

A Proposed Approach for Evaluating Harm
Reduction in Adult Smokers after Switching from
Cigarettes to Tobacco Heating System (THS):
Biomarkers of Potential Harm

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PMI's Director Clinical Research & Execution

[Harm Reduction](#)

[Tobacco and sugar: Is there a third way](#)

12 December 2020

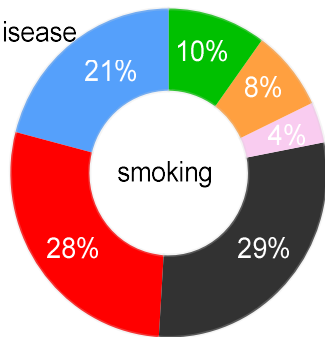


PMI SCIENCE
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Tobacco Harm Reduction in Adult Smokers

- lung cancer
- COPD (chronic obstructive pulmonary disease)
- other diagnosis
- other cancers
- ischemic heart disease
- stroke



number of deaths attributable to smoking per disease type

Smokers

Smoking cessation is the gold standard for reducing risk



<https://www.hhs.gov/sites/default/files/2020-cessation-sgr-full-report.pdf>



Former smokers

BUT

Still 1 billion smokers

TOBACCO HARM REDUCTION?

“Tobacco harm reduction has been defined as “minimizing harms and decreasing total mortality and morbidity, without completely eliminating tobacco and nicotine use”.

Institute of Medicine: Clearing the Smoke: Assessing the Science Base for Tobacco Harm Reduction. 2001.

No consensus on how to evaluate harm/risk reduction in the absence of long-term epidemiological data



The Role of Nicotine in Smokers

“It is primarily the toxins and carcinogens in tobacco smoke –not the nicotine –that cause illness and death.”

-NICE Public Health Guidance: Tobacco: Harm Reduction Approaches to Smoking (2013)

Nicotine, though addictive and not risk-free, is not the primary cause of smoking-related diseases



“Nicotine is the core of the problem but also the centerpiece of the solution.”

-Mitch Zeller, director of US FDA's Center for Tobacco Products; Presentation at Food and Drug Law Institute Conference (Washington 26 October 2017)



Public Health
England



FDA

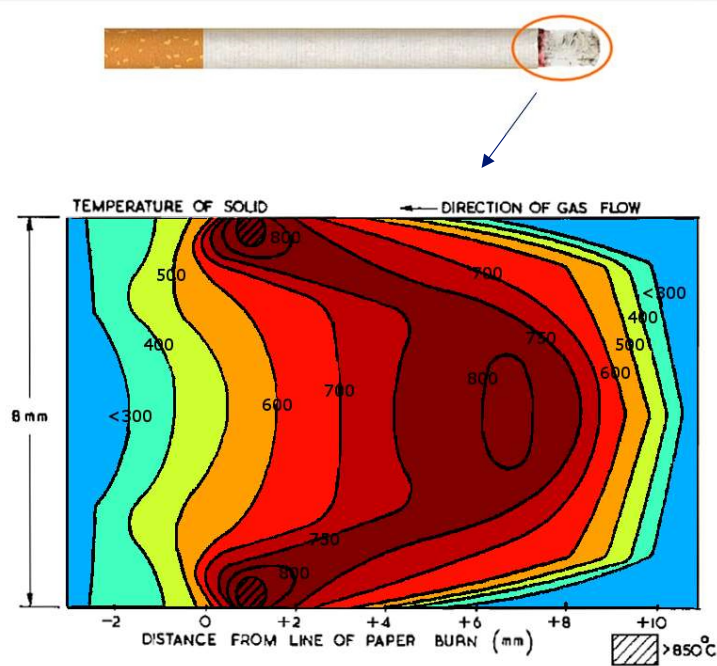


Royal College
of Physicians

NICE National Institute for
Health and Care Excellence



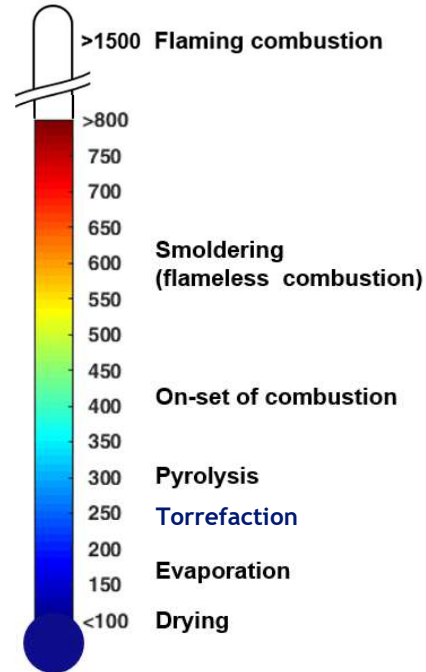
Elimination of Combustion is Key



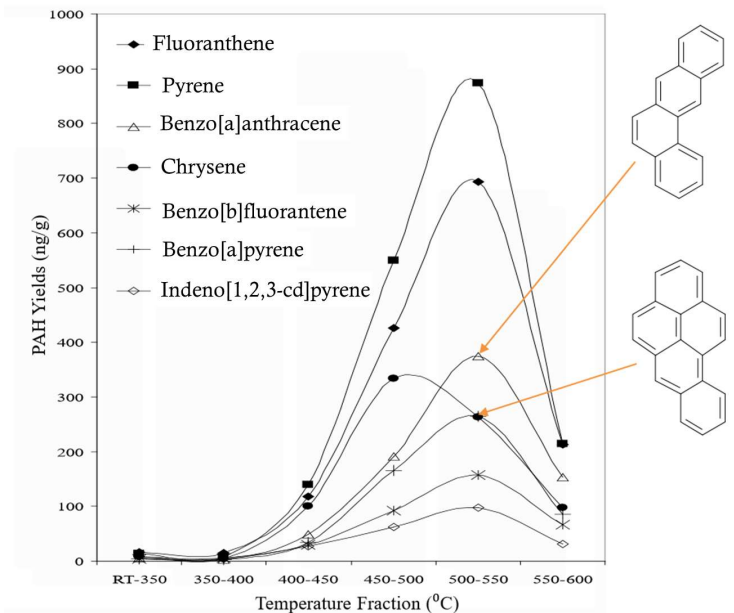
Source: Baker R. R., 1975, Temperature variation within a cigarette combustion coal during the smoking cycle, High Temp. Sci., 7, 236-247. Coloration by PMI.

- More than 6,000 constituents identified in cigarette smoke
- About 100 of these constituents are categorized as harmful or potentially harmful constituents ("HPHC")

Temperature ($^{\circ}\text{C}$)



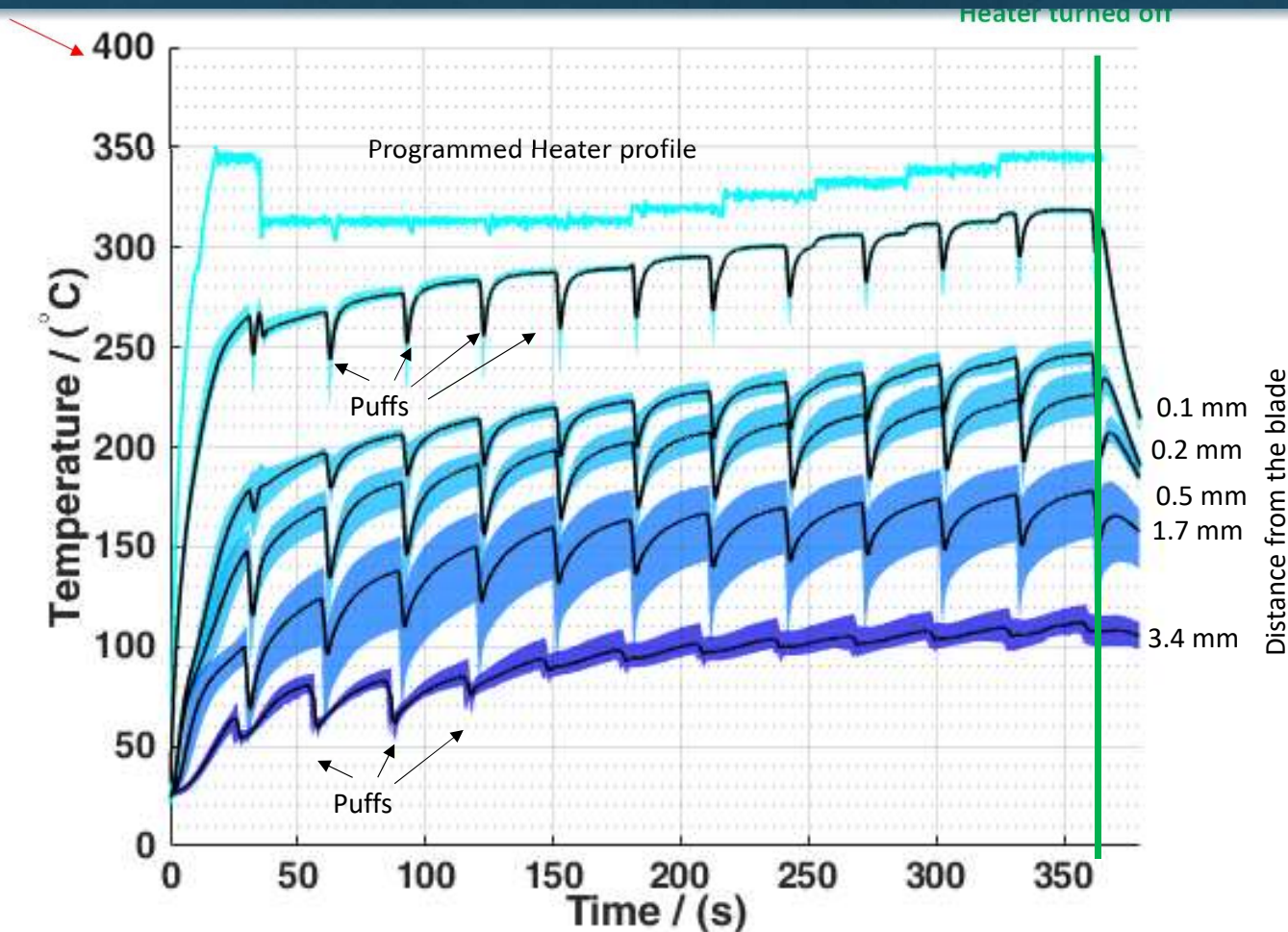
- Scientific studies have shown that, as the temperature of tobacco increases, the levels of harmful chemicals formed increases



Source: McGrath, T.E., Wooten, J.B., Chan W.G. and Hajaligol, M.R., 2007, Formation of polycyclic Aromatic Hydrocarbons from Tobacco: the "Link" between Low Temperature Residual Solid and PAH Formation, Food and Chemical Toxicology, 45,6,1039-1050



Absence of Combustion in the Tobacco Heating System (THS)



The tobacco touching the heater surface reaches a maximum temperature of 320°C, well below the temperatures required for combustion of the tobacco to occur.

Drop in temperature when the heater is stopped while puffing. This indicates that no self-sustaining combustion occurs.

Drop in temperature each time a puff is taken. The system needs to compensate by bringing in heat.



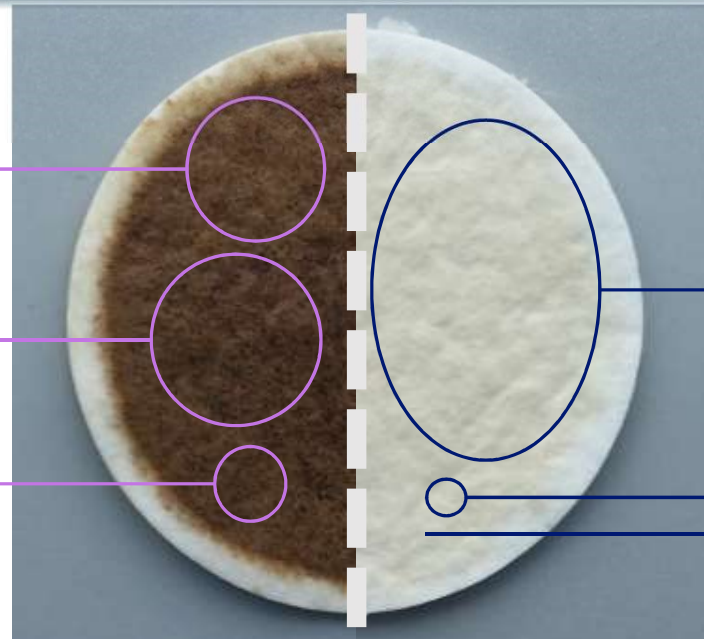
Aerosol Chemistry: Differences Between THS Aerosol and Cigarette Smoke



Water and glycerin form 50% of smoke mass

Toxicants

Contains carbon-based solid particles



Water and glycerin form 90% of aerosol mass

Toxicants reduced by >90%

No carbon-based solid particles



Smoke and aerosol were collected on a Cambridge filter pad in accordance with the Health Canada Intense smoking regimen

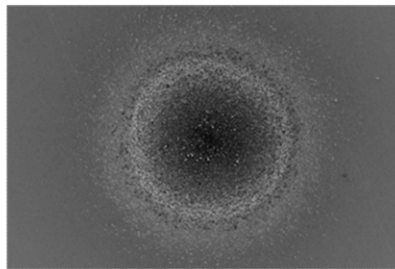
Note: THS stands for Tobacco Heating System and refers to a commercialized version of IQOS

Ghosh D, et al. An improved Cambridge filter pad extraction methodology to obtain more accurate water and "tar" values: In situ Cambridge filter pad extraction methodology. Beiträge zur Tabakforschung/Contributions to Tobacco Research. 2014;26(2):38-49 ([link](#))



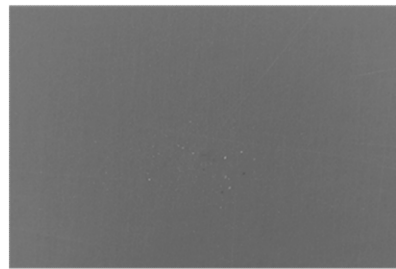
No Carbon-Based Solid Particle Emission in THS

Scanning Electron Microscopy images of the collected smoke/aerosol after passing through a thermodenuder

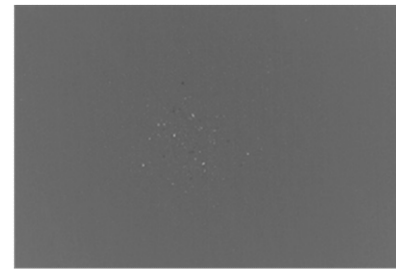


Cigarette smoke

Carbon-based nanoparticles
Median diameter = 75 nm
Amount: 6×10^{11} particle \approx 0.7 mg*



**Blank
(Air)**



THS aerosol
No solid particles



Scanning electron microscopy images of the collected smoke/aerosol, after being passed through a thermodenuder set at 300°C to remove the volatile portion/collected material characterized by electron diffusive X-ray radiography

*Under the Health Canada Intense Smoking regimen.

Pratte et al. *Hum. Exp. Toxicol*, 2017; 36:1115-1120

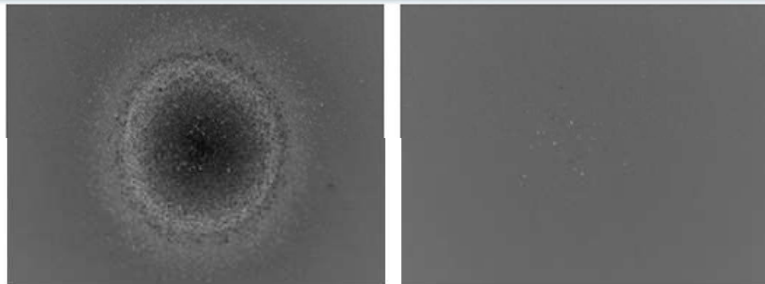
Cohen et al. *Lancet* 2017; 1907-1918.



No Nanoparticle Deposition in the Lungs In Vivo Post-Exposure to THS

Cigarette Smoke

Carbon-based nanoparticles
 6×10^{11} particle ≈ 0.7 mg*



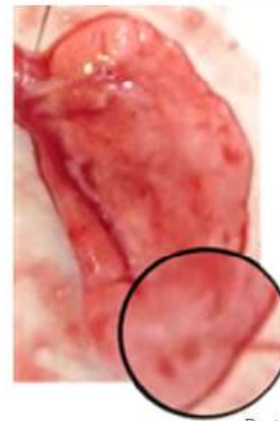
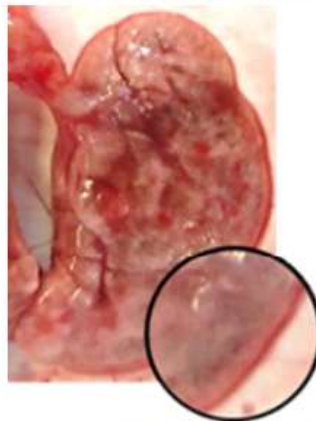
THS Aerosol

No solid particles



Lung Deposition after 6 months

Cigarette smoke
(600 mg/m³ TPM)

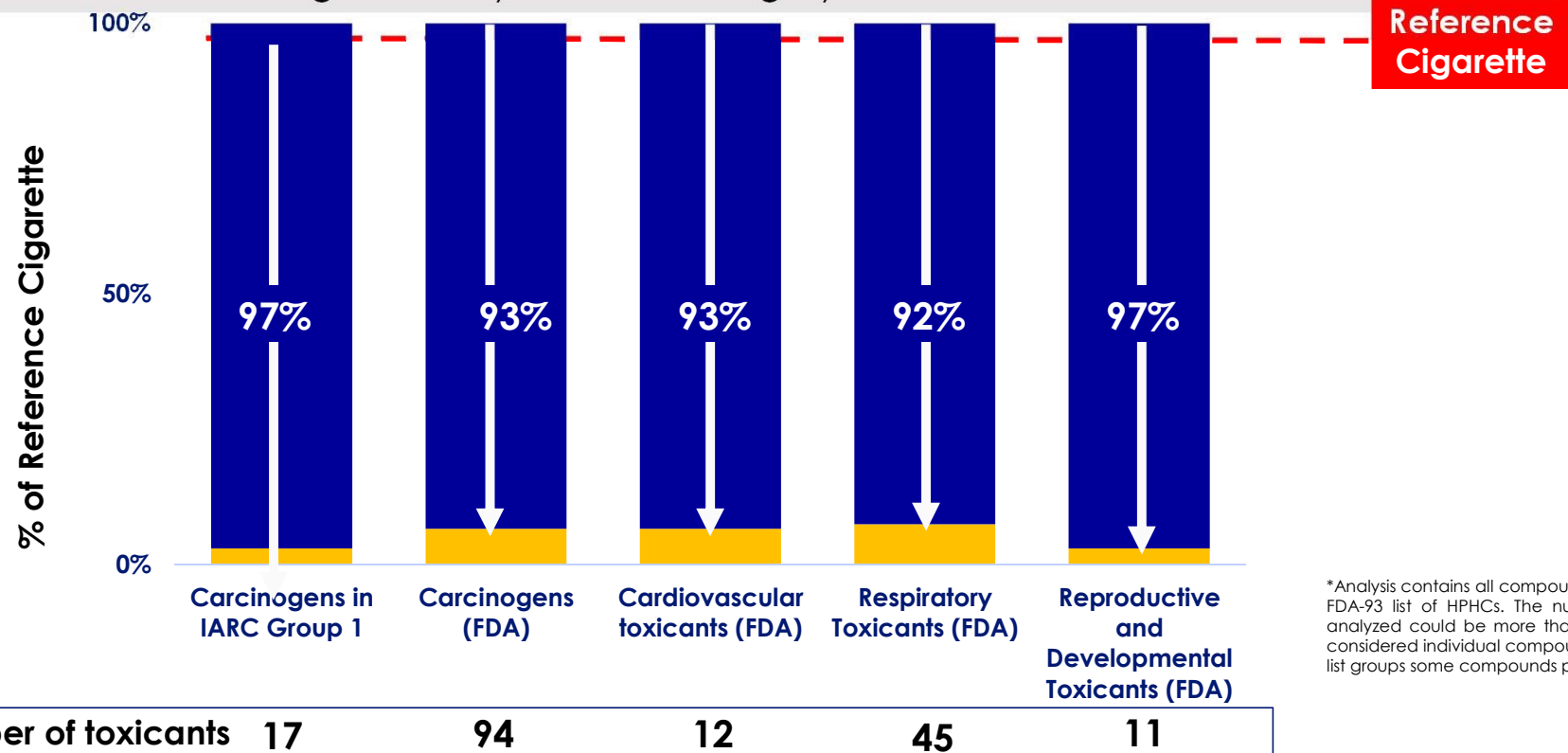


Corresponding
concentration of
THS aerosol



Classification Of Toxicants per Disease Toxicity

Average reductions in the **formation** of HPHCs with THS2.2 relative to the levels measured in smoke from the 3R4F reference cigarette, by disease category*



*Analysis contains all compounds included in the FDA-93 list of HPHCs. The number of toxicants analyzed could be more than 93, because we considered individual compounds, as the FDA-93 list groups some compounds per class or isomer

Note:

- THS 2.2 stands for Tobacco Heating System version 2.2 and refers to a commercialized version of IQOS.
- Health Canada Intense Smoking regimen; comparison on a per-stick basis; excludes nicotine

FDA's list of HPHCs: Comparison between HPHC levels in THS 2.2 aerosol and cigarette smoke <https://www.pmscience.com/whats-new/fda-s-list-of-hphcs>



Clinical Program to Assess the Reduced Risk of THS



Pharmacokinetics
4 PK studies

Nicotine absorption
similar to that of cigarette

**5-day confinement
reduced exposure
2 REXC studies**

Exposure to toxicants is reduced
Exposure to nicotine is similar

**90-day ambulatory
reduced exposure
2 REXA studies**

**Exposure response
ZRHR-ERS-09-US** **Exposure response
ZRHR-ERS-09-EXT**

Smoking Cessation Study
As actually used, exposure to toxicants is reduced,
which leads to changes in clinical risk endpoints

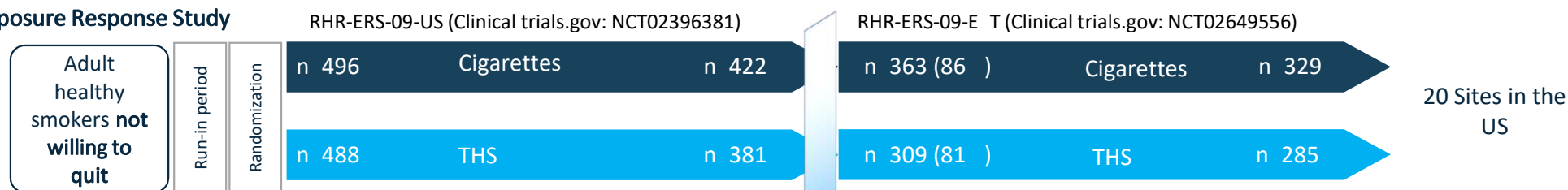
Changes in Biomarkers of Potential Harm (BoPH) upon THS Use, Smoking Cessation, and Continued Smoking



Research Questions:

- Product use patterns, nicotine exposure, reduction in exposure?
- Trajectory response compared with continued smoking and smoking cessation?
- Dose–response of BoPHs to number of cigarettes smoked in THS users?
- How much of the magnitude of changes after smoking cessation is preserved?

Exposure Response Study



Smoking Cessation Response Study





Our Approach for Evaluating Tobacco Harm Reduction: Biomarkers of Potential Harm

1. Biomarkers of potential harm (BoPH) definition

“Measurement of an effect due to exposure; these include biological effects, alterations in morphology, structure, or function, and clinical symptoms consistent with harm, also include pre-clinical changes”

Institute of Medicine (IOM), Clearing the Smoke; Assessing the Science Based for Tobacco Harm Reduction, 2001

2. Rationale for selection

Biomarkers of Potential Harm: Summary of an FDA-Sponsored Public Workshop

¹Office of Science, Center for Tobacco Products, Food and Drug Administration, Silver Spring, MD; ²Department of Psychiatry, Tobacco Research Programs, University of Minnesota, Minneapolis, MN

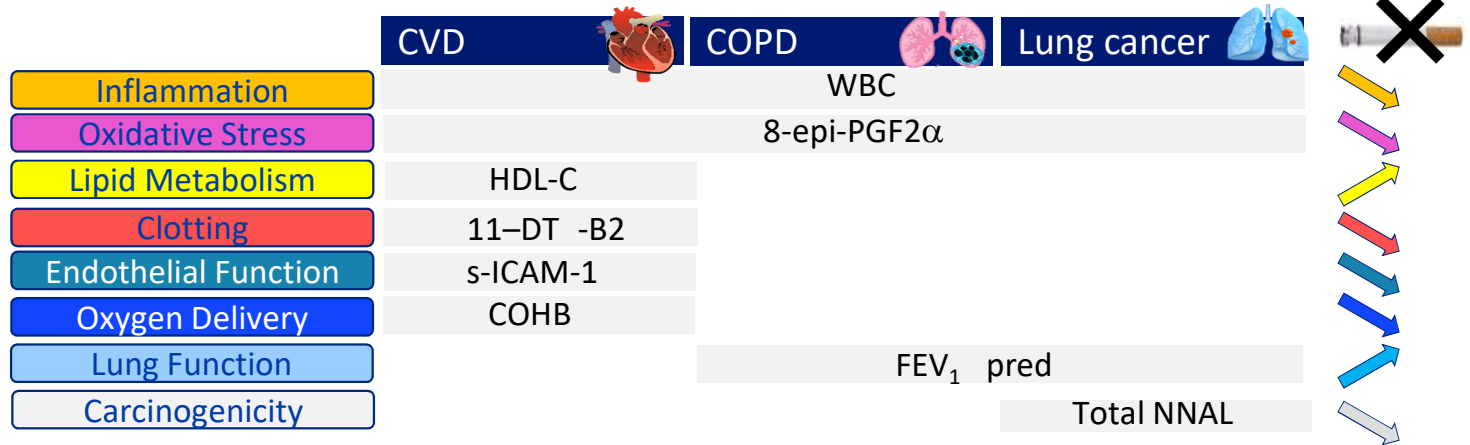
Criteria for Adequate Selection (IOM)

Criteria

Reflective of pathological process as a consequence of exposure

- Sensitivity
- Predictive
- Temporality
- Experiment
- Biological gradient
- Specificity
- Analogy
- Consistency

Selection of BoPHs linked to morbidity and sensitive to smoking cessation

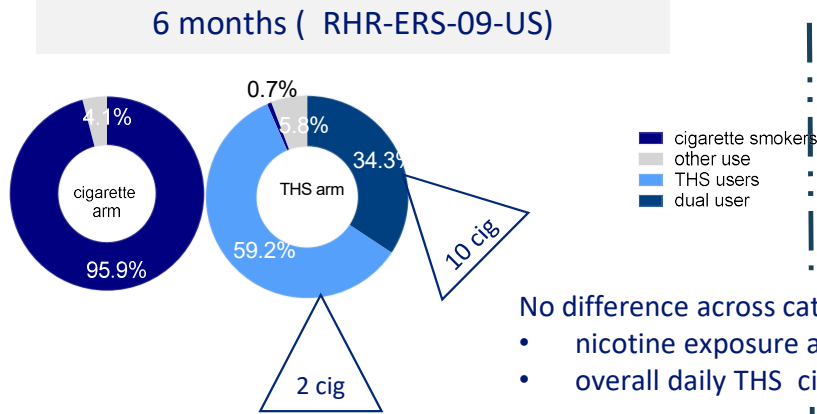


CVD: cardiovascular disease; COPD: Chronic obstructive pulmonary disease; WBC: white blood cell; 8-epi-PGF2α: 8-epi-prostaglandin-F2a; HDL-C: high-density lipoprotein-C; 11-DT B2: 11-dehydrothromboxane B2; s-ICAM-1: soluble intercellular molecule adhesion-1; COHB: carboxyhemoglobin; FEV₁ pred: predicted forced expiratory volume in one second; total NNAL: total 4-(methylnitrosamino)-1-(3-pyridyl)-1-butanol (NNAL)

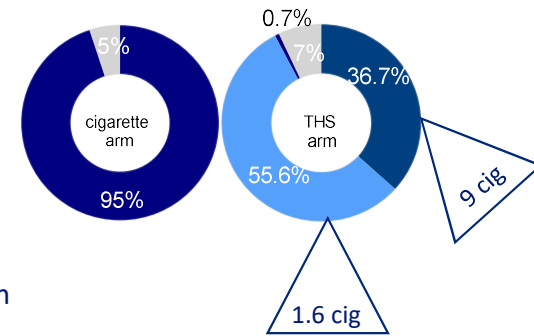


Results: Product Use Patterns and Exposure to Nicotine and Toxicants

Product Use Patterns and Nicotine Exposure



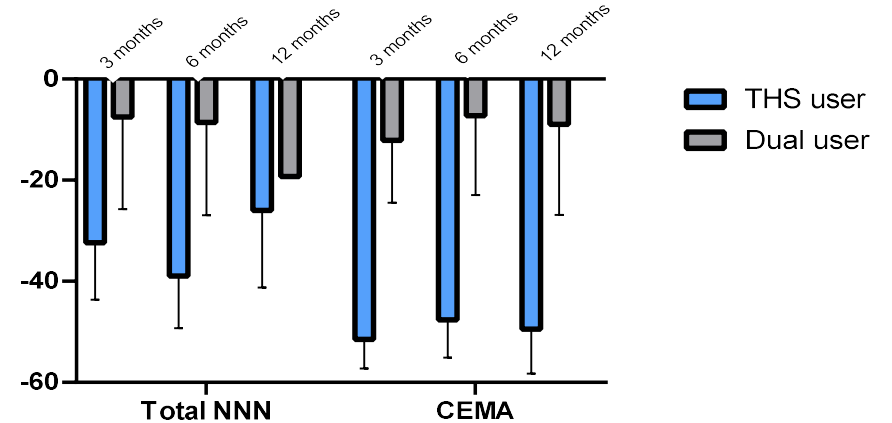
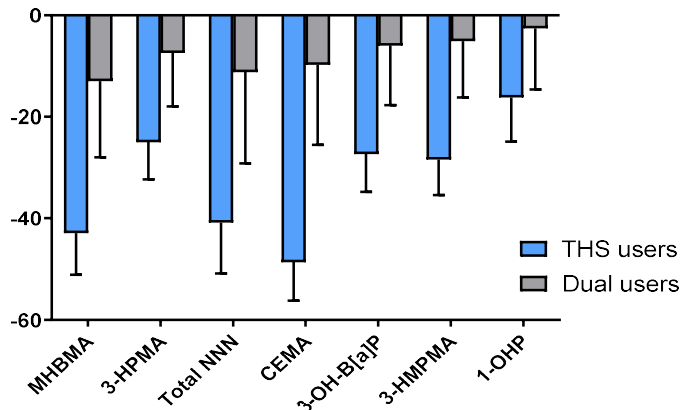
12 months (RHR-ERS-09-US-E T)



No difference across categories in

- nicotine exposure and
- overall daily THS cig consumption

Reduction in Exposure Relative to Cigarettes (%)



MHBMA: monohydroxybutyl mercapturic acid; 3-HPMA: 3-hydroxypropyl mercapturic acid; total NNN: *N*-nitrosonorcotine; CEMA: cyanoethyl mercapturic acid; total 3-OH-B[a]P: 3 hydroxyl benzo a pyrene; 3-HMPMA; hydroxymethyl propylmercapturic acid; 1-OHP: 1- hydroxypyrene

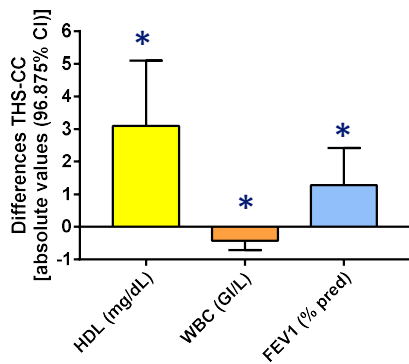


Results: Changes in BoPHs Related to Disease

Favorable Biological Impact

Favorable Biological Impact

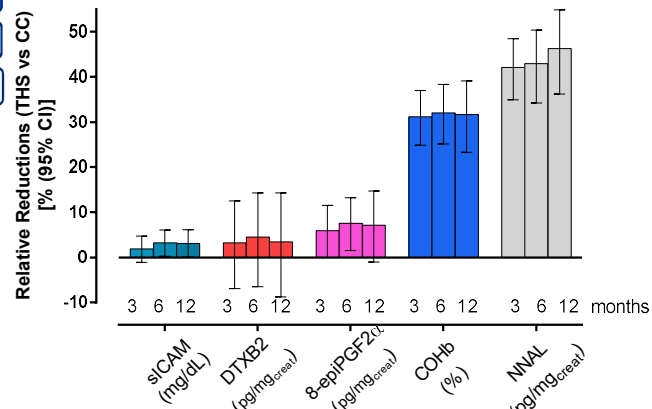
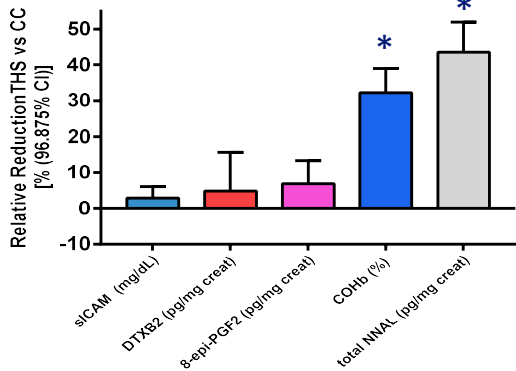
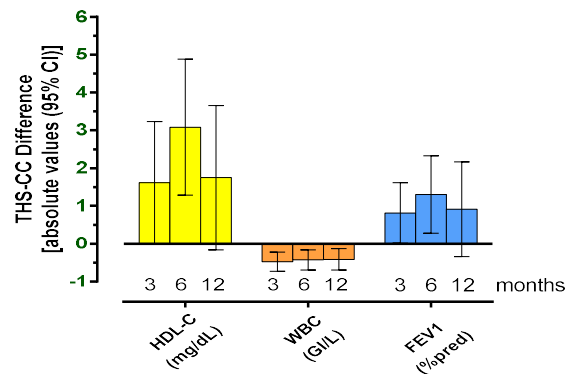
6 months (RHR-ERS-09-US)



Differences between THS and cigarettes

- Inflammation
- Oxidative Stress
- Lipid Metabolism
- Clotting
- Endothelial Function
- Oxygen Delivery
- Lung Function
- Carcinogenicity

Time course up to 12 months (RHR-ERS-09-US-E T)

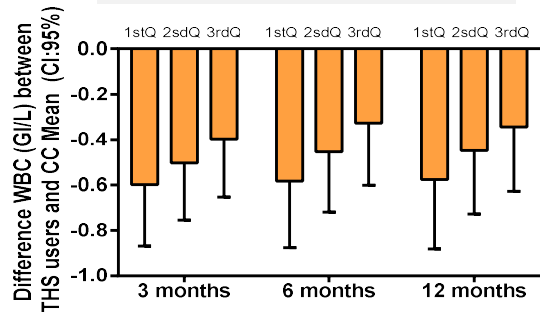


WBC: white blood cell; 8-epi-PGF2 α : 8-epi-prostaglandin-F2 α ; HDL-C: high-density lipoprotein-C; 11-DT B2: 11-dehydrothromboxane B2; s-ICAM-1: soluble intercellular molecule adhesion-1; COHb: carboxyhemoglobin; FEV1 pred: predicted forced expiratory volume in one second; total NNAL: total 4-(methylnitrosamino)-1-(3-pyridyl)-1-butanol (NNAL)

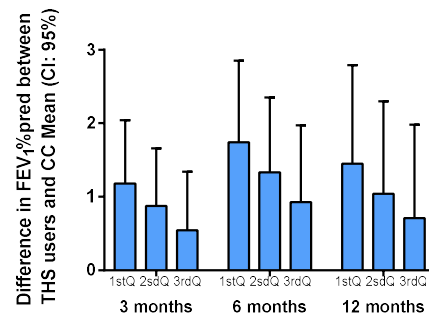


The Intensity of Smoking Decreases the Favorable Effects of THS on BoPHs

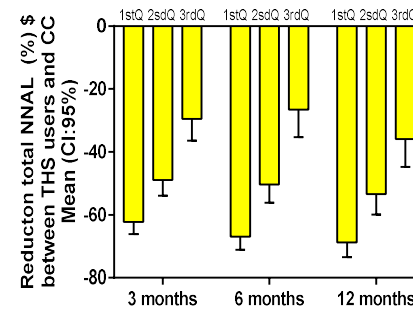
WBC: Inflammation



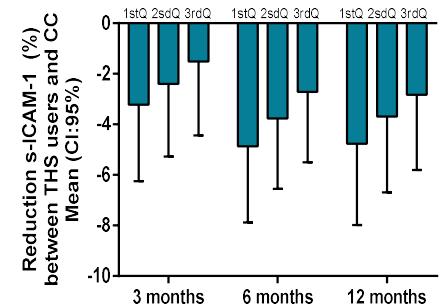
FEV₁ pred: Lung Function



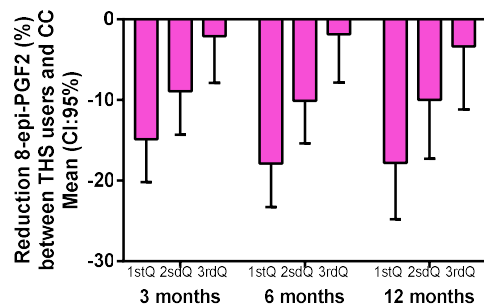
HDL-C: Lipid Metabolism



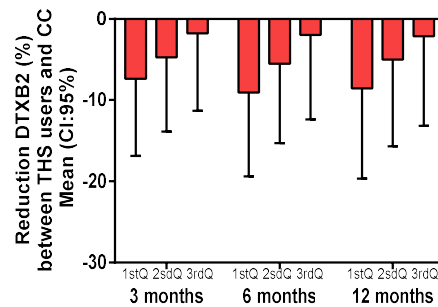
s-ICAM-1: Endothelial Function



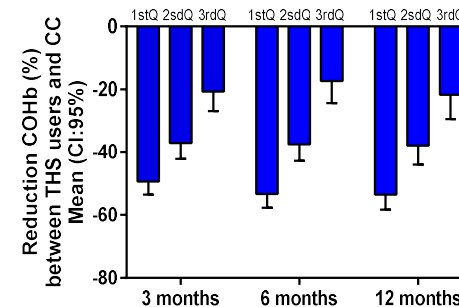
8-epi-PGF2α: Oxidative Stress



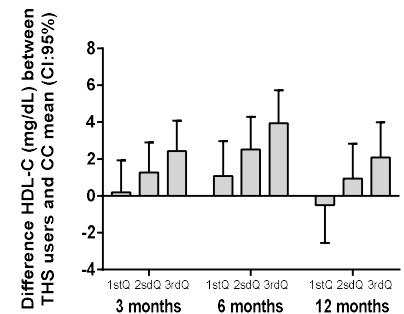
11-DT B2: Clotting



COHb: Oxygen Delivery



Total NNAL: Carcinogenicity

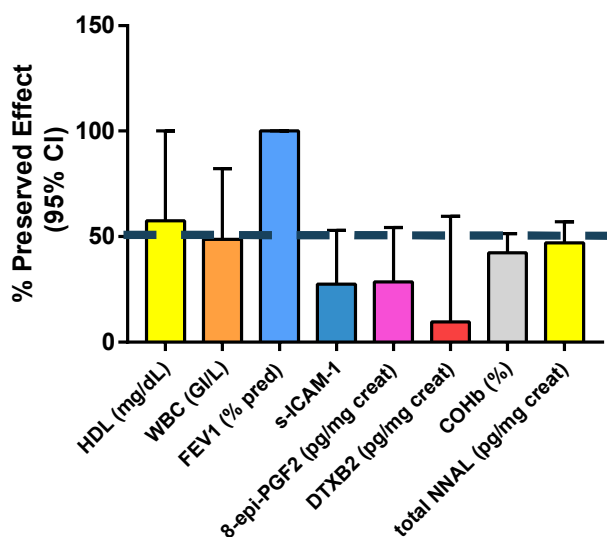


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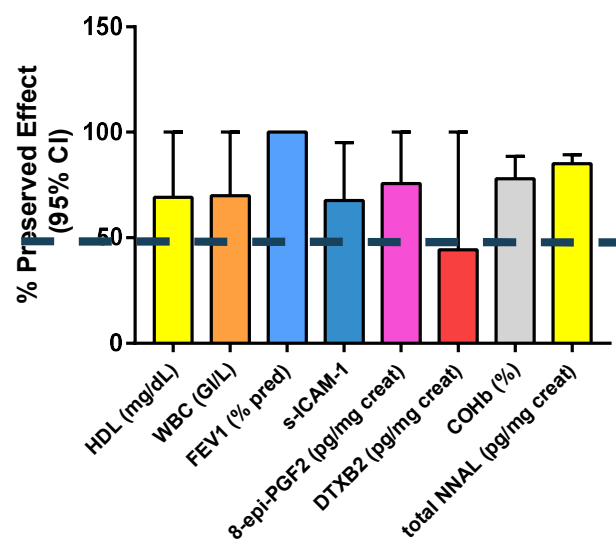


Does THS Preserve the Smoking Cessation Effect after 6 Months: Relevance of BoPHs in Evaluating Tobacco Harm Reduction

Self-Reported Product Use Classification Analysis in complete switchers to THS



CEMA Verification to Detect Cigarette Smoking in THS users Analysis in complete switchers to THS by using CEMA a cutoff value of 40ng/mg creatinine to detect cigarette smoking



50

- Inflammation
- Oxidative Stress
- Lipid Metabolism
- Clotting
- Endothelial Function
- Oxygen Delivery
- Lung Function
- Carcinogenicity

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Conclusions

- Among subjects randomized to THS use, 55 switched predominantly to THS (70 THS) and 35 to dual use of both THS and cigarettes over 12 months. Daily overall tobacco use and nicotine exposure were comparable to baseline, while exposure to toxicants was reduced.
- Both smoking cessation and complete THS switching led to favorable shifts in the core set of eight BoPHs relative to smoking.
- In complete THS switchers, classified on the basis of self-reporting, 40 of the smoking cessation effect was preserved in 5/8 BoPHs relative to smoking, with 50 of preserved effect in FEV₁ and HDL-C level.
- Chemical verification for detecting cigarette smoking in predominant THS switchers showed that 67 of the smoking cessation effect was preserved in 7/8 BoPHs.
- Dual users exhibited less favorable effects, both in exposure and BoPHs, than complete switchers



FDA NEWS RELEASE

FDA Authorizes Marketing of IQOS Tobacco Heating System with ‘Reduced Exposure’ Information

Agency Will Closely Monitor Real-World Data to Assess if Marketing Continues to be Appropriate

“Through the modified risk tobacco product application process, the FDA aims to ensure that information directed at consumers about reduced risk or reduced exposure from using a tobacco product is supported by scientific evidence and understandable,” said Mitch Zeller, J.D., director of the FDA’s Center for Tobacco Products. **“Data submitted by the company shows that marketing these particular products with the authorized information could help addicted adult smokers transition away from combusted cigarettes and reduce their exposure to harmful chemicals, but only if they completely switch. The FDA will closely monitor how IQOS is used by consumers to determine if these products meet this potential and do not cause increased use among youth. It is important to note that these products are not safe, so people, especially young people, who do not currently use tobacco products should not start using them or any other tobacco product.”**

<https://www.fda.gov/news-events/press-announcements/fda-authorizes-marketing-iqos-tobacco-heating-system-reduced-exposure-information>

Key Takeaways

- The best option for every smoker is to quit
- Tobacco harm reduction i.e., offering smoke-free alternatives to adult smokers is a recommended approach for smokers who would otherwise continue smoking
- Changes in BoPHs provide relevant insights for evaluating the tobacco harm reduction associated with switching to THS use, when evaluated in light of smoking cessation and in the absence of epidemiological data.
- Although addictive and not risk-free, THS has the potential for harm reduction, as demonstrated by the totality of the robust and multifaceted scientific data on THS