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Effects of Cigarette Smoking, Tobacco Heating System Use, and Smoking Cessation on Cough

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July 2020

These slides are presented to the Annual Vietnamese Pulmonary Conference

www.pmisience.com

WHAT ARE THE KEY CAUSES OF COUGH?

- Cough is a reflex action of the respiratory tract that is used to clear the upper airways
- Chronic cough lasting for more than 8 weeks is common in the population
- Causes include cigarette smoking, exposure to cigarette smoke, and exposure to environmental pollution, especially particulates
- Diseases causing chronic cough include asthma, eosinophilic bronchitis, gastro-oesophageal reflux disease, postnasal drip syndrome or rhino-sinusitis, chronic obstructive pulmonary disease, pulmonary fibrosis, and bronchiectasis

WHAT ARE THE KEY CAUSES OF COUGH?

Chronic Cough Due to Chronic Bronchitis

ACCP Evidence-Based Clinical Practice Guidelines

Sidney S. Braman, MD, FCCP

(CHEST 2006; 129:104S–115S)

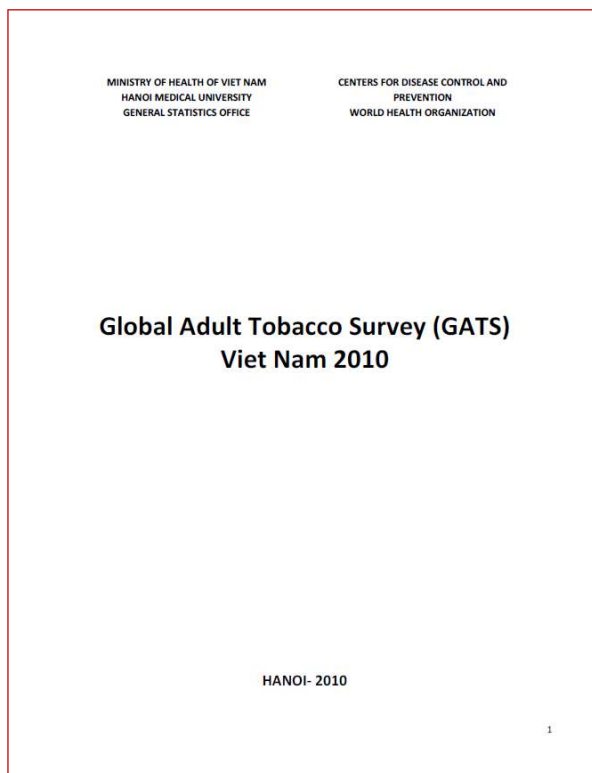
Epidemiology

Chronic bronchitis before age 50 years predicts incident airflow limitation and mortality risk

S Guerra,¹ D L Sherrill,² C Venker,¹ C M Ceccato,¹ M Halonen,¹ F D Martinez¹

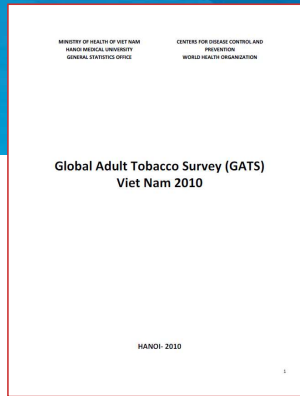
Thorax 2009;**64**:894–900. doi:10.1136/thx.2008.110619

WHO VIETNAM – TOBACCO USE



- 47.4% of men, 1.4% of women (23.8% overall, 17 million adults) smoked tobacco.
- 81.8% smoked on a daily basis
- 83.7% smoked cigarettes, and 26.9% smoked water pipes
- 1.3% of adults (0.3% of males and 2.3% of females) currently used smokeless tobacco (e.g. snuff, chewing tobacco, etc)
- About 69.0% of daily cigarette smokers smoked >10 cigs/day; 29.3% smoked >20 cigs/day

WHO VIETNAM – RECCOMENDATIONS



- PROTECT PEOPLE FROM TOBACCO SMOKE
- IMPROVE ENFORCEMENT OF EXISTING TOBACCO CONTROL REGULATIONS ON SMOKE-FREE ENVIRONMENTS.
- ADVOCATE FOR SMOKE-FREE HOMES INITIATIVES

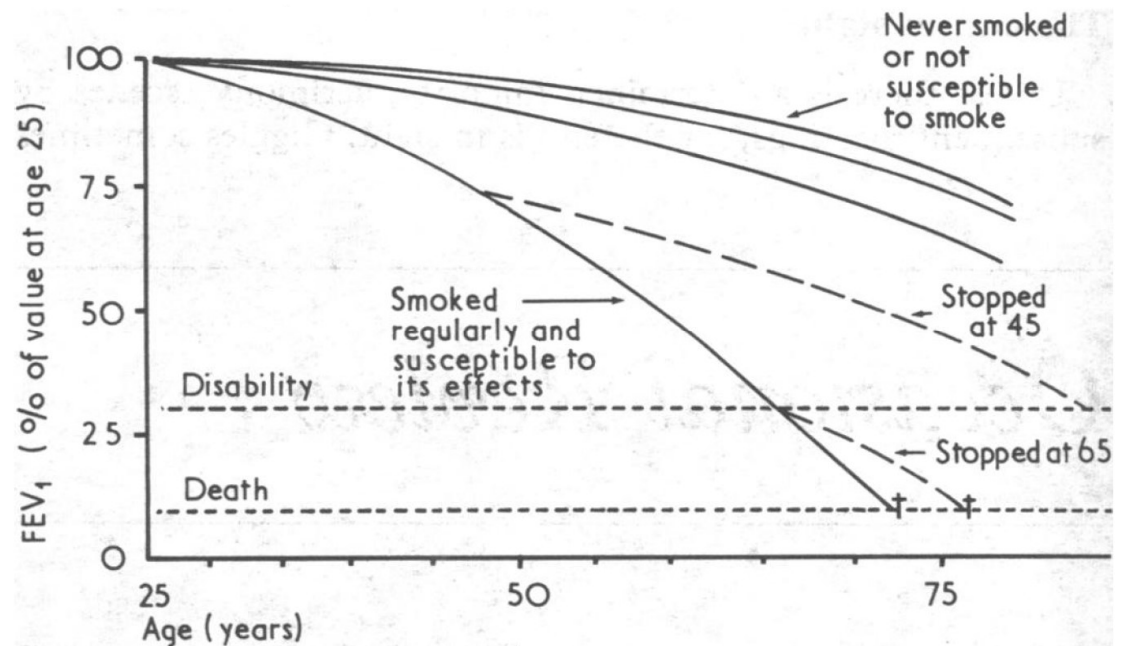
THE IMPACT OF SMOKING CESSATION

Occasional Review

The natural history of chronic airflow obstruction

CHARLES FLETCHER, RICHARD PETO

British Medical Journal, 1977, 1, 1645-1648



THE IMPACT OF SMOKING CESSATION

International Journal of COPD

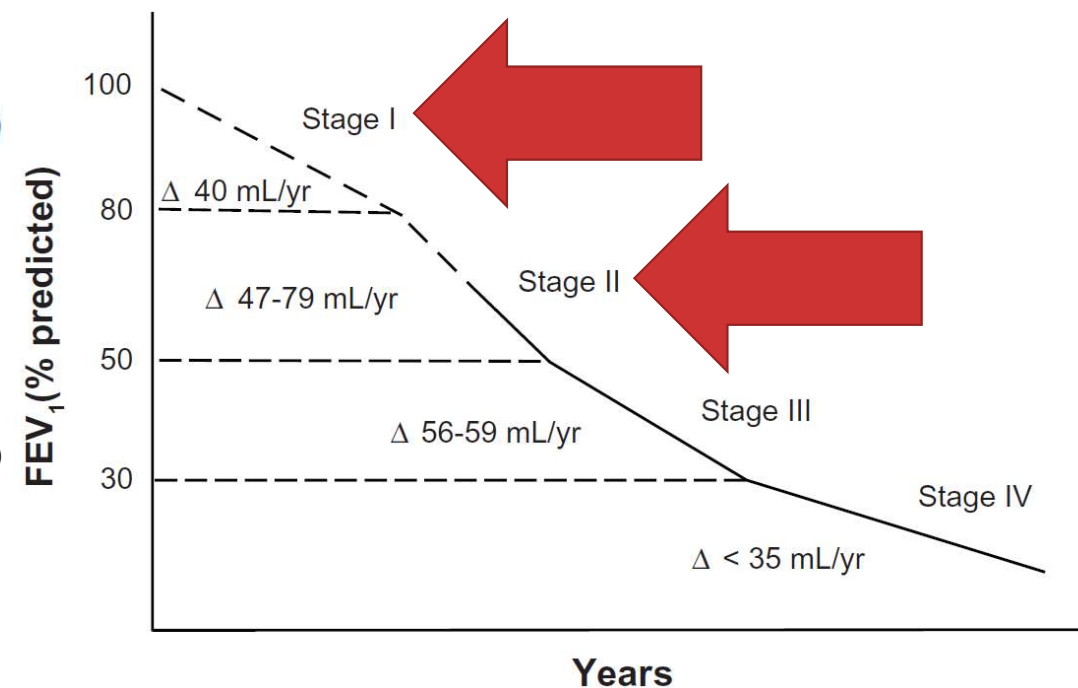
Open Access Full Text Article

Lung function decline in COPD

Claudio Tantucci

Conclusion

- The faster progression of functional impairment in COPD occurs early and it particularly occurs in GOLD stage II.
- To make efforts for an early (spirometric) detection of COPD, based on risk factors rather than symptoms.



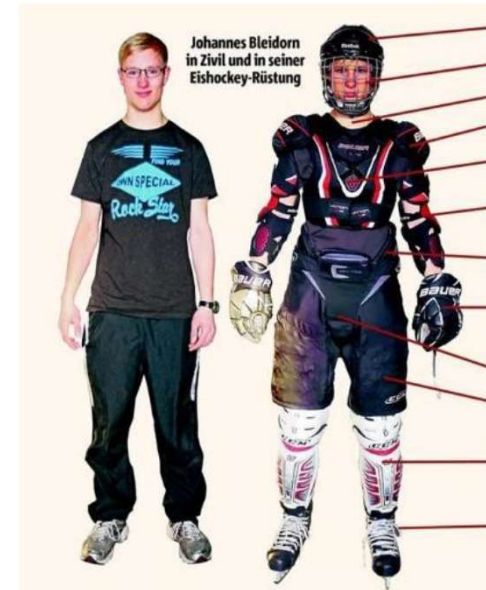
THE CONCEPT OF HARM REDUCTION

What is harm reduction?

Harm reduction is a strategy in medicine and social policy for the minimization of harm to individuals and/or a population by harmful behaviors that cannot be avoided or prevented completely.

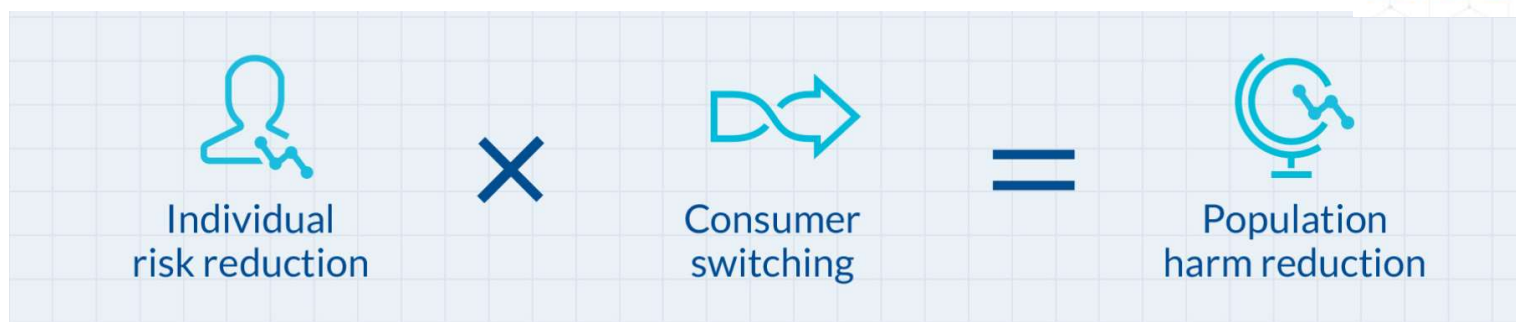
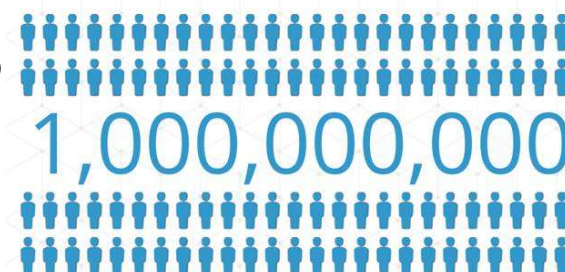
Examples:

- Protective clothing for sports
- Seatbelts
- Laws against drunk driving



TOBACCO HARM REDUCTION

- Smoking is addictive and causes a number of serious diseases
- Worldwide, it is estimated that more than **1 billion** people will continue to smoke in the foreseeable future*
- Offering smoke-free alternatives to adult smokers is a sensible, complementary addition to existing tobacco control strategies



- Successful harm reduction requires that current adult smokers be offered a range of satisfactory Reduced-Risk Products they can fully switch to, should they otherwise continue to smoke

THE ROLE OF NICOTINE

"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)

"Nicotine is the very same compound FDA has approved for over 30 years as a safe and effective medication. People are dying from the tobacco-related diseases from the smoke particles, not the nicotine... Can we start to take a different look at this?"

Mitch Zeller, Director of US FDA's Center for Tobacco Products; Presentation at Legacy Foundation



Royal College
of Physicians

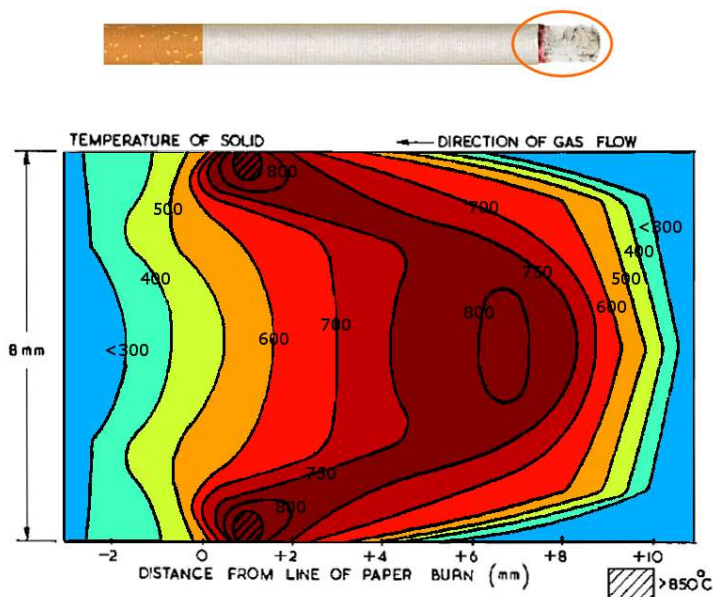
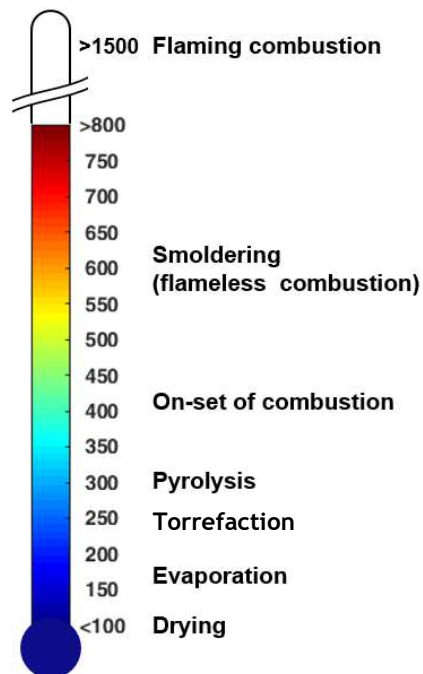
NICE

National Institute for
Health and Care Excellence

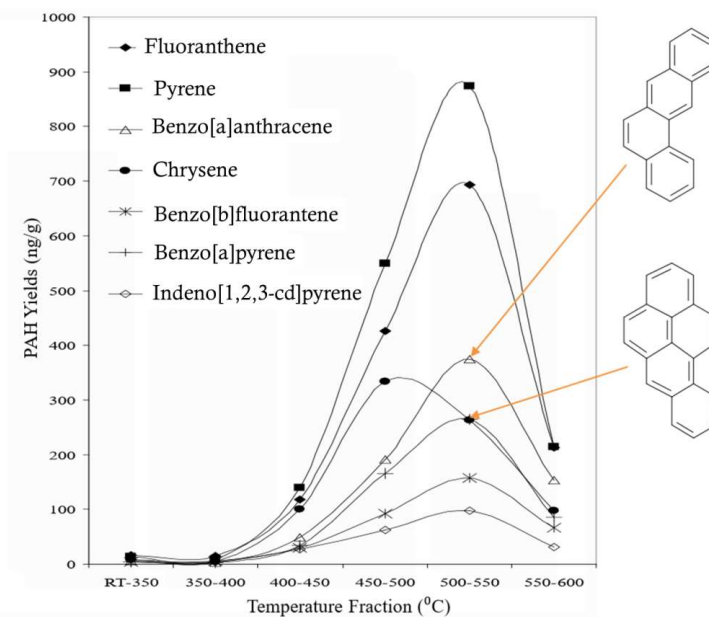
ELIMINATION OF TOBACCO COMBUSTION IS KEY

AS THE TEMPERATURE OF TOBACCO INCREASES, THE LEVELS OF HARMFUL CHEMICALS FORMED INCREASES

Temperature (°C)



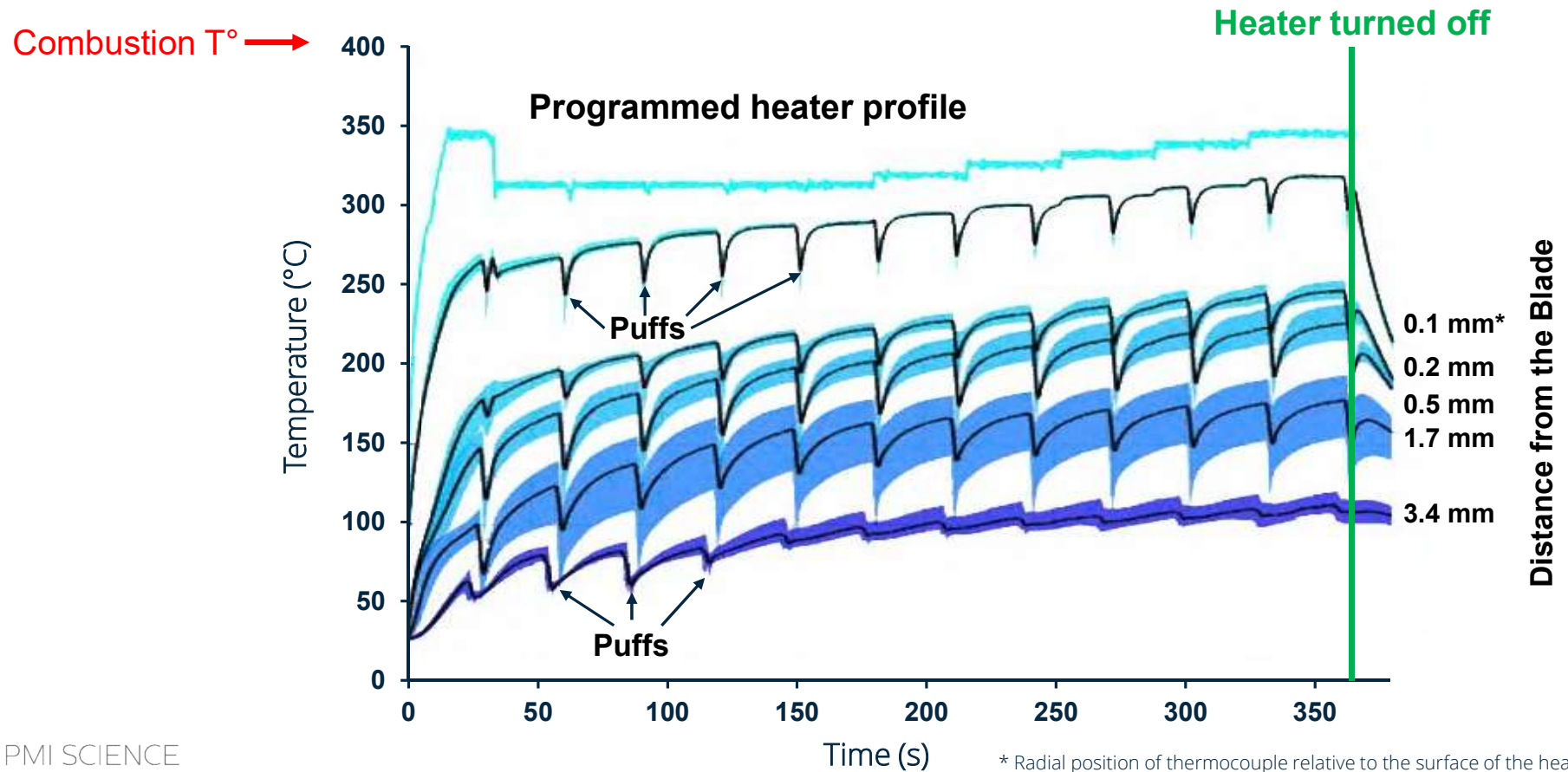
Reference 1



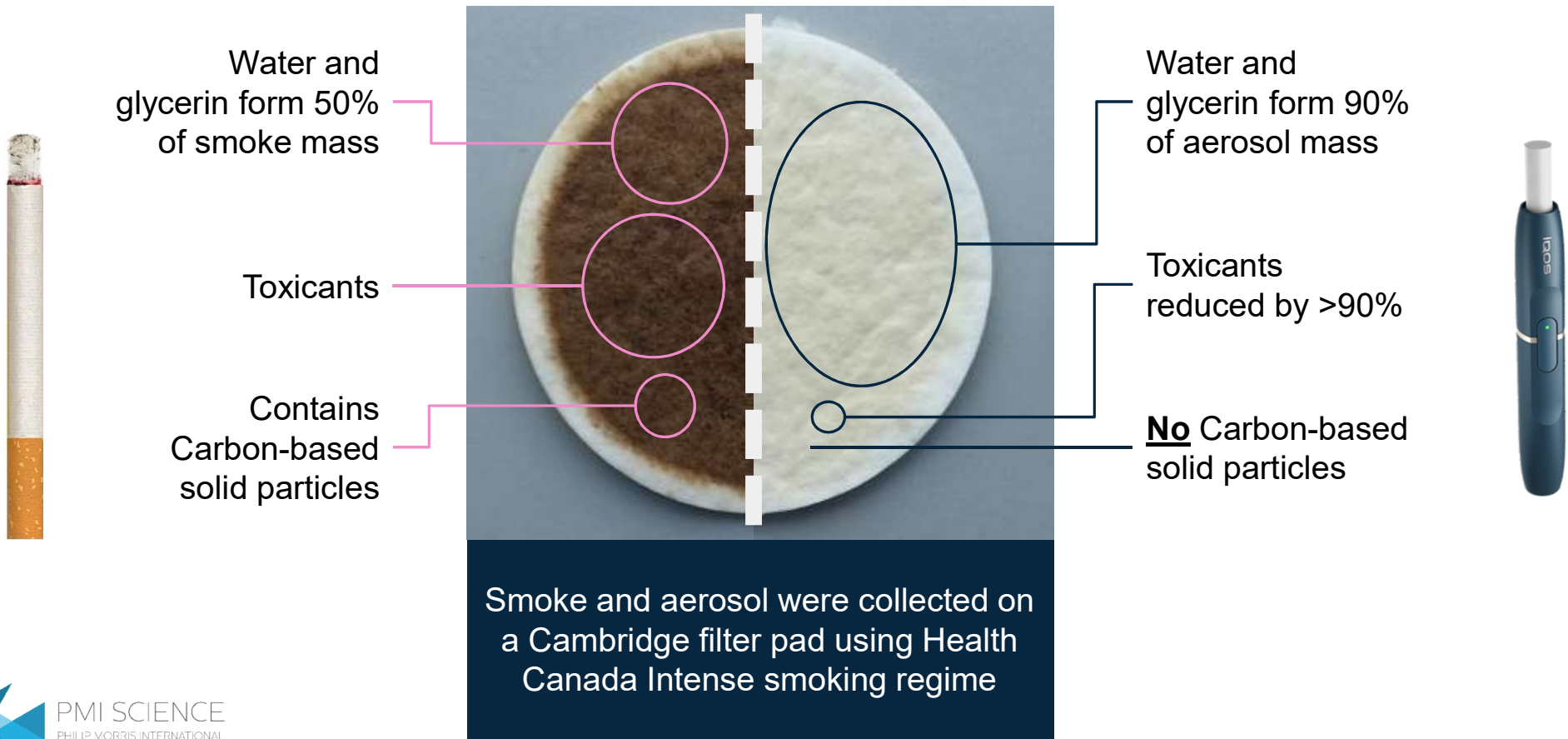
Reference 2

1. Baker RR. High Temp Sci, 1975;7:236-247. Coloration by PMI.
2. McGrath TE, et al. Food and Chemical Toxicology, 2007; 45:1039-1050

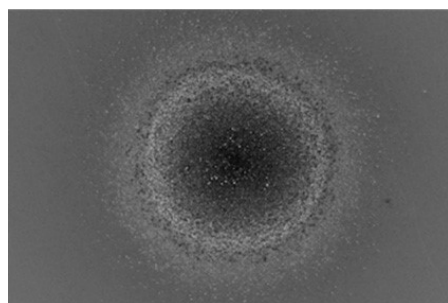
THS: ABSENCE OF COMBUSTION



DIFFERENCES BETWEEN THIS AEROSOL AND CIGARETTE SMOKE



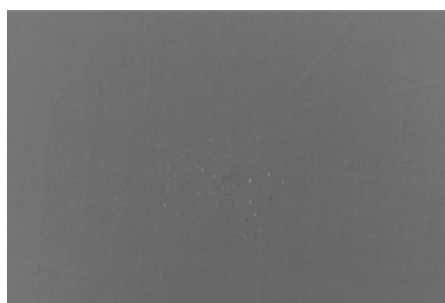
THS: NO CARBON-BASED SOLID PARTICLES EMISSION



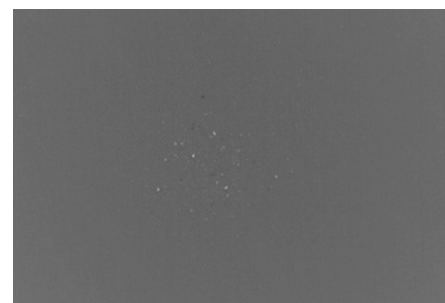
Cigarette smoke

Carbon-based nanoparticles
Median diameter = 75 nm

Amount: 6×10^{11} particles $\approx$ 0.7 mg*



Blank (Air)



THS aerosol

No solid particles

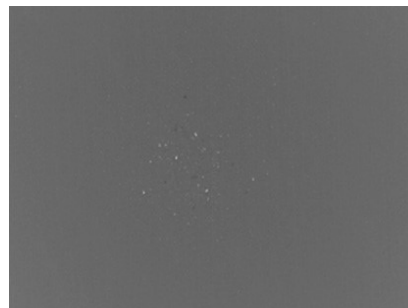
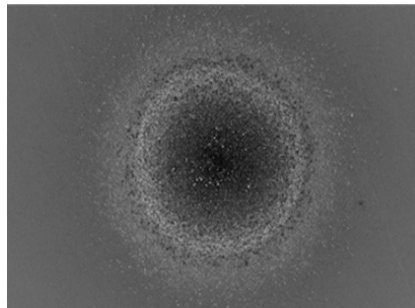


Scanning Electron Microscopy images of the collected smoke/aerosol after passing through a thermodenuder set at 300° C to remove the volatile portion / collected material characterized by Electron Diffusive X-ray.

NANOPARTICLES DEPOSIT IN THE LUNG

Cigarette Smoke

Carbon-based nanoparticles
 6×10^{11} particles $\approx$ 0.7 mg*



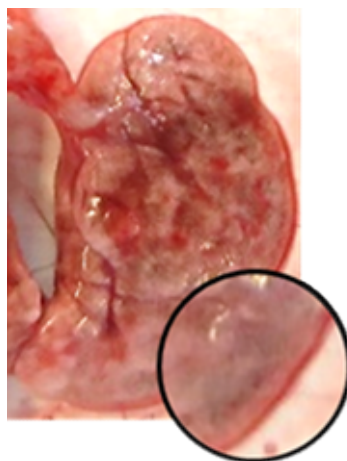
THS Aerosol

No solid particles



Lung Deposition after 6 months

Cigarette smoke
(600 mg/m³ TPM)



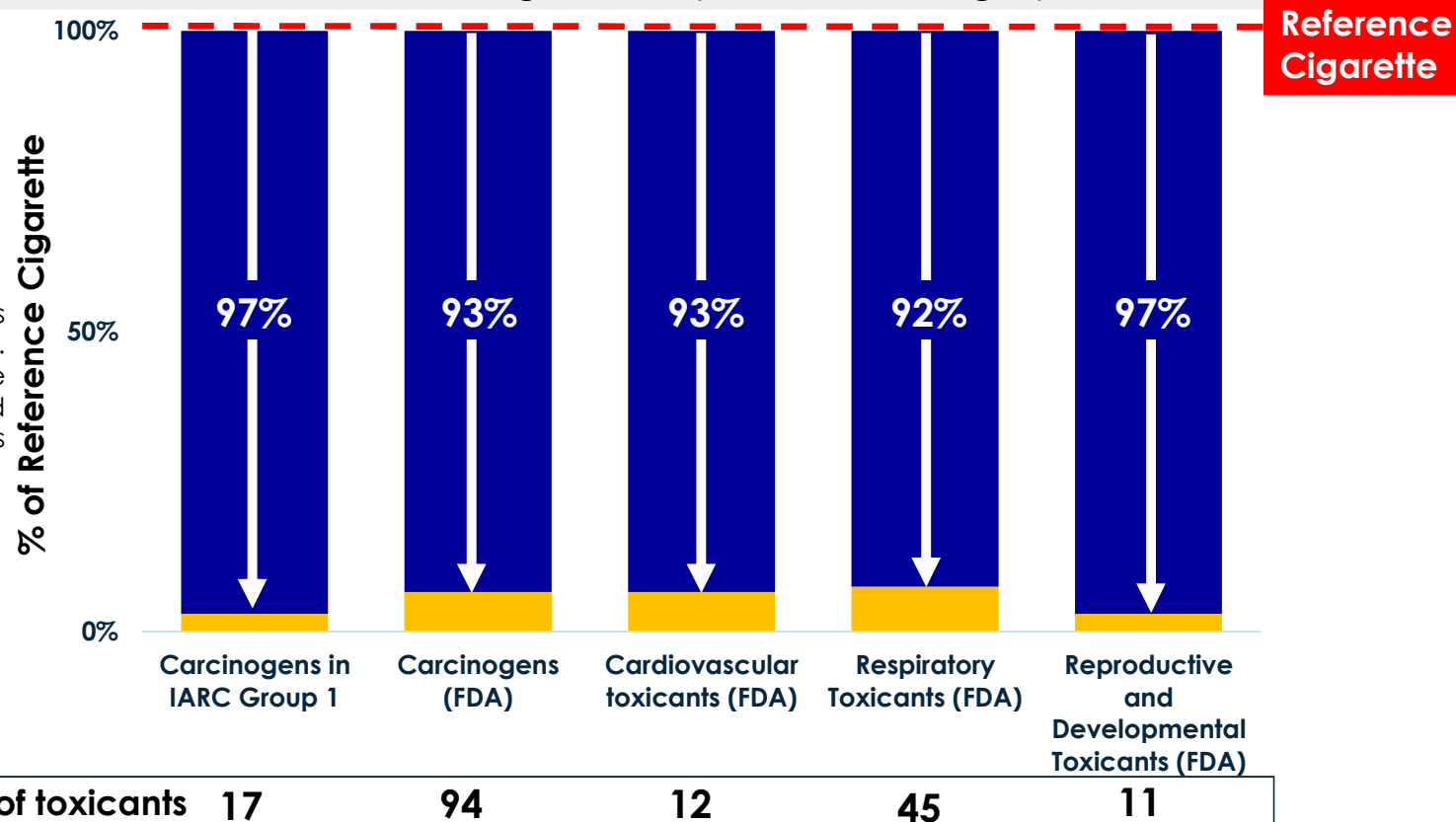
Corresponding
concentration of
THS aerosol

REDUCTIONS OF TOXICANTS BY DISEASE CATEGORY

Average reductions in **formation** of harmful or potentially harmful constituents for THS2.2 compared to levels measured in smoke from the 3R4F reference cigarette by disease category*



*Analysis contains all compounds included in the FDA-93 list of HPHCs. Number of toxicant analyzed can be more than 93 because we considered individual compounds as FDA-93 groups some compounds per classes or isomers



Note:

- THS 2.2 stands for Tobacco Heating System version 2.2 and refers to a commercialized version of IQOS.
- Intense Health Canada's Smoking Regime; 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.pmisceince.com/whats-new/fda's-list-of-hphcs>

INDOOR AIR QUALITY

Regulatory Toxicology and Pharmacology 80 (2016) 91–101



Contents lists available at ScienceDirect

Regulatory Toxicology and Pharmacology

journal homepage: www.elsevier.com/locate/yrtph



Comparison of the impact of the Tobacco Heating System 2.2 and a cigarette on indoor air quality



Maya I. Mitova*, Pedro B. Campelos, Catherine G. Goujon-Ginglinger, Serge Maeder, Nicolas Mottier, Emmanuel G.R. Rouget, Manuel Tharin, Anthony R. Tricker

Philip Morris International R&D, Philip Morris Products S.A., Quai Jeanrenaud 5, 2000 Neuchâtel, Switzerland (part of Philip Morris International group of companies)

CONCLUSIONS

Under the simulated conditions the **concentrations** of most **measured indoor air constituents** with the exception of acetaldehyde and nicotine during use of THS 2.2 were **similar to background levels**, suggesting **no negative impact** on the Indoor Air Quality when using THS in an indoor environment

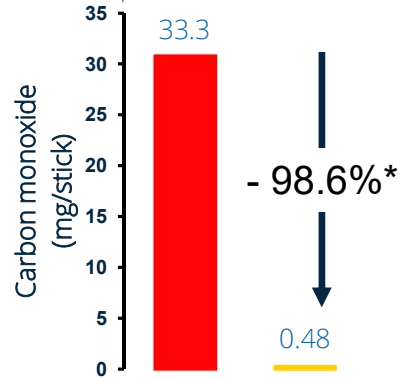
Indoor air constituents measured:

- respirable suspended particles < 2.5 mm in diameter,
- ultraviolet particulate matter,
- fluorescent particulate matter,
- solanesol,
- 3-ethenylpyridine,
- nicotine,
- 1,3-butadiene,
- acrylonitrile,
- benzene,
- isoprene,
- toluene,
- acetaldehyde,
- acrolein,
- crotonaldehyde,
- formaldehyde,
- Carbon monoxide,
- nitrogen oxide,
- combined oxides of nitrogen

CHANGES IN EXPOSURE TO HPHCS WITH THS USE IN HEALTHY HUMAN SUBJECTS

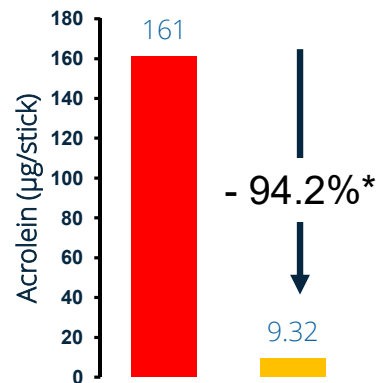
HPHCs are Drastically Reduced in THS Aerosol

* On equivalent nicotine basis



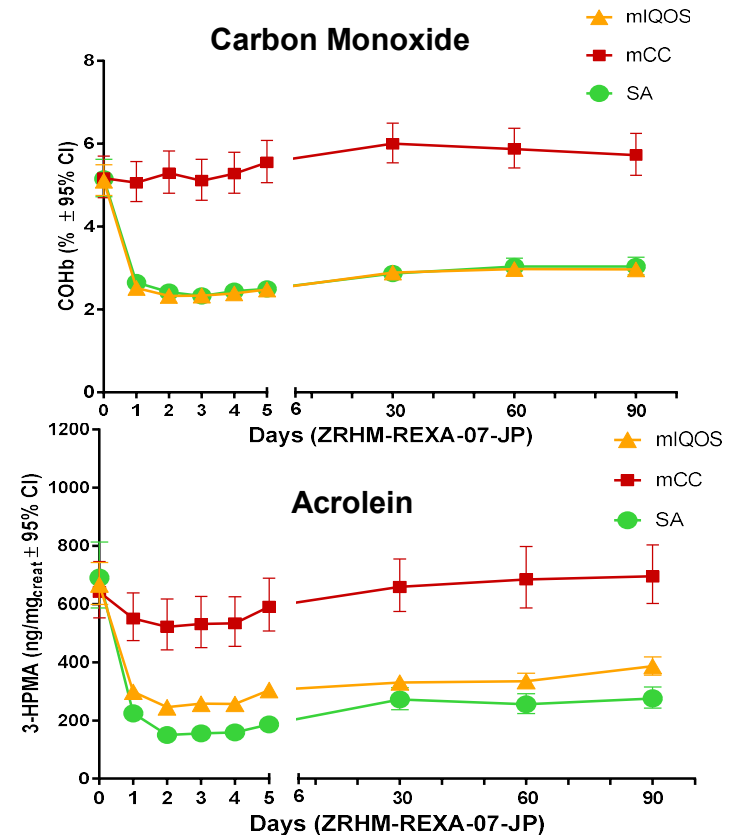
Leads to

■ Cigarette
■ THS
■ Smoking Abstinence



Leads to

Exposure is Significantly Reduced After Switching to THS



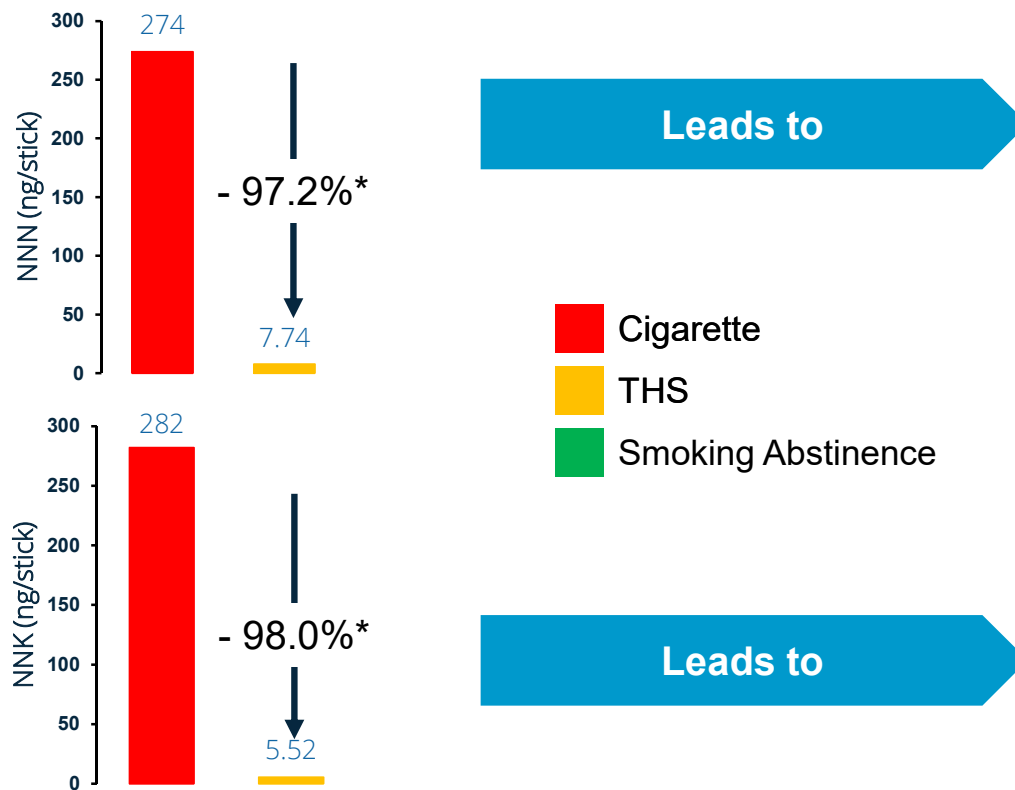
Note: These data alone do not represent a claim of reduced risk.
Registered on clinicaltrials.gov: NCT01989156

Luedicke et al. Effects of Switching to the Tobacco Heating System 2.2 Menthol, Smoking Abstinence, or Continued Cigarette Smoking on Biomarkers of Exposure: A Randomized, Controlled, Open-Label, Multicenter Study in Sequential Confinement and Ambulatory Settings. Nicotine & Tobacco Research, Volume 20, Issue 2, February 2018, Pages 161–172 <https://doi.org/10.1093/ntr/ntw287>

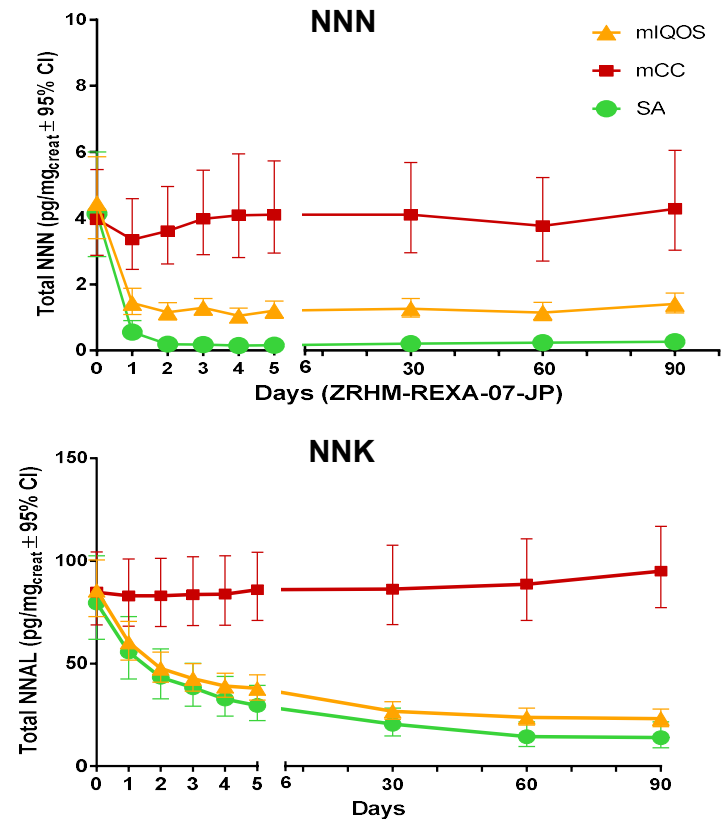
CHANGES IN EXPOSURE TO HPHCS WITH THS USE IN HEALTHY HUMAN SUBJECTS

HPHCs are Drastically Reduced in THS Aerosol

* On equivalent nicotine basis



Exposure is Significantly Reduced After Switching to THS

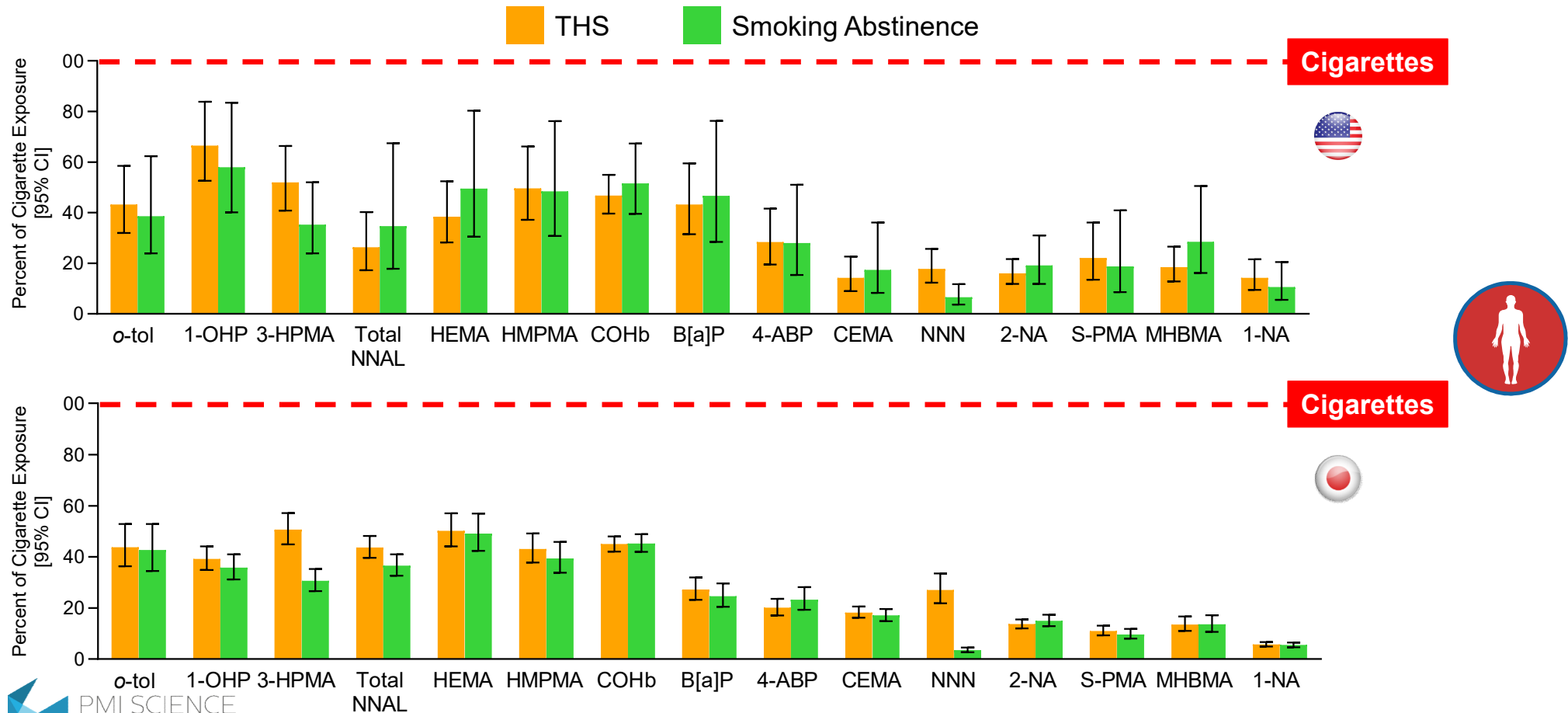


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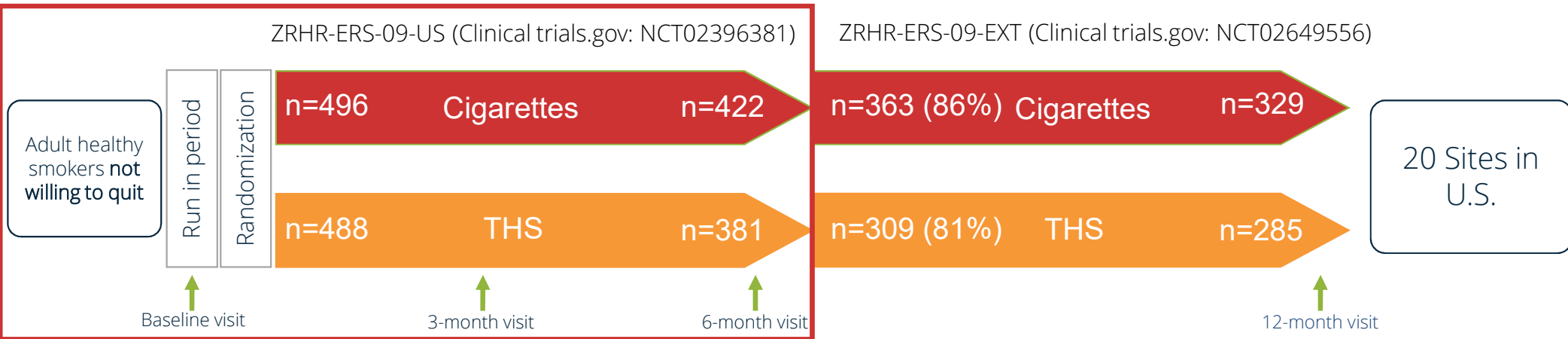
Luedicke et al. Effects of Switching to the Tobacco Heating System 2.2 Menthol, Smoking Abstinence, or Continued Cigarette Smoking on Biomarkers of Exposure: A Randomized, Controlled, Open-Label, Multicenter Study in Sequential Confinement and Ambulatory Settings. Nicotine & Tobacco Research, Volume 20, Issue 2, February 2018, Pages 161–172. <https://doi.org/10.1093/ntr/ntw287>

REDUCED EXPOSURE TO HPHCs WITH THS USE IN HEALTHY HUMAN SUBJECTS

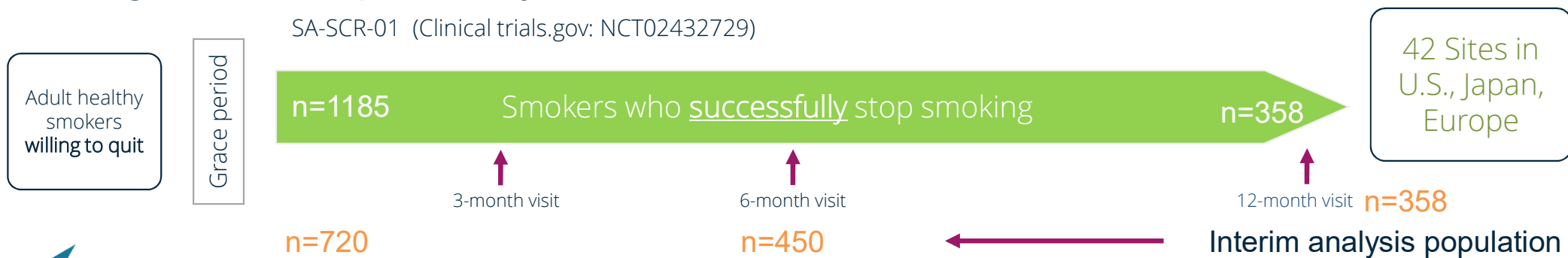


Haziza et al. Reduction In Exposure To Selected Harmful And Potentially Harmful Constituents Approaching Those Observed Upon Smoking Abstinence In Smokers Switching To The Menthol Tobacco Heating System 2.2 For Three Months (Part 1) (2019) Nicotine & Tobacco Research, 2020, 539–548 <https://doi.org/10.1093/ntn/ntz013>

EXPOSURE RESPONSE STUDY ERS-09 STUDY DESIGN



Smoking Cessation Response Study



Published OnlineFirst July 3, 2019; DOI: 10.1158/1055-9965.EPI-18-0915

Research Article

Cancer
Epidemiology,
Biomarkers
& Prevention

Effects of Switching to a Heat-Not-Burn Tobacco Product on Biologically Relevant Biomarkers to Assess a Candidate Modified Risk Tobacco Product: A Randomized Trial



Frank Lüdiche, S. Michael Ansari, Nicola Lama, Nicolas Blanc, Marija Bosilkovska, Andrea Donelli, Patrick Picavet, Gizelle Baker, Christelle Haziza, Manuel Peitsch, and Rolf Weitkunat

1934 Cancer Epidemiol Biomarkers Prev; 28(11) November 2019

AAGR

EXPOSURE RESPONSE STUDY ERS-09

PRIMARY OBJECTIVE AND CO-PRIMARY ENDPOINTS



Smoking cessation

Epidemiologic link
to smoking-
related disease?

Affected by
smoking status

Reversible upon
smoking cessation



Co-Primary Endpoints Representative of Pathomechanisms

Lipid metabolism	HDL-C
Clotting	11-DTX-B2
Endothelial function	sICAM-1
Acute effect	COHb
Inflammation	WBC
Oxidative stress	8-epi-PGF _{2α}
Lung function	FEV ₁ %pred
Genotoxicity	Total NNAL

Assess the changes across a set of the “8 co-primary clinical risk endpoints (CRE)” in smokers who switch from smoking cigarettes to using THS (*/QOS*) as compared with those continuing to smoke cigarettes for six months

ERS-09: PRIMARY ANALYSIS RESULT COMPARISON WITH SMOKING

	Type of Change	Observed Change*	alperin-Rüger Adjusted CI	1-sided <i>p</i> -value** (0.0156)	Statistical Significance
HDL-C	Difference	3.09 mg/dL	1.10, 5.09	< 0.001	✓ significant
WBC Count	Difference	-0.420 GI/L	-0.717, -0.123	0.001	✓ significant
sICAM-1	% Reduction	2.86%	-0.426, 6.04	0.030	✓
11-DTX-B2	% Reduction	4.74%	-7.50, 15.6	0.193	✓
8-epi-PGF _{2α}	% Reduction	6.80%	-0.216, 13.3	0.018	✓
COHb	% Reduction	32.2%	24.5, 39.0	< 0.001	✓ significant
FEV ₁ %pred	Difference	1.28%pred	0.145, 2.42	0.008	✓ significant
Total NNAL	% Reduction	43.5 %	33.7, 51.9	< 0.001	✓ significant

- All Clinical Risk Endpoints shifted in the same direction as smoking cessation effect observed in the literature
- 5 out of 8 biomarkers of potential harm were statistically significant compared to continued smoking



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* Observed change presented as LS Mean Difference / Relative Reduction

** Denotes significant *p* value at the 1.5625% level, following test multiplicity adjustment using the Hailperin-Rüger approach

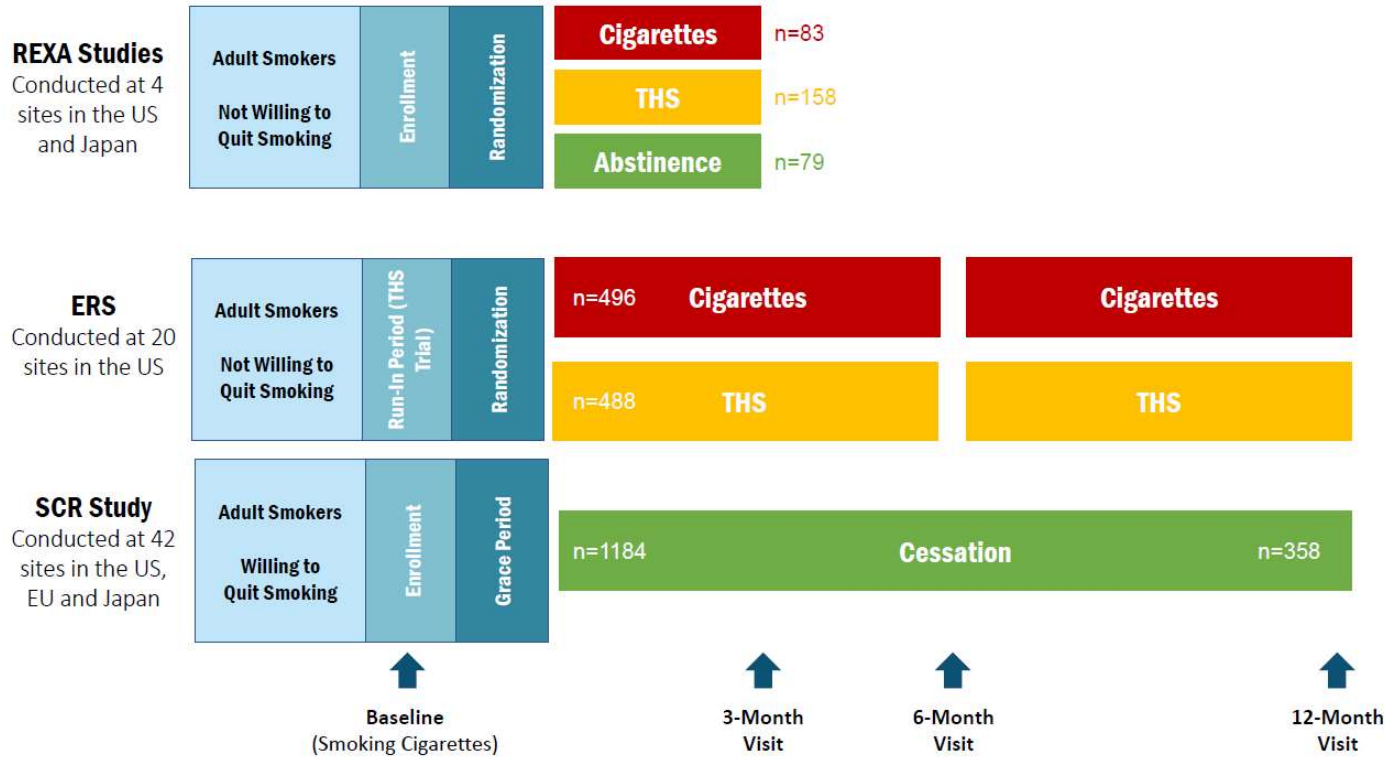
Lüdicke et al. Effects of Switching to a Heat-Not-Burn Tobacco Product on Biologically Relevant Biomarkers to Assess a Candidate Modified Risk Tobacco Product: A Randomized Trial (2019)
Cancer Epidemiol Biomarkers Prev. 28(11):1934-43 DOI: [10.1158/1055-9965.EPI-18-0915](https://doi.org/10.1158/1055-9965.EPI-18-0915)

ERS-09: STUDY CONCLUSIONS AND IMPACT

Conclusions: All endpoints showed favorable changes in the same direction as with smoking cessation and improved biological effects were observed in smokers who predominantly used THS compared with continued cigarette smoking, with similar nicotine levels in both groups.

Impact: Improvements in 5 of 8 biomarkers of effect are supportive of the research hypothesis, suggestive of disease risk reduction potential for smokers switching to THS instead of continuing to smoke cigarettes.

COUGH: EFFECTS OF CIGARETTE SMOKING, TOBACCO HEATING SYSTEM USE, AND SMOKING CESSATION

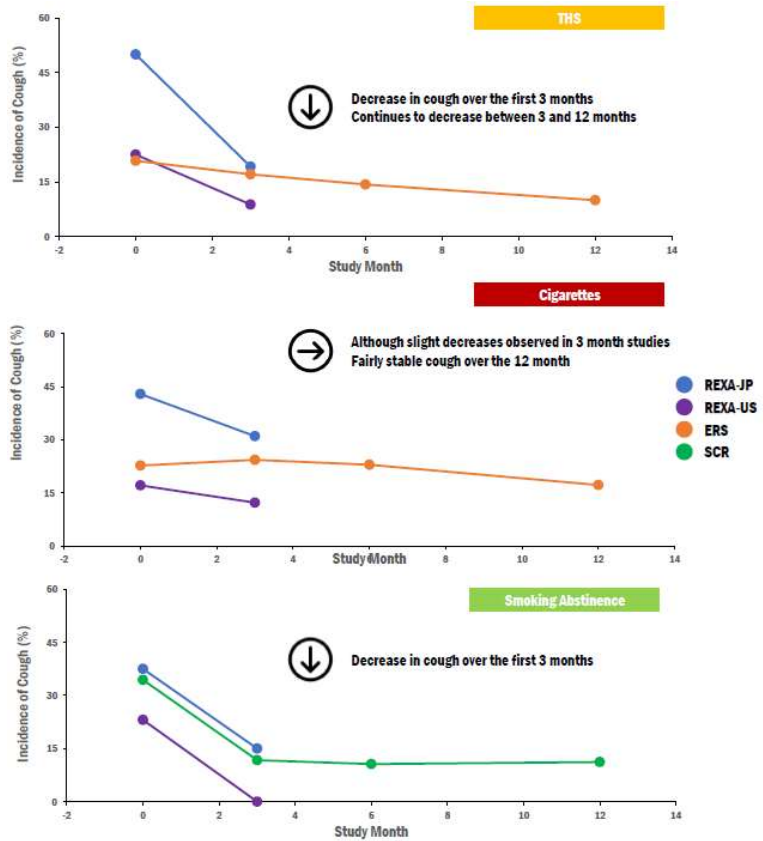


Cough symptom:

- Experience a **regular** need to cough within the 24 hours prior to visit
- Assessed by using a questionnaire and visual analog scale (VAS).

Felber L, et al. GFN conference 2020

COUGH: EFFECTS OF CIGARETTE SMOKING, TOBACCO HEATING SYSTEM USE, AND SMOKING CESSATION



Within a few weeks after switching to THS, one to two thirds of the subjects who reported a regular need to cough at baseline reported that they no longer felt the need to cough.

The decline in need to cough was observed among subjects in THS group and who abstained from smoking but not among those who continued to smoke cigarettes.

Felber L, et al. GFN conference 2020

COUGH: EFFECTS OF CIGARETTE SMOKING, TOBACCO HEATING SYSTEM USE, AND SMOKING CESSATION

CONCLUSIONS

- There is a consensus among epidemiological studies in smokers that chronic cough has a significant link with COPD development.
- The decline in the incidence of reported cough after switching to THS in several clinical studies could indicate a potential for decreasing the risk of COPD and limiting the global burden of the disease.

US FDA AUTHORISE SALE OF THS – OVERALL CONCLUSION



"FDA's scientific evaluation of the company's applications, peer-reviewed published literature and other sources, found that the aerosol produced by the IQOS tobacco heating system contains fewer toxic chemicals than cigarette smoke, and many of the toxins identified are present at lower levels than in cigarette smoke. Additionally, IQOS delivers nicotine in levels close to combustible cigarettes suggesting a likelihood that IQOS users may be able to completely transition away from combustible cigarettes and use IQOS exclusively. Available data, while limited, also indicate that few non-tobacco users would be likely to choose to start using IQOS, including youth."



CONCLUSIONS

- Smoking remains a challenge for the prevention of respiratory diseases and the best option for every smoker is to quit.
- Tobacco Harm Reduction, i.e. offering smoke-free alternatives to adult smokers, is a sensible, complementary addition to existing tobacco control strategies.
- Although addictive and not risk free, scientific data on smoke-free products provide clear evidence of their potential for harm reduction.
- The totality of the scientific evidence on THS demonstrates that switching completely to THS presents less risk of harm than continuing to smoke.



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THANKS FOR YOUR ATTENTION

In case of further questions:
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