THE UK ELECTRONIC CIGARETTE RESEARCH FORUM

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Electronic cigarette research briefing – December 2015 & January 2016

This first research briefing of 2016 is part of a series of monthly updates aiming to provide an overview of new studies on electronic cigarettes. The briefings are intended for researchers, policy makers, health professionals and others who may not have time to keep up to date with new findings and would like to access a summary that goes beyond the study abstract. The briefing also aims to provide a critical overview of individual studies and put them in the context of what we already know from previous research.

The studies selected in these briefings do not form an exhaustive list of every e-cigarette-related study published each month. Instead they include those most relevant to key themes identified by the UK Electronic Cigarette Research Forum. This includes mechanisms and safety, cessation, population level impact, marketing and unintended consequences. For an explanation of the search strategy used, please see the end of this briefing.

The text below provides an overview of the aims, key findings and limitations of each of the highlighted studies. The briefing concludes with a section that puts the study findings in the context of the wider literature and what we know about existing research gaps.

If you would prefer not to receive this briefing in future, just let us know.

1. **Electronic cigarettes induce DNA strand breaks and cell death independently of nicotine in cell lines**

- **Study aims**
  This US study aimed to evaluate the cytotoxicity and genotoxicity of e-cigarette vapour from two brands of cig-a-like e-cigarette, both with and without nicotine, on epithelial and head and neck squamous cell carcinoma (HNSCC) cell lines. These cell lines were grown for between 48 hours and 8 weeks on media exposed to tobacco flavour vapour (re-treated every 3 days) and compared to cells treated with tobacco smoke, nicotine or untreated.

- **Key findings**
  In terms of cytotoxicity, a 53-258% increase in necrotic and apoptotic cells was seen in e-cigarette treated cells compared to untreated controls. There was a 5-fold increase in cell death in e-cigarettes without nicotine and 10-fold with nicotine. However the cigarette-treated cells could only be treated for 24 hours because of the high levels of cytotoxicity so the later comparisons could not be made.

The genotoxicity tests showed increased single- and double- strand DNA breaks in the e-cigarette treated lines compared to the untreated control in most experiments and similar or increased levels of DNA damage to the nicotine treated cells.

- **Limitations**
  This was a lab-based study it's not clear how relevant this would be *in vivo*. As the growth medium was treated with e-cigarette vapour, the cells were exposed continuously which is likely to be more intense exposure than would be achieved in the real-world. It was not possible to compare e-cigarette to cigarette treated cells in all assays because some were conducted on cells which had been treated with vapour for 8 weeks but the cigarette treated cells died after 24 hours.

Yu V, Rahimy M, Korrapati A, Xuan Y, Zou AE, Krishnan AR, Tsui T, Aguilera JA, Advani S, Crotty Alexander LE, Brumund KT, Wang-Rodriguez J, Ongkeko WM. Electronic cigarettes induce DNA strand breaks and cell death independently of nicotine in cell lines. Oral Oncol. 2016 Jan; 52:58-65. doi: 10.1016/j.oraloncology.2015.10.018.

2. **E-cigarettes and smoking cessation in real-world and clinical settings: a systematic review and meta-analysis**

- **Study aims**
  This US systematic review and meta-analysis combined all identified studies looking at e-cigarette use and smoking cessation to assess the impact of using these products. This included randomised trials alongside longitudinal and cross-sectional studies.

- **Key findings**
  38 studies were identified and reviewed and the 20 with control groups were combined in a meta-analysis which found significantly lower odds of quitting in those using e-cigarettes (OR= 0·72, 95% CI 0·57-0·91). However when studies were limited to only those where e-cigarettes were used for smoking cessation, the result became non-significant.

- **Limitations**
  The studies included in the meta-analysis were not homogenous, in respect to study design, participant selection, control arm and control for confounders, other products/support used concurrently and measurements used.

  This is particularly important for definition of e-cigarette use as many of the studies looked only at ever use. As the authors noted, results have shown a significant improvement in smoking cessation outcomes for use of some types of devices and when these are used daily, as shown in the subgroup analyses of some studies. However in the meta-analysis, e-cigarettes and any users are treated as a single entity despite large variation in devices, especially over time and by country.

  Motivation for e-cigarette use also varied so smoking cessation is not the aim for all participants included here and results were non-significant when this was the focus.

Kalkhoran S, Glantz SA. E-cigarettes and smoking cessation in real-world and clinical settings: a systematic review and meta-analysis. Lancet Respir Med. 2016 Jan 13. pii: S2213-2600(15)00521-4. doi: 10.1016/S2213-2600(15)00521-4.

3. **Views from the Coalface: What Do English Stop Smoking Service Personnel Think about E-Cigarettes?**

- **Study aims**
  This study looked at the impact of e-cigarettes in English Stop Smoking Services. Firstly quarterly returns (n=207,883) were used to explore which quit aids were used in services and 4 week quit rates. An online survey was also conducted with practitioners, managers and commissioners in late 2014 (n = 1,801) to measure attitudes towards e-cigarettes and perceived reasons for the decline in Stop Smoking Service attendance over recent years.

- **Key findings**
  A small minority 2% (n=4,750) of Stop Smoking Service clients were using unlicensed nicotine-containing products as part of their quit attempt (mainly e-cigarettes) and most were using an e-cigarette alongside other licensed medication. Average self-reported 4 week quit success for all users was 50%, for anyone using an e-cigarette (with or without other medication) it was 59% and for those just using an e-cigarette it was 65% - this was the highest success rate group, though the group was small. The most successful non-e-cigarette group was those using varenicline at 60%.

  The survey revealed high variation in attitudes and behaviour towards e-cigarettes among Stop Smoking Service personnel. Only 24.4% thought e-cigarettes were a good thing. 5% would recommend e-cigarettes to all of their clients, 20.2% only to those who had tried and failed to quit many times and 55.8% to none of their clients. The survey found managers and commissioners were more positive about e-cigarettes than practitioners, those in London were more likely to be positive than elsewhere and those employed by GPs/hospitals were more negative.

  When asked why they thought there had been a decline in Stop Smoking Service attendance, 83% thought smokers were choosing to use e-cigarettes, 53.8% that remaining smokers are harder to reach and 27.7% thought reduced funding contributed to the decline.

- **Limitations**
  Use of quit aid was not randomised so users are likely to be different in terms of demographic variables and other factors such as previous quit experience, smoking dependence and motivation. There were only small numbers of e-cigarette users compared to those using licensed products and it's possible they are self-selected vapers in supportive services who may be highly motivated to quit, so these results may not be generalisable across services or users as a whole.

  It's worth noting that longer-term quit success is far lower. A recent national evaluation found it was 8% at one year. We don't know what longer term quit rates would be for service clients using e-cigarettes and how these might differ from quit rates for clients using other quit aids.

  Response rate for the survey was low, at 7% and personnel with particularly strong opinions may have been more motivated to respond.

Hiscock R, Bauld L, Arnott D, Dockrell M, Ross L, McEwen A. Views from the Coalface: What Do English Stop Smoking Service Personnel Think about E-Cigarettes? Int J Environ Res Public Health. 2015 Dec 21;12(12):16157-67. doi: 10.3390/ijerph121215048

4. **Impact of advertisements promoting candy-like flavoured e-cigarettes on appeal of tobacco smoking among children: an experimental study**

- **Study aims**
  This UK study examined the appeal of tobacco cigarettes and e-cigarettes in children (aged 11-16, n=471) who hadn't used either of these products before and the impact of printed advertisements which either included flavoured e-cigarettes or non-flavoured-e-cigarettes or a control with no adverts shown.

- **Key findings**
  Exposure to either set of adverts did not increase the appeal of tobacco smoking, the appeal of using e-cigarettes, or susceptibility to tobacco smoking or reduce the perceived harm of tobacco smoking, which was high.

  The group which viewed the flavoured e-cigarette adverts rated these adverts as significantly more appealing than those viewing the non-flavoured adverts. Interest in buying e-cigarettes was also significantly higher in this group but still negative on average.

- **Limitations**
  This study was investigated attitudes of young people in two schools only (one in Cambridgeshire and one in Hampshire) so these results may not be generalisable to all young people in the UK. It also tested impact of printed e-cigarette adverts in a non-realistic setting; it may be that celebrity endorsement, TV adverts or printed ones places next to sweets in a shop, for example, illicit different responses.

  It measured only attitudes and not behaviour. There are many other factors which could influence e-cigarette trial (and views of the products) including any other advertisements seen as well as peer and family influences.

Vasiljevic M, Petrescu DC, Marteau TM. Impact of advertisements promoting candy-like flavoured e-cigarettes on appeal of tobacco smoking among children: an experimental study. Tob Control. 2016 Jan 17. doi:10.1136/tobaccocontrol-2015-052593

5. **Adolescents' responses to the promotion and flavouring of e-cigarettes**

- **Study aims**
  This UK study examined adolescents' awareness of e-cigarette marketing and investigated the impact of e-cigarette flavours on perceptions of product harm and user image. 1,205 11 – 16 year olds from the 2014 Youth Tobacco Policy Survey were asked about e-cigarettes, awareness of brands was tested and perceptions of product harm and likely users in relation to flavours was explored.

- **Key findings**
  12% of participants had tried e-cigarettes but regular use was low (2%) and confined to adolescents who had also smoked tobacco. 82% of young people were aware of at least one promotional channel (by far the most common being displays in shops) and 69% knew that e-cigarettes came in different flavours (with fruit and sweets the most commonly mentioned).

  The vast majority of participants were aware that e-cigarettes were advertised, but brand awareness was low and only 16% of participants named a brand. Overall e-cigarettes were

perceived as harmful but this was moderated by product flavours with tobacco viewed as most harmful, followed by coffee and then cherry and candy. Fruit and sweet flavours were perceived as more likely to be tried by young never smokers than adult smokers trying to quit.

- **Limitations**
  The cross-sectional nature of the study means we can't infer causal relationships between the awareness of marketing and perceptions of e-cigarettes. The study didn't explore possible reasons for perceptions of harm, what the harm might be or how this compares to the harm of tobacco.

  Not all types of promotion or flavour perceptions were tested and attitudes were tested in a non-realistic setting. Behaviour also relies on self-report.

Ford A, MacKintosh AM, Bauld L, Moodie C, Hastings G. Adolescents' responses to the promotion and flavouring of e-cigarettes. Int J Public Health. 2015 Dec 9. doi: 10.1007/s00038-015-0769-5

Overview

A significant number of new e-cigarette studies have been published since the last bulletin. This month we've selected five papers that may be of particular interest to UKECRF members. The first two generated headlines around the world and are on the themes of potential harms and smoking cessation. The last three are from the UK, so directly relevant to our context, and examine e-cigarettes and Stop Smoking Services, and then marketing and flavourings.

The first paper is a cell study examining the toxicity of e-cigarette vapour. Damage was observed in cells of the type that lines the mouth and lungs (including some cancer cells) that were exposed to vapour for up to 8 weeks. Some of the cells died. Cell death was more common in those treated with nicotine-containing vapour but also occurred in those exposed to non nicotine-containing vapour. It wasn't possible to compare the effects on the cells of tobacco smoke with e-cigarette vapour because the cells treated with tobacco died within 24 hours. The paper therefore provides some evidence that the constituents of e-cigarette vapour may be harmful to cells in a lab environment although not necessarily in humans, as the study wasn't designed to look at this. Unfortunately the study couldn't compare the toxicity of e-cigarette vapour with tobacco smoke. The press release accompanying the paper included a quote from the lead author who stated that the evidence to date suggested e-cigarettes were no less harmful than tobacco. Arguably the data in the paper do not support this claim, and readers may be interested in a critique of the paper that was published in The Guardian newspaper at the end of December.

The second paper includes a systematic review and meta-analysis of e-cigarettes and smoking cessation conducted by researchers in California. This follows on from a Cochrane review on this topic and also the Public Health England report that examined similar literature up to early 2015. The current review reaches different conclusions from the Cochrane and PHE reports and found that e-cigarette users were less likely to stop smoking than others when study results were combined. The review is useful in the breadth of literature it covers, but has significant limitations because a meta-analysis was conducted on many studies (20) with varying designs, only two of which were trials. Also some the individual studies within the review have been criticised because of very weak measures of e-cigarette use (only recording 'ever' rather than sustained use, for example) or that people who had stopped smoking (possibly some with e-cigarettes) were excluded and only continuing smokers were involved and followed up. Another big challenge for this body of research

is the wide range of type of devices and nicotine content used, so comparing them is very difficult. Future research is urgently needed that would provide the field with a standardised (or at least consistent) set of measures to allow better comparisons to be made.

In the UK e-cigarettes are currently the most popular aid to stopping smoking and services that help people quit are seeing some clients who use these devices. The third paper summarises routine Stop Smoking Service data that shows e-cigarette users who also access behavioural support have good chances of quitting, even when compared with other clients who use NRT or varenicline for example. However the numbers are very small and this pattern needs monitoring over time. The paper also includes a survey of Stop Smoking Service staff, illustrating their views on e-cigarettes. Many advisers remain very unsure about these devices and hesitant to engage with clients about them. In the next few weeks, we are expecting a briefing paper from the National Centre for Smoking Cessation and Training which will provide practical advice to staff regarding what they can say and what we know about e-cigarettes. We'll provide a link to this briefing in a future bulletin.

The last two papers examine the controversial issue of e-cigarette marketing and flavourings. The first was an experimental study in the East of England that examined the response of 11-16 year olds to ads with flavoured or non flavoured e-cigarettes and a control group. Ads showing flavoured e-cigarettes were more appealing to participants, and media coverage of the article focused on this issue. However, the authors were careful to point out that neither set of e-cigarette adverts increased the actual appeal of using e-cigarettes. More importantly, there was no increase in the appeal of tobacco cigarettes in those shown the ads, and no increase in the participants' susceptibility to starting smoking (as measured in the study). This is consistent with the second paper, a UK wide survey of 11-16 year olds which found very low levels of reported regular use of e-cigarettes and this was only found in children who already smoked tobacco. Also participants thought e-cigarettes were, overall, harmful, but their views on harm did vary and e-cigarettes that had fruit or sweet e-liquid flavours were seen as potentially less harmful. The paper didn't compare perceptions of harm between e-cigarettes and tobacco cigarettes amongst the sample, which is an area that requires ongoing research and surveillance.

Colleagues may also be interested to read a CRUK blog which addressed science communication issues around the first two and the fourth paper in this bulletin. See http://scienceblog.cancerresearchuk.org/2016/01/20/headlines-about-e-cigarettes-dont-mean-theyre-not-safer-than-tobacco/

Other studies from the last month that you may find of interest:

- Perceptions towards electronic cigarettes for smoking cessation among Stop Smoking Service users.
- Characteristics of users, and usage of different types of electronic cigarettes: findings from an online survey.
- Exposure to Electronic Nicotine Delivery Systems (ENDS) Visual Imagery Increases Smoking Urge and Desire.
- Flavoring Chemicals in E-Cigarettes: Diacetyl, 2,3-Pentanedione, and Acetoin in a Sample of 51 Products, Including Fruit-, Candy-, and Cocktail-Flavored E-Cigarettes.
- Diffusion of Messages from an Electronic Cigarette Brand to Potential Users through Twitter.
- Nicotine and Cotinine Levels With Electronic Cigarette: A Review.
- How does electronic cigarette access affect adolescent smoking?
- Preferred flavors and reasons for e-cigarette use and discontinued use among never, current, and former smokers.
- Smokers' sources of e-cigarette awareness and risk information.

- Levels of Selected Groups of Compounds in Refill Solutions for Electronic Cigarettes.
- An Examination of Electronic Cigarette Content on Social Media: Analysis of E-Cigarette Flavor Content on Reddit.
- Patterns of Alternative Tobacco Product Use: Emergence of Hookah and E-cigarettes as Preferred Products Amongst Youth.
- Comparison of beliefs about e-cigarettes' harms and benefits among never users and ever users of e-cigarettes.
- Transdermal nicotine absorption handling e-cigarette refill liquids.
- Throat Hit in Users of the Electronic Cigarette: An Exploratory Study.
- Enjoyment and other reasons for electronic cigarette use: Results from college students in New York.
- A qualitative assessment of the perceived risks of electronic cigarette and hookah use in pregnancy.
- E-cigarette Dual Users, Exclusive Users and Perceptions of Tobacco Products.

Search strategy

The Pubmed database is searched in the middle of each month, for the previous month using the following search terms: e-cigarette*[title/abstract] OR electronic cigarette*[title/abstract] OR e-cig[title/abstract] OR (nicotine AND (vaporizer OR vapourizer OR vaporiser OR vapouriser))

Based on the titles and abstracts new studies on e-cigarettes that may be relevant to health, the UK and the UKECRF key questions are identified. Only peer-reviewed primary studies and systematic reviews are included – commentaries will not be included. Please note studies funded by the tobacco industry will be excluded.

This briefing is produced by Nicola Smith from Cancer Research UK with assistance from Professor Linda Bauld and Kathryn Angus at the University of Stirling and the UK Centre for Tobacco and Alcohol Studies, primarily for the benefit of members of the CRUK & PHE UK E-Cigarette Research Forum. If you wish to circulate to external parties, do not make any alterations to the contents and provide a full acknowledgement. Kindly note Cancer Research UK cannot be responsible for the contents once externally circulated.