Regulatory Toxicology and Pharmacology 93 (2018) 1–3

Contents lists available at ScienceDirect

Regulatory Toxicology and Pharmacology

journal homepage: www.elsevier.com/locate/yrtph

Assessment of tobacco heating product THP1.0. Part 1: Series introduction

Christopher Proctor

British American Tobacco, R&D Centre, Southampton, SO15 8TL, UK

ARTICLE INFO

Article history:
Received 26 May 2017
Received in revised form
14 August 2017
Accepted 10 September 2017
Available online 1 October 2017

Keywords:
Comprehensive assessment framework
Modified risk tobacco products
Tobacco harm reduction
Tobacco heating product

ABSTRACT

We have recently developed a Tobacco Heating Product (THP) comprising an electrical heating device, commercially known as Glo™, and consumable tobacco rods, commercially known as Kent Neostiks™. We refer to this system as THP1.0; Bright tobacco-flavoured variant THP1.0(T), or THP1.0(M) Menthol-flavoured variant. In this issue, we present a series of seven pre-clinical studies conducted on THP1.0,covering the following aspects of its design, development, safety and toxicological assessment, and a paper on placing THPs on an emissions continuum.

© 2017 The Author. Published by Elsevier Inc. This is an open access article under the CC BY-NC-ND license (http://creativecommons.org/licenses/by-nc-nd/4.0/).

Despite the known health risks, tobacco products continue to be used on a global scale: there are currently an estimated 1 billion smokers worldwide (WHO, 2016), and 5.8 trillion cigarettes were consumed globally in 2014 (Eriksen et al., 2015).

The associations between cigarette smoking and human diseases, such as cardiovascular disease, lung disease and cancer, are well established (US DHHS, 2010; US DHHS, 2014). When a cigarette is lit, the tobacco burns to form smoke containing more than 6500 compounds (Rodgman and Perfetti, 2013). Approximately 150 of these are thought to be toxicants (Fowles and Dybing, 2003), some of which form through incomplete combustion and pyrolysis of the tobacco (Baker, 2006). Indeed, most smoking-related diseases are not caused by the addictive substance nicotine but by these toxicants, which are present in the inhaled smoke (Farsalinos and Le Houezec, 2015).

In 2001, the US Institute of Medicine (IOM) defined the concept of harm reduction in tobacco use as “decreasing total morbidity and mortality, without the complete elimination of tobacco and nicotine use” (Stratton et al., 2001). They also proposed the development of potential reduced-exposure products (PREPs) — namely, products that result in a substantial reduction in exposure to one or more tobacco toxicants and provide nicotine in a “cleaner form”. Subsequently, McNeil and Munafò (2013) devised the concept of a risk continuum for tobacco and nicotine products, with cigarettes placed at the high-risk end of the continuum and nicotine replacement therapy at the low-risk end.

The US Food and Drug Administration is currently the only national regulator to have provided a draft guidance document (FDA, 2012) outlining a framework to assess novel tobacco and nicotine products as Modified Risk Tobacco Products (MRTPs), a term that replaced the original IOM term of PREPs. Based on that draft guidance, several groups (Berman et al., 2015; Breheny et al., 2017; Murphy et al., 2017a; Poynton et al., 2017; Smith et al., 2016) have proposed scientific assessment frameworks comprising pre-clinical, clinical and population studies to assess the risk reduction potential of novel tobacco and nicotine products both at the individual and population level.

Previously, British American Tobacco has examined several approaches in the development of reduced-exposure products (Branton et al., 2009, 2011a, 2011b; Branton and Bradley, 2010; Dittrich et al., 2014; Liu et al., 2011; McAdam et al., 2011), and applied them in various combinations to produce reduced toxicant prototype cigarettes (Combes et al., 2013; Dittrich et al., 2014; McAdam et al., 2012; Proctor et al., 2011; Shepperd et al., 2013a, 2013b, 2015). While many of these technologies achieved some toxicant reductions in pre-clinical assessment, clinical studies to assess the level of biomarkers of exposure did not demonstrate sufficient reductions to support their potential translation into reduced health risks to the smoker. A key learning from those

Abbreviations: MRTP, modified risk tobacco product; NGP, next-generation product; THP, tobacco heating product.

E-mail address: christopher_proctor@bat.com.

https://doi.org/10.1016/j.yrtph.2017.09.010
0273-2300/© 2017 The Author. Published by Elsevier Inc. This is an open access article under the CC BY-NC-ND license (http://creativecommons.org/licenses/by-nc-nd/4.0/).

studies was that the relationship between emission, exposure and risk is essential to assessing the risk profile of MRTPs relative to cigarettes.

By contrast, next-generation products (NGPs), which heat rather than combust the tobacco consumable or use liquids that contain nicotine, have considerable potential to reduce the levels of toxicants in emissions and subsequently the exposure and risk beyond anything that could practically be achieved in a modified cigarette. Today, there exist various NGP platforms, including electronic cigarettes, tobacco heating products (THPs) and hybrids. The first commercial THP, Premier™ (R. J. Reynolds), was introduced in 1988, followed by Eclipse™ (R. J. Reynolds) and Accord™ (Philip Morris) in the 1990s, Heat Bar™ (Philip Morris) in 2007, and iQOS™ (Philip Morris International) in 2016.

British American Tobacco has recently developed a THP comprising an electrical heating device, commercially known as Glo™, and consumable tobacco rods, commercially known as Kent Neostiks™. We refer to this system as THP1.0; Bright tobacco-flavoured variant (T), or THP1.0(M) Menthol-flavoured variant. In this issue, we present a series of seven pre-clinical studies conducted on THP1.0, covering the following aspects of its design, development, safety and toxicological assessment, and a paper on placing THPs on an emissions continuum.

- Part 2. Product design rationale and product stewardship considerations, with evaluation of the main physical and chemical processes underlying aerosol formation in THP1.0 (Eaton et al., 2017).
- Part 3. Targeted chemical analyses of the levels of toxicant emissions in THP1.0 aerosol and comparison with those in Kentucky 3R4F (3R4F) reference mainstream cigarette smoke. The comprehensive list of toxicants assessed was based on known tobacco and cigarette smoke constituents as well as any toxicants considered to form during tobacco heating (Forster et al., 2017a).
- Part 4. Indoor air quality assessment, evaluating the levels of toxicants emitted in the aerosol under controlled environmental conditions when THP1.0 is used by regular smokers, coupled with a novel sensory evaluation of residual tobacco odour intensity on fingers, hair and fabric (Forster et al., 2017b).
- Part 5. Levels of nicotine, glycerol and selected volatile organic constituents in the aerosol emissions of THP1.0 at multiple locations between the point of aerosol generation and the point of aerosol exposure in *in vitro* biological assays to evaluate tissue dosimetry (Jaunky et al., 2017).
- Part 6. Further *in vitro* assessments on the emissions of THP1.0 using contemporary screening approaches with eight different biological endpoints (Taylor et al., 2017).
- Part 7. Comparison of responses in a range of regulatory toxicological tests (Ames, NRU, MLA and Bhas) between the aerosol emissions of THP1.0 and mainstream smoke from 3R4F (Thorne et al., 2017).
- Part 8. Puffing topography results and mouth level exposure among a group of Japanese consumers of THP1.0(T) or THP1.0(M) and comparator products, providing a basis on which to assess the machine-puffed emission data and *in vitro* toxicological results (Gee et al., 2017).
- Part 9. Placement of a range of NGPs on the emissions spectrum relative to cigarettes via a pre-clinical assessment of their emissions (Murphy et al., 2017b).

This compendium describes THP1.0 and its operation, and provides a comprehensive pre-clinical assessment of its emissions and the impact of these emissions on indoor air quality and on some toxicological end points relative to a reference cigarette. These studies suggest that THP1.0 has the potential to be a reduced risk product relative to conventional cigarettes, but that further studies will be needed to determine whether this potential is likely to be realised. Ongoing work is focusing on clinical and population studies assessing the exposure and risk profile of THP1.0 relative to cigarettes that will be presented in future papers.

Transparency document

Transparency document related to this article can be found online at https://doi.org/10.1016/j.yrtph.2017.09.010.

References

Baker, R.R., 2006. Smoke generation inside a burning cigarette: modifying combustion to develop cigarettes that may be less hazardous to health. Prog. Energy Combust. Sci. 32 (4), 373–385.

Berman, M.L., Connolly, G., Cummings, M.K., Djordjevic, M.V., Hatsukami, D.K., Henningfield, J.E., Myers, M., O'Connor, R.J., Parascandola, M., Rees, V., Rice, J.M., Shields, P.G., 2015. Providing a science base for the evaluation of tobacco products. Tob. Regul. Sci. 1, 76–93.

Branton, P., Lu, A.H., Schuth, F., 2009. The effect of carbon pore structure on the adsorption of cigarette smoke vapour phase compounds. Carbon 47, 1005–1011.

Branton, P., Bradley, R.H., 2010. Activated carbons for the adsorption of vapours from cigarette smoke. Adsorpt. Sci. Technol. 28, 3–21.

Branton, P.J., McAdam, K.G., Winter, D., Liu, C., Duke, M.G., Proctor, C.J., 2011a. Reduction of aldehydes and hydrogen cyanide in mainstream cigarette smoke using an amine functionalised ion exchange resin. Chem. Cent. J. 5, 15.

Branton, P., McAdam, K.G., Duke, M.G., Liu, C., Curle, M., Mola, M., Proctor, C.J., Bradley, R.H., 2011b. Use of classical adsorption theory to understand the dynamic filtration of volatile toxicants in cigarette smoke by active carbons. Adsorpt. Sci. Technol. 29, 117–138.

Breheny, D., Adamson, J., Azzopardi, D., Baxter, A., Bishop, E., Carr, T., Crooks, I., Hewitt, K., Jaunky, T., Larard, S., Lowe, F., Oke, O., Taylor, M., Santopietro, S., Thorne, D., Zainuddin, B., Gaça, M., Liu, C., Murphy, J., Proctor, C., 2017. A novel hybrid tobacco product that delivers a tobacco flavour note with vapour aerosol (Part 2): in vitro biological assessment and comparison with different tobacco-heating products. Food Chem. Toxicol. 106, 533–546.

Combes, R., Scott, K., Crooks, I., Dillon, D., Meredith, C., McAdam, K., Proctor, C., 2013. The in vitro cytotoxicity and genotoxicity of cigarette smoke particulate matter with reduced toxicant yields. Toxicol. In Vitro 27 (5), 1533–1541.

Dittrich, D.J., Fieblekorn, R.T., Bevan, M.J., Rushforth, D., Murphy, J.J., Ashley, M., McAdam, K.G., Liu, C., Proctor, C.J., 2014. Approaches for the design of reduced toxicant emission cigarettes. Springerplus 3, 374.

Eaton, D., Jakaj, B., Forster, M., Nicol, J., Mavropoulou, E., Scott, J.K., Liu, C., McAdam, K.G., Murphy, J., Proctor, C.J., 2017. Assessment of tobacco heating product THP1.0. Part 2: product design, operation and thermophysical characterisation. Regul. Toxicol. Pharmacol. in (this issue).

Eriksen, M., Mackay, J., Schluger, N., 2015. The Tobacco Atlas, fifth ed. American Cancer Society http://www.tobaccoatlas.org/. accessed 16, January 2017.

Farsalinos, K.E., Le Houezec, J., 2015. Regulation in the face of uncertainty: the evidence on electronic nicotine delivery systems (e-cigarettes). Risk Manag. Healthc. Policy 8, 157–167.

Food and Drug Administration, 2012. Guidance for Industry Modified Risk Tobacco Product Applications. Draft Guidance. http://www.fda.gov/downloads/TobaccoProducts/GuidanceComplianceRegulatoryInformation/UCM297751.pdf. accessed 20/02/17.

Forster, M., Mariner, D., Wright, C., Fiebelkorn, S., Liu, C., Yurteri, C., McAdam, K.G., Proctor, C.J., 2017a. Assessment of tobacco heating product THP1.0. Part 3: comprehensive chemical characterisation—harmful and potentially harmful aerosol emissions. Regul. Toxicol. Pharmacol. in (this issue).

Forster, M., McAughey, J., Prasad, K., Mavropoulou, E., Proctor, C.J., 2017b. Assessment of tobacco heating product THP1.0. Part 4: characterisation of indoor air quality and odour analysis. Regul. Toxicol. Pharmacol. in (this issue).

Fowles, J., Dybing, E., 2003. Application of toxicological risk assessment principles to the chemical constituents of cigarette smoke. Tob. Control 12 (4), 424–430.

Gee, J., Prasad, K., Slayford, S., Gray, A., Nother, K., Mavropoulou, E., Cunningham, A., roctor, C.J., 2017. Assessment of tobacco heating product THP1.0. Part 8: study to determine puffing topography, mouth level exposure and consumption among Japanese users. Regul. Toxicol. Pharmacol. in (this issue).

Jaunky, T., Adamson, J., Santopietro, S., Terry, A., Thorne, D., Breheny, D., Proctor, C.J., Gaça, M., 2017. Assessment of tobacco heating product THP1.0. Part 5: in vitro dosimetric and cytotoxic assessment. Regul. Toxicol. Pharmacol. in (this issue).

Liu, C., DeGrandpré, Y., Porter, A., Griffiths, A., McAdam, K., Voisine, R., Côté, F., Proctor, C., 2011. The use of a novel tobacco treatment process to reduce toxicant yields in cigarette smoke. Food Chem. Toxicol. 49 (9), 1904–1917.

McAdam, K.G., Gregg, E.O., Liu, C., Dittrich, D.J., Duke, M.G., Proctor, C.J., 2011. The use of a novel tobacco-substitute sheet and smoke dilution to reduce toxicant yields in cigarette smoke. Food Chem. Toxicol. 49 (8), 1684–1696.

McAdam, K.G., Gregg, E.O., Bevan, M., Dittrich, D.J., Hemsley, S., Liu, C., Proctor, C.J.,

2012. Design and chemical evaluation of reduced machine-yield cigarettes. Regul. Toxicol. Pharmacol. 62 (1), 138–150.
Murphy, J., Gaça, M., Lowe, F., Minet, E., Breheny, D., Prasad, K., Camacho, O., Fearon, I., Liu, C., Wright, C., McAdam, K., Proctor, C., 2017a. Assessing modified risk tobacco and nicotine products: description of the scientific framework and assessment of a closed modular electronic cigarette. Regul. Toxicol. Pharmacol. https://doi.org/10.1016/j.yrtph.2017.09.008.
Murphy, J., Liu, C., McAdam, K., Gaça, M., Prasad, K., McAughey, J., Proctor, C.J., 2017b. Assessment of tobacco heating product THP1.0. Part 9: the quantitative placement of a range of next generation products on the risk spectrum relative to cigarettes via a pre-clinical assessment of their emissions. Regul. Toxicol. Pharmacol. in (this issue).
McNeill, A., Munafò, M.R., 2013. Reducing harm from tobacco use. J. Psychopharmacol. 27 (1), 13–18.
Proctor, C., Shepperd, J., Eldridge, A., McAdam, K., Errington, G., 2011. Cigarette Smoke Toxicant Exposure Estimates in Smokers Switched to Reduced Toxicant Prototype ('RTP') Cigarettes. CORESTA, Graz, Austria. October 2011. https://www.coresta.org/sites/default/files/abstracts/2011_ST35_Proctor.pdf. accessed 16, January 2017.
Poynton, S., Sutton, J., Goodall, S., Margham, J., Forster, M., Scott, K., Liu, C., McAdam, K., Murphy, J., Proctor, C., 2017. A novel hybrid tobacco product that delivers a tobacco flavour note with vapour aerosol (Part 1): product operation and preliminary aerosol chemistry assessment. Food Chem. Toxicol. 106, 522–532.
Rodgman, A., Perfetti, T.A., 2013. The Chemical Components of Tobacco and Tobacco Smoke, second ed. CRC Press, Boca Raton, USA.
Shepperd, C.J., Eldridge, A., Camacho, O.M., McAdam, K., Proctor, C.J., Meyer, I., 2013a. Changes in levels of biomarkers of exposure observed in a controlled study of smokers switched from conventional to reduced toxicant prototype cigarettes. Regul. Toxicol. Pharmacol. 66 (1), 147–162 erratum in Regul. Toxicol. Pharmacol. 2013, 67(3), 536.
Shepperd, C.J., Newland, N., Eldridge, A., Graff, D., Meyer, I., 2013b. A single-blinded, single-centre, controlled study in healthy adult smokers to identify the effects of a reduced toxicant prototype cigarette on biomarkers of exposure and of biological effect versus commercial cigarettes. BMC Public Health 13, 690.
Shepperd, C.J., Newland, N., Eldridge, A., Haswell, L., Lowe, F., Papadopoulou, E., Camacho, O., Proctor, C.J., Graff, D., Meyer, I., 2015. Changes in levels of biomarkers of exposure and biological effect in a controlled study of smokers switched from conventional cigarettes to reduced-toxicant-prototype cigarettes. Regul. Toxicol. Pharmacol. 72 (2), 273–291.
Smith, M.R., Clark, B., Lüdicke, F., Schaller, J.P., Vanscheeuwijck, P., Hoeng, J., Peitsch, M.C., 2016. Evaluation of the Tobacco Heating System 2.2. Part 1: description of the system and the scientific assessment program. Regul. Toxicol. Pharmacol. 81, S17–S26.
Stratton, K., Shetty, P., Wallace, R., Bondurant, S. (Eds.), 2001. Clearing the Smoke: Assessing the Science Base for Tobacco Harm Reduction. National Academies Press, Washington, DC, 2001.
Taylor, M., Thorne, D., Carr, T., Breheny, D., Walker, P., Proctor, C.J., Gaça, M., 2017. Assessment of tobacco heating product THP1.0. Part 6: a comparative in vitro study using contemporary screening approaches. Regul. Toxicol. Pharmacol. in (this issue).
Thorne, D., Breheny, D., Proctor, C.J., Gaça, M., 2017. Assessment of tobacco heating product THP1.0. Part 7: comparative *in vitro* toxicological evaluation. Regul. Toxicol. Pharmacol. in (this issue).
US Department of Health and Human Services, 2010. How Tobacco Smoke Causes Disease: the Biology and Behavioral Basis for Smoking-attributable Disease: a Report of the Surgeon General. Atlanta, USA. https://www.cdc.gov/tobacco/data_statistics/sgr/2010/. accessed 16 January 2017.
US Department of Health and Human Services, 2014. The Health Consequences of Smoking 50 Years of Progress: a Report of the Surgeon General, 2014. Atlanta, USA. http://www.surgeongeneral.gov/library/reports/50-years-of-progress/index.html. accessed 16, January 2017.
WHO, 2016. Tobacco Fact Sheet. http://www.who.int/mediacentre/factsheets/fs339/en/. accessed 17, January 2017.