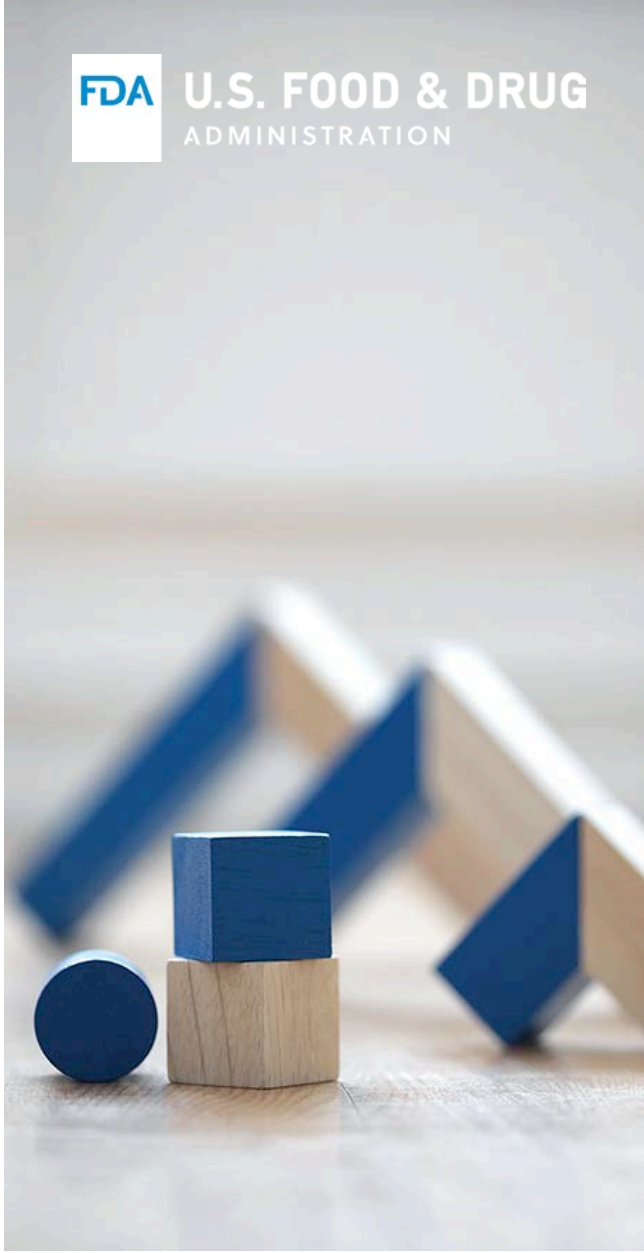
EVIDENCE RELATED TO THE HEALTH RISK OF *IQOS* USE

EVALUATION OF PRODUCT CHEMISTRY

Presented by
Karina Zuck, PhD
Chemist
Office of Science
Center for Tobacco Products
U.S. Food and Drug Administration

Disclaimer: This is not a formal dissemination of information by FDA and does not represent Agency position or policy.



DISCLAIMER

The information in these materials is not a formal dissemination of information by FDA and does not represent agency position or policy. The information is being provided to TPSAC to aid in its evaluation of the issues and questions referred to the committee.

This presentation contains information prepared by the FDA for the members of the TPSAC. The presentation describes assessments and/or conclusions and recommendations written by individual FDA reviewers. Such conclusions and recommendations do not necessarily represent the final position of the individual reviewers, nor do they necessarily represent the final position of the Review Division or Office. This presentation may not include all issues relevant to FDA's decision on the applications and instead is intended to focus on issues identified by FDA for discussion by TPSAC. The FDA will not make its determination on the issues at hand until input from TPSAC and from the public comments has been considered and all FDA reviews have been finalized. FDA's determination may be affected by issues not discussed at the TPSAC meeting.

OUTLINE

- Summary of evidence from applicant
- FDA preliminary assessment

IQOS DESCRIPTION

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

- *IQOS HeatStick*
- *IQOS* Holder
- *IQOS* Charger

HEATSTICKS INGREDIENTS

- The tobacco blend in the *HeatSticks* includes only reconstituted tobacco
- Combusted cigarettes typically include tobacco leaf (e.g., flue cured, burley, oriental tobacco leaf), expanded tobacco, and reconstituted tobacco
- The *HeatSticks* contain the humectants glycerol (52.3 mg/*HeatStick*) and propylene glycol (2.04 - 2.57 mg/*HeatStick*)

OVERVIEW OF AEROSOL AND TOBACCO FILLER TESTING

Analytical Studies Submitted:

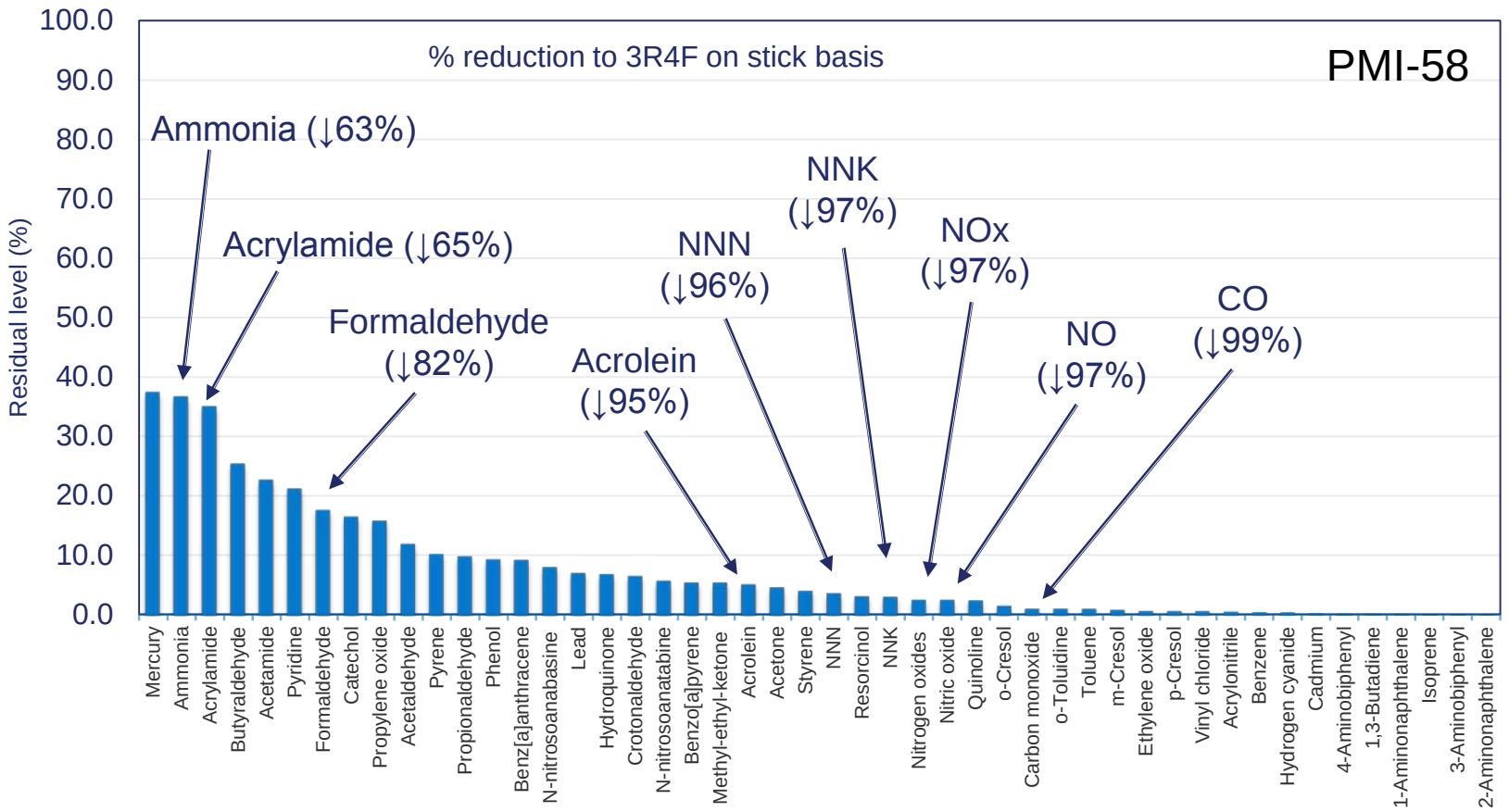
1. “PMI-58”: yields of glycerol, nicotine, tar, TPM, and water; plus 54 HPHCs (“modified” Canadian Intense regimen)
2. Non-Targeted Differential Screening: constituents present in the aerosol of the IQOS at higher concentrations than in the smoke of Kentucky reference cigarette 3R4F
3. Tar, Nicotine, Carbon monoxide (TNCO) yields using ISO smoking regimen
4. “FDA 18 + 6”: yields of 18 HPHCs in aerosol (ISO and “modified” Canadian Intense smoking regimens) and 6 HPHCs in tobacco filler

- HPHC: Harmful and Potentially Harmful Constituents

HPHC TESTING IN “PMI-58”

- “PMI-58” data includes yields of 54 HPHCs in the aerosol of the three *HeatSticks*
- The applicant compared the quantity of each HPHC in the *HeatSticks* with data obtained from the Kentucky reference cigarette 3R4F. The comparison is performed per unit (quantity in aerosol of *HeatSticks* vs. quantity in mainstream cigarette smoke)
- Aerosol generated using “modified” Canadian Intense smoking regimen. The method is modified because the *HeatSticks* have no ventilation holes to block. Modified Canadian Intense smoking regimen: Puff volume: 55 mL, puff frequency: 30 s, duration: 2 s, vents: no vent blocking applied

HPHC REDUCTION COMPARED TO KENTUCKY REFERENCE CIGARETTE 3R4F



Marlboro HeatSticks. Similar graphs are obtained for *Marlboro Smooth Menthol HeatSticks* and *Marlboro Fresh Menthol HeatSticks*

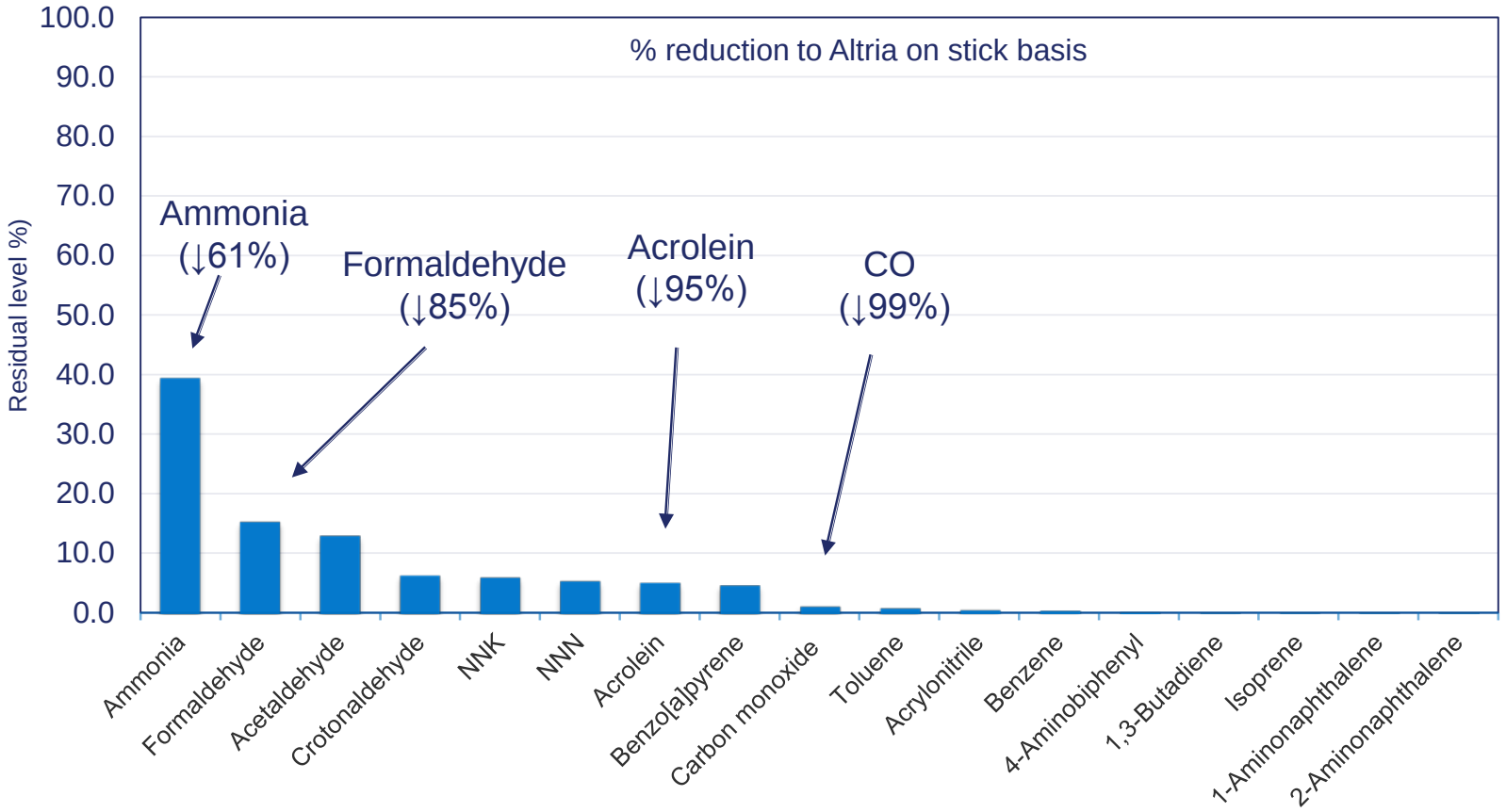
NNN: N-Nitrosonornicotine
NNK: 4-(Methyl-nitrosamino)-1-(3-pyridyl)-1-butanone

Data Source: Section 3.3.2 of MRTPAs

HPHC LEVEL COMPARISON BETWEEN THE *HEATSTICKS* AND PHILIP MORRIS U.S. MARKET

- The applicant compared the quantity in aerosol of 18 HPHCs from the PMI-58 dataset with the median quantity in mainstream smoke from 31 Philip Morris USA cigarettes.

HPHC REDUCTION COMPARED TO PHILIP MORRIS U.S. MARKET



Marlboro HeatSticks. Similar graphs are obtained for *Marlboro Smooth Menthol HeatSticks* and *Marlboro Fresh Menthol HeatSticks.*

Data Source: Section 6.1.1.3.4 of MRTPAs

NICOTINE LEVEL IN THE AEROSOL OF THE *IQOS*

- "PMI-58" includes nicotine level in the aerosol of the three *HeatSticks* by "modified" Canadian Intense smoking regimen

- Nicotine level is 1.29 mg/*HeatStick* in *Marlboro HeatSticks,* 1.19 mg/*HeatStick* in *Marlboro Smooth Menthol HeatSticks,* and 1.17 mg/*HeatStick* in *Marlboro Fresh Menthol HeatSticks*

- Nicotine level in the Kentucky reference cigarette 3R4F is 1.74 – 1.93 mg/cigarette

- Nicotine level in the mainstream smoke of 31 Philip Morris USA cigarettes is 1.06 – 3.35 mg/cigarette

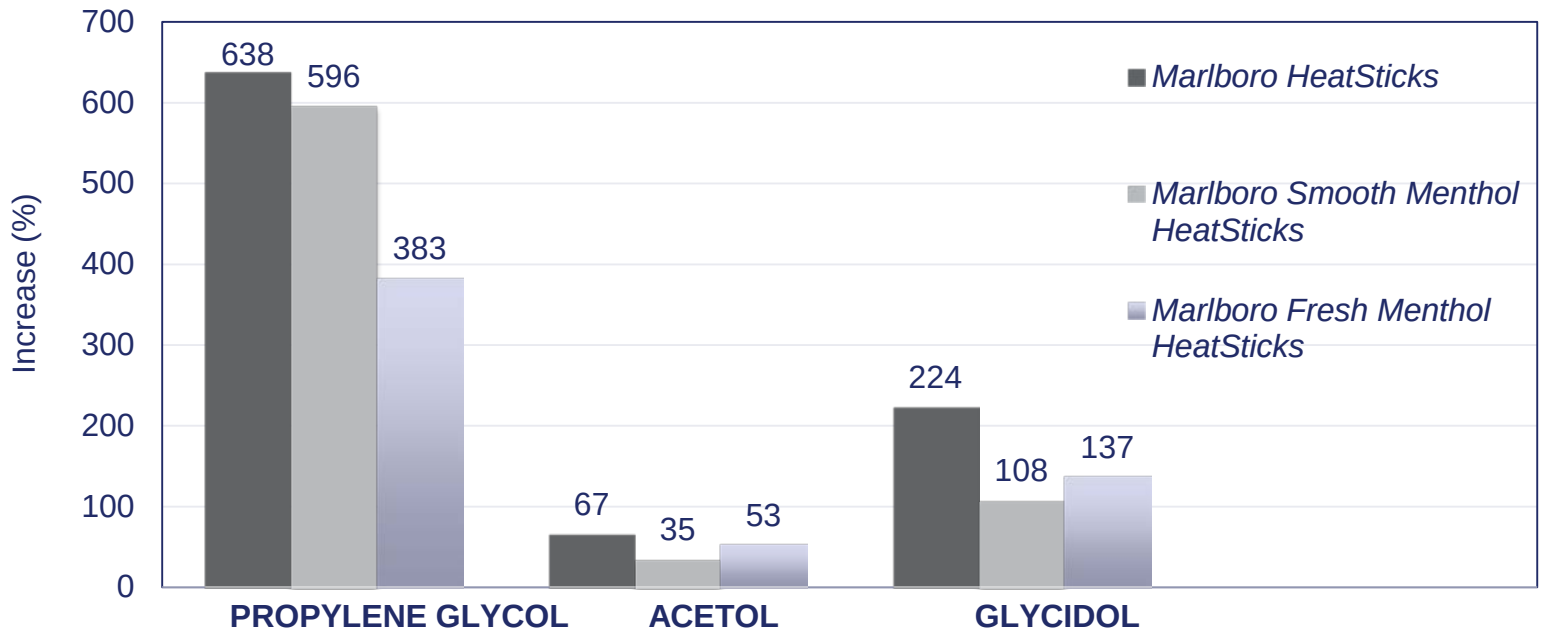
NON-TARGETED DIFFERENTIAL SCREENING

- The applicant states that the goal is to identify and semi-quantify any constituent present in the aerosol of the *HeatSticks* at higher concentration compared to the smoke of Kentucky reference cigarette 3R4F
- Aerosol generated by “modified” Canadian Intense smoking regimen. Analysis performed by GCxGC-TOFMS* and LC-HRAM-MS** in full scan modes. Semi-quantification based on the relative peak areas
- The applicant lists 53 compounds in the *Marlboro HeatSticks*, 58 compounds in the *Marlboro Smooth Menthol HeatSticks*, and 61 compounds in the *Marlboro Fresh Menthol HeatSticks* with higher quantities in the aerosol of the *Heatsticks* compared to mainstream smoke of Kentucky reference cigarette 3R4F
- The compounds listed include menthol related constituents, alkaloids, and flavors

*GCxGX-TOFMS: Two dimensional Gas Chromatography Time-Of-Flight Mass Spectrometry

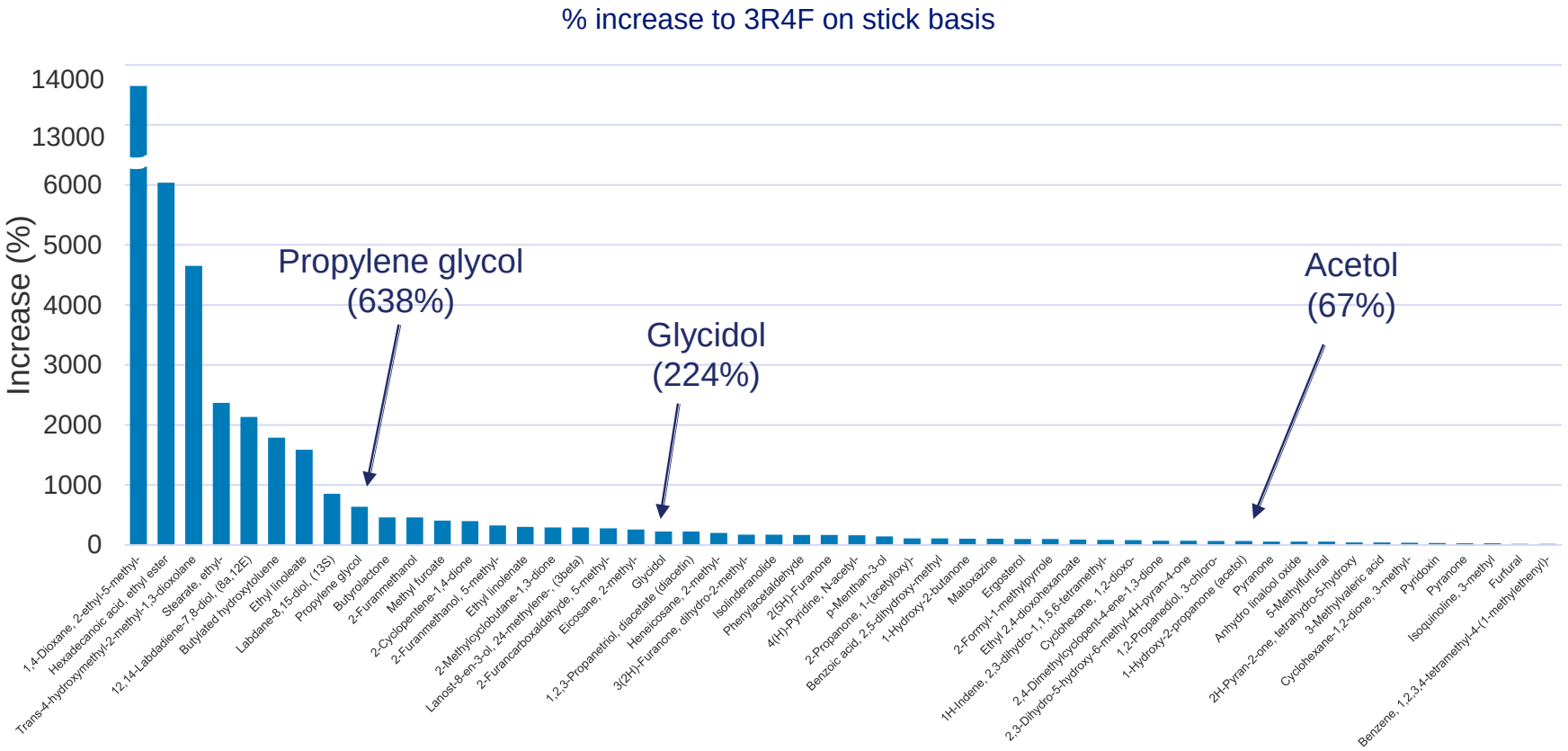
**LC-HRAM-MS: Liquid Chromatography High Resolution Accurate Mass Spectrometry

SELECT COMPOUNDS INCREASED IN *IQOS* AEROSOL COMPARED TO KENTUCKY REFERENCE CIGARETTE 3R4F



Data source: MRTPAs amendment submitted December 8, 2017

COMPOUNDS INCREASED COMPARED TO KENTUCKY REFERENCE CIGARETTE 3R4F



Marlboro HeatSticks. Similar graphs are obtained for *Marlboro Smooth Menthol HeatSticks* and *Marlboro Fresh Menthol HeatSticks*

Data source: MRTPAs amendment submitted December 8, 2017

TNCO AND HPHC INDEPENDENT TESTING

- Independent testing was conducted at FDA's Southeast Tobacco Laboratory (STL) to verify the applicant's data
- Analytical testing of tar, nicotine, acrolein, formaldehyde, and benzo[a]pyrene in mainstream aerosol and ammonia, NNN, and NNK in the tobacco filler. The analytes tested were selected based on characteristics, such as constituents produced in mainstream cigarette smoke compared to similar constituents produced in the aerosol of *HeatSticks*
- The applicant used a 20-port linear smoking machine while an e-cigarette smoking machine was used by the independent laboratory
- The levels of acrolein, formaldehyde, and benzo[a]pyrene measured by STL are higher compared to the values reported by the applicant, but significantly lower than the levels in the Kentucky reference cigarette, 3R4F. A reduction of >90% is observed for acrolein and benzo[a]pyrene, and >77% for formaldehyde in the *HeatSticks* compared to Kentucky reference cigarette 3R4F

TNCO AND HPHC INDEPENDENT TESTING

MRTPA	Analytes	Matrix/ Smoking regimen	PMP SA data			STL# results	Difference between PMP and STL data (%)
			FDA 18 + 6	PMI-58	3R4F		
Marlboro HeatSticks	Tar (mg/stick)	Aerosol/ HCI	21.9 – 23.7	19.4	25.0	15.1	↓28
	Nicotine (mg/stick)		1.15 – 1.19	1.29	1.74	1.25	0
	Acrolein (µg/stick)		8.9 – 11.5	8.3	158	12.25	↑24
	Formaldehyde (µg/stick)		13 – 14	14.1	85.2	19.6	↑45
	NNN (ng/stick)	Tobacco filler	88.4-104	-		86.3	↓10
	NNK (ng/stick)		44.9-47.7	-		38.6	↓15
	Ammonia (µg/stick)		105-111	-		130.1	↑20
Smooth Menthol HeatSticks	Acrolein (µg/stick)	Aerosol/ HCI	8.4-10.3	9.8	157	10.1	0
	Formaldehyde (µg/stick)		13.8-14.1	15.2	79.4	18.7	↑29
	Ammonia (µg/stick)	Tobacco filler	105-113	-		123.3	↑13
Fresh Menthol HeatSticks	Benzo[a]pyrene (ng/stick)	Aerosol/ HCI	0.51-0.55	0.45	14.4	0.99	↑98
	NNN (ng/stick)	Tobacco filler	65-68	-		81.4	↑22
	NNK (ng/stick)		51-54	-		40.0	↓24

*#STL: Southeast Tobacco Laboratory

REVIEW OF PUBLISHED LITERATURE

- Auer *et al*. (2017): reported lower reduction of acrolein (18%) and formaldehyde (26%) in the aerosol of the *HeatSticks* than the reduction reported by the applicant. In addition, reported high quantity of acenaphthene (295%).
- Bekki et al. (2017): found carbon monoxide (99%), NNN (90-94%), and NNK (87-95%) lower in the aerosol of *HeatSticks* compared to the reference cigarettes 3R4F and 1R5F
- Savareear *et al.* (2017), British American Tobacco: reported 205 compounds in the aerosol of *HeatSticks*, including flavor and fragrance agents, humectants, natural substances, and a plasticizer. The paper lists 82 compounds that were not previously reported in cigarette smoke. From those 82 compounds, 43 compounds were previously reported in tobacco filler but not in cigarette smoke.

SUMMARY

- According to the applicant, 54 HPHCs are 54-99.9% lower in the *IQOS* system when compared per unit (*HeatStick* vs. cigarette).
- FDA's independent testing found lower levels of selected HPHCs in the aerosol of the *HeatSticks* compared to mainstream cigarette smoke.
- The applicant reported 53 compounds in the *Marlboro HeatSticks*, 58 compounds in the *Marlboro Smooth Menthol HeatSticks*, and 61 compounds in the *Marlboro Fresh Menthol HeatSticks* with higher quantities in the aerosol of the *HeatSticks*. Compounds other than HPHCs, such as glycidol, acetol, and propylene glycol, are higher in the aerosol of the *HeatSticks* compared to the mainstream cigarette smoke of the Kentucky reference cigarette 3R4F.

CLARIFYING QUESTIONS?