Philip Morris Products S.A. Renewal Modified Risk Tobacco Product Applications

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Agenda

- History of modified risk granted orders (MRGOs) for exposure modification issued to Philip Morris Products S.A. (PMPSA) under Section 911(g)(2) of the Federal Food, Drug, & Cosmetic Act (FD&C Act)
- Summary of PMPSA renewal modified risk tobacco product applications (MRTPAs) under review
- Lines of scientific evidence in renewal MRTPAs

Standard for a 911(g)(2) Exposure Modification Order

The FD&C Act requires FDA to determine if the applicant, among other determinations, has demonstrated that:

- Such an order would be appropriate to promote the public health
- The scientific evidence that is available without conducting long-term epidemiological studies demonstrates that a measurable and substantial reduction in morbidity or mortality among individual tobacco users is reasonably likely in subsequent studies
- The product as actually used by consumers will not expose them to higher levels of other harmful substances compared to similar types of tobacco products on the market, unless such increases are minimal and the reasonably likely overall impact of product use remains a substantial and measurable reduction in overall morbidity and mortality among individual tobacco users
- The advertising and labeling of the modified risk tobacco product (MRTP) enable the public to comprehend the information concerning modified risk and to understand the relative significance of such information in the context of total health and in relation to all the tobacco diseases and health-related conditions associated with the use of tobacco products (section 911(h)(1))

Questions Relevant to the MRTPA Evaluation

These questions are relevant to the evaluation of whether the applicant has met the applicable 911(g)(2) standard for an exposure modification order

- Are the proposed modified exposure claims scientifically accurate?
- Are measurable and substantial reductions in morbidity and mortality among individual tobacco users reasonably likely in subsequent studies?
- How do consumers perceive and understand the modified exposure claims?
- What are the potential benefits and harms to the health of the population as a whole?

IQOS System

The applicant describes the IQOS Tobacco Heating System as a "heat-not-burn tobacco product," consisting of:

- IQOS HeatStick: A filtered non-combusted cigarette containing a tobacco plug. It is designed to function with the IQOS Holder to produce an aerosol when the plug is heated.
- IQOS Holder: The HeatStick is inserted into the Holder which heats the tobacco material by means of an electronically controlled heating blade.
- IQOS Charger: The Charger is used to recharge the Holder after each use.

Components of IQOS Tobacco Heating System

IQOS 2.4 System Holder and Charger	*IQOS* 3.0 System Holder and Charger
	

Figure 2 *Marlboro* Amber *HeatSticks*

Figure 3 *Marlboro* Blue Menthol *HeatSticks*

Figure 4 *Marlboro* Green Menthol *HeatSticks*

Image of IQOS System and packs of HeatSticks from MRTPA section 2.4
Image of individual HeatSticks from FDA Authorizes 3 Marlboro HeatSticks Products | NACS accessed 7.24.2025

History of PMPSA's Exposure Modification Orders

- July 7, 2020: FDA issued four MRGOs (valid for 4 years, until July 2024)
  - IQOS 2.4 System Holder and Charger
  - Marlboro Amber HeatSticks
  - Marlboro Green Menthol HeatSticks
  - Marlboro Blue Menthol HeatSticks
- March 11, 2022: FDA issued one MRGO (valid until July 2024)
  - IQOS 3.0 System Holder and Charger
- July 5, 2023: PMPSA submitted renewal MRTPAs to continue marketing IQOS with the same reduced exposure claim
- May 9, 2024: FDA filed the renewal MRTPAs and began review
- November 22, 2024: FDA issued an Advice/Information Request Letter (AI Letter) to PMPSA asking for clarification about several scientific topics
- December 20, 2024: PMPSA responded to the AI Letter

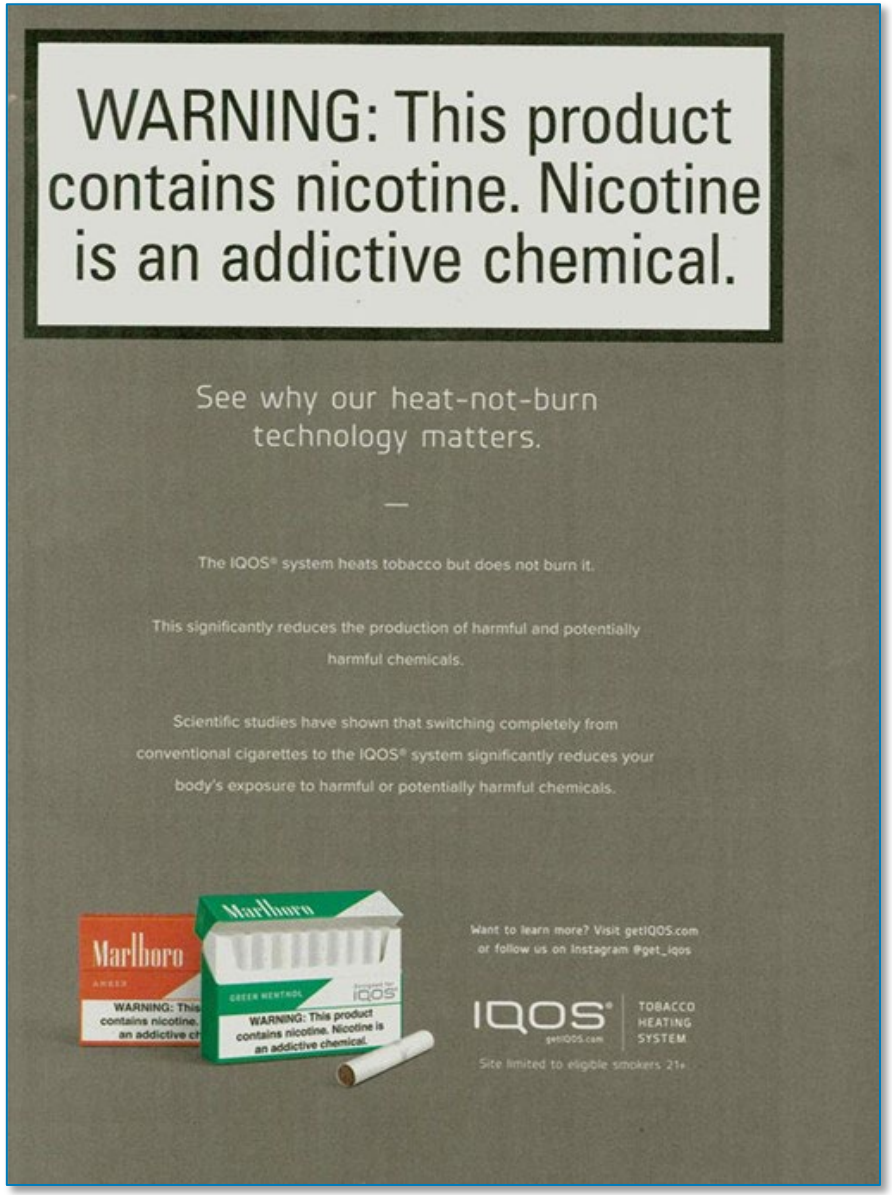
Modified Exposure Claim

AVAILABLE EVIDENCE TO DATE:

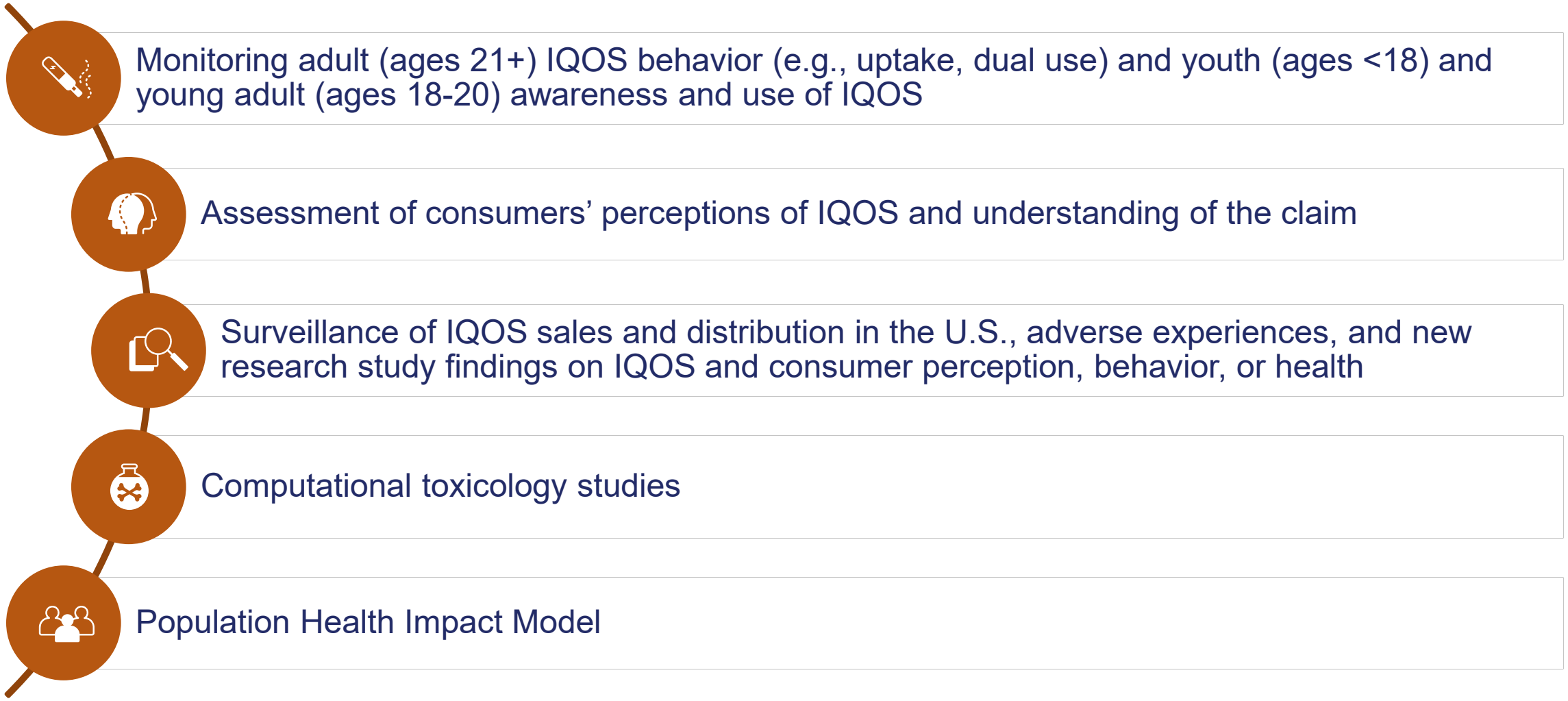
The IQOS system heats tobacco but does not burn it.

This significantly reduces the production of harmful and potentially harmful chemicals.

Scientific studies have shown that switching completely from conventional cigarettes to the IQOS system significantly reduces your body's exposure to harmful or potentially harmful chemicals.

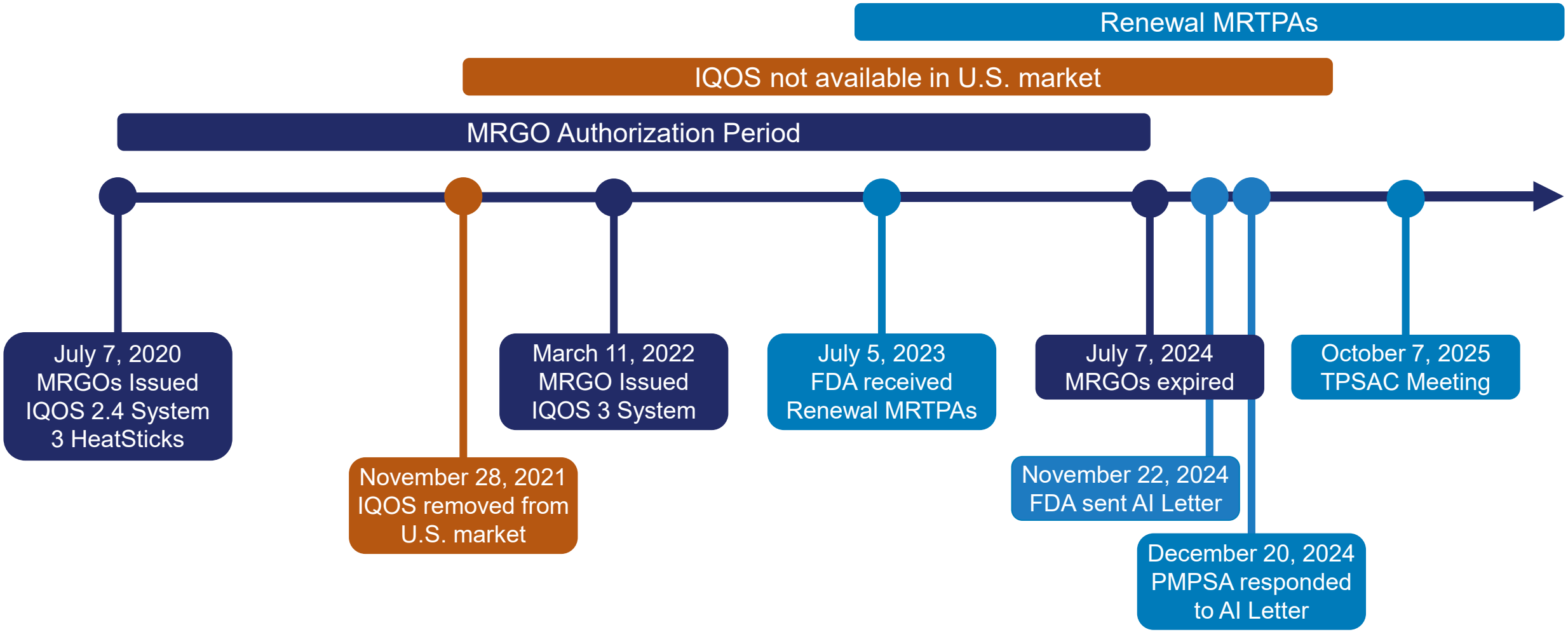


Postmarket Surveillance and Studies (PMSS) Requirements



- Monitoring adult (ages 21+) IQOS behavior (e.g., uptake, dual use) and youth (ages <18) and young adult (ages 18-20) awareness and use of IQOS
- Assessment of consumers' perceptions of IQOS and understanding of the claim
- Surveillance of IQOS sales and distribution in the U.S., adverse experiences, and new research study findings on IQOS and consumer perception, behavior, or health
- Computational toxicology studies
- Population Health Impact Model

Timeline


Renewal MRTPAs
IQOS not available in U.S. market
MRGO Authorization Period
July 7, 2020
MRGOs Issued
IQOS 2.4 System
3 HeatSticks
November 28, 2021
IQOS removed from
U.S. market
March 11, 2022
MRGO Issued
IQOS 3 System
July 5, 2023
FDA received
Renewal MRTPAs
July 7, 2024
MRGOs expired
November 22, 2024
FDA sent AI Letter
December 20, 2024
PMPSA responded
to AI Letter
October 7, 2025
TPSAC Meeting

Adjustments to PMSS

Awareness and Use

- IQOS with Marlboro HeatSticks Cross-sectional Postmarket Adult Consumer Study (PACS)
- IQOS with Marlboro HeatSticks Cohort Postmarket Adult Consumer Study (PACS)
- U.S. IQOS Owners Panel
- Underage Tobacco Use Survey (UTUS)
- Adult Tobacco Consumer Tracker (ATCT)

Perceptions and Understanding

- IQOS with Marlboro HeatSticks Cross-sectional Postmarket Adult Consumer Study (PACS)
- IQOS with Marlboro HeatSticks Cohort Postmarket Adult Consumer Study (PACS)

Computational Toxicology

- 3-Phase Computational Toxicology study assessing the chemicals that were higher in HeatSticks aerosols than combusted cigarettes

Population Health Impact Model

- Updated probabilistic population health modeling to incorporate long-term health impacts, additional functionality, and in-market data sources for the estimation of transition probabilities

No adjustments | Limited data collection | Unable to be completed

Evidence Presented in the Renewal MRTPAs

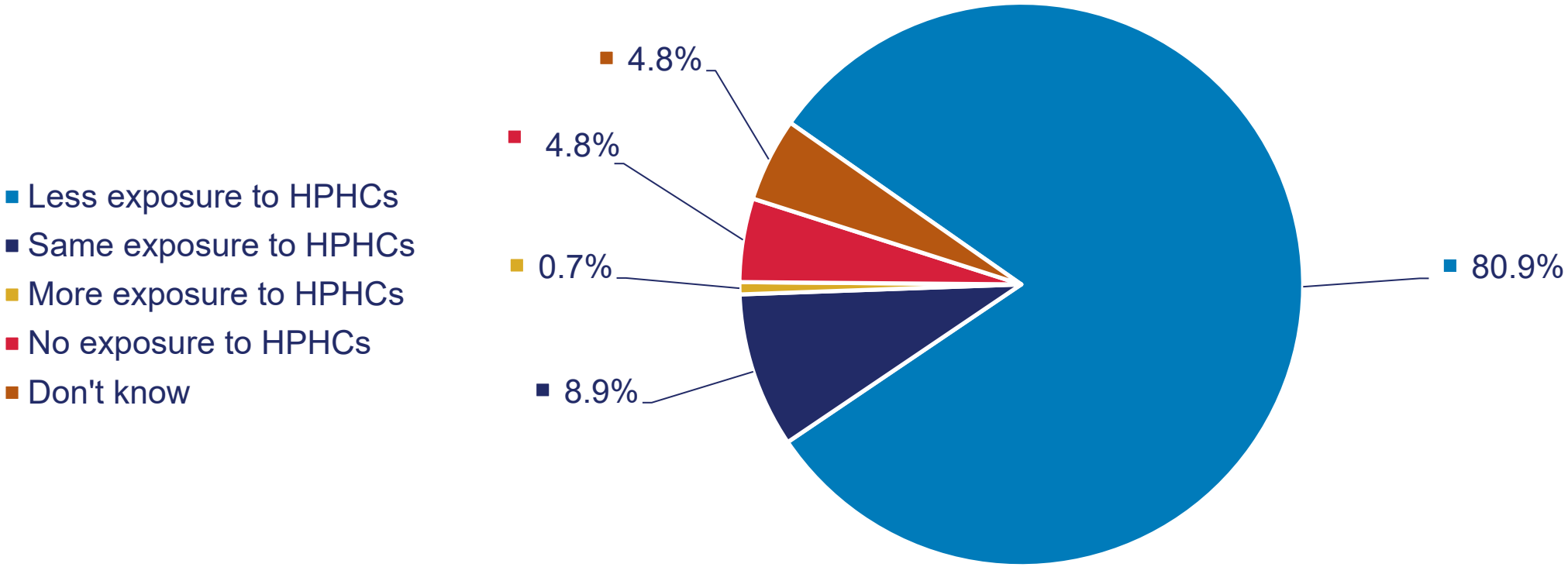
Outline

- Consumer Understanding and Perceptions
- Patterns of IQOS Use
  - Impact on users of tobacco products
  - Impact on non-users of tobacco products including youth
- Health risks of IQOS relative to combusted cigarettes
  - Biomarker and other clinical data
  - Toxicological evidence
    - Constituents
    - Cancer risk
    - Noncancer risks

Consumer Understanding and Perceptions

Findings from 1 Wave of IQOS Cross-sectional PACS (n = 439)

Perceptions of switching completely from cigarettes to IQOS on exposure to HPHCs among current established IQOS users



Patterns of Use: Impact on Users of Tobacco Products

Findings from 1 Wave of IQOS Cross-sectional PACS (n = 439)

IQOS User Demographics

- 98.2% ever established users of tobacco products other than IQOS
- 50.6% formerly used cigarettes; 48.8% currently used cigarettes

Frequency and Intensity of IQOS Use

- 70.4% of current IQOS users used IQOS daily in the past 30 days
  - On those days they used a median of 15 HeatSticks per day
- 29.2% dual used IQOS and cigarettes
- 19.6% poly used IQOS, cigarettes, and one or more other tobacco products

Likelihood of Switching from Cigarettes to IQOS

- Among current IQOS users, 31.2% reported having completely switched from cigarettes to IQOS after first trying IQOS
- 83.1% of current IQOS users who were established users of cigarettes in the 30 days before trying IQOS stated they now smoked fewer cigarettes per day than before trying IQOS

Patterns of Use: Impact on Non-Users of Tobacco Products

2021-2022 Adult Tobacco Consumer Tracker and Underage Tobacco Use Survey

Initiation of IQOS

- Only 3 adult (ages 21+) current users of IQOS (N~28,800)
- Among underage individuals (ages 13-20) (national sample, N~5,195, weighted):
  - 0.4% reported ever use
  - 0.1% reported past 30-day use
- Among underage individuals (ages 13-20) (regional sample where IQOS was available, N~929, weighted):
  - 1% reported ever use
  - 0.2% reported past 30-day use

Summary of Patterns of Use

IQOS Cross-sectional PACS (September - October 2021) demonstrated that

- IQOS is predominately used by people who were ever established combusted cigarette users
- Combusted cigarette use was common among IQOS users, with 48.8% of current established IQOS users using both IQOS and cigarettes
- 31.2% of current IQOS users reported having completely switched from cigarettes to IQOS, based on recall of their past behavior
  - In contrast, evidence submitted with the original MRTPAs found that 7.5% of participants exclusively used IQOS (≥95% HeatSticks use) by the end of a six-week study

Overall, results from the IQOS cross-sectional PACS, ATCT, and UTUS suggested low levels of use among adults and youth, consistent with published literature

Relative Health Risks: Biomarker and Other Clinical Data

U.S. Clinical Study, International Studies, and Cross-study Post-hoc Analyses

Biomarkers of Exposure

- Continued significant reductions in select biomarkers of exposure related to HPHCs at 3, 6, and 12 months

Biomarkers of Potential Harm

- Continued favorable but small changes in biomarkers of potential harm compared to cigarette smoking at month 12
- Clinical significance of these changes is unclear

Relative Health Risks: Nonclinical Studies

Nonclinical Studies Related to the Health Risks of IQOS Use

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- Summary of original MRTPA findings
- IQOS aerosol constituents
- Cancer risk associated with IQOS aerosols
- Literature findings: Noncancer toxic effects
  - In vitro studies
  - In vivo studies
    - Respiratory toxicity
    - Cardiovascular toxicity

Original MRTPA Conclusions from Nonclinical Studies

- The applicant provided data from genotoxicity/carcinogenicity studies for the original MRTPA.
  - IQOS aerosols were genotoxic in mouse lymphoma assays.
  - The applicant's genotoxicity studies did not provide comparative information regarding the genotoxic potency of IQOS aerosols or cigarette smoke.
  - The mouse model used in the applicant's carcinogenicity study had limitations and provided inconclusive results regarding the carcinogenic potential of IQOS aerosols.
- The applicant also provided findings from rodent exposure studies that evaluated noncancer toxic effects of IQOS aerosol exposure for the original MRTPA.
- Overall, data from the nonclinical studies submitted by the applicant suggested that IQOS aerosol had lower toxic potential than cigarette smoke under the conditions used in the assays and for the endpoints measured.
- The applicant's studies had significant limitations that limited stronger conclusions about the relative health risks of using the IQOS system.

IQOS Aerosol Constituents

- In IQOS aerosols, most harmful and potentially harmful constituents (HPHCs) on FDA's established HPHC list are either below the limits of detection or quantification or lower than the levels in cigarette smoke and are 20% - 99.8% lower when compared to normalized nicotine levels. Some of these HPHCs are also found at levels below the limit of detection or quantification in cigarette smoke.
- The applicant identified 80 chemicals not on FDA's established list of HPHCs that are found at higher levels in IQOS aerosols in a Non-Targeted Differential Screening.
- The applicant's Non-Targeted Differential Screening was semi-quantitative, and the absolute quantities of most of these 80 chemicals in IQOS aerosols are unclear.
- The toxic potential of some of these 80 chemicals is poorly characterized.

Post-market Computational Toxicology Study

- In part, the applicant's post-market computational toxicology study evaluated the potential genotoxicity/carcinogenicity of the 80 chemicals found to be higher in IQOS aerosols than in 3R4F reference cigarette smoke.
- This study found that 36 of the 80 chemicals found at higher levels in IQOS aerosols were potentially genotoxic/carcinogenic.
- These findings suggest that cancer risks associated with IQOS aerosols may be higher than initially indicated by information available for the original MRTPA review.

Cancer Risk Evaluation

- The applicant calculated excess lifetime cancer risks (ELCRs) for IQOS aerosols and 3R4F reference cigarette smoke.
  - IQOS was associated with an ELCR of 2,683 per 100,000 users.
  - 3R4F reference cigarettes were associated with an ELCR of 12,244 per 100,000 users.
- However, due to limitations, it is unclear whether the applicant's calculated ELCRs adequately reflect the cancer risk of IQOS aerosols.
- For example, the applicant's ELCR calculations were partly based on semi-quantitative aerosol constituent quantities.

Summary of the Cancer Risk Evidence

- Experimental data indicate that IQOS aerosols can have genotoxic effects but are inconclusive regarding the relative carcinogenic risks of IQOS and cigarettes.
- Findings from the applicant's post-market computational toxicology study suggested that the cancer risks associated with IQOS aerosols may be higher than initially indicated by information available for the original MRTPA review.
- Compared to cigarettes, IQOS aerosols contain lower levels of carcinogens on FDA's established HPHC (harmful and potentially harmful constituent) list, and higher levels of other potential carcinogens/genotoxicants.
  - For example, acetamide, NNK, and vinyl chloride are found at lower levels in IQOS aerosols than cigarette smoke.
  - Other potential carcinogens or genotoxicants, such as 2-furanmethanol and glycidol are found at higher levels in IQOS aerosols than cigarette smoke.

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- Literature findings: Noncancer toxic effects
  - **In vitro studies**
  - In vivo studies
    - Respiratory toxicity
    - Cardiovascular toxicity

Literature Review: In Vitro Findings

35 in vitro studies and 1 ex vivo study evaluated toxic effects of IQOS.

- 18 studies evaluated effects in respiratory cells.
- 5 studies evaluated effects in cardiovascular cells or tissues, such as endothelial cells.
- Most of these studies found that IQOS exposure had less severe toxic effects than cigarette exposure.
- Most of these studies had limitations, such as the use of aerosol or smoke extracts that are not expected to contain all of the constituents in whole smoke or aerosols.
- Comparisons of cell culture media toxicant concentrations to actual toxicant doses in animals or humans are difficult due to effects of the portal of entry, absorption, distribution, metabolism, and excretion on the development of toxicity.

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- Summary of original MRTPA findings
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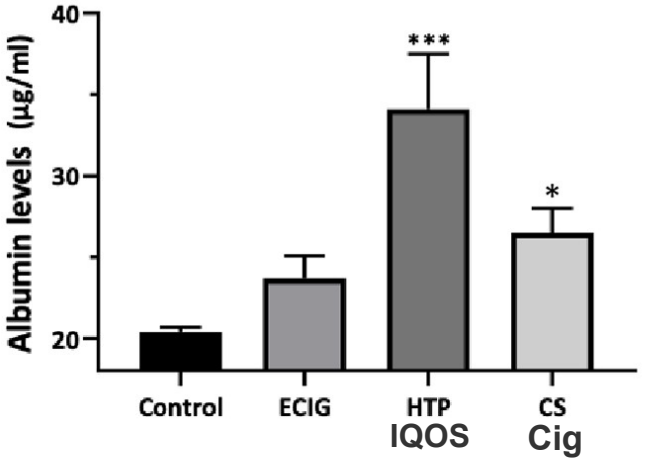
  - In vivo studies
    - **Respiratory toxicity**
    - Cardiovascular toxicity

Findings on Subacute Respiratory Effects

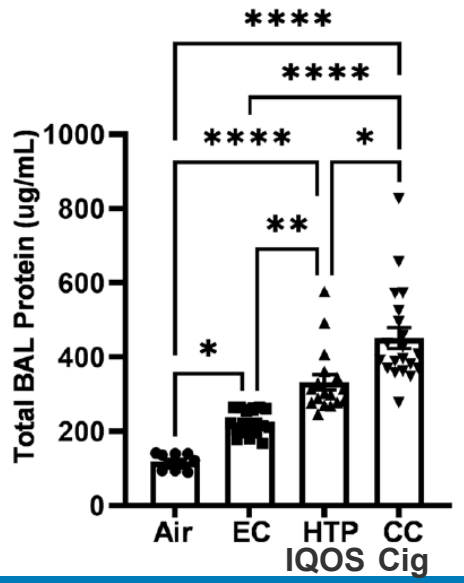
- The literature review performed by toxicology reviewers identified new studies that evaluated respiratory effects of rodent exposures to IQOS aerosols or cigarette smoke for 90 days or less.
- Two studies found that 7-day exposures to cigarette smoke, but not IQOS aerosols, led to increased levels of cell death and reactive oxygen species in the lungs (Daou et al., 2021; Husari et al., 2023). Reactive oxygen species cause oxidative stress, which may contribute to the development of emphysema.
- Four studies included data based on lung histology.
  - Mice exposed to cigarette smoke for 7 days had higher histological inflammation scores than mice exposed to IQOS aerosols (Heluany et al., 2022).
  - Mice exposed to IQOS aerosols for 7 days had patches of alveolar wall edema (Daou et al., 2021). Acute lung injury was observed in mice exposed to cigarette smoke.
  - Mice exposed to IQOS aerosols for 4 weeks had significantly lower histological severity of lung injury than mice exposed to cigarette smoke (Kastratovic et al., 2024).
  - Based on qualitative assessments, mice exposed to IQOS aerosols for 7 days had limited lung injury, while mice exposed to cigarette smoke had more severe lung injury (Husari et al., 2023).

IQOS Aerosol Exposure Led to Increased Lung Vascular Permeability in Studies Published after MRGO Issuance

- Four new studies evaluated protein levels in bronchoalveolar lavage fluid (BAL fluid) in mice exposed to cigarette smoke and IQOS aerosols.
- Increased BAL protein levels are an indication of increased lung vascular permeability, which is associated with lung injury.
- In general, the studies found that IQOS aerosol exposure led to increased BAL protein levels compared to air-exposed mice. Findings regarding the relative effects of IQOS aerosol or cigarette smoke exposure on BAL protein levels indicated that in two studies, IQOS exposure appeared to produce similar or greater effects, while in two other studies, cigarettes generated a higher response.



Female FVB-Tg mice
1 week exposure
(Daou et al., 2021)



Male and female
C57BL/6NCr mice
8 week exposure
(Bhat et al., 2023)

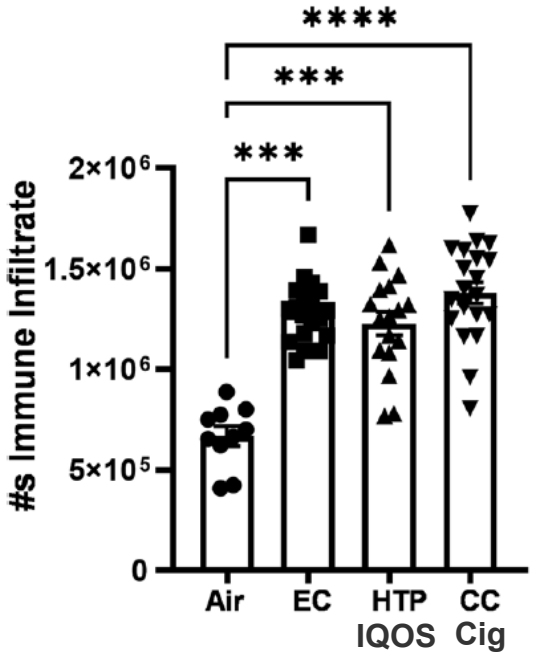
IQOS Aerosol Exposure Led to Increased Levels of Inflammatory Mediators in Bronchoalveolar Lavage Fluid in New Studies

- Two new studies from the same research group evaluated bronchoalveolar lavage fluid (BAL fluid) cytokine levels in mice exposed to cigarette smoke and IQOS aerosols.
- Increased levels of proinflammatory cytokines in BAL fluid are an indication of lung inflammation, which may contribute to the development of emphysema.
- There were no significant differences in the levels of multiple cytokines in mice exposed to IQOS aerosols compared to mice exposed to cigarette smoke.

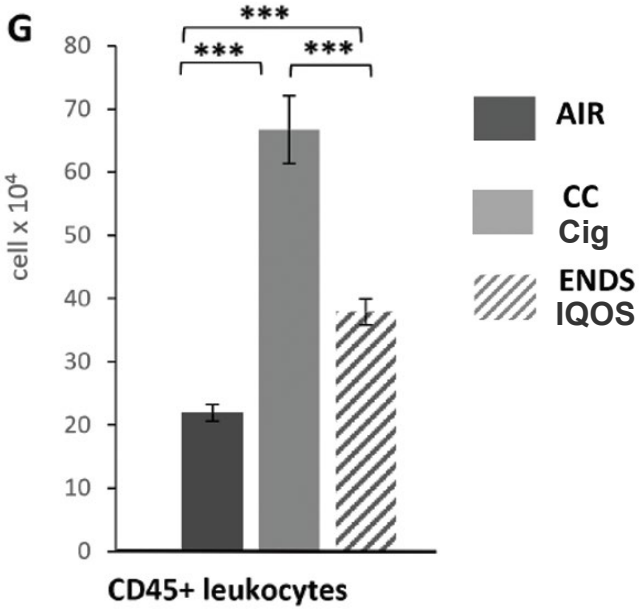
	2 week exposure (Bhat et al., 2021)	8 week exposure (Bhat et al., 2023)
Cig > control IQOS > control No difference between Cig and IQOS	IL-2, TNF-α, IL-9, IL-13, IL-5, RANTES, KC, Eotaxin, MIP1β	IL-6, LIX, G-CSF, KC, VEGF
IQOS > control No difference between Cig and control	IFN-γ	MIP-1α
Cig > control No difference between IQOS and control	IL-6, G-CSF, MIP-1α	Eotaxin, IL-1α, IL-2, MIP-2, IL-9
No difference between control, Cig, IQOS	IL-17A	IP-10, MIP-1β

IQOS Aerosol Exposure Led to Increased Lung Immune Infiltration in Studies Published after MRGO Issuance

- Three new studies evaluated immune infiltration into the lungs in mice exposed to cigarette smoke and IQOS aerosols.
- Increased lung immune infiltration is an indication of lung inflammation, which may contribute to the development of emphysema.
- In general, the studies found that IQOS aerosol exposure led to increased lung immune infiltration compared to air-exposed mice. Findings from these studies did not reveal a clear difference between exposures to IQOS and cigarettes. IQOS exposures had similar effects as cigarettes in two studies, and cigarettes had more severe effects than IQOS in one other study.



Male and female C57BL/6NCr mice
8 week exposure
(Bhat et al., 2023)



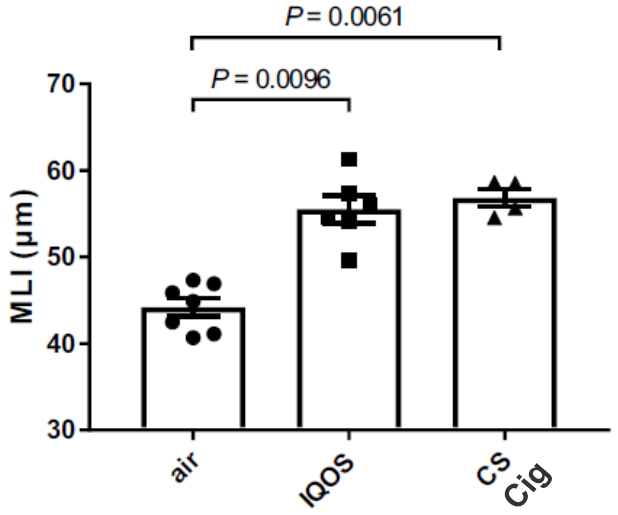
Male and female BALB/c mice
4 week exposure
(Kastratovic et al., 2024)

Findings in Emphysema Studies Published after MRGO Issuance

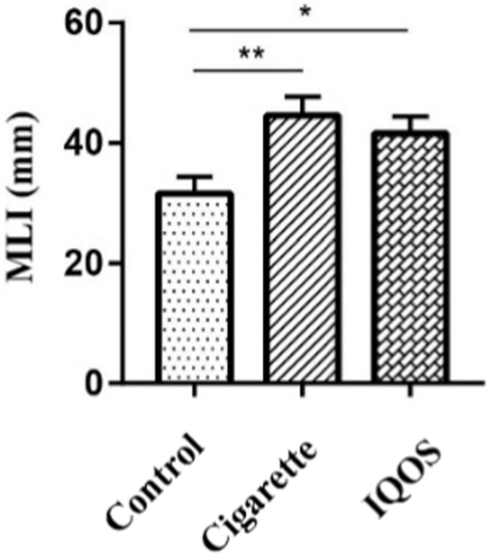
- The literature review performed by toxicology reviewers identified a total of 3 studies that evaluated emphysema in mice exposed to cigarette smoke and IQOS aerosols.
- One study was published by authors affiliated with Philip Morris Products S.A (Wong et al., 2020; Titz et al., 2020). A/J mice were exposed to cigarette smoke or IQOS aerosols for up to 18 months.
- Levels of inflammatory cytokines increased in bronchoalveolar lavage fluid (BAL fluid) from mice exposed to cigarette smoke, but not in mice exposed to IQOS aerosols.
- Mice exposed to cigarette smoke, but not IQOS aerosols, developed histological signs of emphysema when compared to air-exposed mice.
- This study has certain limitations.
  - A/J mice develop spontaneous lung tumors at a high rate, which may confound the evaluation of relative effects related to respiratory toxicity.
  - Based on aerosol data provided by the applicant for the original MRTPA, IQOS contains 66% - 106% higher levels of total particulate matter than cigarettes when normalized to nicotine. However, the exposure atmosphere for IQOS aerosols in this study contained ~53% lower levels of total particulate matter than the exposure atmosphere for cigarette smoke at the same nicotine concentrations. This discrepancy raises the question of whether the IQOS aerosol exposures in this study fully reflected the constituent levels found in IQOS aerosols.

IQOS Aerosol Exposure Led to Histological Emphysematous Changes in New Studies

- In the two other studies, male C57BL/6J mice were exposed to cigarette smoke or IQOS aerosols for 6 months (Nitta et al., 2022; Gu et al., 2023).
- Mice exposed to cigarette smoke or IQOS aerosols developed histological signs of emphysema (Nitta et al., 2022; Gu et al., 2023).



(Nitta et al., 2022)

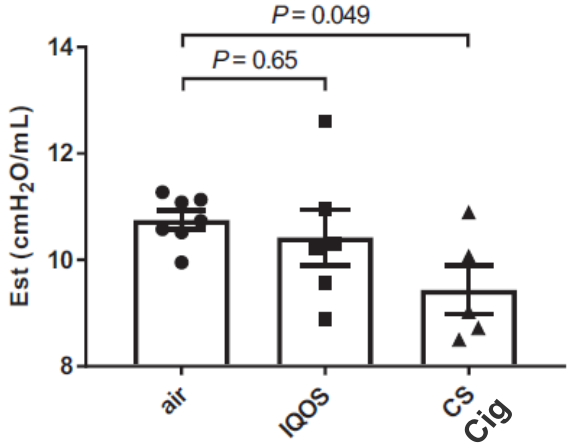


(Gu et al., 2023)

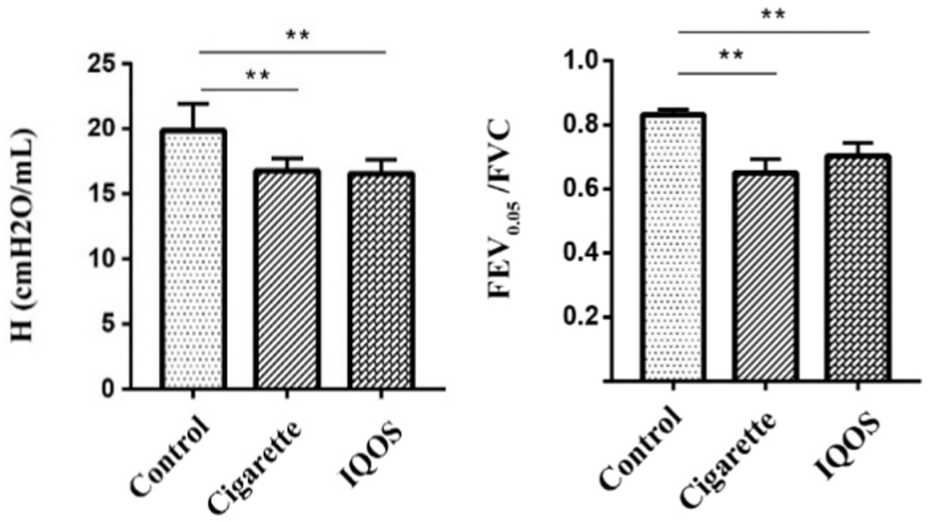
MLI = mean linear intercept

Findings Regarding Emphysematous Lung Function Changes Following IQOS Aerosol Exposure in New Studies

- In Nitta et al., 2022, mice exposed to cigarette smoke for 6 months had significant changes in lung function that are associated with emphysema. Lung function was not significantly altered in mice exposed to IQOS aerosols when compared to air-exposed mice.
- In Gu et al., 2023, mice exposed to cigarette smoke or IQOS aerosols for 6 months had significant changes in lung function that are associated with emphysema. For most of the parameters that were evaluated, there were no significant differences between mice exposed to IQOS aerosols and mice exposed to cigarette smoke.



(Nitta et al., 2022)



(Gu et al., 2023)

Est = static lung elastance
H = tissue elastance
FEV = forced expiratory volume
FVC = forced vital capacity

Study Limitations

- There were histology limitations in Gu et al., 2023 and Nitta et al., 2022 (i.e. no information on whether samples were evaluated by board-certified pathologists, use of small numbers of images for evaluation).
  - These two independent studies had similar histopathology findings.
- Biomarkers of exposure were not evaluated in Gu et al., 2023.
  - Mice in this study were exposed to aerosols generated from 5 HeatSticks or 5 cigarettes, which may have resulted in comparable exposures.
- Although Gu et al., 2023 and Nitta et al., 2022 have limitations, each of these two studies independently found that exposure to cigarette smoke or IQOS aerosols led to similar emphysematous changes.

Respiratory Toxicants in IQOS Aerosols

- Based on one of the HPHC studies provided by the applicant, 18 respiratory toxicants on the established harmful and potentially harmful constituent (HPHC) list are found at 60% -> 99% lower levels in IQOS aerosols than 3R4F reference cigarette smoke on a per stick basis.
  - Examples include acrolein, formaldehyde, and phenol.
- Compared to 3R4F reference cigarette smoke, IQOS aerosols contain higher levels of potential respiratory toxicants that are not on the established HPHC list.
  - Examples include propylene glycol, glycerol, glycidol, and butylated hydroxytoluene.
  - The absolute quantities of most of the constituents that are higher in IQOS aerosols are unclear.

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- Summary of original MRTPA findings
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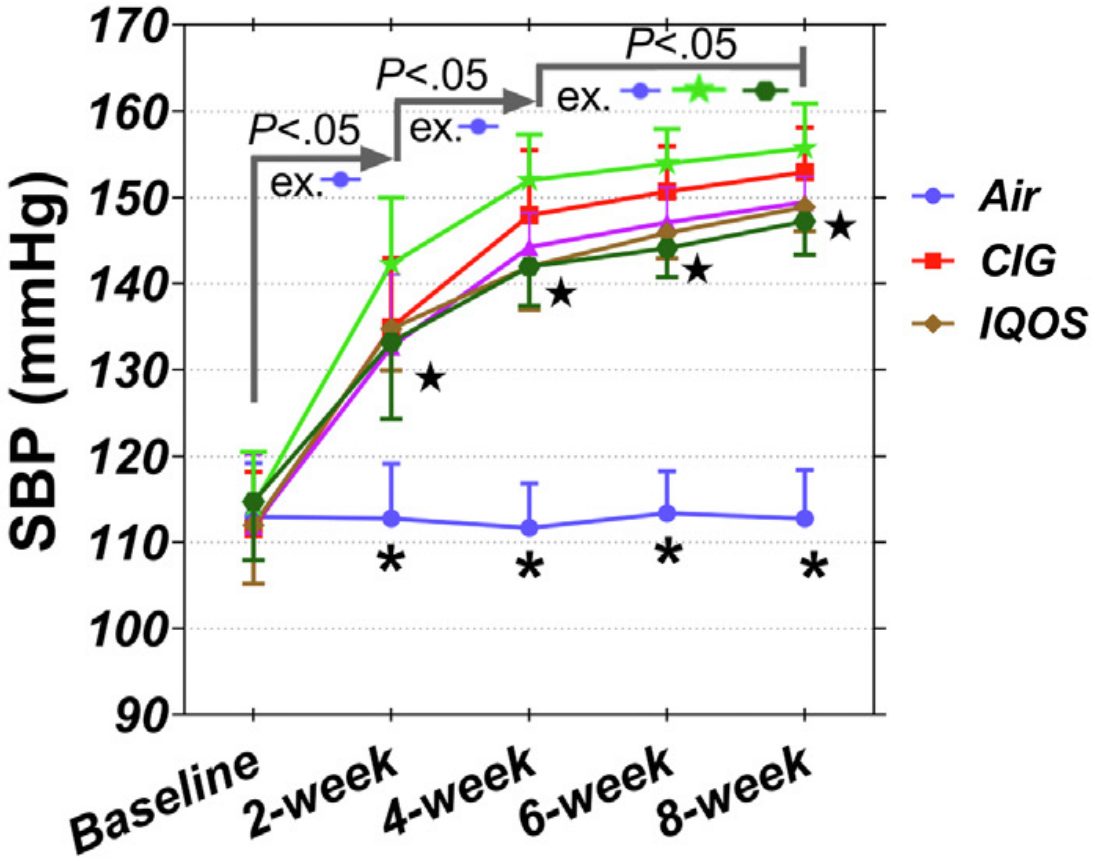
- Cancer risk associated with IQOS aerosols
- Literature findings: Noncancer toxic effects
  - In vitro studies
  - In vivo studies
    - Respiratory toxicity
    - **Cardiovascular toxicity**

IQOS Aerosol Exposure Led to Increased Blood Pressure in a Study Published after MRGO Issuance

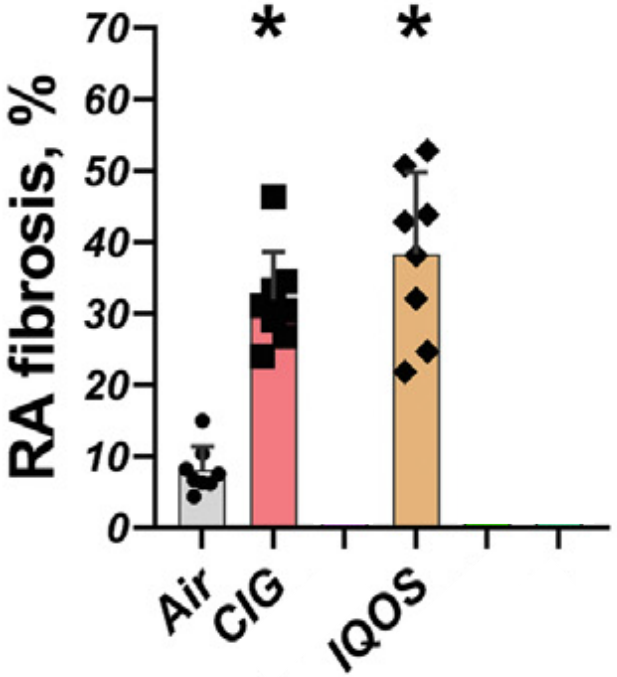
- The literature review performed by toxicology reviewers identified a total of 2 studies in animals that evaluated cardiovascular toxicity.
- One study found that exposure to cigarette smoke or IQOS aerosols led to impaired flow-mediated dilation in rats (Rao et al., 2022).
- In another study from the same research group, male and female Sprague-Dawley rats were exposed to cigarette smoke, IQOS aerosols, or other aerosols during 5 minutes daily for 8 weeks (Qiu et al., 2022).
- Systolic blood pressure increased in rats exposed to cigarette smoke or IQOS aerosols (Qiu et al., 2022).

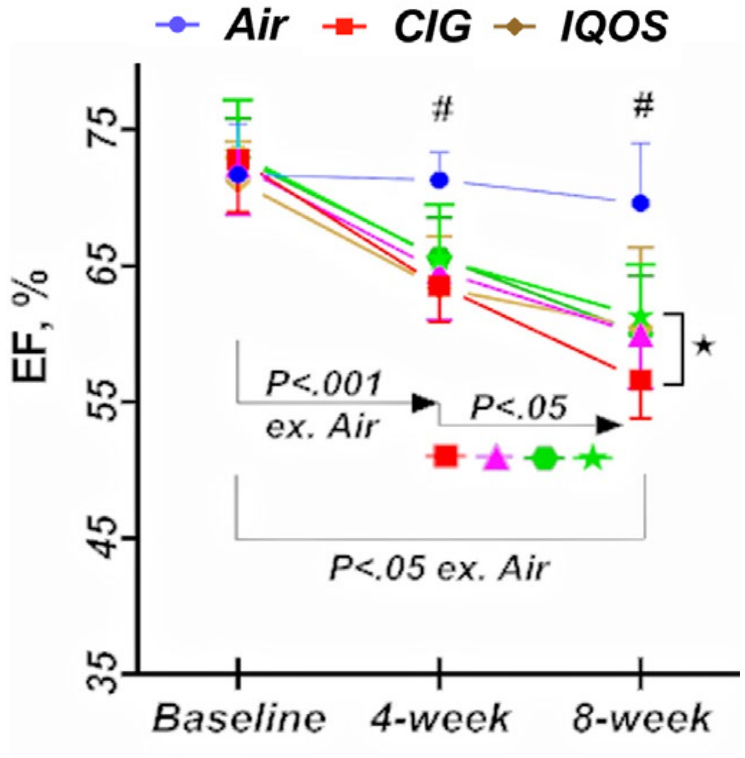


SBP = systolic blood pressure
(Qui et al., 2022)

IQOS Aerosol Exposure Led to Fibrosis and Decreased Ejection Fraction in a Study Published after MRGO Issuance

- Exposure to IQOS aerosols or cigarette smoke led to cardiac fibrosis and decreased ejection fractions.
- Exposure to cigarette smoke or IQOS aerosols led to hypertension, cardiac fibrosis, and impaired cardiac function.
- This study did not include measurements of biomarkers of exposure.





RA = right ventricle
EF = ejection fraction
Sprague-Dawley rats
(Qiu et al., 2022)

Cardiovascular Toxicants in IQOS Aerosols

- Based on one of the HPHC studies provided by the applicant, 7 cardiovascular toxicants on the established harmful and potentially harmful constituent (HPHC) list are found at 89% - 99% lower levels in IQOS aerosols than 3R4F reference cigarette smoke on a per stick basis.
  - Examples include benzene, lead, and hydrogen cyanide.
- IQOS aerosols contain higher levels of other potential cardiovascular toxicants than 3R4F reference cigarette smoke.
  - Examples include glycidol and 3-chloro-1,2-propanediol.
  - The absolute quantities of most of the constituents that are higher in IQOS aerosols are unclear.

Additional Literature Review Findings

- 1 animal study evaluated developmental toxicity.
  - 5-week old male CD-1 mice that had been prenatally exposed to IQOS aerosols on days 7 and 14 of gestation had significantly increased levels of seminiferous tubule damage and reduced daily sperm production. These effects were not seen in mice that were prenatally exposed to cigarette smoke.
  - These effects were transient, and no significant differences were observed between any of the exposure groups in 15-week old male mice.
- 7 additional animal studies evaluated effects of exposure to IQOS aerosols, but did not include animals exposed to cigarette smoke for comparison. Therefore, it was unclear how the toxic effects of IQOS aerosol exposures in these studies compare to the effects of cigarette smoke exposure.
- 2 animal studies evaluated immunotoxic effects of IQOS aerosols and cigarette smoke. For most of the endpoints that were evaluated, IQOS aerosol exposure had less severe effects than cigarette smoke exposure.

Overall Summary

- The applicant's post-market computational toxicology study suggested that cancer risks associated with IQOS aerosols may be higher than initially indicated by information available for the original MRTPA review. The lack of clear absolute quantities for most of the IQOS constituents that are not present or present at lower levels in cigarettes prevents the calculation of an excess lifetime cancer risk (ELCR) that encompasses the overall cancer risk associated with IQOS.
- Studies published after the issuance of the MRGO evaluated respiratory, reproductive/developmental, and cardiovascular toxic effects of exposure to IQOS aerosols and cigarette smoke.
- Compared to cigarettes, IQOS aerosols contain lower levels of most HPHCs on FDA's established list. IQOS aerosols also contain higher levels of other potential toxicants that are not on FDA's established list than cigarettes. Examples include glycerol, glycidol, butylated hydroxytoluene, and 2-furanmethanol.

Overall Conclusions about Relative Health Risk

- Evidence continues to support the modified exposure claim that “Scientific studies have shown that switching completely from conventional cigarettes to the IQOS system significantly reduces your body’s exposure to harmful or potentially harmful chemicals.”
- The overall long-term relative health risks of IQOS compared to cigarettes are still largely unknown.
- The new computational toxicology study identifies 36 potentially genotoxic/carcinogenic compounds found at higher levels in IQOS aerosol than in RCS.
- Several studies that were published after the MRGOs raise questions about the toxic effects of the complete IQOS aerosol mixture in rodent models.

Questions to the Committee

Discussion Questions for TPSAC: IQOS and Nonclinical Toxicity Evidence

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

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

Discussion Questions for TPSAC: Totality of Evidence and Long-term Disease Risk

- **Background:** There is evidence of large overall reductions in harmful and potentially harmful constituents (HPHCs) in IQOS aerosols compared to combusted cigarette smoke; however, newly available nonclinical data from predictive computational toxicology studies and rodent models raise questions about the genotoxic and noncancer toxicological effects of exposure to IQOS aerosols.
- **Consider** the totality of the toxicological evidence that is now available and **discuss** the implications for long-term disease risks of exposure to IQOS aerosols relative to combusted cigarettes.

Discussion Questions for TPSAC: IQOS Patterns of Use

- **Background:** The applicant was unable to conduct all planned postmarket studies, including the cohort study designed to evaluate the impact of marketing IQOS with the modified risk claim on tobacco product use behavior. Accordingly, FDA received limited evidence regarding the impact of marketing IQOS with the claim on patterns of tobacco use.
- **Discuss** the likely patterns of IQOS use behavior when marketed as an MRTP in the U.S. Based on the available evidence, **consider** the likely patterns of use with a specific focus on the likelihood that people who use combusted cigarettes will switch completely to IQOS and the likelihood that they will dual use IQOS and combusted cigarettes.