes' [link] which recommended a new regulatory framework for ENDS.

The Act includes provisions to protect youth from nicotine addiction and tobacco use while allowing adults to access vaping products as likely less harmful alternatives to tobacco use.

The legislation will make nicotine legal when used for vaping and provides a balanced regulatory framework to maximise the benefits to current smokers while minimizing the risks to non-smokers with appropriate controls and monitoring.

Please do not hesitate to contact me if you would like any further information.

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Clearing the Air: A systematic review on the harms and benefits of e-cigarettes and vapour devices

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January 2017

University of Victoria
Centre for Addictions Research of BC

Acknowledgements

We thank our Knowledge User partners for their involvement and contributions to this study:
Dr. Perry Kendall, Provincial Health Officer, BC Ministry of Health
Frank Welsh, Director of Policy, Canadian Public Health Association
Matt Herman, Executive Director, Healthy Living Branch, BC Ministry of Health

We gratefully acknowledge the participation of our Stakeholders:
Deanne Chafe, MSW RSW, Addictions Specialist, Canadian Armed Forces
Kim Bulger, Social Worker, Canadian Forces Health Services Group
Dr. Richard Stanwick, Chief Medical Officer, Island Health
Dr. Mark Tyndall, Executive Medical Director, BC Centre for Disease Control

Suggested Citation

O'Leary, R., MacDonald, M., Stockwell, T., & Reist, D. (2017). Clearing the Air: A systematic review on the harms and benefits of e-cigarettes and vapour devices. Victoria, BC: Centre for Addictions Research of BC.

Clearing the Air is a Knowledge Synthesis project funded by the Canadian Institutes of Health Research, Grant KRS-138211. PROSPERO registration CRD42015025267.

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Executive Summary

Clearing the Air is a Canadian Institutes of Health Research funded knowledge synthesis project that examines the debate around vapour devices (e-cigarettes) through a synthesis and evidence review. In the literature search we queried 15 databases and retrieved 1,622 journal articles through April 26, 2016. This library was searched for articles on cessation, youth use, second-hand exposure, and the toxicity of vapour devices compared to cigarettes. In a number of instances, the research studies provided conflicting data. The overriding caveat for evaluating the findings is that the plethora of different devices and liquids means that the findings of a particular study may not be generalizable to other devices.

Regarding cessation with vapour devices, the limited number of studies to date do not allow for a definitive judgement about their efficacy for cessation. However, evidence from higher quality studies is encouraging, and many researchers found an appreciable number of vapour device users are quitting tobacco. The research is mixed as to whether vapour device use had an effect on the desire or ability of those who smoke to quit tobacco use, but based on the preponderance of findings, it is clear that claims for a negative impact on cessation are unjustified. Newer models (for example, tank systems) provide more effective nicotine delivery, and with earlier models rapidly falling out of favour, studies on earlier devices could be reasonably excluded in evaluations of vapour device use for cessation.

A key issue around vapour devices is the concern that youth use of vapour devices could lead to their uptake of tobacco products. This does not appear to be occurring as tobacco use in the US, Canada, and other countries is declining significantly among 12 – 19 year olds as vapour device use is increasing. Two independent regression analyses provide solid evidence against a gateway effect. Comparing rates of youth tobacco use in US states with and without bans on sales to minors, where adolescents had access to vapour devices, the prevalence of tobacco use was lower. In addition, addiction may not always be a factor as 23% - 72% of teens have reported consuming non-nicotine liquids. Based on the studies, we suggest a common liabilities model with vapour device use and tobacco use driven by the same psycho-social factors, particularly adolescent sensation seeking and the influence of family and peers who are themselves tobacco users.

Another critical issue is the potential risks from second hand exposure to vapour. Several studies found that vapour did produce a measureable absorption of nicotine in bystanders, but it is not yet clear how to frame the extent of risk from transient exposure to nicotine. Tests determined that second hand vapour is far less toxic than cigarette smoke, often by several orders of magnitude, and that it does not contain carbon monoxide or volatile organic compounds. Yet more testing is urgently needed to clarify the conflicting findings on the emissions of particulate matter, polycyclic aromatic hydrocarbons, and metals, and to determine the levels of passive exposure that may put vulnerable populations at risk, such as children and persons with smoke-sensitive morbidities.

Comparing the emissions of vaping to smoking, the studies are very encouraging for the potential of vapour devices for tobacco harm reduction. Vapour devices do not deliver tar, and emissions do not contain 61 of 79 cigarette toxins. Vaping produced exponentially lower levels of cancer causing agents, tobacco-specific nitrosamines, and volatile organic compounds. Nevertheless, the reduction in emissions most likely differs between products and may be influenced by user behaviours. Unfortunately, no independent research has measured vapour device emissions of 1,3-butadiene (BDE), the highest source of cancer risk in cigarettes. The lower level emissions of metals and particulate matter remain of concern, and could possibly be addressed by manufacturing standards or improvements in product design.

Based on our systematic reviews of literature published up to April 2016, we conclude with the following four observations:

1. Overall, there is encouraging evidence that vapour devices can be at least as effective as other nicotine replacements as aids to help tobacco smokers quit.
2. There is no evidence of any gateway effect whereby youth who experiment with vapour devices are, as a result, more likely to take up tobacco use. The available evidence is that tobacco use by youth has been declining while use of vapour devices has been increasing.
3. Second hand exposure to vapour is more transient than exposure to tobacco smoke. However, it has been shown to create measurable but small exposure to nicotine and no significant exposure to carcinogens such as found in tobacco smoke. It is unclear whether low level nicotine exposure poses any risk to health.
4. Vapour from e-cigarettes contains substantially fewer toxicants than does smoke from regular tobacco cigarettes, however there has been insufficient research regarding some significant carcinogens that may still be present.

In conclusion, we recommend that Canadian regulation of vapour devices be driven by best available evidence with a view to supporting improved public health outcomes. Policy should not be driven by ungrounded fears of a 'gateway effect' but, rather, be geared towards helping tobacco smokers quit and ensuring that only the safest devices are legally available, thereby reducing harm for both direct and second hand exposure.

About the Clearing the Air Project

Under the shadow of the tobacco epidemic, the sale and use of e-cigarettes and other vapour devices is increasing dramatically. A contentious debate has risen within public health over the harms and benefits of these devices. The Clearing the Air research teams seeks to clarify the issues with an even-handed systematic review of the health and social impacts of vapour device use and its harm reduction potential. Our research design used an integrated knowledge translation model in which public health researchers and knowledge users (e.g., policy and decision makers) worked collaboratively to identify the research questions, interpret the results, make recommendations, and engage in knowledge translation. The goal of our project is to generate a research synthesis that can inform the pressing regulatory and public health decisions to be made, specifically in British Columbia and Canada but also internationally. We seek to "clear the air" in this contentious public health debate with an appeal to the available evidence, and by offering clear-headed recommendations for policy, regulation, and future research.

Research Questions

1. What are the health risks and benefits of vapour devices, and how do these compare to cigarettes?
2. What is the harm reduction potential of vapour devices for individuals, the environment, and society?
3. Does youth vapour device experimentation lead to cigarette use?
4. Can vapour devices be effective tools for tobacco cessation?
5. What is the potential toxicity of second-hand vapour?

In this evidence review we examined the research studies applicable to questions 1, 3, 4, and 5, and this evidence does have implications for question 2 on harm reduction. A fuller examination of the debate over harm reduction among different research traditions will be conducted later in the project through a meta-narrative analysis.

Search Processes and Quality Assessments

Search Strategy

The Research Coordinator (RC) developed the initial search strategy. In consultation with a Research Librarian, each database was searched for subject headings that were retrieved and pilot tested for accuracy by the RC. The search strings and 15 databases are reported in Table 1, with the search covering 2007 (date of the first published peer reviewed article) to April 26, 2016. The search was conducted on four dates, allowing time for articles to be reviewed, classified, and assigned to the research questions as applicable. Search dates and retrieval counts are reported in Table 2. Initially, conference abstracts and posters were to be included, but the quantity of available articles made this unnecessary. In total, 1622 journal publications were retrieved.

Table 1: Search Strings and Databases

Database	Search fields	Terms
Academic Search Complete (EBSCO) CINAHL with full text (EBSCO) Cochrane Central Register of Controlled Trials (CENTRAL) (EBSCO) LGBT Life with full text (EBSCO) MEDLINE with full text (EBSCO) PsycArticles (EBSCO)	abstract OR title	[electronic cigarettes OR (e-cigarettes AND multiple topics) OR e-cigs OR vapor cigarettes] OR [electronic nicotine AND (delivery systems OR delivery device OR devices)]

PsycINFO (EBSCO) Social Sciences Citation Index (H.W. Wilson) Women's Studies International (EBSCO)		
Business Source Complete (EBSCO), limited to scholarly (peer reviewed) journals	subject terms	electronic cigarettes
LILACS (Latin American and Caribbean Literature on Health Sciences)	abstract words	vaporizer
MEDLINE 1996 – on (OVID)	keyword	electronic cigarette*
PubMed	title/abstract	electronic cigarette* (AND sub headings) OR electronic nicotine delivery (AND sub headings OR e-liquid* OR vaping
ScienceDirect (Elsevier)	abstract, title, keywords	electronic cigarette* OR "electronic nicotine" OR vaping
Web of Science (Thomson Reuters)	topic	"electronic cigarette*" OR e-cigarette* OR "electronic nicotine" OR vaping

Table 2: Search Retrievals

Search Date	Count	Deletions	Additions	Total
14 Apr 2015	1059	**170 DELETIONS** 53 conference abstracts 1 book review 10 unable to locate 4 continuing medical ed. 8 erratum 9 issue introductions 2 table of contents 3 grey literature 80 < 3 sentences on devices	1	890
1 Oct 2015	379	**51 DELETIONS** 10 conference abstracts 1 call for papers 1 continuing medical ed. 4 erratum 2 issue introduction 8 final publication 23 < 3 sentences on devices 2 unable to locate	0	328
2 Jan 2016	242	**62 DELETIONS** 1 erratum 25 conference abstracts 1 withdrawn 23 final publication 12 < 3 sentences on devices	0	180

26 Apr 2016	266	**43 DELETIONS** 5 unable to locate 1 erratum 1 issue introduction 11 final publication 11 conference abstracts 14 < 3 sentences on devices	1	224
TOTAL				1622

Search Process for Research Questions

As each round of the search was performed, the RC searched all articles retrieved by hand for their relevance to the research questions, and tagged them in the EndNote libraries. To assure that all articles had been located for each question, the entire library was searched with keywords for the sections, see Table 2A below.

Table 2A: Subject Keywords for Research Questions

Research Question	**Keywords**
Cessation	cessation, quit
Youth Transition	youth, adolescent*, teen*, student*, young people
Second Hand	second hand, passive
Comparison	toxicology

Quality Assessment

Quality assessments were performed on the studies based on the following standards. For the cessation studies, we applied the modified GRADE criteria used by Malas et al. (2016) in their systematic review of cessation studies. We accepted their quality assessments for the articles they rated, and applied their criteria to additional studies retrieved in our review. The Youth Transition studies were assessed with the National Institute for Health and Care Excellence (NICE) 2012 Quality Appraisal Checklists. The Second Hand studies were assessed with the criteria of the Fernández et al. (2015) systematic review for passive vapour exposure. We accepted their quality assessments for the articles they rated, and applied their criteria to the other studies included in our review of second hand exposure. The quality assessments for the Comparison review were based on the assessments of testing methods by Bansal and Kim (2016) in their review of quantitation methods for vapour device testing.

The quality assessment of each study is noted after its citation with the following symbols from the NICE reporting method: [++] for strong studies, [+] for moderate or acceptable studies, [-] for weak or poor quality studies. Studies conducted or funded by commercial interests as stated in the publication's conflict of interest statement or author's affiliation are indicated with [I] for industry studies. It is possible that some studies may have been supported by industry without being declared, therefore we cannot guarantee that all commercial interests have been identified. Systematic reviews and background articles were not assessed for quality.

Systematic Review 1: Effectiveness of Vapour Devices for Smoking Cessation

Can vapour devices be effective tools for tobacco cessation? For this research question, we examined five systematic reviews and 63 publications (60 research studies) on topics germane to vapour devices and tobacco cessation. We assessed the cessation studies based on the systematic review by Malas et al. (2016), and included an additional six cessation studies. We classified 18 publications as strong or moderate quality studies, and 25 studies as weak. Our evidence review also incorporates 10 surveys, five case studies, and three qualitative studies not included in other reviews. The research on cessation with vapour devices encompassed a broad spectrum of populations: cessation treatment patients, non-treatment seeking smokers, cancer patients, hospitalized smokers, persons with schizophrenia or depression, methadone patients, pregnant women, adolescent students, young adults, homeless parents, and vape shop customers.

Systematic Reviews

In this section we discuss three meta-analyses conducted on two RCTs, and two systematic reviews published in 2016. The two reviews covered a large number of studies on cessation in adults, but the reviewers did not work with an identical set of publications. These two research teams came to differing conclusions on the efficacy of vapour devices for cessation.

The first two RCTs: Bullen et al. (2013), and Caponnetto et al. (2013)

In three reviews, the authors performed a meta-analysis of the same two RCTs, Bullen et al. (2013) ASCEND, and Caponnetto et al. (2013) ECLAT. The Cochrane review by McRobbie, Bullen, Hartmann-Boyce, and Hajek (2014) and the meta-analysis by Rahman, Hann, Wilson, Mnatzaganian, and Worrall-Carter (2015) produced almost identical results, showing significantly higher quit rates for nicotine compared to non-nicotine vapour devices. The Cochrane review team pooled cessation outcomes with an intention-to-treat analysis (ITT, participants lost to follow-up computed as smokers) and determined that 9% of nicotine vapour device users achieved six month tobacco abstinence, versus 4% for non-nicotine devices, a significantly greater likelihood for cessation with nicotine vapour devices over non-nicotine ones RR 2.29, 95% CI [1.05, 4.96]. Rahman et al. (2015) produced the same figures for pooled relative risk as the Cochrane review. In addition, their meta-analysis of six studies calculated a small effect size of 0.20, 95% CI [0.11, 0.28] (small, approaching medium, ITT) for 1,242 smokers with 224 (18%) reporting cessation at six months. A third meta-analysis by Khoudigian et al. (2016) did not find a statistically significant difference between nicotine and non-nicotine devices for smoking cessation for these two RCTs.

Two comprehensive systematic reviews: Kalkhoran and Glantz (2016) and Malas et al. (2016)

Two systematic reviews, Kalkhoran and Glantz (2016) and Malas et al. (2016) each covered a substantial number of studies (see Table 3 below), but came to differing conclusions on the effectiveness of vapour devices for cessation.

Table 3: Cessation Studies in Kalkhoran and Glantz (2016) and Malas et al. (2016)

Study	Kalkhoran	Malas
Adkison (2013)	x	x
Adriaens (2014)	*	x
Al-Delaimy (2015)	x	x
Berg (2014)	*	x
Biener (2015)	x	x
Borderud (2014)	x	x
Brose (2015)		x
Brown (2014)	x	x
Bullen (2013)	x	x

Study	Kalkhoran	Malas
Harrington (2015)	x	x
Hitchman (2015)	x	x
Humair (2014) [conference abst]	*	x
Lechner (2015)		x
Manzoli (2015)	x	x
McQueen (2016)	x	x
Nides (2014)		x
O'Brien (2015)		x
Pavlov (2015) [conference abst]	x	

Caponnetto, Campagne (2013)		x	Pearson (2014)	x	x
Caponnetto, Auditore (2013)		x	Polosa (2011) 6 month	*	x
Choi (2014) [letter]	x		Polosa (2014) 24 month	*	x
Christensen (2014)	x	x	Polosa (2014) asthmatic smokers		x
Dawkins (2013)	*	x	Polosa (2015) vape shop	*	x
Etter (2010) survey of users		x	Prochaska (2014) mental illness	x	x
Etter (2011) users profile		x	Shi (2015) [conference abstract]	x	
Etter (2014) dependence		x	Siegel (2011)	*	x
Etter (2014) longitudinal	*	x	Stein (2016)		x
Gmel (2016)		x	Sutfin (2015)	x	
Goniewicz (2013)		x	Tackett (2015)	*	x
Grana (2014)	x	x	Vickerman (2013)	x	x
Hajek (2015)	x				

* Excluded for absence of a non-vapour device control group.

Kalkhoran and Glantz (2016) performed a meta-analysis of 16 cohort studies, three cross-sectional studies, and two clinical trials retrieved through June 17, 2015. The authors' meta-analysis calculated that the odds of quitting were 28% lower for vapour device users compared to those who did not use vapour devices, OR 0.72, 95% CI [0.57, 0.91]. Yet 12 of the 21 studies demonstrated a positive impact for vapour device use on cessation rates: four showed improved cessation outcomes with vapour devices, and an additional eight reflected a positive effect for cessation within their 95% CI.

The study selection by Kalkhoran and Glantz for their meta-analysis may well have influenced the findings. To begin with, no quality assessment was conducted. In addition, data were drawn from three studies without a full report of the research, one letter and two conference presentations (see Table 3), all with non-favourable outcomes for cessation, which accounted for 12.57% of the weighting of the meta-analysis. Of note, the reviewers did not include any studies by Etter or Polosa who are both known as pro-harm-reduction researchers, nor did it include the Capponetto (2013) RCT or the Adriaens (2014) RCT. These studies were excluded because they lacked a non-vapour device control group (see Table 3 above).

On the contrary, Malas et al. (2016) found improved quit rates with vapour devices compared to NRT or no aid. The authors examined 62 studies retrieved through February 2016 with data on the outcomes of smoking abstinence, smoking reduction, withdrawal symptoms, and urges to smoke. They appraised the studies for quality with a modified GRADE system. The Malas et al. team shared their assessment tool with our research team, and we used to it assess 6 additional studies (see Table 6). Among the 39 cessation studies included in the Malas et al. review, only Brown (2014) was rated as strong, with 14 rated as moderate, and 24 as weak (two were conference abstracts not included in this review). The weak studies were excluded from the meta-analysis (see Tables 4 and 5).

Their meta-analysis of five studies with duration of abstinence not reported showed an AOR for vapour devices at 1.63, 95% CI [1.17, 2.27] compared to NRT and 1.61 [1.19, 2.18] compared to no aid. Yet overall, the authors rated the strength of the evidence as low due to the small number of studies. The six studies reporting abstinence at 6 months or more post-treatment were non-significant due to insufficient power for the combined studies. In their narrative review, the authors observed that only two studies did not support the use of vapour devices for cessation, and both had limitations: Christensen (2014) did not account for users in the process of quitting, and Grana's (2014) calculations were based on a small subsample and was not statistically significant. In addition, our Research Coordinator noted that the Borderud (2014) data were not favourable for cessation when based on an ITT calculation.

Table 4: Malas et al. Strong and Moderate Quality Cessation Studies

First Author, Year, Title, Country	Study Design	Findings
Adkison (2013) Electronic nicotine delivery systems: International Tobacco Control Four-Country Survey. Canada, US, UK, and Australia	Survey in 2008-09 with one year f/u for current and former smokers, N=5939. 7.6% ever use, 2.9% current use.	85.1% reported using ENDS as a cessation aid. 11% had quit at one year f/u. No significant difference in quit rates between ENDS users and non-users.
Adriaens (2014) Effectiveness of the electronic cigarette: An eight-week Flemish study with six-month follow-up on smoking reduction, craving and experienced benefits and complaints.	RCT with 3 arms, one control. N=48, mean age 44, no quit intentions. 3 sessions in 2 months. EC use after 4 hours of abstinence. Analysis measured craving, eCO levels, and reduction in cigarette use.	10 drop outs. 21% of remaining participants quit 6 months post-test, verified eCO.
Biener (2015) A longitudinal study of electronic cigarette use among a population-based sample of adult smokers: association with smoking cessation and motivation to quit. US	Population-based survey of 2 US metro area adult smokers, n=695 at f/u (51% response rate), telephone interviews in 2011/12 and 2014. n=227 discontinuers of 493 ever triers.	Daily EC users 6 times more likely to quit smoking (30 day abstinence) than non-EC users, while non-daily EC users displayed reduced motivation to quit.
Borderud (2014) Electronic cigarette use among patients with cancer. US	Case analysis (observational study) of n=414 cancer patients in tobacco cessation treatment at 6 month f/u. Tobacco users screened=4505, enrolled in treatment n=1074 (26.5% EC past 30day use), n=699 eligible for 6 month f/u, (285 lost to f/u, calculated ITT).	Quit of 1+ days in past 7 days, complete case analysis, no significant difference between users and non-users. ITT analysis, EC users twice as likely to continue smoking.
Brown (2014) Real-world effectiveness of e-cigarettes when used to aid smoking cessation: a cross-sectional population study. England Strong quality rating.	Cross-sectional study, representative population sample of N=5863 smokers with at least 1 quit attempt in past 12 months. EC quit attempt=46, NRT=1922, and no aid=3477.	Self-report of quit: 20.0% for EC, 10.1% for NRT, and 15.4% no aid. EC users AOR 1.55, 95% CI [1.19, 2.27] more likely to have quit than no aid, and 1.58 [1.14, 2.11] for NRT.
Bullen (2013) Electronic cigarettes for smoking cessation: A randomised controlled trial. NZ	RCT N=657 randomized (289 nicotine EC, 295 patches, 73 placebo EC), plus telephone counselling (fidelity not reported). 13 week trial. Outcome: 6 months post-treatment verified abstinence.	ITT quit rates were 7.3% for nicotine EC, 5.8% patches, 4.1% placebo. Insufficient power to calculate significance.
Caponnetto (2013) Impact of an electronic cigarette on smoking reduction and cessation in schizophrenic smokers: A prospective 12-month pilot study. Italy	Quantitative before and after study (clinical trial). 14 participants with adlib use of EC, 12 week trial.	2 of 14 participants (14.3%) quit at 52 weeks.

Christensen (2014) Profile of e-cigarette use and its relationship with cigarette quit attempts and abstinence in Kansas adults. US	Telephone survey of N=9656 adults. 11.8% ever used EC, 3.4% used past month. For smokers, 45% ever use, 14% past month use. Data combines EC and smokeless tobacco as cessation aid.	22.1% of past month users had made quit attempt in prior year, compared to 9.2% of non-users. Past month use negatively associated with past month (POR=0.05) and past year (POR=0.08) cigarette abstinence.
Dawkins (2013) 'Vaping' profiles and preferences: An online survey of electronic cigarette users. Multi-country, 72% European	Cross-sectional online survey of EC users N=1347.	74% self-reported quit.
Goniewicz (2013) Patterns of electronic cigarette use and user beliefs about their safety and benefits: An internet survey. Poland	Cross-sectional survey of EC users, N=173.	64%, 95% CI [56, 72] self-reported quitting.
Grana (2014) A longitudinal analysis of electronic cigarette use and smoking cessation. [letter] US	Panel survey of smokers from 2012 Knowledge Network (GfK) N=949. EC users n=88 with 9 quitters.	EC past 30 day use not significant for quit within 1 year.
Lechner (2015) Effects of duration of electronic cigarette use. US	Cross-sectional survey, N=159 current users.	Increased duration of EC use increased likelihood of quit, OR 1.003 (p=0.012).
Pearson et al. (2015) E-Cigarettes and smoking cessation: Insights and cautions from a secondary analysis of data from a study of online treatment-seeking smokers. US	Observational study. Data analysis of 30 day abstinence (self-report) at 3 months for web-based free US cessation program BecomeAnEx, N=2,123, with 672 using EC.	EC users significantly less likely to have 30 day abstinence than non-EC users (15.8% vs 22.0%), and lower odds of quitting for EC users, OR 0.66, 95% CI [0.53, 0.87].
Polosa (2014) Success rates with nicotine personal vaporizers: a prospective 6-month pilot study of smokers not intending to quit. Italy	Proof of concept trial of 50 smokers (15+ cigarettes/day) not quitting supplied free EC for 24 weeks. Self-report diary for reduction; eCO verified abstinence at 24 weeks.	36% (18) abstinent with 15 of 18 still using EC at 24 weeks.
Tackett (2015) Biochemically verified smoking cessation and vaping beliefs among vape store customers. US	Cross-sectional survey of N=215 US adult vape store customers, with n=181 biochemically verified eCO.	86% reporting EC use for cessation. 66% of 181 had verified quit. Quit success correlated with use of new generation devices, and non-tobacco and non-menthol flavours.

EC = e-cigarette (vapour device)

Table 5: Malas et al. Weak Cessation Studies

First Author, Year, Title, Country	**Study Design**	**Findings**
Al-Delaimy (2015) E-cigarette use in the past and quitting behavior in the future: A population-based study. US	Longitudinal survey California Smokers Cohort, baseline 2011/2012 to 1 year f/u, response rate 23.4% for telephone/cell survey. N=1000 smokers at baseline, N=236 ever use EC.	Ever-users of EC less likely to be 1 month abstinent at 1 year follow-up 0.41, 95% CI [0.186, 0.93].

O'Leary et al. (2017)

Berg (2014) Attitudes toward e-cigarettes, reasons for initiating e-cigarette use, and changes in smoking behavior after initiation: A pilot longitudinal study of regular cigarette smokers. US	Pilot longitudinal study, N=36, measured at 0, 4, and 8 weeks (72.2% response rate).	At week 8, 30 day point prevalence 16.7% (ITT) or 23.1%.
Brose (2015) Is the use of electronic cigarettes while smoking associated with smoking cessation attempts, cessation and reduced cigarette consumption? A survey with a 1-year follow-up. UK	Web survey, 2012 of N=4064 UK adult smokers with one year follow-up n=1759 (43%). EC users n=348.	Daily EC use (dual use) associated with increased cessation attempts compared to non-users OR 2.11, 95% CI [1.24, 3.58], but not with cessation. Non-daily EC use not significant for quit attempts or cessation.
Caponnetto (2013) EffiCiency and Safety of an eLectronic cigAreTte (ECLAT) as tobacco cigarettes substitute: A prospective 12-month randomized control design study. Italy	RCT of 7.2 mg nicotine EC, 5.4 mg nicotine EC, and 0 nicotine EC. 190 males, 110 females, no intention to quit. Study design: ad lib use of EC for 12 weeks, with participants keeping journals, CO level tests, and saliva samples.	At 52 weeks, quit rates 13% for high nicotine EC, 9% for nicotine EC, and 4% for placebo EC. 26.9% continuing EC use at 52 weeks.
Etter (2014) A longitudinal study of electronic cigarette users. Multi-country, US 34%	Longitudinal survey, self-selected N= 773 baseline EC daily users, 3+ months. F/u at 1 month (n=477, 62%) and 1 year (n=367, 47%).	Former smokers: 6% relapsed at 1 month, 6% at 1 year. Dual users 22% quit at 1 month and 46% quit at 1 year.
Etter (2015) Dependence levels in users of electronic cigarettes, nicotine gums and tobacco cigarettes. Multi-country, 36% France	Survey data from multiple sources. N=1284 daily use.	N=911 (70.9%) no tobacco use past 7 days.
Etter (2011) Electronic cigarette: Users profile, utilization, satisfaction and perceived efficacy. Multi-country 62% US	Cross-sectional survey, N=3587 users.	36% former smokers.
Etter (2010) Electronic cigarettes: A survey of users. Multi-country, 81% France	Cross-sectional survey from smoking cessation site, N=81.	79% self- reported that EC helped them quit.
Gmel (2016) E-cigarette use in young Swiss men: is vaping an effective way of reducing or quitting smoking?	Survey of N=5,128, 20 year old Swiss men reporting for military service registration. F/U at 15 months, 91.5% response. EC prevalence 5.0%.	2.9% EC users had quit smoking at 12 month f/u, compared to 6.5% of non-vapers.
Hitchman (2015) Associations between e-cigarette type, frequency of use, and quitting smoking: Findings from a longitudinal online panel survey in Great Britain.	1 year longitudinal on-line survey N=1643 current smokers to observe quit rates for EC users. At f/u (43.3% response rate), 27% using cigalikes and 9% tank systems.	Compared to no-EC use, non-daily cigalikes users less likely to quit OR 0.35 (5.23% quit); daily cigalike (10.57% quit) and non-daily tank users (8.57% quit) no more or less likely to have quit; and daily tank users more likely to have quit (OR 2.69) (27.54% quit).

Manzoli (2015) electronic cigarettes efficacy and safety at 12 months: Cohort study. Italy	Prospective cohort study, 60 months; article presents 12 month f/u. Adults 30-75 years old, n=491 smokers (1+ cigarettes/day), 236 EC users, and 232 dual users. 396 losses to follow-up and discontinuers from 1355 eligible subjects (29%) – no ITT analysis. eCo verified quit in 25% random sample (4% false self-report).	EC users: 15.7% quit both, 10.6% relapsed to dual use, and 27.5% quit EC and relapsed to smoking. Dual users: 11.6% quit all use, 10.3% quit tobacco and continued EC, and 53.5% quit EC and continued smoking. Smokers: 13.6% quit all use, 6.9% quit smoking and started EC, 1.8% started dual use, and 77.6% continued smoking.
McQueen (2016) Smoking cessation and electronic cigarette use among head and neck cancer patients. US	In-office survey of 106 cancer patients. EC use for quit n=23 (21.7%), and 70% of EC users also used nicotine patch.	Non-user quit rate (30+ day abstinence) 72% vs 39% for EC users.
Nides (2014) Nicotine blood levels and short-term smoking reduction with an electronic nicotine delivery system. US	Before and after trial. Novice EC use N= 29, smoking 20 cigarettes/ day. Baseline first visit, training visit, and third visit 1 week f/u for biochemical measurement.	4 participants with 7 day cessation.
O'Brian (2015) E-Cigarettes versus NRT for smoking reduction or cessation in people with mental illness: Secondary analysis of data from the ASCEND trial. NZ	Secondary analysis of Bullen et al. (2013) trial, n=86 participants on medication for mental illness.	No significant differences in 6 month f/u quit rates between participants with and without mental illness. Relapse rate 85%.
Polosa (2015) Quit and smoking reduction rates in vape shop customers: A prospective 12-month survey. Italy	Survey of 71 adult first time vape shop customers recruited from 7 Italian vape shops. Self-report at 12 months follow-up, 69%, with ITT analysis.	40.8% quitters. At f/u 66.2% using EC. Study presents few data details.
Polosa (2014) Effectiveness and tolerability of electronic cigarette in real-life: A 24-month prospective observational study. Italy	Continuation of study Polosa (2011) (listed below) to 24 month follow-up.	Quit rate 12.5%.
Polosa (2014) Effect of smoking abstinence and reduction in asthmatic smokers switching to electronic cigarettes: Evidence for harm reversal. Italy	Retrospective study, N=18 patients with mild-moderate asthma. F/U at 6 and 12 months.	55% (n=10) quit at 12 month f/u.
Polosa (2011) Effect of an electronic nicotine delivery device (e-cigarette) on smoking reduction and cessation: A prospective 6-month pilot study. Italy	Proof of concept trial N=40 adult smokers, 15+ cigarettes/day, 10+ years. Supplied 7.4 mg nicotine liquid. 5 visits: baseline, week 4, 8, 12, and 24. eCo verification, participant diaries.	At week 24 (N=27), 9 no cigarette use (6 continuing EC use). ITT analysis: 22.5% no cigarette use.
Prochaska (2014) E-cigarette use among smokers with serious mental illness. US	Observational study of EC users in RCT for smoking cessation by patients with serious mental illness, N=956. Overall 11%, n= 101 reported EC use (appears to be any use).	21% of EC users reported abstinence past 7 days vs. 19% of non-users (not significant).

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Siegel (2011) Electronic cigarettes as a smoking-cessation tool: Results from an online survey. US	Cross-sectional on-line survey, N=216 respondents (4.5% response rate), 71.5% men and 28.5% women. Effectiveness of smoking cessation after 6 months for first time users of Blu EC.	At 6 months, 31% not smoking (95% CI [24.8, 37.2]) with 56.7% of the non-smokers using nicotine EC. 26.8% discontinued EC.
Stein et al. (2016) An open trial of electronic cigarettes for smoking cessation among methadone-maintained smokers. US	Pilot trial, 6 week EC use (NJOY), N= 12 methadone-maintained smokers. Adherence 89.1%.	1 verified quit.
Vickerman (2013) Use of electronic cigarettes among state tobacco cessation quitline callers. US	Survey of quit line callers, 7 months after treatment (34.6% response rate) N= 2,476 respondents.	At 7 month follow-up, 30 day self-report quit rate. 21.7% quit rate for EC use 1+ months, 16.6% quit rate for EC use < 1 month.

Table 6: Additional Included Cessation Studies and Quality Assessment

First Author, Year, Title, Country	Study Design	Findings
Moderate quality studies		
Hajek (2015) Adding e-cigarettes to specialist stop-smoking treatment: City of London pilot project. England	Clinical trial of 100 smokers at smoking clinic. 69% used EC, 4 weeks free supply.	65% validated abstinence at 4 weeks for EC users. EC+varenicline quit rate 85% vs. 54% for EC only.
James (2016) E-Cigarettes for immediate smoking substitution in women diagnosed with cervical dysplasia and associated disorders. US	Clinical trial N=28 diagnosed women aged 18-65 years old. 2 sessions of motivational interviewing and a 6 week supply of EC. N=26 completed 12 week f/u.	7 day point prevalence quit, 8 quit at 12 weeks.
Nolan (2016) Feasibility of electronic nicotine delivery systems in surgical patients. US	Clinical trial of N=75 patients provided with 1 week preoperative and 2 week post-operative supply of EC. 30 day f/u n=67 (89%).	At 30 day f/u by telephone, 11 of 67 (16% complete case, 14.6% ITT) self-reported 7 day point prevalence quit.
Weak studies		
Ramo (2015) Feasibility and quit rates of the Tobacco Status Project: A Facebook smoking cessation intervention for young adults. US	A Facebook based cessation trial, 79 smokers aged 18-25. 13% had 7 day point prevalence during 12 month follow-up, half verified with saliva testing.	Although not part of the program, 18% (14/79) reported using EC for a quit attempt. No subgroup data on success rate for EC users.
Sutfin (2015) The impact of trying electronic cigarettes on cigarette smoking by college students: A prospective analysis. US	Longitudinal survey of N=271 first year college students, smokers with no EC use. 44% had tried EC by end of 3rd year.	Author supplied data in Kalkhorn meta-analysis reported 0.40 (95% CI [0.21-0.76]) odds of quitting. 19% reported using EC for quitting.
Vickerman (2016) Reasons for electronic nicotine delivery system use and smoking abstinence at 6 months: a descriptive study of callers to employer and health plan-sponsored quitlines. US	Observational study of n=6,029 participants 18+ years old (n=821 EC users). 6 month f/u telephone survey (52.4% response rate) after participating in Alere Wellbeing's Quit for Life cessation program. n=477 reported using EC for quit attempt, n=355 using EC for "other reasons."	30 day point prevalence: 55.1% for EC for quit users, 43.1% for EC other reason users, and 50.8% of no EC users. 7 day point prevalence: 60.4% of EC for quit users, 49.2% of EC other reason users, and 57.4% of no EC users. 40% of EC for quit users and 28% of EC for other reason users continuing EC use at 6 month f/u (all participants).

Individual Study Findings

In this section we discuss the studies that addressed the reasons why vapour devices were used as a quit aid, the impacts of vapour device use on quit attempts and quit success, quit rates and relapse, and the best practices for using vapour devices for cessation. Details of the studies are presented in Tables 4, 5, and 6 above, and in Table 7 at the end of this section.

Reasons for use of vapour devices as a quit aid

So why do dual users select vapour devices as a cessation aid? Two qualitative studies have explored their reasons. Pokhrel and Herzog (2015 [-]) surveyed 292 Hawaiian US adults and uncovered that, surprisingly, health reasons, desire for self-control, and social pressure were not motivators; rather it was concerns about the expense of smoking and personal smoke odour. In the other study, 11 US vapers said they used vapour devices as a quit aid because they found it similar to smoking, they enjoyed being part of a community of vapers, they were happy to have discarded their identity as a smoker, and they did not want to give up nicotine (Barbeau, Burda, & Siegel, 2013 [+]). More qualitative studies are required to understand why some smokers turn to vapour devices for quitting tobacco.

Impact of vapour device use on quitting attempts and success

Among the better quality studies, the data are mixed on the effect of vapour device use on successful quitting. Biener and Hargraves (2015 [+]) and Brown et al. (2014 [++]) concluded that vapour device users were more likely to quit. On the other hand, data from three studies (Adkison et al., 2013 [+]; Borderud et al., 2014 [+]; Grana et al., 2014 [+]) showed no difference in quit rates, while data in two studies (Christensen et al., 2014 [+]; Pearson et al., 2015 [+]) found less successful quitting among vapour device users.

Including the data from the weak studies does not produce a clearer picture about the impact of vapour device use on quitting attempts and success. Data from three weak studies found vapour device users less likely to quit than non- users (Al-Delaimy et al., 2015 [-]; Gmel et al., 2016 [-]), and were less successful in quitting (McQueen et al., 2016 [-]). On the contrary, quit data from five studies (Brose et al., 2015 [-]; Kasza et al., 2014 [+]; O'Brien et al., 2015 [-]; Prochaska & Grana, 2014 [-]; Unger, Soto, & Leventhal, 2016 [-]) pointed to similar quit rates for vapour device users and non-users, and another study (Pokhrel, Fagan, Little, Kawamoto, & Herzog, 2013 [-]) found that users were more likely to consider quitting. In addition, motives for vapour devices use appear to have an impact on quit rates, with higher quit rates for vapour device users who were intentionally using them for quitting compared to those who used vapour devices for other reasons (Vickerman, 2016 [-]).

Based on all these studies of both higher quality and weak studies, there is no consistent evidence that vapour device use influences a dual user to be less likely to quit cigarettes.

Quit rates and relapse

From the best available studies conducted in four Western countries, an estimated 85% of adult smokers have used a vapour device in a cessation attempt (Adkison et al., 2013 [+]; Tackett et al., 2015 [+]). The range of quit rates in the better quality studies, from lowest to highest, were 7.3% (Bullen et al., 2013 [+]), 11% (Adkison et al., 2013 [+]), 15.8% (Pearson et al., 2015 [+]), 20% (Brown et al., 2014 [++]), and 36% (Polosa et al., 2014 [+]). In three studies (Dawkins et al., 2013 [+]; Goniewicz et al., 2013 [+]; Tackett et al., 2015 [+]), 64% to 74% of current vapour device users stated they used vapour devices to quit smoking. The point prevalence (duration) of abstinence measured in these studies varied greatly, from seven days to one year.

Three clinical trials of vapour device use for cessation were not yet published so they were not included in the Malas et al (2016) review. The number of quitters in two of these trials was eight of 28 women (31%, ITT) with cervical disease (James et al., 2016 [+]), and 11 of 75 surgical patients (16% complete case, 14.6% ITT) (Nolan et al., 2016 [+]). These participants almost certainly had an increased motivation to quit due to illness. In the third trial, a UK smoking clinic offered 100 clients a trial of vapour devices for cessation (Hajek et al., 2015 [+]), and 54% of those using only vapour devices reported 7 day point prevalence abstinence at four weeks – nevertheless, the abstinence rate was 85% for those receiving treatment with both vapour devices and varenicline. These clinical trials demonstrated that vapour device use can be a supportive component of a formal cessation treatment program.

In these cessation studies, the substantial differences in reported quit rates were due to the participant populations recruited, the study designs, and the differing point prevalences defined as cessation. The follow-up timeframe for measuring abstinence varied from seven days to one year. Several researchers did not include an ITT calculation, and instead based their findings on completed cases. Few research designs included biochemical verifications of cessation, with most utilizing self-report. The most frequent point prevalence measured was any period of abstinence at the time of follow-up. These multiple factors combined have resulted in a wide range of quit rates between the studies.

None of the higher quality studies addressed relapse, a common occurrence in the cessation process. In two weak studies, researchers calculated relapse rates of 27.5% (Manzoli, 2015 [-]) and 85% (O'Brian, 2015 [-], a secondary analysis of Bullen, 2013). More studies need to evaluate the relapse rates for cessation with vapour devices. Another factor to consider: does continuing vapour device use after cessation improve or decrease the rates of ongoing abstinence? Six weak studies (Caponnetto et al., 2013 [-]; Harrell et al., 2015 [-]; Polosa et al., 2015 [-]; Polosa et al. 2014 [-]; Siegel, Tanwar, & Wood, 2011 [-]; Vickerman et al., 2013 [-]) published data on the continued use of vapour devices after cessation, and 26.9% to 66.2% of quitters stated that they were continuing to use vapour devices. No study to date has addressed the potential positive or negative impact of the continuing use of vapour devices on relapse.

Best practices for cessation with vapour devices

Patterns of use and the type of device have been shown to result in improved rates of cessation. For patterns of use, daily use (Biener & Hargraves, 2015 [+]) and a longer duration of use (Lechner et al., 2015 [+]) resulted in higher quit rates. As for the type of device, Tackett et al. (2015 [+]) reported improved quit rates among those using newer generation devices compared to older products, and better quit rates for those who consumed non-tobacco and non-menthol flavours. Three weak studies (Chen, Zhuang, & Zhu, 2016 [-]; Etter, 2015 [-]; Hitchman et al., 2015 [-]) echoed these same factors for improved cessation rates, with the finding that tank devices in particular appeared to be the most effective for cessation support. The Cochrane review team (McRobbie et al., 2014) also suggested that different devices and liquids most likely have an impact on quit rates.

Table 7: Additional Cessation Studies

First Author, Year, Title, Country	Study Design	Findings
Case studies or series		
Bowker (2016) [-] Understanding pregnant smokers' adherence to nicotine replacement therapy during a quit attempt: A qualitative study. UK	Qualitative interviews with 10 pregnant women using NRT for a quit attempt; 5 EC users.	3 women discontinued EC on the advice of friends or smoking counsellor. 2 used NRT + EC, and continued smoking, and reported that EC were not helpful for their quit attempt.
Caponnetto (2011) [-] Smoking cessation with e-cigarettes in smokers with a documented history of depression and recurring relapses. Italy	Case reports of prior patients with history of major depression at smoking clinic. Quit biochemically verified at 6+ months.	51 year old male reported quit after a "few weeks" of EC use, and discontinued EC after a "couple" of months. 50 year old female, reported quit with 3 months of EC use, and continuing EC use.
Caponnetto (2011) [-] Successful smoking cessation with electronic cigarettes in smokers with a documented history of recurring relapses: A case series. Italy	3 case studies, (2 male, ages 47 and 65; 1 female aged 38) selected from author's smoking cessation clinic, with multiple failed quit attempts. Subjects had taken up EC use on their own.	Male 47, "a few weeks" of EC use for cessation, and "a few months" of EC use; 6 months complete abstinence. Female, 3 months of EC use for cessation, followed by EC for 7 months EC use. Male 65, cessation with 2 months with EC use, and continuing to use EC.
Farsalinos (2013) [-] Chronic idiopathic neutrophilia in a smoker, relieved after smoking cessation with the use of electronic cigarette: A case report. Greece	Single case study. Patient had 2 prior failed quit attempts.	Patient quit cigarette use after 10 days of EC use, and continued EC use.
Heydari (2015) [+] Assessment of different quit smoking methods selected by patients in tobacco cessation centers in Iran.	Random sample of patients at all national quit centres.	5% of quitters used EC as a cessation aid.
Qualitative studies		
Barbeau (2013) [+] Perceived efficacy of e-cigarettes versus nicotine replacement therapy among successful e-cigarette users: A qualitative approach. US	Qualitative focus groups (two, 90 minutes), 11 participants (9 men, 2 women) recruited from 2 on-line vaper forums.	Themes: bio-behavioral feedback (EC mimic cigarette smoking), social benefits (belonging to a vaping community), hobby elements (device collections), personal identity (vaper, not smoker), and smoking cessation without nicotine cessation ("reducing nicotine dependence is optional").
Farsalinos (2013) [-] Evaluating nicotine levels selection and patterns of electronic cigarette use in a group of "vapers" who had achieved complete substitution of smoking. Greece	Interviews of EC users N=111 (84% male) 20-55 years old, former smokers (25 cigarettes/day), quit from 4-11 months, blood carboxyhemoglobin verified.	Self-report 42% quit in first month of EC use.
Stewart (2015) [-] Attitudes toward smoking cessation among sheltered homeless parents. US	Qualitative focus group of N=33 parents.	An unreported number of participants expressed a positive interest in vapour devices for cessation.

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First Author, Year, Title, Country	Study Design	Findings
Surveys		
Farsalinos (2014) [-] Characteristics, perceived side effects and benefits of electronic cigarette use: A worldwide survey of more than 19,000 consumers. Multi-country, 74.4% Europe	Online survey, 18+ years old, N=19,441.	81.0% self-report quit at time of survey.
Harrell (2015) [+] E-cigarettes and expectancies: Why do some users keep smoking? US	US on-line survey, N=1815 current EC users with n=1434 former smokers.	52.1% no intention of stopping EC use. 10% planned to stop vapour device use within the next year
Kasza (2014) [+] Cigarette smokers' use of unconventional tobacco products and associations with quitting activity: Findings from the ITC-4 U.S. cohort. US	Survey of N=6,110 adult smokers in from 2002 - 2011. Data on EC only for 2011. 16% ever use EU.	No significant difference in quit rates between EC ever users and cigarette-only users.
Lippert (2015) [+] Do adolescent smokers use e-cigarettes to help them quit? The sociodemographic correlates and cessation motivations of U.S. adolescent e-cigarette use.	Cross-sectional survey from 2011 National Youth Tobacco Survey Probability sample of 15,264 smokers in grades 6-12. 3.2% had tried EC.	Desire to quit and recent quit attempts not associated with EC use.
Pokhrel (2013) [-] Smokers who try e-cigarettes to quit smoking: Findings from a multiethnic study in Hawaii. Pokhrel (2014) [-] Correlates of use of electronic cigarettes versus nicotine replacement therapy for help with smoking cessation. US Pokhrel (2015) [-] Reasons for quitting cigarette smoking and electronic cigarette use for cessation help. US	Cross-sectional survey, N=1567 daily adult smokers (3+ cigarettes/ day).	13% report using EC to quit (n=292). EC users significantly more likely to be motivated to quit, OR 1.14 -1.21, and higher perceived self-efficacy for quit , OR 1.03-1.36.
Popova (2013) [-] Alternative tobacco product use and smoking cessation: A national study. US	On-line survey of 1836 US adult current smokers and recent quitters (<2 years). Analysis of rates of alternative tobacco use correlated with quitting success, non-success, and no quit attempts.	For EC, only significant result was unsuccessful quitters more likely to ever use EC, OR 1.78, 95% CI [1.25, 2.53 CI].
Pulvers (2015) [-] Tobacco use, quitting behavior, and health characteristics among current electronic cigarette users in a national tri-ethnic adult stable smoker sample. US	Cross-sectional stratified survey of stable smokers, n=219 dual users.	44% reported using EC in the past year as a cessation aid.
Unger (2016) [-] E-cigarette use and subsequent cigarette and marijuana use among Hispanic young adults. US	Longitudinal panel survey, Project RED 2014-2015, N=1332 Hispanic young adults aged 22-23 years old. In 2014, n=276 (21%) for cigarettes, with n=76 dual users.	Cigarette smokers who used EC past month in 2014 not significantly more or less to remain cigarette smokers in 2015.

First Author, Year, Title, Country	Study Design	Findings
Surveys of vapour devices used for cessation		
Chen (2016) [+] E-Cigarette design preference and smoking cessation: A U.S. population study.	Online survey of N=923 current EC users, former (n=212, quit 1+ years) or current (n=711) smokers.	Among former smokers, 53.8% used tank systems, 41.4% used disposable or cartridge devices, 4.8% used both. For quitters < 1 year, 55.1% used tank systems vs. 34.8% of non-quitters. For those with a quit attempt past year, 40.1% used tank systems vs. 28.2% of non-quitters.
Etter (2015) [+] Explaining the effects of electronic cigarettes on craving for tobacco in recent quitters. Multi-country, France 39%	Cross-sectional survey. N=374 daily EC users, 18+ years old who had quit tobacco past 62 days, Oct 2012-Sep 2014 recruited on smoking cessation website.	Type of device and nicotine liquid strength associated with craving suppression.

Conclusion

We located eighteen research studies on vapour devices for tobacco cessation rated as strong to moderate quality: two RCTs (plus one RCT rated as weak), five clinical trials, two cross-sectional studies, two observational studies, one longitudinal survey, and six surveys. The limited amount of data from these studies does not allow for a definitive judgement about the efficacy of vapour devices for cessation. Nonetheless, researchers in many of the cessation studies and surveys found that an appreciable number of vapour device users are quitting tobacco. Also, it appears that as many as half or more of tobacco quitters continued to use vapour devices after cessation. The research is mixed as to whether or not vapour device use had any effect on the desire or ability of those who smoke to quit tobacco use, but based on the preponderance of findings, it is clear that claims for a negative impact of vapour devices on cessation are unjustified. In a small number of studies researchers have suggested that newer devices are likely more effective for cessation, so studies performed with earlier models (which are rapidly falling out of favour among consumers) could reasonably be excluded in future evaluations of the effectiveness of vapour devices for cessation. The generalizability of the research findings is constrained by the large number of different devices and liquids used in the studies.

Systematic Review 2: Youth Vapour Device Use and Transition to Tobacco Use

Does youth vapour device experimentation lead to cigarette use? Youth in this review are the age group of 12-19 year olds, roughly encompassing the years when young people are attending middle and high school. Where study designs included both youth and adults, we extracted the datasets only on youth. Overall, in this section we review 47 studies, with 33 studies (34 publications) on factors for youth initiation of vapour device use and transitions to tobacco use, nine population data studies, and five surveys.

Vapour Device Use Initiation by Youth

Schneider and Diehl (2016) developed a theoretical model for youth transition from vapour devices to cigarette and/or tobacco product use. In their "catalyst" model they have broken down the trajectory into two research questions: (1) why may initiating e-cigarette use be easier than starting cigarette use? and (2) why may e-cigarette use promote subsequent tobacco use? Based on this model, the conditions for a transition to tobacco use originate with non-smoking youth taking up vapour devices, and then the pattern of vapour device use leads to tobacco use. In this section, we first consider the evidence for vapour device experimentation influenced by flavours, advertising, and psycho-social factors. We then examine patterns of vapour device use, frequency and nicotine addiction, which could shape the potential transition to tobacco use.

Flavours

A frequent claim in the public health debate is that flavours attract youth to use vapour devices. Shiffman, Sembower, Pillitteri, Gerlach, and Gitchell (2015) [+] dispute this claim. US teens (n=216), with no vapour device use whatsoever and no tobacco use in the past six months, were shown lists of flavours, including the youth-oriented flavours of bubble gum, cotton candy, and gummy bear. These abstinent teens exhibited almost no interest in trying vapour devices, regardless of flavour. A qualitative study from Scotland (de Andrade, 2016 [-]) contained unsolicited quotes from two participants mentioning that they tried vapour devices because of their flavour. Our search retrieved no other research on flavours and youth vapour device use, only numerous editorials and opinion pieces with claims.

Table 8: Youth and Interest in Flavours

First Author, Year, Title, Country	Study Design	Findings
de Andrade (2016) Teenage perceptions of electronic cigarettes in Scottish tobacco-education school interventions: Co-production and innovative engagement through a pop-up radio project. [-]	Qualitative study drawn from non-solicited comments about EC from N=182 schoolchildren aged 13-16 (tobacco use status not reported) participating in 2014 tobacco education project.	Flavours were mentioned by "most" students, with one quoted as stating that he/she tried them for the flavour, and another stating that the variety of flavours was a reason to try EC.
Shiffman (2015) The impact of flavor descriptors on nonsmoking teens' and adult smokers' interest in electronic cigarettes. [+]	2014 before and after test (n= 216, aged 13 – 17), with no vapour device use whatsoever and no tobacco use in the past six months, exposed to 15flavour descriptions for water, ice cream, and vapour devices to measure interest in trying the product.	Mean score for all flavours for vapour devices was 0.41 $\pm$ 0.14 on a 10 point scale, from 0 "not at all interested" to 10 "very interested." No individual flavour had a score of 1 or more.

Advertising

Advertising aimed at youth is often claimed to be a factor in the initiation of vapour device use. No longitudinal studies have been published, so a causal pathway from advertising exposure to initiation of use cannot be established. Four cross-sectional studies, one qualitative study, and one exposure trial offered data on the association of advertising exposure to vapour device use intentions or experimentation.

In three countries, youth advertising viewing rates were 68.9% in the US (Singh, Marynak, et al., 2016 [+]); 50% in Mexico, where e-cigarettes are banned (Thrasher et al., 2016 [+]); and young teens reported seeing "loads" of ads in Scotland (de Andrade et al., 2016 [-]). In Finland, where advertising is banned, the prevalence of advertising exposure was only 10.5% (Kinnunen et al., 2015 [+]). The 2014 US National Youth Tobacco Survey (US-NYTS) indicated a small increase, AOR 1.11, in the correlation for advertising exposure and "susceptibility" to vapour device use, but not actual experimentation (Singh, Marynak, et al., 2016 [+]). Among ever triers, only those Mexican youth with frequent exposure to advertising were significantly more likely to have tried vapour devices, AOR 1.45 (95% CI [1.12, 1.86]) compared to youth who were sometimes, rarely, or never exposed to ads (Thrasher et al., 2016 [+]). US youth with past 30 day use of vapour devices had an AOR 1.22 (95% CI [1.15, 2.02]) of having advertising exposure compared to non-users (Mantey, Cooper, Clendennen, Pasch, & Perry, 2016 [+]). The large confidence intervals in these latter two studies preclude estimating the strength of the association between advertising exposure and actual uptake of vapour devices by youth.

All of these advertising studies could have been influenced by recall bias, as the youth who recalled ads may have had a prior, underlying interest in vapour devices. But on the other hand, the Scottish students could recall specific brand names - advertising has made an impression. The research also speaks to how the internet can bypass national advertising bans and market to youth directly, as was reported by youth in Finland and Mexico.

The last study in this section on advertising was a trial of ad exposure that was reported in two publications (Duke, Allen, Eggers, Nonnemaker, & Farrelly, 2016 [-]; Farrelly et al., 2015 [-]). In this experiment, youth were shown four actual vapour device TV commercials. The researchers concluded that youth who perceived a greater effectiveness of the ads had a higher intention to try vapour devices, with the advertising treatment group increasing their positive attitude towards vapour devices by 14% on the test's attitude scale. However, this information is of limited value as the results indicated only the immediate, short-term influence of viewing ads in an experimental setting, and actual behavioural outcomes were not included in the study. In addition, some members of the research team expressed possible ethical concerns about the study design as it exposed the underage participants to actual vapour device advertising.

Table 9: Youth Exposure to Vapour Device Advertising

First Author, Year, Title	Study Design	Findings
De Andrade (2016) Teenage perceptions of electronic cigarettes in Scottish tobacco-education school interventions: co-production and innovative engagement through a pop-up radio project. [-]	Qualitative study of non-solicited comments about EC from N=182 schoolchildren aged 13-16 participating in 2014 tobacco education project.	Students reported "loads" of advertising: posters, magazines and newspapers, in-store ads, and TV. Some ads demonstrated product use, and others promoted free trials. Several students exhibited brand awareness.
Duke (2016) Exploring differences in youth perceptions of the effectiveness of electronic cigarette television advertisements. AND Farrelly (2015) A randomized trial of the effect of e-cigarette TV advertisements on intentions to use e-cigarettes. US [-]	2014, n=3665 aged 13-17 never EC use. Random assignment, half viewed 4 EC advertisements aired in 2013-2014 and completed survey, second group completed survey and then viewed ads. Intention to use questions try in next year, use one if friend offered. Four point scale.	Greater perceived effectiveness resulted in higher intention to use EC (b=0.16)
Kinnunen (2015) Awareness and determinants of electronic cigarette use among Finnish adolescents in 2013: a population-based study. [+]	2013 survey N=3535 Finnish adolescents aged 12-18. Advertising is banned except for point of sale.	10.5% had seen EC ad in past month, 41.4% internet and 21.8% Facebook.
Mantey (2016) E-cigarette marketing exposure is associated with e-cigarette use among US youth. [+]	2014 US-NYTS N=22,007 Susceptibility with three questions, may try, friend offer, and curious, with all responses "definitely no" to be classified not susceptible.	For non-EC user, susceptibility to use when exposed to advertising, AOR 1.11 (95% CI [1.08, 1.15]) and OR 1.81 when exposed to all 4 mediums: internet, print, retail, and TV/movies, Past 30 day use EC, AOR 1.22 (95% CI [1.15, 2.02]) for advertising exposure.

Singh (2016) Vital signs: Exposure to electronic cigarette advertising among middle school and high school students - United States, 2014. [+]	2014 US-NYTS N=22,007	Any advertising exposure: 68.9%. Retail stores: 54.8% Internet: 39.8% TV/movies: 36.5% Newspapers/magazines: 30.4%
Thrasher (2016) Prevalence and correlates of e-cigarette perceptions and trial among early adolescents in Mexico. [+]	2015 survey of N=10,146 middle school students, stratified sampling, from 3 largest cities. EC are banned in Mexico. EC ever try 10%.	Internet ad exposure: 50% never 42% rarely/sometimes 8% mostly/always. Only "mostly/always" significant for EC ever use: AOR 1.45 (95% CI [1.12, 1.86].

Psycho-social factors in youth initiation

We located and included seven studies that examined psycho-social factors associated with the ever use of vapour devices. A strong longitudinal cohort study by Hampson, Andrews, Severson, and Barckley (2015) [++] measured tobacco use risk factors in a cohort of 862 US students in 8th and 9th grade in 1998, and when surveyed 14 years later (84% response rate among the original participants), 6.6% had used vapour devices 20 times or more. Yet the prevalence of use of "novel" tobacco products in this cohort was much higher than vapour devices, with hookah use by 21.7% and 16.8% using little cigars. The two significant risk factors for vapour device use were the mother's use of cigarettes and sensation seeking. Of note, the cohort's 9th grade intentions to use cigarettes, alcohol, or cannabis, or early use of these substances were *not* associated with subsequent vapour device use.

Four other studies addressed the psychological profiles of youth who try vapour devices. Sensation seeking was found to be associated with vapour device use by the German researchers Hanewinkel and Isensee (2015) [+] as well as by Hampson et al. Other psychological factors determined to be influential on vapour device experimentation were, in Finland, poor school performance (Kinnunen et al., 2015 [+]), and in the US, executive function problems defined as an inability to regulate emotions and inhibit impulsive behaviours (Pentz et al., 2015 [-]). Curiosity about vapour devices was more frequently reported by US students who had ever tried tobacco products at 43% than by never tobacco users at 22% (Margolis, Nguyen, Slavit, & King, 2016 [+]), but this may be a reflection of other psychological factors such as sensation seeking.

Another psycho-social factor at work is gender, as every study in this Report with gender data showed that males had higher rates of experimentation and use of vapour devices than females. This same disparity in prevalence is also found among male and female cigarette users. It is important to bear in mind that psychological traits and gender social roles may function as potential risk or protective factors for vapour device use but not necessarily be causal factors. Which psycho-social factors exert a strong influence varies by culture, and most likely by gender as well.

Other social factors influencing vapour device trial or use are the relationships youth have with family and friends who are tobacco users. Perhaps surprisingly, parental smoking was not always associated with vapour device experimentation in the research. Hampson et al. (2015 [++]) located maternal smoking as a distal influence on the increased uptake of vapour device use, and researchers in two other studies (Cardenas et al., 2015 [+]; Hanewinkel & Isensee, 2015 [+]) concluded that parental smoking had a significant influence in increasing the risk for vapour device experimentation. Contrary to these findings, in two other studies (Pentz et al., 2015 [-]; Thrasher et al., 2016 [+]) the researchers did not find a strong relationship between parental smoking and youth experimentation with vapour devices. Perhaps the influence of parental relationships is a cultural factor.

Additional social relationships associated with higher rates of vapour device experimentation include youth having peers or siblings who smoke. Having a friend who smoked increased the odds of experimenting with vapour devices among German youth (Hanewinkel & Isensee, 2015 [+]) and Mexican youth (Thrasher et al., 2016 [+]). Having a sibling who smoked was a significant factor for vapour device experimentation among Mexican youth (Thrasher et al., 2016 [+]). No studies have investigated the social influence of parents or peers who themselves use vapour devices.

Table 10: Psycho-Social Factors in Youth Vapour Device Initiation

First Author, Year, Title	Study Design	Findings
Cardenas (2015) The smoking habits of the family influence the uptake of e-cigarettes in US children. [+]	2012 US-NYTS n=14,861 never cigarette users.	For never EC users, living with a cigarette smoker doubled the prevalence of ever EC use, PR 2.3 (95% CI [1.4, 3.9]).
Hampson (2015) Prospective predictors of novel tobacco and nicotine products in emerging adulthood. US. [++]	Longitudinal cohort study N=862. Risk factors measured in 1998 and 1999 in grades 8 and 9, and use measured in 2013 (age 22). F/U participation 84%. EC use ≥ 20 times, 6.6%: 9.9% male, 3.6% female.	Higher prevalence of the 20+ time use of hookahs 21.7% and little cigars 16.8%. Mother's cigarette use (distal) and sensation seeking (proximal) were risk factors for EC uptake, but not early use of cigarettes, alcohol or cannabis, and not intentions to use these substances.
Hanewinkel (2015) Risk factors for e-cigarette, conventional cigarette, and dual use in German adolescents: A cohort study. [+]	Longitudinal cohort study Oct. 2010 retested 26 months later. N=2,693 Adolescents, mean age 12.5 years at baseline.	Ever EC use 4.7%. EC and cigarette use associated with higher sensation seeking scores, and higher odds of cigarette smoking parents or friends.
Kinnunen (2015) Awareness and determinants of electronic cigarette use among Finnish adolescents in 2013: a population-based study. [+]	2013 survey N=3535 Finnish adolescents aged 12-18.	Vocational school education and poor school performance associated with EC use.
Margolis (2016) E-cigarette curiosity among U.S. middle and high school students: Findings from the 2014 national youth tobacco survey. US [+]	2014 US-NYTS n=17,268 never EC users.	For never tobacco users 10.58% high curiosity 11.58% some curiosity 77.84 % no curiosity For ever tobacco users 26.38% high curiosity 16.50% some curiosity 57.12 % no curiosity
Pentz (2015) Parent, peer, and executive function relationships to early adolescent e-cigarette use: A substance use pathway? US [-]	2013 survey of 7th grade students in Southern California, N=410. Ever EC use 11.0% (n=45).	Executive function problems OR 4.99, (95% CI [1.80, 13.86]) compared to no EC use.
Thrasher (2016) Prevalence and correlates of e-cigarette perceptions and trial among early adolescents in Mexico. [+]	2015 survey of N=10,146 middle school students, stratified sampling, from 3 largest cities. EC are banned in Mexico. EC ever try 10%.	Sibling tobacco user, EC ever try, AOR 1.47 (95% CI [1.23, 1.76]), and friend tobacco user AOR 1.37 [1.16, 1.61]. Parent smoking not significant for EC ever try.

Patterns of Use

Infrequent use of a vapour device is unlikely to create a pattern of use that could act as a potential behavioural conduit for regular tobacco use. Most of the literature employs the measurement of "ever use" or "ever try" for vapour device use, but ever use is not a measure of current use (Bauld, MacKintosh, Ford, & McNeill, 2016). How many adolescents are actually using vapour devices more than simply trying them just once, a few times, or using them infrequently? Past 30 day use is another measure utilized by researchers, and as such it is frequently presented as an indicator of current vapour device use.

Findings from 13 surveys (with the most current country data) indicated that the prevalence of past 30 day use varies between countries, and by age and gender. The highest prevalence ranged from Polish 16-18 year olds at 29.6% (Goniewicz et al., 2016), followed by US male high school students at 19.0% (Singh, Arrazola, et al., 2016), to the lowest prevalence for Greek female youth at 0.1% (Fotiou, Kanavou, Stavrou, Richardson, & Kokkevi, 2015). Seven countries posted a past 30 day use prevalence under 3% for youth. See Table 11 below.

Table 11: Youth Prevalence of Vapour Device Use > Ever Try

Country Year	N Ages	Prevalence of Past 30 Day Use (except as noted)	Source
Canada (2 provinces) 2013-2014	44,163 Ages 14 – 18	4.7% 14 years old 6.8% 15 years old 8.6% 16 years old	Czoli (2015)
Canada 2013	14,565 Ages 15-19	2.6%	Reid (2015)
China (Hong Kong) 2012-2013	45,128 Age 14.6 ± 1.9	1.1% (95% CI [1.0, 1.2])	Wang (2015)
Greece 2014	1,320 Age 15	"I use it now" (undefined survey question) 0.8% males 0.1% females	Fotiou (2015)
Finland 2013	3,535 Ages 12-18	2.0% used > 20 times 0.7% girls aged 14 1.0% boys aged 14 1.7% girls aged 16 5.3% boys aged 16	Kinnunen (2015)
France (Paris) 2013	3,279 Ages 12-19	5.6%	Dautzenberg (2015)
Great Britain 2014	1,952 Ages 11-18	1.7% ≥ monthly use	Eastwood (2015)
Ireland 2014	821 Ages 16-17	3.2% ≥ monthly use	Babineau (2015)
Poland 2014	1,785 16-18	29.6%	Goniewicz (2016)
South Korea 2014	37,192 High School	7.0%	Cho (2016)
Switzerland 2014	621 Age 16	2% (n=12) "regular use" undefined	Suris (2015)
UK 2014	1,205 Ages 11-16	2% (n=21) ≥ monthly use	Ford (2016)

US 2015	17,711 Grades 6-12	High School 16.0% (95% CI [14.1, 18.0]) 12.8% [11.0, 15.0] female 19.0% [16.5, 21.7] male Middle School 5.3% [4.6, 6.2] 4.8% [4.0, 5.6] female 5.9% [4.7, 7.2] male	Singh (2016)
Wales 2013-2014	9055 Ages 11-16	1.5%≥ monthly use	Moore (2015)

Yet the measurement of past 30 day use grossly overestimates the number of current users, by as much as 90% for adult never-smokers (Amato, Boyle, & Levy, 2016). A more accurate marker of regular use would be more than five times per month (ibid). Three youth studies provided a more detailed reporting of the frequency of use in the past 30 days, and their data demonstrates the overestimation of regular use with this metric. For US high school students with past 30 day use, the US-NYTS 2014 data showed only 40% of past 30 day users had vaped five or more times a month (Neff et al., 2015 [+]). Data from two weak studies corroborate this overestimation of current users. Among Polish youth with past 30 day use, 71.9% used vapour devices less than once a week (Goniewicz et al., 2016 [-]), and for Hawaiian youth with past 30 day use, only 4% were weekly or daily users (Wills, Knight, Williams, Pagano, & Sargent, 2015 [-]). A more finely detailed reporting of patterns of vapour device use revealed that few youth have established a regular pattern of consumption that could serve as the behavioural basis for regular tobacco use.

Table 12: Detailed Rates of Youth Vapour Device Past 30 Day Use

First Author, Year, Title	Study Design	Findings
Goniewicz (2016) Dual use of electronic and tobacco cigarettes among adolescents: a cross-sectional study in Poland. [-]	Survey of N=1785 students aged 16-18 conducted Dec. 2013 – Feb. 2014. Past 30 day EC use 29.6%.	12.2% daily use 11.5% a “few times” a week 71.9% less than once a week.
Neff (2015) Frequency of tobacco use among middle and high school students--United States, 2014 [+]	2014 US-NYTS N=22,007 [Overall prevalence of past 30 day use not reported.]	High school past 30 day users: 1-2 days: 45.4% ,95% CI [41.9, 49.0] 3-5 days: 16.2% [14.0, 18.5] 6-9 days: 12.0% [10.0, 14.3] 10-19 days: 10.9% [9.1, 13.0] 20-29 days: 5.8% [4.5, 7.5] All 30 days: 9.7% [7.5, 12.5] Middle school past 30 day users: 1-2 days: 54.5% ,95% CI [49.4, 59.3] 3-5 days: 17.3% [13.7, 21.6] 6-9 days: 9.2% [7.0, 12.0] 10-19 days: 7.3% [5.2, 10.1] 20-29 days: 3.9% [statistically unreliable] All 30 days: 7.9% [5.4, 11.4]
Wills (2015) Risk factors for exclusive e-cigarette use and dual e-cigarette use and tobacco use in adolescents. [-]	2013 survey of N=1941 Hawaii high school students.	3% Monthly users n=58 2% Weekly users n=45 2% Daily users n=33

Nicotine use

Finally, a major premise for youth vapour device users transitioning to cigarettes or tobacco is that vapour device use induces nicotine addiction. Yet not all vapour device liquids contain nicotine, although some liquids labeled as not containing nicotine do, in fact, contain trace amounts (Goniewicz et al., 2015). Four studies have estimated the consumption of non-nicotine liquids among youth vapour device users. In Canada and Switzerland, non-nicotine devices are legal while nicotine liquids are prohibited, and consequently in one study 72% of Ontario high school students said they used non-nicotine liquids (Hamilton et al., 2015 [+]), and 70.2% of Swiss 16 year olds reported using non-nicotine liquids (Surís et al., 2015 [-]). Even in countries where nicotine liquids are not banned, a survey of Connecticut middle and high school student vapour device users counted 22% using non-nicotine liquids (Krishnan-Sarin, Morean, Camenga, Cavallo, & Kong, 2015 [-]), and in a Finnish survey, 23.5% of adolescent vapour device users reported consuming non-nicotine liquids (Kinnunen et al., 2015 [+]). For those youth consuming vapour devices without nicotine, addiction is eliminated as a potential pathway to tobacco use.

Table 13: Prevalence of Non-Nicotine Use by Youth

First Author, Year, Title	Study Design	Findings
Hamilton (2015) Ever use of nicotine and nonnicotine electronic cigarettes among high school students in Ontario, Canada. [+]	Survey 2013 Ontario Student Drug Use and Health Survey. N=2,892 high school students, aged ≤ 19.	15% ever use. 72% used EC without nicotine.
Kinnunen (2015) Awareness and determinants of electronic cigarette use among Finnish adolescents in 2013: a population-based study. [+]	2013 survey N=3535 Finnish adolescents aged 12-18.	EC use ≥ 20 times. Females 1.0% Males 2.0%. Non-nicotine use 23.5% (95% CI [20.3, 27.0]) for ever users. For those with 2+ times use, 83.6% used nicotine liquids
Krishnan-Sarin (2015) E-cigarette use among high school and middle school adolescents in Connecticut. [-]	2013 survey of high school students n=3,614 and middle school students n=1,166.	Past 30 day use 1.5% middle school (5.82±7.36 days) and 12.0% (9.49±10.03 days) high school. Non-nicotine use 22.0%.
Suris (2015) Reasons to use e-cigarettes and associations with other substances among adolescents in Switzerland. [-]	2014 representative sample from internet survey of N=621 aged 16, French-speaking. Nicotine EC illegal, non-nicotine legal.	Used "several times" n=136, and "regular users" (undefined) n=12 (2%), 70.2% used non-nicotine EC.

Population Data Research

Researchers have examined population level data in nine regularly recurring survey studies comparing changes in the rates of vapour device and cigarette use. These studies are described in Table 14 at the end of this section.

Population prevalence surveys

Population studies provide strong data informing the question of the prevalence of youth transitioning from vapour device use to tobacco. In two regression analysis studies the researchers calculated the effect of vapour device bans on US youth smoking rates. Three studies were based on established youth tobacco surveys, and one study was based on an independent survey conducted by the researchers themselves.

The strongest evidence available testing the association of vapour device use and tobacco use came from two studies in which the researchers conducted regression analysis comparing the smoking rates of adolescents in US states with and without bans on vapour device sales to youth. Friedman (2015 [+]) calculated the rates of decline in tobacco use of 12-17 year olds (and other age groups) from 2003 to 2013, and states with bans had a significant (adjusted R-square = 0.922) 0.9% smaller decline in 12 – 17 year olds smoking rates compared to states without a ban. The youth age sale bans counteracted 70% of the downward trend in youth smoking rates in the prior two years. A 2016 regression analysis by Pesko, Hughes, and Faisal (2016) [+] of the 2007-

2013 US Youth Risk Behavior Survey also found similar figures, with a 0.8% increase in regular cigarette use by youth in states with vapour device age sales restrictions compared to states without them. Friedman observed that "policy discussions to date have not considered that banning e-cigarette sales to minors might *increase* teen smoking" (p. 306).

The three population level studies (US national, US regional, and Paris) based on established tobacco use surveys showed an increase in youth vapour device use rates and a concurrent decrease in tobacco use rates. One independent survey from Poland showed an increase in both vapour device and cigarette use, but we have assessed it as a weak study, as will be discussed shortly.

The US-NYTS prevalence data showed that past 30 day use of vapour devices increased from 1.5% in 2011 to 16.0% in 2015, and in the same period, past 30 day use of cigarettes decreased from 15.8% to 9.3%. Past 30 day use of other tobacco products significantly decreased as well: smokeless tobacco use declined from 7.9% in 2011 to 6.0% in 2015, cigars from 11.6% to 8.6%, pipe tobacco from 4.0% to 1.0%, and bidis from 2.0% to 0.6% (Singh, Arrazola, et al., 2016 [+]).

A similar pattern has occurred in Florida, as studied by Porter et al. (2015). Among Florida middle school students vapour device ever use increased from 3.0% in 2011 to 8.5% in 2014, and past 30 day use increased from 1.5% to 4.0%. Concurrently, ever cigarette use decreased from 14.3% to 10.3%, and past 30 day tobacco use decreased from 4.2% to 2.9%. For the high school students, vapour device ever use increased from 6.0% in 2011 to 20.5% in 2014, and past 30 day use increased from 3.1% to 10.8%, while ever cigarette use decreased from 34.2% to 25.8%, and past 30 day tobacco use decreased from 13.0% to 8.7%.

The same trend of an increasing use of vapour devices coupled with a decreasing use of tobacco products has taken place among Paris teenagers. Dautzenberg et al. (2016 [+]) compared prevalence rates from 2012 and 2014 youth tobacco surveys (N=3279), and the prevalence of vapour device triers increased from 7.9% to 26.3% for 12-15 year olds, and from 12.2% to 47.9% for 16-19 year olds. In the same two year period, regular and occasional smoking decreased from 15.3% to 10.9% for ages 12-15, and from 38.3% to 33.5% for ages 16-19. The decreases in tobacco use rates in the US and France is welcome news, but these surveys also showed that vapour device experimentation is increasing very rapidly among these teenagers.

As well, the prevalence of youth using vapour devices in the past 30 days has been increasing rapidly among Polish youth, yet the rates of cigarette use also increased in the surveys by Goniewicz, Gawron, Nadolska, Balwicki, and Sobczak (2014 [-]) conducted in 2010 and 2013. In their survey, past 30 day vapour device use rose from 5.5% to 29.9%, while cigarette use increased from 23.9% to 38.0%. Yet these data need to be viewed with caution as the lead author acknowledged in another publication that the survey was not a representative sample (Goniewicz et al., 2016).

Longitudinal cohort studies

Two weak longitudinal cohort studies followed youth vapour device triers and their experimentation with tobacco one year later: Leventhal et al. (2015 [-]) with 9th grade students in Los Angeles (n=222 vapour device triers), and Wills et al. (2016 [-]) with Hawaiian of 9th and 10th grade students (N=2338, 31% past 6 month vapour device use).

In the Leventhal study [-], baseline vapour device triers had a 2.65 (95% CI [1.73, 4.05]) higher odds ratio of smoking experimentation one year later compared to non-users, with 25.2% of vapour device users progressing to smoking (any use) compared to 9.3% of non- users. Yet the tobacco products that the vapour device triers experimented with was rather surprising – it was cigars and hookahs, with cigarettes comprising less than 23% of the tobacco products. This observation of preference among vapour device triers for tobacco experimentation with products other than cigarettes is in accord with the patterns of use found by Hampson et al. (2015) [++] in their 6 year longitudinal cohort study. While vapour device experimenters were also trying other tobacco products, cigarettes were not the popular choice.

In a second longitudinal cohort study, Wills et al. (2016 [-]) calculated an odds ratio of 1.67 for vapour device users to progress to smoking (any) over students with no vapour device use. Yet only 14% of vapour device triers experimented with smoking (any) after one year, compared to 5% of prior abstainers. Weekly and daily vapour device users were at a higher risk to progress to smoking (any) with an odds ratio of 4.09 over prior abstainers. This higher risk of tobacco experimentation among regular vapour device users may confirm that a regular pattern of vapour device use, not simply experimentation, is necessary for the creation of a potential behavioural pathway for subsequent tobacco experimentation.

Both of these studies were limited in their analysis by their small sample sizes of youth who had ever tried vapour devices but never tried tobacco, and the even smaller number of vapour device triers who actually progressed to any tobacco experimentation. In addition, Wills et al. (2016 [-]) did not report the numbers of youth in their reporting of percentages or odds ratios, making it difficult to interpret the study's findings. Furthermore, it is also plausible to suggest that young people with higher risk-taking tendencies are more attracted to experimenting both with vapour devices and tobacco than abstainers, i.e., there is no underlying causal association suggested by these studies.

Cross-Sectional study

Cardenas et al. (2016 [+]) conducted a retrospective cross-sectional study based on the 2011-2013 US-NYTS, and calculated that the multivariate prevalence ratio of past year cigarette use (even one puff) for those who tried vapour devices decreased with the subjects' age, with 11-13 year olds at 4.1 PR decreasing to 1.4 PR for 16-18 year olds. The overall numbers for past year tobacco experimentation were low, with 6.6% of vapour device ever-users trying smoking in the past year, but were higher than the 2.9% of prior abstainers. Again, psychological risk-taking tendencies may be a factor in the higher rate of trying cigarettes among vapour device ever-users. Like all cross-sectional research, this study cannot show directionality or causality.

Table 14: Population Studies of Youth Vapour Device and Tobacco Use

First Author, Year, Title	Study Design	Findings
Population survey studies		
Dautzenberg (2015) [The e-cigarette disrupts other consumptions in Parisian teenagers (2012-2014)] [+]	Cross-sectional survey, N=3279 students aged 12-19, comparing rates in 2012 with 2014.	EC trier increased from 7.9% to 26.3% for ages 12-15 and 12.2% to 47.9% for ages 16-19. Regular and occasional smoking decreased from 15.3% to 10.9% for ages 12-15 and 38.3% to 33.5% for ages 16-19.
Friedman (2015) How does electronic cigarette access affect adolescent smoking? US [+]	Regression analysis of 12-17 year old smoking rates (any cigarette past 30 day use) between US states with and without bans on EC sales to minors. 24 states had such bans prior to 2014, regressions based on National Survey on Drug Use and Health. Regressions calculated from 2002 – 2013 smoking rates.	States with bans yielded a statistically significant 0.9% increase in recent smoking among 12-17 year olds, countering 70% of decrease in youth smoking rates.

Goniewicz (2014) Rise in electronic cigarette use among adolescents in Poland. [-]	Comparison of two cross-sectional studies from Poland, students 15-19 years old, 2010-2011 (N=1,760) and 2013-2014 (N=1,970).	Past 30 day use of EC increased from 5.5% to 29.9%. Dual use increased from 3.6% to 21.8%. Cigarette use increased from 23.9% to 38.0%.
Pesko (2016) The influence of electronic cigarette age purchasing restrictions on adolescent tobacco and marijuana use. US [+]	Regression analysis of 2007-2013 US Youth Risk Behavior Surveillance System, ages 10-19 years old. Controlled for age-race cohorts, cigarette excise taxes, and indoor smoking bans.	ENDS age restrictions associated with an increase of 0.8% in regular cigarette use (20 of past 30 days) and 0.7% increase in heavy cigarette use (every day in past 30 days) in states with ENDS age restrictions compared to those without.
Porter (2015) Electronic cigarette and traditional cigarette use among middle and high school students in Florida, 2011–2014. [+]	Florida Youth Tobacco Surveys 2011-2014 middle school and high school students. N varied greatly by year (n=5,972-38,972 middle school, 6,097-36,578 high school).	Middle school EC ever use increased from 3.0% in 2011 to 8.5% in 2014, and past 30 day EC use increased from 1.5% to 4.0%. Any cigarette use decreased from 14.3% to 10.3%, and past 30 day use decreased from 4.2% to 2.9%. High school ever EC use increased from 6.0% in 2011 to 20.5% in 2014, and past 30 day use increased from 3.1% to 10.8%. Ever cigarette use decreased from 34.2% to 25.8% and past 30 day use decreased from 13.0% to 8.7%.
Singh (2016) Tobacco use among middle and high school students - United States, 2011-2015. [+]	2011-2015 US-NYTS 2015 N=17,711	Past 30 day use of EC increased from 1.5% in 2011 to 16.0% in 2015. Significant decreases in past 30 day use of cigarettes from 15.8% to 9.3%. Past 30 day use of other tobacco products significantly decreased: smokeless tobacco use from 7.9% to 6.0%, cigars from 11.6% to 8.6%, pipe tobacco from 4.0% to 1.0%, bidis from 2.0% to 0.6%.

O'Leary et al. (2017)

Longitudinal cohort studies		
Leventhal (2015) Association of electronic cigarette use with initiation of combustible tobacco product smoking in early adolescence. [-]	Longitudinal assessment of school-based cohort starting at 9th grade (mean age 14 years old), with f/u at 6 and 12 months. Never use of tobacco at baseline, N=2530, EC use (any use in prior 6 months) at baseline n=222.	Baseline EC use positively associated with any tobacco use, OR 2.65 (95% CI [1.73, 4.05]) with 25.2% of EC users reporting tobacco use vs. 9.3% with no EC use. For EC triers with tobacco product any use at 12 months: cigarettes (n=17), cigars (n=33), and hookahs (n=25).
Wills (2016) Longitudinal study of e-cigarette use and onset of cigarette smoking among high school students in Hawaii. [-]	Longitudinal survey of N=2338 students in 9th and 10th grade in 2013 with one-year f/u. 31% ever use EC at baseline, and 38% at f/u. 5% weekly + very day EC users at baseline and f/u.	EC only user at baseline more likely to have ever-smoked cigarettes at f/u (14%) compared to non-users (5%), complete case analysis OR 2.87 (95% CI [2.03, 4.05]). Full analysis OR 1.67 [1.17, 2.39]. Tobacco use at f/u highly correlated with frequency of EC use with daily/ weekly users OR 4.09 compared to non-users.
Cross-Sectional study		
Cardenas (2016) Use of electronic nicotine delivery systems and recent initiation of smoking among US youth. [+]	2011-2013 US-NYTS n=54,677 55.0% had tried cigarette (even 1 puff) in past 3 years. EC ever use 5.9% EC use past 30 days: 2.0%.	EC ever use more likely to have tried cigarette smoking in the past year. 4.1 (95% CI [2.6, 6.4]) multivariate prevalence ratio for ages 11-13; PR 3.0 [2.2, 3.9] for ages 14-15; 1.4 PR [1.1, 1.8] for ages 16-18. Overall, 2.9% of non-users had tried smoking compared to 6.6% of ever use EC.

Surveys

In five surveys, youth were asked which product they used first, vapour devices or tobacco, and five surveys measured smoking intentions among vapour device ever triers.

Sequence of use.

In five surveys (see Table 15 below), a substantial majority of youth self-reported trying tobacco before vapour devices. The highest percentage of teens who tried a vapour device before tobacco was 15.7% in Poland [-], and the percentages of teens trying vapour devices before tobacco were 11.6% in France [+] and 8.2% in Great Britain [-], to a low of 0.5% among US teens [-] – see Table 15 below. These self-reports may be influenced by recall bias, but this handful of studies indicated that for the great majority of youth, tobacco experimentation preceded vapour device use, and not the other way around.

Table 15: Surveys with Sequence of Use

First Author, Year, Title	Study Design	Findings
Dautzenberg (2015) [The e-cigarette disrupts other consumptions in Parisian teenagers (2012-2014)] [+]	Cross-sectional survey, N=3279 students aged 12-19, comparing rates in 2012 with 2014.	Of those using tobacco, 3.1% used EC first.

Eastwood (2015) Electronic cigarette use in young people in Great Britain 2013-2014. [-]	2013-2014 two wave cross-sectional online study, N=1952, aged 11-18. 8.2% ever try EC.	Of EC ever triers, 69.8% (95% CI [62.2, 77.3]) smoked cigarette first, 8.2% [4.1, 12.2] smoked EC first, and 18.3% [11.7, 24.8] have never smoked a cigarette.
Goniewicz (2016) Dual use of electronic and tobacco cigarettes among adolescents: a cross-sectional study in Poland. [-]	Survey of N=1785 students aged 16-18 conducted Dec. 2013 – Feb. 2014. Past 30 day EC use 29.6%.	15.7% of dual users tried EC first.
Soneji (2016) Multiple tobacco product use among US adolescents and young adults. [-]	2012-2013 web-based survey, N=927 ever tobacco user, n=32 aged 10-14, and n=201 aged 15-17.	EC as first tobacco product used, 0% for ages 10-14, and 0.5% for ages 15-17.
Stenger (2015) [Survey on the use of electronic cigarettes and tobacco among children in middle and high school.] France [+]	2014 survey of N=3319 middle and high school students. 56% ever tried EC; 3.4% daily EC use.	88.4% used tobacco before trying EC.

Smoking intentions.

Five surveys examined smoking intentions (also called smoking susceptibility) in youth in three countries: Bunnell et al. (2015 [-]) for US 6-12 grade students; Moore et al. (2016 [-]) for Welsh 10-11 year olds; Park, Seo, & Lin (2016 [-]) for US 6–12 grade students; Wang, Ho, Leung, & Lam (2015 [+]) for Hong Kong 12-17 year olds, and Wills et al. (2015 [-]) for US 9-10 grade students. Smoking intention was measured with two questions (except as noted): (1) will you use tobacco in the next year ("next two years" in Moore et al.; "soon" in Park et al.), and (2) would you use tobacco if it were offered by a friend. Park asked only the first question, and Wills asked only the second question. The four responses offered are definitely yes, probably yes, probably no, and definitely no. Only those with "definitely no" responses to the question(s) were classified not having a smoking intention, and all others were counted as having an intention to smoke tobacco.

All studies found that participants who had ever tried a vapour device to have higher "intention to smoke" scores than non-device users. The studies computed odds ratios ranging from 1.70 to 3.62 for vapour device triers as compared to non-users to have any use (even one puff) of tobacco products.

Like the longitudinal cohort studies, these studies were limited in their analysis by their very small sample sizes, resulting in very wide confidence intervals. Four of the five studies were based on a very small number of youth who had ever tried a vapour device but had never used tobacco: Park et al. (2016 [-]) found only 146 of 16,238 never-smoking US youth had ever used a vapour device; Wang et al. (2015 [+]) reported 0.13% of past 30 day vapour devices users in Hong Kong had never smoked; Bunnell et al. (2015 [-]) determined that 0.9% of US youth who had ever used a vapour device had never used tobacco; and Moore et al. (2016 [-]) counted 5.3% of very young Welsh students having tried a vapour device, but not tobacco. In other words, the vast majority of youth who have tried a vapour device have also experimented with tobacco. All studies acknowledged that their cross-sectional research design could not determine a causal direction between vapour device use and tobacco use. Smoking intentions were not a marker for vapour device uptake in the strong longitudinal cohort study by Hampson et al. (2015) [++].

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Table 16: Smoking Intentions of Vapour Device Ever Triers

First Author, Year, Title	Study Design	Findings
Bunnell (2015) Intentions to smoke cigarettes among never-smoking US middle and high school electronic cigarette users: National Youth Tobacco Survey, 2011–2013. [-]	2013 US-NYTS Non-smoking students N=53,873. Non-smoking + EC ever-use = 0.9% Non-smoking + EC past 30 days = 0.3%.	Ever EC use more likely to have intention to smoke than never users, 43.9% (AOR=1.70, (95% CI [1.24, 2.32]) vs 21.9% of all non-smokers. 58.2% [47.5-68.1] current EC users had smoking intention.
Moore (2016) E-cigarette use and intentions to smoke among 10-11-year-old never-smokers in Wales. [-]	Cross-sectional survey of 10-11 year old children, Child Exposure to Tobacco Smoke survey 2014, n=1601. 21 reported ever tobacco use, 10 reported ever use of tobacco and EC, and 5.3% reported ever EC use.	Ever EC use associated with higher intention to smoke OR=3.21 (95% CI [1.66, 6.23]). Non-EC triers 0.3% (n=4) had any yes response to intention to smoke in next 2 years; EC triers 2.6% (n=2) had any yes response.
Park (2016) E-Cigarette use and intention to initiate or quit smoking among US youths. [-]	2012 US-NYTS Never smoker, no EC use n=16092 Never smoker, ever EC use n=146 Experimenters < 100 cigarettes, no use past 30 days, no EC use n=2856 Experimenters, EC ever use n=392. Current smoker > 100 cigarettes, past 30 day use, no EC use n = 277, current smoker, ever EC use n=430.	Never smokers, EC triers 3.62 AOR (95% CI [2.04, 6.45]) more likely to report smoking intention. Experimenters, EC triers 1.99 AOR [1.50-2.64] more likely to report smoking intention.
Wang (2015) Electronic cigarette use and its association with smoking in Hong Kong Chinese adolescents. [+]	Random cross-sectional survey N=45,128 students aged 12-17. Prevalence of past 30 day EC use was 1.1%.	4.12% (95% CI [3.72, 4.54]) EC users measured intention to smoke. Compared to all students, EC users AOR 1.74 [1.30, 2.31].
Wills (2015) E-cigarette use and willingness to smoke: A sample of adolescent non-smokers. US [-]	Cross-sectional survey N=2309 high school students. N=418 non-smokers had ever used EC. Willingness based on friend offer question.	EC ever users 2.35 (95% CI [1.73-3.19]) more likely to report willingness to smoke (26%) than never tobacco users (11%).

Conclusion

It is surprising that so few studies have used the available data from national surveys to track and compare trends in the rates of youth vapour device use and tobacco use considering the many editorials and commentaries expressing their concern on the matter. Four population survey studies found that tobacco use rates among youth were declining as vapour device prevalence increased. The two regression analysis studies provided the strongest evidence that vapour device use does not lead to tobacco use among youth, as US adolescents with access to vapour devices had lower rates of tobacco uptake than those who were banned from the legal purchase of vapour devices. Other studies will need to be reviewed to see if this pattern of decline in tobacco experimentation and use continues as youth move into young adulthood.

Many studies reviewed were biased by the size of the study populations with only a very small subset of the study population, from well under 1% to 5%, who had tried vapour devices but had not experimented with smoking. It is not surprising that this class of participants was difficult to locate as the five surveys with data on the sequence of use reported that for dual users, approximately 90% had used tobacco before trying vapour devices.

For our research question, three research teams have concluded that there is no causal pathway from vapour device use to tobacco use. Hampson et al. (2015) proposed a common liability model for the use of tobacco and other nicotine products, particularly based on sensation seeking traits (also suggested by Friedman, 2015). Cardenas et al. (2016) conjectured that youth who have tried vapour devices may have "behavior phenotypes" that put them at higher risk for smoking. Pentz et al. (2015) reasoned that cigarette and vapour device experimentation occur concurrently. Based on their conclusions, we can suggest that vapour device experimentation does not cause tobacco experimentation because the psycho-social factors that influence youth tobacco uptake appear to be the same ones influencing youth vapour device experimentation.

The impact of vapour device use on youth smoking is a critical question for public health, regardless of which product was used first. With the availability of numerous population level surveys of adolescent tobacco and vapour device use, regression analysis could provide more reliable answers to the question of the relationship of current vapour device use to actual tobacco uptake, particularly for subgroups of youth at higher risk for substance use.

Systematic Review 3: Second Hand Exposure from Vapour Devices

What is the potential toxicity of second-hand vapour? In our search we retrieved one systematic review and 26 studies on this research question. For the individual studies, 17 involved environmental testing (one very strong, two strong, six moderate, eight weak), seven assessed physiological reactions to second hand exposure (three moderate, four weak), and two offered data in both areas (one very strong and one strong).

A potential conflict of interest was noted for four of the studies: three conducted by tobacco corporations, and one funded by the vapour device industry. They are hereafter noted as [I]; see Table 17 below.

Table 17: Industry Funded or Conducted Studies on Second Hand Exposure

First Author, Date, Title	Study Design	Findings and Conclusions
Long (2014) Comparison of selected analytes in exhaled aerosol from e-cigarettes with exhaled smoke from a conventional cigarette and exhaled breaths.	Tested 2 blu products, 20-24 mg nicotine for major components, phenolocs, and carbonyls. 9 sessions of 2 hours, up to 99 puffs by 10 subjects – pad collection.	Lorillard Tobacco Co. study. Phenolics and total carbonlys not significantly different that exhaled breaths and or room blanks.
Maloney (2016) Insights from two industrial hygiene pilot e-cigarette passive vaping studies.	6 one hour vaping sessions in test room, EC prototype, 6 days of testing, up to 9 users in room.	Study by Altria. Nicotine and menthol below limit of quantitation. Formaldehyde below limit of detection; the authors proposed that background building levels responsible for emissions.
McAuley (2012) Comparison of the effects of e-cigarette vapor and cigarette smoke on indoor air quality.	Smoking machine testing of 4 liquids. Tested for nicotine, TSNAs, PAHs, PG, DEG, VOCs, and carbonyls. Risk analysis of Total Cumulative Hazard Indices and Excess Lifetime Cancer Risks also calculated for children. Found "no significant risk" for bystanders.	Testing found "no significant risk" for bystanders and "no discernible health impacts" (p. 855) Study funded by the National Vapers Club (US), including EC retailer contributions.

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O'Connell (2015) An assessment of indoor air quality before, during, and after unrestricted use of e-cigarettes in a small room.	Business room, 3 EC users and 2 non-users, 165 minute vaping sessions, 7 hours. Measured nicotine, VOCs, glycerol, carbonyls, PAHs, trace metals, nitrosamines. WHO Air Quality Guidelines or UK Workplace Exposure Limits	Imperial Tobacco Co. study. Formaldehyde and acetaldehyde below WHO guidelines. Did not detect acrolein or increases PAHs or nitrosamines from vapour. Acetone and metals substantially lower than UK limits.

Systematic Review

The systematic review by Fernández et al. (2015) was originally undertaken for the World Health Organization. The literature search was conducted through January 27, 2015. Their exclusion criteria removed studies with machine generated vapour, and included studies with human-generated vapour due to its "real-life" conditions. The authors rated Schripp et al. (2013 [++]) and Balbe et al. (2014 [++]) as the studies of major importance, and rated Czogala et al. (2014 [++]) and Schober et al. (2014 [++]) as important. The Fernandez et al. review covered eight studies, plus the authors conducted a small study themselves (see Table 18 below). The Long (2014) industry study is listed in Table 17 above. In addition to the information presented in Table 18 below, we refer you to Fernández et al. Table 1, page 426 for additional details.

The authors concluded that second hand (or passive) vapour does contain particulate matter, but at lower levels than cigarettes. They also cautioned that the level of exposures may differ by the type of device, and the amount of the potential variation cannot be determined with the limited number of studies available.

Table 18: Fernandez et al. Systematic Review Studies

First Author, Date, Title	Study Design	Findings and Conclusions
Ballbe (2014) Cigarettes vs. e-cigarettes: Passive exposure at home measured by means of airborne marker and biomarkers. [++]	Observational study of 54 homes, 5 testing EC. Airborne nicotine markers 5.7 times higher in cigarette homes than EC homes. Salivary cotinine and urinary cotinine markers in non-smokers similar for cigarette and EC homes.	"Non-smokers passively exposed to e-cigarettes absorb nicotine" (p. 79).
Bertholon (2013) [Comparison of the aerosol produced by electronic cigarettes with conventional cigarettes and the shisha.] [French] [English abstract] [+]	Tested exhalation of EC vapour. 26% was absorbed by vaper. Airborne half-life is 11 seconds due to evaporation, compared to 19-20 minutes for tobacco smoke.	"the risk of 'passive' smoking exposure from e-cigarettes is modest" [English abstract]
Czogala (2014) Secondhand exposure to vapors from electronic cigarettes. [++]	Exposure chamber study of 3 devices w/18 mg nicotine generated by users. Measured nicotine, PM2.5, CO, and VOC.	Bystanders are exposed to nicotine, but not CO or VOC. EC nicotine levels 1/10 that of cigarettes. EC PM2.5 levels 7X lower than cigarettes.
Fernandez (2015) Particulate matter from electronic cigarettes and conventional cigarettes: A systematic review and observational study. [+]	Measured PM2.5 in homes of 1 cigarette smoker (3 cigarettes), 1 EC user (42 puffs), and two non-smokers. Measurement for 1 hour with user 2 m from the monitor	Median concentrations similar for EC and non-smoker homes, under the threshold for the WHO Air Quality Guidelines.

Ruprecht (2014) Comparison between particulate matter and ultrafine particle emission by electronic and normal cigarettes in real-life conditions. [+]	Real-time measurement performed in office space, vapour and smoke generated by user. PM significantly lower for EC than cigarettes, 479X less for nicotine and 363X less for non-nicotine.	All EC PM below European Air Quality Standards and US EPA Air Quality Index.
Saffari (2014) Particulate metals and organic compounds from electronic and tobacco-containing cigarettes: comparison of emission rates and secondhand exposure. [+]	Air sampled from indoor office with smoke/vapour generated by users. Measured black carbon, CO, PM, 32 alkanes and organic acids, and compared to outdoor air and cigarettes. Organic compound emissions 100 times less than cigarettes, and 10 times less for elements. Nickel and silver emissions minimally higher than cigarettes. No detectable black carbon, PAHs, or hopanes in EC.	"with the exception of Ni, Zn, and Ag, e-cigarettes resulted in a remarkable decrease in secondhand exposure to all metals and organic compounds" (abstract). Authors state that manufacturing standards could potentially reduce metal particulates.
Schober (2014) Use of electronic cigarettes (e-cigarettes) impairs indoor air quality and increases FeNO levels of e-cigarette consumers. [++]	For indoor air quality testing of a small room, exposure produced by users. PAH average of 7 chemicals increased by 20%; aluminum increased 2.4-fold. No change in CO and CO2 levels. No increase in lanthanum and cerium (in secondhand cigarettes). No increase in cadmium, arsenic, thallium, formaldehyde, benzene, acrolein, or acetone.	"substantial amounts" of 1,2-propanediol, glycerine, nicotine, and PM2.5 found in tests.
Schripp (2013) Does e-cigarette consumption cause passive vaping? [++]	Emission test chamber study, 3 liquids with vapour produced by user. Found low levels of formaldehyde, acetaldehyde, isoprene, acetic acid, 2-butanodione, acetone, propanol, PG, and diacetin (from flavouring), apple oil (3- methylbutyl-3-methylbutanoate), and nicotine. 1,2-propanediol below detectable limits.	"the e-cigarette is a new source of VOCs and ultrafine/fine particles in the indoor environment. Therefore, the question of 'passive vaping' can be answered in the affirmative" (p. 31).

Our search retrieved seven additional studies not included in the Fernández et al. review, listed below in Table 19.

Table 19: Environmental Testing Studies

First Author, Date, Title	Study Design	Findings and Conclusions
Human generated vapour – quality studies		
Soule (2016) Electronic cigarette use and indoor air quality in a natural setting. [+]	Measured PM2.5 in a 4023 m3 hotel room during an EC convention with 59-86 active users.	Baseline concentration 1.92-3.20 µg/m3 increased to concentrations ranging from 311.68 – 818.88 µg/m3.
Trassierra (2015) On the interaction between radon progeny and particles generated by electronic and traditional cigarettes. [+]	Walk-in radon chamber testing of co-exposure of radon progeny and second hand vapour. Attached Potential Alpha Energy Concentration was higher for EC (69%) than cigarettes (31%). Appears to be human generated vapour.	Second hand EC increases exposure risk for radon.

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Machine generated vapour – weak studies		
Geiss (2015) Characterisation of mainstream and passive vapours emitted by selected electronic cigarettes. [-]	Indoor environmental testing using 30 m3 emission chamber, 2 types of devices and 7 different refill liquids. Tested for nicotine, PG, glycerol, VOC, and particulate concentrations of <0.3µm and 0.02-1µm. Emissions varied greatly between different liquids. Smoking machine.	Relatively low concentrations of nicotine "deemed to be negligible" (p. 173). "The additional amount of carbonyls… can be deemed to be negligible when compared to levels of the same substances typically found indoors." (p. 176)
Offerman (2015) Chemical emissions from e-cigarettes: Direct and indirect (passive). [-]	Used published data (unclear which studies) to calculate 24 hour passive exposures for worst-case scenarios to small office space, 8 hour exposure (125 puffs of 24 mg/ml nicotine in PG), assumed 100% of inhaled aerosol was exhaled. Applied 1% of California OSHA Permissible Exposure Guideline as standard for nicotine and PG, and CA EPA No Significant Risks levels for all other chemicals.	Acetaldehyde, acrolein, formaldehyde, cadmium, lead, nickel, and NNK below exposure criteria (0.001-0.17). Nicotine (X5.4) and PG (X23) exceeded 1% of CA OSHA criteria. PG exposure causes acute eye and upper respiratory tract irritation.
Offerman (2014) The hazards of e-cigarettes. [-]	Applied NSRL and CREL health exposure guidelines to data from Goniewicz (2013) and Schripp (2013). Assumed 100% non-absorption by user, modeled 8 hour exposure in a small office space.	Nicotine and PG exposures exceeded guidelines. "Ventilation is not a solution and e-cigarette use will have to be…prohibited indoors" (p. 42).
Third hand nicotine exposure		
Bush (2015) A pilot study on nicotine residues in houses of electronic cigarette users, tobacco smokers, and non-users of nicotine-containing products. [+]	Environmental testing, 3 surface wipes from the floor, wall, and window for third hand nicotine in the homes of 8 e-cig users, 6 cigarette users, and 8 non-users.	Nicotine was not found in 4 e-cig homes; in the remaining 4 homes the levels were almost 200 times lower than in the cigarette user homes. Nicotine was also detected in half of the non-users homes, and no significant difference in nicotine in EC users homes compared to non-smokers homes.
Goniewicz (2015) Electronic cigarettes are a source of third hand exposure to nicotine. [-]	Chamber testing of 100 puffs, 4 tests with 4 EC brands with 20 mg/ml-32mg/ml nicotine. Syringe generated vapour. Surface wipes tested from 5 locations.	3 of 4 tests showed significant increases of nicotine. "Nicotine from e-cigarettes can stick to various surfaces" (p. 258), particularly tile floors.

Individual Studies - Environmental Testing

The composition of second hand vapour is quite distinct from cigarette smoke in that vapour is airborne for under 30 seconds, compared to 18-20 minutes for tobacco smoke, substantially reducing the time of exposure to second hand vapour (Bertholon et al., 2013 [+]). No studies applied this metric when evaluating exposure levels.

Many researchers found a substantially lower level of particulate matter ($PM_{2.5}$) from vapour device emissions compared to cigarettes. Environmental testing by Czogala et al. (2014 [++]) determined PM emissions to be 7 times (10 times per Saffari et al., 2014 [+]) lower than cigarettes, and ultra-fine particles hundreds of times lower than cigarettes (Ruprecht et al., 2014 [+]). One small test conducted on in-home $PM_{2.5}$ found similar levels in the homes of vapour device users and non-smokers, which were below WHO Air Quality Guidelines (Fernandez et al., 2015 [+]). Testing by Ruprecht et al. (2014 [+]) in an office space determined that the particulate matter levels were below the European Air Quality Standards and the US EPA Air Quality Index.

Yet other researchers who conducted rigorous studies found PM emissions. Schrober et al. (2014 [++]) and Schripp et al. (2013 [++]) reported detectable particulate matter emissions from vapour devices, and Soule et al. (2016 [+]) measured a large increase of PM in a vapers' convention hotel room (readings which could possibly be used as a metric for maximum exposure). Also of serious concern, it appears that the particle size of vapour increases the exposure risk for radon (Trassierra, Cardellini, Buonanno, & de Felice, 2015 [+]).

Volatile organic compounds (VOC) were not detected in two strong studies (Czogala et al., 2014 [++]; Schober et al., 2014 [++]), or at negligible levels in a very strong study (Schripp et al., 2013 [++]) and one weak study (Geiss, Bianchi, Barahona, and Barrero-Morenno, 2015 [-]). Saffari et al (2014 [+]) measured VOC for vapour devices at 100 times less than cigarettes. Acetaldehyde was measured at below published guidelines or at low levels (not quantified) by Schripp et al. (2013 [++]) as well as in two other studies (O'Connell et al., 2015 [I], Offerman, 2015 [-]). Acrolein emissions were found to be at low levels in testing by Schrober, 2014 [++], and in the test results of one other study (Offerman, 2015 [-]). The data from these studies demonstrated that vapour devices are not a significant source of VOCs.

For polycyclic aromatic hydrocarbons (PAH) and metals, testing results were mixed regarding the levels of exposure. One strong study measured an increase of 20% in PAH exposure (Schrober et al., 2014 [++]), while two studies did not detect PAH (O'Connell et al., 2015 [I]; Saffari et al., 2014 [+]). As for metals in second hand emissions, in one strong study environmental levels of cadmium did not increase (Schrober et al., 2014 [++]). Nevertheless, Saffari et al. (2014 [+]) found nickel emission levels were three times higher for vapour devices than cigarettes, yet overall, the emissions of elements were 10 times lower in vapour devices than cigarettes.

Environmental testing for nicotine measured second-hand (airborne) and third hand (surface) exposures. Vapour device disposition of nicotine in homes was measured at 5.7 times lower in vapour device user homes than those of cigarette smokers (Balbe et al., 2014 [++]), and one study did not detect nicotine in half of the homes of vapour device users (Bush & Lee, 2015 [+]). Two studies determined that second hand vapour device nicotine levels were 10% (Czogala et al., 2014 [++]) to 20% (Gallart-Mateu, Elbal, Armenta, & de la Gardia, 2016 [-]) of the level of emissions from cigarettes. Figures from Saffari et al. (2014 [+]) compared the nicotine concentrations of cigarettes at 1542 ng m^{-3} (±80.4) to vapour devices at 123.0 ng m^{-3} (±34.5).

Vapour device disposition of nicotine in homes was measured at 5.7 times lower in vapour device user homes than those of cigarette smokers (Balbe et al., 2014 [++]), and one study did not detect nicotine in half of the homes of vapour device users (Bush & Lee, 2015 [+]). Third hand exposure was found by Goniewicz and Lee (2015 [-]), yet nicotine appeared to be a common environmental toxin in homes, even in those without cigarette smokers or vapour device users (Bush & Lee, 2015 [+]).

Physiology Studies

Physiology studies have reported effects of second hand vapour exposure on bystanders for nicotine exposure, breath composition, and medical emergencies. Findings of four studies showed that second hand exposure to vapour devices does result in the measureable absorption of nicotine in bystanders: Balbe et al., 2014 [++]; Czogala et al., 2014 [++]; Flouris et al., 2013 [-], Gallart-Mateau et al., 2016 [-]). Additionally, Casanova-Chafer, Gallart-Mateu, Armenta, & de la Gardia (2016 [+]) found no changes in the composition of the breath of bystanders exposed to vapour. For medical complications from second hand exposure, three years of FDA reports had 35 acute reaction reports, nine of which were determined to be related to pre-existing conditions; one hospitalization reported (Durmowicz, Rudy, & Lee, 2016 [+]).

Table 20: Physiology Studies of Passive Exposure to Vapour

First Author, Date, Title	Study Design	Findings and Conclusions
Second hand exposure – moderate quality studies		
Casanova-Chafer (2016) Preliminary results about the breath of passive smokers and vapers based on the use of portable air monitoring devices. [+]	Real-life conditions room study. Measured PM, CO2, CO, VOC, and formaldehyde.	"exposition to EC vapers does not affect the breath composition of passive vapers" (p. 457).
Durmowicz (2016) Electronic cigarettes: Analysis of FDA adverse experience reports in non-users [letter]. [+]	Reports from 1 Jan 2012 – 31 Dec 2014.	35 reports, 26 of respiratory symptoms (9 related to pre-existing condition) with 6 receiving medical attention and 1 hospitalization.
Second hand exposure studies - weak		
Flouris (2013) Acute impact of active and passive electronic cigarette smoking on serum cotinine and lung function. [-]	Chamber study to approximate "a smoky bar" with vapour generated by machine. Bystanders had similar levels of serum cotinine for exposure to EC and cigarette.	1 hour of passive exposure did not significantly effect lung function.
Flouris (2012) Acute effects of electronic and tobacco cigarette smoking on complete blood count. [-]	15 smokers and 15 never smokers exposed in chamber for 1 hour, vapour generated with air pump.	No change in complete blood count.
Gallart-Mateu (2016) Passive exposure to nicotine from e-cigarettes. [-]	Room based exposure of 5 minutes at a distance of <2 m. Oral fluid samples at 30 and 60 minutes after exposure for 16 non-smokers for nicotine. Machine-generated exposure.	Found levels of 7-16 μgL-1of nicotine (approximately 20% of the exposure produced by cigarettes). Nicotine amounts 4X-9X lower for EC exposure compared to tobacco.
Marco (2015) A rapid method for the chromatographic analysis of volatile organic compounds in the exhaled breath of tobacco cigarette and electronic cigarette smokers. [-]	Tested 2 ECs, exhaled breath tested with collection bag.	Vapour mainly composed of PG, glycerin, nicotine, and vanillin in sample 2. VOCs "virtually absent" except for nicotine.

Conclusions

Data from all available studies showed that second hand vapour, also called passive exposure, did produce a measurable absorption of nicotine in bystanders. There is no evidence as of yet that nicotine present in vapour (in very low and transient exposures) poses significant second-hand health risks. It is theoretically possible that enduring exposure to second-hand nicotine might have some harmful effects, but this remains to be determined.

Environmental testing studies found that second hand vapour is far less toxic than cigarette smoke, often by several orders of magnitude. Second hand vapour did not contain the carbon monoxide and volatile organic compounds generated by second hand tobacco smoke. Of course, compared to ambient air, vapour devices do have emissions, and further studies are needed to assess their potential risks.

First and foremost, particulate matter testing is urgently needed as the available studies had mixed results regarding the level of their second hand emissions. More testing is needed on the emissions of polycyclic aromatic hydrocarbons (PAH) and metals. Levels of risk for vulnerable populations, such as children and persons with respiratory illnesses, need to be evaluated. Just as for cigarettes, vapour devices certainly vary widely in their levels of emissions. More devices should be tested, and in the US, individual models are now required to be tested under the newly enacted regulations.

Systematic Review 4: Comparison of Vapour Devices and Cigarettes for Emissions and Physiology

What are the health risks and benefits of vapour devices, and how do these compare to cigarettes? The studies reported here directly compare vapour devices and cigarettes on their emissions and their effects on the physiological functions of the users. Ten studies compared emissions and 11 studies examined physiological responses. The limited number of studies was due to the absence of comparative cigarette data in most research.

Emissions

Ten studies were located that compared the emissions of vapour devices and cigarettes; one study (Tayyarah & Long, 2014) was conducted by the tobacco industry. The studies could not be directly compared due to their differing sample sizes (i.e., number of puffs) and measurements. Almost all substances tested were substantially lower, or not detected, in vapour devices compared to cigarettes. No publications discussed the possible health impacts for the reduced level of emissions in vapour devices.

The major caveat for interpreting the results of these studies is that there is a wide range of vapour devices, and hundreds of different flavouring agents. The large majority of the studies tested only one device. The type of device and how it is used (topology) results in substantial differences in emissions. For example, increasing the voltage of a vapour device from 3.2 to 4.8V increased formaldehyde, acetaldehyde, and acetone levels from 4-200 times (Kosmider et al., 2014), and higher vapour device voltage resulted in increased carbonyl production in two other studies (Bekki et al., 2014; Ohta, Uchiyama, Inaba, Nakagome, & Kunugita, 2011). Direct dripping, in which the user drops the liquid directly on the heating element, has been measured with dramatically increased emissions of three volatile organic compounds (VOC) to levels above those of cigarettes (Talih, Balhas, Salman, Karaoghlanian, & Shidadeh, 2015 [++]).

Overall, vapour devices emissions were several orders of magnitude lower than those produced by cigarettes, or eliminated altogether. Unlike cigarettes, the vapour devices tested did not emit tar (Blair et al., 2015 [+]), and 61 of the 79 compounds in tobacco smoke measured by Marco and Grimalt (2015 [++]) were not found in vapour (RC tally of the study's Table 1). Two major chemicals for cancer risk are acrylonitrile and benzene (Fowles & Dybing, 2003). Acrylonitrile was measured at levels 3-10 times lower than cigarettes by Blair, Epstein, Nizkorodov, and Staimer (2015 [+], and benzene at 1800 times lower than cigarettes by Marco and Grimalt (2015 [++]). Emissions of tobacco specific nitrosamines cancer agents NNN (N'-nitrosonornicotine) and NNK [4-(methylnitrosamino)-1-(3-pyridyl)-1-butanone] from tobacco were approximately 100 times lower for vapour devices than cigarettes (Goniewicz et al., 2014 [++]). Jo and Kim (2016 [+]) determined that VOCs were 234 times lower per puff of vapour than in cigarettes. The substantial difference in the number of VOCs between vapour devices and cigarettes were made plain in the chromatograms by Marco and Grimalt (2015 [++]).

Two studies reported higher exposures of particulate matter and metals in the emissions of vapour devices than in tobacco smoke. Higher particulate matter emissions were found in the Fuoco, Buonanno, Stabile, and Vigo (2014) [+] study, but these findings were contradicted by the measurements in the Pellegrino et al. (2012) [++] and Blair et al. (2015 [+]) studies. For metals, lead and chromium levels in vapour device emissions were similar to cigarettes while, iron, nickel, and aluminum levels were higher than cigarettes as measured by Williams, Villarreal, Bozhilov, Lin, and Talbot (2013) [+]. The authors believe that the metal emissions likely came from the wires and metal components of the vapour devices, and they stated that these emissions could be substantially reduced with improvements in manufacturing of the devices.

Vapour device emissions of formaldehyde and acrolein at the high end of their recorded range could be higher than the lowest level measurements of these compounds in cigarette smoke. Nevertheless, when these vapour device emissions were compared to the highest range of emissions for cigarette smoke, the vapour device emissions of formaldehyde were 9 times lower than cigarettes, and acrolein emissions were 13 times lower (Goniewicz et al., 2014 [++]). Formaldehyde was also higher in the top range of emissions in tank systems emissions when compared to cigarettes, yet 100 times lower than cigarettes at the lowest levels recorded for vapour device emissions (Talih, Balhas, Salman, Karaoghlanian, & Shidadeh, 2015 [++]). These findings of higher levels of these VOC in vapour devices were contradicted by the testing by Laugensen (2015 [-]), and Tahih et al. (2015 [++]) who did not find these levels of emissions for acrolein.

The research team observed a major gap in the research. No independent studies to date have measured the emissions of 1,3-butadiene (BDE) in vapour devices, the highest source of cancer risk in cigarette smoke (Fowles & Dybing, 2003; Hatsukami & Parascandola, 2005). A British American Tobacco conference presentation (Wright, Mariner, Williams, & Proctor, 2014) did suggest that BDE emissions from vapour devices were approximated five times lower than from cigarettes.

Table 21: Toxicology Emissions Comparisons of Vapour Devices and Cigarettes

First Author, Date	Substance	Vapour Device	Cigarettes
Blair (2015) [+]	Tar mg/cig Acetaldehyde μg/9 puffs Acetone μg/9 puffs Acetonitrile μg/9 puffs Acrolein μg/9 puffs Methanol μg/9 puffs VOC, 9 puffs	0 95.9 22.0 8.85 32.0 0.292 $1.2x10^{12}$	1.67-25.0 269-578 150-322 25.7-90.0 40.9-78.9 5.80-48.9 $(1.4-7.4)x10^{12}$
Fuoco (2014) [+]	Total particles, per puff	$4.39 \pm 0.42 \times 10^9/cm^{-3}$	$3.14 \pm 0.61x10^9/cm^{-3}$
Goniewicz (2014) [++]	Formaldehyde μ/g Acetaldehyde Acrolein Toluene NNN NNK	0.20-5.61 0.11-1.36 0.07-4.19 0.02-0.63 0.00008-0.00043 0.00011-0.00283	1.6-52 52-140 2.4-62 2.4-62 0.005-0.19 0.012-0.11

<table>
<tr><td>Jo (2016) [+]</td><td>Sum of formaldehyde, acetaldehyde, and acrolein.
Sum of all above plus propionaldehyde, crotonaldehyde, butyraldehyde, and methyl ethyl ketone.</td><td colspan="3">345-1,112 ng L^{-1}

<0.9 µg puff</td><td>11,357-31,865 ng L^{-1}

211 µg puff</td></tr>
<tr><td>Laugensen (2015) [-]</td><td>Formaldehyde mcg/L
Acetaldehyde
Acrolein</td><td colspan="3">1.07
0.81
1.06</td><td>116
2282
231</td></tr>
<tr><td>Marco (2015) [++]
ND=not detected
Two vapour devices tested</td><td>Pent-1-ene µg/m^3
n-Pentane
Pent-2-ene
Isoprene
Pent-2-ene
n-Hexane
Benzene
n-Heptane
Toluene
n-Octane
Ethylbenzene
m-Xylene
p-Xylene
o-Xylene
Naphthalene</td><td colspan="3">ND
ND
ND
ND
ND
ND
0.6/ND
ND/1
ND/4
ND
1/ND
ND
0.6/ND
0.4/ND
ND</td><td>700
1200
625
2700
460
975
1100
890
1400
560
660
980
420
590
240</td></tr>
<tr><td>Pellegrino (2012) [++]</td><td>PM_1 µg/m^3
$PM_{2.5}$
PM_7
PM_{10}
Total Suspended P</td><td colspan="3">14
43
50
52
63</td><td>80
901
919
922
933</td></tr>
<tr><td>Talih (2015) [++]
NR=not reported

BDL=below detectable limit

BQL=below quantifiable limit</td><td>15 puffs

Formaldehyde

Acetaldehyde

Acetone

Acrolein

Propionaldehyde

Crotonaldehyde

Methacroline

Butyraldehyde

Valaradehyde</td><td>Direct Drip
88.06
±9.43
1172.23
±87.04
196.55
±49.91
1.75
±0.71
314.54
±32.58
BQL

0.95
±0.44
6.30
±0.36
92.49
±10.28</td><td>Cigalike

0.20-5.61

0.11-
1.36
NR

0.07-4.19
NR

NR

NR

NR

NR</td><td>Tank

0.02-27
0.17-4.23
0.34-7.59
NR

BDL

BQL

NR

NR

BQL</td><td>Cigarette

21.5±7.8

540.3±135.3

214.1±43.4

49.6±14.1

42.6±8.0

13.2±5.2

NR

26.7±6.2

NR</td></tr>
</table>

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Tayyarah (2014) [I] Lorillard study Cig=mg/cig EC=mg/99 puffs	CO Carbonyls Phenolics Volatiles Metals TSNAs PAA PAH	<0.1 <0.09 <0.003 <0.008 <0.00006 <0.00002 <0.000014 <0.00016	20-27 1.18-1.92 0.17-0.26 0.94-1.43 <0.0003 0.000185-0.000550 0.000017-0.000024 0.00153-0.00222
Williams (2013) [+]	Sodium μg/10 puffs Iron Aluminum Potassium Copper Magnesium Zinc Lead Chromium Nickel Manganese	4.18 0.52 0.394 0.292 0.203 0.066 0.058 0.017 0.007 0.005 0.002	1.3 0.042 0.22 70 0.19 0.070 0.12-1.21 0.017-0.98 0.004-0.069 0.0014-0.003 0.003

Physiology

The physiological impacts of vapour devices and cigarettes were compared in 11 studies, with nine studies comparing two groups of users, and two measuring changes in physiological markers in smokers who switched to vapour devices.

In one substitution study by van Staden, Groenewald, Engelbrecht, Becker, and Hazelhurst (2013 [-]), smokers who switched to vapour device use for two weeks had a reduction in blood CO and an increase in oxygen uptake, demonstrating improvements in physiological functioning. In another substitution study, research on the effect of vapour device use on asthma outcomes by Polosa et al. (2016 [+]) found improvements at 24 months in symptoms and no significant changes in exacerbation rates in smokers who switched to vapour devices, and dual users also experienced improvements in their asthma symptoms.

In the studies comparing the physiological responses of vapour device users and tobacco smokers, unlike cigarettes, vapour device use had no significant acute impacts on lung function (Chorti et al., 2012 [-]; Ferrari et al., 2015 [+]), blood composition (Farasalinos et al., 2013; Flouris et al., 2012 [+]), myocardial function (Farsalinos, Tsiapras, Kyrzopoulos, Savvopoulou, & Voudris, 2014 [+]), inflammatory markers (Tzatzarakis et al., 2013 [-]), or coronary circulation (Farsalinos et al., 2013 [-]), and significantly lower impact on vascular function (Carnevale et al., 2016 [+]) compared to cigarette smoking.

Data on biomarkers of carcinogens in two studies (Hecht et al., 2015 [+]; Kotandeniya, Carmella, Pillsbury, & Hecht, 2015 [++]) found levels significantly lower for vapour device users than for smokers. Particularly of interest, the nicotinic carcinogens biomarker of total NNAL ([4-(methylnitrosamino)-1-(3-pyridyl)-1-butanol], metabolite of NNK) for vapour device users was 1/100 of that of smokers in both studies, with just under 30% of the vapour device users testing below the limit of detection for any NNN exposure in the Kotandeniya (2015 [++]) study. These are important findings because NNAL is a biomarker for the exposure risk for cancer (Fowles & Dybing, 2003; Hatsukami & Parascandola, 2005). Yet caution is needed in interpreting these findings because there are no data on the amount of reduction or threshold levels required to reduce risk (Hatsukami et al., 2007). Biomarkers are surrogate outcomes, not actual health outcomes (Boyd et al., 2012).

Table 22: Physiological Function Comparisons between Vapers and Smokers

First Author, Date	Function	Vapers	Smokers
Carnevale (2016) [+]	Oxidative stress and vascular function	Significantly lower impact than cigarettes for sNox2-dp, 8-isoPGF2a, and NO bioavailability.	Similar level of effect as vaping on vitamin E levels and flow-mediated dilation.
Chorti (2012) [-]	Lung function	No significant changes.	Significantly decreased FEV1, FEVi/FVC, FEF25-75, FeNO. Significantly increased CO.
Farsalinos (2013) [-]	Coronary circulation and blood carboxyhemoglobin levels	No significant changes.	Significant decrease in CFVR, and significant increase in CVRI and HbCO.
Farsalinos (2014) [+]	Myocardial function	No immediate effects.	Significant delay in LV myocardial relaxation: IVRT and IVRTc prolonged, Em and SRe decreased, and MPI and MPlt elevated.
Ferrari (2015) [+]	Lung function	Non-nicotine device, no significant changes.	Significant decreases in FEF25, FEF50, FEF50, FEF75 FEV_1, and PEF, and significant increase in FeCO.
Flouris (2012) [+] also Kouretas (2012)	Complete blood count	No changes.	Significant increases in white blood cell, lymphocyte, and granulocyte counts.
Hecht (2015) [+]	Toxicant and carcinogen metabolites in urine. 1-HOP [95% CI] total NNAL 3-HPMA 2-HPMA SPMA	All significantly lower levels than smokers. 0.38 [0.26-0.55] 0.02 [0.02-0.03] 1,100 [766-1590] 141 [80-252] 0.29 [0.18-0.46]	0.97 [0.80-1.17] 1.21 [0.99-1.47] 4,040 [3,380-4,830] 399 [255-626] 2.85[2.24-3.63]
Kotandeniya (2015) [++]	Total NNN and total NNAL levels.	Total NNN below limit of detection in 21 of 27 vapers; mean level 0.0055pmol/mL. Total NNAL below limit of detection in 17 of 27 vapers; mean level 0.024 pmol/mL.	Total NNN 0.060±0.035 Total NNAL 2.41±1.41. Both significantly higher in smokers than vapers.
Polosa (2016) [+]	Asthma outcomes	At 24 months, improvements in respiratory symptoms, lung function, AHR, and ACQ. No significant changes in exacerbation rates.	Dual users decreased tobacco consumption, and also obtained improvements.
Tzatzarakis (2013) [-]	Inflammatory markers	No significant changes.	Interleukins 2 and epidermal growth factor significantly increased.

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Van Staden (2013) [-]	COHb and SpO_2 changes in 13 smokers who used vapour device for 2 weeks	2 weeks of vapour device substitution COHb 2.71±1.35 SpO_2 97.49±1.34 Both changes significant.	Baseline 4.66±1.99 96.15±1.76

Conclusion

Overall, these studies are very encouraging for the potential of vapour devices for harm reduction. Vapour devices do not emit tar, and eliminated 61 of 79 tested compounds found in cigarettes. Vapour devices exponentially decreased exposure levels of the cancer causing agents of acrylonitrile and benzene found in cigarettes. Vapour device use did not cause several adverse physiological effects that occur with cigarette use. The substantial reduction in NNAL and NNN (tobacco toxins) biomarkers demonstrated the possibility that vapour devices may offer tobacco smokers a far less toxic alternative. Nevertheless, the amount of reduction in emissions most likely differs between products, and user behaviours such as increasing the device's voltage and use of direct dripping increases emissions.

Unfortunately, no independent research has measured 1,3-butadiene (BDE) in vapour devices, the compound which is the highest source of cancer risk in cigarettes. The presence of metal emissions remains of concern, and could possibly be addressed with manufacturing standards and improvements in product design. Overall, we conclude that vapour devices present lower risks than conventional cigarettes for those using vapour devices as a substitute for smoking, and there is strong evidence of benefit. For non-tobacco users, however, vapour devices do expose them to some toxicants, but the level of increased risk has yet to be studied.

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