Brief Technical Report

Potential Range of Relative Harm from E-cigarettes for Major Health Conditions for use in Modelling Work: Based on Recent Biomarker Studies

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Summary

This document examines recent biomarker studies (published since 1 January 2015) in which the biomarker levels in e-cigarette users (vapers) are compared to those from tobacco smokers. The results are highly variable but all suggest lower levels of risk to vapers relative to tobacco smokers. Yet as the situation with vaping is very dynamic (new products, changing ways people vape) and there is no evidence yet about long-term effects of e-cigarette use on health outcomes, a lot more future research will be needed to get a reasonable understanding of the relative harms.

Introduction

Estimating the potential harm to health from using e-cigarettes is very complex given the ongoing changes and large diversity of e-cigarette products in the international market. How vapers actually use these products is also a likely determinant of what toxicants they inhale. For example, there is evidence that vapers take longer inhalations than do smokers (eg,(Lee *et al.* 2015) (Spindle *et al.* 2015) (Behar *et al.* 2015; Talih *et al.* 2015)). Further, many models of vaporisers have adjustable features such as variable voltage/wattage and air flow. Users may also customise the coil resistance, nicotine strength and flavourings of the liquid used to fill the device. These issues may suggest that past estimates of harm based on e-cigarette aerosol may not reflect the range of exposures users experience at the current point in time (mid-2016). Also past estimates (as per reports by Public Health England(McNeill *et al.*) and the Royal College of Physicians in the UK(Royal College of Physicians)) largely relied on expert opinion and relatively few biomarker studies. A systematic review in 2014 reported that "due to many methodological problems, severe conflicts of interest, the relatively few and often small studies, the inconsistencies and contradictions in results, and the lack of long-term follow-up no firm conclusions can be drawn on the safety of ECs."(Pisinger & Dossing 2014) Furthermore, the only published model of e-cigarette harm has used very large ranges for the harm from e-cigarettes relative to that of tobacco cigarettes (ie, from 1% to 50%).(Kalkhoran & Glantz 2015) This static model also did not account for transitions in use beyond the baseline year, such as quitting smoking or vaping, hence the modelled patterns did not represent realistic patterns of long-term use.

Methods

Given the changing technology of e-cigarettes we decided to restrict our literature searches to only very recent studies (since 1 January 2015) and to focus only on biomarker studies –

which are more likely to capture the impacts from what vapers actually inhale than studies of just aerosols or e-cigarette product constituents. Different search strategies were used to identify the likely relative harm (compared to tobacco smoking) for: (i) cancer causation in general; (ii) and harm to the cardiovascular and respiratory systems.

For carcinogens we used a list of the top eight most important carcinogens from tobacco smoking based on Cunningham et al[(Cunningham *et al.* 2011)]: acrolein; formaldehyde; acrylonitrile; 1,3-butadiene; cadmium; acetaldehyde; ethylene oxide; and isoprene. Although this was a tobacco industry funded study, these specific carcinogens are reported as relevant in other scientific literature as well and so seem reasonable to use. In PubMed searches, the specific names of these carcinogens were combined with the words "electronic cigarettes" or e-cigarettes (with searches restricted to 1 January 2015 to 5 May 2016). The metabolites of the most important carcinogen (acrolein) were also included in these searches (ie, "HPMA" [*N*-(2-Hydroxypropyl)methacrylamide]).

Tobacco-specific nitrosamines are also described in the literature as important carcinogens,[(Xue *et al.* 2014)] [(Yalcin & de la Monte 2016)] so we repeated the above searches with the terms "nitrosamine", "NNN", "NNAL", and "NNK". (NNK is the nicotine-derived nitrosamine ketone, NNN is *N*-nitrosonornicotine, and NNAL is a metabolite of NNK [4-(methylnitrosamino)-1-(3-pyridyl)-1-butanol]).

For cardiovascular disease (CVD) and respiratory harm we searched for all recent biomarker based studies by using the words "electronic cigarettes" or e-cigarettes and "blood or urine or biomarker" (with searches restricted to 1 January 2015 to 5 May 2016). A specific search was also done for "carbon monoxide" as this is also relevant for CVD risk from tobacco smoking.[(US Department of Health and Human Services)]

We did not focus on nicotine and cotinine results, given that nicotine is probably less important than other toxicants in the pathogenesis of CVD.[(US Department of Health and Human Services)] Similarly for the results for changes in blood pressure, heart rate and other measures of blood flow, all of which may be largely influenced by nicotine intake (eg, Farsalinos et al 2016,[(Farsalinos *et al.* 2016)] flow mediated dilation in Carnevale et al[(Carnevale *et al.* 2016)]; and blood flow to oral mucosa[(Reuther *et al.* 2016)]). Studies of airway resistance (eg, FEV) were also not included as these might also reflect short-term effects as opposed to long-term respiratory damage.

All the above searches were also repeated for the Abstracts of the most relevant tobacco-related conference held in March 2016 (Society for Research on Nicotine and Tobacco).

Abstracts of the identified studies were then examined for determining if comparisons with tobacco smoking were included and to ensure a biomarker measurement in humans was involved (eg, measurement in human urine or exhaled breath).

Results

The results suggest a very diverse range of values as shown in Table 1, but all suggest lower levels of risk for vapers compared to tobacco smokers. In particular, the risk associated with carbon monoxide seems likely to be close to 0% or a few percent at most. However, preliminary evidence (ie, one study by Carnevale et al[(Carnevale et al. 2016)]) suggests that the effect of vaping on three other inflammatory markers associated with CVD may be at least half that of tobacco smoking. The results for cancer-related toxicants are less variable – but the range

is still large at 0% to 23% that of tobacco smoking.

Table 1: Results of identified biomarker studies where vaping is compared to tobacco smoking (ordered within disease categories by relative level and for studies reported since 1 January 2015)

Disease group relevance	Measure	% level in vapers vs tobacco smokers	Study	Extra details
Mainly cancer relevant				
Cancer	NNAL	Around 0%	Martin et al 2016(Martin *et al.* 2016)	The 12 vapers had NNAL levels in their urine at non-smoker levels, except for one subject (where the level was above the cut-off point for distinguishing smokers from non-smokers).
Cancer	Total NNAL	1.5%	Hecht et al 2015(Hecht *et al.* 2015)	Measured in urine. The results also have wide uncertainty. The comparative results for smokers were based on the average of three separate studies.
Cancer	Total NNAL	2.5%	Kotandeniya et al 2015(Kotandeniya *et al.* 2015)	Measured in urine. Total of 27 vapers and 38 smokers.
Cancer	Total NNAL	14.3%	Wagener et al 2016(Wagener *et al.*)	The study included 10 smokers and 20 vapers (9 used a Generation 2 device and 11 used a Generation 3 device). The relative value for the latter is shown (14.3%). For the Generation 2 device users the equivalent value was 11.6%.
Cancer (& CVD & respiratory*)	3-HPMA (from acrolein)	20.7%	Hecht et al 2015(Hecht *et al.* 2015)	See above for other results from this study.
Cancer (& CVD & respiratory*)	3-HPMA (from acrolein)	21.1%	McRobbie et al 2015(McRobbie *et al.* 2015)	Measured in urine. The results were relative to levels at baseline when smoking tobacco four weeks before (albeit with wide uncertainty). At this four week point the 3-HPMA levels of the vapers were just over a third (35.4%; 343/969) that of dual users in the study.
Cancer	Total NNN	22.9%	Kotandeniya et al 2015(Kotandeniya *et al.* 2015)	See above for other results from this study (NNAL)
Mainly CVD relevant				
CVD (& respiratory*)	Exhaled carbon monoxide (eCO)	Around 0%	Yan and D'Ruiz 2015(Yan & D'Ruiz 2015)	A joint tobacco and e-cigarette company (Lorillard) funded study which found the five types of e-cigarettes had a non-significant impact on the eCO levels in study participants, whereas the tobacco cigarettes significantly increased the eCO more than eight times above the baseline (from 3.00 ppm to 25.14 ppm). While detailed data were not provided for CO levels from e-cigarettes in the publication, the study reported "basically no changes in exhaled CO after use of any of the 5 blu e-cigs" and CO levels were within the range for non-smokers (2.86–3.52 ppm).

Disease group relevance	Measure	% level in vapers vs tobacco smokers	Study	Extra details
CVD (& respiratory*)	eCO	Around 0%	Wagener et al 2016(Wagener *et al.*)	The levels in vapers for 2nd and 3rd generation devices were 2.3 and 3.4 ppm (both in the <4 ppm range consistent with not smoking). This compared to 13.9 ppm in the smokers. See other results from this study above.
CVD (& respiratory*)	Fractional eCO	Around 0%	Ferrari et al 2015(Ferrari *et al.* 2015)	The level did not increase after vaping among either non-smokers or smokers (in marked contrast to tobacco cigarettes).
CVD (& respiratory*)	eCO	Around 0%	McRobbie et al 2015	The levels for vapers were within the range for non-smokers at the four week point (<4 ppm). At this time the eCO levels of vapers were 27.3% (3/11) that of the dual users in the study.
CVD (& respiratory*)	eCO	Around 0%	Walele et al 2016(Walele *et al.* 2016)	The level only increased in conventional cigarette users, not in vapers. This was a tobacco industry funded study.
CVD (& respiratory*)	eCO	Around 0%	Pacifici et al 2015(Pacifici *et al.* 2015)	The level in vapers appeared to be in the normal range for non-smokers. The level in vapers was 20%, 7% and 18% that of smokers at the 1 month, 4 month and 8 month points. The levels were also lower than for dual users.
CVD (& respiratory*)	eCO	10.4%	Washington-Krauth et al 2016(Washington-Krauth *et al.*)	This comparison used the amount of increase after vaping/smoking.
CVD (& cancer & respiratory*)	eCO, NNAL	Reduced levels	Pulvers et al 2016(Pulvers *et al.*)	Significantly lower levels in people who switched from smoking to become vapers or dual users (using second generation devices). The presented results were not quantified. Lower levels of a metabolite of benzene were also reported.
CVD and probably chronic respiratory disease				
CVD & respiratory	Four biomarkers of oxidative stress: sNox2-dp, 8-isoPGF2α, NO bioavailability, vitamin E	67.3% (median results)	Carnevale et al 2016(Carnevale et al. 2016)	After vaping, the levels of all these biomarkers were reported as more favourable (from a health perspective) than after a tobacco cigarette (except for 8-isoPGF2α in the non-smoker group). The e-publication had some errors in Table 2 so an updated table was supplied to us by the authors (with some changes in the vitamin E results). From their reported results we could calculate the effect of vaping on these biomarkers as being 67% that of smoking tobacco cigarettes (using the median result for the combined smoker and non-smoker group for the four measures). The mean was 67.8%.

* When considering chronic obstructive pulmonary disease (COPD), both acrolein and CO have been described as markers for oxidative damage (amongst a range of other molecules).(Antus & Kardos 2015) The US Surgeon General also states the likely role of acrolein in CVD risk.(US Department of Health and Human Services)

Discussion

Given the evolving nature of e-cigarettes and how vapers use these products (typically with longer inhalations than smokers), a focus on the most recent biomarker studies probably gives the most reliable current estimates of potential chronic disease harm to human health.

Nevertheless, the human biomarker studies to date are relatively small and it is generally difficult to interpret the results in terms of long-term disease risk. It is also difficult to interpret the potential biases in work funded by tobacco/e-cigarette manufacturers –as discussed elsewhere.(Pisinger & Dossing 2014)

In modelling work, it is possible to not assign any values for relative harm and just use the modelling to answer the questions around thresholds (eg, how much reduced harm from vaping would there need to be to balance out any possible harms of vaping such as any reduction in quit rates associated with dual use)? Nevertheless, scenario analyses could consider using the values in Table 2. Such use still needs to note the large uncertainty levels and that this knowledge base only represents that available as of June 2016 (and noting the dynamic market of changing products and changing vaping practices).

Table 2: Summary of the results from Table 1 with values that could be potentially used for modelling

Disease group	Median (mean) values for relative level	Range of values for relative level	Possible values for use in modelling*	Uncertainty (for possible use in modelling)
Cancers	14.3% (11.9%)	0% to 23%	10%	SD = +/-30% of the central estimate, beta distribution
Cardiovascular disease (CVD)	0%** (9.7%)**	0% to 67%	10%	As above
Chronic respiratory disease	Probably just 1 study that also applies to CVD		Using values for CVD given the lack of data	

* There are many ways these could be selected. Here the mean values are rounded to the nearest 10% increment.

** Calculated using all the non-cancer group values in Table 1 (ie, six zero values, 10.4% and 60.8%)

Further work to improve such estimates could be obtained from considering other types of biomarker eg, those considering the expression of inflammatory response genes in vapers.(Martin et al. 2016) There are also laboratory studies of relevance which suggest that e-cigarette aerosol may have constituents that could be harmful to human tissues in terms of triggering inflammatory responses,(Rubenstein *et al.* 2015) causing cytotoxicity,(Ji *et al.* 2016) and inducing oxidative stress.(Lerner *et al.* 2015) However, the validity of these studies are also reliant on the aerosol extracts being representative of what vapers are exposed to and translation into disease risk may not be straightforward. A review of the animal biomarker studies done to date may also be helpful (we note at least 21 such mouse studies and 17 rat studies in PubMed as per 10 June 2016). However, the relevance of animal models to human health risk is not always clear and it is often difficult to translate these animal model results into a quantitative estimate of human health risk. Similarly, the animals used in these experiments may not be exposed to aerosol levels that accurately reflect human exposure levels under naturalistic operating conditions.

Ultimately there is a need for well-designed cohort studies that follow vapers through to actual CVD and other disease incidence and death. There would need to careful attention to both exposure assessment (repeatedly) and confounder assessment (smoking proper, socioeconomic position, BMI, etc).

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