PART 3 – SUPPORTING DATA

SUPPORTING DATA SUMMARY

This application refers to tobacco rather than nicotine as a pure chemical substance, and the requested change to Schedule 7 is a class exemption for tobacco prepared and packed for heating rather than a specific product.

That being the case, much of the information contained in this application is focused on comparing HTP products which conventional cigarettes.

Supporting data is by way of reference to published papers, regulatory decisions and policy statements, as noted in the bibliography. This includes peer reviewed journal papers relating to studies performed by the tobacco industry and other researchers.

The supporting data and references fall into four general categories

1) Published statistics and peer reviewed papers of independent research on the effects (including use, misuse and abuse) of nicotine and tobacco, in various forms.
2) Information on studies performed by industry such as Philip Morris International and British American Tobacco on HTP vs conventional cigarettes.
3) Regulatory opinions and decisions from comparable overseas regulators including, but not limited to, the U.S. FDA, New Zealand Ministry of Health, UK Committees on Toxicology, Carcinogenicity and Mutagenicity of Chemicals in Food, Consumer Products and the Environment, WHO and the Japanese National Fire Agency.
4) Policy statements and opinion pieces from other government agencies, UK Royal College of Physicians, Royal Australian College of General Practitioners and other peak bodies and stakeholders.

In particular, in the Risks and Benefits Section A, there is compelling evidence provided by independent researchers and the tobacco industry in relation to the reduced level of HPHCs in HTPs, relative to conventional cigarettes and, how this may affect overall health outcomes and indoor air quality. These are illustrated in the following publications: (Schaller et al. 2016a; Schaller et al. 2016b; Li et al. 2018; Jaccard et al. 2017; Mallock et al. 2018; Forster et al. 2018, Bekki et al. 2017; Uchiyama et al. 2018; FDA TPL Report, 2019, PMI 2018, Pratte et al 2017, FDA 2019, FDA 2016, Royal College of Physicians 2016, WHO 2009, WHO 2000, Nordlund et al 2019). There is also supporting details on the impact of HTP aerosol on the environment and bystanders (Appendix 4).

Additional information on some current brands of HTPs, relevant to Section D of the application, is located in Appendix 2. PMI's HTP is one of the most studied HTPs and Appendix 3 lists publications and reviews for the product.

The risks of abuse and misuse (including attractiveness to youth, never-smokers or former smokers) are summarised in Section A and thoroughly discussed in Section E. THS abuse liability was assessed based on the review of available information from various sources, including product design and content, aerosol chemistry, human clinical and behavioural data and an example comparison is provided between IQOS and conventional cigarettes using the methodology of Carter 2009.

Section C provides evidence on reduced toxicity of HTPs in comparison to CCs, as well as additional details on independent assessments by comparable regulators and agencies (Appendix 5).

An overview of recent independent studies giving insight into the use patterns and misuse/abuse potential of different tobacco products has been provided with reference to Queloz and Etter, 2019, Delgrande et al., 2019 and Osaki, 2019.

Section E also includes reference to Appendix 6 which provides the full abuse liability assessment provided by PMI to the U.S. FDA as part of PMI's Modified Risk Tobacco Product application for THS.

Section F discusses the concept of tobacco harm reduction as well as the approach taken by comparable regulators.

Studies by PMI that are included in this application are peer reviewed publications or information in the public domain such as FDA submission dockets. Study reports are available for all studies relating to PMI's HTP and can be supplied if required.

All references used within the body of the document are hyperlinked to the Bibliography for ease of readability.

SUPPORTING DATA DETAILS

Additional data to substantiate indicated data points in the submission has been included as addenda in the following appendices:

Appendix 1: Countries that Regulate Heated Tobacco Products
Appendix 2: Marketed HTP Devices and Consumable
Appendix 3: List of independent studies and reviews of PMI's HTP
Appendix 4: Impact of HTP aerosol on the environment and on bystanders
Appendix 5: Examples of research conducted by independent researchers or regulatory authorities on the mainstream aerosol of the HTPs and reference cigarette smoke
Appendix 6: Abuse Liability

A Glossary of terms and abbreviations is also provided for ease of reference.

Data, including independent studies that have been conducted by medical institutions, have been provided by way of reference to peer reviewed journals and published papers, regulatory decisions and policy statements.

COPIES OF PAPERS REFERENCED

Copies of papers referenced are included as separate attachments and have been uploaded with the application.

All work referenced, copied and submitted for the purposes of this application, and used by the Commonwealth, can be taken to be authorised by the Commonwealth under section 183 of the Copyright Act 1968 (Cth).

PART 4 – BIBLIOGRAPHY

Abrams DB., Glasser AM., Pearson JL., Villanti AC., Collins LK., Niaura RS., 2018, Harm Minimization and Tobacco Control: Reframing Societal Views of Nicotine Use to Rapidly Save Lives, 39 Ann. Rev. Pub. Health 193

Abrams et al. (2017) Submission to Tobacco Products Scientific Advisory Committee on Modified Risk Tobacco Product Applications for IQOS System (Dec. 14, 2017), available at https://www.fda.gov/media/110535/download

Afolalu EF, Langer P, Prieto L, Skiada D, Dobrynina M, Sponsiello-Wang Z, Weitkunat R, Lüdicke F (2018) Patterns of Use Behaviors in a Sample of Japanese "Heat-Not-Burn" Tobacco Product (IQOS), presented at CORESTA 2018, available at: https://www.pmiscience.com/library/publication/patterns-of-use-behaviors-in-a-sample-of-japanese

American College of Medical Toxicology, Nicotine, available at: https://www.acmt.net/_Library/Public_Affairs/ACMT_FAQ_Nicotine_.pdf

Australian Bureau of Statistics, 2015, 4364.0.55.001 - National Health Survey: First Results 2014-15.

Australian Bureau of Statistics, 2018, 4364.0.55.001 - National Health Survey: First Results 2017-18.

Baker, R.R., 1987 A review of pyrolysis studies to unravel reaction steps in burning tobacco. J. Anal. Appl. Pyrolysis 11, 555-573.

Bekki, K., et al., Comparison of Chemicals in Mainstream Smoke in Heat-not-burn Tobacco and Combustion Cigarettes. Journal of UOEH, 2017. 39(3): p. 201-207.

Benhamou E, Benhamou S, Auquier A, Flamant R. Changes in patterns of cigarette smoking and lung cancer risk: results of a case-control study. British Journal of Cancer. 1989; 60(4):601-4.

Berthet A. Jacot Sadowski I., Zurcher K., Guenin V., Gendre A., Auer R., Vernez D., Cornuz J.; "Heated" tobacco products: what you need to know; Rev Med Suisse 2018; 14:1935-41

Bibra Toxicology advice and consulting. EU Classification of nicotine mixtures under CLP Regulation 1272/2008. 2014. Available at https://echa.europa.eu/documents/10162/76d24a79-e356-483e-9bae-16c241002684

Bronstein, A.C. et al. 2008 Annual Report of the American Association of Poison Control Centers' National Poison Data System (NPDS): 25th Annual Report. Clin Toxicol (Phila) 46, 927-1057 (2008)

Brossard, P. et al., 2017 Nicotine pharmacokinetic profiles of the Tobacco Heating System 2.2, cigarettes and nicotine gum in Japanese smokers. Regul Tox and Pharm. 89, 193-199.

Carter LP, Stitzer ML, Henningfield JE, O'Connor RJ, Cummings KM, Hatsukami DK.; Abuse Liability Assessment of Tobacco Products Including Potential Reduced

Exposure Products (PREPs); Cancer Epidemiology, Biomarkers & Prevention; 2009 Dec;18(12):3241-62. doi: 10.1158/1055-9965.EPI-09-0948

Charrier, Lorena, Berchialla, Paola, Galeone, Daniela, Spizzichino, Lorenzo, Borraccino, Alberto, Lemma, Patrizia, Dalmasso, Paola, and Cavallo, Franco, Smoking Habits among Italian Adolescents: What Has Changed in the Last Decade?, Hindawi Publishing Corporation, BioMed Research International, Volume 2014, Article ID 287139, 8 pages http://dx.doi.org/10.1155/2014/287139

Christensen L. Three cases of attempted suicide by ingestion of nicotine liquid used in e-cigarettes. Clinical Toxicology. 2013;51:290

Coates, L., Kaandorp, G., Harris, J., van Leeuwen, J., Avci, A., Evans, J., George, S., Gissing, A., van den Honert, R. and Haynes, K., 2019, Preventable residential fire fatalities: July 2003 to June 2017, Bushfire and Natural Hazards CRC

Committees on Toxicity, Carcinogenicity and Mutagenicity of Chemicals in Food, Consumer Products and the Environment, Statement on the toxicological evaluation of novel heat-not-burn tobacco products (Dec. 2017), available at https://cot.food.gov.uk/cotstatements/cotstatementsyrs/cot-statements-2017/statement-on-heat-not-burn-tobacco-products.

Czoli CD, White CM, Reid JL, RJ OC, Hammond D. Awareness and interest in IQOS heated tobacco products among youth in Canada, England and the USA. Tob Control. 2019:0:1-7. doi: 10.1136/tobaccocontrol-2018-054654. PubMed PMID: 30696783.

Daston, Life, Chance & Life Chances, 137 DAEDALUS 5 (2008), Volume 137, Issue 1, Winter 2008 p.5-14

Delgrande Jordan, M., Schneider, E., Eichenberger, Y, & Kretschmann, A. (2019). La consommation de substances psychoactives des 11 à 15 ans en Suisse – Situation en 2018 et évolutions depuis 1986 - Résultats de l'étude, Health Behaviour in School-aged Children (HBSC) (rapport de recherche No 100). Lausanne: Addiction Suisse. https://www.hbsc.ch/pdf/hbsc_bibliographie_342.pdf.

Department of Health in Australia, Nicotine Replacement Therapy, available at: https://www.health.gov.au/internet/main/publishing.nsf/Content/tobacco-nicotine-replacement (Accessed on 1 August 2019)

Djurdjevic S, Lee PN, Weitkunat R, Sponsiello-Wang Z, Lüdicke F, Baker G, 2018. Modeling the Population Health Impact of Introducing a Modified Risk Tobacco Product into the U.S. Market. Healthcare 2018, 6(2), 47; https://doi.org/10.3390/healthcare6020047

Drovandi A, Salem S, Barker D, Booth D, Kairuz T, Human Biomarker Exposure from Cigarettes versus Novel Heat-Not-Burn Devices: A Systematic Review and Meta-Analysis, Nicotine & Tobacco Research, ntz200, https://doi.org/10.1093/ntr/ntz200

Eaton, D., et al., 2018 Assessment of tobacco heating product THS1.0. Part 2: Product design, operation and thermophysical characterization. Regul. Tox and Pharm 93, 4-13.

Eichler et al, The Risks of Risk Aversion in Drug Regulation, NATURE REVIEWS, DRUG DISCOVERY, VOLUME 12, DECEMBER 2013

Food and Drug Administration (FDA) (2016), Deeming Tobacco Products To Be Subject to the Federal Food, Drug, and Cosmetic Act, as Amended by the Family Smoking Prevention and Tobacco Control Act; Restrictions on the Sale and Distribution of Tobacco Products and Required Warning Statements for Tobacco Products. 21 CFR Parts 1100, 1140, and 1143. Available from: https://www.federalregister.gov/articles/2016/05/10/2016-10685/deeming-tobacco-products-to-be-subject-to-the-federal-food-drug-and-cosmetic-act-as-amended-by-the

Food and Drug Administration (FDA) (2019), Nicotine: The Addictive Chemical in Tobacco Products, available at: https://www.fda.gov/tobacco-products/products-guidance-regulations/nicotine-addictive-chemical-tobacco-products (Accessed on 6 September 2019)

Food and Drug Administration (FDA) (2019), Technical Project Lead Report for the IQOS PMTA submitted by Philip Morris Products S.A. on May 15, 2017 available at: https://www.fda.gov/tobacco-products/premarket-tobacco-product-applications/premarket-tobacco-product-marketing-orders

Food and Drug Administration (FDA) press release (2019) FDA permits sale of IQOS Tobacco Heating System through premarket tobacco product application pathway, April 30, 2019, available at https://www.fda.gov/news-events/press-announcements/fda-permits-sale-iqos-tobacco-heating-system-through-premarket-tobacco-product-application-pathway.

Forster M., McAughey J., Prasad K., (2018) Assessment of tobacco heating product THP1.0. Part 4: Characterisation of indoor air quality and odour. Regul Toxicol Pharmacol 2018;**93**:34–51. doi:10.1016/j.yrtph.2017.09.017

Forster, M., et al., Assessment of novel tobacco heating product THP1.0. Part 3: Comprehensive chemical characterisation of harmful and potentially harmful aerosol emissions. Regulatory Toxicology and Pharmacology, 2018. 93: p. 14-33.

Frost and Sullivan, Understanding of and Attitudes Towards Tobacco Harm Reduction Products, Insights from the Australian Public and Healthcare Professionals, December 2018

Fujita, O. (2017) Report Review of IQOS Tobacco Heating Device Model:2.4 Device Safety Report.

Fujita, O. and Y. Hui, Final Report for Collaborative Research between HU-PMI. Will a used and discarded Electrically Heated Tobacco Product cause fire in a trash box, forest and grass-land? Technical expert report dated July 22, 2016.

Gale N, McEwan M, Eldridge AC, Fearon IM, Sherwood N, Bowen E, McDermott S, Holmes E, Hedge A, Hossack S, Wakenshaw L, Glew J, Camacho OM, Errington G, McAughey J, Murphy J, Liu C, Proctor CJ, Changes in Biomarkers of Exposure on Switching From a Conventional Cigarette to Tobacco Heating Products: A Randomized, Controlled Study in Healthy Japanese Subjects, Nicotine & Tobacco Research, Volume 21, Issue 9, September 2019, Pages 1220–1227, https://doi.org/10.1093/ntr/nty104

Godtfredsen NS, Prescott E, Osler M. Effect of smoking reduction on lung cancer risk. JAMA 2005; 294(12):1505-10.

Goepferd, S.J. Smokeless tobacco: a potential hazard to infants and children. J Am Dent Assoc 113, 49-50 (1986).

Goldfrank LR, N.L., Howland & MA, L.N., Flumenbaum NE, Hoffman RS,. Goldfrank's Toxicologic Emergencies. 8th ed. New York, NY: McGraw-Hill; 1221–1230 (2006)

Gonzalez Suarez I, Martin F, Marescotti D, Guedj E, Acali S, Johne S, Dulize R, Baumer K, Peric D, Goedertier D, Frentzel S, Ivanov N, Mathis C, Hoeng J and Peitsch MC (2016) In vitro Systems Toxicology assessment of a candidate Modified Risk Tobacco Product shows reduced toxicity compared to a conventional cigarette. **Chemical Research in Toxicology**, 29:3-18. (PMID: 26651182)

Gottlieb S, Zeller M, (2017) Nicotine-Focused Framework for Public Health, N Engl J Med 2017; 377:1111-1114
DOI: 10.1056/NEJMp1707409

Greenhalgh EM, Stillman S, & Ford C, 7.16 Pharmacotherapies, In Scollo, MM and Winstanley, MH [editors], Tobacco in Australia: Facts and issues. Melbourne: Cancer Council Victoria; 2018, available from: http://www.tobaccoinaustralia.org.au/chapter-7-cessation/7-16-pharmacotherapy

Greenhalgh, EM Stillman S, & Ford C, Chapter 1, Prevalence of smoking—adults. In Scollo, MM and Winstanley, MH [editors]. Tobacco in Australia: Facts and issues. Melbourne: Cancer Council Victoria (2019), available from: http://www.tobaccoinaustralia.org.au/chapter-1-prevalence/1-3-prevalence-of-smoking-adults (accessed 10 Oct. 2019).

Hart C, Gruer L, Bauld L. Does smoking reduction in midlife reduce mortality risk? Results of 2 long-term prospective cohort studies of men and women in Scotland. Am J Epidemiol. 2013; 178(5):770-9.

Haziza C, de La Bourdonnaye G, Donelli A, Poux V, Skiada D, Weitkunt R, Baker G, Picavet P, Lüdicke F (2019) Reduction In Exposure To Selected Harmful And Potentially Harmful Constituents Approaching Those Observed Upon Smoking Abstinence In Smokers Switching To The Menthol Tobacco Heating System 2.2 For Three Months (Part 1). Nicotine Tob Res. doi: 10.1093/ntr/ntz013.

Haziza C, de La Bourdonnaye G, Merlet S, Benzimra M, Ancerewicz J, Donelli A, Baker G, Picavet P and Luedicke F. (2016a) Assessment of the reduction in levels of exposure to harmful and potentially harmful constituents in Japanese subjects using a novel tobacco heating system compared with conventional cigarettes and smoking abstinence: a randomized controlled study in confinement. **Regulatory Toxicology and Pharmacology**, 81:489-499. (PMID: 27693654).

Haziza C, De La Bourdonnaye G, Skiada D, Ancerewicz J, Baker G, Picavet P and Luedicke F (2016b) Evaluation of the Tobacco Heating System 2.2. Part 8: 5-day randomized reduced exposure clinical trial in Poland. **Regulatory Toxicology and Pharmacology**, 81 Suppl 2:S139-S150. (PMID: 27816672).

IARC Handbook of Cancer Prevention Volume 12, Methods for Evaluating Tobacco Control Policies, Chapter 3.1, 2008 .

Inoue-Choi M, Hartge P, Park Y, Abnet CC, Freedman ND. Association Between Reductions of Number of Cigarettes Smoked per Day and Mortality Among Older Adults in the United States. Am J Epidemiol. 2019; 188(2):363-371.

Inoue-Choi M, McNeel TS, Hartge P, Caporaso NE, Graubard BI, Freedman ND (2018) Non-Daily Cigarette Smokers: Mortality Risks in the U.S., Am J Prev Med. 2019 Jan;56(1):27-37. doi: 10.1016/j.amepre.2018.06.025

Institute of Medicine, Scientific Standards for Studies on Modified Risk Tobacco Products (2012), available at: https://www.nap.edu/catalog/13294/scientific-standards-for-studies-on-modified-risk-tobacco-products

Iskandar AR, Titz B, Sewer A, Leroy P, Schneider T, Zanetti F, Mathis C, Elamin A, Frentzel S, Schlage W, Martin F, Peitsch MC, and Hoeng J (2017) Systems Toxicology Meta-Analysis of In Vitro Assessment Studies: Biological Impact of a Modified-Risk Tobacco Product Aerosol Compared with Cigarette Smoke on Human Organotypic Cultures of the Aerodigestive Tract. **Toxicology Research (Cambridge)**, 6:631-653. (PMID: 30090531).

Iskandar, A. et al., 2017b Comparative effects of a candidate modified-risk tobacco product Aerosol and cigarette smoke on human organotypic small airway cultures: a systems toxicology approach. Toxicol. Res**.**, 2017, **6**, 930-946

Jaccard, G., et al., Comparative assessment of HPHC yields in the Tobacco Heating System THS2.2 and commercial cigarettes. Regulatory Toxicology and Pharmacology, 2017. 90: p. 1-8.

Jaccard, Guy, Tafin Djoko, Donatien, Korneliou, Alexandra, Stabbert, Regina, Belushkin, Maxim, Esposito, Marco (2019) Mainstream smoke constituents and in vitro toxicity comparative analysis of 3R4F and 1R6F reference cigarettes. Toxicology ReportsVolume 6, Pages 222-231

Jaunky, T. et al., 2018 Assessment of tobacco heating product THP1.0. Part 5: In vitro dosimetric and cytotoxic assessment. Reg. Tox. Pharm., 93,52-61.

Johnson, C.P. & Blasco, P.A. Infant growth and development. Pediatr Rev 18, 224-42 (1997).

Kamboj, A., Spiller, H.A., Casavant, M.J., Chounthirath, T. & Smith, G.A. Pediatric Exposure to ECigarettes, Nicotine, and Tobacco Products in the United States. Pediatrics 137(2016).

Kiviniemi M.T., Kozlowski L.T (2015) Deficiencies in public understanding about tobacco harm reduction: results from a United States national survey. Harm Reduction Journal 2015, 512:21 (July 2015).

Kogel, U., Titz, B., Schlage, W. K., Nury, C., Martin, F., Oviedo, A., Lebrun, S., Elamin, A., Guedj, E., Trivedi, K., Ivanov, N. V., Vanscheeuwijck P, Peitsch, MC and Hoeng J (2016) Evaluation of the Tobacco Heating System 2.2. Part 7: Systems toxicological assessment of a mentholated version revealed reduced cellular and molecular exposure effects compared with cigarette smoke. **Regulatory Toxicology and Pharmacology**, 81 Suppl 2:S123-S138. (PMID: 27818347).

Kotz, D. & Kastaun, S. Bundesgesundheitsbl (2018) 61: 1407. https://doi.org/10.1007/s00103-018-2827-7

Langer P, Prieto L, Rousseau C, Formey A, Skiada D, Afolalu E, Sponsiello Z, Fischer K, Baker G, Weitkunat R, Tobacco product use after the launch of a heat-not-burn alternative in Japan: results of two cross-sectional surveys, presented at GFN Europe, Warsaw 13 –16 June 2019, available at: https://www.pmiscience.com/library/publication/tobacco-product-use-after-the-launch-of-a-heat-not-burn-alternative-in-japan-results-of-two-cross-sectional-surveys

Lee PN. The effect of reducing the number of cigarettes smoked on risk of lung cancer, COPD, cardiovascular disease and FEV1 – A review. Regul Toxicol Pharmacol. 2013; (67):372-81.

Li et al., Chemical Analysis and Simulated Pyrolysis of Tobacco Heating System 2.2 Compared to Conventional Cigarettes. Nicotine & Tobacco Research, 2018: p. 1-8.

Liu X, Lugo A, Spizzichino L, et al. Heat-not-burn tobacco products: concerns from the Italian experience; Tob Control January 2019 Vol 28 No 1

Liu X, Lugo A, Spizzichino L, Tabuchi T, Pacifici R, Gallus S, (2018). Heat-not-burn tobacco products: Concerns from the Italian experience. Tobacco Control. 28. tobaccocontrol-2017. 10.1136/tobaccocontrol-2017-054054.

Lo Sasso, G., B. Titz, C. Nury, S. Boué, B. Phillips, V. Belcastro, T. Schneider, S. Dijon, K. Baumer, D. Peric, R. Dulize, A. Elamin, E. Guedj, A. Buettner, P. Leroy, S. Kleinhans, G. Vuillaume, E. Veljkovic, N. V. Ivanov, F. Martin, P. Vanscheeuwijck, M. C. Peitsch and J. Hoeng (2016a). Effects of cigarette smoke, cessation and switching to a candidate modified risk tobacco product on the liver in Apoe$^{-/-}$ mice – a systems toxicology analysis. Inhal Toxicol 28(5): 226-240. (PMID: 27027324)

Luedicke F, Ansari SM, Lama N, Blanc N, Bosilkovska M, Donelli A, Picavet P, Baker G, Haziza C, Peitsch M, Weitkunat R (2019) Effects of Switching to a Heat-Not-Burn Tobacco Product on Biologically-Relevant Biomarkers to assess a Candidate Modified Risk Tobacco Product: A Randomized Trial. **Cancer Epidemiology, biomarkers and prevention**, e-pub ahead of print. (PMID: 31270101).

Luedicke FP, Picavet P; Baker, G.; Haziza, C.; Poux, V.; Lama, N.; Weitkunat, R. (2018) Effects of Switching to the Tobacco Heating System 2.2 Menthol, Smoking Abstinence, or Continued Cigarette Smoking on Biomarkers of Exposure: A Randomized, Controlled, Open-Label, Multicenter Study in Sequential Confinement and Ambulatory Settings (Part 1). Nicotine & Tobacco Research.;20(2):161-172. doi: 10.1093/ntr/ntw287. PubMed PMID: 28177489

Mallock et al., 2019 Heated Tobacco Products: A Review of Current Knowledge and Initial Assessments. Frontiers in Public Health. 7:287. doi: 10.3389/fpubh.2019.00287

Mallock et al., Levels of selected analytes in the emissions of "heat not burn" tobacco products that are relevant to assess human health risks. Archives of Toxicology, 2018. 92(6): p. 2145-2149

Market Research Report. Heated Tobacco Products Market Size, Share & Trends Analysis Report By Product (Stick, Leaf), By Distribution Channel (Online, Offline), By Region, And Segment Forecasts, 2019 – 2025, Grand View Research, 2019,

available at: https://www.grandviewresearch.com/industry-analysis/heated-tobacco-products-htps-market

Mayer B., How much nicotine kills a human? Tracing back the generally accepted lethal dose to dubious self-experiments in the nineteenth century. Arch Toxicol. 2014;88(1):5-7. doi: 10.1007/s00204-013-1127-0. PubMed PMID: 24091634; PubMed Central PMCID: PMCPMC3880486.

Mitova MI, Bielik N, Campelos PB, Cluse C, Goujon-Ginglinger C, Jaquier A, Gomez Lueso M, Maeder S, Pitton C, Poget L, Polier-Calame J, Rotach M, Rouget EGR, Schaller M, Tharin M and Zaugg V (2019) Air quality assessment of the Tobacco Heating System 2.2 under simulated residential conditions. **Air Quality, Atmosphere & Health,** 12:807-823.

Mitova MI, Campelos PB, Goujon-Ginglinger CG, Maeder S, Mottier N, Rouget EG, Tharin M and Tricker AR (2016) Comparison of the impact of the Tobacco Heating System 2.2 and a cigarette on indoor air quality. **Regulatory Toxicology and Pharmacology**, 80:91-101. (PMID: 27311683).

MSD Manuals, Kenilworth, NJ, USA: Merck Sharp & Dohme Corp.; 2018 [cited 2018], available from: https://www.msdmanuals.com/professional .

National Drug Strategy Household Survey (NDSHS) 2016—key findings, available at: https://www.aihw.gov.au/reports/illicit-use-of-drugs/ndshs-2016-key-findings/contents/tobacco-smoking

Niaura R, Re-thinking nicotine and its effects, Dec. 02, 2016, available at: https://www.truthinitiative.org/sites/default/files/media/files/2019/08/ReThinking-Nicotine_0.pdf

Nordlund, M., et al., (2019) Scientific substantiation of the absence of combustion and no smoke formation in the Electrically Heated Tobacco Product (EHTP), version 1.0. Scientific substantiation report dated January 21, 2019, Philip Morris Products S.A. https://www.pmiscience.com/library/publication/scientific-substantiation-of-the-absence-of-combustion-and-no-smoke-formation-in-the-electrically-heated-tobacco-product-ehtp

Nordlund, M., Kuczaj, A.K. 2016. Modeling aerosol formation in an electrically heated tobacco product. Int. J. Chem. Mol. Nucl. Mater. Metal. Eng. 10, 334-346

Osaki Y., Chief investigator, Professor, Division of Environmental and Preventive Medicine, Faculty of Medicine, Tottori University. http://researchers.adm.tottori-u.ac.jp/html/100000120_en.html

Oviedo A, Lebrun S, Kogel U, Ho J, Tan WT, Titz B, Leroy P, Vuillaume G, Bera M, Martin FT, Rodrigo G, Esposito M, Dempsey R, Ivanov NV, Hoeng J Peitsch MC and Vanscheeuwijck P (2016) Evaluation of the Tobacco Heating System 2.2. Part 6: 90-day OECD 413 rat inhalation study with systems toxicology endpoints demonstrates reduced exposure effects of a mentholated version compared with cigarette smoke. **Regulatory Toxicology and Pharmacology**, 81 Suppl 2:S93-S122. (PMID: 27818348)

Petrović-van der Deen FS, Wilson N, Crothers A, Cleghorn CL, Gartner C, Blakely T, Potential Country-level Health and Cost Impacts of Legalizing Domestic Sale of

Vaporized Nicotine Products, Epidemiology: May 2019, Vol 30, Issue 3, p 396-404, doi: 10.1097/EDE.0000000000000975

Philip Morris Products S.A., Experimental Report for P1 Characterization. Version N°: 1.0. 2018; Available from: https://www.fda.gov/tobacco-products/advertising-and-promotion/philip-morris-products-sa-modified-risk-tobacco-product-mrtp-applications September 21, 2018 Amendment: Submission of an Amended Study Report as part of "P1 Characterization" and an Updated Clinical Study (.zip – 376 MB) **(**added November 29, 2018**)** (April 26, 2018 Amendment: Submission of "P1 Characterization" Study (.zip – 25 MB) (added October 1, 2018)).

Phillips, B., E. Veljkovic, S. Boue, W. K. Schlage, G. Vuillaume, F. Martin, B. Titz, P. Leroy, A. Buettner, A. Elamin, A. Oviedo, M. Cabanski, E. Guedj, T. Schneider, M. Talikka, N. V. Ivanov, P. Vanscheeuwijck, M. C. Peitsch and J. Hoeng (2016). An 8-month systems toxicology inhalation/cessation study in Apoe-/- mice to investigate cardiovascular and respiratory exposure effects of a candidate modified risk tobacco product, THS 2.2, compared with combustible cigarettes. Toxicol Sci 149(2): 411-432. (https://www.pmiscience.com/library/8-month-systems-toxicology-inhalationcessation-study-apoe-mice-investigate-cardiovascular) (PMID: 26609137)

Poussin C, Laurent A, Peitsch MC, Hoeng J and De Leon H (2016) Systems toxicology-based assessment of the candidate modified-risk tobacco product THS2.2 for the adhesion of monocytic cells to human coronary arterial endothelial cells. **Toxicology**, 339:73-86. (PMID: 26655683)

Pratte, P., S. Cosandey, and C. Goujon Ginglinger, Investigation of solid particles in the mainstream aerosol of the Tobacco Heating System THS2.2 and mainstream smoke of a 3R4F reference cigarette. Human & Experimental Toxicology, 2017. 36(11): p. 1115-1120.

PubChem, Nicotine, Compound Summary, available at: https://pubchem.ncbi.nlm.nih.gov/compound/Nicotine (Accessed on 6 September 2019)

Public Health England, Evidence review of e-cigarettes and heated tobacco products 2018 (Feb. 2018), available at https://www.gov.uk/government/publications/e-cigarettes-and-heated-tobacco-products-evidence-review

Queloz, S. and Etter, J.F. (2019); An online survey of users of tobacco vaporizers, reasons and modes of utilization, perceived advantages and perceived risks. BMC Public Health 19:642 https://doi.org/10.1186/s12889-019-6957-0

Ramst, L. & Wikmans, T., Mortality Attributable to Tobacco Among Men in Sweden and Other European Countries: An Analysis of Data in a WHO Report, Tobacco Induced Diseases, 12:14 (2014)

Regulatory impact statement, Supporting smokers to switch to significantly less harmful alternatives, Ministry of Health, New Zealand, January 7, 2019, available at: https://www.health.govt.nz/about-ministry/legislation-and-regulation/regulatory-impact-statements/supporting-smokers-switch-significantly-less-harmful-alternatives

Rodgman, A., Perfetti, T.A. 2013. The chemical component of tobacco and tobacco smoke. Second edition CRC Press, Boca Raton, USA.

Royal Australian College of General Practitioners, Supporting smoking cessation, available at: https://www.racgp.org.au/clinical-resources/clinical-guidelines/key-racgp-guidelines/view-all-racgp-guidelines/supporting-smoking-cessation/pharmacotherapy/nicotine-replacement-therapy (Accessed on 1 August 2019)

Royal College of Physicians (2007) Harm reduction in nicotine addiction: helping people who can't quit. Available from: http://shop.rcplondon.ac.uk/products/harm-reduction-in-nicotine-addiction-helping-people-who-cant-quit?variant=6509405637

Royal College of Physicians (2012) Fifty Years since Smoking and Health: Progress, lessons and priorities for a smoke-free UK. UK Centre for Tobacco Control Studies. Available from: https://www.rcplondon.ac.uk/projects/outputs/fifty-years-smoking-and-health

Royal College of Physicians (2016) Nicotine without smoke, Tobacco harm reduction, A report by the Tobacco Advisory Group of the Royal College of Physicians, April 2016, available at: https://www.rcplondon.ac.uk/news/next-steps-long-journey-tobacco-harm-reduction

Schaller, J.-P., et al., Evaluation of the Tobacco Heating System 2.2. Part 2: Chemical composition, genotoxicity, cytotoxicity, and physical properties of the aerosol. Regulatory Toxicology and Pharmacology, 2016. 81(Supplement 2): p. S27-S47.

Schaller, J.-P., et al., Evaluation of the Tobacco Heating System 2.2. Part 3: Influence of the tobacco blend on the formation of harmful and potentially harmful constituents of the Tobacco Heating System 2.2 aerosol. Regulatory Toxicology and Pharmacology, 2016. 81(Supplement 2): p. S48-S58.

Schipper EM, de Graaff LC, Koch BC et al. A new challenge: suicide attempt using nicotine fillings for electronic cigarettes. Br J Clin Pharmacol. 2014;78(6):1469

Schneider NG, Olmstead RE, Franzon MA, Lunell E, The nicotine inhaler: clinical pharmacokinetics and comparison with other nicotine treatments. Clinical Pharmacokinetics 2001;40:661–84.8

Simmons MS, Connett JE, Nides MA, Lindgren PG, Kleerup EC, Murray RP, Bjornson WM, Tashkin DP. Smoking reduction and the rate of decline in FEV(1): results from the Lung Health Study. Eur Respir J. 2005; 25(6):1011-7

Simonavicius E., McNeill A., Shahab L., Brose; Heat-not-burn tobacco products: a systematic literature review; Tob Control 2018;0:1–13. doi:10.1136/tobaccocontrol-2018-054419

Song YM, Cho HJ. Risk of stroke and myocardial infarction after reduction or cessation of cigarette smoking: a cohort study in Korean men. Stroke. 2008; 39(9):2432-8. Epub 2008 Jul 10.

Stead LF, Perera R, Bullen C, Mant D, Hartmann-Boyce J, Cahill K, Lancaster T, Nicotine replacement therapy for smoking cessation, Cochrane Database of Systematic

Reviews 2012, Issue 11. Art. No.: CD000146. DOI: 10.1002/14651858.CD000146.pub4 available at: https://www.cochranelibrary.com/cdsr/doi/10.1002/14651858.CD000146.pub4/full

Stinn, W., Berges, A., Meurrens, K., Buettner, A., Gebel, S., Lichtner, R.B., Janssens, K., Veljkovic, E., Xiang, Y., Roemer, E., and Haussmann, H.J. (2013a). Towards the validation of a lung tumorigenesis model with mainstream cigarette smoke inhalation using the A/J mouse. Toxicology 305, 49-64.

Stinn, W., Buettner, A., Weiler, H., Friedrichs, B., Luetjen, S., van Overveld, F., Meurrens, K., Janssens, K., Gebel, S., Stabbert, R., Haussmann HJ (2013b). Lung inflammatory effects, tumorigenesis, and emphysema development in a long-term inhalation study with cigarette mainstream smoke in mice. Toxicol Sci 131, 596-611.

Stoklosa M, Cahn Z, Liber A, et al. (2019) Effect of IQOS introduction on cigarette sales: evidence of decline and replacement, Tob Control 2019;0:1–7. doi:10.1136/tobaccocontrol-2019-054998

Streller K, Roth S, Starker Tobak - Unsere Lust und Last mit der Zigarette, Chem. Unserer Zeit **2013**, 47, 248–268. DOI: 10.1002/ciuz.201300636, available at: https://www.chemistryviews.org/details/ezine/7164151/The_Chemistry_of_Tobacco__Part_4.html

Surgeon General's Report (2014): The Health Consequences of Smoking—50 Years of Progress, available at: https://www.cdc.gov/tobacco/data_statistics/sgr/50th-anniversary/index.htm

Taylor, M. et al., 2018 Assessment of novel tobacco heating product THP1.0. Part 6: A comparative in vitro study using contemporary screening approaches. Reg. Tox. Pharm., 93, 62-70.

The Japan Times, June 30, 2018. No authors listed. Japan to restrict heated tobacco use but give up on indoor smoking ban ahead of 2020 Tokyo Olympics, available from: https://www.japantimes.co.jp/news/2018/01/30/national/science-health/japan-restrict-heated-tobacco-use-give-indoor-smoking-ban-ahead-2020-tokyo-olympics/#.WnE2WrllKUm

Therapeutic Goods Administration (TGA), Scheduling Handbook – Guidance for amending the Poisons Standard (version 1.0, January 2018), TGA, available at: https://www.tga.gov.au/book-page/version-history

Thorne, D. et al., 2018 Assessment of novel tobacco heating product THP1.0. Part 7: Comparative in vitro toxicological evaluation. Reg. Tox. Pharm., 93, 71-83.

Titz, B., S. Boue, B. Phillips, M. Talikka, T. Vihervaara, T. Schneider, C. Nury, A. Elamin, E. Guedj, M. J. Peck, W. K. Schlage, M. Cabanski, P. Leroy, G. Vuillaume, F. Martin, N. V. Ivanov, E. Veljkovic, K. Ekroos, R. Laaksonen, P. Vanscheeuwijck, M. C. Peitsch and J. Hoeng (2016). Effects of cigarette smoke, cessation and switching to two heat-not-burn tobacco products on lung lipid metabolism in C57BL/6 and Apoe-/- mice - an integrative systems toxicology analysis. Toxicol Sci 149(2): 441-457. (https://www.pmiscience.com/library/effects-cigarette-smoke-cessation-and-switching-two-heat-not-burn-tobacco-products-lung) (PMID: 26582801).

Toorn, M. et al., 2018 The biological effects of long-term exposure of human bronchial epithelial cells to total particulate matter from a candidate modified-risk tobacco product. Toxicology In Vitro 50, 95-108

Torero, J.L., Review of "The Electrically Heated Tobacco System and the Electrically Heated Tobacco Product", Technical expert report dated October 27, 2017.

U.S. Department of Health and Human Services (HHS). Surgeon General's Report: How Tobacco Smoke Causes Disease: The Biology and Behavioral Basis for Smoking-Attributable Disease, Executive Summary [Internet]. 2010 [updated 2010; cited 2016 Jun 23]. Available from: http://whyquit.com/CDC/SGR_2010_How_Tobacco_Smoke_Causes_Disease.pdf

Uchiyama, S., et al., Simple Determination of Gaseous and Particulate Compounds Generated from Heated Tobacco Products. Chemical Research in Toxicology, 2018. 31(7): p. 585-593

UK House of Commons, Science and Technology Committee, E-Cigarettes, 7th Report of Session 2017-2019 (Aug. 17, 2018), available at: https://publications.parliament.uk/pa/cm201719/cmselect/cmsctech/505/505.pdf.

Vardavas, C.I. et al. Characteristics and outcomes of e-cigarette exposure incidents reported to 10 European Poison Centers: a retrospective data analysis. Tob Induc Dis 15, 36 (2017).

Wald NJ, Watt HC. Prospective study of effect of switching from cigarettes to pipes or cigars on mortality from three smoking related diseases. BMJ. 1997; 314(7098):1860-3.

WHO Report on the Global Tobacco Epidemic, 2009, Implementing smoke-free environments, ISBN: 978 92 4 156391 8

WHO Study Group on Tobacco Product Regulation. Report on the scientific basis of tobacco product regulation: seventh report of a WHO study group, 24 October 2019, https://www.who.int/publications-detail/who-study-group-on-tobacco-product-regulation-report-on-the-scientific-basis-of-tobacco-product-regulation-seventh-report-of-a-who-study-group

Witschi, H., A/J mouse as a model for lung tumorigenesis caused by tobacco smoke: strengths and weaknesses. Exp Lung Res, 2005. 31(1): p. 3-18.

Wong ET, Kogel U, Veljkovic E, Martin F, Xiang Y, Boue S, Vuillaume G, Leroy P, Guedj E, Rodrigo G, Ivanov NV, Hoeng J, Peitsch MC, Vanscheeuwijck P. (2016)

Evaluation of the Tobacco Heating System 2.2. Part 4: 90-day OECD 413 rat inhalation study with systems toxicology endpoints demonstrates reduced exposure effects compared with cigarette smoke. Regul Toxicol Pharmacol. 81 Suppl 2: S59-S81

World Health Organization (WHO) Regional Office for Europe Copenhagen, Air Quality Guidelines for Europe. Second ed. 2000: WHO Regional Publications, European Series, No. 91.

World Health Organization (WHO), Heated Tobacco Products (HTPs), Market Monitoring Information Sheet, July 2018, WHO/NMH/PND/18.7, available at:

https://apps.who.int/iris/bitstream/handle/10665/273459/WHO-NMH-PND-18.7-eng.pdf?ua=1

Zeller M, The Strategic Dialogue on Tobacco Harm Reduction: A Vision and Blueprint for Action in the U.S., Tobacco Control, 18(4): 324–332, (Aug. 2009), doi: 10.1136/tc.2008.027318.

Glossary

Abbreviation	Definition
3R4F	Reference cigarette produced by the University of Kentucky
ABS	Australian Bureau of Statistics
ANDS	Alternative Nicotine Delivery Systems
ANPRM	Advance Notice of Proposed Rulemaking, FDA (U.S.)
AUC	Area under the concentration-time curve
$AUC_{(0\text{-}24\ h)}$	Area under the concentration-time curve from 0 to 24 hours
$AUC_{(0\text{-}last)}$	Area under plasma concentration-time curve from start of product use to time of last quantifiable concentration
$AUC_{(0\text{-}t')}$	Partial AUC, where t' is the subject-specific time of maximum nicotine concentration
BAT	British American Tobacco
BfR	German Federal Institute for Risk Assessment
BoExp/ BoE	Biomarker(s) of exposure. A chemical, its metabolite, or the product of an interaction between a chemical and some target molecule or cell that is measured in the human body (e.g. cotinine in blood or urine for second-hand tobacco smoke, benzene metabolites in urine for traffic-related pollution)
CC	Conventional cigarette, Combustible cigarette
CI	Confidence interval
CISPR	International Special Committee for Radio Protection
CLP	Classification, Labelling and Packaging (E.U.)
C_m	Maximum nicotine concentration
C_{max}	Maximum plasma concentration
C_{min}	Minimum plasma drug concentration
CNS	Central Nervous System
COAG	Council of Australian Government
COHb	Carboxyhemoglobin
COPD	Chronic obstructive pulmonary disease
COT	Committee of Toxicology (U.K.)
CROs	Contract Research Organisation
CTP	Center of Tobacco Products, FDA (U.S.)
CVD	Cardiovascular disease
DoH or DOH	Commonwealth Department of Health

EAC	Eurasian Conformity standards
EHTP	Electrically Heated Tobacco Product. Typically consists of a consumable product (such as tobacco sticks or *HeatSticks*) that contains tobacco which is electrically heated
EHTS	Electrically Heated Tobacco Systems
EN	European Norm standards
ENDS	Electronic Nicotine Delivery Systems
ETS	Environmental tobacco smoke. Also known as secondhand smoke, it is a complex mixture of chemicals generated during the burning and smoking of tobacco products to which a person is unintentionally exposed, most commonly in the home, formerly in public places. It comes from both the smoke from the tip of the cigarette and the smoke that the smoker is exhaling
FCTC	Framework Convention of Tobacco Control (W.H.O.)
FDA	Food and Drug Administration (U.S.)
FDA-18	Abbreviated FDA list of 18 HPHCs in smoke/aerosol
FDA-18 + 6	Abbreviated FDA list of 18 HPHCs in smoke/aerosol + 6 tobacco constituents
FDA-93	Established FDA list of 93 HPHCs in tobacco products and tobacco smoke
FEV_1	Forced expiry volume in 1 second
FFC	Federal Communications Commission (U.S.)
HC	Health Canada (including Health Canada list of 44 constituents in the mainstream smoke of tobacco products)
HCI	Health Canada Intense (puffing regime). First described by Health Canada, when taking one puff of 55 ml volume and 2 s duration every 30 s with 100 % of the ventilation zone on the cigarette filter blocked
HD	Heart Disease
HDL-C	High Density lipoprotein-C
HeatSticks	Specially designed heated tobacco consumables that contain tobacco and is intended for exclusive use with the *IQOS* holder
HNB or HnB	Heat-not-burn. Refers to tobacco that is heated instead of lit or burnt. Also referred to as a Heated Tobacco Product (HTP)
HPHCs	Harmful and potentially harmful constituent(s). Chemical compounds in tobacco products or tobacco smoke that cause or could cause harm to smokers or nonsmokers
HTP	Heated Tobacco Product. The consumable product (such as tobacco sticks or *HeatSticks*) that contains tobacco for heating
IAQ	Indoor air quality
IARC	International Agency for Research on Cancer
IC	Integrated Circuit

IEC	International Electrotechnical Commission
IOM	Institute of Medicine
iQOS and *IQOS*	Commercial names (both registered trademarks) of PMI's Tobacco Heating Device
ISO	International Organization for Standardization
JNFA	Japanese National Fire Authority
JTI	Japan Tobacco International
KT&G	Korean Tobacco & Ginseng
LOQ	Limit of Quantitation/ Quantification
MFDS	Ministry of Food and Drug Safety (Korea)
MLA	Mouse Lymphoma Assay
MRTP	Modified risk tobacco product
MRTPA	Modified risk tobacco product application
NFDPM	Nicotine-Free Dry Particulate Matter
NNAL	4-(methylnitrosamino)-1-(3-pyridyl)-1-butanol
NNS	Nicotine Nasal Spray
NTDA	Non Targeted Differential Analysis
NRT	Nicotine replacement therapy
OECD	Organization for Economic Co-operation and Development
PHE	Public Health England
PK	Pharmacokinetics
PK/PD	The relationship between blood plasma nicotine (PK) concentration and suppressing the urge to smoke (PD) in adult smokers
PM USA	Philip Morris U.S.A.
PMI	Philip Morris International, which is comprised of the following entities: (1) Philip Morris International Inc., (2) Philip Morris Products S.A., (3) Philip Morris International Management S.A., (4) Philip Morris International Research Laboratories Pte. Ltd., and (5) Philip Morris Manufacturing & Technology Bologna S.p.A
PMI-58	List of constituents and analytes defined by PMI that are quantified in the THS aerosol
PML	Philip Morris Limited, the Australian Philip Morris International subsidiary
PMTA	Premarket tobacco product application
R&D	Research and Development
RCP	Royal College of Physicians (U.K.)
REX	Reduced exposure studies
REXA	Reduced exposure studies in ambulatory settings

REXC	Reduced exposure studies in confinement settings
RACGP	Royal Australian College of General Practitioners
RRP	Reduced risk product(s)
SA	Smoking Abstinence
SmPC	Summary of Product Characteristics
To	Time point of first product use during study day
"Tar"	Nicotine-Free Dry Particulate Matter (NFDPM)
THD	Tobacco Heating Device (Holder and Charger)
THS	Tobacco Heating System (Tobacco Heating Device + HTP/Tobacco Sticks). Combination of consumable product (HTP) plus heating device. Also referred to as an EHTS (Electrically Heated Tobacco System) if the heat source is electronic.
Tobacco Sticks	Tobacco containing sticks (resembling cigarettes) manufactured to be used as part of the THS. May also be sometimes referred to as Heat Sticks.
T_{max}	Time to the maximum concentration
TPM	Total particulate matter
TSNA	Tobacco-specific N-nitrosamines
Type II Error	A Type I error is the rejection of a true null hypothesis, whereas Type II error describes the error that occurs when one fails to reject a null hypothesis *that is actually false.* In other words, it produces a false positive. The error rejects the alternative hypothesis, even though it does not occur due to chance.
UL	Underwriters Laboratories standards
US SURG	United States Surgeon General
WBC	White blood cell (count)
WHO	World Health Organization

APPENDIX 2: MARKETED HTP DEVICES AND CONSUMABLES

Appendix 2: Marketed HTP Devices and Consumables

Company	Product	Brand	Markets available
BAT	Consumable	Dunhill (for glo)	Bulgaria
BAT	Consumable	Kent (for glo)	Romania, Japan, Russia, Azerbaijan, Ukraine
BAT	Consumable	Kool (for glo)	Japan
BAT	Consumable	Neo (for glo)	Switzerland, Japan, Croatia, South Korea, Malaysia, Ukraine, Greece, Czech Republic, Kazakhstan, Poland, Serbia, Italy
BAT	Device	Glo Express	Italy, Romania
BAT	Device	Glo nano	Romania, Italy
BAT	Device	Glo series 1	Malaysia. Switzerland, Serbia
BAT	Device	Glo series 2	Poland, Romania, Malaysia, Japan, Croatia, Ukraine, Greece, Kazakhstan, Russia, Bulgaria, South Korea, Czech Republic, Azerbaijan
BAT	Device	Glo series 2 mini	Japan, Croatia, South Korea, Ukraine, Greece, Kazakhstan, Russia, Bulgaria,
CNTC	Consumable	COO (for MOK)	South Korea, Maldives
CNTC	Consumable	Kuanzhai (for KungFu)	South Korea
CNTC	Consumable	MC (for MC)	South Korea
CNTC	Device	MOK	South Korea, Maldives
CNTC	Device	MOK mini	South Korea, Maldives
CNTC	Device	KungFu	South Korea
CNTC	Device	MC 2.0 (Mate)	South Korea
Imperial	Consumable	iD (for Pulze)	Japan
Imperial	Device	Pulze	Japan
JTI	Consumable	Mevius (for Ploom S)	Japan
JTI	Device	Ploom S	Japan
KT&G	Consumable	Fiit (for lil)	South Korea
KT&G	Device	lil mini	South Korea

KT&G	Device	lil Plus	South Korea
PMI	Consumable	HEETS	Japan, Korea, Malaysia, New Zealand, Albania, Armenia, Belarus, Bosnia & Herz., Israel, Kazakhstan, Moldova, Russia, Serbia, Ukraine, Andorra, Azores, Bulgaria, Canary Islands, Corsica, Croatia, Cyprus, Czech Republic, Denmark, France, Germany, Greece, Hungary, Italy, Latvia, Lithuania, Madeira, Netherlands, Poland, Portugal, Romania, Slovak Republic, Slovenia, Spain Mainland, Sweden, Switzerland, United Kingdom,, Canada, Caribbean Other, Colombia, Dominican Republic, Guatemala, PMIDF (PMI Duty Free), Palestine Auth. Area, Reunion, South Africa, Turkish Cyprus, UAE
PMI	Consumable	Marlboro	Japan
PMI	Device	iQOS	As per HEETS consumables

Note: As at September 2019

APPENDIX 3 – INDEPENDENT PUBLICATIONS

2019

1. Andrikopoulos, G.I., Zagoriti, Z., Topouzis, S. et al. (2019). Oxidative stress induced by electronic nicotine delivery systems (ENDS): Focus on respiratory system. Curr Opin Toxicol. 13:81-89.
2. Barben, J., Künzli, N. (2019). [Smoking prevention: new trends and challenges]. Swiss Medical Forum 19(3334): 531-536.
3. Barben, J., Schuurmans, M.M., Zürcher, A., et al. (2019). [Reduced-Risk, ineffective strategy against tobacco]. Bulletin des médecins suisses, 100(3132):1041-1044. [Article in French].
4. Bar-Zeev, Y., Levine, H., Rubinstein, G. et al. (2019). IQOS point-of-sale marketing strategies in Israel: a pilot study. Isr J Health Policy Res. 8(1):11.
5. Beatrice, F., Massaro, G. (2019). Exhaled Carbon Monoxide Levels in Forty Resistant to Cessation Male Smokers after Six Months of Full Switch to Electronic Cigarettes (e-Cigs) or to A Tobacco Heating Systems (THS). Int J Environ Res Public Health. 16(20).
6. Biondi-Zoccai, G., Sciarretta, S., Bullen, C. et al. (2019). Acute Effects of Heat-Not-Burn, Electronic Vaping, and Traditional Tobacco Combustion Cigarettes: The Sapienza University of Rome-Vascular Assessment of Proatherosclerotic Effects of Smoking (SUR - VAPES) 2 Randomized Trial. J Am Heart Assoc. 8(6):e010455.
7. Cancelada, L., Sleiman, M., Tang, X. et al. (2019). Heated Tobacco Products: Volatile Emissions and Their Predicted Impact on Indoor Air Quality. Environ Sci Technol. 53(13):7866-7876.
8. Clapp, P. W., Jadelis, C. T., Wu, J. et al. (2019). Characterization of the physical and thermal properties of new and emerging tobacco product (NETP) emissions. J. Aerosol. Med. Pulm. Drug. Deliv. 32(3):A31.
9. Conklin, D.J., Schick, S., Blaha, M.J. et al. (2019). Cardiovascular injury induced by tobacco products: assessment of risk factors and biomarkers of harm. A Tobacco Centers of Regulatory Science compilation. Am J Physiol Heart Circ Physiol. 316(4):H801-H827.
10. Crooks, I. (2019). In vitro mutagenicity of gas-vapour phase extracts from flavoured and unflavoured heated tobacco products. Toxicology Rep. doi: 10.1016/j.toxrep.2019.10.007.
11. Davis B., To V., Talbot P. (2019). Comparison of cytotoxicity of IQOS aerosols to smoke from marlboro Red and 3R4F reference cigarettes. Toxicol In Vitro. doi: 10.1016/j.tiv.2019.104652.
12. Drovandi, A., Salem, S., Barker, D. et al. (2019). Human Biomarker Exposure from Cigarettes versus Novel Heat-Not-Burn Devices: A Systematic Review and Meta-Analysis. Nicotine Tob Res. doi: 10.1093/ntr/ntz200.
13. Eke, B.C., Başaran, R., Güven, N.M. (2019). An overview of iQOS® as a new heat-not-burn tobacco product and its potential effects on human health and environment. Turk J Pharm Sci. 16(3):371-374.
14. Farsalinos, K., Diamantopoulou. E., Panagiotopoulou, E. et al. (2019). Patterns of use, past smoking status, and biochemically verified current smoking status of heated tobacco product (IQOS) shops customers: preliminary results. Chest. 155(6):A387.
15. Formoso, G., Celani, M.G., Minozzi, S. et al. (2019). Heated tobacco and politics in Italy. BMJ. 365:l4189.
16. Freeman, B., Hefler, M., Hunt, D. (2019). Philip Morris International's use of Facebook to undermine Australian tobacco control laws.Public Health Res Pract. 29(3):e2931924.
17. Gong, S., Liu, W., Huang, P. et al. (2019). Puff-by-puff release of main aerosol components from two commercial heat-not-burn tobacco products.Tobacco Science and Technology. 52(2):62-71.
18. Górski, P. (2019). E-cigarettes or heat-not-burn tobacco products - advantages or disadvantages for the lungs of smokers. Adv Respir Med. 87(2):123-134.

19. Gravely, S., Driezen, P., Ouimet, J. et al. (2019). Prevalence of awareness, ever-use and current use of nicotine vaping products (NVPs) among adult current smokers and ex-smokers in 14 countries with differing regulations on sales and marketing of NVPs: cross-sectional findings from the ITC Project. Addiction. 114(6):1060-1073.
20. Gupta, R., Gupta, S., Sharma, S. et al. (2019). Risk of Coronary Heart Disease Among Smokeless Tobacco Users: Results of Systematic Review and Meta-Analysis of Global Data. Nicotine Tob Res. 21(1):25-31.
21. Hitosugi, M., Tojo, M., Shiomi, N., et al. (2019). Criminal mercury vapor poisoning using heated tobacco product. Int J Legal Med. 133(2):479-481.
22. Hwang, J.H., Ryu, D.H., Park, S.-W. (2019). Heated tobacco products: cigarette complements, not substitutes. Drug Alcohol Depend. 204:107576.
23. Ibañez, M.P., Martin, D., Gonzálvez, A.G. et al. (2019). A Comparative Study of Non-Volatile Compounds Present in 3R4F Cigarettes and iQOS Heatsticks Utilizing GC-MS. Am J Analyt Chem. 10:76-85.
24. Ishizaki, A., Kataoka, H. (2019). A sensitive method for the determination of tobacco-specific nitrosamines in mainstream and sidestream smokes of combustion cigarettes and heated tobacco products by online in-tube solid-phase microextraction coupled with liquid chromatography-tandem mass spectrometry. Analytica Chimica Acta. 1075:98-105.
25. Ito, S., Taylor, M., Mori, S., et al. (2019). An inter-laboratory in vitro assessment of cigarettes and next generation nicotine delivery products. Toxicol Lett. 315:14-22.
26. Jabba, S.V., Jordt, S.E. (2019). Risk Analysis for the Carcinogen Pulegone in Mint- and Menthol-Flavored e-Cigarettes and Smokeless Tobacco Products. JAMA Intern Med. doi: 10.1001/jamainternmed.2019.3649.
27. Jackson, S.E., Shahab, L., Kock, L. et al. (2019). Expenditure on smoking and alternative nicotine delivery products: a population survey in England. Addiction. 114(11):2026-2036.
28. Jacob, M. (2019). Looking Back and Ahead: The Food and Drug Administration's Regulation of the Tobacco Industry and Next-Generation Products. Adv Dent Res. 30(1):22-25.
29. Jankowski, M., Brożek, G.M., Lawson, J. et al. (2019). New ideas, old problems? Heated tobacco products – a systematic review. Int J Occup Med Environ Health. 32(5):595-634.
30. Jeong, W.T.; Cho, H.K.; Lee, H.R. et al. (2019). Comparison of the content of tobacco alkaloids and tobacco-specific nitrosamines in 'heat-not-burn' tobacco products before and after aerosol generation. Inhalation Inhal Toxicol. 11:1-7.
31. Kang, H., Cho, S.H. (2019). Heated tobacco product use among Korean adolescents. Tob Control. doi: 10.1136/tobaccocontrol-2019-054949.
32. Kastaun, S., Kotz, D. (2019). [Should advertising for electronic cigarettes and heated tobacco products be banned in Germany? Results of a representative survey (DEBRA study)]. Bundesgesundheitsbl. doi: 10.1007/s00103-019-03017-6.
33. Kaunelienė, V., Meišutovič-Akhtarieva, M., Prasauskas, T. et al. (2019). Impact of Using a Tobacco Heating System (THS) on Indoor Air Quality in a Nightclub. Aerosol Air Qual. Res. 19(9):1961-1968.
34. Kistler, C.E., Ranney, L.M., Sutfin, E.L. et al. (2019). Product attributes important to US adult consumers' use of electronic nicotine delivery systems: a discrete choice experiment. BMJ Open. 9(8):e027247.
35. Kopa, P.N., Pawliczak, R. (2019). IQOS - a heat-not-burn (HnB) tobacco product - chemical composition and possible impact on oxidative stress and inflammatory response. A Systematic Review. Toxicol Mech Methods. doi: 10.1080/15376516.2019.1669245.
36. La Torre, G., Dorelli, B., Ricciardi, M. (2019). Smoking E-CigaRette and HEat-noT-burn products: validation of the SECRHET questionnaire. Clin Ter. 170(4):e247-e251.

37. Lauterstein, D., Savidge, M., Chen, Y. et al. (2019). Nonanimal toxicology testing approaches for traditional and deemed tobacco products in a complex regulatory environment: Limitations, possibilities, and future directions. Toxicol In Vitro. doi: 10.1016/j.tiv.2019.104684.
38. Lee, A., Lee, K.-S., Park, H. (2019). Association of the Use of a Heated Tobacco Product with Perceived Stress, Physical Activity, and Internet Use in Korean Adolescents. National Survey. Int. J. Environ. Res. Public Health. 16(6):965.
39. Lee, J.G.L., Blanchflower, T.M., O'Brien, K.F. et al. (2019). Evolving IQOS packaging designs change perceptions of product appeal, uniqueness, quality and safety: a randomised experiment, 2018, USA. Tob Control. doi: 10.1136/tobaccocontrol-2018-054910.
40. Li, X., Luo, Y., Jiang, X. et al. (2019). Chemical analysis and simulated pyrolysis of Tobacco Heating System 2.2 compared to conventional cigarettes. Nicotine Tob Res. 21(1):111-118.
41. Liu, X., Lugo, A., Spizzichino, L. et al. (2019). Heat-not-burn tobacco products: concerns from the Italian experience. Tob Control. 28(1):113-114.
42. Malela, S., Scott, A., Thickett, D. (2019). Effects of IQOS on macrophage viability and function. ERJ Open Research 5(suppl 2):PP130.
43. Mallock, N., Hutzler, C., Henkler-Stephani, F. et al. (2019). Heated Tobacco Products: A review of current knowledge and initial assessments. Front Public Health. 7:287.
44. Marsden, D.G., Loukas, A., Chen, B. et al. (2019). Associations between frequency of cigarette and alternative tobacco product use and depressive symptoms: A longitudinal study of young adults. Addict Behav. 99:106078.
45. McAlinden, K.D., Sohal, S.S, Sharma, P. (2019). There can be smoke without fire: warranted caution in promoting electronic cigarettes and heat not burn devices as a safer alternative to cigarette smoking. ERJ Open Res. 5: 00114-2019.
46. Meehan-Atrash, J., Duell, A.K., McWhirter, K.J. et al. (2019). Free-Base Nicotine Is Nearly Absent in Aerosol from IQOS Heat-Not-Burn Devices, As Determined by 1H NMR Spectroscopy. Chem Res Toxicol. 32(6):974-976.
47. Meišutovič-Akhtarieva, M., Prasauskas, T., Čiužas, D. et al. (2019). Impacts of exhaled aerosol from the usage of the tobacco heating system to indoor air quality: A chamber study. Chemosp. 223:474-482.
48. Mendes. A. (2019). Smoking cessation in 2019. Br J Community Nurs. 24(3), pp. 144–145.
49. Mohanty, D.; Lippmann, S. (2019). We must counsel against heat-not-burn cigarettes. J Fam Pract. 68(1):E2-E3.
50. Muhammad-Kah, R.S., Pithawalla, Y.B., Boone, E.L. et al. (2019). A Computational Model for Assessing the Population Health Impact of Introducing a Modified Risk Claim on an Existing Smokeless Tobacco Product. Int J Environ Res Public Health. 16(7):E1264.
51. Newland, N., Lowe, F.J., Camacho, O.M. et al. (2019). Evaluating the effects of switching from cigarette smoking to using a heated tobacco product on health effect indicators in healthy subjects: study protocol for a randomized controlled trial. Intern Emerg Med. 14(6):885-898.
52. Nistorescu, N., Pop Ananda, D., Croitoru Mircea, D. (2019). Difficulties in measuring the amount of cyanide by various method and their application in the toxicological risk assessment of classic cigarettes versus IQOS system. Acta Medica Marisiensis. 65(S1):58.
53. Ozga-Hess, J.E., Felicione, N.J., Ferguson, S.G. et al. (2019). Piloting a clinical laboratory method to evaluate the influence of potential modified risk tobacco products on smokers' quit-related motivation, choice, and behavior. Addict Behav. 99:106105.
54. Pisinger, C., Mackay, J. (2019). New Tobacco Products Do Not Protect Public Health. Ann Am Thorac Soc. doi: 10.1513/AnnalsATS.201905-411PS.

55. Polosa, R., Farsalinos, K. ,Prisco, D. (2019). Health impact of electronic cigarettes and heated tobacco systems. Intern Emerg Med. 14(6):817-820.
56. Polosa, R., Urso, S., Farsalinos, K. E. (2019). Response to "New tobacco products, a threat for tobacco control and public health of Mexico". Salud Publica Mex. 61(4):552-553.
57. Poynton, S., Sutton, J., Goodall, S. et al. (2019). 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(Pt A):522-532.
58. Prochaska, J.J, Henriksen, L. (2019). PMI reduced-risk claims and upselling of IQOS via Reviti life insurance. Tob Control. doi: 10.1136/tobaccocontrol-2019-055145.
59. Queloz, S., Etter, J.F. (2019). An online survey of users of tobacco vaporizers, reasons and modes of utilization, perceived advantages and perceived risks. BMC Public Health. 19(1):642.
60. Quinto, C. B. (2019).[Promoter of health]. Bulletin des médecins suisses, 100(34):1099-1099.
61. Ravara S. (2019). The ERS position paper on heated tobacco products. Tob Prev Cessation. 5(Supplement):A29. doi:10.18332/tpc/105322. doi: 10.18332/tpc/105322.
62. Reynales-Shigematsu L.M., Roa-Rodríguez, R., Barrington-Trimis, J.L., et al. (2019). [Current and emerging issues in tobacco prevention and control]. Salud Publica Mex. 61:436-447.
63. Savareear, B., Escobar-Arnanz, J., Brokl, M. et al. (2019). Non-targeted analysis of the particulate phase of heated tobacco product aerosol and cigarette mainstream tobacco smoke by thermal desorption comprehensive two-dimensional gas chromatography with dual flame ionisation and mass spectrometric detection. J Chromatogr A. 1603:327-337.
64. Schober, W.; Fembacher, L.; Frenzen, A. et al. (2019). Passive exposure to pollutants from conventional cigarettes and new electronic smoking devices (IQOS, e-cigarette) in passenger cars. Int J Hyg Environ Health. 222(3):486-493.
65. Shein, M., Jeschke, G. (2019). Comparison of Free Radical Levels in the Aerosol from Conventional Cigarettes, Electronic Cigarettes, and Heat-Not-Burn Tobacco Products. Chem Res Toxicol. 32(6):1289-1298.
66. Signes-Costa, J., de Granda-Orive, J,I, Ramos Pinedo, Á. et al. (2019). Official Statement of the Spanish Society of Pulmonology and Thoracic Surgery (SEPAR) on Electronic Cigarettes and IQOS®. Arch Bronconeumol. doi: 10.1016/j.arbres.2019.
67. Sohal; S.; Eapen, M.; Naidu, V.; (2019). IQOS exposure impairs human airway cell homeostasis: direct comparison with traditional cigarette and e-cigarette. ERJ Open Res. 11;5(1). pii: 00159-2018.
68. St Helen, G., Benowitz, N.L., Ko, J. (2019). Differences in exposure to toxic and/or carcinogenic volatile organic compounds between Black and White cigarette smokers. J Expo Sci Environ Epidemiol. doi: 10.1038/s41370-019-0159-9.
69. Stone, E., Marshall, H. (2019). Tobacco and electronic nicotine delivery systems regulation. Transl Lung Cancer Res. 8(Suppl 1):S67-S76.
70. Strong, D.R., Messer, K., White, M. et al. (2019). Youth perception of harm and addictiveness of tobacco products: Findings from the Population Assessment of Tobacco and Health Study (Wave 1). Addict Behav. 92:128-135.
71. Thorne, D., Leverette, R., Breheny, D. et al. (2019). Genotoxicity evaluation of tobacco and nicotine delivery products: Part Two. In vitro micronucleus assay. Food Chem Toxicol. 132:110546.
72. Wu, Y.S., Wang, M.P., Ho, S.Y. et al. (2019). Heated tobacco products use in Chinese adults in Hong Kong: a population-based cross-sectional study. Tob Control. doi: 10.1136/tobaccocontrol-2018-054719.

2018

73. Adriaens, K., Van Gucht, D., Baeyens, F. (2018). IQOS™ vs. e-Cigarette vs. Tobacco Cigarette: A Direct Comparison of Short-Term Effects after Overnight-Abstinence. Int J Environ Res Public Health. 15:2902.
74. Berthet, A., Jacot Sadowski, J., Zurcher, K. et al. (2018). Heated tobacco products: what do you need to know? Rev Med Suisse, 14(625):1935-1941.
75. Bialous, S.A., Glantz S.A. (2018). Heated tobacco products: another tobacco industry global strategy to slow progress in tobacco control. Tob Control. 27(Suppl 1):s111-s117.
76. Brose, L.S., Simonavicius E., Cheeseman, H. (2018). Awareness and use of 'heat-not-burn' tobacco products in Great Britain. Tob Regul Sci. 4(2):44-50.
77. Caponnetto, P., Maglia, M., Prosperini, G., et al. (2018) Carbon monoxide levels after inhalation from new generation heated tobacco products. Respir Res. 19(1):164.
78. Cho, Y.J., Trasher, J.F. (2018). Flavour capsule heat-sticks for heated tobacco products. Tob Control. doi:10.1136/tobaccocontrol-2018-054472 .
79. Chun, L., Moazed, F., Matthay, M., et al. (2018). Possible hepatotoxicity of IQOS. Tob Control. 27:s39–s40.
80. Crooks, I., Neilson, L., Scott, K., et al. (2018). Evaluation of flavourings potentially used in a heated tobacco product: Chemical analysis, in vitro mutagenicity, genotoxicity, cytotoxicity and in vitro tumour promoting activity. Food and Chemical Toxicol. 118: 940-952.
81. Czoli, C.D., White, C.M., Reid, J.L., et al. (2018). Awareness and interest in IQOS heated tobacco products among youth in Canada, England and the USA. Tob Control. doi: 10.1136/tobaccocontrol-2018-054654.
82. Dautzenberg, B., Dautzenberg, M.D. (2018). Le tabac chauffé : revue systématique de la littérature. Rev Mal Respir. 36(1):82-103.
83. Davis, B., Williams, M., Talbot, P. (2018). iQOS: evidence of pyrolysis and release of a toxicant from plastic. Tob Control. 28:34-41.
84. Eaton, D., Jakaj, B., Forster, M. et al. (2018). Assessment of tobacco heating product THP1.0. Part 2: Product design, operation and thermophysical characterisation. Regul Toxicol Pharmacol. 93:4-13.
85. Elias, J., Dutra, L.M., St Helen, G., et al. (2018). Revolution or redux? Assessing IQOS through a precursor product. Tob Control. 27:s102–s110.
86. Elias, J., Ling, P.M. (2018). Invisible smoke: third-party endorsement and the resurrection of heat-not-burn tobacco products. Tob Control. 27:s96–s101.
87. El-Toukhy, S., Baig, S.A., Jeong, M., et al. (2018). Impact of modified risk tobacco product claims on beliefs of US adults and adolescents. Tob Control. 27:s62–s69.
88. Farsalinos, K.E., Yannovits, N., Sarri, T et al. (2018). Carbonyl emissions from a novel heated tobacco product (IQOS): comparison with an e-cigarette and a tobacco cigarette. Addiction. 113(11):2099-2106.
89. Farsalinos, K.E., Yannovits, N., Sarri, T. et al. (2018). Nicotine delivery to the aerosol of a heat-not-burn tobacco product: comparison with a tobacco cigarette and e-cigarettes. Nicotine Tob Res. 20(8):1004-1009.
90. Forster, M., McAughey, J., Prasad, K. et al. (2018). Assessment of tobacco heating product THP1.0. Part 4: Characterisation of indoor air quality and odour. Regul Toxicol Pharmacol. 93:34-51.
91. Foster, M., Fiebelkorn, S., Yurteri, C. et al. (2018). Assessment of novel tobacco heating product THP1.0. Part 3: Comprehensive chemical characterisation of harmful and potentially harmful aerosol emissions. Regul Toxicol Pharm. 93:14-33.

92. Gale, N., McEwan, M., Eldridge, A.C. et al. (2018). Changes in Biomarkers of Exposure on Switching From a Conventional Cigarette to Tobacco Heating Products: A Randomized, Controlled Study in Healthy Japanese Subjects. Nicotine Tob Res. 21(9):1220-1227.
93. Gasparyan, H., Mariner, D., Wright, C. et al. (2018). Accurate measurement of main aerosol constituents from heated tobacco products (HTPs): Implications for a fundamentally different aerosol. Regul toxicol Pharmacol. 99:131-141.
94. Gee, J., Prasad, K., Slayford, S. et al. (2018). 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. 93:84-91.
95. Glantz, S.A. (2018). Heated tobacco products: the example of IQOS. Tob Control. 27(Suppl 1):s1-s6.
96. Glantz, S.A. (2018). PMI's own in vivo clinical data on biomarkers of potential harm in Americans show that IQOS is not detectably different from conventional cigarettes. Tob Control. 27:s9–s12.
97. Hair, E.C., Bennett, M., Sheen, E. et al. (2018). Examining perceptions about IQOS heated tobacco product: consumer studies in Japan and Switzerland. Tob Control. 27(Suppl 1):s70-s73.
98. Haswell, L.E., Corke, S., Verrastro, I., et al. (2018). In vitro RNA-seq-based toxicogenomics assessment shows reduced biological effect of tobacco heating products when compared to cigarette smoke. Sci Rep. 8:1145.
99. Humbel, F., Sattler, A., Schuurmans, M.M. (2018). Erhitzter Tabak und «Heat not Burn»-Tabakprodukte. Praxis. 107:315-322.
100. Jenssen, B.P., Walley, S.C., McGrath-Morrow S.A. (2018). Heat-not-burn tobacco products: tobacco industry claims no substitute for science. Pediatrics. 141(1):e20172383.
101. Kauneliene, V., Meisutovic-Akhtarieva, M., Martuzevicius, D. (2018) A Review of the Impacts of Tobacco Heating System on Indoor Air Quality versus Conventional Pollution Sources. Chemosphere. 206:568-578.
102. Kaur, G., Muthumalage, T., Rahman, I. (2018). Mechanisms of toxicity and biomarkers of flavoring and flavor enhancing chemicals in emerging tobacco and non-tobacco products. Toxicol Lett. 288:143-155.
103. Kawamura, K., Yamada, K., Morioka, I. (2018). Health Effects Accompanying the Transition from Cigarettes to Heat-not-burn Tobacco: Nicotine Dependence, Nicotine Withdrawal Symptoms, and Changes in Smoking Behaviors. Nihon Eiseigaku Zasshi. 73(3): 379-387.
104. Kim, J., Yu, H., Lee, S. et al. (2018). Awareness, experience and prevalence of heated tobacco product, IQOS, among young Korean adults. Tob Control. 27(Suppl 1):s74-s77.
105. Kioi, Y., Tabuchi, T. (2018). Electronic, heat-not-burn, and combustible cigarette use among chronic disease patients in Japan: A cross-sectional study. Tob Induc Dis. 16:41.
106. Kotz, D., Kastaun, S. (2018) E-Zigaretten und Tabakerhitzer: repräsentative Daten zu Konsumverhalten und assoziierten Faktoren in der deutschen Bevölkerung (die DEBRA-Studie). Bundesgesundheitsblatt Gesundheitsforschung Gesundheitsschutz. 61(11): 1407-1414.
107. Kreitzberg, D.S., Murthy, D., Loukas, A., et al. (2018). Heat not burn tobacco promotion on Instagram. Addict Behav. 91:112-118.
108. Lachenmeier, D.W., Anderson, P., Rehm, J. (2018). Heat-Not-Burn Tobacco Products: The Devil in Disguise or a Considerable Risk Reduction?. The International Journal of Alcohol and Drug Research, 7(2):8-11.
109. Leigh, N.J., Palumbo, M.N., Marino, A.M. et al. (2018). Tobacco-specific nitrosamines (TSNA) in heated tobacco product IQOS. Tob Control. 27(Suppl 1):s37-s38.
110. Leigh, N.J., Tran, P.L., O'Connor, R.J. et al. (2018). Cytotoxic effects of heated tobacco products (HTP) on human bronchial epithelial cells. Tob Control. 27(Suppl 1):s26-s29.

111. Lempert L.K., Glantz, S.A. (2018). Heated tobacco product regulation under US law and the FCTC. Tob Control. 27(Suppl 1):s118-s125.
112. Liber, A.C. (2018). Heated tobacco products and combusted cigarettes: comparing global prices and taxes. Tob Control. doi: 10.1136/tobaccocontrol-2018-054602.
113. Lindblom, E.N. (2018). Should FDA Try to Move Smokers to E-Cigarettes and Other Less-Harmful Tobacco Products and, If So, How. Food Drug Law J. 73(2):276-318.
114. Liu, X., Lugo, A., Spizzichino, L. et al. (2018) Heat-Not-Burn Tobacco Products Are Getting Hot in Italy. J Epidemiol 28(5):274-275.
115. Mallock, N., Böss, L., Burk, R. et al. (2018). Levels of selected analytes in the emissions of "heat not burn" tobacco products that are relevant to assess human health risks. Arch Toxicol. 92:2145-2149.
116. Mathers, A., Schwartz, R., O'Connor, S. et al. (2018). Marketing IQOS in a dark market. Tob Control. 28(2):237-238.
117. Max, W.B., Sung, H., Lightwood, J., et al. (2018). Modelling the impact of a new tobacco product: review of Philip Morris International's Population Health Impact Model as applied to the IQOS heated tobacco product. Tob Control. 27:s82–s86.
118. McKelvey, K., Popova, L., Kim, M. et al. (2018). IQOS labelling will mislead consumers. Tob Control. 27(Suppl 1):s48-s54.
119. Miyashita, L., Grigg, J. (2018). Effect of the iQOS electronic cigarette device on susceptibility *to S. pneumoniae* infection. J Allergy Clin Immunol, 141(2):AB28.
120. Miyazaki, Y., Tabuchi, T. (2018). Educational gradients in the use of electronic cigarettes and heat-not-burn tobacco products in Japan. PLoS One 13(1):e0191008.
121. Moazed, F., Chun, L., Matthay, M.A. et al. (2018). Assessment of industry data on pulmonary and immunosuppressive effects of IQOS. Tob Control. 27:s20–s25.
122. Munakata, S., Ishimori, K., Kitamura, N. et al. (2018). Oxidative stress responses in human bronchial epithelial cells exposed to cigarette smoke and vapor from tobacco- and nicotine-containing products. Regul Toxicol Pharmacol. 99:122-128.
123. Murphy, J., Liu, C., McAdam, K. et al. (2018). 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. Regul Toxicol Pharm. 93:92-104.
124. Nabavizadeh, P., Liu, J., Havel, C.M. et al. (2018). Vascular endothelial function is impaired by aerosol from a single IQOS HeatStick to the same extent as by cigarette smoke. Tob Control. 27(Suppl 1):s13-s19.
125. Pacitto, A., Stabile, L., Scungio, M. et al. (2018). Characterization of airborne particles emitted by an electrically heated tobacco smoking system. Environ Pollut. 240:248-254.
126. Pemberton, M,N. (2018). Oral cancer and tobacco: developments in harm reduction. Br Dent J. 225: 822–826.
127. Pieper, E., Mallock, N., Henkler-Stephani, F. et al. (2018). "Heat not burn" tobacco devices as new tobacco industry products: health risks". Bundesgesundheitsblatt Gesundheitsforschung Gesundheitsschutz. 61(11):1422-1428.
128. Popova, L., Lempert, L.K., Glantz, S.A. (2018). Light and mild redux: heated tobacco products' reduced exposure claims are likely to be misunderstood as reduced risk claims. Tob Control. 27(Suppl 1):s87-s95.
129. Rosen, L.J., Kislev, S. (2018). IQOS campaign in Israel. Tob Control. 27:s78–s81.

130. Rychert, M. (2018). New Zealand court dismisses ministry of health case against 'heat-not-burn' tobacco products, highlighting the need to future-proof tobacco control laws. Addiction. 113(10):1953-1954.
131. Salman, R., Talih, S., El-Hage, R., et al. (2018). Free-Base and Total Nicotine, Reactive Oxygen Species, and Carbonyl Emissions From IQOS, a Heated Tobacco Product. Nicotine Tob Res. 21(9):1285-1288.
132. Sharman, A., Zhussupov, B., Sharman, D., et al. (2018). Lung Function in Users of a Smoke-Free Electronic Device With HeatSticks (iQOS) Versus Smokers of Conventional Cigarettes: Protocol for a Longitudinal Cohort Observational Study. JMIR Res Protoc. 7(11):e10006.
133. Si, X., Tang, J., Zhu, R. et al. (2018). Aerosol particle size distribution from an electrical heat-not-burn product under ISO and HCI smoking regimes. Tobacco Science and Technology, 51(8):47-52.
134. Simonavicius, E., McNeill, A., Shanab, L. et al. (2018). Heat-not-burn tobacco products: a systematic literature review. Tob Control. 240:248-254.
135. Smitha, T.T., Hatsukamib, D., Benowitzc, N.L., et al. (2018). Whether to push or pull? Nicotine reduction and non-combusted alternatives - Two strategies for reducing smoking and improving public health. Prev. Med. 117:8-14.
136. St. Helen, G., Jacob III, P., Nardone, N., et al. (2018). IQOS: examination of Philip Morris International's claim of reduced exposure. Tob Control. 27:s30–s36.
137. Staal, Y.C., van de Nobelen, S., Havermans, A. et al. (2018). New Tobacco and Tobacco-Related Products: Early Detection of Product Development, Marketing Strategies, and Consumer Interest. JMIR Public Health Surveill. 4(2):e55.
138. Stepanov, I., Woodward, A. (2018). Heated tobacco products: things we do and do not know. Tob Control. 27:s7–s8.
139. Stephens, W.E. (2018). Comparing the cancer potencies of emissions from vapourised nicotine products including e-cigarettes with those of tobacco smoke. Tob Control. 27:10-17.
140. Tabuchi, T., Gallus, S., Shinozaki, T. et al. (2018). Heat-not-burn tobacco product use in Japan: its prevalence, predictors and perceived symptoms from exposure to secondhand heat-not-burn tobacco aerosol. Tob Control. 27:e25-e33.
141. Tabuchi, T., Shinozaki, T., Kunugita, N. et al. (2018). Study Profile: The Japan "Society and New Tobacco" Internet Survey (JASTIS): A longitudinal internet cohort study of heat-not-burn tobacco products, electronic cigarettes and conventional tobacco products in Japan. J Epidemiol. doi: 10.2188/jea.JE20180116.
142. Takahashi, Y., Kanemaru, Y., Fukushima, T. et al. (2018). Chemical analysis and in vitro toxicological evaluation of aerosol from a novel tobacco vapor product: A comparison with cigarette smoke. Regul Toxicol Pharmacol. 92:94-103.
143. Thorne, D., Breheny, D., Proctor, C. et al. (2018). Assessment of novel tobacco heating product THP1.0. Part 7: Comparative in vitro toxicological evaluation. Regul Toxicol Pharm. 93:71-83.
144. Uchiyama, S., Noguchi, M., Tagaki, N. et al. (2018). Simple Determination of Gaseous and Particulate Compounds Generated from Heated Tobacco Products. Chem Res Toxicol. 31(7):585-593.
145. Yoshida, J. (2018). Abstract. The Rise of Heat-Not Burn Tobacco in Japan: A "Hot" Issue for Tobacco Control. J Thorathic Oncol. 13(10):S271.
146. Yuki, D., Takeshige, Y., Nakaya, K., et al. (2018). Assessment of the exposure to harmful and potentially harmful constituents in healthy Japanese smokers using a novel tobacco vapor product compared with conventional cigarettes and smoking abstinence. Regul Toxicol Pharmacol. 96:127-134.

2017

147. Auer, R., Concha-Lozano, N., Jacot-Sadowski, I. et al. (2017). Heat-not-burn tobacco cigarettes: smoke by any other name. JAMA Intern Med. 177(7):1050-1052.
148. Auer, R., Cornuz, J., Berthet, A. (2017). Perplexing conclusions concerning heat-not-burn tobacco cigarettes—reply. JAMA Intern Med. 177(11):1699-1700.
149. Bekki, K., Inaba, Y., Uchiyama, S. et al. (2017). Comparison of chemicals in mainstream smoke in heat-not-burn tobacco and combustion cigarettes. J UOEH 39(3):201-207.
150. Breheny, D., Adamson, J., Azzopardi, D. et al. (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(Pt A):533-546.
151. Caputi, T.L. (2017). Heat-not-burn tobacco products are about to reach their boiling point. Tob Control. 26:609-610.
152. Caputi, T.L., Leas, E., Dredze, M. et al. (2017). They're heating up: Internet search query trends reveal significant public interest in heat-not-burn tobacco products. PLoS One. 12(10):e0185735.
153. Caruso, M., Polosa, R. (2017). Perplexing conclusions concerning heat-not-burn tobacco cigarettes. JAMA Intern Med. 177(11):1699.
154. Chen, C. (2017). Change and challenge: outlook for development of new tobacco products. Acta Tabacaria Sinica. 23(3):14-18.
155. Gale, N., McEwan, M., Eldridge, A.C. et al. (2017). A randomised, controlled, two-centre open-label study in healthy Japanese subjects to evaluate the effect on biomarkers of exposure of switching from a conventional cigarette to a tobacco heating product. BMC Public Health. 17(1):673.
156. Ichitsubo, H., Kotaki, M. (2017). Indoor air quality (IAQ) evaluation of a Novel Tobacco Vapor (NTV) product. Regul Toxicol Pharmacol. 92:278-294.
157. Jaunky, T., Adamson, J., Santopietro, S. et al. (2017). Assessment of tobacco heating product THP1.0. Part 5: In vitro dosimetric and cytotoxic assessment. Regul Toxicol Pharm. 93:52-61.
158. Kim, M. (2017). Philip Morris International introduces new heat-not-burn product, IQOS, in South Korea. Tob Control. 27:e76-e78.
159. Kvasha, Y.A. (2017). Evaluation of electronic nicotine delivery system (ENDS) effects on cardiovascular disease risk, based on endothelium function as factor of its determination. Health of Ukraine Medical Newspaper.
160. Marynak, K.L., Wang, T.W., King, B.A. et al. (2018). Awareness and Ever Use of "Heat-Not-Burn" Tobacco Products Among U.S. Adults, 2017. Am J Prev Med. 55(4):551-554.
161. Nau, J.Y. (2017). Que penser du tabac chauffe «a moindre nocivite»? Rev Med Suisse. 13:972-973.
162. Protano, C., Manigrasso, M., Avino, P. et al. (2017). Second-hand smoke generated by combustion and electronic smoking devices used in real scenarios: Ultrafine particle pollution and age-related dose assessment. Environ Int. 107:190-195.
163. Ruprecht, A., Sioutas, C., De Marco, C. et al. (2017). Comparative assessment of the side-stream aerosols emitted from heat-not-burn tobacco devices, e-cigarettes and traditional cigarettes. Eur Respir. J. 50:OA1977.
164. Ruprecht, A.A., De Marco, C., Saffari, A. et al. (2017). Environmental pollution and emission factors of electronic cigarettes, heat-not-burn tobacco products and conventional cigarettes. Aerosol Sci Technol. 51(6):674-684
165. Rychert, M. (2017). New Zealand's legal action against IQOS postponed, consultation with big tobacco follows. New Zealand Med. J. 130(1465):109-111.

166. Savareear, B., Lizak, R., Brokl, M., et al. (2017). Headspace solid-phase microextraction coupled to comprehensive two-dimensional gas chromatography–time-of-flight mass spectrometry for the analysis of aerosol from tobacco heating product. J Chromatogr A. 1520:135-142.
167. Taylor, M., Thorne, D., Carr, T. et al. (2017). Assessment of novel tobacco heating product THP1.0. Part 6: A comparative in vitro study using contemporary screening approaches. Regul Toxicol Pharm. 93:62-70.
168. Veronese, C., Ruprecht, A.A., de Marco, C. et al. (2017). Fumo di sigaretta, vapore di e-cig e "fumo freddo": un confronto tra le emissioni di sostanze nocive (Cigarette smoke, e-cig vapor and "heat-not-burn": a comparison between the emissions of toxic compound). Tabaccologia. 1:17-23.

2016

169. Kamada, T., Yamashita, Y., Tomioka, H. (2016). Acute eosinophilic pneumonia following heat-not-burn cigarette smoking. Respirol Case Rep. 4(6).
170. Nyman, A.L., Weaver, S.R., Popova, L. et al. (2018). Awareness and use of heated tobacco products among US adults, 2016-2017. Tob Control. 27(Suppl 1):s55-s61.
171. Protano, C., Manigrasso, M., Avino, P. et al. (2016). Second-hand smoke exposure generated by new electronic devices (IQOS® and e-cigs) and traditional cigarettes: submicron particle behaviour in human respiratory system. Ann Ig 28(2):109-112.
172. Tabuchi, T., Kiyohara, K., Hoshino, T. et al. (2016). Awareness and use of electronic cigarettes and heat-not-burn tobacco products in Japan. Addiction. 111(4):706-713.

2015

173. Miura, N., Yuki, D., Minami, N. et al. (2015). A study to investigate changes in the levels of biomarkers of exposure to selected cigarette smoke constituents in Japanese adult male smokers who switched to a non-combustion inhaler type of tobacco product. Regul Toxicol Pharmacol. 71(3):498-506.
174. O'Connell, G., Wilkinson, P., Burseg, K.M.M. et al. (2015). Heated tobacco products create side-stream emissions: implications for regulation. J Environ Anal Chem. 2(5):163.

2014

175. Sakaguchi, C., Kakehi, A., Minami, N. et al. (2014). Exposure evaluation of adult male Japanese smokers switched to a heated cigarette in a controlled clinical setting. Regul Toxicol Pharmacol. 69(3):338-47.

APPENDIX 5 – Examples of research conducted by independent researchers or regulatory authorities on the mainstream aerosol of the HTPs and reference cigarette smoke.

1. Japan: National Institute of Public Health (Bekki et al., 2017)
The Department of Environmental Health, National Institute of Public Health in Japan, one of the WHO Tobacco Laboratory Network (TobLabNet) laboratories analyzed nicotine, tar, carbon monoxide (CO) and tobacco-specific nitrosamines (TSNAs) in the mainstream aerosol and tobacco fillers of IQOS regular and IQOS menthol, and compared their concentrations with those from reference cigarettes (3R4F and 1R5F) using WHO TobLabNet methods.
The authors conclude "*In this study we could provide important information* ***showing that the concentration levels of hazardous compounds in the mainstream smoke of IQOS are much lower than those in conventional combustion cigarettes****." Although it is low concentration, toxic compounds are definitely included in the mainstream smoke of IQOS.*

2. UK: Independent Scientific Advisory Committees on Toxicity (COT), Carcinogenicity (COC) and Mutagenicity (COM)
The UK Committee on Toxicity (COT), with support from the Committee on Carcinogenicity (COC) and Committee on Mutagenicity (COM) assessed the toxicological risks from novel heat-not-burn tobacco products and compared these risks to those from conventional cigarettes. The Committee has reviewed evidence on two heated tobacco products, *IQOS* (PMI) and *iFUSE* (BAT). The Committees stated *"For both products, there were some HPHCs where the reduction was approximately 50%, but the reduction in a number of other HPHCs was greater than 90%, with many of the compounds being below the limits of detection or quantification for the assays used"* and *"Overall, the Committees conclude that while there is a likely reduction in risk for smokers switching to heat-not-burn tobacco products, there will be a residual risk and it would be more beneficial for smokers to quit smoking entirely."* Statement on the toxicological evaluation of novel heat-not-burn tobacco products published on the 12th of December 2017 by the UK Committee on Toxicity (COT):
https://cot.food.gov.uk/sites/default/files/heat_not_burn_tobacco_statement.pdf

3. The China National Tobacco Quality Supervision and Test Centre ("CNTQSTC"), a member of the WHO Tobacco Laboratory Network (TobLabNet), published on the 8th of January 2018 an independent study in Nicotine & Tobacco Research comparing the HPHCs present in IQOS aerosol and 3R4F reference cigarette smoke (Li et al, 2018)
This peer reviewed publication by Li et al (2018) "Chemical Analysis and Simulated Pyrolysis of Tobacco Heating System 2.2 Compared to Conventional Cigarettes" includes % reduction results of carbon monoxide and 25 Harmful and Potentially Harmful Constituents (HPHCs) in *IQOS* aerosol versus 3R4F reference cigarette smoke using the ISO and Health Canada intense testing regime. The authors stated "*The majority of mainstream constituents of THS 2.2 were reduced compared to 3R4F [reference cigarette]*." Specifically, they found that compared to the 3R4F reference cigarette, *IQOS* produced "*more than 90% [lower levels of] HPHCs, except for carbonyls, ammonia, and NAB, which were about 50–80% lower*." The authors cautioned *"that reduction of harmful constituent emissions cannot be interpreted as equivalent to a proportionate harm/risk reduction for smokers."*

4. Laboratory studies performed by The German Federal Institute for Risk Assessment (BfR)

On 5 May 2018, the German Federal Institute of Risk Assessment (BfR) published the results of their independent assessment of *IQOS*. The study, published in *Archives of Toxicology*, analysed the *IQOS* aerosol using the Health Canada Intense Smoking Regimen. In its report, BfR concludes:

Our study confirms that levels of major carcinogens are markedly reduced in the emissions of the analysed HNB product in relation to the conventional tobacco cigarettes and that monitoring these emissions using standardized machine smoking procedures generates reliable and reproducible data which provide a useful basis to assess exposure and human health risks. Importantly, our data confirms absolute values for selected toxicants in the emissions of the analysed HNB that are in agreement with data published by the manufacturer (Schaller et al. 2016). The herein confirmed reductions of relevant toxicants by about 80% - 99% are substantial, leading to the relevant question of putatively reduced health risks.

Link to the report: https://link.springer.com/epdf/10.1007/s00204-018-2215-y?author_access_token=m2gTAwzR8lN1XHHPyz2Egve4RwlQNchNByi7wbcMAY7B4pkXqsqfUkMAy

5. Independent Testing by FDA

In order to verify chemical and physical data submitted to the U.S. FDA as part of PMI's Modified Risk Tobacco Product Applications (MRTPAs) for IQOS, the U.S. FDA commissioned independent testing at the FDA's Southeast Tobacco Laboratory (STL) in October 2017. The constituents tested were selected based on the characteristics of the EHTP. STL reported the value for NFDPM as "tar". There were some differences between the applicant's analytical and aerosol generation methods and those used by STL. Preliminary assessment of the data indicated that the levels of acrolein, formaldehyde and benzo[a]pyrene measured by STL were higher than the values reported by the applicant; however, these three HPHCs were still significantly lower than the levels in the mainstream smoke of the reference cigarette 3R4F. Greater than 90% reduction was observed for acrolein and benzo[a]pyrene, and greater than 80% reduction was observed for formaldehyde in the aerosol compared to 3R4F. The levels of NFDPM (quoted by STL as tar) and nicotine determined by STL were similar to the levels reported by the applicant. Finally, the levels of ammonia, NNN, and NNK in the EHTP measured by STL were similar to the levels reported by the applicant.

Link to the FDA Briefing Document published on the 22nd of January 2018:
https://www.fda.gov/downloads/AdvisoryCommittees/CommitteesMeetingMaterials/TobaccoProductsScientificAdvisoryCommittee/UCM593109.pdf