
# U.S. FOOD AND DRUG ADMINISTRATION

## Tobacco Products Scientific Advisory Committee

## BRIEFING MATERIALS

Philip Morris Products S.A.

*IQOS* 2.4, *IQOS* 3.0, and *HEETS*

**MR0000254.PD1, MR0000254.PD3,**
**MR0000254.PD5 – MR0000254.PD7**

October 7th, 2025

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# Acronyms

| | |
|---|---|
| 1-OHP | 1-Hydroxypyrene |
| 3-HMPMA | 3-Hydroxy-1-Ethylpropylmercapturic Acid |
| 3-HPMA | 3-Hydroxypropylmercapturic Acid |
| 3-OH-B[a]P | 3-Hydroxybenzo[a]pyrene |
| AE | Adverse Experience |
| ALCS | Altria Client Services |
| APPH | Appropriate for the Protection of Public Health |
| ATCT | Adult Tobacco Consumer Tracking Study |
| BoE | Biomarker of Exposure |
| BoPH | Biomarker of Potential Harm |
| CC | Combusted Cigarettes |
| CI | Confidence Interval |
| CEMA | 2-Cyanoethylmercapturic Acid |
| CPD | Cigarettes Per Day |
| ELCRc | Excess Lifetime Cancer Risk cumulated |
| ENDS | Electronic Nicotine Delivery System |
| ERS | Exposure Response Study |
| FDA | Food and Drug Administration |
| FD&C | Food, Drug, and Cosmetic |
| HBSC | National Health Behavior in School-Aged Children |
| HDL-C | High Density Lipoprotein-Cholesterol |
| HPHCs | Harmful and Potentially Harmful Constituents |
| HTP | Heated Tobacco Product |
| ICSR | Individual Case Safety Report |
| ITC | International Trade Commission |
| LYS | Life-Years Saved |
| MedDRA | Medical Dictionary for Regulatory Activities |
| MGO | Marketing Granted Order |
| MHBMA | Monohydroxy-3-Butenyl Mercapturic Acid |
| MRGO | Modified Risk Granted Order |
| MRTP | Modified Risk Tobacco Product |
| MRTPA | Modified Risk Tobacco Product Application |
| NEQ | Nicotine Equivalents |
| NNAL | 4-(Methylnitrosamino)-1-(3-Pyridyl)-1-Butanol |
| NNN | N-Nitrosonornicotine |
| NTDS | Non-Targeted Differential Screening |
| NYTS | National Youth Tobacco Survey |
| PACS | Postmarket Adult Consumer Study |
| PAH | Polycyclic Aromatic Hydrocarbon |
| PATH | Population Assessment of Tobacco and Health |
| PHIM | Population Health Impact Modeling |
| PK | Pharmacokinetic |
| PMSS | Postmarket Surveillance and Studies |
| PMTA | Premarket Tobacco Product Application |
| POU | Patterns of Use |
| RMC | Risk marker Cross-Sectional Study |

| | |
|---|---|
| SA | Smoking Abstinence |
| SAE | Serious Adverse Experience |
| S-BMA | S-Butyl Mercapturic Acid |
| SCR | Smoking Cessation Response |
| sMRTPA | Supplemental Modified Risk Tobacco Product Application |
| sPMTA | Supplemental Premarket Tobacco Product Application |
| SOCs | System Organ Classes |
| SUR | Safety Update Report |
| THS | Tobacco Heating System |
| TNP | Tobacco and Nicotine Product |
| TPL | Technical Project Lead |
| TPSAC | Tobacco Products Scientific Advisory Committee |
| TSNA | Tobacco-Specific Nitrosamine |
| U.S. | United States |
| UTUS | Underage Tobacco Use Survey |
| $VO_{2max}$ | Maximal Rate of Oxygen Consumption |
| VOC | Volatile Organic Compound |

# 1. EXECUTIVE SUMMARY

On July 7, 2020, FDA issued MRGOs[1] for the *IQOS* 2.4 System Holder and Charger *(IQOS* 2.4*)* with three *HEETS* consumables. On March 11, 2022, FDA issued an MRGO[2] for the *IQOS* 3.0 System Holder and Charger *(IQOS* 3.0*)* (**Table 1**). The MRGOs were issued under section 911(g)(2) of the FD&C Act for a fixed period of 4 years based on the July 7, 2020, MRGO issuance date. Given that FDA recommends requests for renewals be received at least 360 days prior to the expiration date, we, Philip Morris Products S.A. (PMP S.A.), submitted applications on July 5, 2023, requesting renewal of the MRGOs.[3]

**Table 1. Product Name and FDA Authorization Information**

| Product Name[4] | Product Category | Product Subcategory | Original Authorized STNs |
|---|---|---|---|
| *IQOS* 2.4 System Holder and Charger | HTP | Closed HTP | MR0000133 |
| *IQOS* 3.0 System Holder and Charger | HTP | Closed HTP | MR0000192 |
| *HEETS* Amber | HTP | HTP Consumable | MR0000059 |
| *HEETS* Green | HTP | HTP Consumable | MR0000060 |
| *HEETS* Blue | HTP | HTP Consumable | MR0000061 |

Both *IQOS* 2.4 and *IQOS* 3.0 are similar in design and have the same operating principles (**Figure 1**). *IQOS* 2.4 was updated and replaced to make the more user-friendly *IQOS* 3.0, with improved ergonomics, a buttonless side opening, a more robust outer shell, a USB-C charging port, and a doubled battery lifetime. These ergonomic and aesthetic differences do not impact the composition of the aerosols produced by the two devices.

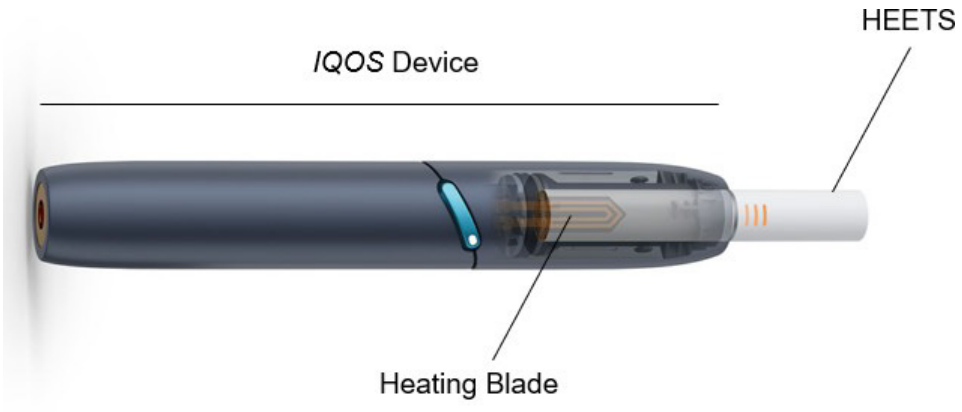
**Figure 1. *IQOS* 2.4 and *IQOS* 3.0 System Holders and Chargers**


[1] July 7, 2020, MRGO letter
[2] March 11, 2022, MRGO letter
[3] 77 Fed. Reg. 20226, April 3, 2012 (MRTP Draft Guidance). We submitted applications that conform to this nonbinding guidance.
[4] MR0000059 - MR0000061: Products were authorized under the names *Marlboro Heatsticks®*, *Marlboro Smooth Menthol Heatsticks®*, and *Marlboro Fresh Heatsticks®*. They were subsequently renamed as *HEETS* Amber, *HEETS* Blue, and *HEETS* Green, respectively. MR0000192 was authorized under the name IQOS 3.0 System Holder and Charger and renamed as *IQOS* Originals. Given that product name changes do not render the tobacco products to be new tobacco products for which premarket authorization is required, PMP S.A. notified the FDA of this change on March 27, 2024, through the 30-day notification process.

*IQOS* 2.4 and *IQOS* 3.0 can be used with any of the three authorized *HEETS* consumables (**Figure 2**) which are inserted into the *IQOS* System Holder and heated by a heating blade to a temperature below the threshold of combustion (**Figure 3**).

**Figure 2. *HEETS* Consumable Packaging and Labeling**


**Figure 3. Heating Blade Technology Used in *IQOS* 2.4 and IQOS 3.0**




The MRGOs authorized the ability to market these products for a period of four years with the following reduced exposure claim:

- *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.*

When authorizing the products, FDA concluded that:

> *With respect to the exposure modification order request, the applicant **has demonstrated** that the products sold or distributed with the proposed modified risk information meet the standard under section 911(g)(2) of the FD&C Act, including that a measurable and substantial reduction*

*in morbidity or mortality among individual tobacco users is reasonably likely 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*.

As a function of receiving MRGOs, FDA required us to conduct PMSS and submit data in Annual Reports in order to monitor the impact of the MRTPs and the respective reduced exposure claim on public health. To evaluate such impact, PMSS focused primarily on individual health risks, consumer understanding and perceptions, tobacco use behavior, and population as a whole. FDA reviewed and approved all studies designed before PMSS were conducted. Based on our PMSS and additional postmarket evidence, the available data shows:

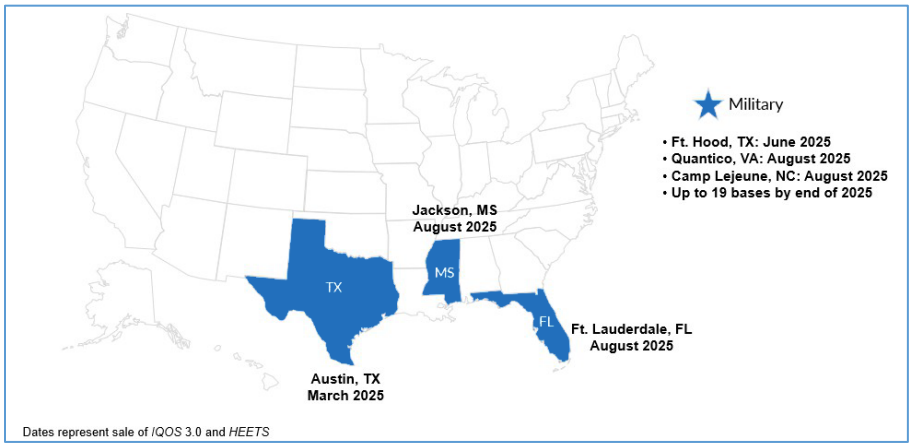
- **Much lower genotoxicity and carcinogenicity** from *IQOS* aerosol than from cigarette smoke
- Nearly **80% reduction in estimated cumulative lifetime cancer risk** of *IQOS* relative to the 3R4F cigarette
- **AEs remain low** and are similar to those observed in *IQOS* premarket clinical studies
- **Significantly reduced BoEs and BoPHs** associated with predominate *IQOS* use and exclusive *IQOS* use compared to combustible cigarette use
- **Substantial reduction in exposure to HPHCs** when smokers completely switch to *IQOS*
- **High consumer comprehension** of the *IQOS* reduced exposure claim
- *IQOS* promotes **complete switching from, and reduction of, combustible cigarette use**
- **Adult cigarette smokers** are the population **most likely to use** *IQOS*
- *IQOS* **does not appeal to non-users** of tobacco and nicotine products, including those below the legal age of purchase

During the post-authorization period, the *IQOS* products were marketed in select U.S. locations[5] from October 2019-November 2021 (25 months) by Philip Morris USA Inc. and further impacted by a patent proceeding before the U.S. International Trade Commission (ITC). As a result of a decision by the ITC pertaining to a dispute brought by affiliates of British American Tobacco plc (BAT), the authorized *IQOS* products were subject to a mandatory withdrawal from the U.S. market, effective November 29, 2021. Therefore, U.S. sales of *IQOS* products ended on November 28, 2021.

With the patent dispute resolved, we are seeking MRTP renewals of the *IQOS* products for which we have reintroduced to select U.S. locations beginning in Q1 2025 (**Figure 4**). For all commercialized *IQOS* products, we employ effective and responsible marketing controls to guard against use by unintended user populations (e.g., below legal age of purchase). As confirmed by nationally representative surveys during the time periods of initial commercialization, there has been no significant use of heated tobacco products (HTPs) by those under the legal age of purchase. In order to purchase *IQOS* 3.0 and *HEETS* consumables, adult consumers must be verified either in-person via a valid ID check when purchasing in physical location, or online through a credible third-party database. In addition, adult consumers who are purchasing *IQOS* in the U.S. for the first time are registered and verified through a credible third-party database, regardless of whether they are purchasing in-person or online.

[5] Atlanta, GA; Charlotte, NC; Richmond, VA

**Figure 4. U.S. Re-Commercialization of *IQOS* Products**




Nationwide reintroduction of *IQOS* products into the U.S. market holds tremendous potential to accelerate progress in reducing the devastating toll of deaths and diseases caused by combustible tobacco by providing adult smokers with a scientifically substantiated, non-combustible alternative. The scientific basis for FDA's MRGO decision of these products has not changed. The comprehensive review of postmarket evidence continues to support FDA's previous conclusions regarding *IQOS* use and health risks, consumer understanding, consumer perception, consumer use behavior, and the potential impact on population health. No new information has emerged which contradicts or materially changes the scientific foundation on which FDA's conclusions were based.

Instead, the postmarket evidence further reinforces FDA's original decision to authorize these products as modified risk with the reduced exposure claim. The available data continues to support FDA's prior MRGO conclusion that completely switching from combustible cigarettes to *IQOS* products can significantly reduce exposure to HPHCs. As such, we have demonstrated that the requirements for the exposure modification order under section 911(g)(2) continue to be satisfied.

For these reasons, the TPSAC should recommend FDA authorize the MRGO renewal for *IQOS* 2.4*,* *IQOS* 3.0*, HEETS* Amber*, HEETS* Green, and *HEETS* Blue.

## 2. SUMMARY OF PRIOR AUTHORIZATIONS

On November 18, 2016, and May 15, 2017, we submitted MRTPAs and PMTAs, respectively, for *IQOS* 2.4 and *HEETS.* On April 30, 2019, FDA issued MGOs[6] for these products, concluding that the products meet the APPH standard. The FDA MGO decisions[7] were primarily predicated on the following:

- *IQOS* product aerosols show **substantially lower numbers and yields of harmful and potentially harmful constituents (HPHCs)** compared to combusted cigarette smoke.
- Based on pharmacokinetic (PK) studies, *IQOS* products have **similar nicotine delivery**, addiction potential, and abuse liability to combusted cigarettes, which signifies that *IQOS* products can provide an adequate nicotine source for adult smokers.

[6] April 30, 2019, MGO letter
[7] April 19, 2019, PMTA Technical Project Lead Review

- Based on biomarkers of exposure (BoE) studies, smokers who switch completely to the *IQOS* products show **reduced toxicant exposures**.
- The most likely user population of *IQOS* products is **current, adult smokers**.
- Proposed marketing information **restricts youth exposure and access** to *IQOS* products, and international data demonstrates low youth appeal and uptake of the products.
- *IQOS* products are made using **well-controlled manufacturing and packaging processes** that consistently deliver aerosols with low levels of HPHCs.

On July 7, 2020, FDA issued MRGOs[1] for the submitted modified risk reduced exposure claim for a period of four years. The FDA decision[8] was based on many of the same reasons listed above for the MGO, as well as evidence demonstrating the products are *reasonably likely* to reduce tobacco-related disease among smokers who switch completely from cigarettes to *IQOS*, and consumers understand the reduced exposure claim and relative health risks of the products. The FDA MRGO decisions were primarily predicated on the following:

- The *IQOS* system produces **fewer HPHCs** compared to cigarette smoke.
- There is a **substantial reduction in BoEs** in smokers who switch completely to *IQOS* across a range of chemical classes (carbonyls, aromatic amines, polycyclic aromatic hydrocarbons, nitrosamines) and toxicity classes (carcinogenic, cardiovascular, respiratory, reproductive).
- The substantial reductions in HPHCs and BoEs are *reasonably likely* to translate to **lower risk of tobacco-related disease**.
- When shown the reduced exposure claim, **consumers understand the relative health risks** of the products that are *reasonably likely*, while not interpreting the claim to mean the product causes no risk.

On March 30, 2020, and March 18, 2021, we submitted an sPMTA and an sMRTPA for *IQOS* 3.0. FDA relied heavily on their prior understanding and assessment of *IQOS* 2.4, resulting in the issuance of an MGO[9,10] and MRGO[2,11] for *IQOS* 3.0 on December 7, 2020, and March 11, 2022, respectively. On March 24, 2025, FDA issued updated MGO letters[12,13] categorizing *IQOS* products as Heated Tobacco Products in lieu of non-combusted cigarettes.

In total, FDA reviewed the extensive scientific evidence leading to issuance of five MGOs and five MRGOs for *IQOS* 2.4, *IQOS* 3.0*, HEETS* Amber*, HEETS* Green, and *HEETS* Blue*.*

## 3. SUMMARY OF POSTMARKET SURVEILLANCE AND STUDIES

As conditioned in the MRGO letters[1,2], FDA required us to conduct PMSS to examine the impact of the MRTPs on consumer health risks, perception, and behavior. As part of the PMSS, FDA required the monitoring of awareness and use by youth and other unintended user populations (e.g., nonusers). In accordance with section 911(i)(2) of the FD&C Act, FDA reviewed and approved all PMSS study protocols before executing studies. We submitted comprehensive Annual Reports to the FDA demonstrating compliance with these PMSS requirements over the five years following the first *IQOS* product MRGOs.

[8] July 7, 2020, MRTP Technical Project Lead Review
[9] December 7, 2020, MGO letter
[10] December 7, 2020, sPMTA Technical Project Lead Review
[11] March 11, 2022, sMRTPA Technical Project Lead Review
[12] March 24, 2025, updated MGO letter for IQOS 2.4 and HEETS consumables
[13] March 24, 2025, updated MGO letter for IQOS 3.0

To align with FDA's postmarket requirements, we submitted the following PMSS data (**Table 2**):

**Table 2. PMSS Name and Objective**

| PMSS Name | Objective |
|---|---|
| Computational Toxicology Assessment | Provide hazard identification (genotoxicity and carcinogenicity potential) for the 80 identified compounds from previously reported NTDS that were increased or unique in *IQOS* aerosol compared to 3R4F reference cigarette smoke. |
| Cross-Sectional PACS (ALCS-CMI-17-36-HT) | Cross-sectional study to evaluate (1) adult, ever established *IQOS* users and their tobacco use patterns; (2) risk perceptions of *IQOS*; and (3) initiation, complete switching from cigarette smoking to *IQOS*, transitions to/back to cigarette smoking, and quitting behaviors relevant to *IQOS* use. |
| Cohort PACS (ALCS-CMI-17-37-HT[14]) | Longitudinal study to characterize (1) tobacco product use behaviors; (2) characterize transitions (e.g., initiation, switching, transitioning to/back to cigarettes, and quitting); (3) assess self-reported, health-related, quality-of-life signs and symptoms by product use; and (4) assess risk perceptions of *IQOS* and cigarettes among adult, established *IQOS* users and cigarette smokers over time. |
| *IQOS* Owners Panel | Longitudinal study to evaluate (1) *IQOS* owners' switching behavior over time, (2) the usage of *IQOS* and other tobacco products among adult *IQOS* owners, and (3) the demographic profile of adult *IQOS* owners. |
| Secondary Analysis of ATCT | Cross-sectional study to estimate (1) prevalence of *IQOS* use, (2) prevalence of exclusive, dual- and poly-tobacco use with *IQOS* in adult, (3) days and amount of product use among *IQOS* users, and (4) initiation, quitting, and complete switching behaviors relative to *IQOS* use. |
| Secondary Analysis of UTUS | Cross-sectional study to estimate (1) awareness of *IQOS* and (2) ever and past 30-day *IQOS* use among underage individuals, and to estimate (3) lifetime use behavior and (4) past-30-day use behavior among ever and past-30-day underage *IQOS* users, respectively. |
| Population health impact modeling | Estimate the impact of the *IQOS* products on population health |
| Surveillance of Product Safety | Monitoring and analysis of all adverse experiences associated with use of the *IQOS* products |
| Surveillance of new research study findings | Assessment of any new significant study findings regarding *IQOS* products and consumer perception, behavior, or health |

During the postmarket period, we also conducted the following additional studies and analyses not specifically requested by the FDA (**Table 3**):

**Table 3. Additional Postmarket Studies, Analyses, and Objectives**

| Study/Analysis Name | Objective |
|---|---|
| $ELCR_c$ | Estimate the cumulative excess lifetime cancer risk of *IQOS* aerosol compared to 3R4F reference cigarette smoke using the FDA memorandum 'Calculation of Excess Lifetime Cancer Risk in ENDS Premarket Tobacco Product Applications[15] |
| Exposure Response Study (ZRHR-ERS-09-EXT-US) | Evaluate the impact of a 12-month use period of *IQOS* on BoEs and the eight selected core biomarkers of potential harm (BoPHs). |
| Smoking Cessation Study SA-SCR-01 | Assess BoEs and the eight core BoPHs in smokers abstaining from smoking for 12 months. |

[14] The Cohort PACS (ALCS-CMI-17-37-HT) was never initiated due to the ITC ruling.

[15] Calculating Excess Lifetime Cancer Risk in ENDS Premarket Tobacco Product Applications

| Study/Analysis Name | Objective |
|---|---|
| Post-hoc Analysis (P1-ERS-EXT-SCR-PH-SHP) | A cross-study analysis between the ZRHR-ERS-09-EXT-US and SA-SCR-01 studies conducted to contextualize the changes in BoEs and BoPHs when switching to *IQOS* use or cigarette quitting over 12 months. |
| Post-hoc Analysis (P1-ERS-EXT-SCR-PH-RESP) | A cross-study analysis between the ZRHR-ERS-09-EXT-US and SA-SCR-01 studies conducted to contextualize the changes in lung function and cough when switching to *IQOS* or to cigarette quitting over 12 months. |
| Risk Marker Cross-sectional Study (P1-RMC-03-INT) | Investigate BoPHs related to biological pathways linked to smoking related diseases following at least 2 years of *IQOS* use compared to cigarette smoking and former smoking. |

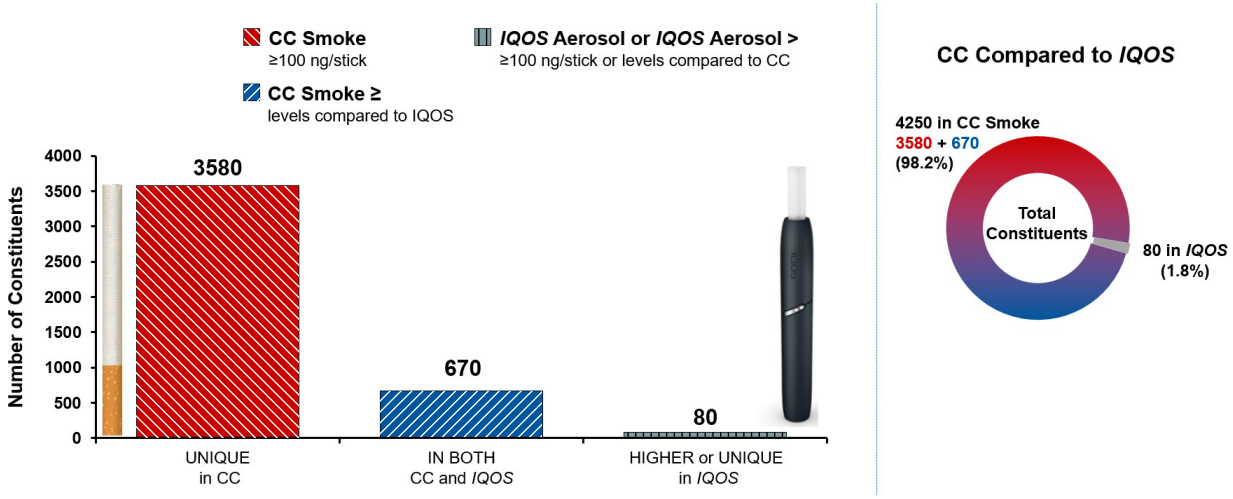
We complied with all PMSS requirements while marketing *IQOS* products and provided additional supplemental evidence when the withdrawal of our products from the market and ITC ruling limited our ability to collect U.S. specific data. The submitted data continues to demonstrate that the authorized MRTPs are appropriate to promote public health and are expected to continue benefiting the health of the population of the whole.

## 3.1. Relative Health Risks of the MRTPs to Individual Tobacco Users

### *3.1.1. Computational Toxicology Assessment*

In the PMTA and MRTP TPL reviews, FDA concluded that the aerosols produced by the three variants of *HEETS* contain far fewer and lower levels of HPHCs compared to combusted reference cigarette smoke.[7,8] This analysis was based on conventional aerosol testing methods following ISO and Health Canada Intense methodologies. In addition, as shown in **Figure 5**, an NTDS of *IQOS* aerosol[16] and 3R4F reference cigarette smoke was performed.

**Figure 5. NTDS of *IQOS* aerosol and 3R4F Cigarette Smoke**




In this respect, it is important to note that these 80 constituents are significantly less in number than the total 4,250 constituents detected and assessed in 3R4F cigarette smoke, for which 3,580 constituents were unique, and 670 constituents were found in higher levels. FDA reviewed these 80 constituents

[16] Representing the combination of *HEETS* Amber, *HEETS* Blue, and *HEETS* Green variants

during the MRTP review process and concluded that when comparing *IQOS* aerosol to 3R4F reference cigarette smoke:[8]

1. The concentration of constituents assessed as carcinogens was reduced by approximately 82%
2. The combined yield of potential respiratory and reproductive toxicants was reduced by approximately 91.7% and 94.0%, respectively

As part of our PMSS, FDA required us to further investigate the toxicological profile of these 80 constituents, and their potentially reactive and toxic metabolites. Given that most of these constituents have very limited or no toxicological data available, hazard identification screening (for genotoxicity and carcinogenicity potential) was done using computational toxicology tools. These tools aid in predicting the toxicity of the constituents and metabolites based on their functional properties and chemical structure (i.e., structural alert or key substructures associated for toxicity) and expert judgement regarding the situational plausibility of any alerting chemical features and potential toxicity. They also reduce applying conventional toxicology testing approaches that may not be appropriate for various reasons, such as time and ethical considerations. Importantly, computational and AI approaches also are consistent with FDA's broader goals under its Predictive Toxicological Road Map. In response, we proposed a multi-year, fundamental research program utilizing predictive computational or in-silico toxicology tools.[17]

The predictive computational toxicology study was conducted in three phases:

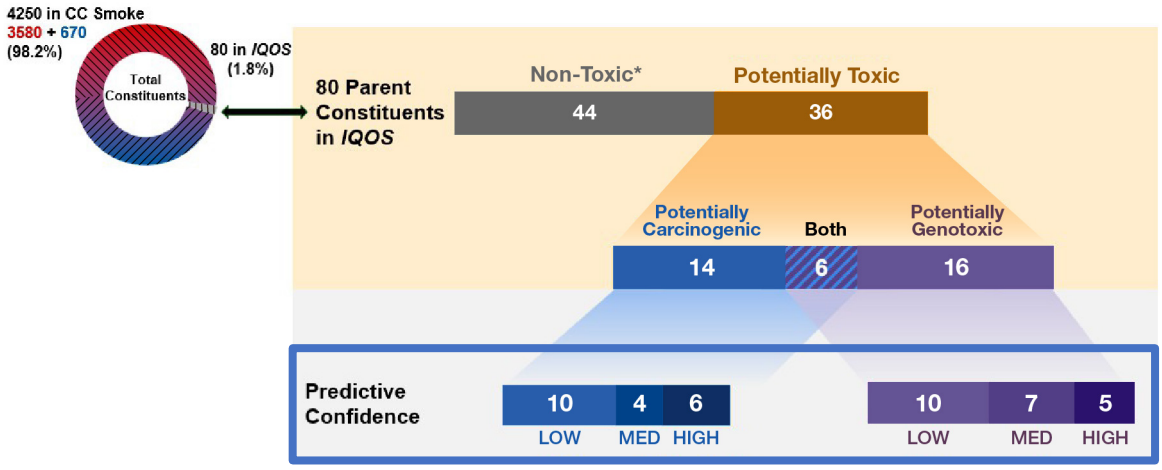
- **Phase 1:** Determine the genotoxicity and/or carcinogenicity potential of the 80 constituents (parent constituents) identified as potentially unique to or higher in *IQOS* aerosol relative to 3R4F cigarette smoke
- **Phase 2**: Determine the potential metabolites of the 80 constituents relevant to humans
- **Phase 3**: Determine the genotoxicity and/or carcinogenicity potential of the relevant metabolites

As shown in **Figure 6**, the majority of parent constituents in *IQOS* aerosol (44 out of 80) were not predicted as being carcinogenic or genotoxic (i.e., without structural alerts for either carcinogenicity or genotoxicity). Of the remaining constituents (36 out of 80), six were predicted to be both genotoxic and carcinogenic, 14 were predicted to be carcinogenic, and 16 were predicted to be genotoxic. Predictive confidence, which measures the extent that the computational method is predictive of experimental results, was high for only five constituents regarding genotoxicity and only six for carcinogenicity. This means that 10[18] constituents out of 80 that are unique to or higher in *IQOS* aerosol compared to cigarette smoke were found to have cancer-related toxicity potential with a high level of certainty. As discussed in Section 3.1.2 below, while these 10 constituents may add to the risk of *IQOS* aerosol inhalation, their combined risk adds only marginally to the ELCRc, considering the total risk due to parent constituents and metabolites included in ELCR calculations add to less than 15% of the ELCRc for 3R4F cigarette smoke.

[17] Hasselgren C, Ahlberg E, Akahori Y, et al Genetic toxicology in silico protocol. Regul Toxicol Pharmacol. 2019 Oct; 107:104403. doi: 10.1016/j.yrtph.2019.104403. Epub 2019 Jun 11. PMID: 31195068; PMCID: PMC7485926

[18] Glycidol was predicted as both potentially genotoxic and carcinogenic. For this reason, Glycidol was considered as one constituent in the total.

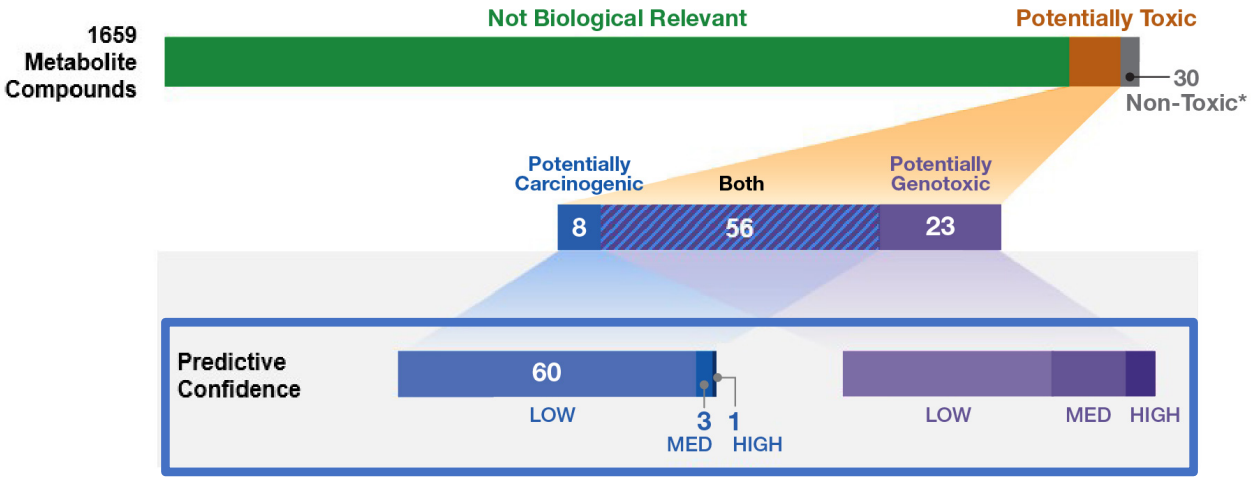
**Figure 6. Genotoxic and Carcinogenic Potential of Parent Constituents in *IQOS* Aerosol**




* Regarding assessments of genotoxicity and carcinogenicity
Source: PMSS - Computational Toxicology Report

As shown in **Figure 7**, we also examined metabolites that could be produced from the 80 parent constituents. The majority of metabolites (1,542 out of 1,659) were not biologically relevant as determined by human expert assessment using established criteria. Thirty (30) of the remaining metabolites had no structural alerts for carcinogenicity or genotoxicity. For the remaining 87 metabolites, 56 were predicted to potentially be both carcinogenic and genotoxic, eight were predicted to be carcinogenic, and 23 were predicted to be genotoxic. Based on prediction confidence, which measures the extent that the computational method is predictive of experimental results, certainty was high that eight metabolites were potentially genotoxic and one metabolite was both potentially genotoxic and potentially carcinogenic. This means that eight[19] of the metabolites in the model were found to have cancer-related toxicity potential with a high level of certainty compared to the total 1,659 metabolites examined.

**Figure 7. Genotoxic and Carcinogenic Potential of Metabolites in *IQOS* Aerosol**




[19] Caffeic acid was predicted as both potentially genotoxic and carcinogenic. For this reason, Caffeic acid was considered as one constituent in the total.

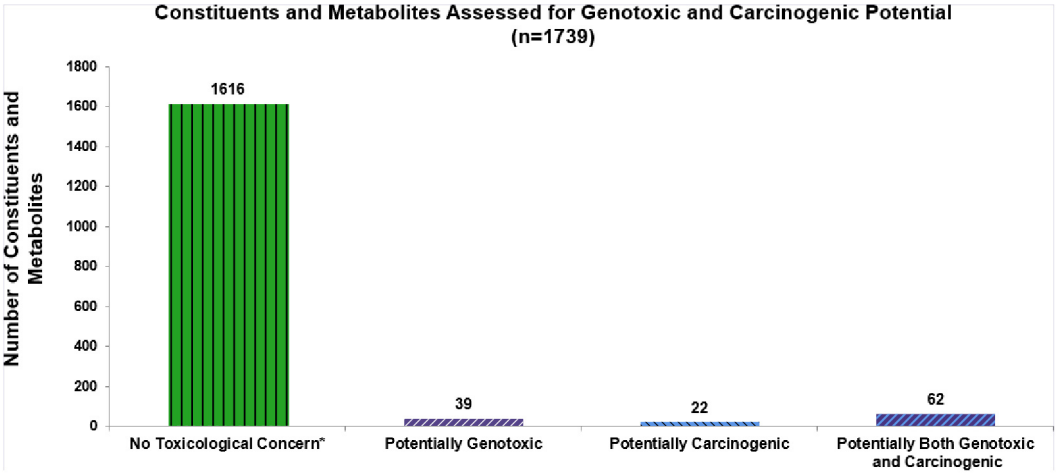
* Regarding assessments of genotoxicity and carcinogenicity
Source: PMSS - Computational Toxicology Report

Taken together, this comparative assessment demonstrates that the vast majority of constituents unique to or at higher levels in *IQOS* aerosol compared to 3R4F cigarette smoke are not causes for toxicological carcinogenicity concern (**Figure 8**). Specifically:

- 44 of 80 parent constituents and 1,572 of 1,659 metabolites have no genotoxicity or carcinogenicity potential (n=1616)
- 16 of 80 parent constituents and 23 of 1,659 metabolites have genotoxic potential (n=39),
- 14 of 80 parent constituents and 8 of 1,659 metabolites have carcinogenic potential (n=22), and
- 6 of 80 parent constituents plus 56 of 1,659 metabolites have both carcinogenic and genotoxic potential (n=62).

When considered in conjunction with the well-characterized reduction of HPHCs in *IQOS* aerosol compared to cigarette smoke, the overall toxicant exposure profile of *IQOS* aerosol is dramatically reduced relative to cigarette smoke. The computational toxicology screening results are also consistent with previous *in vitro* and *in vivo* toxicology studies, **indicating that genotoxicity and carcinogenicity of *IQOS* aerosol continues to be substantially less than that of cigarette smoke.**

**Figure 8. Summary of Computational Toxicology Assessment: 80 Parent *IQOS* constituents and 1,659 Associated Metabolites**




*Regarding assessments of genotoxicity and carcinogenicity
**Source:** PMSS - Computational Toxicology Report

This conclusion is consistent with FDA's 2019 PMTA TPL Review for *IQOS* products and aerosol, where they noted *"[a]lthough some of the chemicals are genotoxic or cytotoxic, these chemicals are present in very low levels and potential effects are outweighed by the substantial decrease in the number and levels of HPHCs found in CC."*[7] Similarly, in the 22nd Century PMTA TPL Review leading to MGOs for VLN King and VLN Menthol combusted cigarettes in 2019, FDA acknowledged levels of some HPHCs were increased in VLN smoke compared to normal nicotine content cigarette smoke, stating *"any increase in respiratory effects due to ammonia, acetaldehyde, and acrylonitrile may be offset by other HPHCs that*

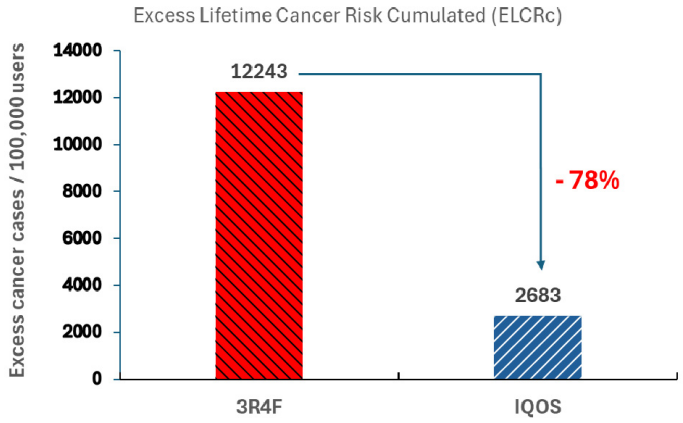
*are decreased."*[20] Therefore, historical FDA decisions demonstrate a consistent approach of balancing the presence of some elevated constituents against the overall reduction in exposure to other known HPHCs. When considering the complete constituent profile of the authorized *IQOS* products, the new toxicological data continues to support the renewal of the MRGOs for *IQOS* products.

### *3.1.2. Calculation of Excess Lifetime Cancer Risk*

Based on the FDA memorandum, 'Calculation of Excess Lifetime Cancer Risk in ENDS Premarket Tobacco Product Applications' we calculated an ELCRc using two sets of constituents found in *IQOS* aerosol: (1) the measured HPHCs (part of the FDA's HPHC list), and (2) additional potentially carcinogenic and/or genotoxic constituents identified through the computational toxicology assessment in *IQOS* aerosol.[16] During FDA's review of the MRTP renewal[21], 58 out of the 80 parent constituents were initially identified as potentially concerning by FDA. Prior to calculating the ELCRc, we conducted a hazard identification of these 58 constituents, focusing specifically on their genotoxicity and carcinogenicity potential. Based on publicly available data and conclusions from international scientific expert committees (e.g., EFSA panel, JECFA committee), 18 constituents were ruled out due to lack of genotoxicity and carcinogenicity concerns. As a result, 40 total constituents from the NTDS were included in the ELCRc assessment alongside the measured 39 HPHCs identified by FDA and IARC as carcinogenic. Additionally, an ELCRc was also calculated for 3R4F reference cigarette smoke using the same selection of constituents.

The calculation revealed an ELCRc of 2,683 (predicted excess cancer cases per 100,000 users), whereas 3R4F cigarette smoke had an ELCRc of 12,243, which translates to a **reduction of cancer potential by approximately 80% for *IQOS* aerosol relative to the 3R4F cigarette smoke** (**Figure 9**). Notably, this aligns with FDA's previous MRGO conclusions when reporting that concentration of carcinogens was reduced by approximately 82% in the *IQOS* aerosol compared to the smoke of the 3R4F reference cigarette. Importantly, the overall cancer risks assessed for the 3R4F cigarette did not include the constituents that were unique to or in higher concentrations in 3R4F cigarette smoke vs *IQOS* (**Figure 5),** indicating the comparative results are very conservative and likely underestimate the actual reduction in cancer risk.

**Figure 9. ELCRc Calculation of *IQOS* Aerosol Compared to 3R4F Cigarette Smoke**




[20] 22nd Century Technical Project Lead Review
[21] FDA Advice and Information Request letter issued on November 25th, 2024

### *3.1.3. Serious and Unexpected Adverse Experiences*

When the *IQOS* products were first internationally commercialized in 2014, we established a worldwide safety surveillance system to collect and manage all safety information related to the use of *IQOS* products. The aim of the safety surveillance process is to monitor and analyze, in a timely manner, all new safety information related to the use of *IQOS* products. We summarize this information in annual SURs detailing all reported AE and SAE[22] , their coding in the MedDRA SOCs, and the percentage of SAEs relative to the total number of AEs. All AE and SAE data are extracted from ICSRs included in the global safety database.

Cumulatively, from the first international launch in November 2014 until the cut-off date of June 30, 2025, a total of 111 ICSRs were reported in the U.S. for *IQOS* products. The reported ICSRs included 259 AEs, all of which were assessed as non-serious. The most frequently reported non-serious AEs (> 5% of total AEs) for *IQOS* products in the U.S. are denoted in **Table 4**. **These AEs remain low in number and are similar to those observed in *IQOS* premarket clinical studies.**

**Table 4. Most Frequently Reported MedDRA Preferred Terms in the U.S. Postmarket Period Through June 30, 2025**

| AEs > 5% | Cumulative Number of AEs | % |
|---|---|---|
| Cough | 17 | 6.56 |
| Headache | 16 | 6.18 |
| **Total No. AEs** | **259** | **100** |

In addition to the U.S., PMP S.A. monitors AEs across the 83 countries where *IQOS* is sold. No actions (e.g., withdrawal or suspension of a marketing authorization) were taken due to safety reasons by regulatory authorities for *IQOS* products in the U.S. or internationally during the postmarket period. Therefore, when considering these data, the cumulative AEs support renewal of MRGOs for the authorized *IQOS* products.

### *3.1.4. Clinical Individual Health Studies*

While FDA did not require additional clinical studies as part of our PMSS, as shown in **Table 5,** we conducted five new postmarket clinical studies and post-hoc analyses to further characterize the *IQOS* products. These clinical studies were conducted across multiple countries, including the U.S., Japan, and Germany.

[22] Per the MGO letters for *IQOS*, "a serious adverse experience means an adverse experience that results in any of the following outcomes: death; a life-threatening adverse event; inpatient hospitalization or prolongation of existing hospitalization; a persistent or significant incapacity or substantial disruption of the ability to conduct normal life functions, a congenital anomaly/birth defect; or any other adverse experience that, based upon appropriate medical judgement, may jeopardize the health of a person and may require medical or surgical intervention to prevent one of the other outcomes listed in this definition."

**Table 5. Summary of Additional Postmarket Clinical Studies and Analyses**

| Study Name | ClinicalTrials.gov ID | Summary of Results |
|---|---|---|
| Exposure Response Study (ZRHR-ERS-09-EXT-US) | NCT02649556 | Compared with the cigarette-use group, the analyzed BoEs for HPHCs were statistically significantly reduced in the *IQOS* user group after 12 months (reductions compared to cigarettes ranging from 26 to 49%).[23] When compared to cigarette smokers, all eight primary BoPHs shifted in the same favorable direction as they would upon smoking cessation in the *IQOS* users group category after 12 months. |
| Smoking Cessation Study (SA-SCR-01) | NCT02432729 | In the overall 12-month abstinent set, BoEs had a marked and sustained reduction from baseline throughout the course of the study (ranging from 54 to 99% change from baseline).[24] Similarly, the smoking cessation study data confirms that all BoPHs levels measured in the exposure response study, when using *IQOS* rather than combusted cigarettes, changed from baseline in the same favorable direction as they would upon smoking cessation and in a time-dependent manner. |
| Post-Hoc Analysis (P1-ERS-EXT-SCR-PH-SHP) | NA | After pooling and weighing of data from the ZRHR-ERS-09-US, ZRHR-ERS-09-EXT-US, and SA-SCR-01 studies, significant favorable differences were observed in all BoEs and BoPHs in both the smoking abstinence and *IQOS* user group vs. the cigarette use group. The magnitude of these changes was, as expected, generally lower in the IQOS user group than that observed in the smoking abstinence group. |
| Post-Hoc Analysis (P1-ERS-EXT-SCR-PH-RESP) | NA | *IQOS* use had a beneficial impact on main lung function parameters relative to continued cigarette smoking at 12 months. *IQOS* use was also associated with a reduction in the reporting of the need to cough. |
| Risk Marker Cross-Sectional Study (P1-RMC-03-INT) | NCT05385055 | The study demonstrated that subjects who had switched to *IQOS* use for at least 2 years showed significant positive differences in all BoEs (reductions compared to cigarettes ranging from 50 to 95%, while former smokers had reductions ranging from 52 to 98%).[25]<br>The study also showed that the levels of the eight core BoPHs (as measured in the exposure response study) in the *IQOS* user group were close to those who had completely quit smoking during the same period and significantly different from the cigarette group. |

[23] BoE assessed at 12 months were 2CyEMA, Total NNN, Total NNAL and COHb

[24] Except for s-butyl mercapturic acid (S-BMA), which was found not to differ between smokers from nonsmokers. The other BoE assessed were MHBMA,3-HPMA, 2CyEMA, Total 3-OH-B[a]P, Total 1-OHP, 3-HMPMA, Total NNN, Total NNAL; COHb and NEQ.

[25] BoE assessed were 2CyEMA, Total NNAL, COHb and NEQ (nicotine equivalent). Levels of NEQ were, as expected, comparable to the levels found in cigarette smokers.

Through a post-hoc cross-studies analysis of the Exposure Response Study (ZHRH-ERS-09-US with its extension; ZRHR-ERS-09-EXT-US) and the Smoking Cessation Study (SA-SCR-01), namely post-hoc analysis P1-ERS-EXT-SCR-PH-SHP, we assessed changes in BoEs associated with various conditions of *IQOS* use (i.e., predominant *IQOS* use [defined as ≥ 70% *IQOS* use and < 30% cigarette use], and exclusive *IQOS* use [defined as users who had levels of 2CyEMA lower than 47 ng/mg$_{creat}$, a threshold proposed in Rostron et al. from the PATH study[26]]) as well as complete cessation, relative to continued combustible cigarette smoking over time (**Figure 10**). In this post-hoc analysis, propensity score weighting was used to adjust for imbalances between study populations. While predominant users of *IQOS* still had statistically significant reductions in all nine measured BoEs compared to cigarettes (25-59% and 20-54% at 3 and 6 months, respectively), exclusive users of *IQOS* (defined as biochemically verified exclusive users of *IQOS* who smoked ≤ 4 cigarettes per day[26]) had even greater reduction that were statistically significant in all nine measured BoEs compared to cigarettes (45-88% and 45-91% at 3 and 6 months, respectively). Given that the full set of BoEs are not expected to change significantly following 6 months as long as product use remains fairly stable, only a subset of BoEs (COHb, NNAL, NNN, and 3-HPMA) were measured at 12 months, which showed similar reductions to what was observed at 3 and 6 months (28-55% and 70-94% in the predominant and exclusive users, respectively). Importantly, the observed reduction in BoE among exclusive *IQOS* users was similar in magnitude compared to that observed in users achieving complete cessation from all tobacco products (55-98%, 54-98%, and 81-99% at 3, 6 and 12 months, respectively). The reductions were rapid (achieved within 3 months) and sustained throughout the follow-up period, **indicating that a reduction in smoking-related diseases in complete switchers to *IQOS* is *reasonably likely*.**

Recently, the results from the risk marker cross sectional study P1-RMC-03-INT built on previous findings from the exposure response study, showing reductions (50-96%) in levels of BoEs and **significant favorable difference in eight core BoPHs in *IQOS* users[27] after at least 2 years of real-life use of *IQOS***. Therefore, the results complement the data from our exposure response study. The data also showed that *IQOS* users had nicotine exposure (as assessed by urinary levels of nicotine equivalents) that was similar to the cigarette smokers, which indicates that there is no increase of nicotine uptake over time.[28]

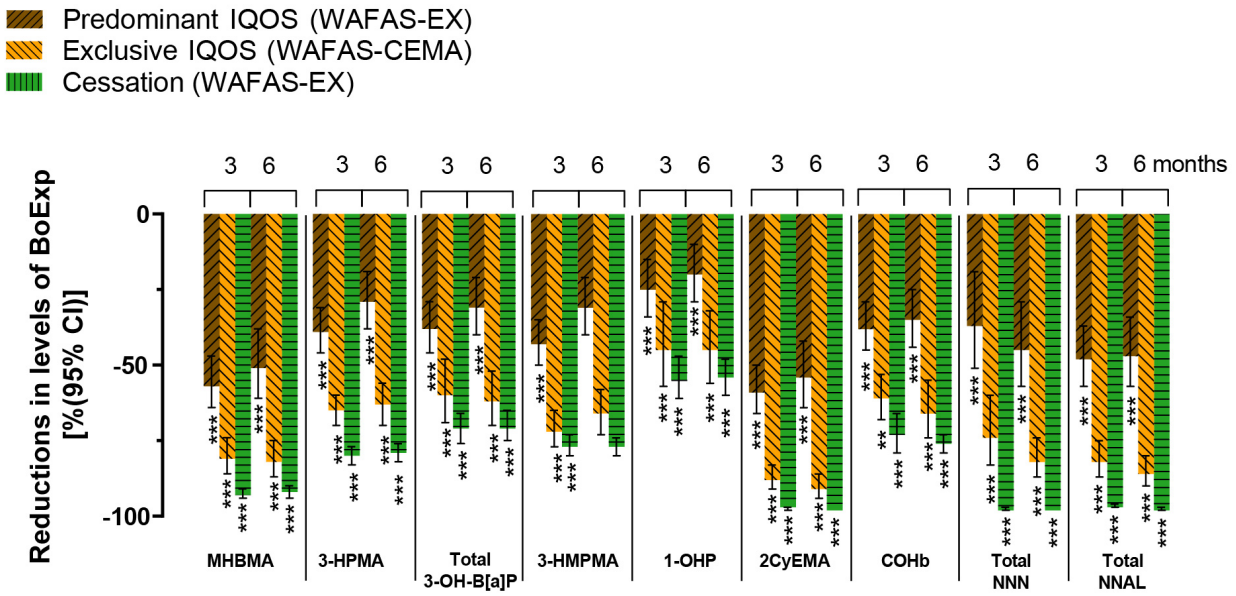
Taken together, the additional postmarket **clinical study findings provide further evidence that there is a substantial reduction in exposure to HPHCs when smokers switch completely to *IQOS*.** These exposure reductions are close to what is observed upon smoking cessation. The data also demonstrates a clear and measurable association and dose response between BoE reduction and the extent to which users successfully substitute *IQOS* for combusted cigarettes, highlighting the need for effective consumer education to encourage complete switching to *IQOS*. For this reason, the renewal of the reduced exposure claim, which is designed to communicate the need for complete switching, is paramount to achieving the full public health benefit of *IQOS*.

[26] Rostron BL, Corey CG, Chang JT, van Bemmel DM, Miller ME, Chang CM. Associations of cigarettes smoked per day with biomarkers of exposure among US adult cigarette smokers in the population assessment of tobacco and health (PATH) study wave 1 (2013-2014). Cancer Epidemiol Biomarkers Prev. 2019.

[27] Subjects in the THS group (i) had used ≥10 sticks/day on average over the past 2 years, (ii) had smoked ≥10 cigarettes/day on average for at least 8 years prior to switching to THS, (iii) had smoked <30 cigarettes/month and did not use other tobacco or nicotine products on a daily basis over the past 2 years, and (iv) had verified product use based on urinary cotinine (≥200 ng/mL) and carbon monoxide breath test (<10 ppm).

[28] Average switching time in this study was 4.5 years.

**Figure 10.Changes in BoEs Associated With *IQOS* Use (Predominant and Exclusive Use) and Cessation – Posthoc Analysis (ZRHR-ERS-09-EXT-US and SA-SCR-01 Studies)**




MHBMA: Monohydroxy-3-butenyl mercapturic acid: 3-HPMA: 3-Hydroxypropylmercapturic acid; 3-OH-B[a]P: 3-Hydroxybenzo[a]pyrene; 3-HMPMA: 3-Hydroxy-1-ethylpropylmercapturic acid; 1-OHP: 1-Hydroxypyrene; NNN: N-Nitrosonornicotine; 2CyEMA: 2-Cyanoethylmercapturic acid; WAFAS-EX: Weighted Augmented Full Analysis Set – As Exposed; WAFAS-CEMA: Weighted Augmented Full Analaysis Set - CEMA
Predominant *IQOS* use is defined as ≥70% *IQOS* use on more than 50% of the days in the analysis period (self-reported from ZRHR-ERS-09-EXT-US)
Exclusive *IQOS* use is defined as predominant *IQOS* use and smoking ≤4 cigarettes per day (biochemically verified from P1-ERS-EXT-SCR-PH-SHP)
Cessation is defined as no use of any tobacco and nicotine consumer products (biochemically verified from P1-ERS-EXT-SCR-PH-SHP)
*p<0.05; **p<0.01; ***p<0.001

## 3.2. Consumer Understanding and Perceptions

FDA required us to conduct PMSS assessing consumer understanding and perceptions to ensure users remain able to adequately understand the reduced exposure claim. This included assessing *IQOS* users' understanding of the relative health risks of the products in relation to combusted cigarettes and the need for complete switching to *IQOS* to achieve a reduction in HPHC exposure.

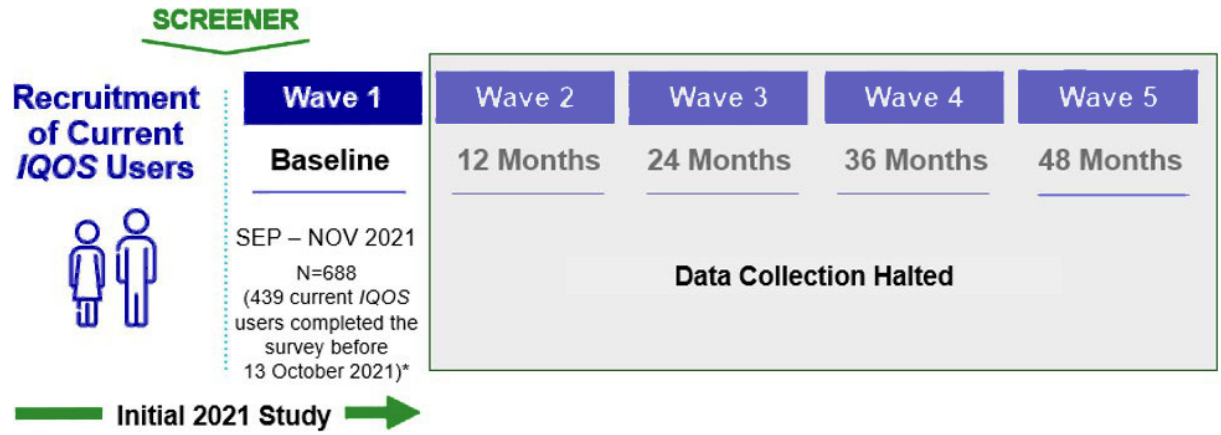
### *3.2.1. Cross-Sectional PACS*

As shown in **Figure 11**, the Cross-Sectional PACS (ALCS-CMI-17-36-HT) is a repeated, cross-sectional survey of adult (ages 21+), ever established *IQOS* users recruited from the *IQOS* consumer database. The Cross-Sectional PACS study began in September 2021 and was paused in November 2021 because of the ITC ruling. This study, also described by Cheng et al.[29], "*provides supportive evidence for the potential of*

[29] Cheng HG, Noggle B, Vansickel AR, Largo EG, Magnani P. Tobacco Use, Risk Perceptions, and Characteristics of Adults Who Used a Heated Tobacco Product (IQOS) in the United States: Cross-Sectional Survey Study JMIR Form Res 2025;9:e57398 doi: 10.2196/57398

*IQOS to help individuals who smoke to switch to IQOS by comprehensively assessing use behaviors and risk perceptions relevant to IQOS use in a real-world setting among established [adult users of IQOS] in the US.*"

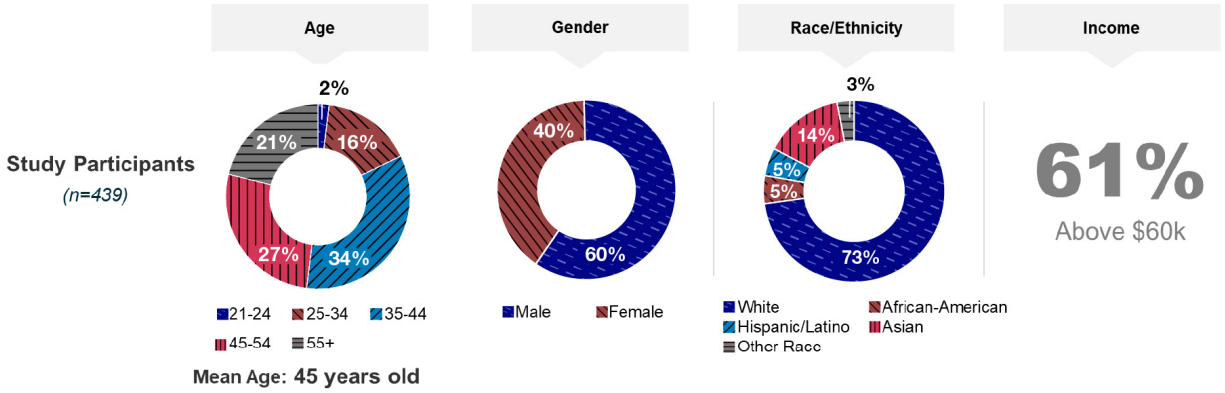
**Figure 11. Study Design of *IQOS* Cross-Sectional PACS**




Source: Cross-Sectional PACS

The Cross-Sectional PACS collected data from 688 established *IQOS* users, 439 of whom were current *IQOS* users as of October 13, 2021.[30] As described in **Figure 12**, *IQOS* was primarily used by middle-aged, legal age consumers. Additionally, less than 2% of *IQOS* users were 21-24 years old, suggesting low prevalence of use by those under 25 years old.

**Figure 12. Demographics of *IQOS* Users in the Cross-Sectional PACS**




Source: Cross-Sectional PACS

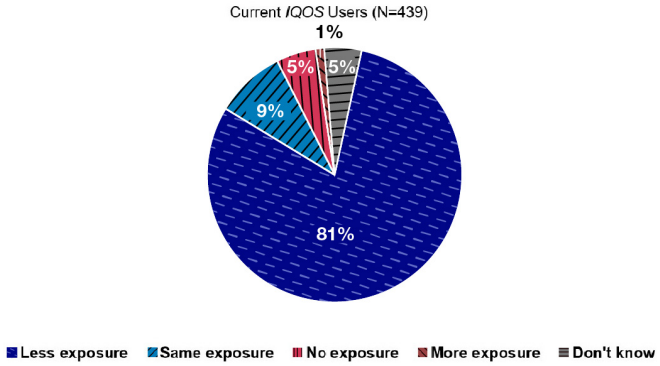
The Cross-Sectional PACS data demonstrates that **consumers continue to understand that the relative risk of using *IQOS* is lower compared to smoking combustible cigarettes and understand the need to**

[30] On October 13th, 2021, an information letter was sent to study participants, stating that *IQOS* would be unavailable for sale in the U.S. as of November 28th, 2021. Considering that the communication may alter consumer behaviors, the study report focuses on the current *IQOS* users (n=439) who completed the study prior to receiving the information letter. We did not observe any substantial differences in tobacco use patterns and perceptions about *IQOS* between those who completed the survey by and after October 13th.

**stop smoking cigarettes and only use *IQOS* (i.e., switch completely) to reduce their exposure to HPHCs.**

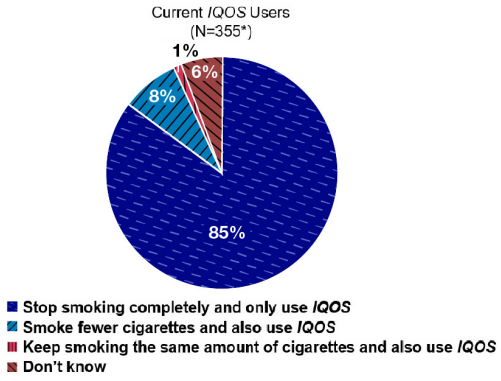
When asked about the relative exposure to HPHCs, the vast majority of adult *IQOS* users (81%) participating in the study correctly stated that completely switching from cigarettes to *IQOS* would result in less exposure to HPHCs (**Figure 13**), demonstrating consumer understanding of the reduced exposure to HPHCs. Further, 85% of those who understood the reduced exposure to HPHCs responded that cigarette smokers must "stop smoking completely and switch to *IQOS*" to reduce their HPHC exposure (**Figure 14**). These results demonstrate the reduced exposure claim effectively communicates that complete switching from cigarettes to *IQOS* significantly reduces exposure to HPHCs.

**Figure 13. Perception About HPHC Exposure When Smokers Switch Completely to *IQOS***




Source: Cross-Sectional PACS

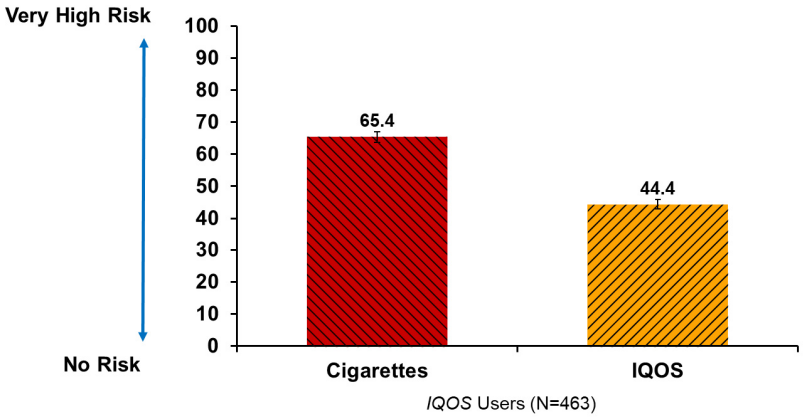
**Figure 14. Understanding of What Smokers Must Do to Reduce Their HPHC Exposure**




* This question was asked of only those respondents who correctly identified that using *IQOS* instead of cigarettes reduces their exposure to harmful or potentially harmful chemicals (**Figure 13**).
Source: Cross-Sectional PACS

As shown in **Figure 15**, risk perceptions for *IQOS* and combustible cigarettes measured in our U.S.-based Cross-Sectional PACS showed that *IQOS* users correctly perceive the health risks of smoking cigarettes to be higher than the health risks associated with using *IQOS*.

**Figure 15. Relative Health Risks Perceptions of Cigarettes and *IQOS***




Error bars: 95% confidence interval
Source: Cross-Sectional PACS
Participants were asked to rate the general perceived risk of getting 18 different diseases or adverse health conditions separately for smoking cigarettes or for using *IQOS* on a 5-point Likert-like scale (ranging from 0 [no risk] to 4 [very high risk]) using PMP S.A.'s psychometrically validated ABOUT–Perceived Risk, General version, Health Risk Instrument (18-item). Based on the 18 rated items, an overall score ranging from 0 [no risk] to 100 [very high risk] was derived from the total raw score by Rasch model analysis.

This postmarket evidence continues to reinforce that consumers understand that the relative health risk of using *IQOS* is lower than smoking cigarettes but is not risk-free. Therefore, the results of postmarket studies continue to support previously submitted premarket evidence showing the following:

- Consumers correctly perceive that the exposure to HPHCs associated with using *IQOS* is lower than the perceived exposure associated with smoking cigarettes.
- There is a high level of consumer understanding that completely switching to *IQOS* reduces exposure to HPHCs compared to smoking.

The availability of *IQOS* along with the reduced exposure claim improves legal age smokers' ability to make informed, personal choices that could reduce their exposure to HPHCs and be *reasonably likely* to reduce their risk of tobacco-related disease by switching completely to *IQOS*.

## 3.3. Tobacco Use Behavior and Impact to the Population as a Whole

As part of the PMSS, FDA required us to also evaluate consumers' use behaviors over time, which were intended to:

> *"...assess the extent to which new MRTP users were never, former, or current smokers, or other tobacco product users before initiating the MRTPs and the extent to which new users of the MRTPs become exclusive IQOS users, dual users with combusted cigarettes or other tobacco products, or transition to combusted cigarette smoking over time."*[1]

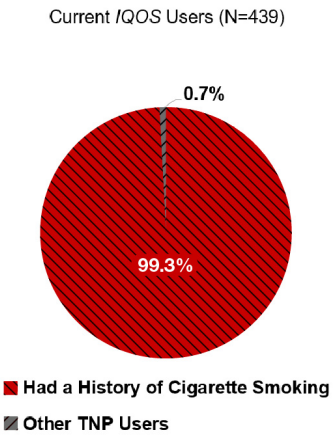
These product use patterns were monitored using a combination of data collected from the Cross-Sectional PACS and the *IQOS* Owners Panel. Additionally, we conducted secondary analyses of the nationally representative Adult Tobacco Consumer Tracking (ATCT) survey data to monitor legal age adult use of HTPs.

### *3.3.1. Benefit to Legal Age Smokers: Cross-Sectional PACS*

Legal age smokers who completely switch from combusted cigarettes to *IQOS* are likely to reduce their exposure to HPHCs and other toxicants. Therefore, it is critical to ensure *IQOS* is being used by the intended consumers (i.e., current, legal age smokers) and to monitor how they are using *IQOS* relative to cigarettes. These data inform the likelihood of consumers becoming complete switchers or dual users of *IQOS* and combusted cigarettes.

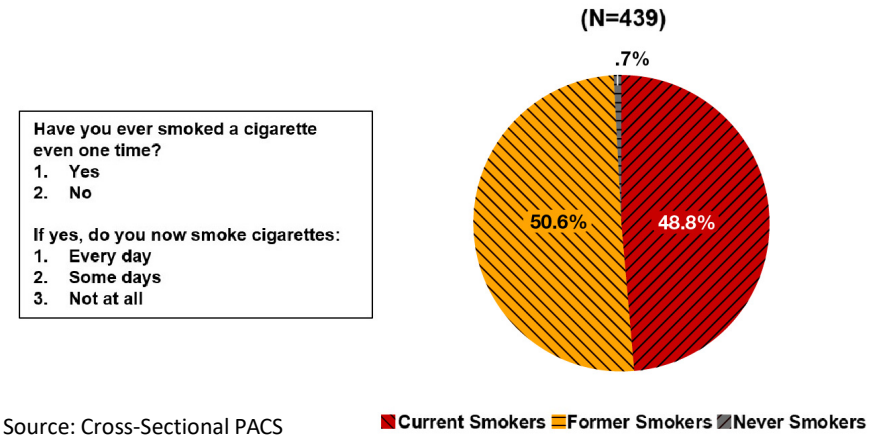
The study data show that over 99% of current established *IQOS* users had a history of cigarette smoking prior to first trying *IQOS* (**Figure 16**). At the time of the survey, over 50% reported that they were no longer smoking (i.e., they became former smokers), while 49% still smoked cigarettes (**Figure 17**). Among *IQOS* users who were still smoking cigarettes, 83% reported smoking fewer cigarettes at the time of the survey compared to before first trying *IQOS* (**Figure 18**).

**Figure 16. Cigarette Smoking History Among Current *IQOS Users***



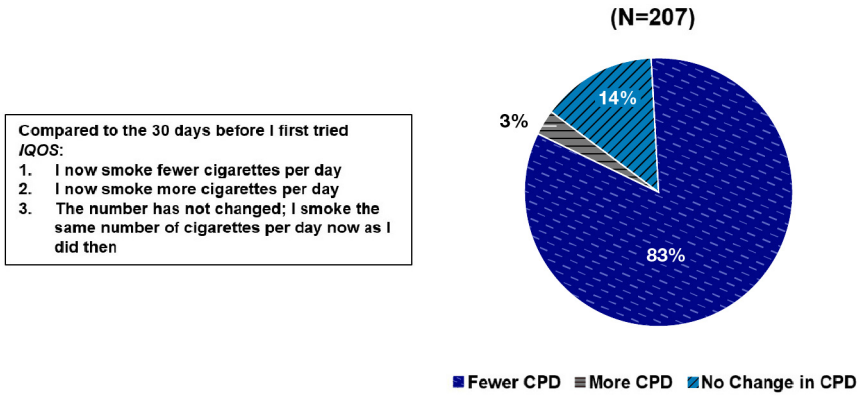

Source: Cross-Sectional PACS

**Figure 17. Cigarette Smoking Status Among Current *IQOS* Users**




Source: Cross-Sectional PACS

**Figure 18. Change in Cigarette Consumption Compared to Before Trying *IQOS***

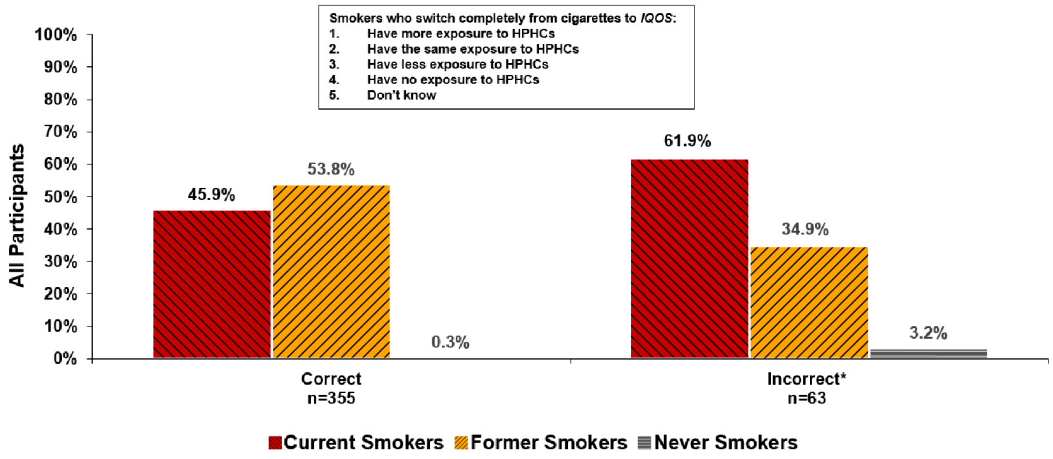



Basis: Current *IQOS* Users who were also current smokers 30 days before trying *IQOS*.
Source: Cross-Sectional PACS

As previously stated, the Cross-Sectional PACS data demonstrates that *IQOS* users understand that the exposure to HPHCs associated with using *IQOS* is lower than smoking cigarettes. They also understand that the relative health risks of using *IQOS* are lower compared to smoking cigarettes, and that they need to stop smoking cigarettes and only use *IQOS* (i.e., switch completely) to reduce their exposure to HPHCs. The Cross-Sectional PACS study data also shows the positive impact of the correct understanding of the claim on cigarette smoking status and cigarette consumption.

As shown in **Figure 19**, the Cross-Sectional PACS data shows that **those who correctly understand the reduced exposure to HPHCs are more likely to completely switch from cigarettes to *IQOS*.** Conversely, *IQOS* users who have a less clear understanding of the reduced exposure to HPHCs are more likely to continue smoking cigarettes.

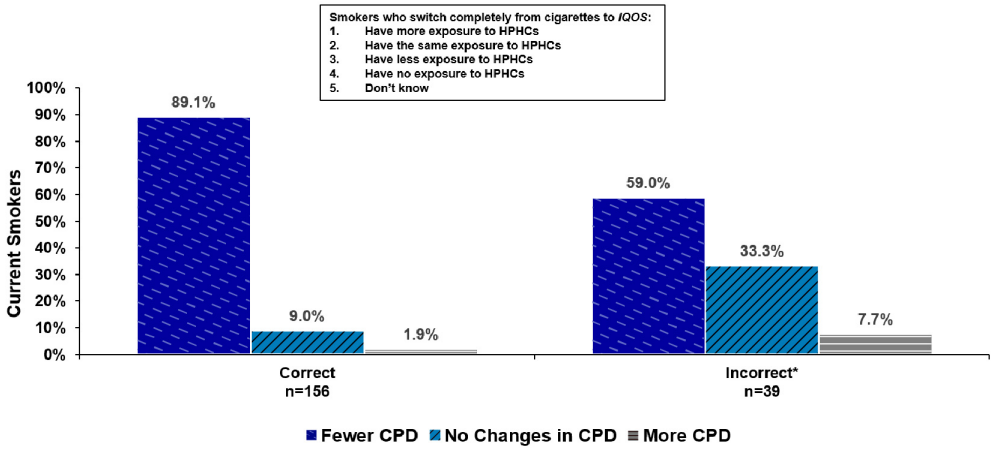
**Figure 19. Cigarette Smoking Status According to Comprehension of Reduced Exposure to HPHCs**




*Incorrect responses include "have more exposure to HPHCs", "have the same exposure to HPHCs", and "have no exposure to HPHCs". This analysis does not include "don't know" (n=21).
Source: Cross-Sectional PACS

As shown in **Figure 20**, a second positive effect of having correctly understood the reduced exposure to HPHCs of *IQOS* is observed among adult *IQOS* users who continued smoking cigarettes. **Among current smokers who correctly understood the reduced exposure benefit of *IQOS*, we observed substantial decrease in the number of cigarettes smoked per day compared to their baseline consumption**. Conversely, those who maintained or increased their cigarette consumption demonstrated lower comprehension of the reduced exposure to HPHCs.

**Figure 20. Changes in Cigarette Consumption According to Comprehension of Reduced Exposure to HPHCs**



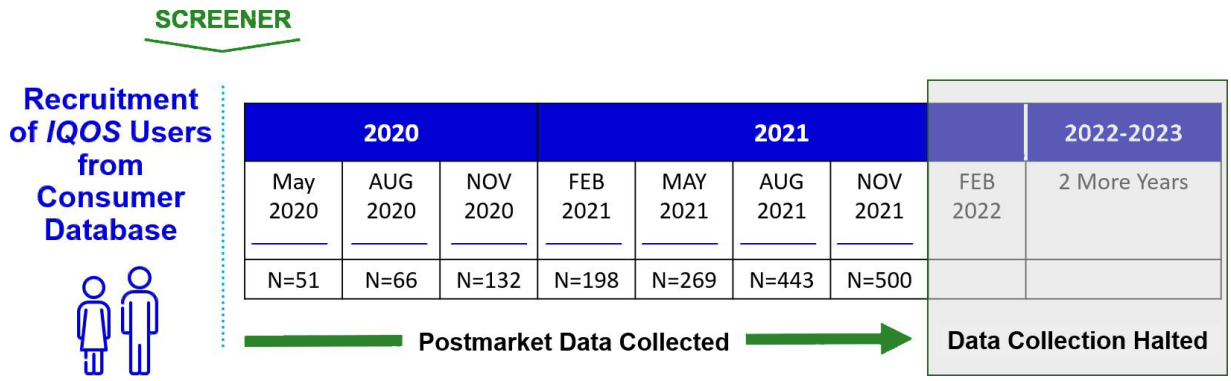

*Incorrect responses include "have more exposure to HPHCs", "have the same exposure to HPHCs", and "have no exposure to HPHCs". This analysis does not include "don't know" (n=12).
Source: Cross-Sectional PACS

### *3.3.2. Benefit to Legal Age Smokers: IQOS Owners Panel*

In addition to the Cross-Sectional PACS, a longitudinal study to measure use behaviors and patterns among *IQOS* owners was carried out. As shown in **Figure 21,** the *IQOS* Owners Panel surveyed *IQOS* owners over 18 months, reaching 500 participants when the study was halted on November 30, 2021.[31]

[31] On October 13th, 2021, an information letter was sent to study participants, stating that *IQOS* would be unavailable for sale in the U.S. as of November 28th, 2021. Considering that the communication may alter consumer behaviors, the study report focuses on the current *IQOS* users (N=443) who completed the study prior to receiving the information letter. We did not observe any substantial differences in tobacco use patterns and perceptions about *IQOS* between those who completed the survey by and after October 13th.

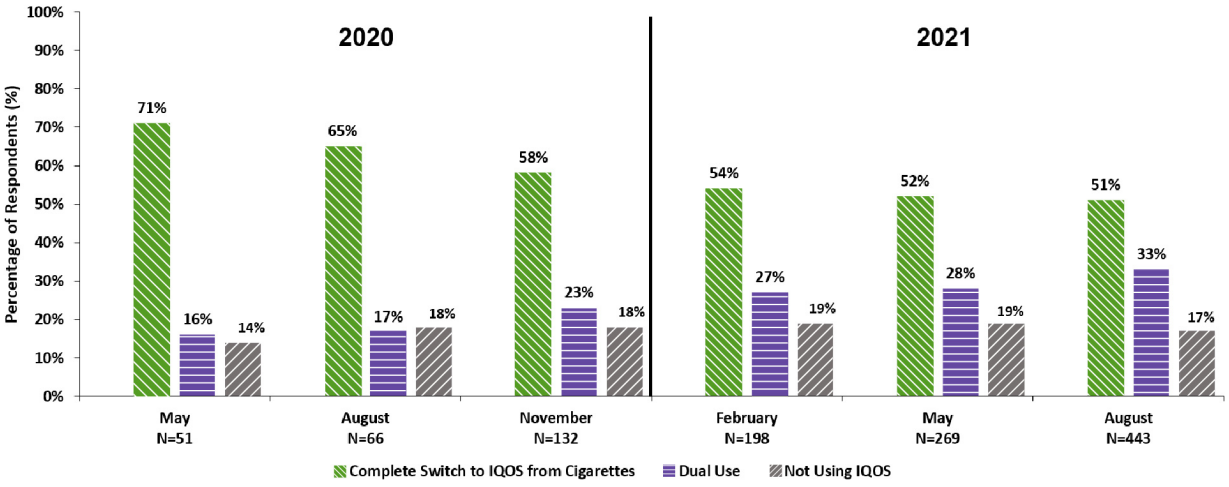
**Figure 21. Study Design of the *IQOS* Owners Panel**




Source: *IQOS* Owners Panel

In agreement with the Cross-Sectional PACS study data, the *IQOS* Owners Panel data (N=443) show that *IQOS* was primarily used by middle-aged, legal age consumers from the Southern region of the U.S. where *IQOS* was marketed**.** The sample size increased from N=51 (May 2020) to N=443 (August 2021), indicating a growing uptake of *IQOS* between May 2020 and August 2021. In August 2021, 51% of *IQOS* users switched completely from cigarettes, 33% were dual using cigarettes and *IQOS*, and 17% reported not using *IQOS* (**Figure 22**). Over the 18-month study period, while the proportion of *IQOS* users switching completely from cigarettes to *IQOS* decreased, the study data still shows that the majority of *IQOS* users switched completely from cigarettes to *IQOS* and reaffirms the critical importance of using the modified exposure information to communicate about complete switching.

**Figure 22. Use Patterns Among Adult *IQOS* Users, May 2020 – Aug. 2021**




Complete Switch is defined as 100% *IQOS* and 0% cigarette consumption.
Dual Use is defined as 5% ≤ *IQOS* usage level < 100% of total *IQOS*/cigarette consumption.
No *IQOS* is defined as *IQOS* usage level < 5% of total *IQOS*/cigarette consumption.
Source: *IQOS* Owners Panel

Collectively, the Cross-Sectional PACS and the *IQOS* Owners panel were the first U.S.-based studies to comprehensively assess *IQOS* user characteristics and behaviors in a postmarket, real-world setting. The data from these postmarket studies are consistent with the data collected in premarket studies and demonstrate that:

- Nearly all *IQOS* users had a history of cigarette smoking prior to first trying *IQOS*.
- Established *IQOS* users displayed cigarette switching and overall reduction in cigarette consumption.
    - The Cross-Sectional PACS data show that **51% of established *IQOS* users** had not smoked a cigarette in the past 30 days prior to the survey and hence **became former smokers.**
    - The *IQOS* Owners Panel data show that **51% of established *IQOS* users completely switched from cigarettes to *IQOS.***
    - Moreover, among *IQOS* users who were still smoking cigarettes, the Cross-Sectional PACS data show that **83% reported smoking fewer cigarettes** at the time of the survey compared to before trying *IQOS*.

These findings are consistent with the prior evidence leading to MRGO authorization and support the renewal of the reduced exposure claim. Finally, data from the ATCT survey show negligible use prevalence of *IQOS* among the general U.S. adult population. Out of 28,856 U.S. adult study participants, only three stated that they were using *IQOS* over the time when *IQOS* was marketed.

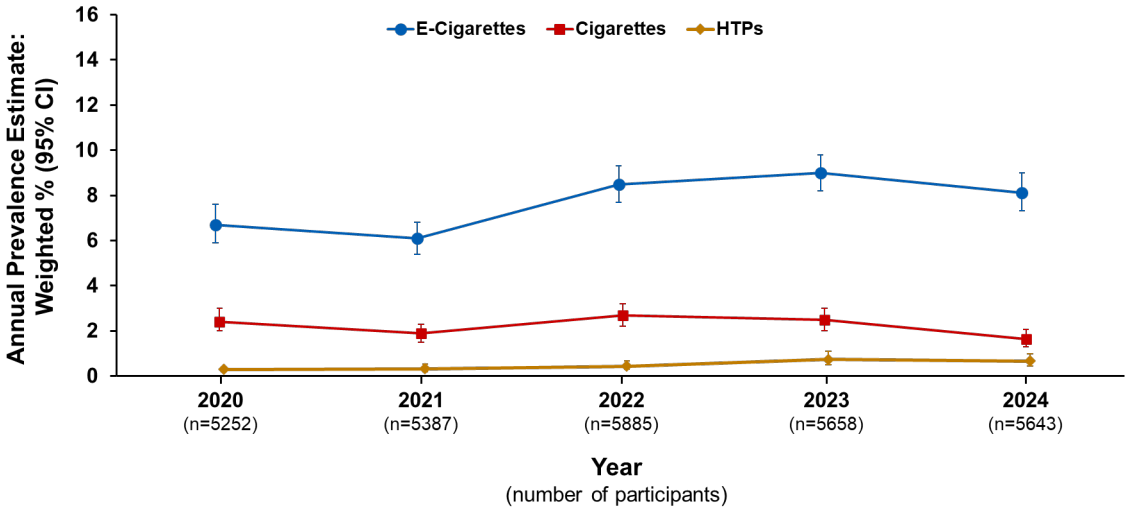
### *3.3.3. Risk to Youth: Secondary Analysis of UTUS and NYTS*

Throughout the postmarket period, we monitored *IQOS* awareness and use prevalence in U.S. youth population. We present data below from a combination of industry- and government-funded nationally representative surveys that collected data during the period when *IQOS* was marketed as well as after *IQOS* was withdrawn from the market. Those data in youth and underage adults have not raised concerns regarding the authorized *IQOS* products.

According to secondary analysis of data collected as part of the UTUS, past-30 -day use of HTP among underage individuals (age 13-20) is low (**Figure 23**). In a 2023 publication, based on UTUS data, the authors note "[t]he lowest levels of awareness and use were observed for heated tobacco products and snus" and "[t]he awareness and use of tobacco products remained relatively stable between May 2020 and August 2022.[32] Further, a review of the most recently available annual UTUS estimates on tobacco product use prevalence shows current (past-30-day) use of HTPs among underage individuals ages 13-20 is less than 1% in 2023 and 2024.

[32] Cheng, H.G., Vansickel, A.R. & Largo, E.G. Awareness and use of tobacco products among underage individuals: findings from the Altria Client Services Underage Tobacco Use Survey 2020–2022. BMC Public Health 23, 662 (2023). https://doi.org/10.1186/s12889-023-15610-1

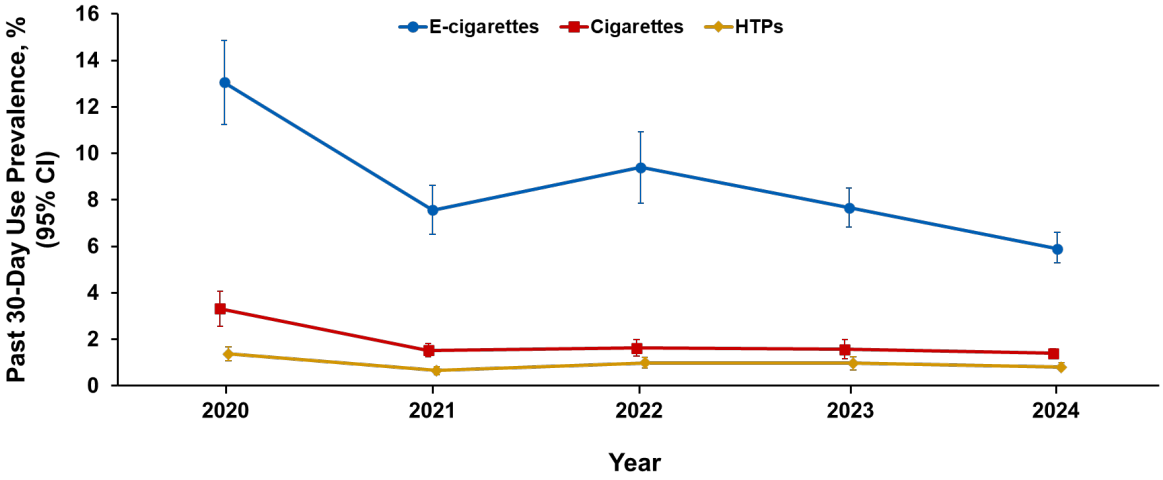
**Figure 23. Past-30-Day Use of HTPs Among U.S. Youth (UTUS)**




Source: UTUS 2020-2024 - US Youth aged 13-20 years old

The NYTS is a repeated cross-sectional study that provides national data about middle school and high school students beliefs, attitudes, behaviors, and exposure to tobacco influences.[33] Similar to UTUS results, low use prevalence of HTPs was observed based on data from NYTS. Since 2020, the estimated past-30-day use of HTPs, among middle school and high school students, has remained low with the most recently available 2024 estimate at 0.8%. The past-30-day prevalence of HTP use is much lower than prevalence of ENDS use (5.9% in 2024) (**Figure 24**).

**Figure 24. Past-30-Day Use of HTPs and Other TNPs Among U.S. Youth (NYTS)**




Source: NYTS estimates calculated directly from publicly available data

To summarize, industry-funded study UTUS and government-funded study NYTS data show **low awareness and prevalence of use of *IQOS* in U.S. youth and young adult population.** In terms of

[33] About National Youth Tobacco Survey (NYTS) | Smoking and Tobacco Use | CDC. (Accessed 14th July 2025)

tobacco use behavior, postmarket surveillance has continued to support the conclusions made in the initial MRGOs:

- The *IQOS* products are primarily used by adult consumers with a history of cigarette smoking, with low rates of uptake among nonusers.
- *IQOS* can facilitate switching from and reduction of combustible products that are high on the continuum of risk (i.e., cigarettes).
- There is a consistently low prevalence of use of HTP in youth.

The evidence demonstrates that *IQOS* can benefit the health of the population as a whole by transitioning legal age cigarette smokers away from cigarettes. Therefore, the continued marketing of *IQOS* as an MRTP will significantly reduce exposure to HPHCs and other toxicants among smokers who completely switch to the *IQOS* products, and renewal of the reduced exposure claim should be granted.

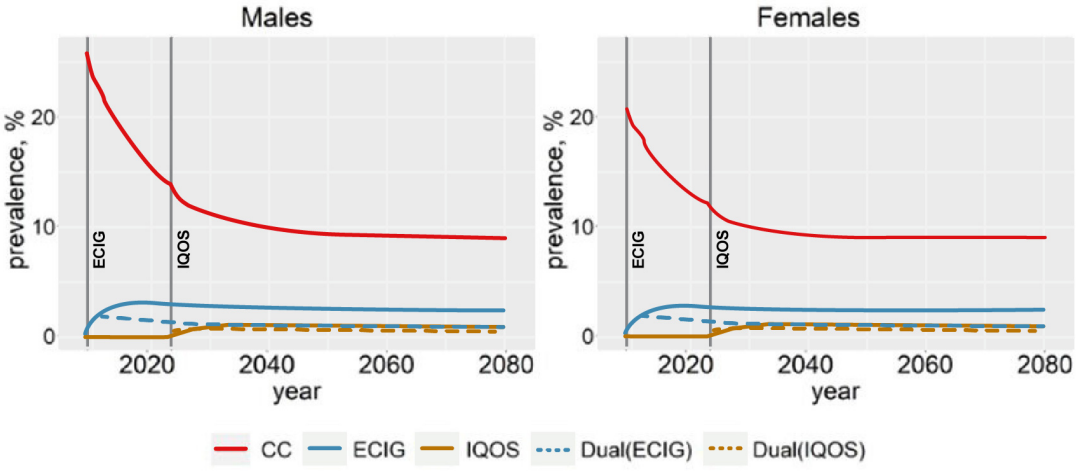
### *3.3.4. Population Modeling and Analysis*

As part of PMSS, FDA required us to model the impact of the MRTP on population health by incorporating information on user behavior and the latest information on acute and long-term health effects of *IQOS* use relative to smoking. Specifically, to assess the potential population impact of marketing *IQOS* products, a modeling framework was developed in which *IQOS* was introduced to a marketplace largely dominated by cigarettes and ENDS products.

The Population Health Impact Model (PHIM) has two components: one related to the TNP prevalence and the other to the epidemiological impact of the estimated new TNP prevalence following the introduction of *IQOS* in the country. The tobacco and nicotine Prevalence component of the model was based on the PATH data with some additional conservative uptake assumptions for *IQOS* (0.7% population prevalence in 2034 and thereafter). As shown in **Figure 25**, the model also took into consideration the existing decreasing trend in CC smoking and the existing use of ENDS. In the second epidemiological component of the model, the impact of TNP use on mortality attributable to smoking (due to lung cancer, chronic obstructive pulmonary disease, ischemic heart disease and stroke) was estimated. As *IQOS* has been consistently shown to significantly reduce HPHCs in aerosol, BoEs, and clinical markers in biospecimens of HTP users compared to CC smokers, an adjustment factor of the excess risk of mortality from one of these diseases was set at 20% for *IQOS* users compared to CC smokers (excess risk of mortality reduction of 80% compared to cigarettes), and 5% for ECIG.[34] Using this adjustment factor into the mortality equation, the model estimated that *IQOS* use would lead to a **reduction of 15,519 smoking attributed deaths** which **translates to 200,000 LYS** compared to continued CC smoking. A less conservative assumption of *IQOS* uptake leading to a 5% population prevalence in 2034 and thereafter would result in a **reduction of 225,000 smoking-attributed deaths** and an **increase of 2.2 million LYS** in the U.S.

[34] Martin F, Vuillaume G, Baker G, Sponsiello-Wang Z, Ricci PF, Lüdicke F, Weitkunat R. Quantifying the risk-reduction potential of new Modified Risk Tobacco Products. Regulatory toxicology and pharmacology. 2018 Feb 1;92:358-69.

**Figure 25. PHIM of Cigarette, ENDS, and *IQOS* Prevalence**




CC: combustible cigarettes; ECIG: ENDS products; Dual: dual use with combustible cigarettes.

# 4. NEW PUBLISHED RESEARCH FINDINGS

In order for FDA to determine whether the tobacco products subject of the MRGOs continue to be appropriate to promote the public health and continue to be expected to benefit the health of the population as a whole, we provided comprehensive literature reviews as part of our Annual Reports. To align with the requirements conditioned in the MRGO letter, this section provides a summary of significant new findings, both in published and unpublished studies, regarding the HTP product category and *IQOS* products. Emphasis is placed on the significant studies released during the post-authorization period, with a focus on health risks, consumer understanding and perception, tobacco use behavior, and impact to the population as a whole.

**The literature revealed no significant new findings**. Pre-clinical and aerosol studies did not present any novel or significant data, supporting earlier reports from our studies. Clinical trials continue to support reduced BoEs and BoPHs among HTP users compared to CC smokers. Behavioral assessments continue to confirm that the consumers comprehend the MRTP reduced exposure claim and that the term "switching completely" means using zero cigarettes. The incidence of unintended audiences using IQOS is negligible, consistent with previously reported findings.

## 4.1. Health Risks

### *4.1.1. Aerosol Chemistry*

As part of our surveillance efforts, we identified numerous postmarket publications that provide additional evidence supporting the reduced exposure claim- The *IQOS* system heats tobacco, which significantly reduces exposure to HPHCs in *IQOS* aerosol. Given the preponderance of evidence on this topic, we chose to include summaries of key literature reviews detailing HPHC exposure findings that best capture the collective postmarket data.

The most recent systematic global review was conducted in 2023 focusing on carbonyl aerosol emissions with an assessment of analytical method suitability, experimental quality, and the physicochemical

properties of HTP aerosols. Reviewing 17 studies, the authors conclude "*[t]he outcomes from the revised studies and regulatory evaluations tend to agree with and converge to a general consensus that HTP aerosols expose users to significantly lower levels of toxicity than tobacco smoke*."[35] Similarly, a 2021 review summarized the literature on *IQOS*, noting the examined studies agree on similar relevant HPHC reductions (e.g., TSNAs, VOCs, PAHs) with respect to the 3R4F reference cigarette under the Canadian Intense regimen.[36] Finally, a 2019 review examined 31 articles on HTPs published between 2009 and 2017. They note substantial differences between studies due to the large variety of methods used to measure and produce HTP aerosols and emphasized the need for the development and use of standardized protocols to allow for optimal comparisons. Despite methodological differences, the collective studies show a reduction in HTP emissions within the 90% range of HPHCs.[37]

Regardless of the differences in aerosol generation techniques and analytical methods, the literature continues to demonstrate a significant reduction in HPHCs emissions for *IQOS* aerosol relative to combusted cigarettes. These studies should be evaluated in context of the totality of evidence surrounding *IQOS* aerosol characterization, and in the context of the modified exposure claim, which communicates a reduced exposure in comparison to cigarette smoking. This postmarket evidence reinforces the validity of the reduced exposure claim.

### *4.1.2. Non-Clinical Toxicology*

While *IQOS* aerosol contains fewer and lower levels of HPHCs compared to cigarette smoke, non-clinical toxicology studies are used to determine if these reductions translate to a reduction in toxicity. In the postmarket period, some non-clinical studies show that exposure to *IQOS* aerosols can induce oxidative stress and inflammation.[38,39,40,42] However, relative to cigarette smoke, both *in vivo* and *in vitro* studies consistently demonstrate lower levels of cytotoxicity, oxidative stress, and inflammatory markers following exposure to *IQOS* aerosol. [38,39,40,41,42,43,44] In cases where *IQOS* aerosol was associated with cytotoxic, oxidative stress, and inflammatory effects, most were transient and resolved more rapidly

[35] Sussman, R.A.; Sipala, F.; Emma, R.; Ronsisvalle, S. Aerosol Emissions from Heated Tobacco Products: A Review Focusing on Carbonyls, Analytical Methods, and Experimental Quality. *Toxics* **2023**, *11*, 947. https://doi.org/10.3390/ toxics11120947
[36] El-Kaassamani M, Yen M, Talih S*, et al* Analysis of mainstream emissions, secondhand emissions and the environmental impact of IQOS waste: a systematic review on IQOS that accounts for data source *Tobacco Control* 2024;**33:**93-102.
[37] Simonavicius E, McNeill A, Shahab L*, et al* Heat-not-burn tobacco products: a systematic literature review *Tobacco Control* 2019;**28:**582-594.
[38] Vivarelli, F., Morosini, C., Rullo, L., Losapio, L. M., Lacorte, A., Sangiorgi, S., ... & Paolini, M. (2024). Effects of unburned tobacco smoke on inflammatory and oxidative mediators in the rat prefrontal cortex. Frontiers in Pharmacology, 15, 1328917.
[39] Husari, A., El-Harakeh, M., Shihadeh, A., Daou, M. A. Z., Bitar, H., Karaoghlanian, N., ... & El-Sabban, M. (2023). 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 and Tobacco Research, 25(7), 1361-1368.
[40] Saha, P., Jain, S., Mukherjee, I., Panda, S. R., Zeki, A. A., Naidu, V. G. M., & Sharma, P. (2023). The effects of dual IQOS and cigarette smoke exposure on airway epithelial cells: implications for lung health and respiratory disease pathogenesis. ERJ Open Research, 9(3).
[41] Rahman, M., Irmler, M., Introna, M., Beckers, J., Palmberg, L., Johanson, G., ... & Ganguly, K. (2022). Insight into the pulmonary molecular toxicity of heated tobacco products using human bronchial and alveolar mucosa models at air–liquid interface. Scientific Reports, 12(1), 16396.
[42] Sawa, M., Ushiyama, A., Inaba, Y., & Hattori, K. (2022). Increased oxidative stress and effects on inflammatory cytokine secretion by heated tobacco products aerosol exposure to mice. Biochemical and Biophysical Research Communications, 610, 43-48.
[43] Ito Y, Oshinden K, et al. Heat-Not-Burn cigarette induces oxidative stress response in primary rat alveolar epithelial cells. PLoS One, 2020, 15(11): e0242789.
[44] Wang L, et al. Harmful chemicals of heat not burn product and its induced oxidative stress of macrophages at air-liquid interface: Comparison with ultra-light cigarette. Toxicology Letters, 2020, 331: 200-207.

compared to the effects observed with cigarette smoke.[45] Overall, the postmarket literature continues to support the prior premarket evidence demonstrating *IQOS* aerosol has reduced cytotoxicity and inflammatory potential compared to cigarette smoke.

### *4.1.3. Clinical*

We examined the available post-market literature on the impact of *IQOS* use on BoEs and BoPHs compared to continued smoking. Across multiple studies, users of HTP had significantly lower levels of BoEs compared to smokers, which, in many cases, were close to the levels seen in those who completely quit smoking. A recent systematic review and meta-analysis, including studies on *IQOS* published by third-party researchers, continues to support the conclusion from a previous systematic review[46] and our own evidence submitted in support of the MRTP Renewal- HTP users had significantly lower levels of BoEs compared to smokers. At the same time, nicotine exposure, as measured by NEQ, was either lower or similar compared to smoking.[47] Additionally, the results from a cross-sectional study of healthy participants (n = 982) showed a reduction (50%-96%) in levels of BoEs in *IQOS* users after at least 2 years of real-life *IQOS* use (average time of IQOS use: 4.5 years) versus smokers and with levels similar to those observed in former smokers.[48] These real-world findings provide additional evidence on *IQOS* and complement the findings in published studies.

Furthermore, two independent systematic reviews (with the majority of studies on *IQOS*) evaluated the effect of HTP use on BoPHs associated with the cardiovascular system. Begic et al. concluded from 25 randomized clinical studies that switching from smoking to HTP is associated with favorable impact on BoPHs, including a decrease in sICAM-1, 8-epi-PGF2α, 11-DTXB2, WBC count, LDL cholesterol, an increase in HDL cholesterol, as well as improvements in cardiac parameters like flow mediated dilation, coronary flow reserve, pulse wave velocity, and heart rate.[49] Ghazaryan et al. also found favorable differences in BoPHs associated with oxidative stress, platelet activation, endothelial dysfunction, inflammation, and antioxidant reserve, between smokers and people using HTPs and reported no relevant difference when comparing the acute effects on arterial stiffness, heart rate, and myocardial function.[50] Both reviews acknowledge the need for further long-term human studies to assess the potential benefits and risks, but the available evidence to date appears promising to the reduced risk potential of HTPs.[49,50]

[45] Dusautoir R, et al. 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-2B cells. Journal of Hazardous Materials, 2021, 401: 123417.
[46] Drovandi, A., Salem, S., Barker, D. et al. (2019). Human Biomarker Exposure from Cigarettes versus Novel Heat-Not-Burn Devices: A Systematic Review and Meta-Analysis. Nicotine Tob Res. doi: 10.1093/ntr/ntz200.
[47] Reaño, J. D. P., Barrinetos-Regala, M., Arimado, R., & Castillo, R. (2022). A Systematic Review and Meta-Analysis on Human Biomarkers of Exposure from Heated Tobacco Products Compared to Conventional Cigarettes among Adult Smokers. Jour Clin Med Res, 3(2), 1-27.
[48] Ansari, S.M., Leroy P., De La Bourdonnaye G., Pouly S., Reese L., Haziza C. (2025). Differences in biomarkers of potential harm after 2+ years of tobacco heating system use compared to cigarette smoking: a cross-sectional study. Biomarkers, Mar;30(2):178-191.
[49] Begic, E., Aziri, B., Omeragic, E. et al. (2023). Heat-not-burn tobacco products and cardiovascular risk reduction: A systematic review of randomized controlled trials. Technol Health Care, 31(4):1457-1491.
[50] Ghazaryan, N., Adamyan, M., Muradyan, N. et al. (2022). Differential Effects of Heated Tobacco Products and Conventional Cigarettes on Cardiovascular System: A Systematic Review of Randomized Trials. Indian Journal of Public Health Research and Development, 12(2):269-276.

The results consistently suggest that switching to *IQOS* results in reductions in BoEs and favorable changes in BoPHs relative to continuing to smoke cigarettes, which in many cases, approach the levels and changes seen with smoking cessation.[46,47,48]

## 4.2. Consumer Understanding and Perception

Among U.S. young adult smokers, the assessment of claims and HTP harm perceptions showed that participants exposed to the claim were more likely to perceive HTPs as less harmful than cigarettes.[51] Other studies conducted in the U.S. also found that the understanding of the reduced exposure claim resulted in lower perceived relative harm, exposure, and disease risk.[52,53]

Moreover, studies show that adult and young adult smokers in the U.S. understand the term "switching completely" to mean zero cigarettes.[54] An investigation of how U.S. youth perceive the modified risk claim for *IQOS* found over 70% of youth understood the term "switching completely" used in the *IQOS* reduced exposure claim. Roughly half of the surveyed youth indicated perceiving *IQOS* as less harmful to their health relative to combusted cigarettes.[55]

[51] Chen-Sankey, JC, A. Kechter, J. Barrington-Trimis, R. McConnell, E. A. Krueger, T. B. Cruz, et al. Effect of a hypothetical modified risk tobacco product claim on heated tobacco product use intention and perceptions in young adults. Tob Control 2023 Vol. 32 Issue 1 Pages 42-50. Accession Number: 34059552 PMCID: PMC8630081 DOI: 10.1136/tobaccocontrol-2021-056479.

[52] Berg, C. J., Duan, Z., Wang, Y., Thrasher, J. F., Bar-Zeev, Y., Abroms, L. C., ... & Levine, H. (2024). Impact of FDA endorsement and modified risk versus exposure messaging in IQOS ads: a randomised factorial experiment among US and Israeli adults. Tobacco control, 33(e1), e69-e77.

[53] Seidenberg, A. B., Boynton, M. H., Brewer, N. T., Lazard, A. J., Sheeran, P., & Ribisl, K. M. (2024). Effects of Modified Risk Tobacco Product Claims on Consumer Responses. Nicotine and Tobacco Research, 26(4), 435-443.

[54] Yang B, Massey ZB, Popova L. Effects of modified risk tobacco product claims on consumer comprehension and risk perceptions of IQOS. Tob Control. 2022 Aug;31(e1):e41-e49. doi: 10.1136/tobaccocontrol-2020-056191. Epub 2021 Mar 9. PMID: 33688084; PMCID: PMC8426425.

[55] McKelvey K, Baiocchi M, Halpern-Felsher B. PMI's heated tobacco products marketing claims of reduced risk and reduced exposure may entice youth to try and continue using these products. Tob Control. 2020 Dec;29(e1):e18-e24. doi: 10.1136/tobaccocontrol-2019-055318.

Several studies focused on harm perceptions related to *IQOS* and HTPs compared to cigarettes and the factors influencing these perceptions. Consistently, these studies demonstrated that a majority of adults and young adults, between ages 21 to 34, accurately perceive *IQOS* and HTPs as less harmful than cigarettes.[56,57,58,59,60,61,62] This perception was shared across various user groups, including ever and current smokers, among exclusive users and dual users of HTPs, and among exclusive and dual e-cigarette users. [63,64,65]

The available evidence indicates that both adults and young adults correctly recognize *IQOS* and HTPs as less harmful alternatives to cigarettes, while understanding *IQOS* was not risk-free, regardless of their smoking status.[66]

Finally, even though there are multiple factors that influence product adoption and continued use, the actual claim and the perceived harm of *IQOS* are often stated as key reasons.[67,68]

The postmarket evidence, therefore, continues to support prior conclusions that reduced exposure claims can effectively inform consumers on the lower risks of HTPs relative to combusted cigarettes.

[56] Laverty, AA, C. I. Vardavas and F. T. Filippidis. Prevalence and reasons for use of Heated Tobacco Products (HTP) in Europe: an analysis of Eurobarometer data in 28 countries. Lancet Reg Health Eur 2021 Vol. 8 Pages 100159. Accession Number: 34557853 PMCID: PMC8454644 DOI: 10.1016/j.lanepe.2021.100159.

[57] Xu, S. S., Meng, G., Yan, M., Gravely, S., Quah, A. C., Ouimet, J., ... & Fong, G. T. (2020). Reasons for regularly using heated tobacco products among adult current and former smokers in Japan: finding from 2018 ITC Japan Survey. International journal of environmental research and public health, 17(21), 8030.

[58] Duan, Z., Wysota, C. N., Romm, K. F., Levine, H., Bar-Zeev, Y., Choi, K., & Berg, C. J. (2022). Correlates of perceptions, use, and intention to use heated tobacco products among US young adults in 2020. Nicotine and Tobacco Research, 24(12), 1968-1977.

[59] Duan, Z., Le, D., Ciceron, A. C., Dickey-Chasins, R., Wysota, C. N., Bar-Zeev, Y., ... & Berg, C. J. (2022). 'It's like if a vape pen and a cigarette had a baby': a mixed methods study of perceptions and use of IQOS among US young adults. Health education research, 37(5), 364-377.

[60] Sutanto, E., Miller, C. R., Smith, D. M., O'Connor, R. J., Gravely, S., Hammond, D., ... & Goniewicz, M. L. (2020). Perceived relative harm of heated tobacco products (IQOS), e-cigarettes, and cigarettes among adults in Canada: Findings from the ITC Project. Tobacco Induced Diseases, 18.

[61] Kim, S. H., Kang, S. Y., & Cho, H. J. (2020). Beliefs about the harmfulness of heated tobacco products compared with combustible cigarettes and their effectiveness for smoking cessation among Korean adults. International Journal of Environmental Research and Public Health, 17(15), 5591.

[62] Suzana AlMoosawi, Martha Bajec, Nelly Mainy, Gerd Kallischnigg, Bertram Zwisele, Karina Fischer, Pierpaolo Magnani, Steve Roulet, Risk perception of IQOS™ and cigarettes: Temporal and cross-country comparisons, SSM - Population Health, Volume 18, 2022, 101123, ISSN 2352-8273, https://doi.org/10.1016/j.ssmph.2022.101123.

[63] Pénzes, M., Joó, T., & Urbán, R. (2022). Perceived harm of heated tobacco products, e-cigarettes, and nicotine replacement therapy compared with conventional cigarettes among ever and current heated tobacco users. Addictive Behaviors Reports, 15, 100432.

[64] Gravely, S., Fong, G. T., Sutanto, E., Loewen, R., Ouimet, J., Xu, S. S., ... & Tabuchi, T. (2020). Perceptions of harmfulness of heated tobacco products compared to combustible cigarettes among adult smokers in Japan: findings from the 2018 ITC Japan Survey. International journal of environmental research and public health, 17(7), 2394.

[65] Kim, CY, K. Lee, C. M. Lee, S. Kim and H. J. Cho. Perceived relative harm of heated tobacco products and electronic cigarettes and its association with use in smoke-free places: A cross-sectional analysis of Korean adults. Tob Induc Dis 2022 Vol. 20 Pages 20. Accession Number: 35280047 PMCID: PMC8859996 DOI: 10.18332/tid/145699.

[66] Tompkins CNE, Burnley A, McNeill A, et al Factors that influence smokers' and ex-smokers' use of IQOS: a qualitative study of IQOS users and ex-users in the UK Tobacco Control 2021;30:16-23.

[67] Fischer, Karina, et al. "How do Risk Perceptions Drive Smokers to Completely Switch to a Smoke-Free Tobacco Product (IQOS™)? A Four-Country Cohort Study" Contributions to Tobacco & Nicotine Research, vol. 32, no. 2, Sciendo, 2023, pp. 50-64. https://doi.org/10.2478/cttr-2023-0007

[68] Seo, H. G., Xu, S. S., Li, G., Gravely, S., Quah, A. C., Lee, S., ... & Fong, G. T. (2023). Reasons for initiation and regular use of heated tobacco products among current and former smokers in South Korea: Findings from the 2020 ITC Korea Survey. International journal of environmental research and public health, 20(6), 4963.

## 4.3. Tobacco Use Behavior and Impact to the Population as a Whole

### *4.3.1. Use Prevalence in Adult*

A systematic global review of publications from 2015 to 2022 found that the prevalence of ever and current use of HTPs increases after HTP market entry across all age groups.[69] A higher prevalence of current use was seen in smokers, males, younger adults (legal age adults under 35 years old), and more affluent populations.[70,71] Virtually all HTP users are current or former smokers, demonstrating a low appeal to never smokers.[72,73] Overall, *IQOS* is the most commonly used HTP in markets where HTPs are marketed.[74,75,76,77,78]

The rates of dual use (HTPs and cigarettes) among HTP users vary across studies. Some studies found dual use to be low, while others report higher rates of dual use. The recent analysis carried out by Scala et al. (2025) show dual use estimates among HTP users ranging between 28.0% (95% CI, 16.2–42.5%) and 96.2% (95% CI, 94.0–97.8%) across the studies included as part of the comprehensive systematic review.[79] The authors further added that *"the definition of HTP use was inconsistent among studies, likely contributing, together with the differences between study populations and socio-demographic characteristics influencing HTP use, to the high heterogeneity observed in each meta-analysis"*.

[69] Sun, T., Anandan, A., Lim, C. C., East, K., Xu, S. S., Quah, A. C., ... & Chan, G. C. (2023). Global prevalence of heated tobacco product use, 2015–22: A systematic review and meta-analysis. Addiction, 118(8), 1430-1444.
[70] Miller, CR, E. Sutanto, D. M. Smith, S. C. Hitchman, S. Gravely, H. H. Yong, et al. Characterizing Heated Tobacco Product Use Among Adult Cigarette Smokers and Nicotine Vaping Product Users in the 2018 ITC Four Country Smoking & Vaping Survey. Nicotine Tob Res 2021 Vol. 24 Issue 4 Pages 493-502. Accession Number: 34669964 PMCID: PMC8887594 DOI: 10.1093/ntr/ntab217.
[71] Lotrean, ML., Trofor, A., Radu-Loghin, C., Eremia, M., Mihaltan, F., Driezen, P., ... & Vardavas, C. I. (2020). Awareness and use of heated tobacco products among adult smokers in six European countries: findings from the EUREST-PLUS ITC Europe Surveys. European Journal of Public Health, 30(Supplement_3), iii78-iii83.
[72] Sutanto, E., Miller, C., Smith, D.M. et al. (2019). Prevalence, Use Behaviors, and Preferences among Users of Heated Tobacco Products: Findings from the 2018 ITC Japan Survey. Int J Environ Res Public Health. 16(23): E4630.
[73] Liu, X.; Lugo, A.; Spizzichino, L. et al. (2019). Heat-not-burn tobacco products: concerns from the Italian experience. Tob Control. 28(1):113-114.
[74] Adamson J, Kanitscheider C, Prasad K, et al. Results from a 2018 cross-sectional survey in Tokyo, Osaka and Sendai to assess tobacco and nicotine product usage after the introduction of heated tobacco products (HTPs) in Japan, Harm Reduct J, 2020, 17(1): 32.
[75] Hori, A., Tabuchi, T., & Kunugita, N. (2021). Rapid increase in heated tobacco product (HTP) use from 2015 to 2019: from the Japan 'Society and New Tobacco' Internet Survey (JASTIS). Tobacco control, 30(4), 474-475.
[76] Tabuchi, T., Shinozaki, T., Kunugita, N. et al. (2019). Study Profile: The Japan "Society and New Tobacco" Internet Survey (JASTIS): A longitudinal internet cohort study of heat-not-burn tobacco products, electronic cigarettes and conventional tobacco products in Japan. J Epidemiol. 29(11): 444-450.
[77] Odani, S. and T. Tabuchi. Prevalence of heated tobacco product use in Japan: the 2020 JASTIS study. Tob Control 2022 Vol. 31 Issue e1 Pages e64-e65. Accession Number: 33707176 DOI: 10.1136/tobaccocontrol-2020-056257.
[78] Gallus, S., Lugo, A., Liu, X., Borroni, E., Clancy, L., Gorini, G., ... & TackSHS Project Investigators. (2022). Use and awareness of heated tobacco products in Europe. Journal of Epidemiology, 32(3), 139-144.
[79] Scala M, Dallera G, Gorini G, Achille J, Havermans A, Neto C, Odone A, Smits L, Zambon A, Lugo A, Gallus S. Patterns of Use of Heated Tobacco Products: A Comprehensive Systematic Review. J Epidemiol. 2025 May 5;35(5):213-221. doi: 10.2188/jea.JE20240189. Epub 2025 Mar 31. PMID: 39805598; PMCID: PMC11979348.

Literature review also shows that HTPs are primarily used by smokers who are interested in stopping or reducing their cigarette use.[80,81,82] Furthermore, a recent analysis from Audrain-Mc-Govern et al. (2025) found out that among adult daily smokers uninterested in quitting cigarette smoking within the next month, *IQOS* use was associated with increased motivation to quit and lead the authors to conclude that *"Motivation to quit smoking may not be a necessary prerequisite for promoting smoking behavior change but rather bolstered by smoking behavior change in the context of HTP use"*.[83] In addition, several published studies found smokers who used *IQOS* were able to significantly reduce their cigarette consumption.[84,85]

In the U.S., awareness of HTPs among young adults was low across studies, with prevalence of ever and current use of *IQOS* and HTPs being similarly low, likely due to the absence of HTPs on the U.S. market.[86,87] Adults who identify themselves as Asian, Hispanic, or White and used cigarettes, ENDS, or other tobacco products in the past month were more likely to have ever used *IQOS*.[88]

Finally, a recent 2024 publication examined the impact of the removal of *IQOS* from the U.S. market on *IQOS* consumers.[89] Data showed the use of *IQOS* was associated with a significant reduction in cigarette smoking; however, after 9 months without *IQOS* on the market, participants reported an increase in cigarette smoking. The authors concluded that *"If unable to find satisfying alternatives, adults who smoke and transition to reduced harm products may return to smoking or purchase products illicitly if their preferred products are removed from the regulated market"*.

In summary, the overall prevalence of HTP use remains low in the United States, while the prevalence of HTP use increases globally among adults of all ages. Nearly all HTP users are current or former smokers, indicating limited appeal to nonsmokers.

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[80] Hussain, S., & Sreeramareddy, C. T. (2022). Smoking cessation behaviors and reasons for use of electronic cigarettes and heated tobacco products among Romanian adults. Scientific reports, 12(1), 5446.

[81] DeAtley T, Stone MD, Strasser AA, Audrain-McGovern J. The role of IQOS risk perceptions on cigarette smoking behaviours: results from a prospective pilot study. Tob Control. 2024 Feb 20;33(2):263-266. doi: 10.1136/tc-2022-057461. PMID: 36002165; PMCID: PMC10394684.

[82] Seo, H. G., Xu, S. S., Li, G., Gravely, S., Quah, A. C., Lee, S., ... & Fong, G. T. (2023). Reasons for initiation and regular use of heated tobacco products among current and former smokers in South Korea: Findings from the 2020 ITC Korea Survey. International journal of environmental research and public health, 20(6), 4963.

[83] Audrain-McGovern J, Klapec O, Paul Wileyto E, Strasser AA. Shifts in motivation to quit cigarette smoking associated with IQOS use. Addict Behav. 2025 Jan;160:108178. doi: 10.1016/j.addbeh.2024.108178. Epub 2024 Sep 26. PMID: 39332230; PMCID: PMC11560473.

[84] Stone, M. D., DeAtley, T., Pianin, S., Strasser, A. A., & Audrain-McGovern, J. (2022). Switching from cigarettes to IQOS: A pilot examination of IQOS-associated reward, reinforcement, and abstinence relief. Drug and Alcohol Dependence, 238, 109569.

[85] Karelitz, J.L., He, Y., Becker, E. *et al.* Switching behavior and changes in smoking behavior by menthol cigarette preference and menthol heated tobacco product use among adults in the United States who smoke cigarettes: an actual use study. *Harm Reduct J* 22, 19 (2025). https://doi.org/10.1186/s12954-025-01170-7

[86] Dunbar, M.S., Seelam, R., Tucker, J.S. et al. (2020). Correlates of Awareness and Use of Heated Tobacco Products in a Sample of US Young Adults in 2018-2019. Nicotine Tob Res.

[87] Berg, CJ, K. F. Romm, B. Patterson and C. N. Wysota. Heated Tobacco Product Awareness, Use, and Perceptions in a Sample of Young Adults in the United States. Nicotine Tob Res 2021 Vol. 23 Issue 11 Pages 1967-1971. Accession Number: 33822111 PMCID: PMC8496465 DOI: 10.1093/ntr/ntab058.

[88] Levine, H., Duan, Z., Bar-Zeev, Y., Abroms, L. C., Khayat, A., Tosakoon, S., ... & Berg, C. J. (2023). IQOS use and interest by sociodemographic and tobacco behavior characteristics among adults in the US and Israel. International journal of environmental research and public health, 20(4), 3141.

[89] Noggle, B., Ball, K.M. & Vansickel, A.R. A reduced exposure heated tobacco product was introduced then abruptly taken off United States shelves: results from a tobacco harm reduction natural experiment. Harm Reduct J 21, 84 (2024). https://doi.org/10.1186/s12954-024-01000-2

### 4.3.2. Use Prevalence in Youth

Postmarket studies on HTP use among youth indicate low use prevalence across various countries. Although HTP awareness has increased with the introduction of HTPs, ever and current HTP use in youth has remained consistently low regardless of the length of time HTPs have been available in the country.[90,91,92,93,94]

Shortly after *IQOS* introduction into the U.S. market, an analysis of 2019 NYTS data showed an increase in awareness of HTPs but low prevalence of ever use and current use among youth.[95] Between 2019 and 2020, HTP awareness among youth in the U.S. increased from 12.8% to 19.3%, while HTP use remains low, with ever use reported as 2.6% in 2019 and 2.4% in 2020, and current use of HTPs being 1.6% in 2019 and 1.4% in 2020.[96] One study analyzing the Underage Tobacco Use Survey (UTUS) in the U.S. found HTPs had the lowest level of awareness, with ever use below 2% and past 30-day use below 1% among youth, aligning with the 2021-2022 NYTS data.[97]

Overall, the prevalence of HTP use in youth is low globally as well as in the U.S. as shown by the 2024 UTUS and NYTS study data (see Section 3.3.3). This further supports the prior evidence that HTPs are not a tobacco product category of particular interest to youth.[8,10]

### 4.3.3. Population Modeling

We also examined the potential impact of HTPs on population health based on published population modeling literature, including assessments in international markets (Italy and Japan) where *IQOS* has achieved sustained market uptake. Researchers have been using complex models to simulate the effects of HTPs on populations, considering factors like initiation rates, dual use, quitting, switching, and cessation. While these models have limitations, they generally indicated that complete switching from cigarettes to HTPs could contribute to the decrease in cigarette smoking and lead to an increase in LYS.

[90] Delgrande Jordan, M., Balsiger, N. & Schmidhauser, V. (2023). La consommation de substances psychoactives des 11 à 15 ans en Suisse – Situation en 2022 et évolution dans le temps - Résultats de l'étude Health Behaviour in School-aged Children (HBSC) (rapport de recherche No 149). Lausanne: Addiction Suisse.
[91] Orth, B. & Merkel, C. (2022). Der Substanzkonsum Jugendlicher und junger Erwachsener in Deutschland. Ergebnisse des Alkoholsurveys 2021 zu Alkohol, Rauchen, Cannabis und Trends. BZgA-Forschungsbericht. Köln: Bundeszentrale für gesundheitliche Aufklärung. https://doi.org/10.17623/BZGA:Q3-ALKSY21-DE-1.0
[92] McNeill, A, Simonavičius, E, Brose, LS, Taylor, E, East, K, Zuikova, E, Calder, R and Robson, D (2022). Nicotine vaping in England: an evidence update including health risks and perceptions, September 2022. A report commissioned by the Office for Health Improvement and Disparities. London: Office for Health Improvement and Disparities.
[93] Ozaki, Y. et al. (2022) Research to understand the actual situation of lifestyle habits such as smoking and drinking and to improve lifestyle habits, Health, Labour and Welfare Science Research https://mhlw-grants.niph.go.jp/project/162312, (accessed 15 August 2025)
[94] Park JE, Jeong WM, Choi YJ, Kim SY, Yeob KE, Park JH. Tobacco Use in Korea: Current Epidemiology and Public Health Issues. J Korean Med Sci. 2024 Nov;39(45):e328. https://doi.org/10.3346/jkms.2024.39.e328.
[95] Dai, H. (2020). Heated tobacco product use and associated factors among US youth, 2019. Drug and alcohol dependence, 214, 108150.
[96] Puvanesarajah, S., Wang, T., Alexander, D. S., Gomez, Y., Head, S. K., Alexandridis, A. A., ... & Trivers, K. (2022). Awareness and use of heated tobacco products among middle school and high school students, United States, 2019–2020. Nicotine and Tobacco Research, 24(8), 1273-1280.
[97] Cheng, H. G., Vansickel, A. R., & Largo, E. G. (2023). Awareness and use of tobacco products among underage individuals: findings from the Altria Client Services Underage Tobacco Use Survey 2020–2022. BMC Public Health, 23(1), 662.

In all models, the uptake of HTPs among smokers was associated with a decreased prevalence of combusted cigarette use and an increase in LYS.[98,99] Based on modeling predicated on HTP use in Italy, simulations projected a lower prevalence of combustible cigarette smoking (4.7% vs. 11.3%) and about 10.7 million LYS compared to continued smoking. Similarly, modeling based on HTP use in Japan, found HTP use in place of continued smoking would result in 13 million LYS.[98,99 98]

Research by Camacho et al. (2021a, 2021b), both BAT funded studies, used dynamic and complex models to assess the population health impact of HTPs in Japan and Italy. For one model, tobacco and HTP use data from two cross-sectional surveys done in 3 prefectures (pilot study) in Japan and then extended nationally in 2019, was used in several scenarios to estimate the nominal risk of HTPs relative to smoking, including initiation by never smokers, potential reduction in cessation due to dual use, and the potential additional risk from dual use of HTPs with cigarettes. The authors noted the established totality of evidence that HTP use reduces user exposure to toxicants compared to smoking cigarettes, and *"that reduction in toxicant exposure can be expected to reduce the risk of smoking related diseases."*[98] The second study designed a complex model to evaluate the population health impact of two reduced risk products (ENDS and HTPs) in the overall population of one country that also includes cigarettes. This more complex model evaluated the public health impact of HTPs and ENDS in Italy, using transition rates estimated for HTPs in Japan (from the same survey than the previous Japanese study) and e-cigarettes from Italian and U.S. PATH data, as well as available national smoking and demographic data.[99] Their results suggested that switching from cigarettes to HTPs or ENDS could significantly improve public health by reducing life years lost. The results estimated that switching completely from combusted cigarettes to HTPs would lead to the largest reduction in life years lost due to a lower assumed initiation rate by never smokers, with a projected 10.7 million LYS among Italians compared to a population in which the two smoke-free products were not introduced as alternatives to smoking. [99]

Overall, these studies suggest that switching from cigarettes to HTPs could be beneficial for public health. Modeling results also suggest that the addition of HTPs as a reduced harm tobacco product could benefit population health when used exclusively instead of cigarettes.

## 5. RESPONSIBLE MARKETING AND CONTROLS

Upon renewal of the MRGO, under section 911(g)(2) of the FD&C Act, we intend to continue marketing *IQOS* products in a manner that restricts access by unintended populations, particularly youth. The target audience for such marketing will continue to be legal age current smokers, and we remain focused on providing legal age smokers with a high level of education and guidance to facilitate complete switching.

As shown in **Table 6,** our responsible marketing practices encompass labeling, advertising, marketing, promotion, and other consumer-directed activities. We conform with the requirements and marketing restrictions included in the MGOs and MRGOs, respectively, for those products, and we report to the FDA annually. We also comply with all FDA-mandated marketing rules and regulations, as well as those

[98] Camacho, O. M., Hill, A., Fiebelkorn, S., Jones, J. D., Prasad, K., Proctor, C., & Murphy, J. (2021a). Modeling the population health impacts of heated tobacco products in Japan. Tobacco regulatory science, 7(3), 221-231.
[99] Camacho, O., Hill, A., Fiebelkorn, S., Williams, A., Murphy, J. (2021b). Investigating the Health Effects of 3 Coexisting Tobacco-Related Products Using System Dynamics Population Modeling: An Italian Population Case Study. Front Public Health 2021 Vol. 9 Pages 700473. Accession Number: 34869141 PMCID: PMC8634955 DOI: 10.3389/fpubh.2021.700473.

required by law. Furthermore, we take additional voluntary measures to ensure responsible marketing practices are applied to our entire portfolio of TNPs, including *IQOS* products.

**Table 6. Summary of U.S. Marketing Practices**

| | |
|---|---|
| Brand website access limited to ONLY those confirmed to be 21+ | ✓ |
| Brand website access limited to self-reported current users of TNP | ✓ |
| Brand website e-commerce limited to U.S. states where *IQOS* is sold | ✓ |
| All models and talent are over the age of 35 | ✓ |
| We do **NOT** advertise in publications for general circulation unless its audience is reasonably estimated to be at least 85% adults (21+) | ✓ |
| We do **NOT** engage via email/direct mail with any consumers who aren't confirmed to be 21+ | ✓ |
| We do **NOT** have branded social media advertising accounts on platforms without age-restriction controls | ✓ |
| We do **NOT** pay social media influencers to endorse our products | ✓ |

In addition to our general responsible marketing practices, we provide responsible use of the authorized MRTP claim and only display in the following channels aimed at directly reaching legal-aged adult consumers:


## 6. CONCLUSIONS

The goal of reducing the harm caused by smoking has traditionally relied on preventing smoking initiation and promoting smoking cessation. While smoking cessation is an important pillar of tobacco harm reduction, smoking cessation has proven difficult for many smokers. Consequently, there is an unmet need for additional products to reduce harm and tobacco-related disease for the approximately 30 million Americans who continue to smoke- According to CDC's latest estimates, 11.6% of the population reported using combustible cigarettes.[100]

[100] TOBACCO PRODUCT USE AMONG ADULTS— United States, 2022

The ability to use MRTP claims, like the reduced exposure claim subject of this renewal, to educate adult smokers creates a significant opportunity to accelerate progress in reducing harm associated with combustible tobacco product use. The combined evidence from the original and renewal applications submitted in support of these products demonstrates that *IQOS* products continue to satisfy the requirements of section 911(g)(2) of the FD&C Act. *IQOS* products are appropriate to promote public health 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.

We remain committed to collecting and publishing evidence to emphasize the importance of offering smoke-free alternatives, like *IQOS* products, to reduce harm for adult smokers who do not quit. Given that the postmarket scientific evidence continues to support FDA's original decision to authorize these products as modified risk with the reduced exposure claim, the TPSAC should recommend FDA authorize the MRGO renewal for *IQOS* 2.4, *IQOS* 3.0, *HEETS* Amber, *HEETS* Green, and *HEETS* Blue.