Scientific Review Article Summary:

A comprehensive evidence review of electronic cigarettes and their role in tobacco harm reduction

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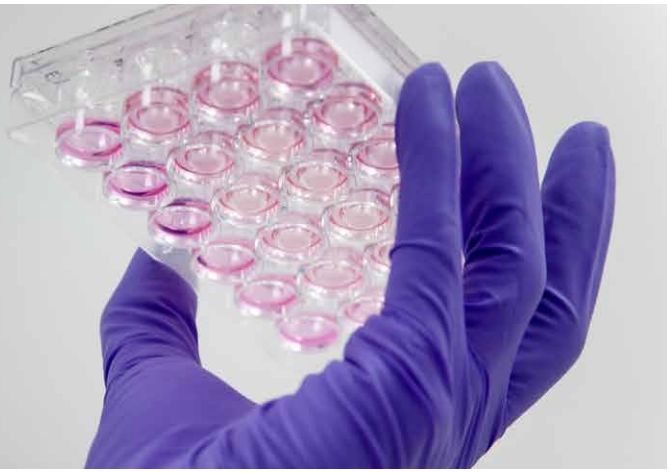
Review Summary

This is a review of over a decade's worth of data from multiple sources to understand and evaluate many different aspects of vapour products (e-cigarettes), including their design, testing, modelling, use, and effects for the entire class of such devices

> **"The review findings support the conclusions of several extensive systematic reviews[i,ii,iii] that vapour products, while addictive and not risk free, are less harmful than conventional cigarettes, and the harm reduction potential can be maximised if smokers who would otherwise continue to smoke switch to using them exclusively"**



There are two issues that will have a critical impact on the effectiveness of E-cigarettes (ECs) to displace smoking:

- The availability of well-built products that compete with conventional cigarettes by satisfying consumers through product performance, sensorial characteristics and nicotine delivery
- That public health institutions should unambiguously and accurately inform smokers about the likely reduced risk character of ECs compared with cigarettes

There are a number of important factors that could maximise the harm reduction potential of the vapour category:

- Vapour products must offer a compelling alternative to smoking in order to encourage smokers, who would otherwise continue to smoke, to switch, including flavours, while mitigating the appeal of such products to young people
- So-called gateway effect claims (that use of ECs leads to use of conventional cigarettes) are generally not supported by public data, which show the lowest levels of smoking initiation ever recorded in key markets such as the US and UK
- Regulatory strategies should promote quality in product development led by robust stewardship, which is essential to identify and eliminate, or minimise, potential hazards
- Emerging evidence in biomarkers of biological effect (those that indicate changes in the body after exposure to EC vapour) point to lower risk for most smoking-related disease endpoints, with further research required particularly for cardiovascular endpoints, where data are conflicting

This summary has been developed based on the review article "Evidence From the Scientific Assessment of Electronic Cigarettes and Their Role in Tobacco Harm Reduction" published in Contributions to Tobacco & Nicotine Research, vol.30, no.2, 2021, pp.63-108. https://doi.org/10.2478/cttr-2021-0007

Evolution of Vapour Products

ECs have been widely available for around a decade and have cycled through several generations and designs already

The aim of each new generation of devices is normally to create an **aerosol delivery system** that is more satisfying to users than the previous version

Standards of testing, manufacturer reporting, and robust testing and monitoring have also developed during this time to **enhance safety features** and prevent accidental harmful exposures (e.g., through e-liquid leaks or overheating)

The adoption of **product stewardship** by manufacturers is helping to protect consumers and provide confidence in the effectiveness and consistency of ECs. However, it is important that product stewardship is universally adopted by manufacturers

“It is important that product stewardship is universally adopted by manufacturers”

The use of Vapour Products

The review shows that the majority of EC users are former smokers who want to avoid returning to smoking, or current smokers aiming to quit or cut down cigarette consumption[iv,v]

For EC use to be successful, and replace smoking entirely, users need to achieve comparable satisfaction in nicotine delivery, use, and sensorial aspects

Satisfactory nicotine delivery is critical to the acceptability of ECs:

- Data from 1,489 current adult smokers reported they discontinued using ECs mostly because the experience was not close enough to smoking[vi]
- Later-generation EC designs have attempted to address these issues through use of higher power, improved coil heating elements, and nicotine delivery without irritation
- Results from some studies suggest that ECs are more successful than NRT in providing smokers with a satisfactory alternative to cigarettes[vii,viii]

Sensorial aspects, such as flavours (e.g., sweetness, coolness) and vapour aerosol visibility or smoothness, also play important parts in product acceptability

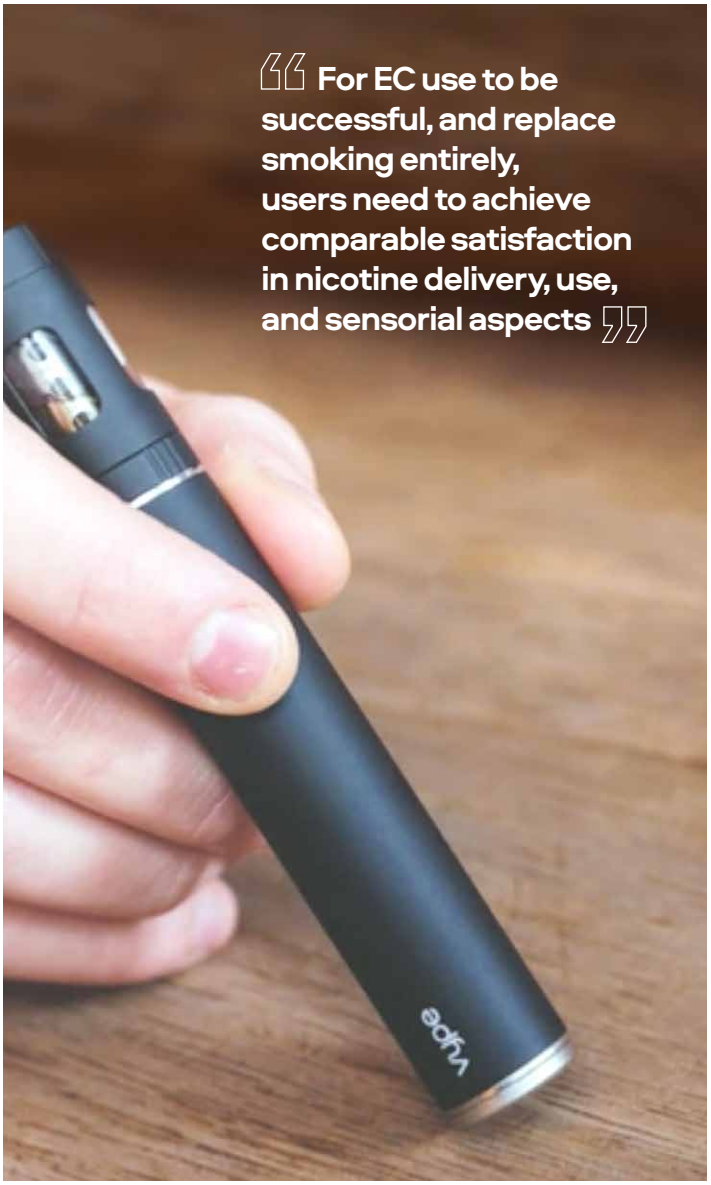
The most common reasons for smokers rejecting ECs relate to performance (mimicking smoking and effectiveness at lessening cravings for smoking) and ease of use

Contrary to some suggestions, national survey data consistently indicate an extremely low gateway effect from ECs[ix,x,xi], and that vaping does not lead to smoking or other more harmful behaviour:

Vapers without smoking history account for a very small proportion of all vapers[iv,viii]

Vaping tends to be seen in older teens who are already smokers, and does not always involve nicotine:[ii]

- Smoking initiation rates among young people in the US indicate absence of a gateway effect, with the lowest rates of smoking initiation on record in 2018 of 2.29%[xiv]. Similar patterns have been observed across European countries where ECs are widely available[xv], and are also suggested by a study commission by Health Canada[xvi]



2019 figures

50%+ of all vapers in the UK used ECs exclusively[xii]

15.8% smoking prevalence was a record low **DOWN** from 16.6% in 2018[xiii]

62.5% of vapers were former smokers. The **HIGHEST** recorded number[viii]

Cigarettes v ECs

Smoking remains one of the leading causes globally of preventable morbidity and mortality, and the World Health Organization (WHO) estimates that around 1.3 billion adults worldwide smoke[xv]

Cigarette smoke is a highly complex aerosol, containing roughly 6,500 different compounds. Some come from the ingredients and materials used, but many are created during combustion at extremely high temperatures (~900°C). Roughly 150 of these compounds are known to be toxic to the human body and to contribute to smoking-related diseases, such as cardiovascular disease, respiratory diseases and cancer, and to the increased risk of disability and death

“Cigarette smoke is a highly complex aerosol”

ECs also create an aerosol, but it arises from heating a simple e-liquid consisting mainly of propylene glycol, vegetable glycerin and flavourings, with or without nicotine. The heat in these devices reaches around 250°C, which means there is no combustion. Due to the low number of ingredients and lower heat, an EC aerosol contains substantially fewer and lower concentrations of compounds than cigarette smoke

“EC aerosol contains substantially fewer and lower concentrations of compounds than cigarette smoke”

Nicotine delivery

Use of pharmacokinetic and behavioural studies have provided insights into the relationship between nicotine concentration and specific consumer responses, including urge for product, craving, and product liking/satisfaction

In response to feedback from vapers, later-generation EC designs have attempted to improve nicotine delivery and user experience through various design and technology changes. These include greater battery power, improved heating elements (the coil) and e-liquid uptake systems (the wick), temperature control, and efficient nicotine delivery without irritation (use of nicotine salts):

- Improved coil designs, wicking materials, and power regulation reduce the risk of 'dry wicking' – the overheating of e-liquid[xiii]
- Acids added to e-liquids form nicotine salts to better mimic the smoking experience and deliver nicotine without increased irritation[xvii,xviii]

> **"EC designs have attempted to improve satisfactory nicotine delivery and user experience"**

Perceptions of risk

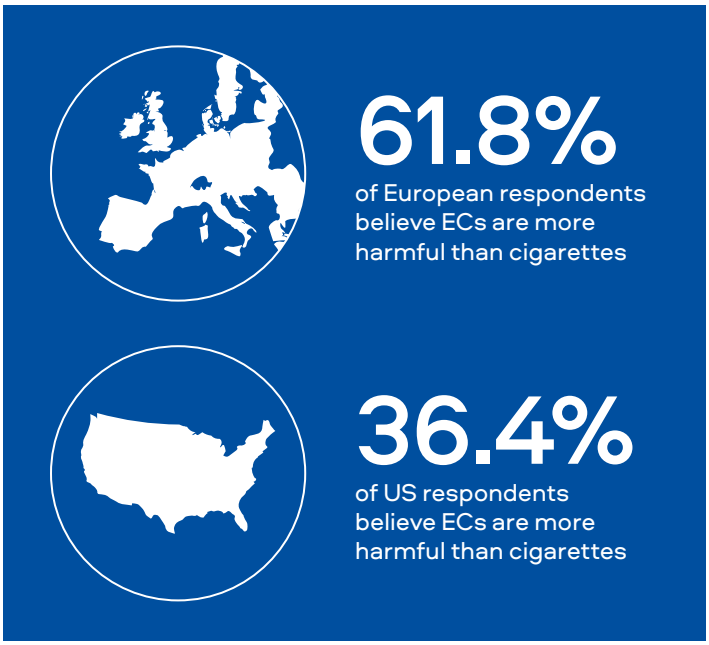
Other systematic reviews have consistently indicated the potential of ECs to offer a substantial reduction in disease risk when used as a complete substitute for continued smoking, through much lower exposure to the tobacco-related toxicants and carcinogens found in smoke

Despite these reviews indicating ECs are reduced risk compared to cigarettes, survey data indicates that consumer misperceptions are a growing reason among smokers to reject them:

- In 2018, 61.8% of survey respondents in six European countries felt that ECs were more harmful than cigarettes, compared with 58.5% in 2016[xix]
- Similarly, this response increased from 11.5% in 2012 to 36.4% in 2017 in a US survey[xx]

To drive acceptance, this critical issue must be addressed. This was reinforced by the results of a survey of smokers which revealed that those who perceived ECs to be less harmful than smoking and started vaping were more likely to be exclusive vapers after 1 year[xxi]

Other perceptions, such as social acceptability, potential to harm others, and environmental impact, may also affect product choice



Evidence & scientific studies

Epidemiological data obtained over many years is the best way to establish real-world use and impact of a substance, device, or medicine, along with the associated risks and benefits. These data are not yet available for ECs due to the short time they have been in use

> **"All available data indicate that the negative health impact of cigarettes arise from combustion, not nicotine. However, nicotine is addictive and not risk free"**

Multiple clinical studies involving vapers have been performed, but so far have been small and/or short, have had variable designs that make comparison of data difficult, and have not always included appropriate control groups (i.e., smokers, former smokers, and non-smokers):

- Most of the information on clinical effects is based on measurement of biomarkers – physiological changes that indicate exposure, risk of disease, etc
- Biomarkers of exposure show substantially lower values with EC aerosol than with cigarettes smoke and are close to those after exposure to nicotine replacement therapies
- Biomarkers of potential harm are measured to try to predict future disease risk
- The reduced risk potential is evidenced by the reversibility of biomarkers of potential harm to levels that are similar to cessation
- However, many biomarkers of potential harm are not smoking specific or even disease specific, so they must be compared with those in former and non-smokers for adequate contextualisation and evaluation of validity

Population modelling has become an important way to understand and estimate potential long-term risks because it uses big data to simulate and make projections based on a continuation of the current situation (base case/status quo) and credible alterations, such as what might happen to smoking prevalence if ECs had different levels of uptake:

- This type of modelling can assess many parameters with complex interactions simultaneously, rather than looking at one aspect of an issue at a time
- Different levels of uncertainty may also be introduced
- Most calculations so far suggest that even if a small proportion of smokers switch exclusively to vaping, millions of potentially lost life years could be avoided through direct and indirect risk reduction

Manufacture & Stewardship

Based on the current situation, the review asserts that, from first design to manufacture, ECs should undergo extensive testing, including chemical, toxicological, pharmacokinetic, and clinical studies and behavioural testing involving real users. These should address not only the device but the individual components and their potential interactions

Given the short time that ECs have been available, much of the testing and evidence reported in the literature has been compared with cigarettes. While in some situations it would be desirable to test ECs against one another, substantial differences between ECs in design, aerosol, use, and effects limit the comparison to high-level assessments of harm

Therefore, new products should be considered relative to those already on the market, and the following parameters used and enhanced:

- **Consistent assessment standards** – The review revealed many variations in measurement techniques, including puffing regime, aerosol collection, and analytical methodology, making data comparisons difficult. International standards for puffing parameters in the laboratory have been developed and published by CORESTA to facilitate assessment, despite differences in product designs and vapers' usage

- **Ingredient quality** – Despite ECs being a rapidly developing product category, responsible product stewardship ensures that manufacturers, suppliers, and sellers offer consumers products of a high standard. Some considerations that the review highlights as being important for maximum performance and safety include:

    - Nicotine should be of pharmaceutical grade purity
    - Flavourings should be food grade purity
    - Ingredients identified as causing potential harm (eg causing cancer or cellular mutations, having reproductive effect, respiratory allergens, etc) should be avoided
    - All regulatory guidance should be followed
    - Toxicological risk assessments should be performed for each e-liquid to demonstrate ingredients and concentrations in e-liquid are supportable. Bridging studies could be used to demonstrate comparability
    - Chemical and toxicological measurements of aerosol should be performed for every device and e-liquid variant. Bridging studies could be used to demonstrate comparability
    - Data from control substances and devices and air versus aerosol, including negative results, should be reported as standard

> "Chemical and toxicological measurements of aerosol should be performed for every device"

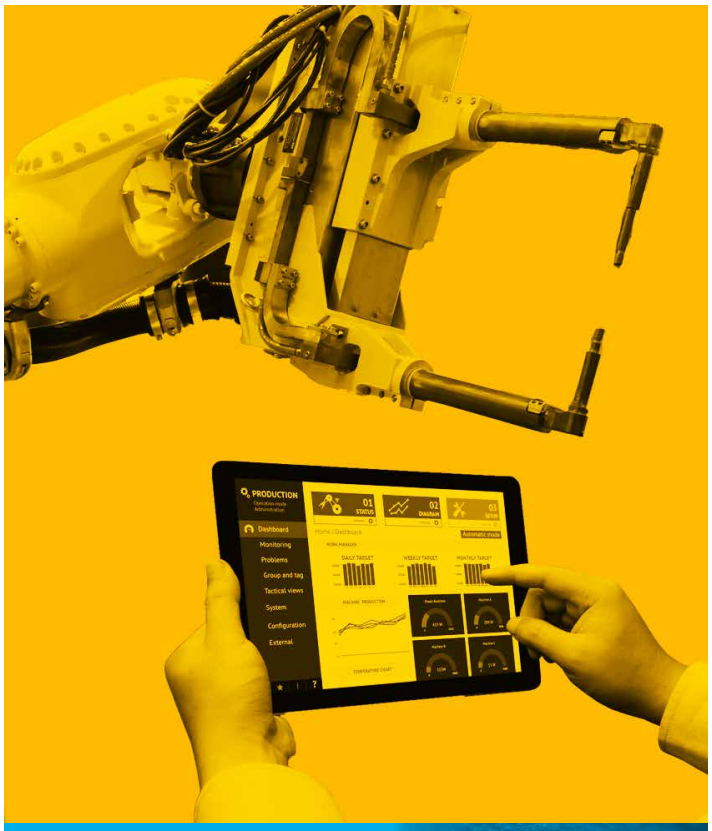
Manufacture & Stewardship

Bridging studies should be utilised. This is an established approach in pharmaceuticals allowing 'validated' data from an existing product to be applied to a new, similar product because of their direct comparability in terms of design and performance. Innovative techniques, such as high-throughput genetic assessments and cell-culture exposure, might enhance this ability:

- High-throughput assessments can help to build a picture of which genes are affected by exposures (aerosol, ingredients, etc)
- As well as specific cell types, cell culture models can closely represent part or whole tissues, such as the lung surface or skin, allowing observance of inter-related effects

Regulations are currently inconsistent between countries. Most regulations tend to consider marketing, labelling, ingredients, and/or taxation. Manufacturing is less well regulated, leading to highly variable product standards globally. However, some authorities, such as the USA Food and Drug Administration (FDA), have begun to request scientific dossiers to support the introduction of products to the market:

- Despite all the evidence supporting ECs as reduced risk products as part of a tobacco harm reduction framework, outright bans and restrictions of ECs or flavoured e-liquids continue in many countries, and others are introducing restrictions, for example on flavours, that are not supported by scientific evidence
- These restrictions or bans can result in poorly made or illegal products entering markets, which can substantially increase the risks of adverse events



Appendix

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