On the Safety of E-cigarettes: "I can resist anything except temptation"1

Article *in* Alternatives to laboratory animals: ATLA · December 2015

Impact Factor: 1.59

2 authors:

Robert Combes

CAVENDISH CONSULTING UK

219 PUBLICATIONS **2,999** CITATIONS

SEE PROFILE

Michael Balls

University of Nottingham

501 PUBLICATIONS **5,502** CITATIONS

SEE PROFILE

Comment

On the Safety of E-cigarettes: "I can resist anything except temptation"[1]

Robert D. Combes and Michael Balls

Strategic policy decisions are being made about e-cigarettes, based on the plausibility of their greater safety, rather than on essential scientific evidence which would permit a proper risk assessment. If e-cigarettes are *really 'safer', then their use should be recommended, but only after an intelligent analysis of their risk to human health, based on integrated* in silico, in vitro *and clinical studies for both scientific and logistical reasons*

Concern Raised by Public Health England's Proposal for ECs to be Available on the NHS

In a Comment article published in the September 2015 issue of *ATLA*,[2] we expressed our concern that, although we welcomed the prospect of new tobacco-related products aimed at reducing harmful exposures, it appeared that new regulations would require that their relatively greater 'safety' would have to be established via complex testing regimes which would be heavily reliant on traditional animal procedures of doubtful relevance and reliance. We argued that, instead, the focus should be on the intelligent and integrated use of non-animal *in silico*, *in vitro* and clinical studies.

Just before our article went to press for publication, Public Health England (PHE; a UK executive agency, sponsored by the Department of Health) proposed that electronic cigarettes (ECs), a non-tobacco alternative to smoking, should be made available via the NHS (National Health Service),[3] as a means of reducing the general incidence of disease and harm attributable to conventional smoking.

We found that there was an increasingly heated debate about the safety of ECs, between those that want their use encouraged and endorsed with little delay, and others who urge caution. The PHE proposal is a classic example of the temptation of short-term gain irrespective of the possibility of long-term pain.[4] It is dangerous, because the relatively greater safety of ECs has not been scientifically established — and regrettable, because it is likely that other authorities, notably those on the other side of the Atlantic, are likely to insist on the introduction of complex testing regimes which will require animal testing, as is the case for new smoking materials.[2]

Background

PHE's proposal is a matter of concern, mainly because of the lack of safety data and the resulting inability to perform any sort of risk assessment of the type normally undertaken for consumer products, as well as doubts concerning the relevance of the data on the impact of ECs on smoking habits. In addition, our review was not specifically on ECs, as a consequence of which there is other, relevant published information on usage and safety, which needs to be considered. We now take this opportunity to elaborate on our initial response, and on our reasons for urging caution, in the light of recent developments regarding ECs, both at home and in the USA.

This issue needs to be resolved urgently, since the popularity of ECs is rapidly gaining ground, especially with young people, at the expense of tobacco smoking, largely on the assumption that ECs either lack many of the toxic constituents, contaminants and by-products to which conventional smokers are exposed, or that these substances are encountered at sufficiently low concentrations so as to cause no health problems. Moreover, an update on the situation with ECs is timely since: a) the FDA is about to be charged with responsibility for regulating ECs in the USA (http://www.fda.gov/TobaccoProducts/ Labeling/ ucm388395.htm); b) as we write, the *Third Summit on Electronic Cigarettes* has just taken place in London (http://www.e-cigarette-summit.com/); and c) the UK (via the Department of Health and the Medicines and Healthcare Products Regulatory Agency [MHRA]) has a deadline of May 2016 to complete the process of transposing into its national legislation, the EU revised Tobacco Products Directive (http://ec.europa.eu/health/ tobacco/ docs/ dir_201440_en.pdf), which came into force in May 2014.

The situation regarding ECs is also highly relevant to the Three Rs, since we have the prospect of significant levels of safety testing, some of which could involve traditional animal tests, highly invasive procedures and the use of non-human primates, to satisfy new regulatory requirements in Europe and the USA.[2] Although, after careful consideration, we believe that more information is required before ECs become incorporated into strategies for tackling the burden of disease and ill-health due to tobacco smoking, we feel that most, if not all, of the required data could be obtained in a more-timely way by implementing a strategy focused on the coordinated use of chemical, *in vitro* and clinical methods. Moreover, because the information will have largely been obtained by using organotypic tissue culture systems comprised of cells from the target tissues and species, it will be of direct relevance to assessing risk levels arising from the use of ECs.

The Controversy

Understandably, PHE's suggestion has provoked considerable discussion and controversy, while being generally welcomed by those who see ECs as a quick solution to the smoking and health problem. To illustrate the type of approach being taken by some stakeholders to address the EC issue, we quote the opening sentence of what looks like an internal report on the burdens of regulating ECs, but dated September 2013,[5] which states that: *E-cigarettes are very low risk alternatives to cigarettes, used by smokers as a pleasurable way of taking the relatively harmless recreational drug, nicotine*. However, we were unable to find any evidence, or citations to original articles presenting toxicity data, in support of such a potentially far-reaching statement by the authors in their 26-page document, which, essentially, urges the UK Government to resist being overburdened with EU regulations for ECs — requirements which, in the authors' opinion, are unnecessary, because they could delay the take-up of ECs by the public. The authors qualify the risk level, by claiming it is 'very low', again without any reference to quantitative hazard data — most extraordinary!

In direct contradiction, and two years following publication of that statement, our in-depth appraisal[2] of the use, safety assessment and regulatory control of tobacco-related products in general, including ECs, leads us to believe that, whatever the long-term consequences of any such policy, or however worthy the ultimate objective of PHE may be, it is, *in the light of current knowledge*, a reckless and irresponsible suggestion.

Poor Reporting

PHE's justification for its proposal relies heavily on two reports which it commissioned, and which were not peer-reviewed.[6,7] It ignores the possibilities that users might be repeatedly exposed to hitherto undetected contaminants and by-products, as well as to carcinogenic chemicals, or their precursors (which have been detected in solvent extracts and vapours, and which are derived from tobacco during solvent extraction or generated during solvent heating), that can have effects at very low dose levels, following repeat exposures, which can occur without clear threshold doses, thus necessitating zero-dose extrapolation.[8] Also, the PHE report contains information on the likely adoption and use of e-cigarettes by existing and potential smokers that could be of questionable relevance to the UK. This is because this information is derived from experience in other countries, with differing attitudes to smoking, or it applies to other tobacco-related products that are used mainly elsewhere, or it is conflicting, or merely circumstantial.

On comparing our Comment[2] with the PHE document, as well as looking at data that were published before the document was released, we have found that some key references are missing from it, or have been selectively covered, with the omission of some important information. For example, we have previously discussed evidence of the presence in vapours of some tobacco-specific nitrosamines (TSNAs), but the PHE report, which included the same reference,[9] omitted any mention of the analytical data for such chemicals. There are several other reports of the detection of TSNAs in ECs,[10,11] but there is no discussion in the PHE report of the potential role of such contaminants, some of which are highly-potent genotoxins[12] in the aetiology of lung cancer. In fact, cancer is not specifically mentioned anywhere in relation to safety, and there is no record of published reports of exposure to additional substances, such as nanoparticles (NPs) derived from metals[13] (also see Combes and Balls[2]). NPs, together with certain other chemicals, have been linked to respiratory sensitisation and mechanistically-related diseases, such as chronic obstructive pulmonary disease. Sensitisation is another endpoint for which clear thresholds for induction doses are difficult to identify.[14] This might be because they do not exist, as with genotoxins, or because of technical deficiencies, but either way, this complicates risk assessment.

The omission by PHE of several key papers and information from a report that was intended to be used to determine public health policy on the basis of the evidence available, is completely inexcusable. This is especially the case, as the above facts combined suggest that there is a tangible, and, at

present, unquantifiable, risk that repeated and prolonged exposure to even low doses of such chemicals, as would be expected to occur as a result of using ECs, could be sufficient to trigger cellular changes eventually culminating in serious conditions, sometimes not manifested until some considerable time following the onset of exposure.

With regard to the possibility of the presence of undetected chemicals, some of which could be toxic, it is worth noting that very few of the analytical methods in use have been validated for the purpose in question, which could, in part, explain the relatively high levels of variation seen between EC brands, and which also could account for the variation experienced within experiments.

The PHE report also fails to mention one of the main findings of the earlier investigations into the safety of ECs, namely, that different brands can vary substantially in the levels of contaminants, by-products and active components (e.g. nicotine), such that there is an urgent need for more harmonisation of the different products available.[3]

A reminder of how difficult it can be to predict the adverse effects of complex mixtures, such as EC aerosols and liquids, is provided by a recent study[15] on the potential modulating influence of nicotyrine, a product present in tobacco which also arises in EC fluids as a result of slow oxidation of nicotine. This chemical is an inhibitor of cytochrome (CYP) isozymes (CYP P450 mixed function oxidases), which clear nicotine from the body and are active in both hepatic and extrahepatic systems. The authors noted that the metabolism of all of the substrates of the respective isozymes will be affected by nicotyrine. It so happens that one of these substrates is the TSNA, nitrosamine 4-(methylnitrosamino)-1-(3-pyridyl)-1-butanone (NNK),[12] one of the most potent of the known lung carcinogens in tobacco smoke. This substance is activated in airway cells, both *in vitro* and *in vivo*, by CYP2A13,[12] suggesting a potential anti-carcinogenic effect of nicotyrine, at least for this particular mechanistic pathway.

Neither our Comment,[2] nor the PHE report, referred to a review, published in April 2014, on the toxicity of ECs.[16] The authors of this review concluded that: *The available evidence suggests that these products are by far a less harmful alternative to smoking and significant health benefits are expected in smokers who switch from tobacco to electronic cigarettes.* However, while this seems to be good news, the authors admitted that only very few toxicological studies were available to them. Also missing from the PHE report is reference to an unpublished, but comprehensive 19-page document, available on the Internet,[17] which summarises various aspects of ECs, including safety issues.

The PHE report went considerably further than merely saying that ECs are safer than conventional smoking, by providing a quantitative estimate of the extent of this alleged greater safety. It claimed that ECs are up to 95% safer than conventional smoking, and that: *Best estimates show e-cigarettes are 95% less harmful to your health than normal cigarettes, and when supported by a smoking cessation service, help most smokers to quit tobacco altogether*. Later on, the report states that: *Acknowledging that the evidence base on overall and relative risks of EC in comparison with smoking was still developing, experts recently identified them as having around 4% of the relative harm of cigarettes overall (including social harm) and 5% of the harm to users.*

Misuse of Information

While these two statements are not referenced, it emerges later in the report that they are based on the outcome of a multi-criteria decision analysis (MCDA) study, in which a small group of experts considered the harms to human health and well-being posed by using a wide range of tobacco products.[18] Each product was ranked on a scale which put cigarette smoking top at almost 100% for several properties, including addiction and cancer. The authors stated that: *Within the tobacco products there was a gradual reduction in harm from water pipe, smokeless unrefined, smokeless refined to snus that has 5% of MRH. Among the purer non-tobacco vehicle products ENDS were rated to have only 4% of MRH and for the even purer NRTs the MRH was only rated at about 2%.* [where ENDS = electronic nicotine delivery systems; MRH = maximum relative harm; and NRTs = pharmacological replacement products.]

PHE then used the outcome of this study, as if it were equivalent to experimental data, to derive the 95% figure. Apart from being baffled by how any quantitative risk assessment can be made with the paucity of available hazard data, we are uncertain as to how to interpret the intended meaning of such a statement, other than by concluding that PHE believes that ECs are almost twice as safe as tobacco smoking. The quantification of risk in toxicology, although not a precise process by any means, implies some greater confidence in a particular prediction than is conveyed by a mere qualitative statement, and it has to be derived from detailed quantitative hazard data. However, in this case, the information was merely generated by an *ad hoc* group of experts, and was based on opinions, rather than being grounded in scientific observation.

Moreover, there are many difficulties with the MCDA approach in general, and in particular, with the above application of it.[2,19] This implies that the validity of its outcome is very questionable, being dependent on the amount and rele-

vance of pre-existing information, subject to much value judgement, and difficult to reproduce with a different set of experts, and with the same ill-defined criteria used to assess relative harm. We also noted one inescapable problem, which relates to the large bias in the overwhelming amount of available data on cigarette smoking compared to that on ECs. It is difficult to see how such an imbalance could be compensated for in practice, but it greatly complicates any comparison of the two types of products. The results from an MCDA study should be used only for what they are, that is, *predictions*, rather than as novel experimental data, which they certainly are not. MCDA is part of the analysis of evidence, rather than being an additional source of evidence *per se*.

Another UK study, investigating the perception of relative harm from the use of ECs,[20] involved recording the views of cohorts of smokers and ex-smokers given ECs, and involved standard statistical methods to estimate changes in perception over a three-year period. It was found that the proportion perceiving ECs to be less harmful than cigarettes decreased significantly over the period 2013 to 2014. Unsurprisingly, a major preliminary conclusion of the study was that: *Clear information on the relative harm of cigarettes and e-cigarettes is needed*. Another human study, a randomised controlled trial,[21] found that ECs, with or without nicotine, were only moderately good at assisting smokers to quit. The authors noted that: *Uncertainty exists about the place of e-cigarettes in tobacco control, and more research is urgently needed to clearly establish their overall benefits and harms.*

Like McKee and Capewell,[22] we doubt that the 95% figure can be given any scientific credibility, mainly due to the way in which it was derived. We go further, in saying that the statement is misguided and misleading. It is tempting to even suspect that the latter was used intentionally, as intimated by Kirby,[23] who summed up the situation well, if somewhat rather benevolently, thus: *While the PHE report contains many caveats, albeit subtle and largely missing from the media coverage, it has uniformly adopted the most favourable interpretation of the very limited evidence, rejecting the precautionary principle.*

In response to criticism of the 95% figure,[24] Professor John Britton (chair of the Royal College of Physicians Tobacco Advisory Group and co-chair of the PHE Tobacco Control Implementation Board, and also a co-author of one of the reports on ECs that was commissioned by PHE), suggested that, rather than dwell on an exact percentage figure, the real point is that ECs are substantially safer than tobacco smoking.[25] This begs the following question: If the 95% figure is not meant to be interpreted literally, why include it in the report, unless the aim was to have a headline for gaining publicity, with a view to persuading us all to accept the proposal without further questioning? However, in truth, as we have argued above, there is no *evidence* for the 95% estimate. Moreover, doubts have been expressed about the integrity and objectiveness of the MCDA study, due to the alleged conflicts of interest of some of its authors.[26] Unfortunately, little further information is available, and this fact, together with the other general drawbacks of implementing MCDA, discussed earlier, suggest that extreme caution should be exercised when considering the outcome. A similar issue with conflict of interest was encountered by Pisinger and Døssing,[27] when they found the problem to have arisen in some 34% of the 76 studies relating to EC safety that they reviewed. These authors could draw no firm conclusions from the information, due to high levels of data inconsistency, but they did state that: *Electronic cigarettes can hardly be considered harmless.* This study, incidentally, is yet another key publication missing from the PHE document.

What is Needed is a Role for Alternative Methods

Predictably, few, if any, of the small number of toxicity studies that have been published to date consist of medium-term to long-term investigations. The issue of chronic toxicity due to vaping has been noted by others, including, for example, Rowell and Tarran,[28] who recently discussed the lack of data relating to the ability of chronic exposures to ECs to induce serious lung disease. The need to take into account long-term consequences of EC use also applies to efficacy as well as safety, as Unger notes in a recent editorial: *Longitudinal studies are not yet available to assess the long term effects of e-cigarettes on health or their usefulness as a cessation tool*.[29] Some four years ago, Etter *et al.*[30] stated that ECs had not been adequately tested for safety or efficacy, and the situation has not altered very much since then. Until further studies of high quality and integrity are conducted, the marketing of ECs poses unknown health and safety concerns, particularly because the products available are extremely diverse, many of them on the market are not regulated, and no oversight of quality control is in operation.

While we understand that there is an urgent need to have more safety information, we believe that there is a better way of obtaining it than having several individuals sitting at a table trying to predict the harms of these products, when they have very little reliable information on which to base their decisions. Instead, we suggest the strategy which we have outlined previously,[2] involving an intelligent, integrated testing scheme, comprised mainly of chemical analysis, *in vitro*

methodologies and human/clinical studies. Such an approach would also expedite testing, particularly since traditional *in vivo* methods are often lengthy and their relevance and reliability are highly questionable.

The numbers of publications on *in vitro* studies with EC vapours are increasing (http://www.ashscotland.org.uk/what-we-do/supply-information-about-tobacco-and-health/tobacco-related-research/research-2015/e-cigarettes-2015/). In general, the data are promising, in that, for example, one paper[31] shows that several vapours exhibit substantially less activity in cytotoxicity testing and in a range of genotoxicity assays, compared with that exhibited by cigarette smoke. Other, more-recent studies, one involving the MatTek™ epithelial airway model, confirm the substantially lower cytotoxicity of vapours, and also demonstrate that this applies to airway cells in culture[32] (http://vaperanks.com/big-tobacco-study-claims-e-cigarette-vapor-is-as-harmless-to-human-airway-tissue-as-plain-air/).

However, while all this is encouraging, a glance at the Vape Ranks website (presenting news on ECs, rankings and reviews [www.http://vaperanks.com/]) shows that there is no shortage of other reports which raise legitimate safety concerns relating to ECs, that warrant further investigation. Among such reports are an increasing number of cases where ECs are being used to 'smoke' marijuana, a potentially worrying development (see, for example, Murphy[33]). Some of the investigations conducted *in vitro* also suggest that acute toxic effects could be caused by vaping. For example, a study in which cultures of human gingival fibroblasts were exposed to nicotine-containing or nicotine-free EC fluids, increased the production of reactive oxygen species (ROS) after 24 hours, along with an elevated expression of the *Bax* gene (an early indicator of apoptosis), followed by apoptosis itself, after 48 hours of exposure.[34] The authors concluded that such exposures could lead to periodontitis, but, in addition, the induction of such cellular changes could presage other, more-serious long-term toxicity.

An important part of the integrated testing strategy that we have proposed, involves human clinical studies, which have been undertaken for both efficacy and safety testing (the latter uniquely possible with tobacco and tobacco-related products, at an early stage), rather than following extensive preclinical testing, as with pharmaceuticals (see Combes and Balls[2]). Encouraging results were obtained in some of the first human studies (reviewed in Caponnetto *et al.*[35]), with high levels of tolerance and acceptance of the new products by existing smokers and non-smokers, as well as low incidences of side-effects or of overt signs of toxicity.

However, some subsequent studies have revealed several potential effects which cause concern. One example is an investigation[36] with smokers and non-smokers that involved monitoring changes in plasma nicotine and carbon monoxide (CO) concentration, and heart rate. One brand of ECs increased each of these parameters within the first five minutes of administration, an example of an acute adverse effect caused by vaping. Other evidence that ECs can exert acute effects on users, following brief exposures, was clearly demonstrated in a clinical study,[37] in which: a) non-smokers, using an EC for ten minutes, experienced elevated airway resistance; b) current regular smokers exhibited a significant rise in airway resistance after using an EC for ten minutes; and c) neither COPD nor asthma patients were affected (www.medicalnewstoday.com/articles/ 249784.php). In a blog, Phillips has questioned the relevance of these results.[38] However, although chemicals causing this effect may not elicit an immune response, the changes seen serve as biomarkers of lung exposure and of changes therein that could result in serious health consequences.

Another investigation, still ongoing, involves cohorts of smokers and non-smokers. At the 12-month stage, the results suggest that vaping has little effect on helping smokers to quit.[39] However, the trial is not scheduled to be completed until 2019. It is monitoring self-reported side-effects, and, hopefully, will include an assessment of biomarkers of disease and toxicity.

Nowhere are conflicting views regarding the safety of ECs more sharply delineated than by the different approaches to their use and regulation that are emerging in markets on either side of the Atlantic (reviewed in Combes and Balls[2]). On the one hand, in the UK, some Government agencies appear too ready to approve and promote the use of such products, without going through the necessary standard checks and balances, while, on the other hand, in the USA, the FDA is about to take over the regulation of ECs by subjecting them to a rigorous and formal assessment.

It was on 25 April 2014 that the FDA published a proposed rule, *Deeming Tobacco Products to be Subject to the Federal Food, Drug, and Cosmetic Act*. The period between then and now has been taken up by: a) a 75-day public comment period, which ended on 9 July 2014; b) an extension of the public comment period by 30 days, taking us to 8 August 2014; c) an unknown time delay for consideration and decision by the Agency of additional requests to extend the comment period a second time (which was not granted); and d) the analysis of comments (undisclosed time). Despite these delays, the question concerning the FDA's regulation of ECs is 'when', rather than 'if'. The latest information we can find is an entry in *The Hill* (the website presenting news of US Congress activities) in May 2015, where it is reported that Senator

Richard Blumenthal (D-Conn.) is giving the FDA until the end of the summer 2015 to finalise its deeming regulations for all tobacco products, including ECs and cigars (http://thehill.com/regulation/242125-fda-has-summer-to-finalize-tobacco-deeming-regs-sen-dem-says).

Once the FDA assumes responsibility for ECs for recreational use (it already regulates such products intended for therapeutic purposes), its approach to ECs would appear to be clear from its website (http://www.fda.gov/NewsEvents/PublicHealthFocus/ucm172906.htm). This states that: *E-cigarettes have not been fully studied, so consumers currently don't know: the potential risks of e-cigarettes when used as intended; how much nicotine or other potentially harmful chemicals are being inhaled during use, or whether there are any benefits associated with using these products. Additionally, it is not known whether e-cigarettes may lead young people to try other tobacco products, including conventional cigarettes, which are known to cause disease and lead to premature death.*

This viewpoint is essentially one that we share, and, although we are not in favour of testing just for the sake of it, we fervently believe that it is very simplistic and premature, at this time, to base important public health decisions of the sort currently being proposed by PHE, on inadequate evidence of safety and/or potentially irrelevant and unreliable extrapolation. On the other hand, while we concur with FDA's overall assessment of the situation regarding ECs, we take issue with the way in which the Agency intends to regulate tobacco-related products, especially via the use of the substantial equivalence concept.[2] In addition, our views on the availability of data are shared by other organisations, notably the American Association for Cancer Research and the American Society of Clinical Oncology,[40] and the BMA.[41]

The official EU position on ECs is not clear at this time. The revised EU Directive on the marketing and use of tobacco products merely requires that manufacturers take responsibility for the safety of such products. However, we understand that, in the UK, once the Directive has been transposed into UK legislation, a process that will be facilitated by the Department of Health, the MHRA will become the competent authority (Dr Ian Hudson, personal communication, 2015) for ECs intended for medicinal purposes, which include quitting smoking. Accordingly, the MHRA will regulate such products in the same way that it does medicines. Indeed, the MHRA website has now documented data requirements for ECs (http://www.mhra.gov.uk/home/groups/commsic/documents/websiteresources/con454361.pdf), where it is stated (for preclinical studies) that: *The potential transformation of the formulation on thermal decomposition, and the potential for the heating element and associated components (including adhesives and solder) to shed metallic and other particles on heating, would warrant further investigation by the applicant to assess the inhalation safety risks and to limit exposure where necessary. In addition, the applicant should provide a detailed safety review of all the components in the formulation from the available literature; in particular a review of the safety following inhalation exposure (including long-term exposure) would be relevant. A comprehensive evaluation of the potential extractables and leachables originating from all components of the electronic cigarette should also be provided, with associated toxicological review.* For clinical studies, for some unaccountable reason, the focus is on the levels of nicotine in the body and its pharmacodynamics, to ensure that endogenous levels do not exceed maximum safe levels. We feel that this represents a missed great opportunity for undertaking biomarker and biomonitoring safety studies on vapours in the clinical setting, as we have explained in more detail elsewhere.[2]

How these regulations are going to be applied in practice after the various stakeholders and pressure groups, including the tobacco industry, have argued their various standpoints remains to be seen. However, if the MHRA sticks to its procedures and requirements for new medicines, it should be the case that: a) if the supporting toxicological data are deemed relevant and suitable, there will be no need for further testing and/or review; and b) where this is not so, or where data are missing, such information would have to be obtained by toxicity testing, according to International Conference on Harmonisation (ICH)-approved regulatory test methods for new medicinal products. Whether any products currently on the market will receive exemption is a matter of conjecture at this time. Therefore, we are now confronted by a ludicrous situation, whereby two UK Government authorities, the MHRA and PHE, both with the responsibility for safeguarding public health, are giving out different messages — the former has the remit of controlling the sale of the ECs according to international regulatory requirements, while the latter endorses the use of ECs now. Furthermore, the PHE report and its associated documents can be downloaded from the MHRA website — no wonder there is so much confusion!

Some notes on the presentations given at the Third E-Cigarette Summit, have been posted on the web (http://www.ecigarettedirect.co.uk/ashtray-blog/wp-content/uploads/2015/11/E-Cig-Summit-3-PDF.pdf). The notes provide a preliminary impression that the debate shows no signs of letting up, although it would appear that there is a growing admission among the protagonists that ECs are not harmless, and, among those looking at health

effects, that they are probably safer than smoking, but by how much it is difficult to tell. Perhaps we could be heading in the right direction, after all. We should get a better idea once the presentations have been uploaded to the resources section of the summit's website.

Concluding Comments

We are puzzled by: a) why there is such a gulf between the UK and the USA in approaches to regulating ECs; and, more importantly, b) why the fundamentals of toxicology, underpinning public health and safety, involving hazard identification and risk assessment,[42] seem to have been ignored by PHE, and are being overlooked in the ongoing debate by a growing number of stakeholders and so-called experts, when the same are usually so rigorously applied to other consumer products.

Calls endorsing the wider usage of ECs are being driven by two main factors, both of which cannot be supported on scientific grounds: a) an understandable, but misguided, wish for having a quick fix for the major health problems associated with smoking; and b) a mistaken belief that there is no need to test complex mixtures, such as EC liquids and vapours, when the levels of ingredients, whose presence and contribution to toxicity are known, are at very low concentrations. If this were possible, most of toxicology would now merely consist of chemical analysis of test samples, except in rare cases where the threshold of regulation concept[43] can legitimately be applied — for example, when synergistic or antagonistic effects between constituents can be accommodated.

One way in which risk assessment can be approached is to derive likely exposure levels from analytical data on the constituents of vapours and compare them with recommended maximum allowable daily intake figures for humans, obtained from safety tests. However, since most of the information relates to data obtained under laboratory conditions, mainly with rodents, sometimes involving different routes of exposure, it has to be extrapolated and scaled up to be relevant to human populations, and adjusted to provide for an extra margin of safety. Moreover, predicting exposure levels is confounded by individual differences in the way in which ECs are used, the extent to which they are used, the differences in design and composition of ECs, the degree of vapour inhalation, and variation in the biotransformation of inhaled constituents, and also by the possible endogenous generation of more TSNAs from vaped nicotine.[44]

It has been noted elsewhere (http://www.tobacco.ucsf.edu/9-chemicals-identified-so-far-e-cig-vapor-are-california-prop-65-list-carcinogens-and-reproductive-t) that nine constituents variously found in EC fluids and/or aerosols, are listed by the Environmental Protection Agency (EPA) of the US State of California as being of concern with regard to human safety, as part of the Agency's drive to improve and simplify the regulation of environmental chemicals. These chemicals are: acetaldehyde, cadmium, formaldehyde, isoprene, lead, nickel, nicotine, N-nitrosonornicotine (NNN) and toluene. NNN is widely considered to be a carcinogen in tobacco smoke. As a worse-case scenario, we have taken the threshold value of concern for this chemical (which the EPA has identified from rodent carcinogenicity studies, after adjustments for species and test system extrapolation), to have a NSRL (non-significant risk level) of 0.5μg/day (NSRL is the level of exposure that would result in no more than one excess case of cancer in 100,000 individuals exposed to the chemical). We have compared this figure with the amount of NNN that different ECs users might be expected to be exposed to, based on the maximum levels of chemical reported in Gureckis and Love,[4] which is 4.3μg/150 puffs (equivalent to 14.3μg/day for a user taking 500 puffs/day). As the respective NSRL value is 0.5μg/day, the expected exposure under these conditions exceeds the level of concern by almost 30-fold. Presumably, such a result would raise the possibility that ECs with similar constituent profiles could prompt the EPA in California to require appropriate product labelling as a precondition for marketing approval. We stress, however, that these are preliminary data, subject to several uncertainties, not the least of which are vaping behaviour and individual susceptibility, and we plan to investigate risk assessment in more detail for more ECs, and also for other risk assessment methods, such as the Margin of Exposure (see Hahn *et al.*[45]).

The more and more we read, the more convinced we are that the whole debate about ECs is premature, and would not be happening with other, equally dangerous consumer products, in the absence of powerful lobbying on behalf of industry. The title of the PHE report includes the phrase *...foundation for evidence-based policy and practice.* This sounds great, until one realises that the foundation is very weak indeed, having been built on sand, in the words of McKee and Capewell,[22] and that the evidence used was incomplete, conflicting, and used selectively. It is crucial that these new types of products are labelled appropriately and accurately, not only with regard to their benefits, but also with appropriate and proportionate warnings of any hazards to which users may be exposed. This will only be possible after there has been a full and scientifically-sound investigation of the toxicity of these products.

We seem to be living in a world now where the term *evidence-based* increasingly seems to be being used to imply some new revelatory approach to

scientific activity that guarantees high quality. We have 'evidence-based medicine' and, more-recently, 'evidence-based toxicology', and now: 'evidence-based public health' and 'evidence-based regulation'. But, in truth, of course, *evidence-based* is not a new concept, nor is it a panacea for quality — any thorough scientific piece of work is only as good as the evidence on which it is based. What does appear to be new is the attempt to use the phrase as a smokescreen for sub-standard scientific investigation, otherwise there would be no need to use it at all!

We leave the last word to the British Heart Foundation (BHF), by quoting from a booklet entitled *10 Minutes to Change Your Life — Time to Quit*, which is available in its high-street charity shops or from its website (https://www.bhf.org.uk/~/media/files/publications/smoking/g925_time_to_quit_01_14_booklet_chart.pdf). This states that: *E-cigarettes allow you to breathe in nicotine vapour. Unlike tobacco smoke, this nicotine [vapour] doesn't contain many of the chemicals that cause cancer and heart disease. But scientists don't know yet if e-cigarettes can help you quit or if they cause any long-term damage to your health.*

Simple, clear, informative and correct — this is where the debate needs to start and it is why the temptation for a quick fix to the smoking issue must be resisted!

Author for correspondence:
Robert D. Combes
Independent Consultant
Norwich
UK
E-mail: robert_combes3@yahoo.co.uk

Michael Balls
c/o FRAME
Russell & Burch House
96–98 North Sherwood Street
Nottingham NG1 4EE
UK

References and Notes

1 Wilde, O. (1892). A quotation from *Lady Windermere's Fan*, a play first performed in 1892 and first published in written form in 1893.

2 Combes, R.D. & Balls, M. (2015). A critical assessment of the scientific basis, and implementation, of regulations for the safety assessment and marketing of innovative tobacco-related products. *ATLA* **43**, 251–290.

3 Anon. (2015). *E-cigarettes: A new foundation for evidence-based policy and practice,* 6pp. Available at: https://www.gov.uk/government/uploads/system/uploads/attachment_data/file/454517/Ecigarettes_a_firm_foundation_for_evidence_based_policy_and_practice.pdf (Accessed 19.08.15).

4 Gureckis, T.M. & Love, B.C. (2009). Short term gains, long term pains: How cues about state aid learning in dynamic environments. *Cognition* **113**, 293–313.

5 Bates, C. & Stimson, G. (2013). *Costs and Burdens of Medicines Regulation for e-Cigarettes. A Report: 20 September 2013*, 26pp. Available at: http://www.e-cigarette-summit.com/files/2014/07/Impacts-of-medicines-regulation-V4-22-09-2013.pdf (Accessed 06.11.15).

6 McNeill, A., Brose, L.S., Calder, R., Hitchman, S.C., Hajek, P. & McRobbie, H. (2015). *E-cigarettes: An evidence update. A report commissioned by Public Health England*, 113pp. London, UK: Public Health England. Available at: https://www.gov.uk/government/uploads/system/uploads/attachment_data/file/457102/Ecigarettes_an_evidence_update_A_report_commissioned_by_Public_Health_England_FINL.pdf (Accessed 07.11.15).

7 Britton, J. & Bogdanovica, I. (2014). *Electronic Cigarettes. A report commissioned by Public Health England*, 30pp. London, UK: Public Health England. Available at: https://www.gov.uk/government/uploads/system/uploads/attachment_data/file/311887/Ecigarettes_report.pdf (Accessed 07.11.15).

8 Hengstler, J.G., Bogdanffy, M.S., Bolt, H.M. & Oesch, F. (2002). Challenging dogma: Thresholds for genotoxic carcinogens? The case of vinyl acetate. *Annual Reviews of Pharmacology* **43**, 485–520.

9 Cheng, T. (2014). Chemical evaluation of electronic cigarettes. *Tobacco Control* **23**, Suppl. ii, 11–17.

10 Williams, M. (2013). *Electronic cigarette liquids and vapors: Is it harmless water vapor?* Webinar presentation. Available at: http://www.trdrp.org/files/e-cigarettes/williams-slides.pdf (Accessed 07.11.15).

11 Kim, H.J. & Shin, H.S. (2013). Determination of tobacco-specific nitrosamines in replacement liquids of electronic cigarettes by liquid chromatography–tandem mass spectrometry. *Journal of Chromatography A* **1291**, 48–55.

12 Akopyan, G. & Bonavida, B. (2006). Understanding tobacco smoke carcinogen NNK and lung tumorigenesis. *International Journal of Oncology* **29**, 745–752.

13 Neuberger, M. (2015). The electronic cigarette: A wolf in sheep's clothing. *Wiener Klinische Wochenschrift, Central European Journal of Medicine,* doi: 10.1007/s00508-015-0753-3. Available at: http://www.forte.or.at/download.php?id=1725 (Accessed 06.11.15).

14 Cochrane, S.A., Arts, J.H.E., Ehnes, C., Hindle, S., Heli, M., Hollnagel, S.H.M., Poole, A. Suto, H. & Kimber, I. (2015). Thresholds in chemical respiratory sensitisation. *Toxicology* **333**, 179–194.

15 Megaraj, V., Zhou, X., Xie, F., Liu, Z., Yang, W. & Ding, X. (2014). Role of CYP2A13 in the bioactivation and lung tumorigenicity of the tobacco-specific lung procarcinogen 4-(methylnitrosamino)-1-(3-pyridyl)-1-butanone: *In vivo* studies using a CYP2A13-humanised mouse model. *Carcinogenesis* **35**, 131–137.

16 Farsalinos, K.E., & Polosa, R. (2014). Safety evaluation and risk assessment of electronic cigarettes as tobacco cigarette substitutes: A systematic review. *Therapeutic Advances in Drug Safety* **5**, 67–86.

17 Gardiner, P. (2013). *E-Cigarettes: The Vapor This Time?* 18pp. Available at: www.trdrp.org/files/e-cigarettes/e-cigarettes-the-vapor-this-time.pdf (Accessed 07.11.15).

18 Nutt, D.J., Phillips, L.D., Balfour, D., Curran, H.V., Dockrell, J.M., Foulds, J., Fagerstrom, K., Letlape, K., Milton, A., Polosa, R., Ramsey, J. & Sweanor, D. (2014). Estimating the harms of nicotine-containing products using the MCDA approach. *European*

Addiction Research **20**, 218–225.

[19] Kujawski, E. (2002). *Multi-criteria decision analysis: Limitations, pitfalls, and practical difficulties*, 9pp. Berkeley, CA, USA: eScholarship, University of California. Available at: http://escholarship.org/uc/item/0cp6j7sj (Accessed 07.11.15).

[20] Brose, L.S., Brown, J., Hitchman, S.C. & McNeill, A. (2015). Perceived relative harm of electronic cigarettes over time and impact on subsequent use. A survey with 1-year and 2-year follow-ups. *Drug & Alcohol Dependence* **157**, 106–111.

[21] Bullen, C., Howe, C., Laugesen, M., McRobbie, H., Parag, V., Williman, J. & Walker, N. (2013). Electronic cigarettes for smoking cessation: A randomised controlled trial. *The Lancet* **382**, 1629–1637.

[22] McKee, M. & Capewell, S. (2015). Evidence about electronic cigarettes: A foundation built on rock or sand? *BMJ* **351**, h4863.

[23] Kirby, T. (2015). E-cigarettes declared 95% less harmful than tobacco by UK health body. *The Lancet Respiratory Medicine* **3**, 750–751.

[24] Culpan, D. (2015). *E-cigarettes 'safer than tobacco' study faces Lancet criticism*. Wired.co.uk, 4 September 2015. Available at: http://www.wired.co.uk/news/archive/2015-09/04/e-cigarette-report-criticised-the-lancet (Accessed 07.11.15).

[25] Britton, J. (2015). E-cigarettes, Public Health England, and common sense. *The Lancet* **386**, 1238–1239.

[26] Knapton, S. (2015). *E-cigarette 'safety' study was written by industry funded scientists, Lancet warns*. The Telegraph, Science News, 28 August 2015. Available at: http://www.telegraph.co.uk/news/science/science-news/11830029/E-cigarette-safety-study-was-written-by-industry-funded-scientists-Lancet-warns.html (Accessed 07.11.15).

[27] Pisinger, C. & Døssing, M. (2014). A systematic review of health effects of electronic cigarettes. *Preventive Medicine* **69**, 248–260.

[28] Rowell, T.R. & Tarran, R.A. (2015). Will chronic e-Cigarette use cause lung disease? *American Journal of Physiology — Lung Cellular & Molecular Physiology*, doi: 10.1152/ajplung.00272.2015. [E-pub ahead of print.]

[29] Unger, J.B. (2015). E-Cigarettes: Introducing new complexities and controversies to the field of nicotine and tobacco research. *Nicotine & Tobacco Research* **17**, 1185–1186.

[30] Etter, J-F., Bullen, C., Flouris, A.D., Laugesen, M. & Eissenberg, T. (2011). Electronic nicotine delivery systems: A research agenda. *Tobacco Control* **20**, 243–248.

[31] Misra, M., Leverette, R.D., Cooper, B.T., Bennett, M.B. & Brown, S.E. (2014). Comparative *in vitro* toxicity profile of electronic and tobacco cigarettes, smokeless tobacco and nicotine replacement therapy products: E-liquids, extracts and collected aerosols. *International Journal of Environmental Research & Public Health* **11**, 11,325–11,347.

[32] Neilson, L., Mankus, C., Thorne, D., Jackson, G., DeBay, J. & Meredith, C. (2015). Development of an *in vitro* cytotoxicity model for aerosol exposure using 3D reconstructed human airway tissue; application for assessment of e-cigarette aerosol. *Toxicology in Vitro* **29**, 1952–1962.

[33] Murphy, N. (2015). *5 Marijuana Vaporizers Offering a Better, Healthier High*. The Cheat Sheet, 28 October 2015. Available at: http://www.cheatsheet.com/business/5-marijuana-vaporizers-offering-a-better-healthier-high.html/?a=viewall#ixzz3lBQ3vxHd (Accessed 06.11.15).

[34] Sancilio, S., Gallorini, M., Cataldi, A. & di Giacomo, V. (2015). Cytotoxicity and apoptosis induction by e-cigarette fluids in human gingival fibroblasts. *Clinical Oral Investigations*, 2015 Aug 4. [E-pub ahead of print.]

[35] Caponnetto, P., Campagna, D., Papale, G., Russo, C. & Polosa, R. (2012). The emerging phenomenon of electronic cigarettes. *Expert Review of Respiratory Medicine* **6**, 63–74.

[36] Vansickel, A.R., Cobb, C.O., Weaver, M.F. & Eissenberg, T.E. (2010). A clinical laboratory model for evaluating the acute effects of electronic "cigarettes": Nicotine delivery profile and cardiovascular and subjective effects. *Cancer Epidemiology, Biomarkers & Prevention* **19**, 1945.

[37] Palamidas, A., Gennimata, S.A., Kaltsakas, G., Tsikrika, S., Vakali, S., Gratziou, C. & Koulouris, N. (2014). Acute effect of an e-cigarette with and without nicotine on lung function. *Tobacco Induced Diseases* **12**, Suppl. 1, A34.

[38] Phillips, C.V. (2012). *The biomarkers lie*. Tobacco Harm Reduction Blog at WordPress.com. Available at: http://antithrlies.com/2012/09/07/the-biomarkers-lie/ (Accessed 06.11.15).

[39] Flacco, M.E., Fiore, M., La Vecchia, C., Marzuillo, C., Gualano, M.R., Liguori, G., Cicolini, G., Capasso, L., Boccia, S., Siliquini, R., Ricciardi, W., Villari, P. & Manzoli, L. (2015). Electronic cigarettes: Efficacy and safety at 12 months: Cohort study. *European Journal of Public Health* **25**, Suppl. 3, 254.

[40] Brandon, T.H., Goniewicz, M.L., Hanna, N.H., Hatsukami, D.K., Herbst, R.S., Hobin, J.A., Ostroff, J.S., Shields, P.G., Toll, B.A., Tyne, C.A., Viswanath, K. & Warren, G.W. (2015). Electronic nicotine delivery systems: A policy statement from the American Association for Cancer Research and the American Society of Oncology. *Journal of Clinical Oncology* **33**, 952–963.

[41] Anon. (2015). *Vaping needs stronger regulation, say doctors leaders*. London, UK: British Medical Association. Available at: http://bma.org.uk/news-views-analysis/news/2015/august/vaping-needs-stronger-regulation-say-doctors-leaders (Accessed 06.11.15).

[42] Combes, R., Balls, M., Illing, P., Bhogal, N., Dale, J., Duvé, G., Feron, V., Grindon, C., Gülden, M., Loizou, G., Priston, R. & Westmoreland, C. (2006). Possibilities for a new approach to chemicals risk assessment. The Report of a FRAME Workshop. *ATLA* **34**, 621–649.

[43] Combes, R.D. (1997). Defining a 'threshold of regulation' the ultimate alternative for safety assessment? *ATLA* **25**, 187–191.

[44] Sepanov, I., Carmella, S.G., Han, S., Pinto, A., Strasser, A.A., Lerman, C. & Hecht, S.S. (2009). Evidence for endogenous formation of N´-nitrosonornicotine in some long-term nicotine patch users. *Nicotine & Tobacco Research* **11**, 99–105.

[45] Hahn, J., Monakhova, Y.B., Hengen, J., Kohl-Himmelseher, M., Schussler, J., Hahn, H., Kuballa, T. & Lachenmeier, D.W. (2014). Electronic cigarettes: Overview of chemical composition and exposure estimation. *Tobacco Induced Diseases* **12**, 23.