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Assessment of tobacco heating product THP1.0. Part 9: The placement of a range of next-generation products on an emissions continuum relative to cigarettes via pre-clinical assessment studies

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ABSTRACT

This series of nine papers described the operation and pre-clinical assessment of a tobacco heating product THP1.0. This last paper contextualises the pre-clinical assessment data on THP1.0 with data from other next generation products relative to cigarette smoke.

The tobacco and nicotine risk continuum is a concept that ranks products according to their potential harm, with cigarettes at the highest risk extreme and Nicotine Replacement Therapy at the least risky extreme. Data generated in pre-clinical studies on THP1.0 and a range of Next Generation Products (NGPs) may provide some initial indication of potential ranking of these products, although importantly, data from such studies are limited and cannot take into consideration several important aspects for risk such as long term product use patterns.

In each of the studies, the responses to the emissions from THP1.0 were substantially reduced relative to cigarette smoke. Additionally, responses from THP1.0 were very similar to those from the other NGP emissions. A comparison of the results clearly showed the emissions from all the NGPs were considerably lower than those from cigarettes and all in around the same emissions level.

These results show that THP1.0 could have the potential to be a reduced risk product compared to cigarettes, though further studies assessing the exposure, individual and population risk reduction profile would be required to substantiate this potential.

1. Introduction

Tobacco has been used by people globally for centuries, and current estimates suggest that over 1 billion people are using products from oral smokeless, through pipe, shisha, factory-made cigarettes and roll-your-own tobacco products. Factory-made cigarettes are overwhelmingly the main form of tobacco used and when smoked. The tobacco is combusted at temperatures in excess of 900 °C, creating smoke that comprises more than 6500 different identified chemicals (Rodgman and Perfetti, 2013), of which around 150 constituents are thought to be toxicants (Fowles and Dybing, 2003). Continued exposure to these chemicals over time can lead to smoking-related diseases, such as cardiovascular disease, chronic obstructive pulmonary disease and cancer (US DHHS, 2014). Detailing the specific toxicants that are the prime causes of disease has been the focus of research for decades, and biological causes linking to specific toxicants or classes of toxicants are far from being fully understood. Presently, different priority toxicant lists have been proposed by the World Health Organization (WHO) (Burns et al., 2008), Health Canada (1999), and the US Food and Drug Administration (FDA), with both their shortened list and a list of harmful and potentially harmful constituents (HPHC) (FDA, 2012a).

Tobacco harm reduction, which was defined by the US Institute of Medicine (IOM) in 2001 as “decreasing total morbidity and mortality, without completely eliminating tobacco and nicotine use” (Stratton et al., 2001), is being considered by some regulators. In many countries, including the USA and European countries, the ability to market next-generation products (NGPs) is subject to regulatory approval. Such approval needs to be obtained by submitting details of a new product's design, performance and impact on users and non-users. In the US, the FDA has outlined the

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Abbreviations

BoE	Biomarker of exposure
E-cigarettes	Electronic cigarettes
HCI	Health Canada intense
HPHC	Harmful and potentially harmful constituent
IOM	Institute of medicine
MMD	Mass median diameter
NGP	Next-generation products
RTP	Reduced toxicant prototype
THP	Tobacco heating product
THS	Tobacco heating system
TPM	Total particulate matter
WA	Whole aerosol
WHO	World Health Organization

requirements to introduce tobacco products onto the market place, either via the Substantial Equivalence pathway where a predicate product exists or the Premarket Tobacco Application approach for novel tobacco products (FDA 2016). In Europe, assessment of product performance and impact on users and non-users may become part of the requirements in the future revisions to the Tobacco Products Directive (European Parliament and the Council of the European Union, 2014). Furthermore, the FDA has detailed the questions and the types of studies that should be considered by a manufacturer to investigate the reduced-risk nature of novel products, and these form part of a Modified Risk Tobacco Products application (FDA, 2012b). In response to these guidelines, product assessment frameworks have been published (Berman et al., 2015; Murphy, 2017; Murphy et al., 2017; Smith et al., 2016) proposing series of pre-clinical, clinical and population studies for the assessment of the relative risk of NGPs versus cigarettes.

A vast number of smokers across the globe are using NGPs to reduce or replace their consumption of cigarettes. Electronic cigarettes (e-cigarettes), tobacco heating products (THPs), such as THP1.0 (British American Tobacco) and iQOS (Philip Morris International) and hybrid THPs that combine both vapour and tobacco technologies are examples of such products (Poynton et al., 2017). Current NGPs are designed and operate differently from cigarettes and, thus, generate very different aerosols (Eaton et al., 2017). THPs contain tobacco but operate at temperatures of typically 250–350 °C, which are much lower than the combustion temperature in cigarettes of around 900 °C (Eaton et al., 2017; Schaller et al., 2016). Recently, a hybrid THP was described as heating a glycerol-based formulation containing nicotine and flavourings at around 250 °C and passing the resulting aerosol over a bed of tobacco at 30-40 °C, eluting volatile tobacco flavourings (Poynton et al., 2017). E-cigarettes, however do not contain tobacco and also operate at temperatures around 250 °C briefly to aerosolise propylene glycol and glycerol based e-liquids (Etter, 2013).

The advent of the array of NGPs has led to questions regarding the relative risk of each of the product categories to cigarettes. McNeill and Munafò (2012) introduced the concept of the product risk continuum, which placed different products that contained tobacco and nicotine, including pipes, oral smokeless, shisha products and e-cigarettes on a continuum of risk, with cigarettes being at the highest risk extreme and nicotine-replacement therapy at the least risky extreme.

Building on this, Nutt et al. (2014) used a Delphi panel approach comprising global public health experts to estimate the relative harms from products across the risk continuum, using a multi-criteria decision analysis model. In this study, cigarettes were estimated to be the most harmful product owing to their associated mortality and morbidity in users and others, whereas the harms from products like snus (5%), e-cigarettes (4%) and nicotine-replacement therapy (2%) were estimated to be substantially less harmful (Nutt et al., 2014).

Currently, in the UK, after reviewing the available evidence, several public health agencies have advocated a potential role for novel nicotine products in tobacco harm reduction. Public Health England (McNeill et al., 2015) has stated that “The wider body of evidence consistently finds that (e-cigarettes) are less harmful than smoking” and that “The current best estimate is that (e-cigarettes) are around 95% less harmful than smoking”. In support of this, the Royal College of Physicians (2016) has urged public health strategies to promote e-cigarettes widely as substitute for smoking. Recently, Cancer Research UK (2017) has also publicly supported the use of e-cigarettes as a less risky product for smokers.

This paper describes the first comparative pre-clinical assessment of a range of tobacco and nicotine products. The data from a series of chemical and *in vitro* studies will enable the ranking of the emission responses to aerosol from THP1.0 against those to other NGPs and cigarettes. Furthermore, this assessment will give insight into the potential risk profiles of the different NGP categories relative to cigarettes, although clinical and population studies would be required to fully assess this risk profile at both the individual and population levels.

2. Product descriptions

This paper describes the results from testing seven products as described in Table 1. Three cigarettes were studied, including the research reference cigarette 3R4F (Center for Tobacco Reference Products, University of Kentucky, Lexington, KY, USA) and two commercial cigarettes, Lucky Strike Regular (LSR; non-mentholated) and DuMaurier Silver (DMS; British American Tobacco, London, UK). The THP1.0 device comprises the glo heating device with Bright Tobacco KENT Neosticks, and was tested with tobacco and menthol variant consumables, all sourced from Japan. The tobacco heating system (THS) was an iQOS heating device with Essence Marlboro HeatSticks (Philip Morris International), both sourced from Japan. The hybrid THP is a commercial product called KENT iFuse used with Neopod tobacco flavour consumables, which were sourced from Romania. The e-cigarette product tested was Vype ePen with blended tobacco flavour e-liquid cartridges (1.8% nicotine), which were sourced from the UK.

3. Methods

The assessments described in this paper utilised a range of puffing regimes and chemical and *in vitro* toxicological methodologies for the assessment of the NGPs relative to cigarettes. Three cigarette controls were used for the studies namely 3R4F, LSR and DMS (Table 1). The scientific reference cigarette from the University of Kentucky, 3R4F, has been widely used in studies on tobacco products for over a decade (Roemer *et al.*, 2012), and was used as the control cigarette throughout all laboratory-based studies. The 3R4F cigarette was designed for research purposes only and not for consumer use. For the consumer-based studies (puffing behaviour and environmental emissions), therefore, only commercially available cigarettes were used. The two most popular styles of cigarettes sold globally are based on a blend of flue-cured Virginia tobacco or a blend of Virginia, Burley and Oriental tobaccos (“United States blended”), for which DSM and LSR were selected as representative examples, respectively.

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