October 7, 2025
Meeting of the Tobacco Products Scientific Advisory Committee (TPSAC)

Renewal Modified Risk Tobacco Product Applications (MRTPAs)
MR0000254
Philip Morris Products S.A.

Office of Science
Center for Tobacco Products
Food and Drug Administration

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The attached briefing document contains information prepared by the Food and Drug Administration (FDA) for the members of the Tobacco Products Scientific Advisory Committee (TPSAC). The FDA background package includes assessments and/or conclusions and recommendations written by individual FDA reviewers. Such conclusions and recommendations do not necessarily represent the final position of the individual reviewers, nor do they necessarily represent the final position of the Review Division or Office. We are referring Philip Morris Products S.A.'s Renewal Modified Risk Tobacco Product Applications (MRTPAs) for five IQOS products to TPSAC to gain TPSAC's insights and recommendations. This briefing package may not include all issues relevant to FDA's decision on the application and instead is intended to focus on issues identified by FDA for discussion by TPSAC. FDA will not make its determination on the issues at hand until input from TPSAC and from the public comments has been considered and all FDA reviews have been finalized. FDA's determination may be affected by issues not discussed at the TPSAC meeting. The information in these materials does not represent agency position or policy. The information is being provided to TPSAC to facilitate its evaluation of the issues and questions referred to the Committee.

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U.S. FOOD & DRUG ADMINISTRATION

Memorandum

To:	Members, Tobacco Products Scientific Advisory Committee (TPSAC)
From:	Benjamin Apelberg, Ph.D., Deputy Director, Office of Science, Center for Tobacco Products, United States Food and Drug Administration
Subject:	Overview of the FDA Briefing Document for October 7, 2025, discussion of Philip Morris Products S.A. renewal MRTPAs for 2 IQOS heating systems and 3 HeatSticks varieties (FDA Submission Tracking Number MR0000254)

Introduction

We would like to thank the TPSAC members in advance for providing recommendations to FDA on the renewal modified risk tobacco product applications (MRTPAs) submitted by Philip Morris Products S.A. ("PMPSA").

On July 7, 2020, FDA issued modified risk granted orders (MRGOs) for the following tobacco products: IQOS 2.4 System Holder and Charger, Marlboro Amber HeatSticks, Marlboro Green Menthol HeatSticks, and Marlboro Blue Menthol HeatSticks. Additionally, on March 11, 2022, FDA issued an MRGO for the IQOS 3.0 System Holder and Charger. These two versions of the heating system and the three varieties of the HeatSticks consumables are collectively referred to as "IQOS" in this document.[1]

On July 5, 2023, FDA received renewal MRTPAs from PMPSA ("applicant") for these five IQOS products. The applicant has requested a renewal of its exposure modification orders under section 911(g)(2) of the Federal Food, Drug, and Cosmetic Act (FD&C Act) to continue to market the products specified with the following reduced exposure claim:

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.*

The aforementioned PMPSA MRGOs are exposure modification orders, meaning the applicant demonstrated that, among other things, as actually used by consumers, the IQOS products sold or distributed with the reduced exposure claim present a substantial reduction in exposure to a harmful substance or substances and that a measurable and substantial reduction in morbidity or mortality among individual tobacco users is reasonably likely to be demonstrated in subsequent studies, and issuance of an order 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 (FD&C Act

[1] IQOS 3.0 System Holder and Charger is also called IQOS 3 Originals; Marlboro Amber HeatSticks were originally Marlboro HeatSticks and are also called HEETS Amber; Marlboro Green Menthol HeatSticks were originally Marlboro Smooth Menthol HeatSticks and are also called HEETS Green; and Marlboro Blue Menthol HeatSticks were originally Marlboro Fresh Menthol HeatSticks and are also called HEETS Blue.

sections 911(g)(2)(A) and (B)). To arrive at this decision, FDA conducted thorough scientific review of the available scientific evidence. See Appendix A for additional information on the statutory requirements for modified risk tobacco products (MRTPs).

1. Postmarket Surveillance and Studies Requirements

Under section 911(g)(2)(C)(ii) of the FD&C Act, an order under 911(g)(2) is conditioned on the applicant's agreement to conduct postmarket surveillance and studies (PMSS) in order to "determine the impact of the order on consumer perception, behavior, and health, and to enable the [FDA] to review the accuracy of the determinations upon which the order was based in accordance with a protocol approved by the [FDA]." FDA communicated the PMSS requirements to PMPSA in the MRGO letters.

PMPSA's PMSS requirements included the following:

1. Monitoring adult (ages 21+) use of the IQOS products that were authorized to be marketed with the reduced exposure claim in terms of uptake, dual use, and complete switching; and monitoring awareness and use of IQOS among youth (ages <18) and young adults (ages 18-20), who are below the legal age to purchase tobacco products.
2. An assessment of consumer perceptions of the products and understanding of the claim, particularly that:
    a. to reduce their exposure to harmful or potentially harmful chemicals[2] relative to combusted cigarettes (CC), users of CC must use IQOS products exclusively and cutting down on CC per day while using IQOS products is not sufficient, and
    b. users of other tobacco products who switch to IQOS products understand that the reduction in exposure to harmful or potentially harmful chemicals is relative to CC use and not to other types of tobacco use.
3. Surveillance of MRTP sales and distribution in the U.S., adverse experiences, and new research study findings on the MRTPs and consumer perceptions, behaviors, or health.
4. Computational toxicology studies utilizing a battery of genotoxicity and carcinogenicity models to assess the chemicals that were higher in HeatSticks aerosols than in CC smoke in order to predict potential adverse effects in users before toxicity may be evident.
5. Postmarket computational modeling of the impact of the MRTPs on population health, including information on acute and long-term health effects of using IQOS relative to CC use, in order to assess the short- and long-term population health impacts of the marketing.

In accordance with sections 911(g)(2)(C)(ii) - (iii), PMPSA received FDA approval in February 2021 of all study protocols for its planned PMSS activities and then submitted five annual reports[3] outlining its progress on the approved PMSS activities. The annual reports included information from consumer surveys, a three-phase computational toxicology study, a population health model, surveillance of MRTP U.S. sales and distribution, adverse experiences, and new research findings (see Table 1).

2. United States International Trade Commission Cease-and-Desist Order

The MRGO authorizations for IQOS were for four years (July 2020 – July 2024). However, on September 29, 2021, the U.S. International Trade Commission issued a Cease-and-Desist Order (CDO) that

[2] In the applicant's claim and in the original PMSS requirements for the MRGOs, the term "chemical" was used rather than "constituent," which we have retained here for accuracy.

[3] The applicant submitted five annual reports over the MRGO authorization period, and each reporting period covered March 1 - February 28 for the previous year. The fifth report covered part of the MRGO authorization period (March 1 - July 7, 2024).

prohibited the importation, marketing, sale, and distribution of IQOS products in the U.S. To comply with the CDO, PMPSA stopped marketing and selling IQOS products in the U.S. by November 28, 2021.[4]

This market removal affected the ongoing PMSS, and PMPSA submitted an updated plan for PMSS data collection in January 2022. Table 1 below lists PMPSA's PMSS and adjustments made due to the removal of IQOS products from the U.S. market.

Table 1: List of PMSS studies and adjustments made due to the market removal of IQOS

Study name	**Original plan for the study**	**Adjustments**
IQOS with Marlboro HeatSticks Cross-Sectional Postmarket Adult Consumer Study (PACS)	Online, cross-sectional survey administered annually over four years beginning in 2021.	The applicant fielded the first wave from September to November 2021. Subsequent data collection was not completed.
IQOS with Marlboro HeatSticks Cohort Postmarket Adult Consumer Study (PACS)	Prospective longitudinal cohort study among adult established users of IQOS and a reference group of adult established users of CC over a closed 24-month period.	Study was not conducted.
Secondary Analysis: Estimation of Prevalence of IQOS Use Adult Tobacco Consumer Tracker (ATCT)	Ongoing nationally representative cross-sectional computer assisted random-digit dialing telephone interview survey. Questions about heated tobacco products (HTPs) were added in October 2019.	There were no adjustments to this data collection or secondary analysis due to the removal of IQOS from the market.
Reporting from the U.S. IQOS Owners Panel	Longitudinal consumer panel recruiting IQOS users from the IQOS consumer database. Planned recruitment wave every 2 weeks on an ongoing basis with participants surveyed weekly for the first 3 months after recruitment and then monthly thereafter.	IQOS Owners Panel data collection ceased as of November 29, 2021, when IQOS became unavailable in the U.S. market. The applicant reported data collected between April 2020 and November 29, 2021.
Secondary Analysis: Estimation of Awareness and Use of IQOS among Underage Individuals using the Underage Tobacco Use Survey (UTUS)	Ongoing nationally representative cross-sectional survey of youth and young adults (ages 13-20) in the U.S., which launched in May 2020 with plans to conduct regular quarterly surveys. This survey planned to oversample youth and young adults in Atlanta, GA, Charlotte, NC, and Richmond,	While data collection relevant to IQOS is ongoing, the applicant halted the oversampling in Atlanta, GA, Charlotte, NC, and Richmond, VA, starting in the second quarter of 2022 because IQOS is no longer available in those markets. The secondary analysis was otherwise unchanged.

[4] The MRGO for the IQOS 3.0 System Holder and Charger was issued after the CDO; the product was authorized to be marketed as an MRTP but was not on the market in the U.S. during PMPSA's compliance with the CDO.

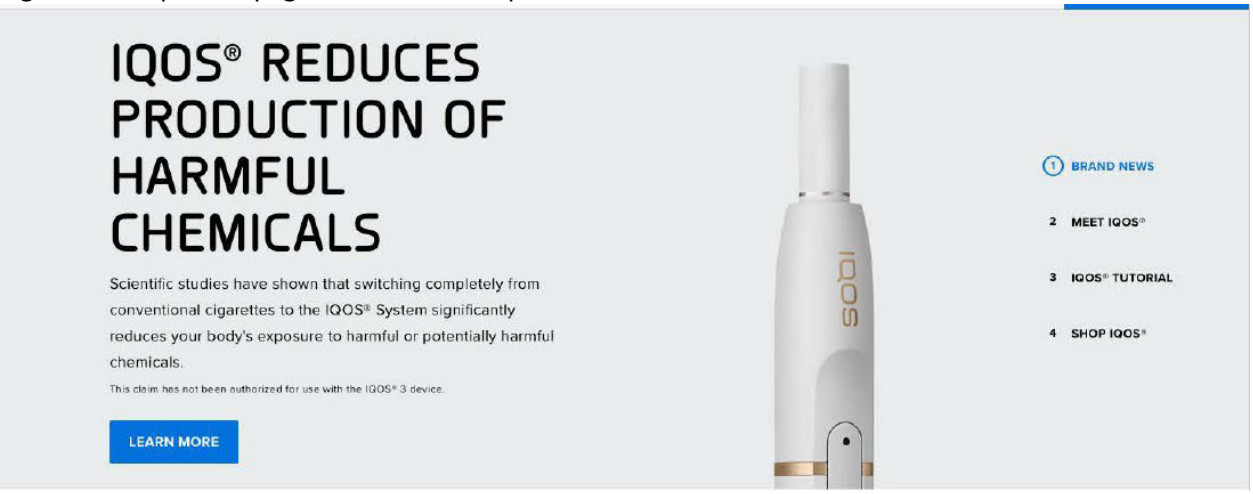
	VA, where IQOS was originally marketed.	
Population Health Impact Model (PHIM)	Update to the PHIM submitted in the original MRTPAs using data from PMSS studies as inputs.	The applicant was unable to utilize PMSS estimates for an updated PHIM, and instead utilized publicly available estimates.
Computational toxicology study	Three-phase computational toxicology study. The first phase evaluated the potential genotoxicity/carcinogenicity of the 80 chemicals found to be higher in HeatSticks aerosols than in 3R4F reference cigarette smoke (RCS) in the original MRTPAs. The second phase identified known and potential metabolites of these 80 parent chemicals. The third phase evaluated the potential genotoxicity/carcinogenicity of certain metabolites.	There were no adjustments to this study due to the removal of IQOS from the market.

Philip Morris International announced on February 2, 2024, that a global settlement was reached that allowed the reintroduction of IQOS products to the U.S. However, these products were not re-launched in the U.S. until March 2025. This means that IQOS products were only available in the U.S. for approximately 17 months during the MRGO authorization period.

3. Marketing and Sales Post-Modified Risk Granted Orders

Before their November 28, 2021, removal from the U.S. market due to the CDO, IQOS products were available from brick-and-mortar stores in Georgia, North Carolina, South Carolina, and Virginia. PMPSA advertised the products via company-owned retail stores, email, direct mail, print media, digital paid media, branded social media pages, point-of-sale signage at third-party retailers, brochures, guides, face-to-face interactions, paid affiliate activities, consumer engagements, and branded websites. See Figure 1 for a sample webpage that includes the reduced exposure claim.

Figure 1. Sample webpage with reduced exposure claim



To satisfy PMSS requirements, PMPSA submitted U.S. data on unit and dollar sales at company-owned stores and through wholesale distribution to third-party retailers ("third-party sales") from Q4 2019 through Q4 2021. Sales of both the IQOS System and HeatSticks show significant growth in quarterly unit sales for these products after the 2020 MRGOs, followed by a rapid decline in sales after the CDO. According to annual PMSS reports, third-party unit sales of HeatSticks grew from just before the MRGOs (b) (4) packs in Q2 2020) until right before the CDO in September 2021 (b) (4) packs in Q2 2021). After the CDO was issued, wholesale sales declined to roughly (b) (4) packs in Q3 2021 before slipping below zero ((b) (4) packs, reflecting returned products according to PMPSA) during Q4 2021. Although PMPSA continued submitting PMSS after the CDO, it reported no sales or distribution of IQOS products between Q1 2022 and February 28, 2025, the end date of the most recent PMPSA annual report.

FDA conducted an internal analysis of IQOS System and HeatSticks sales through NielsenIQ's Retail Measurement Services data[5] and identified a similar pattern of retail sales compared to wholesale data reported by PMPSA. FDA found that quarterly sales of HeatSticks grew from roughly (b) (4) packs during Q2 2020 to roughly (b) (4) packs during Q2 2021. That data also show that retail sales continued to grow into Q3 2021, with sales peaking at approximately (b) (4) packs before falling in Q4 2021 (around (b) (4) packs) and Q1 2022 (b) (4) packs). After Q1 2022, retail sales declined to zero or near-zero for all remaining quarters to date. For comparison, at their peak in Q3 2021, (b) (4) packs of HeatSticks were sold, and about (b) (4) packs of CC were sold during the same quarter. This disparity is to be expected with the introduction of a novel product and limited market availability. Most recently,

[5] FDA analyses and conclusions are informed in part by NielsenIQ Retail Measurement Service (RMS) data for the tobacco product category from the channels Total US Expanded All Outlets Combined (xAOC) and Convenience Stores and covering the time period September 29, 2019, through June 14, 2025. Any analyses, calculations, and conclusions are those of the authors and do not reflect the views of NielsenIQ. NielsenIQ is not responsible for and was not involved in analyzing and preparing the results reported herein, or in developing, reviewing, or confirming the research approaches used in connection with this report. NielsenIQ RMS data consist of weekly purchase and pricing data generated from participating retail store point-of-sale systems in all U.S. markets. See https://NielsenIQ.com/global/en/ for more information. NielsenIQ retail sales data licensed by FDA are not a 1:1 match for applicant-provided sales and distribution data. Notably, the NielsenIQ data do not cover online sales or sales from tobacco specialty stores (including IQOS brand-owned stores). In addition, the third-party sales reported by the applicant reflect wholesale distribution values, while NielsenIQ data reflect final retail point-of-sale values. However, NielsenIQ retail sales data are the most widely used and respected U.S. sales data source in the peer-reviewed scientific literature and are reported here to provide an independent estimate of IQOS sales trends.

NielsenIQ sales data from Nielsen-tracked stores for the 4-week period ending June 14, 2025, reported (b) (4) packs of HeatSticks sold; this data excludes online sales and sales at IQOS-brand owned stores.

Although there have been no studies on IQOS sales in the U.S. published since the MRGOs, there were several studies related to heated tobacco product (HTP) sales in other countries. HTPs, including IQOS, were introduced earlier in some other countries than in the U.S., and sales have increased over time. It is unclear how well these studies reflect what would have happened in the U.S. in absence of the CDO. In total, seven studies were identified that offer mixed findings about HTP sales after market introduction. For example, in Japan and Spain, HTP sales rose to capture a substantial portion of the tobacco market and seemed to replace a large quantity of CC sales (Cummings et al., 2020; Golpe et al., 2022). On the other hand, Liber et al. (2023) found that HTP sales increased in Poland without displacing CC sales. Of note, none of these international studies evaluated the effects of marketing IQOS with the authorized reduced exposure claim on sales, and factors that are unique to each country's tobacco marketplace and regulatory context (e.g., availability of electronic nicotine delivery systems [ENDS]) may limit the studies' applicability to a U.S. setting.

In summary, while IQOS is now back on the U.S. market at pop-up stores and mobile units in select regions and through online sales, little U.S.-based sales data were available to evaluate the effect of marketing IQOS with the authorized reduced exposure claim during the authorization period.

4. Content of the Renewal MRTPAs

The applicant submitted information about relative health risks of IQOS, which included clinical studies assessing biomarkers of exposure and potential harm in CC users who switch from CC to IQOS, a three-phase computational toxicology study, and scientific literature published since the issuance of the original MRGOs. Subsequent sections address patterns of IQOS use, including the potential impact of marketing IQOS as an MRTP on the population as a whole, including both current users and non-users of tobacco, and consumer understanding and perceptions of the MRTP and associated modified risk information.

On November 22, 2024, FDA issued an Advice/Information Request letter to PMPSA asking for clarification about several topics, including manufacturing changes and modifications, absolute quantities of aerosol constituent data, carcinogenic risk of aerosols, and chemical identity. On December 20, 2024, PMPSA responded to this request for information, and pertinent information provided in the response is discussed in the appropriate sections below.
The sections below summarize a subset of the new evidence submitted as part of these renewal MRTPAs and refer to the original MRTPAs as needed for context. PMPSA submitted additional information with the renewal MRTPAs that FDA is considering as a part of the totality of the scientific evidence; however, this document focuses on the evidence that FDA intends to discuss with the Committee. Other evidence submitted includes reports of adverse experiences, a Population Health Impact Model (PHIM), and calculation of excess lifetime cancer risk (ELCR). The PHIM and ELCR provided limited information. The PHIM is limited because the applicant was not able to complete the PMSS that would have provided inputs for this model. Upon review, FDA concluded the ELCR is limited as it was based on values derived from a non-targeted differential screening that did not provide accurate estimates of the absolute quantities of compounds in IQOS aerosol.

Draft Topics for TPSAC Discussion

FDA is reviewing the scientific information submitted in the renewal MRTPAs and scientific information from other sources identified by the Agency to determine whether the standard for issuing the MRGOs continues to be met. FDA will also review public comments submitted in accordance with FD&C Act section 911(e).

FDA intends to raise the following matters for discussion with TPSAC:

Discussion 1: IQOS and nonclinical toxicity evidence
Background: The findings from most nonclinical toxicological studies published since the issuance of the modified risk granted orders (MRGOs) and reviewed by FDA did not identify new toxicological concerns about IQOS. However, four newly published nonclinical studies that used rodent models to study IQOS aerosol exposure found that exposure to IQOS aerosols had respiratory, cardiovascular, and reproductive/developmental toxic effects that were comparable to or more severe than CC smoke exposure (Gu et al., 2023; Nitta et al., 2022; Qiu et al., 2023; Yoshida et al., 2020).

Discuss the strength of the noncancer toxicity evidence from those four animal studies in the context of the totality of toxicological evidence, including any limitations of these and other studies that may limit their conclusions.

Discussion 2: Totality of evidence and long-term disease risk
Background: There is evidence of large overall reductions in harmful and potentially harmful constituents (HPHCs) in IQOS aerosols compared to CC smoke; however, newly available nonclinical data from predictive computational toxicology studies and rodent models raise questions about the genotoxic and noncancer toxicological effects of exposure to IQOS aerosols.

Consider the totality of the toxicological evidence that is now available and discuss the implications for long-term disease risks of exposure to IQOS aerosols relative to CC.

Discussion 3: IQOS patterns of use
Background: The applicant was unable to conduct all planned PMSS, including the cohort study designed to evaluate the impact of marketing IQOS with the authorized modified risk claim on tobacco product use behavior. Accordingly, FDA received limited evidence regarding the impact of marketing IQOS with the claim on patterns of tobacco use.

Discuss the likely patterns of IQOS use behavior when marketed as an MRTP in the U.S. Based on the available evidence, consider the likely patterns of use with a specific focus on the likelihood that people who use CC will switch completely to IQOS and the likelihood that they will dual use IQOS and CC.

Preliminary FDA Review Findings

1. Relative Health Risks

1.1. Biomarker and Other Clinical Data

A. Conclusion from the Original MRTPA Review

In the original MRTPAs, the applicant submitted several randomized clinical studies that measured biomarkers of exposure (BOEs) to assess whether IQOS use resulted in reduced exposure to HPHCs compared to CC use and biomarkers of potential harm (BOPHs) to assess whether IQOS use resulted in biological changes that may indicate a change in long-term disease risk. These studies demonstrated that most BOEs related to HPHCs had statistically significant reductions among participants who switched completely to IQOS. Additionally, these studies demonstrated favorable changes in some BOPHs among participants who switched to IQOS compared to participants who continued CC use, but FDA noted that the clinical significance of these minor changes was unclear.

FDA concluded that the magnitude of difference in BOEs to 15 specific HPHCs when CC users switched completely to IQOS was substantial. The reduced BOEs reflected a range of chemical classes (e.g., carbonyls, aromatic amines, polycyclic aromatic hydrocarbons, nitrosamines) and toxicity classes (e.g., carcinogenic, cardiovascular, respiratory, reproductive). It was reasonable to expect that completely switching to IQOS from CC would lower exposure to other constituents as well. FDA also concluded that longer-term studies are needed to evaluate the overall health impact of switching to IQOS.

B. Postmarket Evidence: Applicant-Conducted Studies

The applicant submitted results from several clinical studies and cross-study post-hoc analyses that evaluated the impact of switching completely from CC to IQOS on changes in BOEs and BOPHs. A U.S. clinical study extended the 6-month randomized, controlled, open-label, two-arm, parallel group, multi-center study of IQOS, the results of which were submitted as part of the original MRTPAs, to 12 months. The statistically significant reduction in select BOEs and the favorable changes in BOPHs that were observed in the original MRTPAs were overall maintained among participants who predominantly used IQOS compared to participants who continued to use CC at month 12. Most changes in the BOPHs continued to be small, and the clinical significance of the BOPH results continues to be unclear.

The results of the post-hoc analyses were consistent with these findings. The post-hoc analyses pooled longitudinal data of participants who predominantly used IQOS, participants who continued to predominantly use CC from the U.S. clinical study, and participants who became abstinent from CC from a separate CC smoking cessation study conducted in the U.S., Japan, and Europe (participants from Japan excluded). The post-hoc analyses examined differences in BOEs and BOPHs, including markers of various disease pathways and lung function, among these three participant categories. Overall, as noted above, the BOEs related to HPHCs were lower at months 3, 6, and 12 (month 12 data available for a subset of BOEs) among the group that predominantly used IQOS compared to the group who continued to use CC, but these reductions were not as large as those for the group who abstained from CC use compared to the group who continued to use CC. There were few differences in BOPHs between the group that predominantly used IQOS and the group that continued to use CC. In contrast, differences in most BOPHs were larger and statistically significant at most time points among the group that abstained from CC use compared to the group that continued to use CC. There were notable limitations to these analyses, including that participants in the group who predominantly used IQOS were not exclusive users of IQOS; the applicant defined IQOS use as at least 70% of the total of self-reported IQOS and CC use over the 12-month study analysis period, which was operationalized as “at least 70% IQOS use and at least 70% IQOS use on over half of the days” for both the first and second six months of the clinical study.

The applicant also submitted results from two international clinical studies. One was a 6-month, randomized, controlled, open-label, two-arm, parallel group study in Japan among people who used CC with generalized chronic periodontitis. This study demonstrated significant reductions in urinary total 4-(methylnitrosamino)-1-(3-pyridyl)-1-butanol (NNAL) and 2-cyanoethylmecapturic acid (CEMA) at 3 and 6 months among participants who predominantly used IQOS compared to participants who continued to use CC. Secondly, a 12-week, randomized, open-label, four-arm, parallel group study of exercise tolerance conducted in Germany among people who used CC demonstrated reductions in total NNAL and CEMA among participants who switched to IQOS use in an ambulatory setting.

C. Postmarket Evidence: Published Literature

Since the issuance of the MRGOs, the literature published on BOEs continues to show that people who switch from CC to HTPs, including IQOS, are generally exposed to lower levels of selected HPHCs than

people who continue to use CC (Drovandi et al., 2020; Nishihara et al., 2024; Tattan-Birch et al., 2022; Yuki et al., 2022).

Since the issuance of the MRGOs, the literature published regarding BOPHs is mixed. In a recent systematic review of the impact of HTPs on BOPHs, analysis of data on 143 BOPHs indicated that short-term use of HTPs had mixed effects compared with CC, CC use abstinence, and ENDS (Braznell et al., 2025). A small cross-over trial with 40 young adults who used CC examined changes in leukocyte count after a single trial use of CC or HTP. Participants who used CC and those who used HTPs both had significant increases in leukocytes (Belkin et al., 2023). Another study that examined BOPHs related to HTP use not specific to IQOS found that, compared to CC use, HTP use was associated with lower levels of six biomarkers (TG, sICAM-1, WBC, 1-DHTXB2, 2,3-d-TXB2, and 8-epi-PGF2α) but higher levels of four biomarkers (HDL-C, FEV1, %FEV1, and FEF25-75) (Sakaguchi et al., 2021).

The literature on the impact of switching from CC to HTPs, including IQOS, on BOPHs has several limitations. Studies tend to be of short duration (e.g., single use in a lab or several months) and often do not specify the exact HTP or IQOS system used in the study. Given these limitations and mixed findings, the clinical significance of the published BOPH data continues to be unclear, particularly as questions remain about the credibility of BOPHs as surrogates or substitutes for disease endpoints.

1.2. Toxicological Assessment

A. Conclusion from the Original MRTPA Review

Results provided in the original MRTPAs demonstrated that there are large reductions in established HPHCs in IQOS compared to 3R4F reference cigarette smoke (RCS). 3R4F cigarettes are reference cigarettes designed for research by the University of Kentucky. FDA stated that the applicant's HPHC testing found that "107 out of 108 HPHCs tested were either found to be below the limit of detection or quantification or lower than the concentrations in mainstream cigarette smoke. With the exception of nicotine and anabasine, HPHCs are 47-99.9% lower in the IQOS system with Heatsticks compared per unit and 20-99.8% lower when compared to normalized nicotine levels.""

Evidence from in vitro and in vivo studies provided in the original MRTPAs indicated that HeatSticks aerosols had reduced cytotoxic potential when compared to 3R4F RCS and indicated less severe histopathological changes in rats exposed to HeatSticks aerosols compared to RCS. In addition, HeatSticks generally produced fewer pathophysiological changes and adverse effects than RCS in studies with human organotypic tissues or produced similar toxicity at higher concentrations. The applicant did identify 80 compounds not on FDA's HPHC list that were either present exclusively or were found in higher quantities in HeatSticks aerosols compared to 3R4F RCS, but FDA concluded that "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."

B. Postmarket Evidence: Computational Toxicology Study

As part of the PMSS requirements, the applicant submitted a postmarket computational toxicology study consisting of three phases. The first phase evaluated the potential genotoxicity/carcinogenicity of the 80 parent chemicals found to be higher in HeatSticks aerosols than in 3R4F RCS in the original MRTPAs. The second phase identified known and potential metabolites of these 80 parent chemicals. The third phase evaluated the potential genotoxicity/carcinogenicity of certain metabolites.

Compared to information submitted in the original MRTPAs, the postmarket computational toxicology study identified additional compounds on the list of 80 chemicals as being potentially genotoxic/carcinogenic. Some of the compounds that were not predicted to be genotoxic/carcinogenic in the computational toxicology study had metabolites with potential genotoxic/carcinogenic effects, such as p-cresol (U.S. EPA, 1986), raising the possibility that some of these parent compounds may act as pro-carcinogens. This new information suggests that genotoxic risks associated with HeatSticks aerosols may be higher than initially indicated by information available as part of the original MRTPA review. Additionally, two rat exposure studies published after the issuance of the MRGOs indicated that exposure to IQOS aerosols may have genotoxic effects in vivo (Vivarelli et al., 2021; Vivarelli et al., 2024).

C. Postmarket Evidence: Published Literature

FDA reviewed 71 studies published since the issuance of the MRGOs that focus on the effects of IQOS and HTPs, including respiratory, cardiovascular, reproductive, and metabolic effects. Of these 71 studies, 35 were in vitro and 25 were in vivo. The largest number of studies, 32 in total, focused on respiratory toxicity; half of these (16) found that CC smoke exposure was worse for respiratory outcomes than HTP/IQOS aerosol exposure. Six studies did not make comparisons between CC smoke exposure and IQOS/HTP aerosol exposure, and one study found that dual exposure of IQOS aerosol and CC smoke was worse than either exposure alone. Four studies found that CC smoke exposure and HTP/IQOS aerosol exposure led to similar respiratory outcomes, and five studies found that the results were mixed when investigating the differences in respiratory outcomes between CC smoke exposure and IQOS/HTP aerosol exposure. See Appendix B for a table of all literature reviewed related to genotoxic and noncancer toxicological effects of IQOS aerosol exposure.

The sections below review a subset of literature related to nonclinical outcomes of IQOS aerosol exposure. Four studies in particular raise questions about the health effects of IQOS aerosols: Gu et al., 2023; Nitta et al., 2022; Qiu et al., 2023; and Yoshida et al., 2020.

i. Respiratory Effects

Thirty-two studies focused on respiratory toxicity. Of these studies, two long-term animal studies (Gu et al., 2023; Nitta et al., 2022) suggest that the use of IQOS aerosols may lead to a significant risk of emphysema relative to CC use. Gu et al. (2023) exposed male C57BL/6J mice to IQOS aerosols or Marlboro Red CC smoke for 5 days per week over 24 weeks. The results for most measured lung function parameters indicated that there were no statistically significant differences between mice exposed to CC smoke and those exposed to IQOS aerosols, and that mice exposed to CC smoke or IQOS aerosols had alveolar enlargement and other changes that were indicative of emphysema.

Nitta et al. (2022) evaluated effects of exposure to IQOS aerosols or Peace nonfilter CC smoke in male C57BL/6J mice. Mice were exposed to CC smoke or IQOS aerosols for 5 days per week over 6 months. Compared to air-exposed controls, there was a statistically significant increase in cell infiltrates in bronchoalveolar lavage fluid in mice exposed to CC smoke but not in mice exposed to IQOS aerosols. There were statistically significant increases in the numbers and percentages of neutrophils and lymphocytes in the bronchoalveolar lavage fluid of mice exposed to CC smoke or IQOS aerosols compared to air-exposed controls. Additionally, exposure to either IQOS aerosols or CC smoke led to airspace enlargement and alveolar wall destruction, which are indicative of emphysema.

Both Gu et al. (2023) and Nitta et al. (2022) had limitations in the morphometrical methodology they used, including the use of a small number of images for quantification, no information on whether images were analyzed in a blinded manner, and no information on whether the histopathological

analysis was performed by a veterinary pathologist. As an additional limitation, Nitta et al. (2022) did not provide statistical evaluations of differences in the measured endpoints between mice exposed to IQOS aerosols and mice exposed to CC smoke. Moreover, statistical analyses of multiple groups in Gu et al. (2023) were based on Student's t-tests that did not account for multiple comparisons, which may lead to type 1 error. Gu et al. (2023) also lacked data for BOEs in exposed mice. Additionally, both Gu et al. (2023) and Nitta et al. (2022) had relatively small group sizes of 5 to 8 mice per group. Despite these limitations, these findings suggest that exposure to IQOS aerosols or CC smoke may have similar effects on the development of emphysema in mouse models.

Although Gu et al. (2023) and Nitta et al. (2022) raise important questions about the respiratory effects of IQOS aerosols, shorter-term acute and subacute studies that evaluated the respiratory effects of IQOS relative to CC smoke provide mixed findings. In one study, Bhat et al. (2023) exposed C57BL/6NCr mice to IQOS aerosols or CC smoke for 8 weeks. There were statistically significant and similar increases from baseline in lung immune infiltrates following exposure to IQOS aerosols or CC smoke. Additionally, mice exposed to IQOS aerosols or CC smoke had statistically significant increases in levels of certain pro-inflammatory chemokines and cytokines in bronchoalveolar lavage fluid. Exposure to IQOS aerosols or CC smoke also led to increased lung vascular permeability, which is associated with lung injury.

In a similar study from the same research group, Bhat et al. (2021) exposed C57BL/6NCr mice to IQOS aerosols or CC smoke for two weeks. There were statistically significant increases in lung immune infiltrates following exposure to IQOS aerosols or CC smoke, and the levels of increase were similar between mice exposed to IQOS aerosols or CC smoke. Additionally, mice exposed to IQOS aerosols or CC smoke had statistically significant increases in levels of pro-inflammatory chemokines and cytokines in bronchoalveolar lavage fluid. The levels of most of these cytokines and chemokines had no statistically significant difference between mice exposed to IQOS aerosols or CC smoke (Bhat et al., 2021). Exposure to IQOS aerosols or CC smoke also led to statistically significant increases in levels of albumin in bronchoalveolar lavage fluid, indicating increased lung vascular permeability, which is associated with lung injury. However, mice exposed to CC smoke had statistically significant higher levels of albumin in bronchoalveolar lavage fluid than mice exposed to IQOS aerosols. In Bhat et al. (2021), mice were exposed to emissions from 20 CC or IQOS HeatSticks for 5 hours per day over 2 weeks, and these exposure levels may have contributed to differences in the effects observed by Bhat et al. (2021) compared to the other studies discussed below (Husari et al., 2023; Kastratovic et al., 2024).

Kastratovic et al. (2024) evaluated the effects of 4-week exposure to IQOS aerosols or 1R6F RCS in BALB/c mice. Mice exposed to IQOS aerosols had statistically significant lower histological scores for lung injury and lower levels of lung immune infiltration than mice exposed to RCS. Based on flow cytometry, mice exposed to IQOS aerosols also had statistically significant lower expression of certain pro-inflammatory cytokines in lung neutrophils and T cells than in mice exposed to RCS. Some similar findings are reported in Husari et al. (2023), a study that exposed C57BL/6 mice to 3R4F RCS, IQOS aerosols, or both for 1 week. Compared to control mice, those exposed to RCS expressed higher lung levels of genes for cytokines associated with inflammation, while the expression of these genes was comparable between mice exposed to IQOS aerosols or controls. Based on qualitative assessments, mice exposed to IQOS aerosols had limited lung injury, while mice exposed to RCS had increased immune infiltration, decreased alveolar spaces, and thickened alveolar walls. Additionally, exposure to RCS, but not IQOS aerosols, led to statistically significant increases in reactive oxygen species production and increased percentages of apoptotic cells in the lungs (Husari et al., 2023). Similarly, a study in which mice were exposed to IQOS aerosols or CC smoke for seven days found that exposure to CC smoke, but not IQOS aerosols, led to increased lung levels of reactive oxygen species compared to unexposed mice. Exposure to CC smoke also led to higher lung levels of pro-inflammatory cytokine gene expression than

IQOS aerosol exposure, but it is unclear whether these differences were statistically significant. Additionally, mice exposed to CC smoke or IQOS aerosols had increased levels of albumin in bronchoalveolar lavage fluid (Daou et al., 2021).

Overall, the evidence for the relative effects of IQOS aerosol and CC smoke exposures on subacute respiratory toxicity is mixed. Several studies indicated that exposure to IQOS aerosols led to lung inflammation and increased lung vascular permeability (Bhat et al., 2023; Bhat et al., 2021; Gu et al., 2023; Nitta et al., 2022), and two of these studies provided evidence that exposure to IQOS aerosols led to outcomes indicative of emphysema. These results of the chronic exposure studies (Gu et al., 2023; Nitta et al., 2022) are more severe than results of the acute studies, which only look at short-term exposure (Daou et al., 2021; Husari et al., 2023; Kastratovic et al., 2024).

ii. Cardiovascular Effects

Seven studies focused on cardiovascular toxicity:: two were in vivo (rodent) studies, and five were in vitro or ex vivo studies. Of these studies, one animal study (Qiu et al., 2023) published since the MRGOs raises questions about the cardiovascular effects of using IQOS relative to CC. Qiu et al. (2023) evaluated the effects of exposures to IQOS aerosols, Marlboro Red CC smoke, or aerosols from other tobacco and marijuana products on cardiac function compared to air-exposed controls. Male and female Sprague-Dawley rats were exposed to IQOS aerosols or CC smoke for 5 minutes once daily, 5 days per week over 2 months. Results indicated that:

- Baseline systolic blood pressure progressively increased over weeks of exposure to either IQOS aerosols or CC smoke.
- Exposure to IQOS aerosols or CC smoke also led to impairments in cardiac function. For example, rats exposed to IQOS aerosols or CC smoke had statistically significant lower ejection fractions and fractional area changes than air-exposed rats.
- Compared to air-exposed rats, rats exposed to IQOS aerosols or CC smoke had statistically significant increases in left ventricular end-systolic volume, left ventricular mass, and left atrial diameter. These changes suggested that exposure to IQOS aerosols or CC smoke led to impaired left ventricular function.
- Rats exposed to IQOS aerosols or CC smoke also had decreased heart rate variability compared to air-exposed rats.
- Exposure to CC smoke or IQOS aerosols led to increased inducibility of atrial fibrillation following ex vivo cardiac stimulation.
- In contrast, rats exposed to CC smoke, but not IQOS aerosols, had statistically significant increases in ventricular tachycardia inducibility compared to air-exposed rats.
- Levels of cardiac interstitial fibrosis showed a statistically significant increase in the left atrium, right atrium, and left ventricles of rats exposed to IQOS aerosols or CC smoke.

These findings suggest that exposure to IQOS aerosols could lead to similar pathophysiological cardiac effects as exposure to CC smoke. One limitation of this study is that it does not include data regarding BOEs in exposed rats, which could have provided relevant information for comparisons of exposure levels between mice exposed to IQOS aerosols or CC smoke.

Other studies also investigated the cardiovascular effects of IQOS aerosols. Rao et al. (2022) evaluated the effects of exposure to IQOS aerosols, Marlboro Red CC smoke, and ENDS aerosols on vascular endothelial function. Exposure to either IQOS aerosols or CC smoke showed statistically significant impairment of flow-mediated dilation, and there was no statistically significant difference between these two groups. Impairments in flow-mediated dilation are predictive of the risk of cardiovascular disease (Conklin et al., 2019). The applicant noted that the results in this study may differ from the

effects of IQOS aerosol exposures in humans, based on a case control study (Ikonomidis et al., 2021) that compared flow-mediated dilation in people who used CC and people who used CC who were instructed to replace CC use with IQOS use for 1 month. Flow-mediated dilation showed a statistically significant increase in people who used CC who were asked to replace CC with IQOS (Ikonomidis et al., 2021). Another randomized study found that CC use had more severe impacts on flow-mediated dilation than IQOS use (Biondi-Zoccai et al., 2019). This study evaluated effects of longer-term IQOS use than Rao et al. (2022). However, given the finding that flow-mediated dilation may improve in people who used CC who replaced CC with IQOS use (Ikonomidis et al., 2021), the results in Rao et al. (2022) raise fewer questions than those of Qiu et al. (2023).

Of the seven studies reviewed that focused on the cardiovascular toxicity of IQOS aerosols, two studies (Qiu et al., 2023; Rao et al., 2022) found that exposure to CC smoke or IQOS aerosols led to similar cardiovascular outcomes. A review of literature by Alarabi et al. (2022) also found that HTP aerosol exposure may lead to similar cardiovascular outcomes as CC smoke exposure. Conversely, four other studies found that CC smoke exposure was worse than IQOS aerosol exposure for cardiovascular toxicity outcomes. Overall, evidence related to the relative effects of IQOS aerosol exposure and CC smoke exposure on cardiovascular toxicity is mixed.

iii. Reproductive Effects

Only one animal study (Yoshida et al., 2020) published since issuance of the MRGOs reviewed by FDA focused on the reproductive effects of IQOS aerosol exposure, and it raises questions about the effect of IQOS relative to CC on the male reproductive system. Yoshida et al. (2020) evaluated the effects of in utero exposure to IQOS aerosols or CC smoke on testicular function. Pregnant CD-1 mice were given whole body exposures to aerosols from four Heatsticks or smoke from four 3R4F reference cigarettes on days 7 and 14 of gestation. Exposure to IQOS aerosols or RCS did not statistically significantly affect fertility or litter size. There were no statistically significant differences in the body weights or testicular weights of offspring that had been exposed to filtered air, IQOS aerosols, or RCS in utero. However, 5-week-old male mice that were exposed to IQOS aerosols in utero had statistically significant higher levels of seminiferous tubule damage and reduced daily sperm production compared to mice exposed in utero to filtered air as a control. In contrast, exposure to RCS in utero did not lead to statistically significant changes in seminiferous tubule damage or daily sperm production. These effects were transient, and at age 15 weeks these outcomes were comparable between mice that had been exposed in utero to filtered air, IQOS aerosols, or RCS. The authors concluded that in utero IQOS aerosol exposure delayed male sexual maturation or impaired testicular function more than RCS exposure (Yoshida et al., 2020).

One limitation of the Yoshida et al. (2020) study is that nicotine absorption was not measured in exposed mice and that BOEs were not reported. Based on published work indicating that prenatal nicotine exposure affects gonocyte maturation, differences in nicotine uptake may have contributed to the effects of IQOS aerosol exposure in this study. An additional limitation is the conservative exposure regimen: pregnant mice were exposed to IQOS aerosols or RCS for only two days, which may not be sufficient to assess the full range of exposure effects on testicular function in offspring. Although this study found that in utero RCS exposure did not show a statistically significant effect on testicular function, other work has identified effects of in utero RCS exposure on testicular histology and sperm counts, suggesting that the sensitivity of the analyses in Yoshida et al. (2020) may be limited.

As only one study was identified that focused on reproductive effects of IQOS aerosol exposure, a definitive conclusion regarding the relative reproductive effects of IQOS aerosol exposure and CC smoke exposure cannot be made. Regardless, and despite the limitations discussed, the findings in Yoshida et

al. (2020) suggest that in utero exposure to IQOS aerosols may have damaging effects on seminiferous tubules and daily sperm production.

iv. *Metabolic Effects*

FDA reviewed two studies addressing the metabolic effects of IQOS that were published since the issuance of the MRGOs, but the strength of the authors' conclusions has been moderated by significant limitations. Curley et al. (2024) evaluated metabolic effects of IQOS aerosol exposure using the HBE-1 immortalized human bronchial epithelial cell line. Submerged cell cultures were exposed to room air, IQOS aerosols, or 1R6F RCS. Cell lysates were then collected and evaluated for primary metabolites, lipids, and biogenic amines. Compared to unexposed cells, cells exposed to IQOS aerosols had unique metabolites that were not seen in cells exposed to RCS. The authors used Ingenuity Pathway Analysis to identify canonical pathways for diseases and disorders associated with the observed metabolites. Based on this analysis, IQOS aerosol exposure induced unique canonical pathways that were not seen following RCS exposure. The pathways induced by IQOS aerosol exposure were associated with human disorders, including developmental and hereditary disorders, organismal injury, and metabolomic diseases (Curley et al., 2024). This study contains limited methodological information, including information regarding the methods used to evaluate levels of primary metabolites, lipids, and biogenic amines. Although Curley et al. (2024) found that IQOS exposures resulted in unique metabolites and pathways compared to RCS exposure, the toxicological consequences of these unique effects is unclear, and more information is necessary to adequately assess the outcomes of this study. Given these limitations, the unique metabolic effects of IQOS in this type of exposure in this study are inconclusive.

In a similar study, BEAS-2B human bronchial epithelial cells were exposed to IQOS aerosols or 3R4F RCS in air-liquid interface cultures for metabolomic evaluation (Lenski et al., 2024). Exposure to two or four puffs of 3R4F or 60 or 120 puffs of IQOS led to metabolic dysregulation. Based on dysregulated metabolites, 3R4F exposures were associated with a metabolomic fingerprint of 51 compounds, while IQOS exposures were associated with a metabolomic fingerprint of 205 compounds. Multiple metabolic pathways were dysregulated following IQOS aerosol exposure, including pathways associated with purine metabolism, glycerophospholipid metabolism, and tryptophan metabolism. As noted by the authors, differences in exposure levels of IQOS aerosols and 3R4F RCS may have contributed to the observed effects. The authors also noted that the analysis in this study served as an initial screening approach, and that additional verification was needed to confirm compound identification.

Although both studies identified unique metabolic effects of IQOS aerosol exposure relative to RCS exposure, limitations of the studies and of the assessed outcomes do not allow for a definitive conclusion.

1.3. Summary of the Relative Health Risks Evidence

Overall, the clinical and toxicological evidence submitted by PMPSA continues to support the authorized claim that "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." The clinical evidence suggests that switching completely from CC to IQOS reduces BOEs to a variety of HPHCs, and the toxicological evidence that IQOS aerosol contains a significantly lower level of a wide variety of HPHCs relative to CC smoke remains unchanged.

The overall long-term relative health risks of IQOS compared to CC are still largely unknown. The clinical evidence of the impact of switching from CC to IQOS on BOPHs is mixed, and the overall clinical significance of BOPHs as a proxy for human health outcomes remains uncertain. Additionally, the

product has not been available in the U.S. or international markets long enough to result in long-term studies of human health outcomes.

The computational toxicology study submitted in the renewal MRTPAs identifies 36 potentially genotoxic/carcinogenic compounds found at higher levels in IQOS aerosols than in RCS, which is more than was identified in the original MRTPAs, increasing uncertainty about the toxicological risks of IQOS.

Additionally, four of 71 studies that were published after the MRGOs and reviewed by FDA raise questions about the toxic effects of the complete IQOS aerosol mixture in rodent models (Gu et al., 2023; Nitta et al., 2022; Qiu et al., 2023; Yoshida et al., 2020). The studies generally found that exposure to IQOS aerosols had similar or more severe effects than exposure to CC smoke on emphysema, cardiovascular toxicity, and one aspect of reproductive/developmental toxicity. As discussed in 1.2.C., these studies have limitations. Additionally, these studies should be assessed as a part of the larger body of non-clinical studies published since the MRGOs that investigated the relative health risks, including the biomarkers of exposure and toxicological effects, of IQOS and HTPs to determine the implications of the long-term health risks of IQOS use relative to CC use.[6]

2. Patterns of Use and Impacts to the Population

2.1. Impact on Users of Tobacco Products

A. Conclusion from the Original MRTPA Review

As part of the original MRTPAs, the applicant submitted U.S. premarket and international studies that evaluated patterns of IQOS use. In both U.S.-based and international studies, dual use with CC was the predominant pattern of IQOS use. Results from a U.S. 6-week actual use study designed to assess IQOS use patterns among people who used CC daily in a near real-world setting showed that by the end of the study, 7.5% of participants exclusively used IQOS (≥95% HeatSticks use) and 29.4% dual-used CC and IQOS (combined participant categories of >30% and <70% HeatSticks use). There were minimal changes in total use of tobacco products between baseline and the end of the observational period, suggesting that participants were replacing a proportion of their CC use with IQOS. Results from an international four-week whole offer test study designed to evaluate the likelihood that adults who used CC daily in Asia and Europe would switch from CC to IQOS showed that by the end of the study, a range of 4-16% of participants exclusively used IQOS (≥95% HeatSticks use), and a range of 38.7-57.8% dual-used CC and IQOS (combined participant categories of >30% and <70% HeatSticks use).

These studies suggested that dual use with CC was the predominant pattern of IQOS use, whereas the rate of exclusive use (≥95% Heatstick use) was relatively low. FDA concluded that because exclusive use is how individuals can most effectively reduce their exposure to HPHCs, these findings did not provide strong support for the potential benefit to the population as a whole. However, FDA noted that these studies were conducted over a relatively short timeframe, and it was unclear whether dual use would be a sustained behavior or transition state. FDA also noted that if the products were authorized as MRTPs, there would be explicit communication that reduced exposure results from "switching *completely* from conventional cigarettes to the IQOS system" (emphasis added).

B. Postmarket Evidence: Study Descriptions

[6] Additional findings and limitations from these studies and other studies that were evaluated as part of the toxicology literature review are summarized in Appendix B. Some of the studies summarized in this table evaluated multiple products, such as ENDS or HTPs other than IQOS. In these cases, only findings regarding effects of IQOS products and any comparisons with CC are summarized.

As part of the PMSS, the applicant was required to monitor patterns of IQOS use, including the likelihood of dual use with CC and complete switching from other tobacco products to IQOS. Because of the removal of IQOS from the U.S. market due to the 2021 CDO, the applicant was not able to complete many of its planned and approved PMSS (see Table 1 for more information). However, the applicant submitted data from the first wave of the IQOS with Marlboro HeatSticks Cross-sectional Postmarket Adult Consumer Study (IQOS Cross-sectional PACS). The IQOS Cross-sectional PACS was designed to be an annual, cross-sectional, self-administered online survey of ever established IQOS users. Participants were recruited from a database of registered IQOS consumers in the U.S. developed and maintained by Altria Client Services. Eligible participants were ever established IQOS users (ages 21+) residing in the U.S., which the applicant defined as having used at least 100 Marlboro HeatSticks in their lifetime. A total of 19,258 individuals were invited to participate, 10.5% responded, and 3.6% (n = 688) were eligible and completed the survey. The applicant reported on the data collected between September 14 and October 13, 2021 (during the MRGO authorization period), when the applicant informed participants that IQOS would soon be taken off the market in the U.S. This subsample consists of 463 individuals, including 439 current and 24 former established IQOS users. The applicant focused on this subsample because the information that IQOS would soon be unavailable could have potentially affected IQOS users' behaviors.

In addition, the applicant submitted information about a Pilot Actual Use Study of IQOS 3.0 in the U.S. and two international studies from Japan. The Pilot Actual Use Study, submitted as part of the 2023 PMSS report, was a six-week home-use study designed to characterize tobacco use patterns among U.S. adults (ages 21+) who used CC when provided with IQOS under near real-world conditions. This study was not part of the original PMSS plan, and the applicant did not provide sufficient information about study methodology to allow its strengths and limitations to be fully evaluated and therefore is not described further here. The two studies in Japan reported data from the fifth year of repeated cross-sectional surveys of the general adult population and a convenience sample of IQOS users registered in the IQOS user database in Japan. The applicant provided little context or justification for why data from Japan are relevant for assessing patterns of use within the U.S. These studies focused on IQOS products that did not include exposure reduction claim, and the applicant did not outline the similarities or differences between the U.S. and Japan with regards to CC use that might inform the impact of IQOS to people in the U.S. who use CC. Therefore, these study findings are not described further here.

C. Postmarket Evidence: IQOS User Demographics

The IQOS Cross-sectional PACS data from October 2021 provided some information about the demographics of current established IQOS users in the U.S. The median age of people who used IQOS was 44 years (interquartile range: 37, 53). Approximately 60% of IQOS users were male; 72.9% were non-Hispanic White and 14.4% were non-Hispanic Asian. Approximately 61% of IQOS users had a household income of $60,000 or more; 78.8% had some college or more education; and 80.6% were employed. Additionally, the vast majority of IQOS users either formerly (50.6%) or currently (48.8%) used CC. Furthermore, 96.6% of the 439 IQOS users were ever established CC users, and 98.2% were ever established users of any tobacco products other than IQOS. Overall, these results suggest that IQOS users in the U.S. tended to be middle-aged men with relatively high socioeconomic status. Additionally, the majority of IQOS users in the U.S. were ever established CC users, many of whom were using CC before using IQOS.

D. Postmarket Evidence: Frequency and Intensity of IQOS Use, and Dual and Poly Use with Other Tobacco Products

The IQOS Cross-sectional PACS suggests that most current IQOS users (70.4%) used IQOS daily in the past 30 days, and on those days, they used a median of 15 HeatSticks per day. Results demonstrated

that 35.1% used IQOS exclusively. The majority (64.9%) of current IQOS users used IQOS with one or more other tobacco products: 42.6% used IQOS and one other tobacco product, and 22.3% used IQOS and two or more other tobacco products. Among current IQOS users, 29.2% dual-used IQOS and CC and 19.6% used IQOS, CC, and one or more other tobacco products. This means that 48.8% of all current established IQOS users used both IQOS and CC. Among those who used both IQOS and CC, approximately 48.1% used CC daily in the past 30 days. On the days they used CC, 68.2% used 2-19 CC per day, and 21% used 20 or more CC per day.

E. Postmarket Evidence: Likelihood of Switching

The applicant did not submit any prospective studies examining the likelihood of switching; therefore, a temporal relationship between IQOS use and changes in CC use behavior could not be established. Instead, the applicant included results from the IQOS Cross-sectional PACS, including current established IQOS users' self-reported past tobacco use behaviors. The applicant reported that 31.2% of current established IQOS users "had switched completely from cigarettes after first trying IQOS." In addition, the applicant reported 83.1% of current IQOS users who also smoked CC at the time of the survey stated they now used fewer CC per day than before trying IQOS.

2.2. Impact on Non-Users of Tobacco Products including Youth

A. Conclusion from the Original MRTPA Review

As part of the original MRTPAs, FDA reviewed two published international studies that provided estimates of the prevalence of IQOS use among youth that suggested that youth use of IQOS was low. Results from consumer perceptions and intentions studies demonstrated that adding the reduced exposure claim to the IQOS labels, labeling, and advertising (LLA) did not increase young adult (ages between state's legal CC use age and 25) never CC users' intentions to use IQOS.

B. Postmarket Evidence: Study Descriptions

In addition to the PMSS requirement to track IQOS product use behavior among tobacco product users, the applicant was also required to track uptake of IQOS among non-users of tobacco products, particularly youth. The applicant submitted two studies designed to better understand IQOS uptake in the general population, including youth. The Adult Tobacco Consumer Tracking (ATCT) Study is an ongoing monthly repeated cross-sectional, telephone-based survey of tobacco use behaviors in U.S. adults ages 21+. Questions about HTPs were added to this study in October 2019. The Underage Tobacco Use Survey (UTUS) is a quarterly cross-sectional survey of tobacco use behaviors in youth and young adults ages 13-20 in the U.S. launched in May 2020. The applicant added an IQOS module to the questionnaire in the second quarter of 2021 and oversampled youth and young adults living in geographic areas where IQOS was sold (Atlanta, GA; Richmond, VA; Charlotte, NC) from the second quarter of 2021 to the second quarter of 2022. Because the product was removed from the U.S. market, the applicant stopped oversampling these areas but did continue to include the IQOS module.

C. Postmarket Evidence: Product Initiation

Each annual sample of the ATCT from 2020/2021 to 2023/2024 identified few current IQOS users in the total population. The 2021/2022 sample, which was conducted while IQOS was still on the U.S. market, identified only three current IQOS users out of a full sample of approximately 28,800. This study did not oversample regions where IQOS was available, so this value does not fully represent the prevalence of IQOS use when it was on the U.S. market. Since its removal from the U.S. market, adult IQOS use has remained low, and only four current IQOS users were identified in the 2023/2024 annual sample of approximately 28,800. Overall, this study suggests low uptake of IQOS among adults in the U.S.

Similarly, the UTUS identified few youth IQOS users. In the 2021/2022 sample conducted when IQOS was available in the U.S., only 0.4% of underage individuals reported ever use of IQOS and only 0.1% reported past 30-day use. In the regions where IQOS was available, 1% of youth reported ever using IQOS and 0.2% reported past 30-day use. In the most recent wave (2023/2024) of reported UTUS data, the applicant found that only 0.7% youth and young adults in the analytic sample had ever used IQOS, with only 0.21% reporting past 30-day use. Overall, the results from the ATCT and UTUS suggest low uptake of IQOS in the U.S.

2.3. Summary of Patterns of Use and Impacts to the Population

The applicant was unable to conduct or complete its approved PMSS intending to monitor IQOS use among U.S. consumers in the presence of the reduced exposure claim because IQOS was removed from the U.S. market (see Table 1 for more information). However, the applicant was able to submit one wave of the IQOS cross-sectional PACS and data from the ongoing ATCT and UTUS studies. The IQOS cross-sectional PACS demonstrated that IQOS is predominately used by people who were ever established CC users. Additionally, it showed that in the U.S., the majority of IQOS users used IQOS with one or more other tobacco products. CC use was common among IQOS users, with 48.8% of current established IQOS users using both IQOS and CC. Among current IQOS users, 31.2% reported having completely switched from CC to IQOS, but this is based on participants' recall of their past behavior. In contrast, the premarket actual use study submitted with the original MRTPAs found that 7.5% of participants exclusively used IQOS (≥95% HeatSticks use) by the end of the study.

For the general population, the applicant's studies suggest very low levels of IQOS use among adults and youth, which is consistent with the published literature. According to the National Youth Tobacco Survey, HTPs broadly (not specifically IQOS) were used by 0.7% (95% CI: 0.6%, 1.0%) and 0.9% (95% CI: 0.7%, 1.1%) of middle and high school students, respectively, over the past 30 days at the time of survey in 2024 (Jamal et al., 2024). Regarding the larger U.S. population, Sun et al. (2023) used data collected between 2016 and 2021 to estimate that 1.22% (95% CI: 0.78%, 1.76%) of individuals ages 9 and older had ever used HTPs. Additionally, youth uptake of HTPs in international markets is generally low, with the prevalence of ever HTP use ranging from 1.8% in Japan to 11.3% in Guatemala, and the prevalence of current HTP use ranging from 0.6% in the UK and Canada to 2.9% in Guatemala (Scala et al., 2025).

3. Consumer Understanding and Perceptions

A. Conclusion from the Original MRTPA Review

In the original MRTPAs, the applicant submitted a study of adult consumers' perceptions of health risks from using IQOS and other tobacco and nicotine products after the consumers viewed IQOS LLA materials with the reduced exposure claim. The study results demonstrated that participants, on average, rated IQOS as a tobacco product that presents moderate risks of a wide range of tobacco-related disease and health effects. Participants also rated, on average, risks of IQOS use to be lower than those presented by smoking CC. Participants who currently used CC rated the health risks of using IQOS as higher than the health risks of quitting CC use and using nicotine replacement therapy (NRT) instead, and participants who formerly used CC rated the health risks of using IQOS as higher than the health risks of using NRT.

FDA concluded that adult consumers understood that IQOS use is not without risks, likely presents moderate risks of a range of tobacco-related diseases and conditions, and is more harmful than quitting smoking and using NRT instead. FDA also concluded that "consumer understanding is in line with the relative health risks of the product that are reasonably likely" (original TPL review). In the MRGOs, FDA

included a PMSS requirement that the applicant assess consumers' understanding that the benefits of reduced HPHC exposure require the user to switch completely from CC to IQOS.

B. Postmarket Evidence: Consumer Understanding and Perceptions

The applicant submitted results from one wave of the IQOS Cross Sectional PACS based on data collected from September to November 2021 (see section 2.1.B. for study description). The survey included items that assessed adult established IQOS users' perceptions of the health risks associated with IQOS use, perceptions of health risks of CC use, and understanding of IQOS-related modified risk information.[7] Participants, overall and categorized by CC use status, rated IQOS users as having moderate risk of experiencing 18 tobacco-related diseases and conditions. On average, they rated the health risks of CC use as higher than the health risks of IQOS use.

Participants were asked to rate their perceptions of HPHC exposure among CC users who switched completely from CC to IQOS, with response options including no exposure to HPHCs, lower exposure to HPHCs compared to CC, same exposure to HPHCs as CC, or more exposure to HPHCs compared to CC. Among participants who were current established IQOS users, 80.9% responded that people who switch completely from CC to IQOS have less exposure to HPHCs. About half of the remaining participants responded that switching completely would lead to the same (8.9%) or more (0.7%) exposure to HPHCs. Notably, 4.8% of participants responded that people who switched completely would have no exposure to HPHCs, and 4.8% responded "don't know." The participants who responded "have less exposure to [HPHCs]" (80.9%) were further asked about their understanding of what people who use CC need to do to reduce their body's exposure to HPHCs. Among these participants, 85.4% responded that people who use CC would need to "stop smoking cigarettes completely and only use IQOS"; 7.9% responded "smoke fewer cigarettes and also use IQOS"; 0.9% responded "keep smoking the same amount of cigarettes and also use IQOS"; and 5.9% responded "don't know."

3.1. Summary of Consumer Understanding

Overall, FDA's conclusions about consumer understanding and perceptions from the original MRTPA review are supported by the limited evidence submitted in the renewal MRTPAs. Survey results from established IQOS users suggest that adult consumers perceive IQOS use to have moderate risk of tobacco-related health effects but to have lower risk than using CC. These results also suggest that a majority of consumers understood that people who use CC would need to switch completely to IQOS use to receive the benefits conveyed by the reduced exposure claim.

[7] The survey did not directly include, nor ask if participants recalled ever seeing, IQOS-related modified risk information.

Appendix A: Statutory Requirements for Modified Risk Tobacco Products (MRTPs) and Overview of FDA Review Process

The Federal Food, Drug, and Cosmetic Act (FD&C Act) defines "modified risk tobacco product" (MRTP) as any tobacco product that is sold or distributed for use to reduce harm or the risk of tobacco-related disease associated with commercially marketed tobacco products [section 911(b)(1)]. With respect to a tobacco product, the term "sold or distributed for use to reduce harm or the risk of tobacco-related disease associated with commercially marketed tobacco products" means a tobacco product:

1) the label, labeling, or advertising of which represents, either implicitly or explicitly, that:
    a) the tobacco product presents a lower risk of tobacco-related disease or is less harmful than one or more other commercially marketed tobacco products;
    b) the tobacco product or its smoke contains a reduced level of a substance or presents a reduced exposure to a substance; or
    c) the tobacco product or its smoke does not contain or is free of a substance;
2) the label, labeling, or advertising of which uses the descriptors "light", "mild", "low", or similar descriptors; or
3) the tobacco product manufacturer of which has taken any action directed to consumers through the media or otherwise, other than by means of the tobacco product's label, labeling, or advertising, after the date of enactment of the Family Smoking Prevention and Tobacco Control Act, respecting the product that would be reasonably expected to result in consumers believing that the tobacco product or its smoke may present a lower risk of disease or is less harmful than one or more commercially marketed tobacco products, or presents a reduced exposure to, or does not contain or is free of, a substance or substances. [section 911(b)(2)]

Before an MRTP can be introduced into interstate commerce, an order from FDA under section 911(g) must be issued and in effect with respect to the tobacco product, and if the proposed MRTP is also a new tobacco product, it must comply with the premarket review requirements under section 910(a)(2).

To request a section 911(g) order from FDA, a person must submit a modified risk tobacco product application (MRTPA) under section 911(d). The MRTPA must include, among other things, information about the various aspects of the tobacco product as well as information to enable FDA to assess the impacts of the proposed MRTP on individual health outcomes and population-level outcomes, such as initiation or cessation of tobacco product use. In March 2012, FDA published a draft guidance for public comment, entitled "Modified Risk Tobacco Product Applications," which when finalized will contain FDA's current thinking on MRTPAs. The draft guidance discusses the submission of applications for an MRTP under section 911 of the FD&C Act and considerations regarding studies and analyses to include in an MRTPA (https://www.fda.gov/media/83300/download).

Section 911(g) of the FD&C Act describes the demonstrations applicants must make to obtain a modified risk granted order (MRGO) from FDA. Sections 911(g)(1) and (2) of the FD&C Act set forth two conditions under which FDA will issue an order.

Risk Modification Order: FDA shall issue an order under section 911(g)(1) of the FD&C Act (risk modification order) only if it determines the applicant has demonstrated that the product, as it is actually used by consumers, will:

- Significantly reduce harm and the risk of tobacco-related disease to individual tobacco users; and
- 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.

FDA may require, with respect to tobacco products for which risk modification orders are issued, that the product comply with requirements relating to advertising and promotion of the tobacco product (section 911(h)(5) of the FD&C Act).

Exposure Modification Order: Alternatively, for products that cannot receive a risk modification order from FDA under section 911(g)(1) of the FD&C Act, FDA may issue an order under section 911(g)(2) of the FD&C Act (exposure modification order) if it determines that the applicant has demonstrated that:

- Such an order would be appropriate to promote the public health;
- Any aspect of the label, labeling, and advertising for the product that would cause the product to be a modified risk tobacco product is limited to an explicit or implicit representation that the tobacco product or its smoke does not contain or is free of a substance or contains a reduced level of a substance, or presents a reduced exposure to a substance in tobacco smoke;
- Scientific evidence is not available and, using the best available scientific methods, cannot be made available without conducting long-term epidemiological studies for an application to meet the standards for obtaining an order under section 911(g)(1); and
- The scientific evidence that is available without conducting long-term epidemiological studies demonstrates that a measurable and substantial reduction in morbidity or mortality among individual tobacco users is reasonably likely in subsequent studies.

Furthermore, for FDA to issue an exposure modification order, FDA must find that the applicant has demonstrated that:

- The magnitude of overall reductions in exposure to the substance or substances that are the subject of the application is substantial, such substance or substances are harmful, and the product as actually used exposes consumers to the specified reduced level of the substance or substances;
- The product as actually used by consumers will not expose them to higher levels of other harmful substances compared to similar types of tobacco products on the market, unless such increases are minimal and the reasonably likely overall impact of product use remains a substantial and measurable reduction in overall morbidity and mortality among individual tobacco users;
- Testing of actual consumer perception shows that, as the applicant proposes to label and market the product, consumers will not be misled into believing that the product is or has been demonstrated to be less harmful or presents or has been demonstrated to present less of a risk of disease than one or more other commercially marketed tobacco products; and
- Issuance of the exposure modification order 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.

Per section 911(g)(4), when evaluating the benefit to health of individuals and of the population as a whole under sections 911(g)(1) and (g)(2) of the FD&C Act, FDA must take into account:

- The relative health risks to individuals of the tobacco product that is subject of the application;
- The increased or decreased likelihood that existing tobacco product users who would otherwise stop using such products will switch to the tobacco product that is subject of the application;
- The increased or decreased likelihood that persons who do not use tobacco products will start using the tobacco product that is subject of the application;
- The risks and benefits to persons from the use of the tobacco product that is the subject of the application as compared to the use of products for smoking cessation and approved under chapter V to treat nicotine dependence; and
- Comments, data, and information submitted to FDA by interested persons.

Once an MRTPA is submitted, FDA performs preliminary administrative reviews to determine whether to accept it and if accepted, whether to file it. In general, after filing an application, FDA begins substantive scientific review. This scientific review process involves soliciting and considering public comments on the application as well as recommendations from TPSAC. FDA intends to review and act on a complete MRTPA within 360 days of its filing. It is important to note that an order authorizing an MRTP pertains to a specific product, not an entire category of tobacco products (e.g., all smokeless products).

An FDA order authorizing an MRTP is not permanent; it is valid for a predetermined period specified in the order. To continue marketing an MRTP beyond this period, the applicant must request renewal of the order and FDA would need to determine that the findings continue to be satisfied. Additionally, section 911(j) specifies when FDA would withdraw an MRTP order after an opportunity for an informal hearing.

Appendix B:Toxicological Studies Published since the MRGOs (2020-2024) Reviewed by FDA

Reference	Study Type
Nishino K, Tamai K, Orita K, Hashimoto Y, Nakamura H. Heated tobacco products impair cell viability, osteoblastic differentiation, and bone fracture-healing. *JBJS*. 2021; 103 (21): https://journals.lww.com/jbjsjournal/fulltext/2021/11030/heated_tobacco_products_impair_cell_viability,.9.aspx	In vivo
Xiang Y, Luettich K, Martin F, Battey JND, Trivedi K, Neau L, Wong ET, Guedj E, Dulize R, Peric D, Bornand D, Ouadi S, Sierro N, Büttner A, Ivanov NV, Vanscheeuwijck P, Hoeng J, Peitsch MC. Discriminating spontaneous from cigarette smoke and THS 2.2 aerosol exposure-related proliferative lung lesions in A/J mice by using gene expression and mutation spectrum data. *Front Toxicol*. 2021; 3: 634035. doi:10.3389/ftox.2021.634035	In vivo
Wong ET, Luettich K, Krishnan S, Wong SK, Lim WT, Yeo D, Büttner A, Leroy P, Vuillaume G, Boué S, Hoeng J, Vanscheeuwijck P, Peitsch MC. 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. *Toxicol Sci*. Nov 1 2020; 178 (1): 44-70. doi:10.1093/toxsci/kfaa131kfaa131	In vivo
Qiu H, Zhang H, Han DD, Derakhshandeh R, Wang X, Goyal N, Navabzadeh M, Rao P, Wilson EE, Mohammadi L, Olgin JE, Springer ML. Increased vulnerability to atrial and ventricular arrhythmias caused by different types of inhaled tobacco or marijuana products. *Heart Rhythm*. 2023/01/01/ 2023; 20 (1): 76-86. doi:https://doi.org/10.1016/j.hrthm.2022.09.021021	In vivo
Rao P, Han DD, Tan K, Mohammadi L, Derakhshandeh R, Navabzadeh M, Goyal N, Springer ML. Comparable impairment of vascular endothelial function by a wide range of electronic nicotine delivery devices. *Nicotine Tob Res*. Jun 15 2022; 24 (7): 1055-1062. doi:10.1093/ntr/ntac019	In vivo
Battey JND, Szostak J, Phillips B, Teng C, Tung CK, Lim WT, Yeo YS, Ouadi S, Baumer K, Thomas J, Martinis J, Sierro N, Ivanov NV, Vanscheeuwijck P, Peitsch MC, Hoeng J. Impact of 6-month exposure to aerosols from potential modified risk tobacco products	In vivo

relative to cigarette smoke on the rodent gastrointestinal tract. *Front Microbiol*. 2021; 12: 587745. doi:10.3389/fmicb.2021.587745	
Granata S, Canistro D, Vivarelli F, Morosini C, Rullo L, Mercatante D, Rodriguez-Estrada MT, Baracca A, Sgarbi G, Solaini G, Ghini S, Fagiolino I, Sangiorgi S, Paolini M. Potential harm of IQOS smoke to rat liver. *Int J Mol Sci*. Aug 5 2023; 24 (15): doi:10.3390/ijms241512462	In vivo
Vivarelli F, Morosini C, Rullo L, Losapio LM, Lacorte A, Sangiorgi S, Ghini S, Fagiolino I, Franchi P, Lucarini M, Candeletti S, Canistro D, Romualdi P, Paolini M. Effects of unburned tobacco smoke on inflammatory and oxidative mediators in the rat prefrontal cortex. *Front Pharmacol*. 2024; 15: 1328917. doi:10.3389/fphar.2024.1328917	In vivo
Yamada H, Yamazaki Y, Takebayashi Y, Yazawa K, Sasanishi M, Motoda A, Nakamori M, Morino H, Takahashi T, Maruyama H. The long-term effects of heated tobacco product exposure on the central nervous system in a mouse model of prodromal alzheimer'sAlzheimer's disease. *Scientific Reports*. 2024/01/02 2024; 14 (1): 227. doi:10.1038/s41598-023-50941-4	In vivo
Sawa M, Ushiyama A, Inaba Y, Uchiyama S, Hattori K, Ogasawara Y, Ishii K. A newly developed aerosol exposure apparatus for heated tobacco products for in vivo experiments can deliver both particles and gas phase with high recovery and depicts the time-dependent variation in nicotine metabolites in mouse urine. *Nicotine Tob Res*. Nov 5 2021; 23 (12): 2145-2152. doi:10.1093/ntr/ntab123ntab123	In vivo
Yoshida S, Ichinose T, Shibamoto T. Effects of fetal exposure to heat-not-burn tobacco on testicular function in male offspring. Article. *Biol Pharm Bull*. 2020; 43 (11): 1687-1692. doi:10.1248/bpb.b20-00390	In vivo
Scharf P, da Rocha GHO, Sandri S, Heluany CS, Pedreira Filho WR, Farsky SHP. Immunotoxic mechanisms of cigarette smoke and heat-not-burn tobacco vapor on jurkat tJurkat T cell functions. *Environ Pollut*. Jan 1 2021; 268: 115863. doi:https://doi.org/10.1016/j.envpol.2020.115863	In vivo
Bhat TA, Kalathil SG, Leigh N, Muthumalage T, Rahman I, Goniewicz ML, Thanavala YM. Acute effects of heated tobacco product (iqos) aerosol inhalation on lung tissue damage and inflammatory changes in the lungs. *Nicotine Tob Res*. Jun 8 2021; 23 (7): 1160-1167. doi:10.1093/ntr/ntaa267	In vivo

Daou MAZ, Shihadeh A, Hashem Y, Bitar H, Kassir A, El-Harakeh M, Karaoghlanian N, Eid AA, El-Sabban M, Zaatari G, Husari A. Role of diabetes in lung injury from acute exposure to electronic cigarette, heated tobacco product, and combustible cigarette aerosols in an animal model. *PLoS One*. 2021; 16 (8): e0255876. doi:10.1371/journal.pone.0255876	In vivo
Gu J, Gong D, Wang Y, Feng T, Zhang J, Hu S, Min L. Chronic exposure to iqos results in impaired pulmonary function and lung tissue damage in mice. *Toxicol Lett*. Feb 1 2023; 374: 1-10. doi:10.1016/j.toxlet.2022.11.022	In vivo
Husari A, El-Harakeh M, Shihadeh A, Daou MAZ, Bitar H, Karaoghlanian N, Zaatari G, El-Sabban M. The substitution of fifty percent of combustible tobacco smoke exposure with either electronic cigarettes or heated tobacco products did not attenuate acute lung injury in an animal model. *Nicotine Tob Res*. 2023; 25 (7): 1361-1368. doi:10.1093/ntr/ntad045	In vivo
Kastratovic N, Markovic V, Harrell CR, Arsenijevic A, Stojanovic MD, Djonov V, Volarevic V. Effects of combustible cigarettes and electronic nicotine delivery systems on the development and progression of chronic lung inflammation in mice. *Nicotine Tob Res*. 2024: doi:10.1093/ntr/ntad235ntad235	In vivo
Koike S, Sato K, Sawa M, Inaba Y, Hattori K, Nakadate K, Ushiyama A, Ogasawara Y. Exposure to heated tobacco products aerosol causes acute stress responses in the lung of mouse. *Antioxidants (Basel)*. Nov 25 2022; 11 (12): doi:10.3390/antiox11122329	In vivo
Nitta NA, Sato T, Komura M, Yoshikawa H, Suzuki Y, Mitsui A, Kuwasaki E, Takahashi F, Kodama Y, Seyama K, Takahashi K. Exposure to the heated tobacco product IQOS generates apoptosis-mediated pulmonary emphysema in murine lungs. *Am J Physiol Lung Cell Mol Physiol*. May 1 2022; 322 (5): L699-l711. doi:10.1152/ajplung.00215.20212021	In vivo
Sawa M, Ushiyama A, Inaba Y, Hattori K. Increased oxidative stress and effects on inflammatory cytokine secretion by heated tobacco products aerosol exposure to mice. *Biochem Biophys Res Commun*. Jun 25 2022; 610: 43-48. doi:10.1016/j.bbrc.2022.04.042	In vivo
Titz B, Sewer A, Luettich K, Wong ET, Guedj E, Nury C, Schneider T, Xiang Y, Trivedi K, Vuillaume G, Leroy P, Büttner A, Martin F, Ivanov NV, Vanscheeuwijck P, Hoeng J, Peitsch MC. Respiratory effects of exposure to aerosol from the candidate modified-risk tobacco product THS 2.2 in an 18-month systems toxicology study with A/J mice. *Toxicol Sci*. Nov 1 2020; 178 (1): 138-158. doi:10.1093/toxsci/kfaa132kfaa132	In vivo

Lavrynenko O, Titz B, Dijon S, Santos DD, Nury C, Schneider T, Guedj E, Szostak J, Kondylis A, Phillips B, Ekroos K, Martin F, Peitsch MC, Hoeng J, Ivanov NV. Ceramide ratios are affected by cigarette smoke but not heat-not-burn or e-vapor aerosols across four independent mouse studies. *Life Sci*. Dec 15 2020; 263: 118753. doi:https://doi.org/10.1016/j.lfs.2020.118753	In vivo
Vivarelli F, Canistro D, Cirillo S, Elias RJ, Granata S, Mussoni M, Burattini S, Falcieri E, Turrini E, Fimognari C, Buschini A, Lazzaretti M, Beghi S, Girotti S, Sangiorgi S, Bolelli L, Ghini S, Ferri EN, Fagiolino I, . . . Paolini M. Unburned tobacco cigarette smoke alters rat ultrastructural lung airways and DNA. *Nicotine Tob Res*. Nov 5 2021; 23 (12): 2127-2134. doi:10.1093/ntr/ntab108ntab108	In vivo
Bhat TA, Kalathil SG, Leigh N, Hutson A, Goniewicz ML, Thanavala YM. Do alternative tobacco products induce less adverse respiratory risk than cigarettes? *Respir Res*. Oct 31 2023; 24 (1): 261. doi:10.1186/s12931-023-02568-2	In vivo
Heluany CS, Scharf P, Schneider AH, Donate PB, dos Reis Pedreira Filho W, de Oliveira TF, Cunha FQ, Farsky SHP. Toxic mechanisms of cigarette smoke and heat-not-burn tobacco vapor inhalation on rheumatoid arthritis. *Science of The Total Environment*. 2022/02/25/ 2022; 809: 151097. doi:https://doi.org/10.1016/j.scitotenv.2021.151097	In vivo
Wölkart G, Kollau A, Russwurm M, Koesling D, Schrammel A, Mayer B. Varied effects of tobacco smoke and e-cigarette vapor suggest that nicotine does not affect endothelium-dependent relaxation and nitric oxide signaling. *Sci Rep*. 2023/09/22 2023; 13 (1): 15833. doi:10.1038/s41598-023-42750-6	Ex vivo
Desorgher L, Berthet A, Rossier J, Bochud F, Froidevaux P. Dosimetry in the lungs of α-particles (^{210}po) and β-particles (^{210}pb) present in the tobacco smoke of conventional cigarettes and heated tobacco products. *J Environ Radioact*. Jul 2023; 263: 107178. doi:10.1016/j.jenvrad.2023.107178	Exposure assessment
Aspera-Werz RH, Ehnert S, Müller M, Zhu S, Chen T, Weng W, Jacoby J, Nussler AK. Assessment of tobacco heating system 2.4 on osteogenic differentiation of mesenchymal stem cells and primary human osteoblasts compared to conventional cigarettes. *World J Stem Cells*. Aug 26 2020; 12 (8): 841-856. doi:10.4252/wjsc.v12.i8.841	In vitro

Bedford R, Smith G, Rothwell E, Martin S, Medhane R, Casentieri D, Daunt A, Freiberg G, Hollings M. A multi-organ, lung-derived inflammatory response following in vitro airway exposure to cigarette smoke and next-generation nicotine delivery products. *Toxicol Lett*. 2023/09/15/ 2023; 387: 35-49. doi:https://doi.org/10.1016/j.toxlet.2023.09.010	In vitro
Bovard D, Renggli K, Marescotti D, Sandoz A, Majeed S, Pinard L, Ferreira S, Pak C, Barbier A, Beguin A, Iskandar A, Frentzel S, Hoeng J, Peitsch MC. Impact of aerosols on liver xenobiotic metabolism: A comparison of two methods of exposure. *Toxicol in Vitro*. 2022/03/01/ 2022; 79: 105277. doi:https://doi.org/10.1016/j.tiv.2021.105277	In vitro
Caruso M, Emma R, Rust S, Distefano A, Carota G, Pulvirenti R, Polosa R, Li Volti G. Screening of different cytotoxicity methods for the assessment of ENDS toxicity relative to tobacco cigarettes. *Regul Toxicol Pharm*. 2021/10/01/ 2021; 125: 105018. doi:https://doi.org/10.1016/j.yrtph.2021.105018	In vitro
Caruso M, Emma R, Distefano A, Rust S, Poulas K, Giordano A, Volarevic V, Mesiakaris K, Boffo S, Arsenijevic A, Karanasios G, Pulvirenti R, Ilic A, Canciello A, Zuccarello P, Ferrante M, Polosa R, Li Volti G. Comparative assessment of electronic nicotine delivery systems aerosol and cigarette smoke on endothelial cell migration: The replica project. *Drug Test Anal*. Oct 2023; 15 (10): 1164-1174. doi:10.1002/dta.3349	In vitro
Curley EO, Abu Aboud O, Chmiel KJ, Nayak AP, Fiehn O, Zeki AA, Sharma P. Heated tobacco product IQOS induces unique metabolic signatures in human bronchial epithelial cells. *ERJ Open Res*. Mar 2024; 10 (2): doi:10.1183/23120541.00805-2023	In vitro
Dusautoir R, Zarcone G, Verriele M, Garçon G, Fronval I, Beauval N, Allorge D, Riffault V, Locoge N, Lo-Guidice J-M, Anthérieu S. Comparison of the chemical composition of aerosols from heated tobacco products, electronic cigarettes and tobacco cigarettes and their toxic impacts on the human bronchial epithelial beas-2bBEAS-2B cells. *J Hazard Mater*. 2021/01/05/ 2021; 401: 123417. doi:https://doi.org/10.1016/j.jhazmat.2020.123417	In vitro
Giebe S, Hofmann A, Brux M, Lowe F, Breheny D, Morawietz H, Brunssen C. Comparative study of the effects of cigarette smoke versus next generation tobacco and nicotine product extracts on endothelial function. *Redox Biology*. 2021/11/01/ 2021; 47: 102150. doi:https://doi.org/10.1016/j.redox.2021.102150	In vitro
Giebe S, Brux M, Hofmann A, Lowe F, Breheny D, Morawietz H, Brunssen C. Comparative study of the effects of cigarette smoke versus next-generation tobacco and nicotine product extracts on inflammatory biomarkers of human monocytes. *Pflügers Archiv*. July 2023; 475 (7): 823-833. doi:10.1007/s00424-023-02809-9	In vitro

Grossmann T, Kirsch A, Gerstenberger C, Steffan B, Gugatschka M. Describing the cellular impact of IQOS™ smoke extract and vibration on human vocal fold fibroblasts. *J Voice*. May 4 2024: doi:10.1016/j.jvoice.2024.04.015	In vitro
Hirata N, Horinouchi T, Kanda Y. Effects of cigarette smoke extract derived from heated tobacco products on the proliferation of lung cancer stem cells. *Toxicol Rep*. June 2022; 9: 1273-1280. doi:https://doi.org/10.1016/j.toxrep.2022.06.001	In vitro
Horinouchi T, Miwa S. Comparison of cytotoxicity of cigarette smoke extract derived from heat-not-burn and combustion cigarettes in human vascular endothelial cells. *J Pharmacol Sci*. Nov 2021; 147 (3): 223-233. doi:10.1016/j.jphs.2021.07.005	In vitro
Ito Y, Oshinden K, Kutsuzawa N, Kohno C, Isaki S, Yokoyama K, Sato T, Tanaka M, Asano K. Heat-not-burn cigarette induces oxidative stress response in primary rat alveolar epithelial cells. *PLoS One*. 2020; 15 (11): e0242789. doi:10.1371/journal.pone.0242789	In vitro
Jaunky T, Thorne D, Baxter A, Hadley S, Frosina J, Breheny D, Murphy J, Gaça M. An experimental analytical and approach to bridge between different heated tobacco product variants. *Contrib Tob Nicotine Res*. 2022; 31 (1): 1-9.	In vitro
Keyser BM, Leverette R, McRae R, Wertman J, Shutsky T, Jordan K, Szeliga K, Makena P. In vitro toxicological evaluation of glo menthol and non-menthol heated tobacco products. *Toxicology*. 2024/05/01/ 2024; 504: 153801. doi:https://doi.org/10.1016/j.tox.2024.153801153801	In vitro
Lenski M, Zarcone G, Maallem S, Garçon G, Lo-Guidice J-M, Allorge D, Anthérieu S. Metabolomics provides novel insights into the potential toxicity associated with heated tobacco products, electronic cigarettes, and tobacco cigarettes on human bronchial epithelial beas-2bBEAS-2B cells. *Toxics*. 2024; 12 (2): 128. https://www.mdpi.com/2305-6304/12/2/128	In vitro
Lyu Q, Jiang L, Zheng H, Hayashi S, Sato K, Toyokuni S. Diluted aqueous extract of heat-not-burn tobacco product smoke causes less oxidative damage in fibroblasts than conventional cigarette. *J Clin Biochem Nutr*. Jul 2022; 71 (1): 55-63. doi:10.3164/jcbn.21-134	In vitro

Marinucci L, Coniglio M, Valenti C, Massari S, Di Michele A, Billi M, Bruscoli S, Negri P, Lombardo G, Cianetti S, Pagano S. In vitro effects of alternative smoking devices on oral cells: Electronic cigarette and heated tobacco product versus tobacco smoke. *Arch Oral Biol*. 2022/12/01/ 2022; 144: 105550. doi:https://doi.org/10.1016/j.archoralbio.2022.105550	In vitro
Mohr T, Probst E, Idel C, Plötze-Martin K, Fleckner J, Rades D, Drömann D, Bohnet S, Bruchhage KL, Franzen KF, Pries R. Different influence pattern of conventional and alternative sources of smoking on adhesion molecules and cytokine secretion in THP-1 monocytes. *Anticancer Res*. Apr 2024; 44 (4): 1455-1464. doi:10.21873/anticanres.16941	In vitro
Morishita Y, Hasegawa S, Koie S, Nakaya S, Goto M, Miyachi H, Naruse K, Nakamura N, Hayashi T, Kawai T, Nagao T. Effects of heated tobacco products and conventional cigarettes on dental implant wound healing: Experimental research. *Ann Med Surg (Lond)*. May 2023; 85 (5): 1366-1370. doi:10.1097/ms9.0000000000000367	In vitro
Nishimoto-Kusunose S, Sawa M, Inaba Y, Ushiyama A, Ishii K, Hattori K, Ogasawara Y. Exposure to aerosol extract from heated tobacco products causes a drastic decrease of glutathione and protein carbonylation in human lung epithelial cells. *Biochem Biophys Res Commun*. Jan22 2022; 589: 92-99. doi:https://doi.org/10.1016/j.bbrc.2021.12.004	In vitro
Otsu W, Ishida K, Chinen N, Nakamura S, Shimazawa M, Tsusaki H, Hara H. Cigarette smoke extract and heated tobacco products promote ferritin cleavage and iron accumulation in human corneal epithelial cells. *Sci Rep*. Sep 17 2021; 11 (1): 18555. doi:10.1038/s41598-021-97956-3	In vitro
Pagano S, Negri P, Coniglio M, Bruscoli S, Di Michele A, Marchetti MC, Valenti C, Gambelunghe A, Fanasca L, Billi M, Cianetti S, Marinucci L. Heat-not-burn tobacco (IQOS), oral fibroblasts and keratinocytes: Cytotoxicity, morphological analysis, apoptosis and cellular cycle. An in vitro study. *J Periodontal Res*. Oct 2021; 56 (5): 917-928. doi:10.1111/jre.12888	In vitro
Poussin C, van der Toorn M, Scheuner S, Piault R, Kondylis A, Savioz R, Dulize R, Peric D, Guedj E, Maranzano F, Merg C, Morelli M, Egesipe A-L, Johne S, Majeed S, Pak C, Schneider T, Schlage WK, Ivanov NV, . . . Hoeng J. Systems toxicology study reveals reduced impact of heated tobacco product aerosol extract relative to cigarette smoke on premature aging and exacerbation effects in aged aortic cells in vitro. *Arch Toxicol*. Oct 2021; 95 (10): 3341-3359. doi:10.1007/s00204-021-03123-y	In vitro
Rahman M, Irmler M, Introna M, Beckers J, Palmberg L, Johanson G, Upadhyay S, Ganguly K. Insight into the pulmonary molecular toxicity of heated tobacco products using human bronchial and alveolar mucosa models at air-liquid interface. *Sci Rep*. Sep 30 2022; 12 (1): 16396. doi:10.1038/s41598-022-20657-y	In vitro

Saha P, Jain S, Mukherjee I, Panda SR, Zeki AA, Naidu VGM, Sharma P. The effects of dual IQOS and cigarette smoke exposure on airway epithelial cells: Implications for lung health and respiratory disease pathogenesis. *ERJ Open Res*. May 2023; 9 (3): doi:10.1183/23120541.00558-2022	In vitro
Sewer A, Talikka M, Calvino-Martin F, Luettich K, Iskandar A. Quantitative modeling of in vitro data using an adverse outcome pathway for the risk assessment of decreased lung function in humans. *Toxicol Lett*. Mar 2024; 393: 107-113. doi:10.1016/j.toxlet.2024.02.001	In vitro
Simms L, Rudd K, Palmer J, Czekala L, Yu F, Chapman F, Trelles Sticken E, Wieczorek R, Bode LM, Stevenson M, Walele T. The use of human induced pluripotent stem cells to screen for developmental toxicity potential indicates reduced potential for non-combusted products, when compared to cigarettes. *Curr Res Toxicol*. Nov 15 2020; 1: 161-173. doi:https://doi.org/10.1016/j.crtox.2020.11.001	In vitro
Simms L, Mason E, Berg EL, Yu F, Rudd K, Czekala L, Trelles Sticken E, Brinster O, Wieczorek R, Stevenson M, Walele T. Use of a rapid human primary cell-based disease screening model, to compare next generation products to combustible cigarettes. *Curr Res Toxicol*. Aug 17 2021; 2: 309-321. doi:https://doi.org/10.1016/j.crtox.2021.08.003	In vitro
Walczak J, Malińska D, Drabik K, Michalska B, Prill M, Johne S, Luettich K, Szymański J, Peitsch MC, Hoeng J, Duszyński J, Więckowski MR, van der Toorn M, Szczepanowska J. Mitochondrial network and biogenesis in response to short and long-term exposure of human beas-2bBEAS-2B cells to aerosol extracts from the tobacco heating system 2.2.*Cell Physiol Biochem*. 2020; 54 (2): 230-251. doi:10.33594/000000216	In vitro
Wang L, Liu X, Chen L, Liu D, Yu T, Bai R, Yan L, Zhou J. Harmful chemicals of heat not burn product and its induced oxidative stress of macrophages at air-liquid interface: Comparison with ultra-light cigarette. *Toxico Lett*. Oct 1 2020; 331: 200-207. doi:https://doi.org/10.1016/j.toxlet.2020.06.017017	In vitro
Weng W, Bovard D, Zanetti F, Ehnert S, Braun B, Uynuk-Ool T, Histing T, Hoeng J, Nussler AK, Aspera-Werz RH. Tobacco heating system has less impact on bone metabolism than cigarette smoke. *Food Chem Toxicol*. Mar 2023; 173: 113637. doi:https://doi.org/10.1016/j.fct.2023.113637113637	In vitro
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Zarcone G, Lenski M, Martinez T, Talahari S, Simonin O, Garçon G, Allorge D, Nesslany F, Lo-Guidice JM, Platel A, Anthérieu S. Impact of electronic cigarettes, heated tobacco products and conventional cigarettes on the generation of oxidative stress and genetic and epigenetic lesions in human bronchial epithelial beas-2bBEAS-2B cells. *Toxics*. Oct 10 2023; 11 (10): doi:10.3390/toxics11100847toxics11100847	In vitro

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