PHILIP MORRIS
LIMITED

10 HAMMERSMITH GROVE · LONDON ·W6 7AP, TEL: +44 (0) 20 8222 0700 FAX: +44(0) 20 8222 0994

Philip Morris Limited ("PML"), the UK & Ireland subsidiary of Philip Morris International (PMI). In 2016, PMI announced our ambition to deliver a smoke-free future and ultimately stop selling cigarettes altogether. We are committed to helping the Government reach its target of a smoke-free England by 2030, by providing less harmful, non-combustible alternatives to the millions of adults who would otherwise continue to smoke. Accordingly, we have developed a portfolio of non-combustible alternatives, which is led by IQOS, our signature heated tobacco system. Heated Tobacco Products (HTPs), together with other less harmful alternatives such as e-cigarettes, nicotine pouches and snus have a vital role to play in meeting the bold ambition for a smoke-free future.

We are writing to update you ahead of the 2022 evidence review of e-cigarettes and other novel nicotine delivery systems which will include a summary of the "Cochrane Collaboration's systematic review of the health effects of heated tobacco products and analysis of data on patterns of use"[1,2]. On 6th January, the Cochrane Library published its paper titled *"Heated tobacco products for smoking cessation and reducing smoking prevalence (Review)"*[3]. The paper primarily aimed to find out "*whether trying to switch to heated tobacco helps people stop smoking cigarettes, and whether it results in unwanted effects"*. The author's performed a literature review of clinical studies or time-series data and they noted that *"Heated tobacco probably exposes people to fewer toxins than cigarettes, but possibly more than not using any tobacco."* The authors did not review the available non-clinical data and called for further independent research.

In light of this paper, and given the forthcoming evidence review, this submission will:

1. Address the assertion that HTP usage in the UK is low by observing HTP usage and trends.
2. Show that when considering the totality of the evidence available there is sufficient scientific evidence to justify a change in the regulatory status of HTPs as a less harmful alternative to continued smoking; and – if the Government's view remains that a further review of the independent evidence is still needed – to call for its undertaking as soon as possible.
3. Finally, we will reiterate our strong commitment to Youth Access Prevention in relation to all nicotine products.

1. HTP USAGE AND TRENDS

It has been suggested by some that the usage of HTPs in the UK remains low. However, a range of figures demonstrate a clear growth trajectory for the category in the UK, despite existing laws making it challenging to proactively communicate with adult consumers about HTPs.

Of particular note:

- *IQOS*, our signature heated tobacco system, and/or *HEETS*[4] are available in over 15,000 supermarkets and conveniences stores, and more than 400 vape stores UK wide[5].

[1] Written Parliamentary Question (2021): https://questions-statements.parliament.uk/written-questions/detail/2021-07-20/36587
[2] Cochrane Collaboration (2020): Heated tobacco products for smoking cessation and reducing smoking prevalence: https://www.cochranelibrary.com/cdsr/doi/10.1002/14651858.CD013790/full
[3] Tattan-Birch H, Hartmann-Boyce J, Kock L, Simonavicius E, Brose L, Jackson S, Shahab L, Brown J. Heated tobacco products for smoking cessation and reducing smoking prevalence. Cochrane Database of Systematic Reviews 2022, Issue 1. Art. No.: CD013790. DOI: 10.1002/14651858.CD013790.pub2.
[4] HEETS consumable: our Electrically Heated Tobacco Product that is intended for use exclusively with IQOS.
[5] AC Nielsen Scan track (Dec-21), Stores in Universe and Numeric Distribution data / and PML internal

PHILIP MORRIS
LIMITED

10 HAMMERSMITH GROVE · LONDON ·W6 7AP, TEL: +44 (0) 20 8222 0700 FAX: +44(0) 20 8222 0994

- There were more than 140,000 estimated users of *IQOS* in the UK as of 31 December 2021, reflecting around 60% growth over the preceding 12 months.[6]
- In Q4 2021, the market share for *IQOS*'s *HEETS* consumables reached 2.7% of the total cigarette and heated tobacco unit market in the UK, representing growth of 0.9 percentage points vs Q4 2020. In addition, *HEETS* reached an offtake share of nearly 6% in London on the same basis, an increase of 2.1 percentage points versus Q4 2020.[7]
- Our estimates as of 31 December 2021 show that 21.2 million people globally were using *IQOS*. Of this number, an estimated 15.3 million – or approximately 72% - had switched to *IQOS* and stopped smoking, with the remainder in various stages of conversion.[8]
- More generally, proprietary data shows that dual use with smoking among UK HTP users is significantly lower than it is for vapers.[9]

While it is true that HTPs are relatively new to the UK market, it should be noted that the market is already sizeable (and growing) and many adult smokers have already successfully made the switch. It is therefore not true that HTP use is rare.

Evidence from other countries is also promising. For example, in Japan the available evidence links the launch of IQOS in 2016 to an accelerated decline in cigarette smoking[10,11]. To build on the published studies looking at the decline in cigarette sales in Japan, we have also:

- Investigated whether the introduction of HTPs was associated with changes in indicators of smoking-related diseases at the population level;
- We obtained hospitalization rates for selected smoking-related endpoints: chronic obstructive pulmonary disease (COPD), COPD exacerbations and ischemic heart disease (IHD)[12]. This data came from two databases: Medical Data Vision (MDV) and Japan Medical Data Center (JMDC);
- For these endpoints, we compared rates of hospitalizations before and after the introduction of HTPs in Japan.

We observed that hospitalization rates started decreasing shortly after the launch. Those decreases so far are modest, but measurable. This makes sense for the population data, considering that it can take years for the excess risk for these endpoints to decrease when an individual quits smoking. This type of real-world data should, therefore, be followed up in the future and reproduced in other countries.

When it comes to the information necessary to inform decision-making as regards the public health impact for introducing HTPs, several lines of evidence come into play and complement each other: evidence from controlled scientific experiments answers precise, pre-defined questions, while evidence collected from the real-world helps understand health effects of a product in real-life

[6] PML Internal estimate as of 31 December 2021
[7] PMI Investor Relations, 2021 Q4 Results: https://www.pmi.com/investor-relations/reports-filings.
[8] PMI Investor Relations, 2021 Q4 Results: https://www.pmi.com/investor-relations/reports-filings
[9] Based on the results of a survey of UK adult and nicotine users conducted by Kantar on behalf of PMI. Please get in touch for further results of this survey.
[10] Stoklosa, M. et al., 2020. Effect of IQOS introduction on cigarette sales: Evidence of decline and replacement. Tob. Control. 29, 381–387. http://dx.doi.org/10.1136/tobaccocontrol-2019-0549
[11] Cummings, K.M. et al., 2020 What is accounting for the rapid decline in cigarette sales in Japan? Int. J. Environ. Res. Public Health 2020, 17, 3570; doi:10.3390/ijerph17103570
[12] Antunes, M. et al., 2022, IHD and COPD Hospitalizations in Japan before and after the Introduction of a Heated Tobacco Product: Interrupted Time Series Analyses using Real-World Data. Scientific Reports. Submitted for publication.

PHILIP MORRIS
LIMITED

10 HAMMERSMITH GROVE · LONDON ·W6 7AP, TEL: +44 (0) 20 8222 0700 FAX: +44(0) 20 8222 0994

settings. So far, the real-world evidence has indicated that introducing HTPs can have a beneficial impact. Launching HTPs in Japan was not only the most likely cause for a reduction in cigarette sales, but it was also related to a decrease in hospitalization rates due to COPD and IHD.

We will continue to gather and evaluate real-world data, in particular, epidemiological data from long-term follow-up studies that include information on other variables that might impact the risk of developing smoking-related diseases as well as lifestyle or other environmental factors (e.g., diet, pollution). The totality of the evidence on IQOS to date, including both experimental and real-life data, point in the direction of harm reduction.

2. THE SCIENTIFIC CASE FOR HTPS

Some suggest that there is insufficient evidence about the efficacy of HTPs, and it is often cited that much of the research on HTPs has been conducted by manufacturers. Indeed, we have invested significant resources in the science and research behind our smoke-free products, including IQOS. This is to be expected given that for any novel consumer or pharmaceutical product, it is essential that manufacturers thoroughly assess potential risks from product use. However, as illustrated below, the body of research on HTPs - be it PMI's or not - is in fact vast. There is substantial independent verification of our proprietary science as well as independent evidence. The science backing HTPs as a less harmful alternative to smoking is clear – and at the centre of this is the absence of combustion. As is the case for e-cigarettes, long-term epidemiological data is not yet available for HTPs. Nevertheless, both product categories deliver nicotine with substantial reduction in harmful and potentially harmful constituents (HPHCs) compared to cigarettes. Therefore, there is sufficient data already to indicate that HTPs and e-cigarettes will be confirmed to be reduced risk products compared to continued smoking.

Research has shown that a majority of HPHCs in cigarette smoke are caused by tobacco combustion. In our HTPs there's no combustion. HTP operation does involve heating tobacco to produce a nicotine-containing aerosol[13]. Furthermore, because of the absence of combustion, the tobacco heating process does not create smoke, which is why the HTP is referred to as a smoke-free product.

By eliminating combustion, we can reduce the number and level of HPHCs produced compared to cigarette smoke. Our studies have also shown an average reduction in HPHCs of 95 percent, compared to cigarette smoke[14]. Additionally, these reductions in HPHC formation result in reduced toxicity in pre-clinical studies [15,16] and reduced exposure in clinical studies[17,18]. By eliminating combustion, such products represent a valuable contribution to a smoke-free future.

[13] Absence of Combustion in PMI-s Heated Tobacco Product | PMI Science
[14] Schaller J-P, et al., 2016 Evaluation of the Tobacco Heating System 2.2. Part 2: Chemical composition, genotoxicity, cytotoxicity, and physical properties of the aerosol. Regul. Toxicol. Pharmacol., 81 Suppl 2:S27-S47.
[15] Wong ET, et al., 2020 Reduced Chronic Toxicity and Carcinogenicity in A/J Mice in Response to Life-Time Exposure to Aerosol from a Heated Tobacco Product Compared with Cigarette Smoke. Toxicological Sciences, 178:44-70. (PMID: 32780830).
[16] Wong ET, et al., 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. http://dx.doi.org/10.1016/j.yrtph.2016.10.015
[17] Ludicke, F. et al., 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 Epidemiol. Biomarkers Prev. 28:1934–43. doi: 10.1158/1055-9965.EPI-18-0915
[18] FDA 2020 FDA Authorizes Marketing of IQOS Tobacco Heating System with 'Reduced Exposure' Information https://www.fda.gov/news-events/press-announcements/fda-authorizes-marketing-iqos-tobacco-heating-system-reduced-exposure-information

PHILIP MORRIS
LIMITED

10 HAMMERSMITH GROVE · LONDON ·W6 7AP, TEL: +44 (0) 20 8222 0700 FAX: +44(0) 20 8222 0994

In addition, independent evidence provides additional support for the reduced risk potential of non-combustible alternatives to smoking. Professor Polosa, for example, has also looked into the evidence surrounding the health impact of such products and noted that:

> *"The key to reducing the negative health effects of smoking is to avoid chronic exposure to chemicals released during the tobacco combustion of conventional cigarettes. This can be achieved either by smoking cessation programs, which include prescription medications (varenicline, bupropion, nicotine replacement therapy) and counselling [3] or by cigarette substitution with combustion-free products, which include e-cigarettes and heated tobacco products (HTPs)."* [19]

PMI Science

We have published over 400 peer-reviewed publications – most open access – and book chapters that relate to our smoke-free product science. Attached at Annex A, we have provided a summary of our key findings on the IQOS heated tobacco system which support its use as a less harmful alternative to smoking. IQOS emits on average 95% lower levels of harmful chemicals compared to cigarettes[20]. Our science conforms to rigorous standards: we follow practices used in the pharmaceutical industry and align with guidance issued by the US Food and Drug Administration (FDA)[21]. We are transparent with our research and welcome the independent review of our work and products, for example we:

- Regularly publish our studies in international journals to allow for independent peer review as well as making them available on PMI Science[22];
- Register all clinical studies on ClincalTrials.gov to uphold transparency over findings; and
- Recently re-opened our Investigator Initiated Studies programme to support external scientists to verify RRP science[23].

Independently verified evidence

It is also important to note that our research on IQOS has been independently reviewed by competent regulators around the world.

Most notably, in July 2020, the US FDA issued its decision on PMI's Modified Risk Tobacco Product (MRTP) Application for IQOS and three HeatStick variants, authorising the products to be marketed in the US with a reduced exposure claim. The FDA has concluded that switching completely from cigarettes to IQOS significantly reduces your body's exposure to harmful or potentially harmful chemicals and they determined that the issuance of the MRTP orders with reduced exposure claims would be *"appropriate to promote the public health and is expected to benefit the health of the population as a whole"*. Furthermore, the MRTP was authorised on the basis that further studies were likely to confirm reduced risk.

[19] Polosa,R., 2021 Examining the evidence for the health impact of combustion-free products: progress and prospects for tobacco harm reversal and reduction. Internal and Emergency Medicine https://doi.org/10.1007/s11739-021-02837-2
[20] Compared to the smoke of a reference cigarette (3R4F). It does not necessarily equal a 95% reduction in risk.
[21] US-FDA 2012 Guidance document: Modified Risk Tobacco Product Applications: *Draft Guidance for Industry.* *https://www.fda.gov/regulatory-information/search-fda-guidance-documents/modified-risk-tobacco-product-applications*
[22] PMI Science: https://www.pmiscience.com/
[23] PMI Investigator Initiated Studies pilot programme: https://www.pmiscience.com/iis

PHILIP MORRIS
LIMITED

10 HAMMERSMITH GROVE · LONDON ·W6 7AP, TEL: +44 (0) 20 8222 0700 FAX: +44(0) 20 8222 0994

The FDA's decision followed a multi-year review of the scientific evidence. The review included FDA's scientific evaluation of PMI's extensive applications, FDA's independent testing of harmful constituents, FDA's inspections of PMI research and manufacturing sites, and assessment of peer-reviewed literature as well as other sources. The scientific evidence package submitted by PMI was published on the FDA's website for review and comment, receiving over 250 comments from experts, researchers, medical professionals and others. The FDA's independent Tobacco Products Scientific Advisory Committee also reviewed the applications made.

Annex B provides further details of the FDA's work and 8 other independent reviews by Government Bodies and Agencies.

Independent evidence

At the same time, the body of literature from studies conducted independently by the broader science community is growing. Such work focuses on a range of topics such as: assessing product performance, physical and chemical analysis of IQOS aerosol, nonclinical assessment, impact on indoor air quality and product use and consumer behavior. The totality of the evidence confirms that tobacco is heated and not combusted during IQOS use, and this results in a substantial lowering of harmful emissions[24] and potentially harmful constituents compared to cigarette smoke, as well as a significant reduction in biological impact. The results and conclusions from most preclinical studies are supportive of PMI results – where studies have not compared results with cigarette smoke or have used extreme dosing regimens that are not of human relevance, conclusions may differ.

There have also been a number of independent studies comparing the effect of IQOS use with cigarette use (and some with e-cigarette use) on indoor air quality in various settings.[25,26,27] The results of these studies expanded and typically confirmed those obtained by PMI, with lower and transient levels of IQOS and e-cigarette aerosols compared to cigarette smoke together with greatly reduced numbers and levels of harmful and potentially harmful constituents detected. Independent clinical studies looking at endpoints associated with smoking related lung and cardiovascular disease have shown improvements in adult smokers switching to IQOS[28,29,30].

A number of independent authors have reported studies on product use and consumer behavior on HTPs from various countries. For example, post-market surveys in Germany[31], Japan[32] and

[24] Mallock N, 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(6):2145-2149. https://doi.org/10.1007/s00204-018-2215-y

[25] Meisutovic-Akhtarieva, M. et al., 2019, Impacts of exhaled aerosol from the usage of the tobacco heating system to indoor air quality: A chamber study. Chemosphere 223 474e482. https://doi.org/10.1016/j.chemosphere.2019.02.095

[26] Schober, W. et al., 2019 Passive exposure to pollutants from conventional cigarettes and new electronic smoking devices (IQOS, e-cigarette) in passenger cars. International Journal of Hygiene and Environmental Health, Volume 222, Issue 3, 486-493. https://doi.org/10.1016/j.ijheh.2019.01.003

[27] Peruzzi,M. et al., 2020 Comparative Indoor Pollution from Glo, Iqos,and Juul, Using Traditional Combustion Cigarettes as Benchmark: Evidence from the Randomized SUR-VAPES AIR Trial. Int.J.Environ.Res and Pub.Health 17, 6029; doi:10.3390/ijerph17176029

[28] Caponnetto P. 2018 Carbon monoxide levels after inhalation from new generation heated tobacco products, Respiratory Research, 19:164.

[29]Biondi-Zoccai, G. 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 (SURVAPES) 2 Randomized Trial. J Am Heart Assoc. 8:e010455. DOI: 10.1161/JAHA.118.010455

[30]Sharman, A & Nurmagambetov, T. (2020) Changes in Respiratory Function and Physical Capacity among Smokers after Switching to IQOS: One Year Follow-Up. Global Journal of Respiratory Care, 6, 22-29. DOI: https://doi.org/10.12974/2312-5470.2020.06.03 (partially funded by a grant from PMI)

[31] Kotz,D. et al., 2018 E-cigarettes and heat-not-burn products: representative data on consumer behaviour and associated factors in the German population (the DEBRA study). Bundesgesundheitsblatt - Gesundheitsforschung - Gesundheitsschutz volume 61, pages1407–1414. https://doi.org/10.1007/s00103-018-2827-7

[32] Kuwabaru, Y. et al., 2020 Heat-not-burn tobacco, electronic cigarettes, and combustible cigarette use among Japanese adolescents: a nationwide population survey 2017. BMC Public Health 20:741 https://doi.org/10.1186/s12889-020-08916-x

PHILIP MORRIS
LIMITED

10 HAMMERSMITH GROVE · LONDON ·W6 7AP, TEL: +44 (0) 20 8222 0700 FAX: +44(0) 20 8222 0994

Switzerland[33,34] suggest that HTPs use among young people, never smokers and re-initiation among former smokers is low.

Overall, the results from independent researchers adds to the total weight of evidence backing the potential for HTPs as a less harmful alternative to continued cigarette smoking.

We have and always will welcome independent review and challenge of our work and products, and that is why we have repeatedly welcomed the Government's commitment to launch a Call for Independent Evidence on HTPs[35]. However, we believe there is enough existing evidence to back HTPs as a less harmful alternative to continued smoking. If the Government's view remains that a call for independent evidence is still needed, and if this is seen as an impediment to fully embracing the potential for HTPs to reduce the harms of smoking, then we urge its undertaking as soon as possible.

3. YOUTH ACCESS PREVENTION

We are clear that non-combustible alternatives are only for adult smokers and nicotine users alone. They should not be used by young people or non-smokers. Promisingly, the data suggests that current use of HTPs among young people in the UK is rare[36]. In other countries where HTPs are prevalent, and where relatively greater regulatory freedoms are afforded to HTPs, the data also supports low youth use/uptake. For example, the German Federal Ministry of Health has found that youth use 12 to 17 year olds was low at 0.1 per cent and has remained unchanged between 2018 and 2019[37]. In its decision authorising the sale of IQOS in the US through the premarket tobacco product application, the U.S. Food and Drug Administration (FDA) opined that: "*Available data, while limited, also indicate that few non-tobacco users would be likely to choose to start using IQOS, including youth.*" [38]

Nonetheless, we have - and will continue to - take robust steps in the UK to prevent youth use/uptake. This includes:

- **Stringent practices to ensure products are not unduly appealing to young people.** For example, ensuring that packaging, branding and flavour names do not mimic youth-oriented products or anything else young people may find unduly appealing; and implementing responsible practices to minimise the potential for communications being seen by unintended audiences.
- **Robust processes to ensure products cannot be sold to youth online or in-person**. For example, we apply a three-pronged approach to age verification for online sales (e.g. soft

[33] 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 .
[34] 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. BMCPublic Health 19:642. https://doi.org/10.1186/s12889-019-6957-0
[35] Department of Health and Social Care, Prevention Green Paper (2019): https://www.gov.uk/government/consultations/advancing-our-health-prevention-in-the-2020s/advancing-our-health-prevention-in-the-2020s-consultation-document
[36] Public Health England, Vaping in England: evidence update February 2021: https://www.gov.uk/government/publications/vaping-in-england-evidence-update-february-2021
[37] Federal Center for Health Education (BZgA), Smoking, Alcohol and Drugs use: prevalence and trends, 2019, July 2020 https://www.bzga.de/fileadmin/user_upload/PDF/studien/Drogenaffinitaet_Jugendlicher_2019_Basisbericht.pdf and Smoking among teenagers and young adults in Germany: Findings from the Alcohol Survey 2018 and trends, Sept. 2018, available at https://www.bzga.de/fileadmin/user_upload/PDF/studien/Alkoholsurvey_2018_Bericht-Rauchen.pdf
[38] U.S. FDA news release, April 30, 2019 https://www.fda.gov/news-events/press-announcements/fda-permits-sale-iqos-tobacco-heating-system-through-premarket-tobacco-product-application-pathway

age verification, hard age verification and point of delivery checks). Refusing entry for anyone under 18 in our stores.

We note the Home Office and the Office for Product Safety and Standards has been considering potential innovative solutions to age verify the retail sale of alcohol[39]. This follows the need to protect children from harm, and reduce abuse faced by retailer workers in performing ID checks. We strongly welcome steps being taken to consider such technology, noting that it may be applied to other age restricted items – including all nicotine products, which we would support.

We are continuing to develop and test age-verification technology to help guard against youth use of our smoke-free devices. We have been looking into solutions such as for example a compulsory age verification on initial use, and allow users to lock/unlock their device to prevent unintended access. Our ambition is to have age verification technology in all of our smoke-free electronic devices in the coming years.

More generally, we also undertake post-marketing surveillance studies in countries where IQOS is commercialized to understand trends and patterns in product use. We monitor how our products are used and by whom, to ensure that our products and commercial activities reach the intended audience of adult consumers while minimising exposure of unintended audiences, such as youth, non-smokers and former smokers. In addition, following market launch, we continuously monitor for any adverse health effects linked to use of our smoke-free products to ensure that any new health risks associated with their use can be identified in a timely fashion and can be managed appropriately.

[39] Home Office (2021) https://www.gov.uk/government/publications/age-verification-technology-in-alcohol-sales-regulatory-sandbox

PHILIP MORRIS
LIMITED

10 HAMMERSMITH GROVE · LONDON ·W6 7AP, TEL: +44 (0) 20 8222 0700 FAX: +44(0) 20 8222 0994

ANNEX A –

PMI'S SCIENTIFIC EVIDENCE ON HEATED TOBACCO PRODUCTS

PMI has invested significant resources into the science and research behind the IQOS heated tobacco system. PMI's scientific assessment is built on a collaborative approach and expertise in the fields of aerosol physics, chemistry, toxicology, biology, informatics, medicine, epidemiology and perception and behaviour[40]. Our practices are inspired by the pharmaceutical industry and aligned with the US Food and Drug Administration's Draft Guidance for Modified Risk Tobacco Product Applications (2012).

Our key findings[41] on the IQOS heated tobacco system include:

- Product development: IQOS is specifically designed to eliminate or reduce the levels of harmful and potentially harmful constituents found in the aerosol compared to those found in cigarette smoke; by eliminating combustion, the levels of harmful chemicals are reduced on average by 95% in the aerosol compared to those in cigarette smoke; moreover, "The scientific evidence shows that the use of HTP in environments, where regulatory norms for adequate ventilation are respected, has no adverse effect on air quality according to the values set forth in air quality guidelines."
- Toxicological assessment: studies show a substantial reduction in toxicity of the aerosol compared to cigarette smoke; in particular, findings have shown reduced toxicity and reduced risk in animal models.
- Clinical assessment: studies show the level of nicotine and the timing of its peak concentration in the blood are comparable for smokers and for those who switch to IQOS. The FDA in its assessment recognized that "*Nicotine exposures appear sufficient to provide user satisfaction, which may facilitate switching from combusted cigarettes to IQOS*".[42] [43]; smokers switching completely were exposed to significantly lower levels of harmful chemicals compared to those who continued smoking; clinical findings indicate that switching to IQOS has a positive impact on smokers' health.
- Perception and behaviour: premarket studies carried out in the USA confirmed that smokers correctly understand that switching to IQOS presents less risk of harm than continued cigarette smoking, while not being risk-free.
- Long-term assessment: as part of PMI's long-term assessment, cross-sectional studies on the adult population from Japan, PMI's most advanced market for IQOS, were conducted in four waves per year, with the first two years' results currently available. Around 70% of IQOS users are using the product either exclusively or in combination with other smoke-free products; the rates of initiation in never smokers and relapse of former smokers are in low single digits.

[40] PMI Science: https://www.pmiscience.com/
[41] PMI Science Booklet (2021): https://www.pmiscience.com/resources/docs/default-source/default-document-library/pmiscience-booklet-2021.pdf
[42] FDA conclusions on user satisfaction : Page 61 and 62 MRTPA TPL, (pages 91 and 92 PMTA)
[43] Nicotine Pharmacokinetic Profile and Safety of the Tobacco Heating System 2.2 Menthol (THS 2.2 Menthol). - Full Text View - ClinicalTrials.gov

PHILIP MORRIS
LIMITED

10 HAMMERSMITH GROVE · LONDON ·W6 7AP, TEL: +44 (0) 20 8222 0700 FAX: +44(0) 20 8222 0994

ANNEX B –

INDEPENDENTLY VERIFIED EVIDENCE ON HEATED TOBACCO PRODUCTS

Overview

The scientific evidence for IQOS has been independently reviewed by competent Government Bodies and Agencies around the world. These include:

1. The US Food and Drug Administration (US FDA) in 2018, 2019 and 2020;
2. Superior Health Council of Belgium in 2020;
3. The National Institute for Public Health and the Environment (RIVM) in the Netherlands in 2018 and 2020;
4. The UK's Public Health England in its 2018 evidence review;
5. The German Federal Institute for Risk Assessment (BFR) in 2018;
6. The Korean Ministry of Food and Drug Safety (MFDS) in 2018;
7. The China National Tobacco Quality Supervision and Test Centre (CNTQSTC) in 2018.
8. The Department of Environmental Health, National Institute of Public Health in Japan in 2017; and
9. The UK Committee on Toxicity of Chemicals in Food, Consumer Products and the Environment (COT) in 2017.

Further details on these are provided below.

1. US Food and Drug Administration (US FDA) (2018/2019/2020): a federal agency of the U.S. Department of Health and Human Services, conducted an assessment of *IQOS* aerosol and concluded "*The independent testing performed by STL confirmed the lower levels of selected HPHCs in the aerosol from the HeatSticks compared to mainstream cigarette smoke.*" These conclusions were included in an FDA Briefing Document for the members of the Tobacco Products Scientific Advisory Committee (TPSAC).

   Subsequently, on April 30, 2019, the U.S. Food and Drug Administration's (FDA) Center of Tobacco Products (CTP) issued a market order letter for the Tobacco Heating Device (THD) and the Electrically Heated Tobacco Product (EHTP) to allow the introduction of the THD and EHTP into the U.S. market. The decision of the U.S. FDA followed "[…] *a rigorous science-based review through the premarket tobacco product application (PMTA) pathway*" based on which, "[…] *the agency determined that authorizing these products for the U.S. market is appropriate for the protection of the public health* […]"[44]

   In their scientific review the U.S. FDA "*found that the aerosol produced by the IQOS Tobacco Heating System*" [EHTP with THD] "*contains fewer toxic chemicals than cigarette smoke, and many of the toxins identified are present at lower levels than in cigarette smoke.*

[44] https://www.fda.gov/news-events/press-announcements/fda-permits-sale-iqos-tobacco-heating-system-throughpremarket-tobacco-product-application-pathway

PHILIP MORRIS
LIMITED

10 HAMMERSMITH GROVE · LONDON ·W6 7AP, TEL: +44 (0) 20 8222 0700 FAX: +44(0) 20 8222 0994

For example, the carbon monoxide exposure from IQOS aerosol is comparable to environmental exposure, and levels of acrolein and formaldehyde are 89% to 95% and 66% to 91% lower than from combustible cigarettes, respectively."[45]

Furthermore, the Agency concluded that "[…] *IQOS delivers nicotine in levels close to combustible cigarettes suggesting a likelihood that IQOS users may be able to completely transition away from combustible cigarettes and use IQOS exclusively*."

Importantly, the US FDA found that "*Available data, while limited, also indicate that few non-tobacco users would be likely to choose to start using IQOS, including youth*".

Moreover, on July 7, 2020, the U.S. FDA issued a decision on the Modified Risk Tobacco Product (MRTP) applications for *IQOS* and the three *HeatSticks* variants submitted by PMI in December 2016.

Following a thorough review of the extensive scientific evidence package PMI submitted to the FDA to support the *IQOS* MRTP applications the Agency found that "*the available scientific evidence demonstrates that the issuance of an exposure modification order for IQOS would be appropriate to promote the public health and is expected to benefit the health of the population as a whole, taking into account both users of tobacco products and persons who do not currently use tobacco products*."[46]

Important to note is that the regulatory framework in the U.S. allows the FDA to issue two types of modified risk orders: a "risk modification" order or an "exposure modification" order. PMI had requested both types of orders for the *IQOS* system. The FDA determined that "*although the non-clinical and clinical studies included in these applications were not sufficient to demonstrate that switching completely lowers the risk of disease compared to combusted cigarette smoking and failed to meet the threshold for issuance of a risk modification order at this time, the totality of evidence presented suggests that a measurable and substantial reduction in morbidity or mortality among individual tobacco users is reasonably likely in subsequent studies. This determination predominantly stems from the substantial reduction in HPHCs relative to combusted cigarette smoke. Although some chemicals of potential concern (not on FDA's HPHC list) may be higher in IQOS users, the increase in these constituents does not impact the conclusion that the substantial reductions in HPHCs and findings from the toxicological evidence are reasonably likely to translate to lower risk of tobacco-related morbidity and mortality*."[47]

This decision follows a stringent process which included:

- A review of the extensive scientific evidence package PMI submitted to the FDA in December 2016 to support its MRTP applications, which included a regular dialogue with PMI scientists to better understand the data submitted and to answer specific questions from the FDA;

[45] Abrams et al. Submission to Tobacco Products Scientific Advisory Committee on Modified Risk Tobacco Product Applications for *IQOS* System (December 14, 2017). Available at: https://www.fda.gov/media/110535/download
[46] FDA News Release "*FDA Authorizes Marketing of IQOS Tobacco Heating System with 'Reduced Exposure' Information*" July 07, 2020, available at: https://www.fda.gov/news-events/press-announcements/fda-authorizesmarketing-iqos-tobacco-heating-system-reduced-exposure-information
[47] The MRTP Technical Project Lead (TPL) Report (page 9), available at: https://www.fda.gov/media/139796/download

PHILIP MORRIS
LIMITED

10 HAMMERSMITH GROVE · LONDON ·W6 7AP, TEL: +44 (0) 20 8222 0700 FAX: +44(0) 20 8222 0994

- Inspections from FDA officials at multiple PMI and study sites, including our factory and research facilities in Neuchatel and Lausanne in 2017;
- A comprehensive review of the independent data and publications around *IQOS* to date;
- A comprehensive review of comments, data, and information submitted to FDA by interested persons (section 911(g)(4) of the FD&C Act).

The modified exposure order granted by the U.S. FDA for 4 years will authorize the communication of the following information to consumers with regards to the *IQOS* system in the United States:

AVAILABLE EVIDENCE TO DATE:

- *The IQOS system heats tobacco but does not burn it.*
- *This significantly reduces the production of harmful and potentially harmful chemicals.*
- *Scientific studies have shown that switching completely from conventional cigarettes to the IQOS system significantly reduces your body's exposure to harmful or potentially harmful chemicals.*

2. The Superior Health Council of Belgium (2020)[48]: issued a scientific advisory report on New Tobacco Products: Heated Tobacco Products, in which it provided a risk assessment for heated tobacco products for smokers and non-smokers and guidance to public health policy-makers.

   The Council concluded that: *"In clinical studies, following a switch from conventional cigarettes to heated tobacco products (IQOS or GLO), significant decreases in biomarker levels of exposure to harmful and potentially harmful constituents have been observed, although they are not considered to be completely safe. Favourable changes have also been noted in several biomarkers with biological impact, suggesting that there is potential for a decreased risk of disease if smokers switch from conventional cigarettes to heated tobacco products."*

3. National Institute for Public Health and the Environment (RIVM) (2018, 2020)[49]: an agency of the Dutch Ministry of Health, Welfare, and Sport published its preliminary assessment of *IQOS*. The assessment, which is presented as a Factsheet, is based on RIVM's aerosol chemistry testing of *IQOS*, as well as published literature.

   RIVM concluded that "*The use of heatsticks with the iQOS is harmful to health, but probably less harmful than smoking tobacco cigarettes*," based on their aerosol chemistry measurements, which are "*of the same order of magnitude as in the data of Philip Morris*."

   The more recent publication from RIVM (Slob et al., 2020)[50] *"A Method for Comparing the Impact on Carcinogenicity of Tobacco Products: A Case Study on Heated Tobacco Versus*

[48] Superior Health Council of Belgium, April 2020, available at: 201026_shc-9538_new_tobacco_products_vweb.pdf (belgium.be)
[49] National Institute for Public Health and the Environment (2018, 2020): https://www.rivm.nl/publicaties?objectid=e1ce3c72-1436-444f-a4d0-e9f93dc30da6&type=pdf&disposition=inline or (English summary): https://www.rivm.nl/en/news/addictive-nicotine-and-harmful-substances-also-present-in-heated-tobacco
[50] Slob, W. et al., 2020 A Method for comparing the Impact on carcinogenicity of tobacco products: A Case Study on Heated Tobacco Versus Cigarettes, Risk Analysis https://onlinelibrary.wiley.com/doi/epdf/10.1111/risa.13482

Cigarettes" compared the carcinogenicity of heated tobacco aerosol versus cigarette smoke. The methodology applied focused on the change in cumulative exposure (CCE) to compare two tobacco/nicotine products instead of performing risk assessments of individual compounds to allow a better understanding on if and how the health impact may differ between the products. The authors concluded that "[*t*]*he CCE was estimated to be 10- to 25-fold lower when using HTPs instead of cigarettes. Such a change indicates a substantially smaller reduction in expected life span, based on available dose-response information in smokers. However, this is a preliminary conclusion, as only eight carcinogens were considered so far. Furthermore, an unfavorable health impact related to HTPs remains as compared to complete abstinence.*"

Even the lower bound of this uncertainty range would be associated with a substantial health impact in favour of the HTP. Assuming that the 8 carcinogens used in this analysis are a representative sample of all carcinogens in smoke, then increasing the number of compounds in the analysis would make the CCE estimate more reliable but would most likely not dramatically change it.

Overall, consuming a HTP such as the one studied instead of cigarettes will be associated with a substantial increase in life expectancy compared to continued smoking, for the subgroup of smokers who would die from cancer. Moreover, the authors also suggest, that the health impact will be greatest for habitual smokers who switch at a young age. It is also important to highlight that the authors make it clear that HTPs, are not risk-free and that there is a negative health impact expected to remain from consuming HTPs as compared to total abstinence from tobacco products.

4. Public Health England (PHE) (2018)[51]: released a report on the evidence behind cigarette alternatives, the fourth such review on e-cigarettes and the first time it included heated tobacco products. PHE's analysis of independent evidence on heated tobacco products, which was heavily focused on *IQOS*, considered eight independent studies in its review.

   Amongst the report's findings on heated tobacco products are a likely reduction in user's exposure to harmful chemicals compared to cigarettes, and that: "*The available evidence suggests that heated tobacco products may be considerably less harmful than tobacco cigarettes and more harmful than* [e-cigarettes]. *With a diverse and mature e-cigarette market in the UK, it is currently not clear whether heated tobacco products provide any advantage as an additional potential harm reduction product."* As reported above since the time of the report there is now an increasing growth trajectory for IQOS in the UK supporting its contribution as potential harm reduction product.

5. German Federal Institute for Risk assessment (BfR) (2018)[52], a branch of the Federal Ministry for Food and Agriculture, is responsible for the assessment of issues related to consumer protection. BfR analyzed *IQOS* aerosol and found reductions in selected toxicants (80-99%) compared to cigarette smoke, which was in line with PMI's own research. The study states

[51] Public Health England, E-cigarettes and heated tobacco products: evidence review (2018): https://www.gov.uk/government/publications/e-cigarettes-and-heated-tobacco-products-evidence-review
[52] German Federal Institute for Risk assessment (2018): https://link.springer.com/article/10.1007/s00204-018-2215-y

PHILIP MORRIS
LIMITED

10 HAMMERSMITH GROVE · LONDON ·W6 7AP, TEL: +44 (0) 20 8222 0700 FAX: +44(0) 20 8222 0994

that while further studies are required to address the magnitude of exposure reduction "the *herein confirmed reductions of relevant toxicants by about 80–99% are substantial, leading to the relevant questions of putatively reduced health risks.*

6. Korean Ministry of Food and Drug safety (MFDS) (2018)[53]: issued a statement on products that heat rather than burn tobacco, based on measurements performed in their own laboratories of three HNB products including *IQOS*. They measured the nine Harmful and Potentially Harmful Constituents (HPHCs) defined by the WHO as a priority list for mandatory reduction, as well as nicotine and "tar".

   MFDS results confirm significant reductions of HPHCs in HNB products compared to cigarettes –but omit to discuss them. In their discussion, MFDS mention that HNB products also contain carcinogens, like benzopyrene and benzene. What they fail to mention is that the levels measured are more than 10 times lower compared to the levels present in cigarette smoke. In fact, their own data show that these 2 carcinogens are reduced by more than 95 % (for benzopyrene) and more than 99 % (for benzene) when comparing the levels of HNB products to the top 5 most sold cigarette brands in Korea. When considering the 9 measured HPHCs, the average reduction of HNB products compared to Korean cigarettes (top 5 most sold brands) is more than 90%.

   Our public comment on the MFDS statement is available here: https://www.pmiscience.com/whats-new/pmi-assessment-of-the-kfda-statement

7. The China National Tobacco Quality Supervision and Test Centre ("CNTQSTC") (2018): a member of the WHO Tobacco Laboratory Network (TobLabNet): published on January 8, 2018 an independent study in Nicotine & Tobacco Research comparing the HPHCs present in IQOS aerosol and 3R4F reference cigarette smoke.

   This peer reviewed publication by Li et al (2018)[54] *"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."*

8. The Department of Environmental Health, National Institute of Public Health in Japan (2017)[55]: one the WHO Tobacco Laboratory Network (TobLabNet) laboratories analysed nicotine, tar, carbon monoxide (CO) and tobacco-specific nitrosamines (TSNAs) in the mainstream aerosol

[53]Korean Ministry of Food and Drug safety: (Korean)
http://www.mohw.go.kr/react/al/sal0301vw.jsp?PAR_MENU_ID=04&MENU_ID=0403&page=1&CONT_SEQ=345119
[54] Li, X. et al 2019 Chemical Analysis and Simulated Pyrolysis of THS 2_2 compared to conventional cigarettes, Nicotine Tob Res 21(1):111-118. doi: 10.1093/ntr/nty005. PMID: 29319815
[55] Bekki, K. et al., 2017 Comparison of Chemicals in Mainstream Smoke in Heat-not-burn Tobacco and Combustion Cigarettes, J. UOEH 39(3) 201-2017

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.*

9. UK Committee on Toxicity of Chemicals in Food, Consumer Products and the Environment (COT) (2017)[56]: reviewed evidence on two heated tobacco products, *IQOS* (PMI) and iFUSE (BAT) as part of their work to assess the risk of heated tobacco products relative to cigarette smoking.

   The assessment concluded that, while still harmful to health, heated tobacco products "*are likely to be less risky than smoking conventional cigarettes." COT also stated that "There would likely be a reduction in risk for conventional smokers deciding to use heat-not-burn tobacco products instead of smoking cigarettes.*"

[56]UK Committee on Toxicity of Chemicals in Food, Consumer Products and the Environment (COT), Statement on the toxicological evaluation of novel heat-not-burn tobacco products (2017): https://cot.food.gov.uk/sites/default/files/heat_not_burn_tobacco_statement.pdf