HARM REDUCTION: THE ROLE OF HEATED TOBACCO PRODUCTS FOR SMOKERS, WITH FOCUS ON CVD AND CHRONIC RESPIRATORY DISEASES

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BULGARIA — SMOKING PREVALENCE AND HEALTH STATUS

Ref. 1





1. WHO Bulgaria factsheet 2016

2. European Commission: State of Health in the EU Bulgaria – Country Health Profile 2017

3. Health and Environment Alliance (HEAL) - www.env-health.org

THE BURDEN OF NON-COMMUNICABLE DISEASES (NCD)

Global NCD Burden

NCDs such as cardiovascular disease (CVD), respiratory disease, and cancer caused:

- > 41 million deaths globally in 2017
- ~18 million CVD deaths in 2017

Bulgarian NCD Burden

NCDs such as CVD, respiratory disease, and cancer caused:

- > 102,000 deaths in Bulgaria in 2017
- >65,000 CVD deaths in Bulgaria in 2017

Institute for Health Metrics and Evaluation (IHME). GBD Compare Data Visualization. Seattle, WA: IHME, University of Washington, 2016. Available from http://vizhub.healthdata.org/gbd-compare. (Accessed October 16th 2020)

CARDIOVASCULAR RISK



Total cardiovascular risk measured with SCORE (Systematic Coronary Risk Evaluation) in men:

- More than 46% over 65 years.
- High in a large proportion of urban population

Dyakova M, et al. Croat Med J. 2008;49:783-91

GLOBAL DISEASE RISK ASSOCIATED WITH $\mathrm{PM}_{2.5}$



Cohen et al. Lancet 2017; 1907-1918.

RESPIRATORY RISK — IMPACT OF SMOKING HABIT



FROM GOLD GUIDELINES 2020

"EXPOSURE TO PARTICLES.

ACROSS THE WORLD, CIGARETTE SMOKING IS THE MOST COMMONLY ENCOUNTERED RISK FACTOR FOR COPD.

CIGARETTE SMOKERS HAVE A HIGHER PREVALENCE OF **RESPIRATORY SYMPTOMS** AND **LUNG FUNCTION ABNORMALITIES**, A GREATER **ANNUAL RATE OF DECLINE IN FEV**₁, AND A GREATER **COPD MORTALITY RATE** THAN NONSMOKERS."

Global Strategy for the Diagnosis, Management and Prevention of COPD, Global Initiative for Chronic Obstructive Lung Disease (GOLD) 2020

COPD DEVELOPMENT DRIVEN BY OXIDATIVE STRESS

- "Oxidative stress is now recognized as a major predisposing factor in the pathogenesis of COPD"
- "Antioxidant capacity in COPD is substantially reduced as a result of cigarette smoking and exacerbations"
- "Oxidative stress persisting long after the cessation of cigarette smoking or exacerbation, due to the continued production of reactive oxygen species from endogenous sources."

CONSEQUENCES OF OXIDATIVE STRESS IN COPD

- "The pathogenesis of COPD involves several oxidative stressinduced cellular and molecular processes"
- "Oxidative stress imposed by inhaled oxidants or produced from endogenous sources can lead to depletion of antioxidants"
- "An oxidant/antioxidant imbalance in favor of oxidants leads to activation of various cellular processes which result in cellular and molecular events involved in pathogenesis of COPD."

THE NATURAL HISTORY OF CHRONIC AIRFLOW OBSTRUCTION



Fletcher and Peto in 1977 described that:

 "The lung function (FEV₁) falls gradually over a lifetime. In most non-smokers and many smokers clinically significant airflow obstruction never develops. In susceptible people smoking causes irreversible obstructive changes. If a susceptible smoker stops smoking he will not recover his lung function but the average further rates of loss of FEV₁ will revert to normal"





- "The faster progression of functional impairment in COPD occurs early, and it particularly occurs in GOLD stage II (stage I: 40 mL/yr, stage II 47-79 mL/yr)"
- "To make efforts for early spirometric detection of COPD on the basis of risk factors rather than symptoms."

COPD IN NONSMOKERS

Nonsmoking risk factors associated with COPD Indoor air pollution:

- Occupational exposures
- Treated pulmonary tuberculosis
- Lower-respiratory-tract infections during childhood
- Chronic asthma
- Outdoor air pollution
- Poor socioeconomic status
- Low educational attainment
- Poor nutrition



Salvi SS, et al. Lancet 2009; 374: 733-43

WHAT IS THE OBJECTIVE OF TOBACCO HARM REDUCTION?

- Smoking is addictive and causes a number of serious diseases
- It is estimated that more than 1 billion people worldwide 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 decide not to quit.

* http://www.who.int/tobacco/publications/surveillance/reportontrendstobaccosmoking/en/index4.html Figure adapted from Clive Bates presentation to E-Cigarette Summit (19 Nov 2013) Note: Reduced Risk Products ("RRPs") is the term PMI uses to refer to products that present, are likely to present, or have the potential to present less risk of harm to smokers who switched to these products versus continued smoking

0.0

WHAT IS THE RISK ASSOCIATED WITH NICOTINE?



-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)





ELIMINATION OF TOBACCO COMBUSTION IS KEY



Temperature (°C)



- 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

WHY HEAT TOBACCO RATHER THAN BURN IT?

The Tobacco Heating System (THS) is designed and has been demonstrated to:

- Heat tobacco without combustion
- Preserve elements of the taste, sensory experience, nicotine delivery profile, and ritual characteristics of cigarettes





R = Radial distance from heater

Note: THS stands for Tobacco Heating System version 2.2 Source: PMI Research and Development

DIFFERENCES BETWEEN THS AEROSOL AND CIGARETTE SMOKE



REDUCTIONS OF TOXICANTS BY DISEASE CATEGORY



THS: NO EMISSION OF CARBON-BASED SOLID PARTICLES





Cigarette smoke

Carbon-based nanoparticles Median diameter = 75 nm Amount: 6x10¹¹ particles = ~0.7 mg*



Blank (Air)



THS aerosol No solid particles

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

Under the Health Canada's Intense Smoking Regime. Pratte et al. Hum. Exp. Toxicol, 2017; 36:1115-1120. Cohen et al. Lancet 2017; 1907-1918.

NANOPARTICLES DEPOSITED IN THE LUNGS



Cigarette Smoke

Carbon-based nanoparticles 6x10¹¹ particles = ~0.7 mg*



THS Aerosol No solid particles

Cigarette smoke (600 mg/m³ TPM)

Lung Deposition after 6 months





Corresponding concentration of THS aerosol

Apoe^{-/-} mice exposed for 6 months, 3 h/day and 5 days/week

Pratte et al. Hum. Exp. Toxicol, 2017; 36:1115-1120. Phillips B, et al. Toxicol Sciences, 2016 149: 411–432

PRECLINICAL EXPOSURE DATA: **REDUCED OXIDATIVE STRESS AND INFLAMMATION**

Log2Ratio 3R4F **THS2.2** Cessation Switch 3 6 8 8 3 6 3 6 8 8 Apo_A_I CD40 CD40 L CRP_Mouse EGF_Mouse Eotaxin Factor_VII FGF 9 FGF basic Fibrinogen GCP_2_Mouse GH GM CSF Haptoglobin IFN_gamma IL 1 alpha IL_1_beta IL_6 IL_7 IL 10 IL_11 IL_12p70 IL_18 Insulin IP_10 KC_GRO Leptin 4 Lymphotactin M_CSF_1 4 MCP 1 MCP_3 MCP_5 MDC 4 MIP 1 alpha MIP 1 beta MIP_1_gamma MIP 2 MIP_3_beta MMP_9 MPO Myoglobin OSM PAI 1 Resistin SAP SCF TIMP 1 Mouse TNF_alpha TPO VCAM_1 VEGF A VWF * After 3months of exposure

Society of Toxicology www.toxsci.oxfordjournals.org

TOXICOLOGICAL SCIENCES, 149(2), 2016, 411-432

doi: 10.1093/toxsci/kfv243 Advance Access Publication Date: November 25, 2015 Research Article

An 8-Month Systems Toxicology Inhalation/Cessation Study in Apoe^{-/-} Mice to Investigate Cardiovascular and Respiratory Exposure Effects of a Candidate Modified Risk Tobacco Product, THS 2.2, Compared With Conventional Cigarettes

Blaine Phillips,* Emilija Veljkovic,† Stéphanie Boué,† Walter K. Schlage,‡

Inflammatory mediators in BALF. Cell-free BALF supernatants were analyzed by using a multiplexed bead array. The ratios are given as the median values of treated mice over the median values of sham-exposed mice at the same time-point (truncated scale).

Only analytes with statistically significant differences compared with the sham under at least one condition are shown.

Phillips B, et al. Toxicological Sciences, 2016 149: 411–432

OXFORD

REDUCED ATHEROSCLEROTIC PLAQUE FORMATION IN THS AEROSOL-EXPOSED MICE



Plaque thickness 0.4 mm 0.3 mm 0.2 mm 0.1 mm 0 mm

Phillips B, et al. Toxicological Sciences, 2016 149: 411-432

PRECLINICAL EXPOSURE DATA: REDUCED IMPACT ON THE LUNGS



Semiquantitative histopathological scoring. Emphysema assessment by morphometry and histopathological evaluation of lung sections.



Macrophage count. Free lung cells in BALF. Light scattering and relative immunofluorescence were measured in BALF cells by flow cytometry.



Reference cigarette THS Cessation Switch

Sham

Morphometric analysis indicates CS-induced emphysema

Phillips B, et al. Toxicological Sciences, 2016 149: 411-432

. 2020 Apr 17;22(4):539-548.

REDUCED EXPOSURE TO HPHCs WITH THS USE IN HEALTHY HUMAN SUBJECTS





1. Ludicke F et al. Cancer Epidem Biomarkers Prev 2019; 28:1934

ERS-09: PRIMARY OBJECTIVE AND CO-PRIMARY ENDPOINTS





Assess the changes across a set of "8 co-primary clinical risk endpoints (CRE)" in smokers who switch from smoking cigarettes to using THS relative to those continuing to smoke cigarettes for 6 months

Ludicke F et al. Cancer Epidem Biomarkers Prev 2019; 28:1934

ERS-09: PRIMARY ANALYSIS RESULT COMPARISON WITH SMOKING

Type of Change Observed Change* Hailperin-Rüger 1-sided p-value** Statistical Significance **Adjusted Cl** (0.0156)✓ significant HDL-C Difference 3.09 mg/dL 1.10, 5.09 < 0.001 ✓ significant WBC Count Difference -0.717, -0.123 -0.420 GI/L 0.001 sICAM-1 % Reduction 2.86% -0.426, 6.04 0.030 \checkmark 11-DTX-B2 % Reduction -7.50, 15.6 0.193 \checkmark 4.74% 8-epi-PGF₂₀ -0.216, 13.3 % Reduction 6.80% 0.018 \checkmark ✓ significant COHb % Reduction 32.2% 24.5, 39.0 < 0.001 FEV₁%pred 1.28%pred 0.145, 2.42 ✓ significant Difference 0.008 √ significant **Total NNAL** % Reduction 43.5 % 33.7, 51.9 < 0.001

• 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

*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

Ludicke F et al. Cancer Epidem Biomarkers Prev 2019; 28:1934-43



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"

Ludicke F et al. Cancer Epidem Biomarkers Prev 2019; 28:1934

ERS-09: POST-HOC ANALYSIS IN MILD COPD PATIENTS

AMERICAN COLLEGE OF CHEST PHYSICIANS



TOBACCO HEATING SYSTEM 2.2 IN MILD TO MODERATE COPD SUBJECTS: AN EXPLORATORY ANALYSIS

S. MICHAEL ANSARI* FRANCESCO SERGIO LOYSE FELBER MEDLIN NICOLA LAMA ASHRAF ELAMIN AND CHRISTELLE HAZIZA

Ansari SM, et al. CHEST 2019, 156, ISSUE 4, SUPPLEMENT: A465-A466 DOI: https://doi.org/10.1016/j.chest.2019.08.485

POPULATION



2. Global Strategy for the Diagnosis, Management and Prevention of COPD, Global Initiative for Chronic Obstructive Lung Disease (GOLD) 2018

STUDY PERIOD



1. Ludicke F et al. Cancer Epidem Biomarkers Prev 2019; 28:1934

RESULTS: RESPIRATORY BIOMARKERS OF EFFECT



Pre-BDR FEV1



ERS: Exposure Response Study SC: Smoking Cessation response study CC: Combustible Cigarette THS: Tobacco Heating System Pre-BDR FEV1: pre-bronchodilator Forced Expiratory Volume in 1 second

Ansari SM, et al. CHEST 2019, 156, ISSUE 4, SUPPLEMENT: A465-A466 DOI: https://doi.org/10.1016/j.chest.2019.08.485

RESULTS: RESPIRATORY AND CARDIOVASCULAR BIOMARKERS OF EFFECT





ERS: Exposure Response Study SC: Smoking Cessation response study CC: Combustible Cigarette THS: Tobacco Heating System Pre-BDR FEV1: pre-bronchodilator Forced Expiratory Volume in 1 second 8-epi PGF 2α: 8-epi Prostaglandin F2α sICAM: Soluble Intercellular Adhesion Molecule WBC: White Blood Cell





Ansari SM, et al. CHEST 2019, 156, ISSUE 4, SUPPLEMENT: A465-A466 DOI: https://doi.org/10.1016/j.chest.2019.08.485

POST-HOC ANALYSIS CONCLUSIONS

- The results indicated a favorable THS–CC difference of 72 mL in FEV₁ among COPD subjects after 12 months.
- They also indicated a reduction of 1.95 GI/L in WBC count, 6.8% in sICAM-1 level, and 28% in 8-epi-PGF2α level for THS relative to CC.
- After 12 months of follow-up, most of the **BoEffs** in subjects with COPD who used the THS showed **favorable shifts** in the direction of the **changes** observed with smoking cessation.
- The magnitude of these shifts was more pronounced than those observed in the ERS, which included a majority of healthy subjects.
- The results of this preliminary analysis are consistent with the findings of the main ERS and suggest a reduced harm potential for THS relative to smoking in subjects with mild to moderate COPD.

US FDA AUTHORIZE MARKETING OF THS OVERALL CONCLUSION



The U.S. Food and Drug Administration authorized the marketing of Philip Morris Products S.A.'s "IQOS Tobacco Heating System" as modified risk tobacco products (MRTPs).

911(g)(2) Exposure Modification Order:

Modified Risk Claim #3:

"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."

DA U.S. FOOD & DRUG

- Home / News & Events / FDA Newsroom / Press Announcements / FDA Authorizes Marketing of IQOS Tobacco Heating System with 'Reduced Exposure' Information

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

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CONCLUSIONS

- Smoking remains a challenge for 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, smoke-free products have a potential for harm reduction, as clearly evident from scientific data.
- The totality of the scientific evidence on THS demonstrates that switching completely to THS presents less risk of harm than continuing to smoke.



THANKS FOR YOR ATTENTION

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