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TOBACCO HEATING SYSTEM VS. COMBUSTIBLE CIGARETTES: CAN LUNG FUNCTION PARAMETERS BE IMPROVED?

Francesco Sergio, MD
30th May 2019

LUNGS: FROM BENCH TO BEDSIDE



Review

Oxidative Stress in COPD: Sources, Markers, and Potential Mechanisms

Adam John Anthony McGuinness * and Elizabeth Sapey

International Journal of COPD

Open Access Full Text Article

Oxidative stress and free radicals in COPD – implications and relevance for treatment

Wolfgang Domej¹

Dovepress

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REVIEW

TASK FORCE REPORT
ERS/ATS GUIDELINES

Prevention of COPD exacerbations: a European Respiratory Society/ American Thoracic Society guideline

Jadwiga A. Wedzicha [ERS co-chair]¹, Peter M.A. Calverley², Richard K. Albert³, Antonio Anzueto⁴, Gerard J. Criner⁵, John R. Hurst⁶, Marc Miravittles ⁷, Alberto Papi ⁸, Klaus F. Rabe⁹, David Rigau¹⁰, Pawel Sliwinski¹¹, Thomy Tonia¹², Jørgen Vestbo¹³, Kevin C. Wilson¹⁴ and Jerry A. Krishnan [ATS co-chair]¹⁵

Global Initiative for Chronic
Obstructive
Lung
Disease

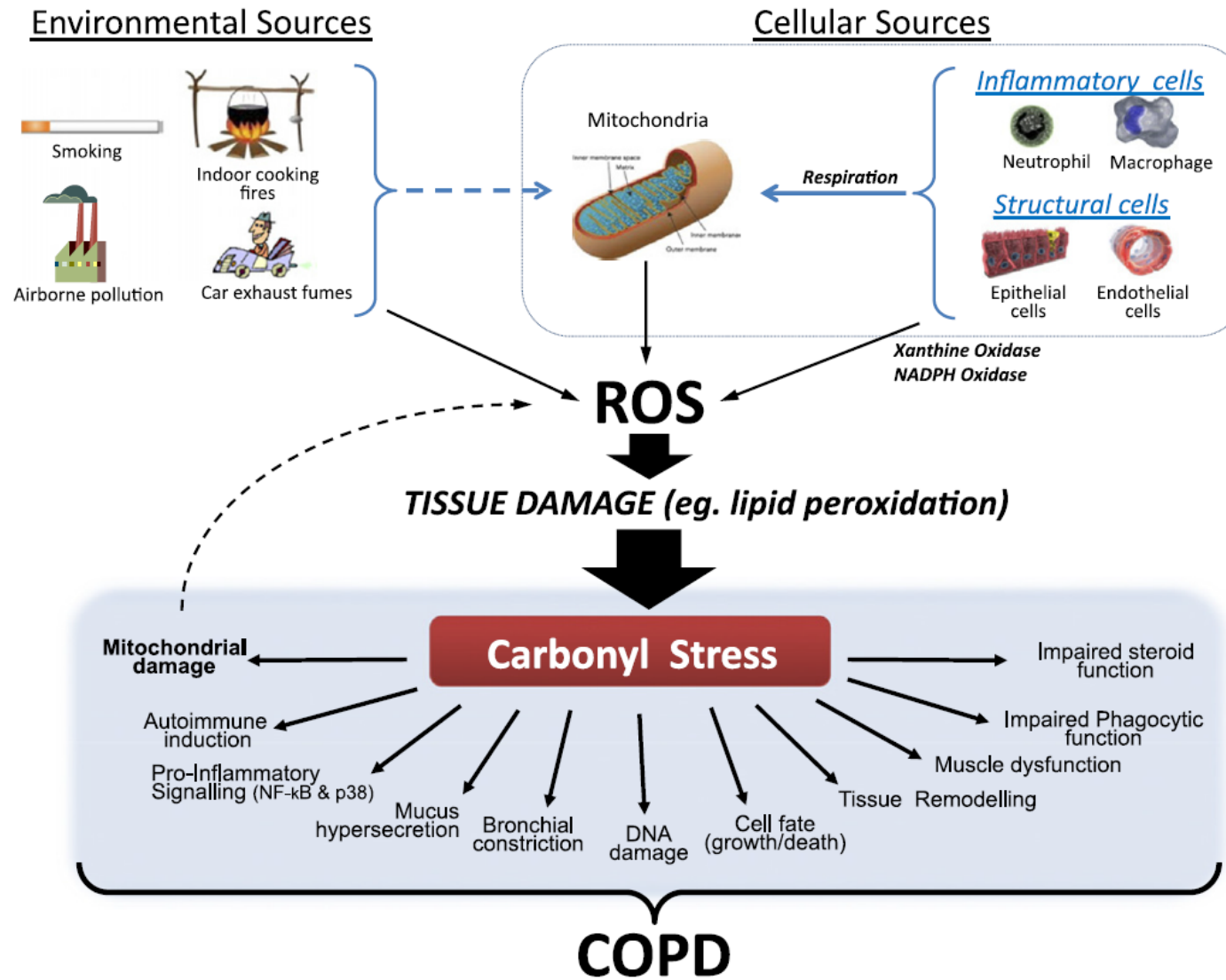


GLOBAL STRATEGY FOR THE DIAGNOSIS,
MANAGEMENT, AND PREVENTION OF
CHRONIC OBSTRUCTIVE PULMONARY DISEASE
2018 REPORT

LUNGS: A HIGH-OXYGEN ENVIRONMENT

- The lungs are constantly in a **high-oxygen environment** due to their high blood supply and large surface area.
- The lung epithelium is also constantly exposed to **oxidants generated endogenously** during respiration from mitochondrial electron transport and **activated inflammatory cells** that influx into the lungs, and **exogenously** from **cigarette smoke** and **air pollutants**, such as **ozone, nitrogen dioxide, and combustion particulates**, as a result of its exposure to the **environment**.

DEVELOPMENT OF COPD DRIVEN BY OXIDATIVE STRESS MECHANISM



ROS: REACTIVE OXIDATIVE SPECIES
Superoxide radical
Hydrogen peroxide

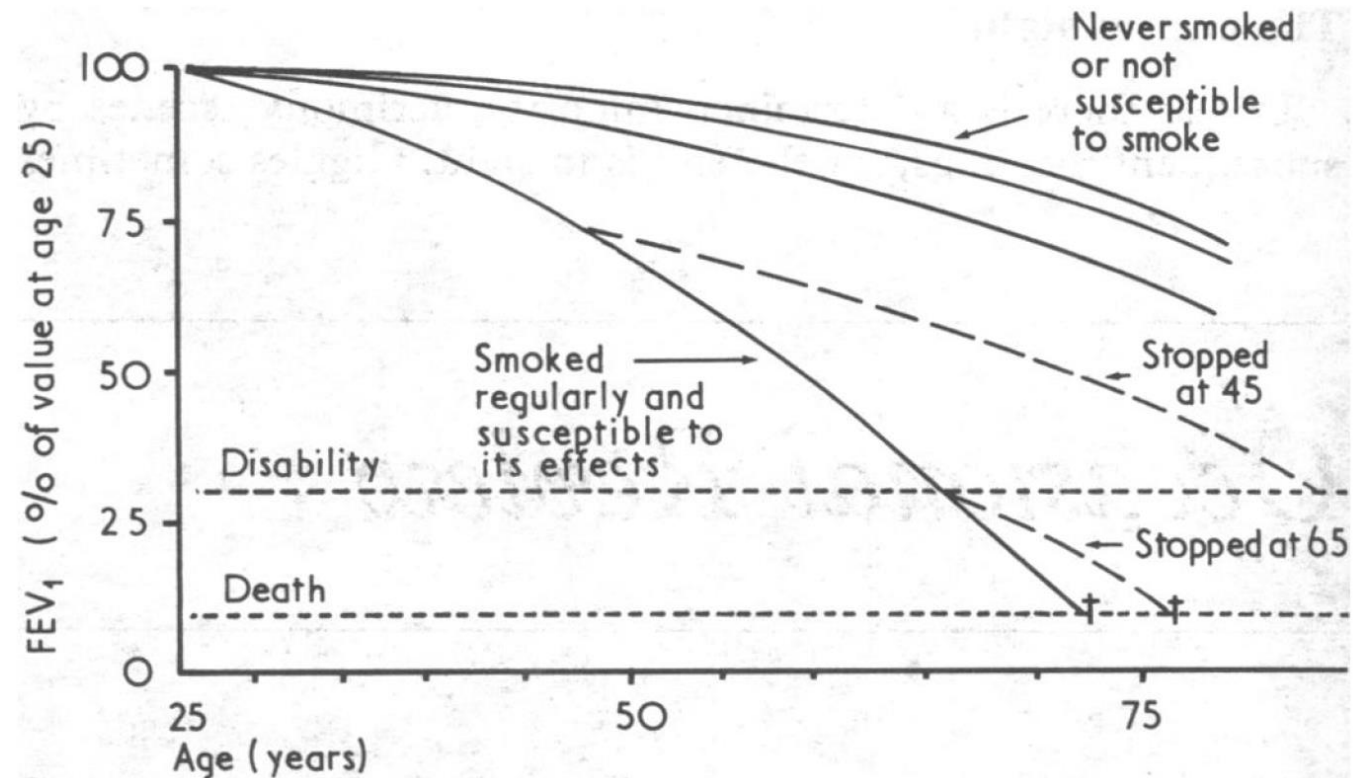
THE IMPACT OF SMOKING CESSATION

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

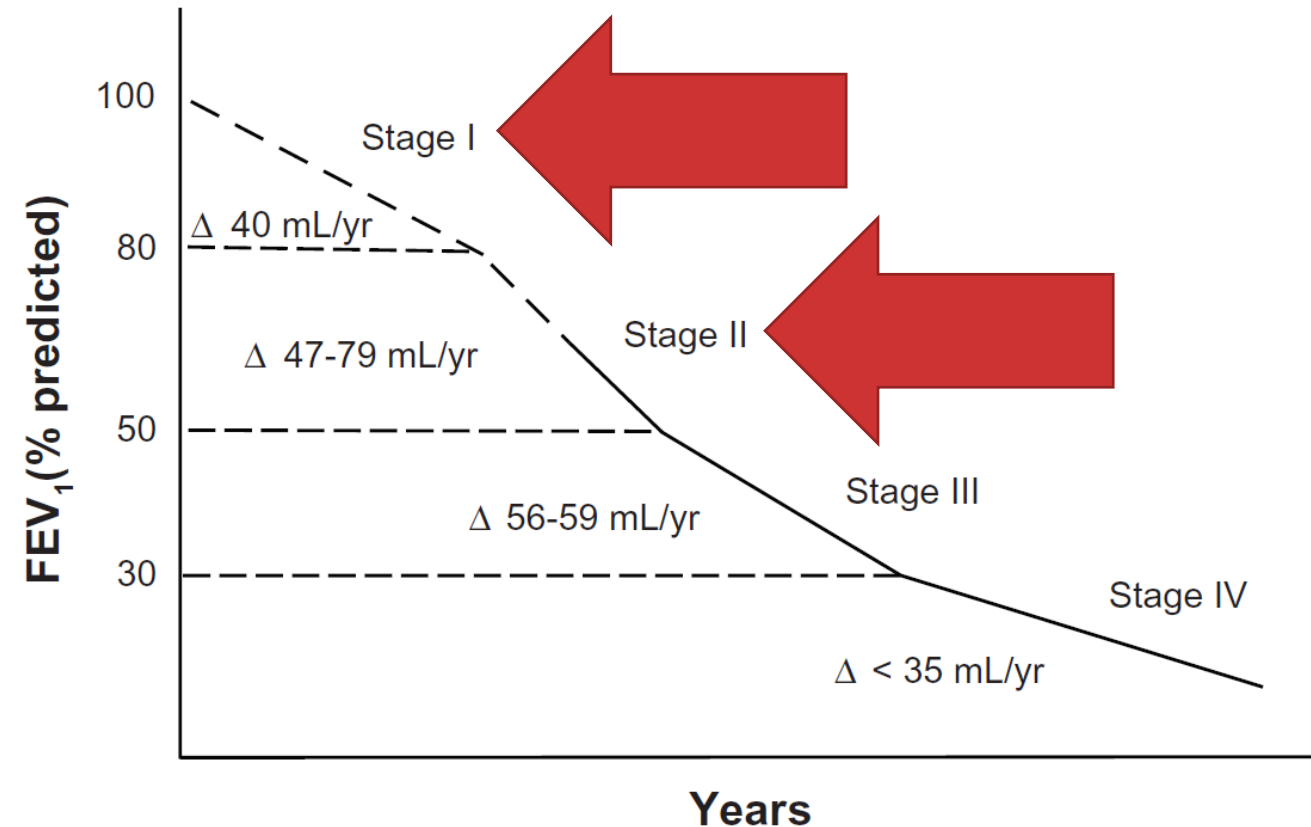
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Lung function decline in COPD

Claudio Tantucci

Conclusion

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



Tantucci C et al. International Journal of COPD 2012;7 95-99

THE IMPACT OF SMOKING CESSATION

International Journal of COPD

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ORIGINAL RESEARCH

Smoking cessation affects the natural history of COPD

Jiu-Wu Bai¹

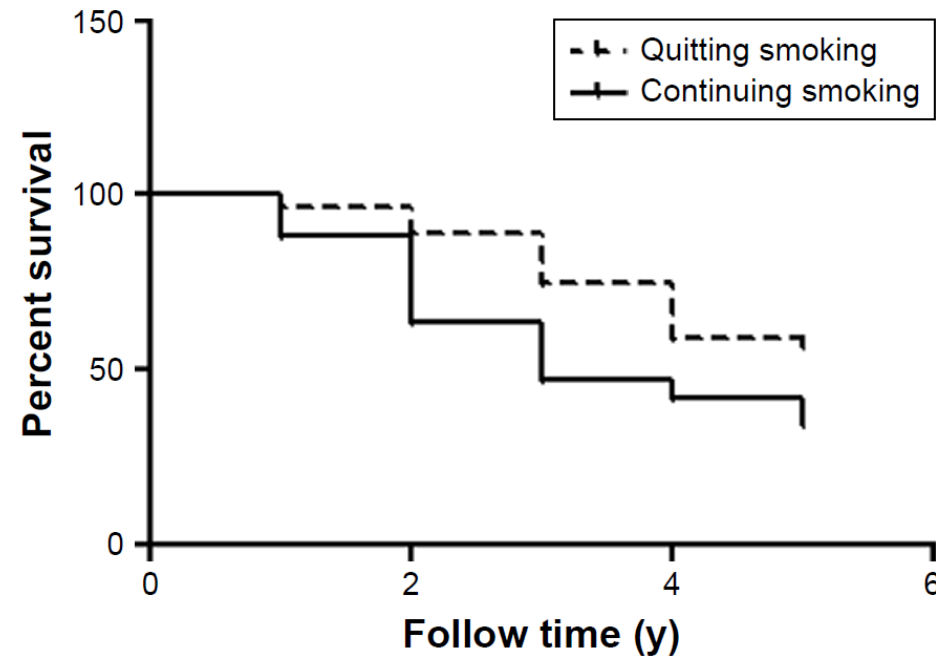
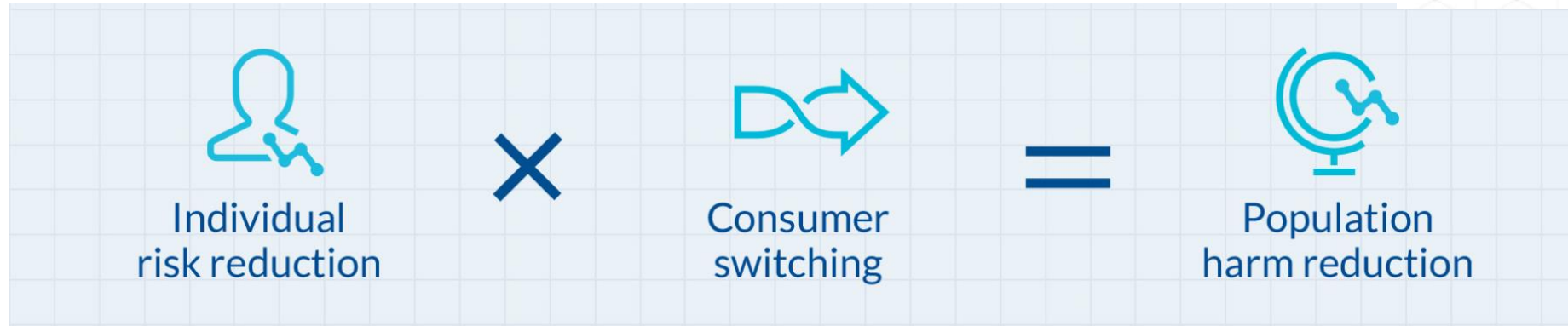
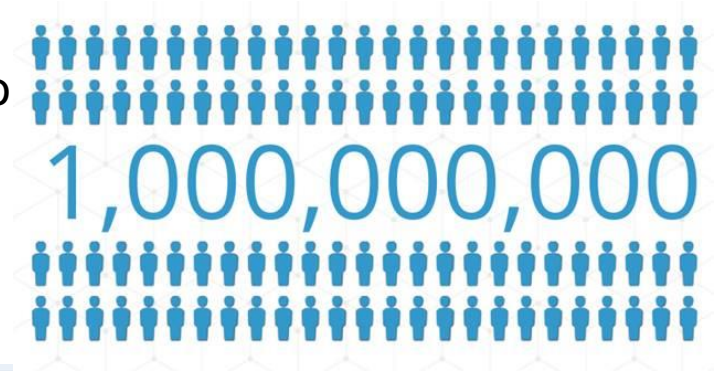


Figure 1 Kaplan–Meier survival curves for COPD patients in the quitting-smoking group (n=92; 40 deaths) and continuing-smoking group (n=112; 73 deaths).

WHAT IS THE OBJECTIVE OF 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

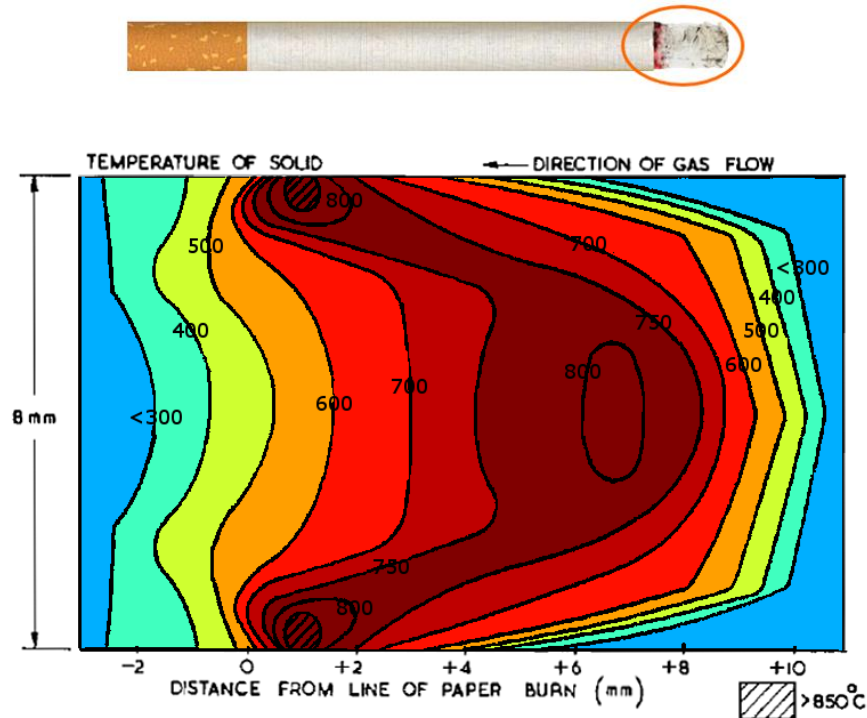
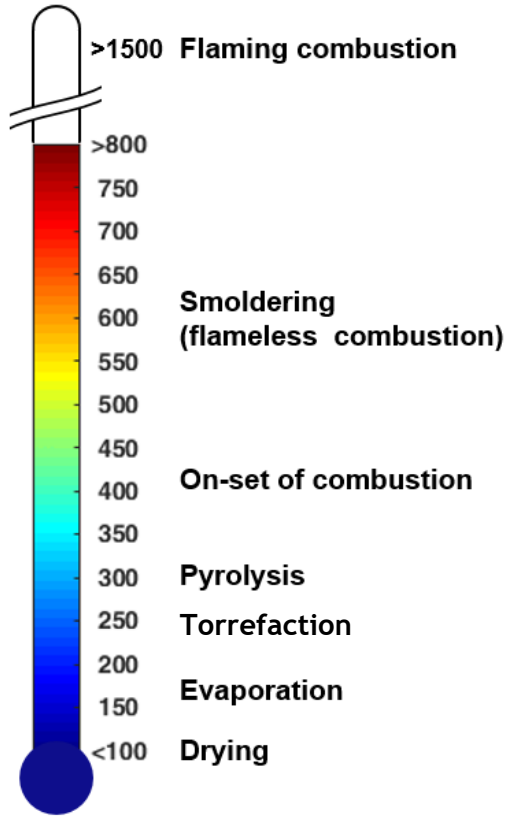


- Successful harm reduction requires that current adult smokers be offered a range of satisfactory Reduced-Risk Products they can fully switch to, should they decide not to quit.

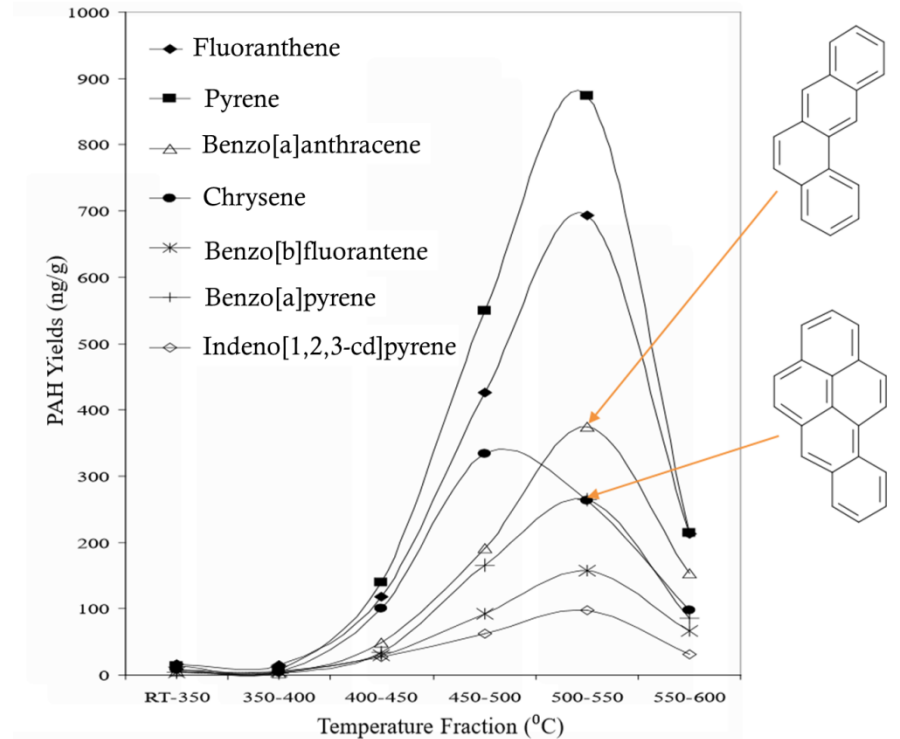
ELIMINATION OF TOBACCO COMBUSTION IS KEY

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

Temperature (°C)



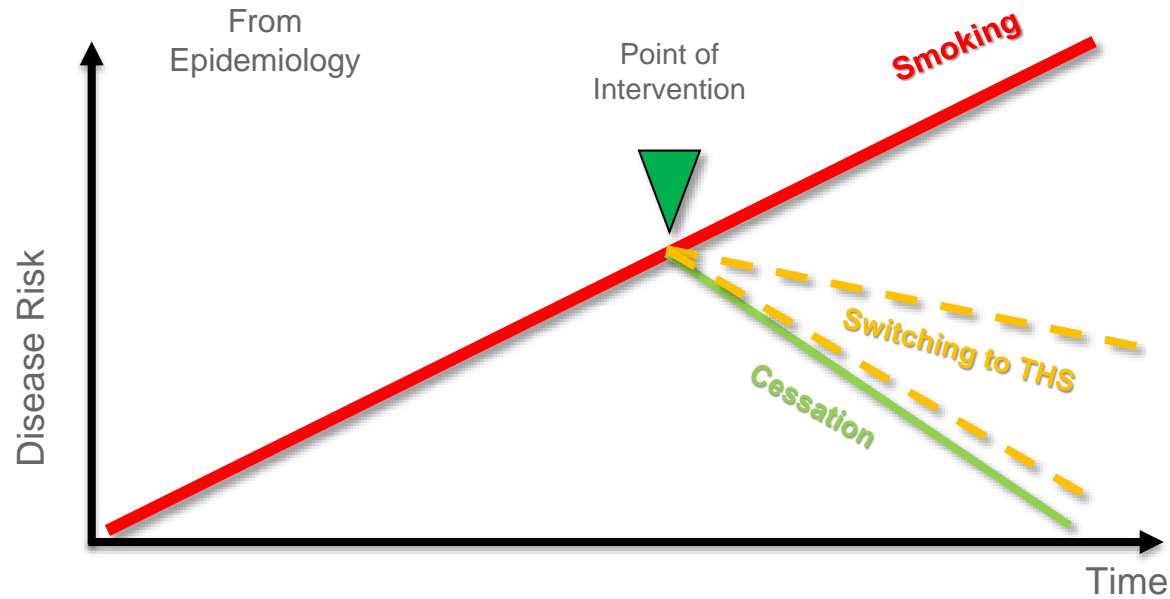
Reference 1



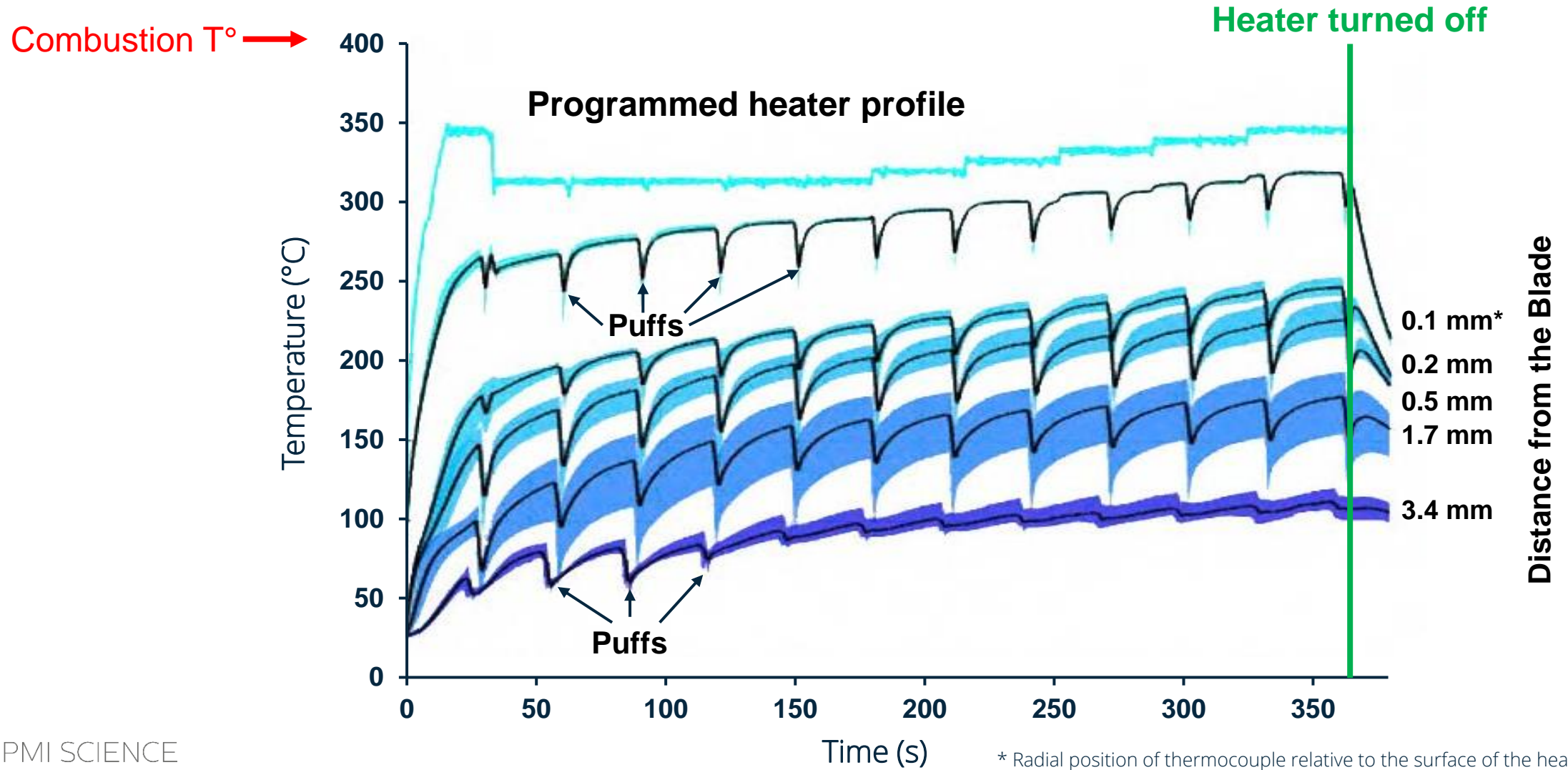
Reference 2

PMI'S REDUCE RISK PRODUCTS (RRPs) SCIENTIFIC ASSESSMENT APPROACH

Assessment Framework



THS: ABSENCE OF COMBUSTION



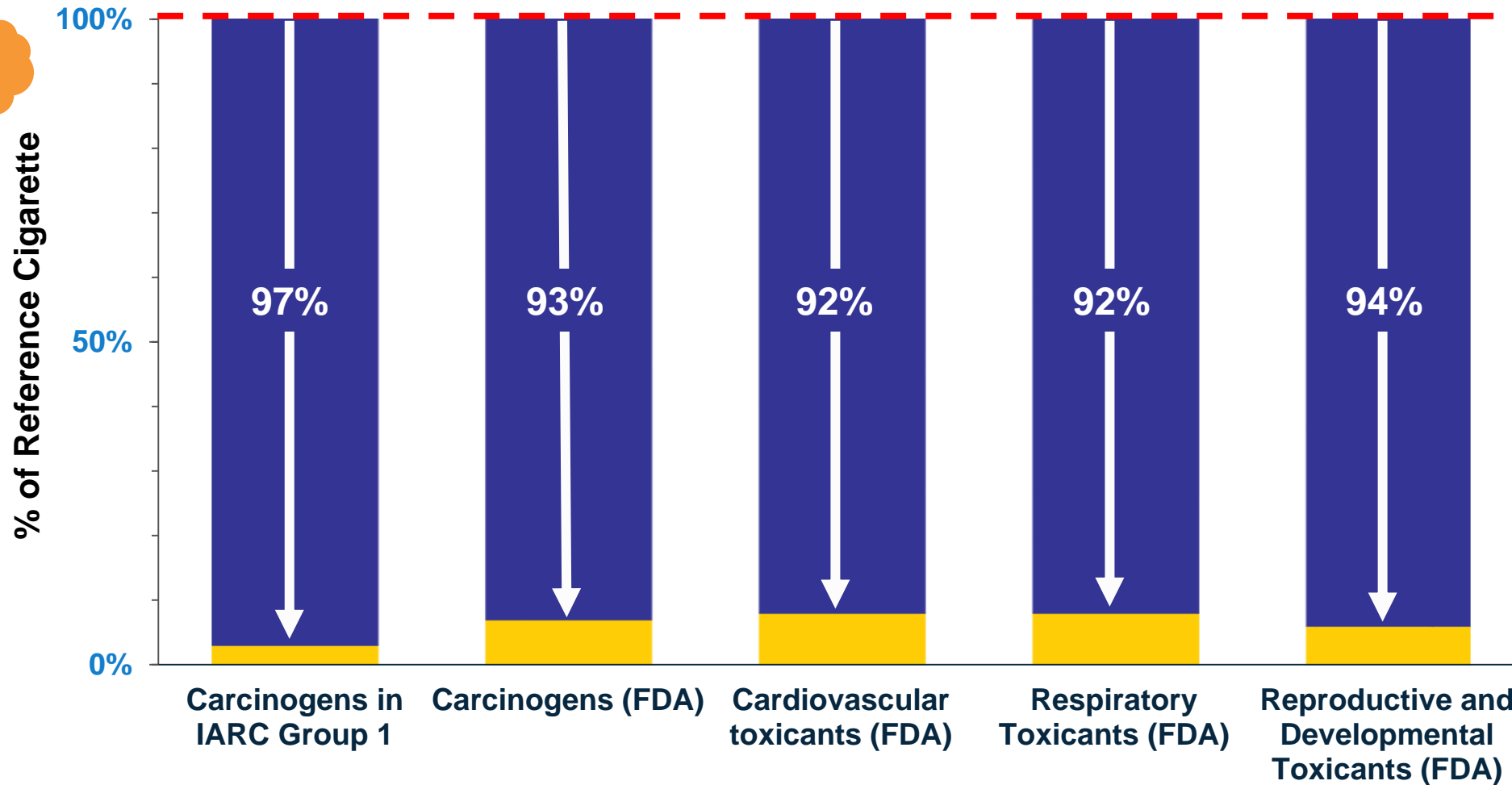
REDUCTIONS OF TOXICANTS BY DISEASE CATEGORY



Reference Cigarette

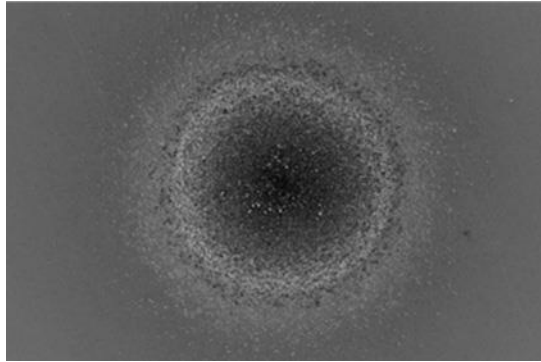
The reductions in the concentrations of most HPHCs in the THS2.2 aerosol were greater than 90% when compared with 3R4F

The ranges for nicotine, formaldehyde, ethyl methyl ketone, acrylonitrile, 1,3-butadiene, benzene, styrene, toluene, o-cresol, p-cresol, NNN, ammonia, and acetamide were lower than the Intermediate Precision (IP)



Number of toxicants	12	29	8	18	7
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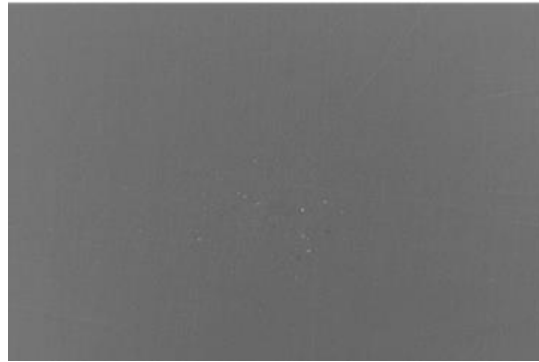
THS: NO CARBON-BASED SOLID PARTICLES EMISSION



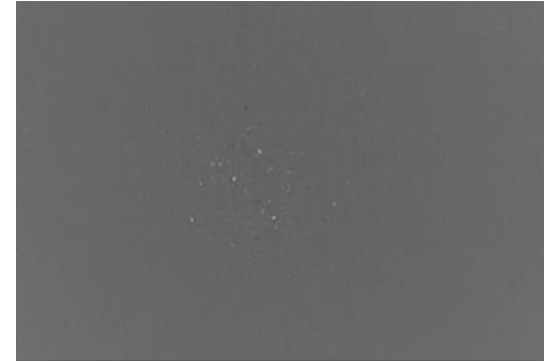
Cigarette smoke

Carbon-based nanoparticles
Median diameter = 75 nm

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



**Blank
(Air)**



THS aerosol

No solid particles

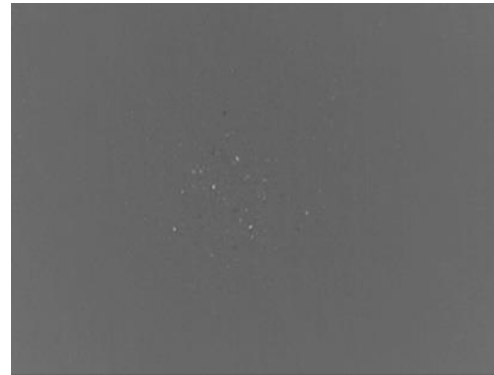
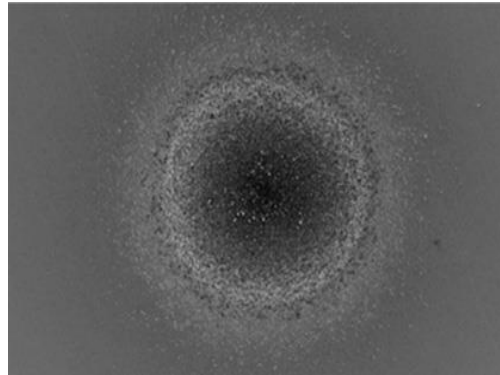


Scanning Electron Microscopy images of the collected smoke/aerosol after passing through a thermodenuder set at 300° C to remove the volatile portion / collected material characterized by Electron Diffusive X-ray.

NANOPARTICLES DEPOSIT IN THE LUNG

Cigarette Smoke

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



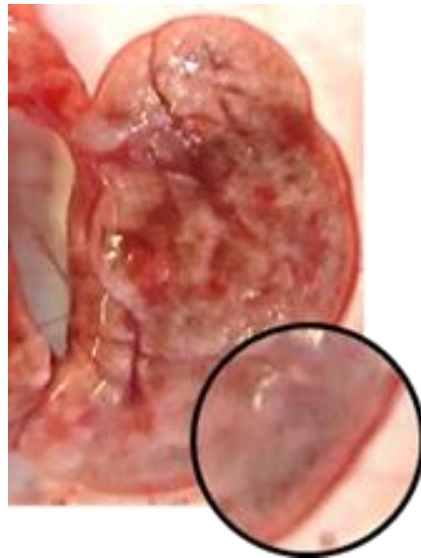
THS Aerosol

No solid particles



Lung Deposition after 6 months

Cigarette smoke
(600 mg/m³ TPM)



Corresponding
concentration of
THS aerosol

PRECLINICAL EXPOSURE DATA AVAILABLE

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

doi: 10.1093/toxsci/kfv243

Advance Access Publication Date: November 25, 2015

Research Article



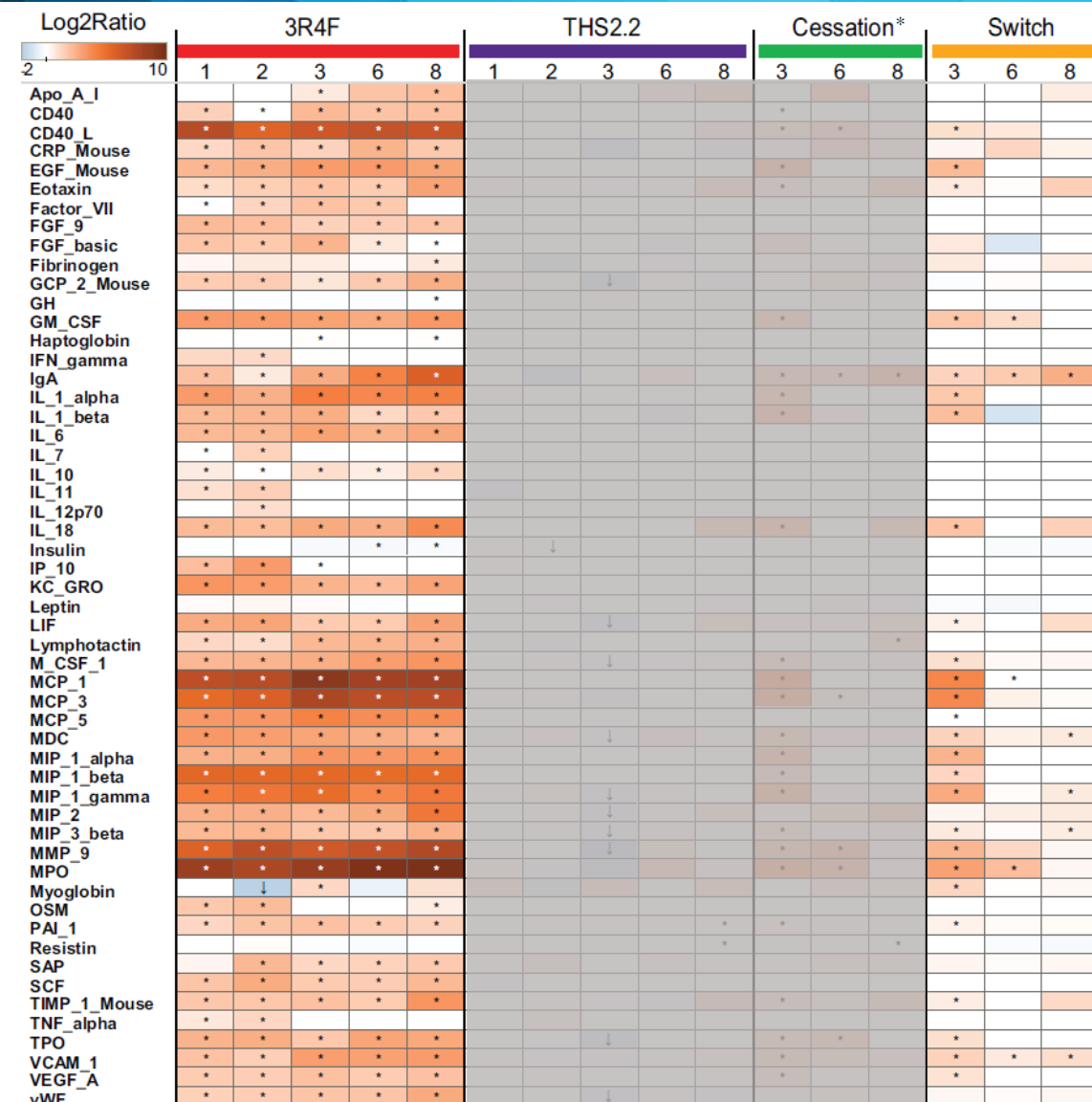
SOT | Society of Toxicology
www.toxsci.oxfordjournals.org

An 8-Month Systems Toxicology Inhalation/Cessation Study in Apo^{e-/-} 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 using a multiplexed bead array. Ratio is given as median of treated mice over median of sham-exposed mice at the same time-point (truncated scale). Only analytes with statistically significant differences compared with sham under at least one condition are shown.

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



* After 3months of exposure

PRECLINICAL EXPOSURE DATA AVAILABLE



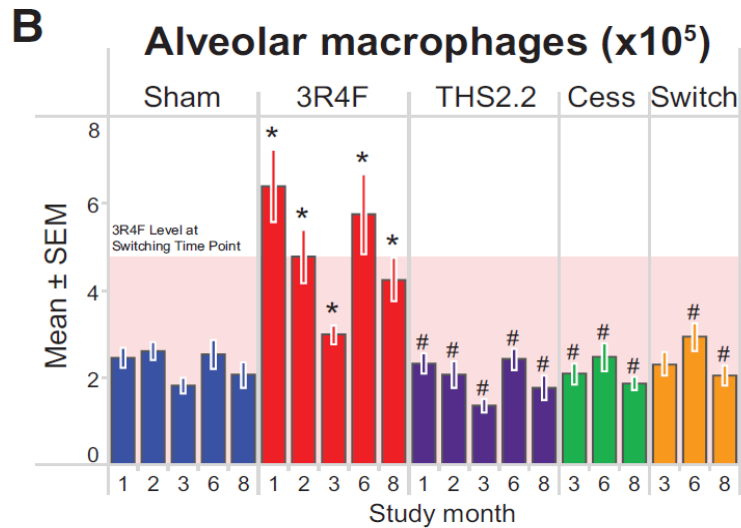
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TOXICOLOGICAL SCIENCES, 149(2), 2016, 411–432

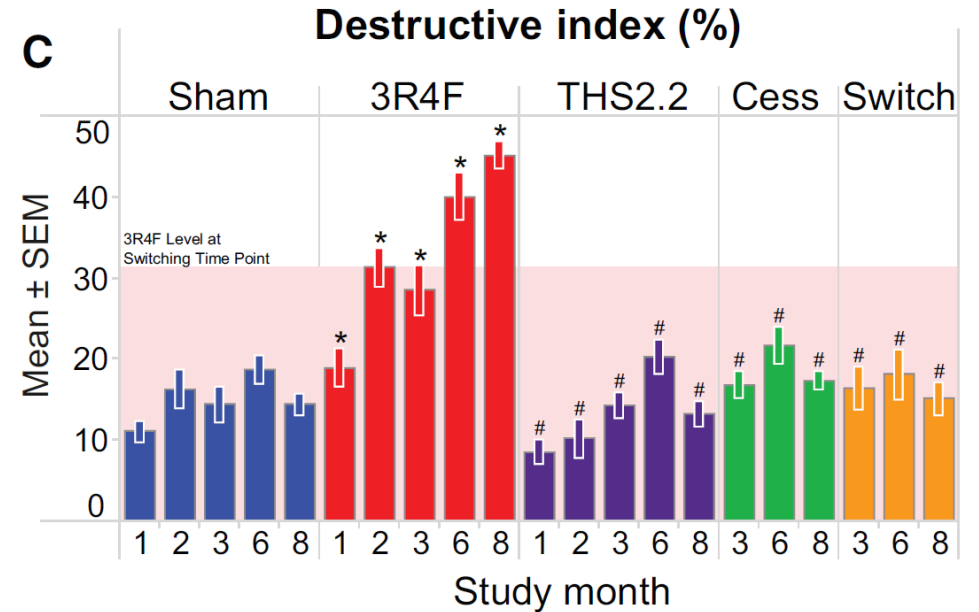
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An 8-Month Systems Toxicology Inhalation/Cessation Study in Apoe^{-/-} Mice to Investigate Cardiovascular and Respiratory Exposure Effects of a Candidate Modified Risk Tobacco Product, THS 2.2, Compared With Conventional Cigarettes

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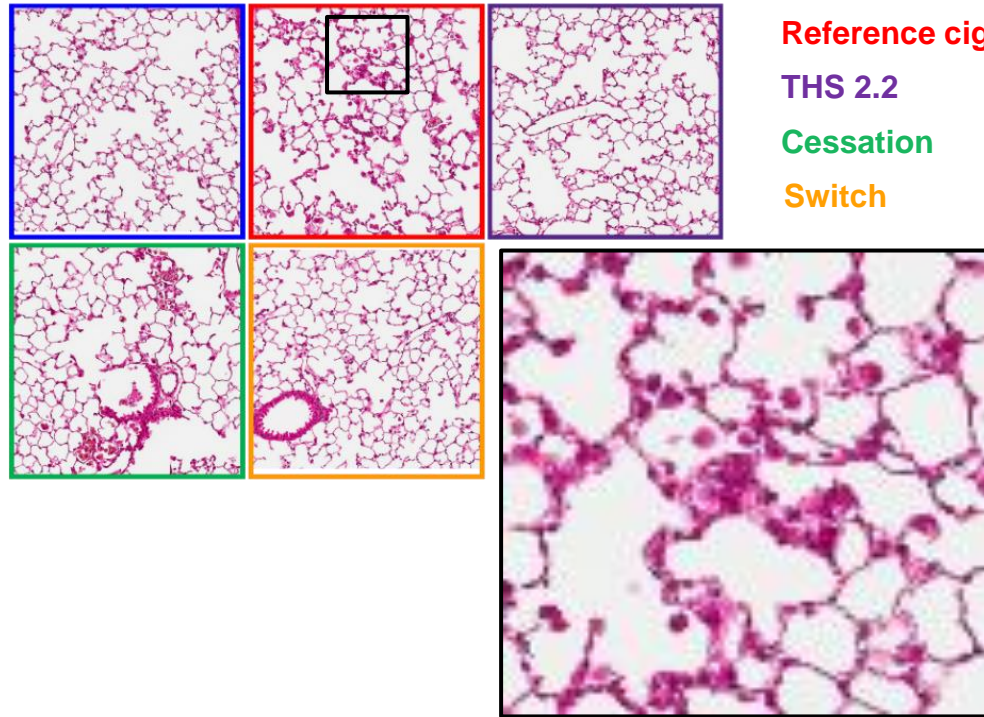


Free lung cells in BALF. Light scatter and relative immunofluorescence were measured in BALF cells by flow cytometry. B, Macrophage count.



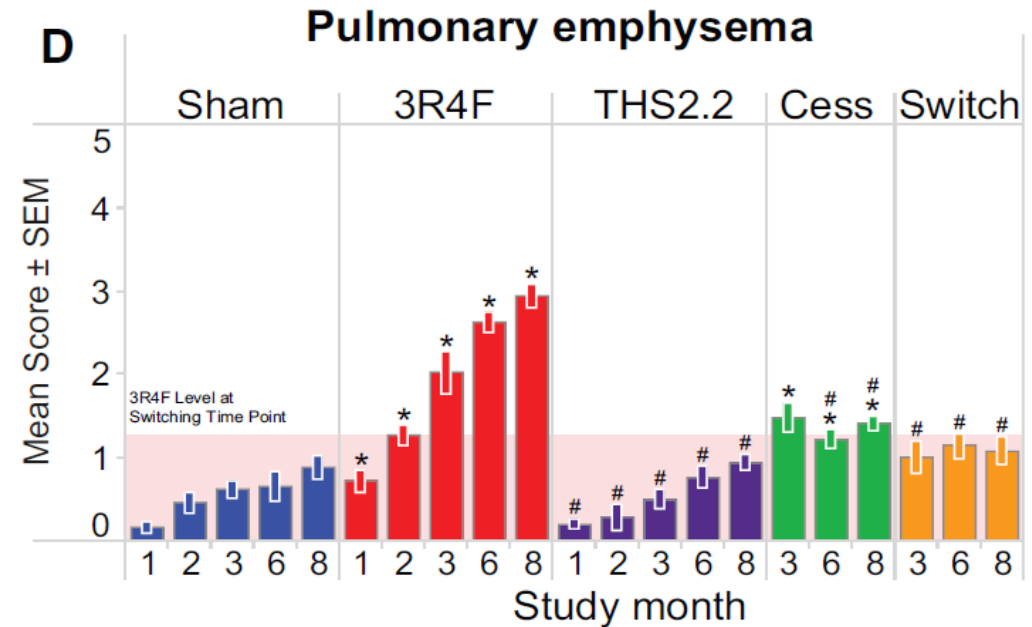
Phillips B, et al. Toxicological Sciences, 2016 149: 411–432

PRECLINICAL EXPOSURE DATA AVAILABLE



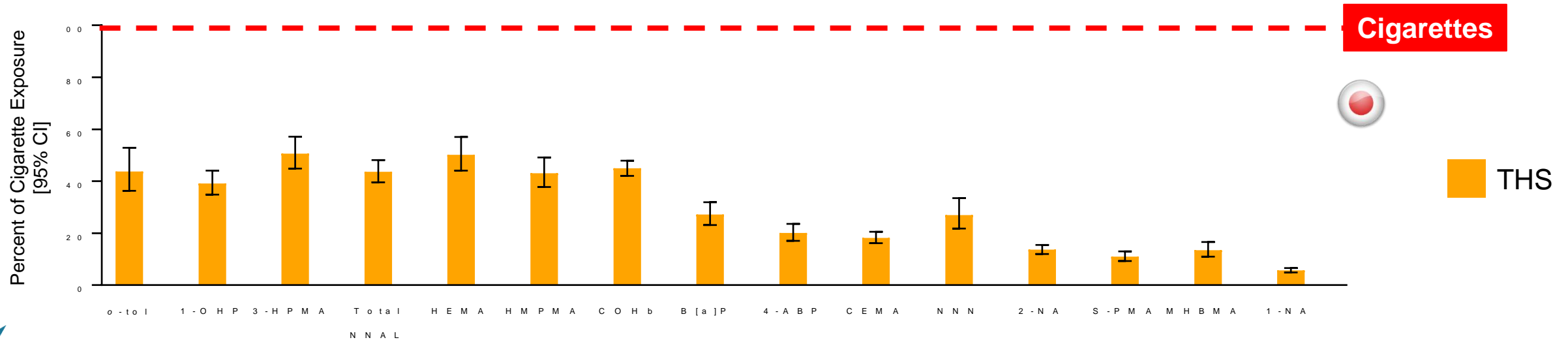
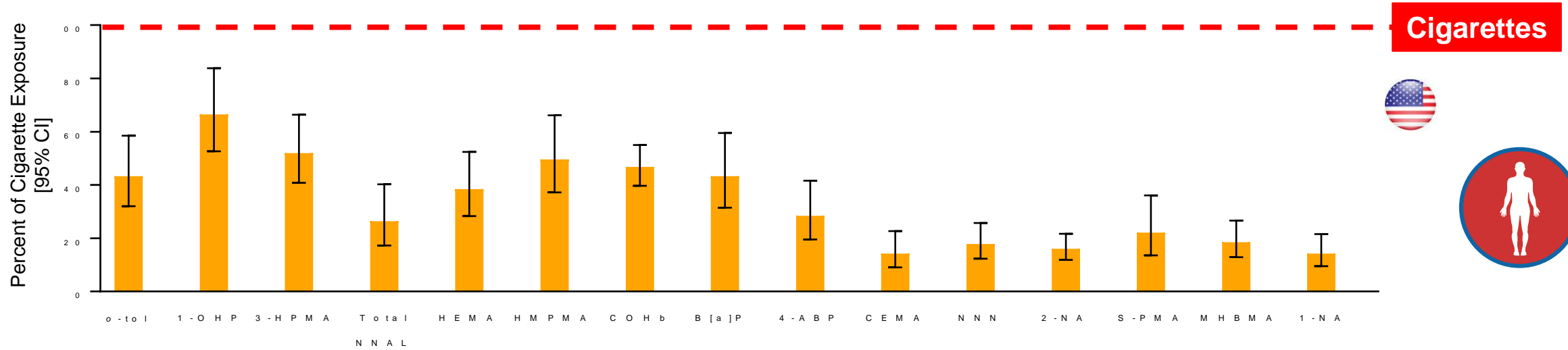
Sham
Reference cigarette
THS 2.2
Cessation
Switch

Morphometric analysis indicates CS-induced emphysema



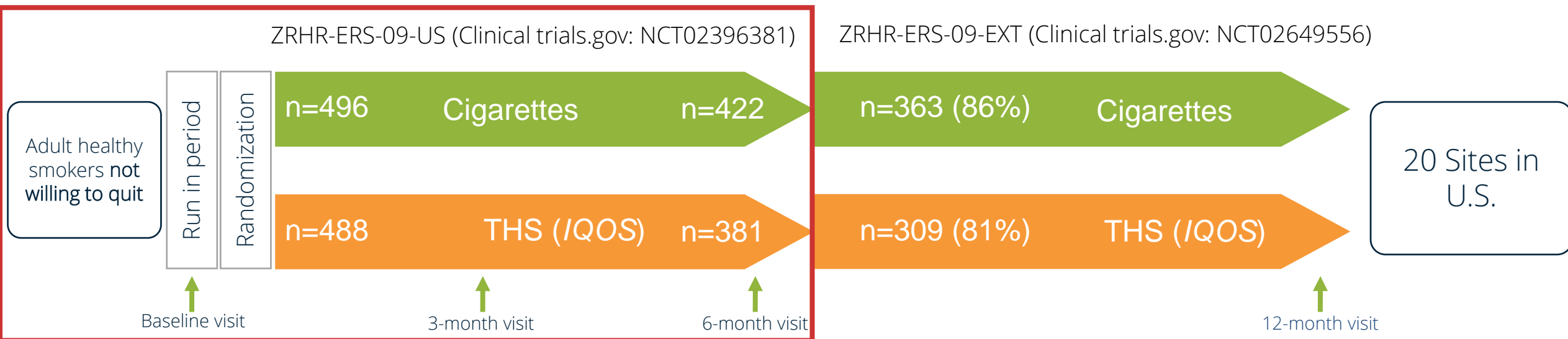
Emphysema assessment by morphometry and histopathological evaluation of lung sections. D, Semiquantitative histopathological scoring.

REDUCED EXPOSURE TO HPHCs WITH THS USE IN HEALTHY HUMAN SUBJECTS

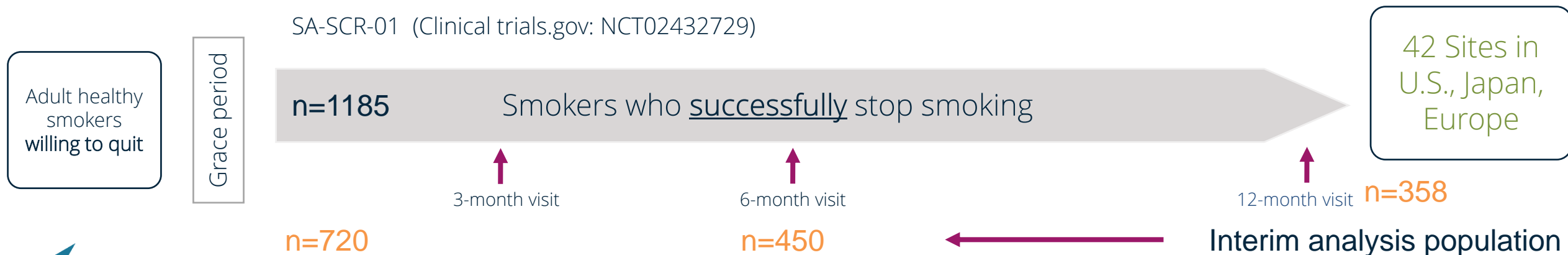


EXPOSURE RESPONSE STUDY ERS-09

STUDY DESIGN



Smoking Cessation Response Study



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

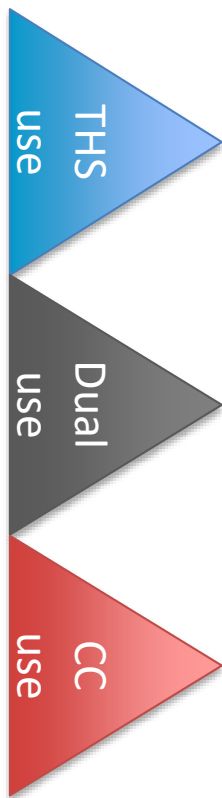


Co-Primary Endpoints Representative of Pathomechanisms

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 (*IQOS*) as compared with those continuing to smoke cigarettes for six months

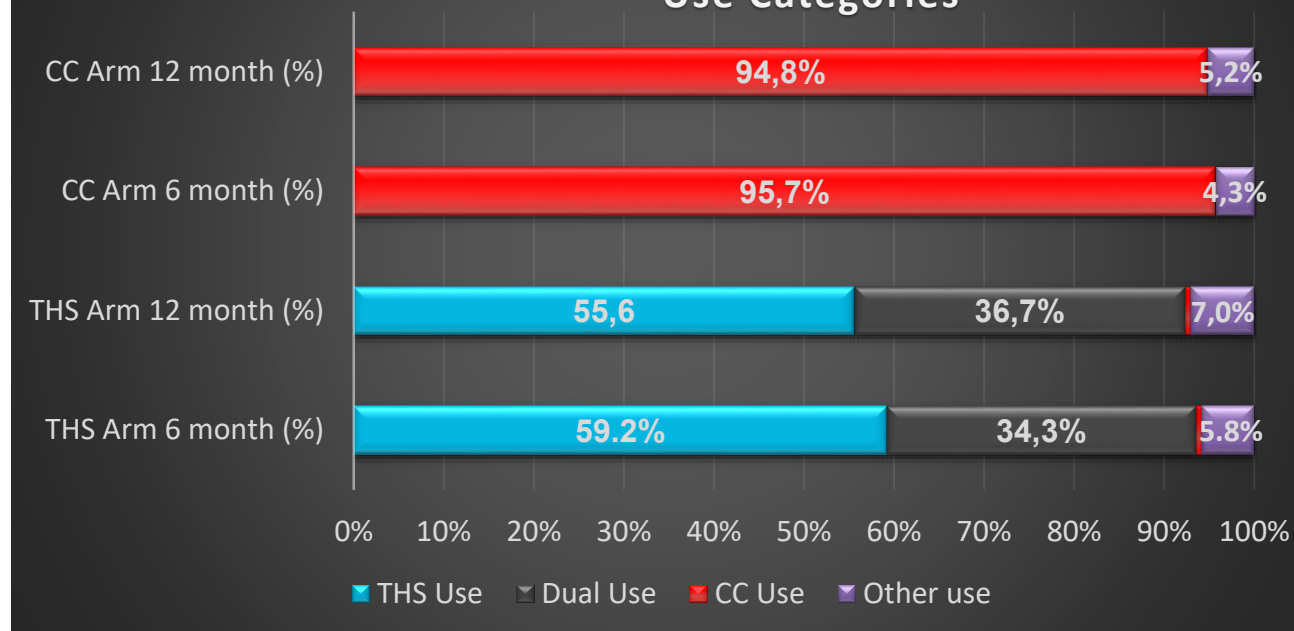
MAIN ANALYSIS POPULATION



- Randomized product use
- $\geq 70\%$ THS use (*)
- Randomized product use
- $1\% \leq$ THS use $< 70\%$ over the period or THS-use and CC-use do not apply $\geq 50\%$ of the days
- Randomized product use
- $< 1\%$ THS use (*)

* Over the whole analysis period and daily on at least 50% of the days period

Distribution of Randomized Subjects by Product Use Categories



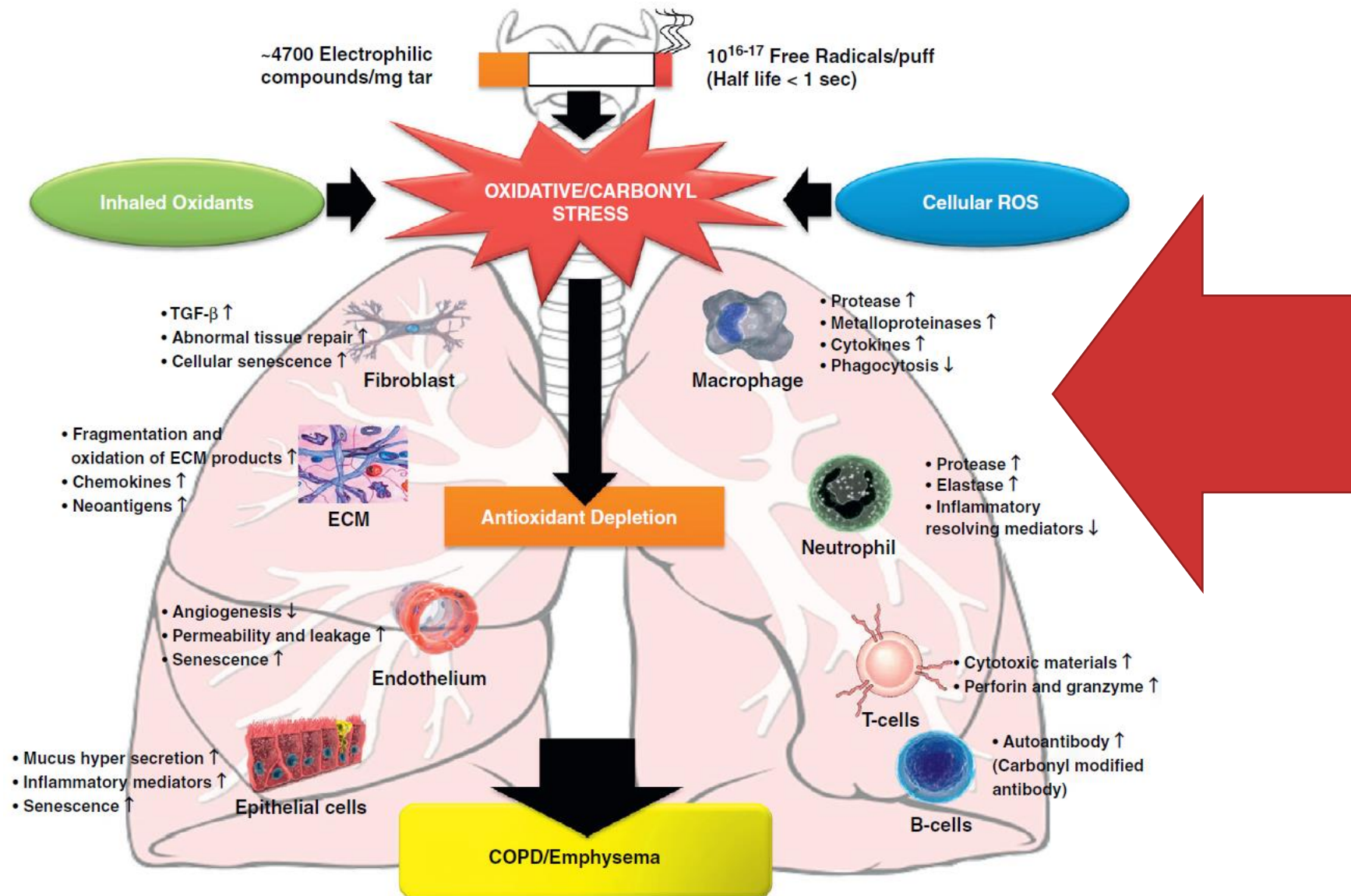
ERS-09: PRIMARY ANALYSIS RESULT COMPARISON WITH SMOKING

	Type of Change	Observed Change*	Halperin-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	✓
WBC Count	Difference	-0.420 GI/L	-0.717, -0.123	0.001	✓
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	✓
FEV ₁ %pred	Difference	1.28%pred	0.145, 2.42	0.008	✓
Total NNAL	% Reduction	43.5 %	33.7, 51.9	< 0.001	✓

* Observed change presented as LS Mean Difference / Relative Reduction

5 of 8 CREs were statistically significant compared with continued smoking

POTENTIAL CONSEQUENCES OF SWITCHING TO THS ON OXIDATIVE STRESS AND COPD



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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