Cancer and its Causes in Korea

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Former President of the National Cancer Institute in France
Harm Reduction Consultant to PMI

Agenda

- Burden of Non-Communicable Diseases

- Causes of cancer in Korea

- Cancer development - a matter of dose and response

- How does cigarette smoke cause cancer

- Smoking Prevalence Globally and in Korea – Or why better, less harmful alternatives are needed

The Burden of Non-Communicable Diseases

The Burden of Non-Communicable Diseases (NCDs)

Global Burden of NCDs

NCDs such as Cardiovascular, Respiratory Disease and Cancer cause:

- > 39 Mio Death globally in 2016

- ~ 9 Mio cancer deaths in 2016

NCD Burden in Korea

NCDs such as Cardiovascular, Respiratory Disease and Cancer cause:

- > 284k death in 2016
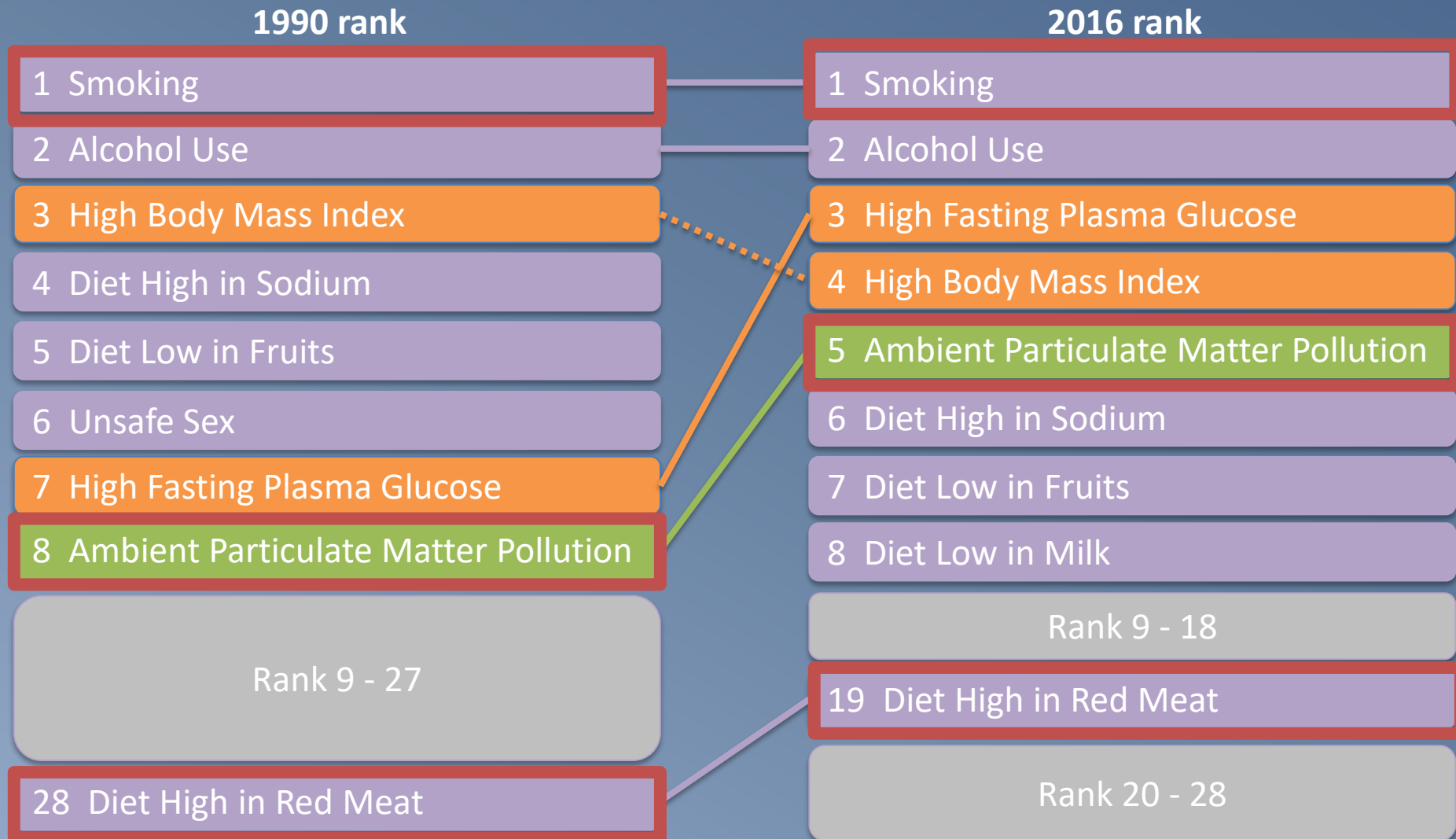
- > 100k cancer deaths in 2016

Numbers are based on public statistics for Korea

Causes of Cancer in Korea

Risk Factors for Cancer in Korea

Korea, All Ages, Both Sexes, Deaths per 100,000

1990 rank

1 Smoking
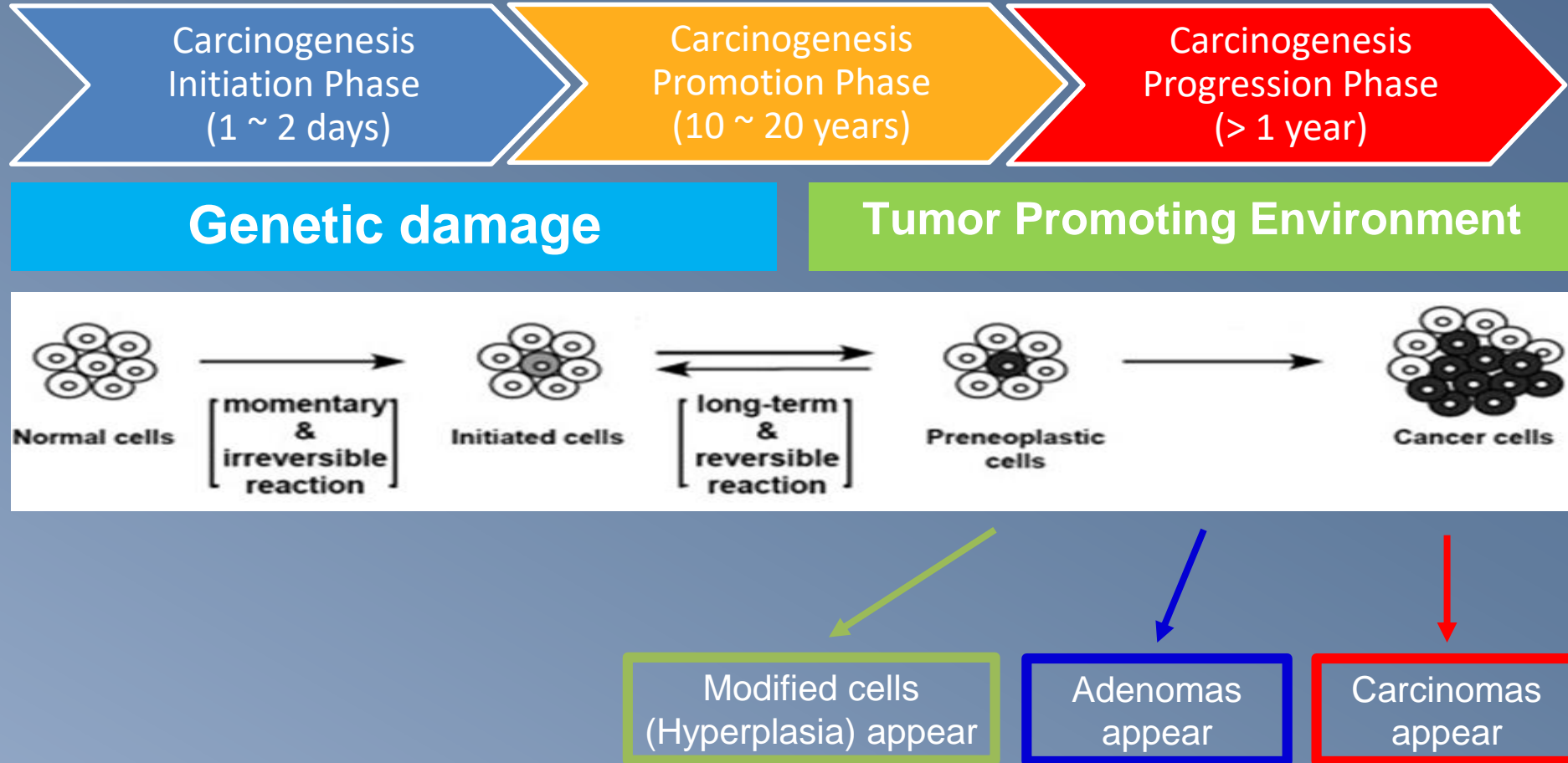2 Alcohol Use
3 High Body Mass Index
4 Diet High in Sodium
5 Diet Low in Fruits
6 Unsafe Sex
7 High Fasting Plasma Glucose
8 Ambient Particulate Matter Pollution

Rank 9 - 27

28 Diet High in Red Meat

2016 rank

1 Smoking
2 Alcohol Use
3 High Fasting Plasma Glucose
4 High Body Mass Index
5 Ambient Particulate Matter Pollution
6 Diet High in Sodium
7 Diet Low in Fruits
8 Diet Low in Milk

Rank 9 - 18

19 Diet High in Red Meat

Rank 20 - 28

Numbers are based on public statistics for Korea

6

Cancer development - a matter of dose response

Events in Carcinogenesis

| Carcinogenesis Initiation Phase (1 ~ 2 days) | Carcinogenesis Promotion Phase (10 ~ 20 years) | Carcinogenesis Progression Phase (> 1 year) |

Genetic damage

Tumor Promoting Environment

Normal cells → [momentary & irreversible reaction] → Initiated cells → [long-term & reversible reaction] → Preneoplastic cells → Cancer cells

Modified cells (Hyperplasia) appear

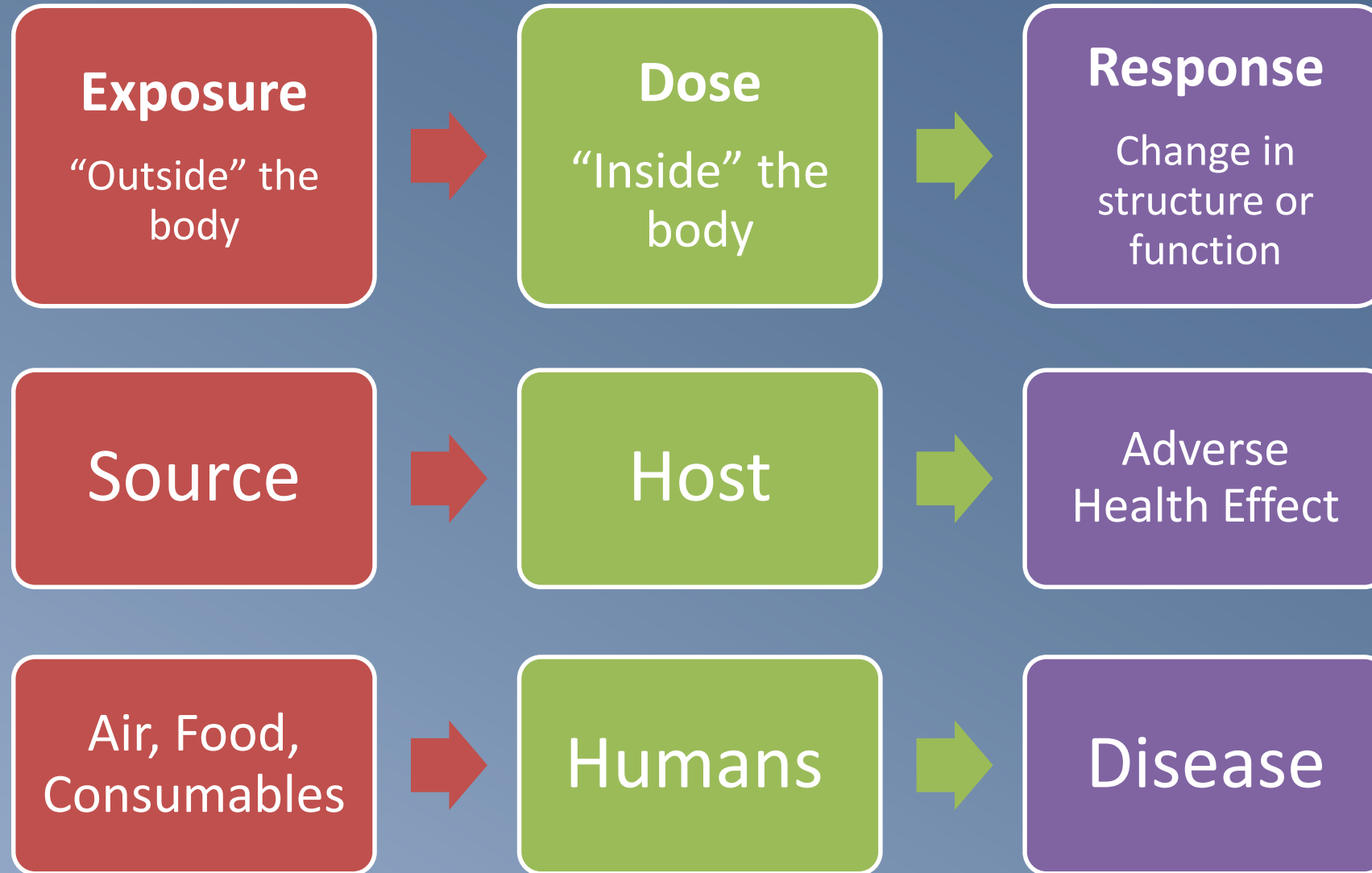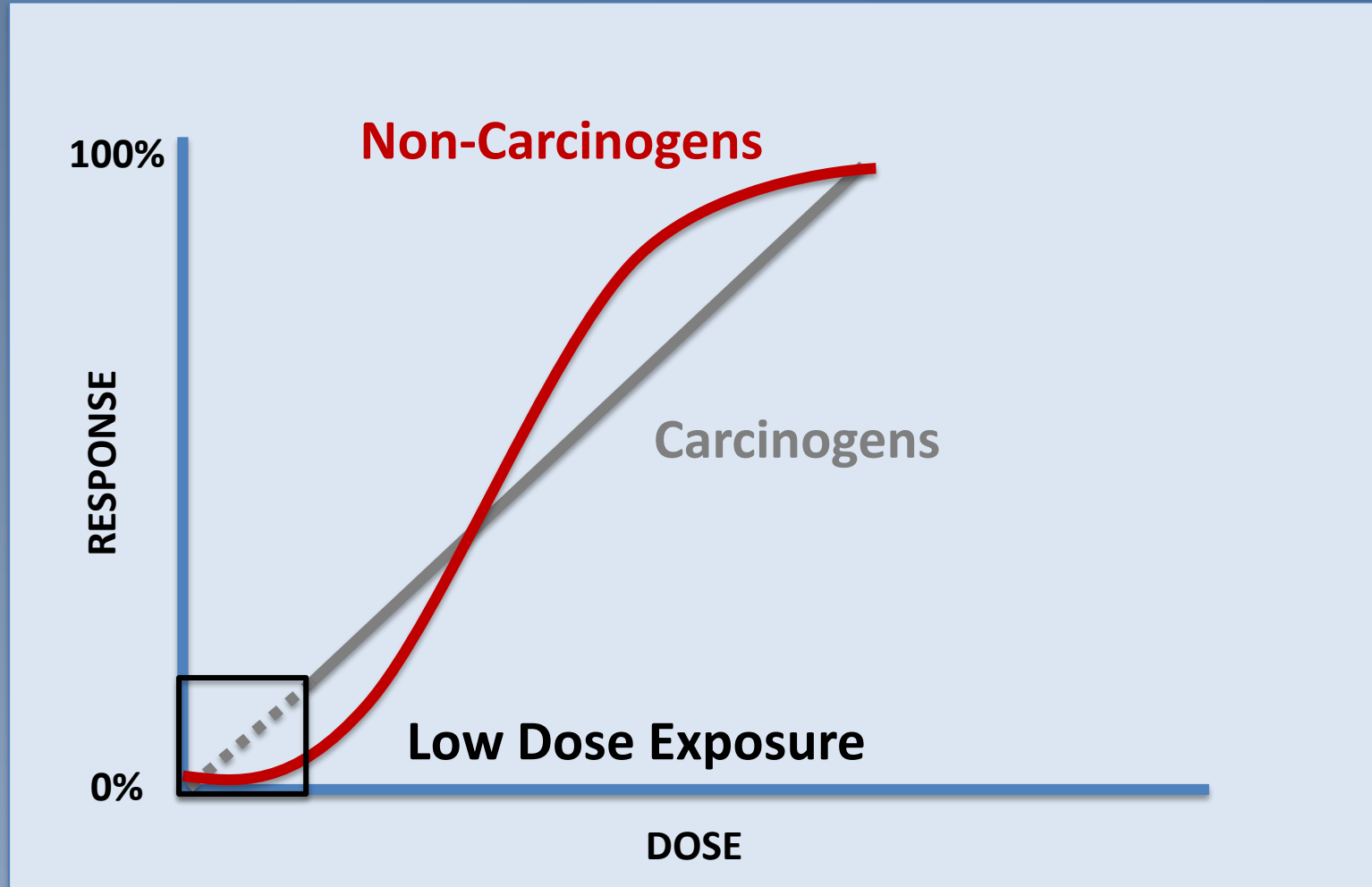Adenomas appear

Carcinomas appear

Dose Response

"What is there that is not poison? All things are poison and nothing is without poison. Solely the dose determines that a thing is not a poison."

Paracelsus

Dose Response

Exposure → **Dose** → **Response**

| Exposure	Dose	Response
Exposure "Outside" the body	**Dose** "Inside" the body	**Response** Change in structure or function
Source	Host	Adverse Health Effect
Air, Food, Consumables	Humans	Disease

Types of Dose Response

The schematic presented here illustrates that the lower the dose, the more reduced is the response and therefore the risk associated with the response

Food: Colorectal Cancer Risk (CRC)

CRC Risk through intake of red and processed meat

CRC risk through intake of Fish
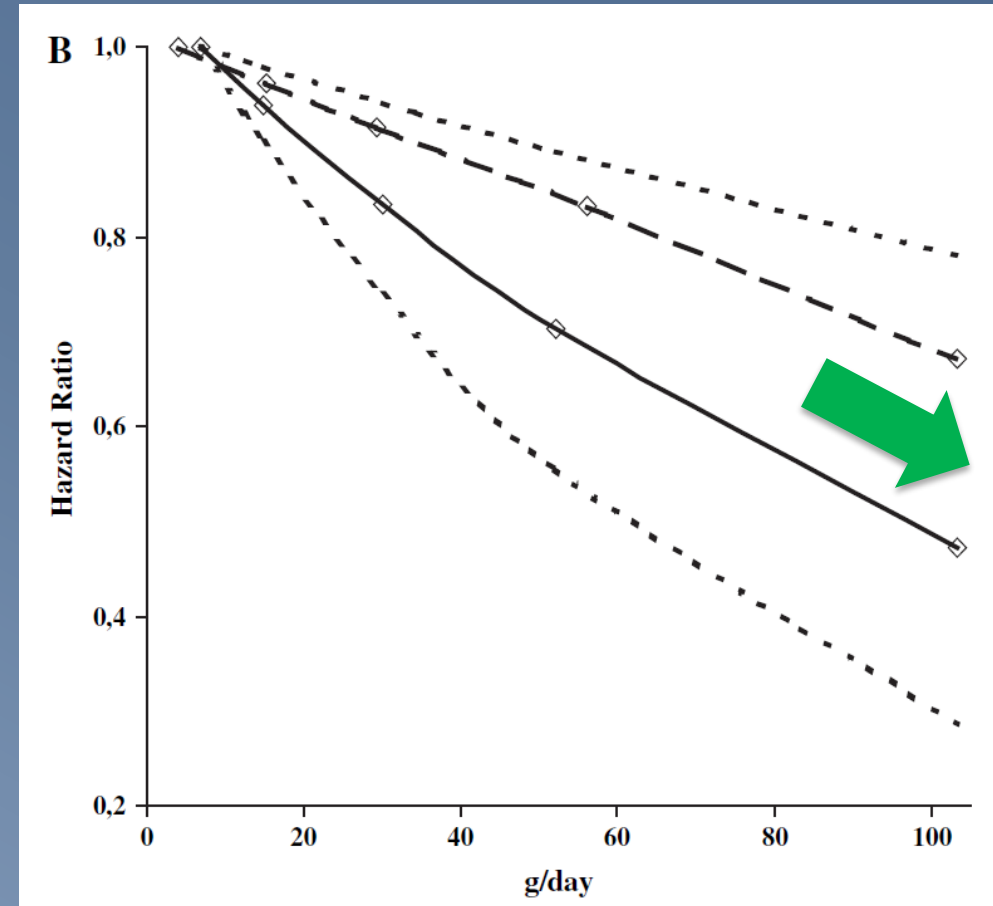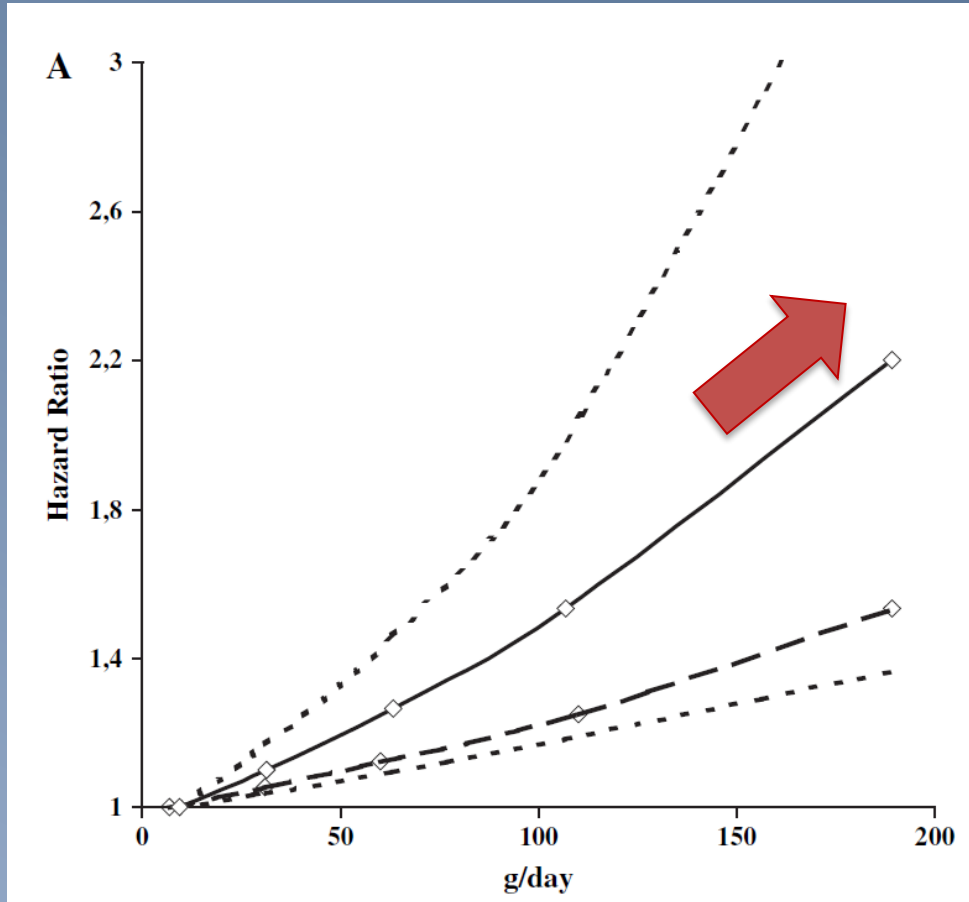
Points in the figure represent median intakes in each category of consumption. Curves generated from calibrated data (**solid line**) and uncalibrated data (**hatched line**) and upper and lower confidence intervals for calibrated data (**dotted lines**) are shown.

Food: Colorectal Cancer Risk (CRC)

- Red meat is classified as "probably carcinogenic" and processed meats as "carcinogenic to humans".[1]

- WCRF/AICR recommendation: Limit red meat consumption to **43 g/day**, for cancer prevention.[2]

- So Young Kim however showed that an intake of 43 g / day of red meat[4] lead to an increase in cancer risk in Korea

- Average consumption in Korea: **~ 109.4 g/day** of red meat.[3]

[1] International Agency for Research on Cancer (IARC); Bouvard, V.; Loomis, D.; Guyton, K.Z.; Grosse, Y.; Ghissassi, F.E.; Benbrahim-Tallaa, L.; Guha, N.; Mattock, H.; Straif, K. Carcinogenicity of consumption of red and processed meat. Lancet Oncol. 2015, 16, 1599–1600.
[2] World Cancer Research Fund and American Institute for Cancer Research. Food, Nutrition, Physical Activity, and the Prevention of Cancer: A Global Perspective; American Institute for Cancer Research (AICR): Arlington, VA, USA, 2007.
[3] Korea National Health and Nutrition Examination Survey (KNHANES). Available online: https://knhanes.cdc.go.kr/knhanes/eng/index.do
[4] Kim, SY; The Role of Red Meat and Flavonoid Consumption on Cancer Prevention: The Korean Cancer Screening Examination Cohort; Nutrients **2017**, 9, 938; doi:10.3390/nu9090938

Smoking: Lung Cancer

Odd Ratio
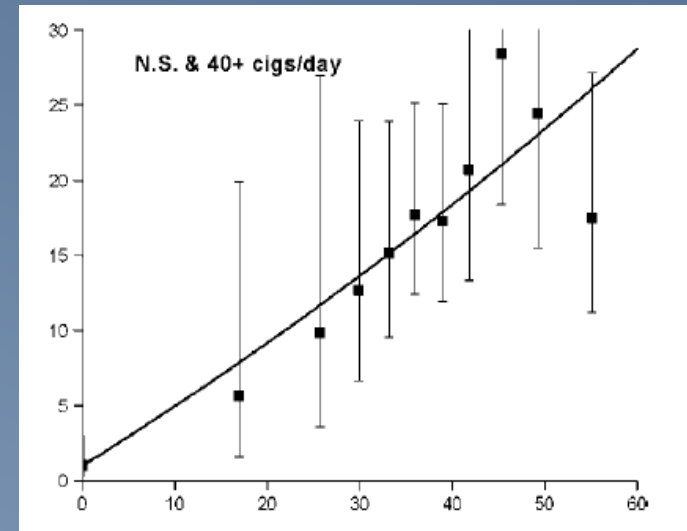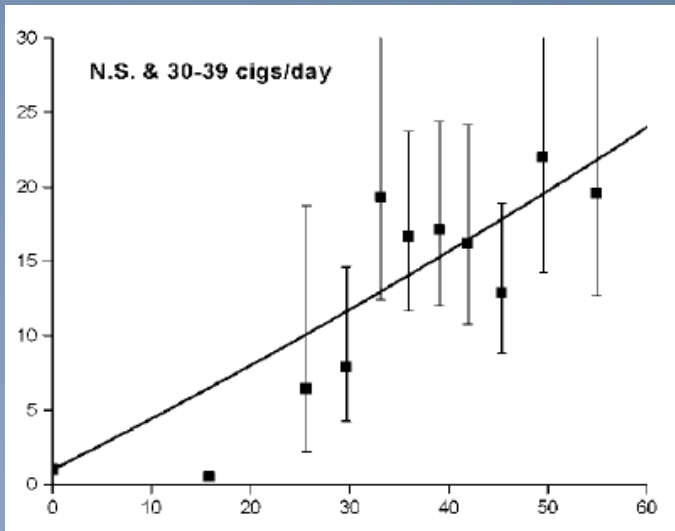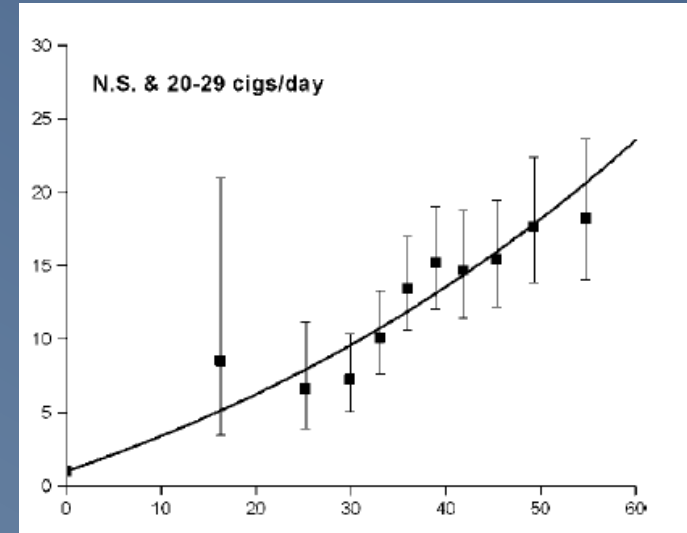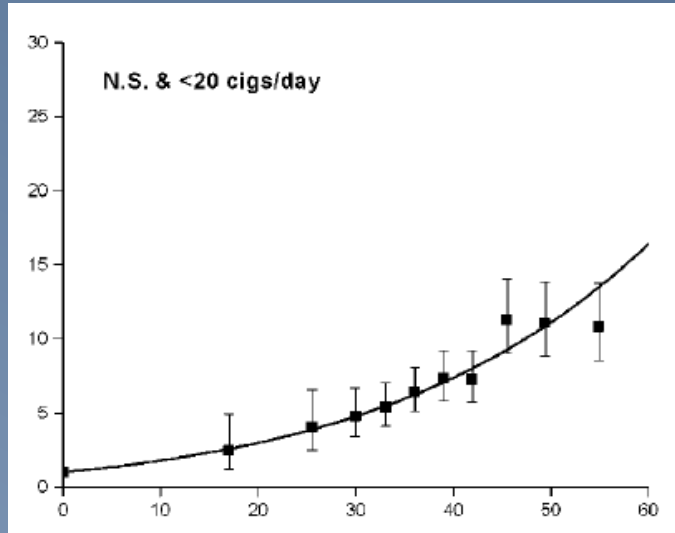
Years of Cigarette Smoking

How does cigarette smoke cause cancer?

Carcinogens in Cigarette Smoke

- Tobacco smoke contains more than 6000 chemicals as well as solid ultrafine particles. [1]

- 93 of them have been listed by the FDA as Harmful and Potentially Harmful Constituents (HPHCs). [2]

- The majority are classified as carcinogens or potential carcinogens. [2]

[1] Rodgman A, Perfetti TA. The chemical components of tobacco and tobacco smoke 2nd ed: CRC Press, Taylor & Francis Inc (United States); 2013.

[2] Reporting Harmful and Potentially   Harmful Constituents in Tobacco Products and Tobacco Smoke Under Section 904(a)(3) of the Federal Food, Drug, and Cosmetic Act; https://www.fda.gov/downloads/TobaccoProducts/Labeling/RulesRegulationsGuidance/ucm297828.pdf

Understanding Cancer Potency of Carcinogens*

Carcinogens		Tobacco Smoke (n=309)	Heat-Not-Burn (n=44)	E-Cigarettes (n=44)	Nicotine Inhaler (n=1)
Compound	IARC Class	Mean Concentration (µg/mL)	% Reduction*	% Reduction*	% Reduction*
Acrylonitrile	2B	4.59×10^{-2}	99.4% ↓	NR	99.8% ↓
1,3 - Butadiene	1	1.83×10^{-1}	99.8% ↓	NR	99.9% ↓

BDL: Below detection limit; NR: Not reported

* compared to Tobacco Smoke

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Acetaldehyde	2B	2.55×10^{-0}	86.4% ↓	99.8% ↓	NR
Formaldehyde	1	1.54×10^{-1}	**93.1%** ↓	**94.7%** ↓	NR
Cadmium	1	1.99×10^{-4}	**BDL** ↓	**94.9%** ↓	**99.5%** ↓

BDL: Below detection limit; NR: Not reported
* compared to Tobacco Smoke

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Cadmium	1	1.99×10^{-4}	BDL ↓	94.9% ↓	99.5% ↓
TSNA - NNN	1	4.63×10^{-4}	94.5% ↓	99.96% ↓	BDL ↓
TSNA - NNK	1	2.88×10^{-4}	94.3% ↓	99.7% ↓	BDL ↓
Mean Life Time Cancer Risk*		1	0.024 ↓	0.004 ↓	0.0004 ↓

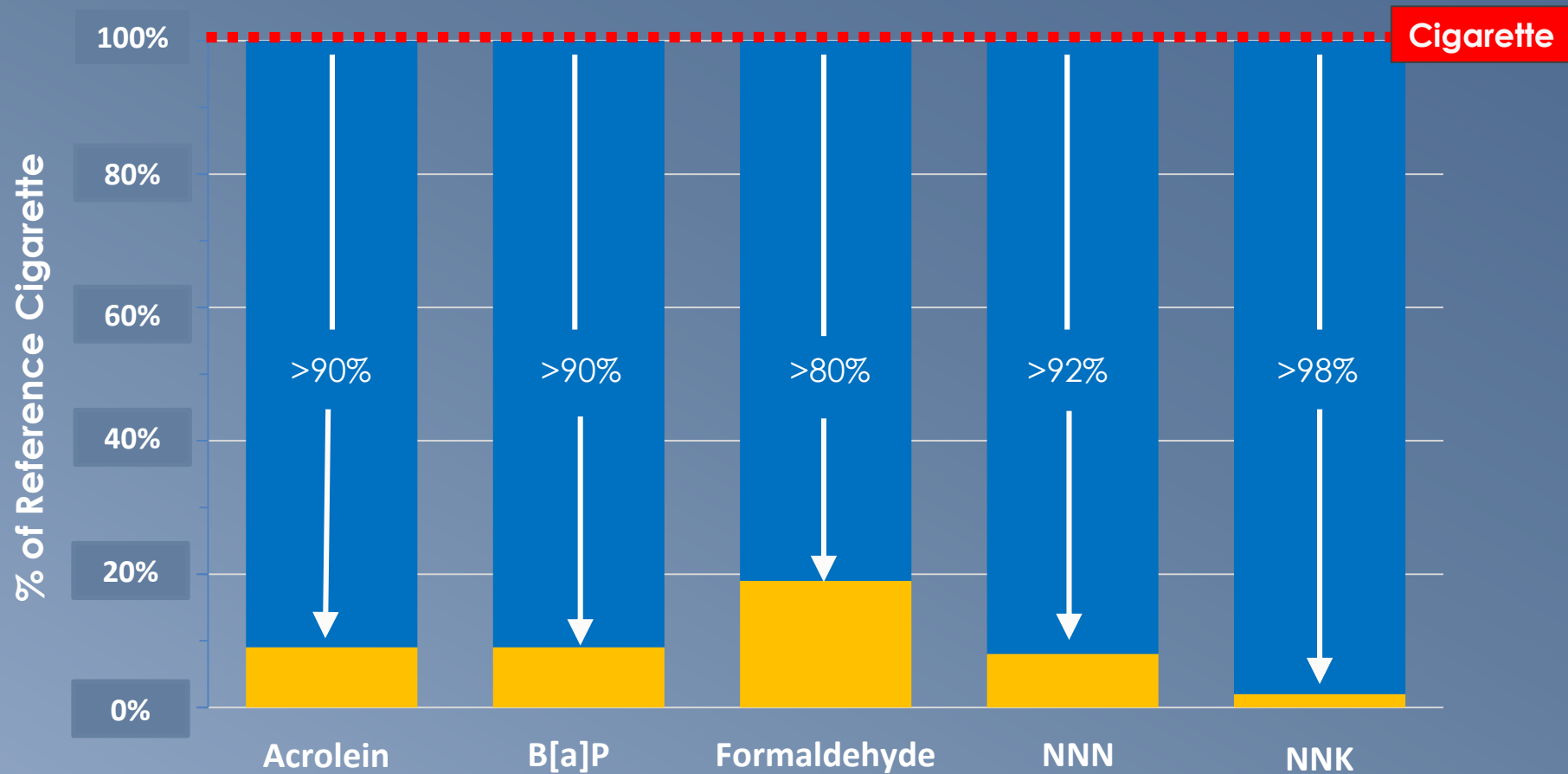BDL: Below detection limit; NR: Not reported

* compared to Tobacco Smoke

Cancer Potency of Carcinogens of Nicotine and Tobacco Containing Products

(Adapted from Stephens, 2017)

21
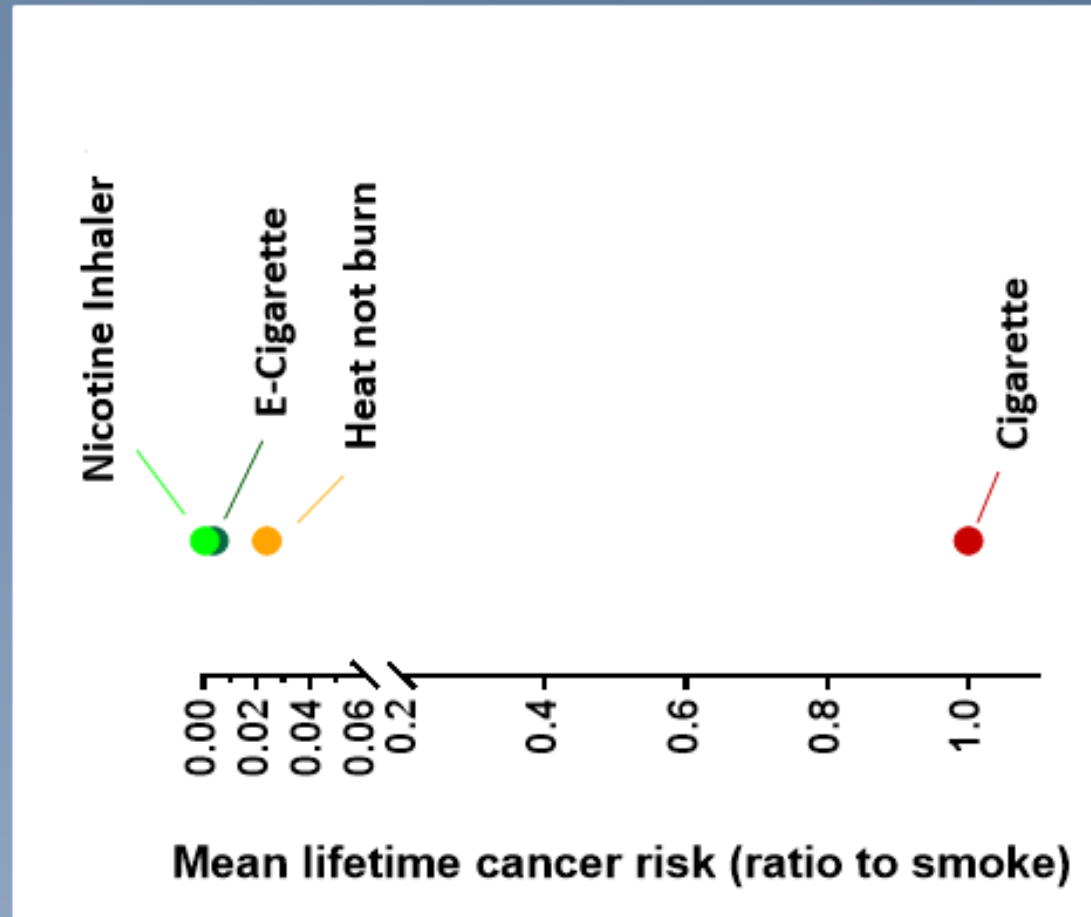
Example: FDA Study on IQOS Emissions

% of Reference Cigarette (y-axis)

100% — Cigarette

- Acrolein: >90%
- B[a]P: >90%
- Formaldehyde: >80%
- NNN: >92%
- NNK: >98%
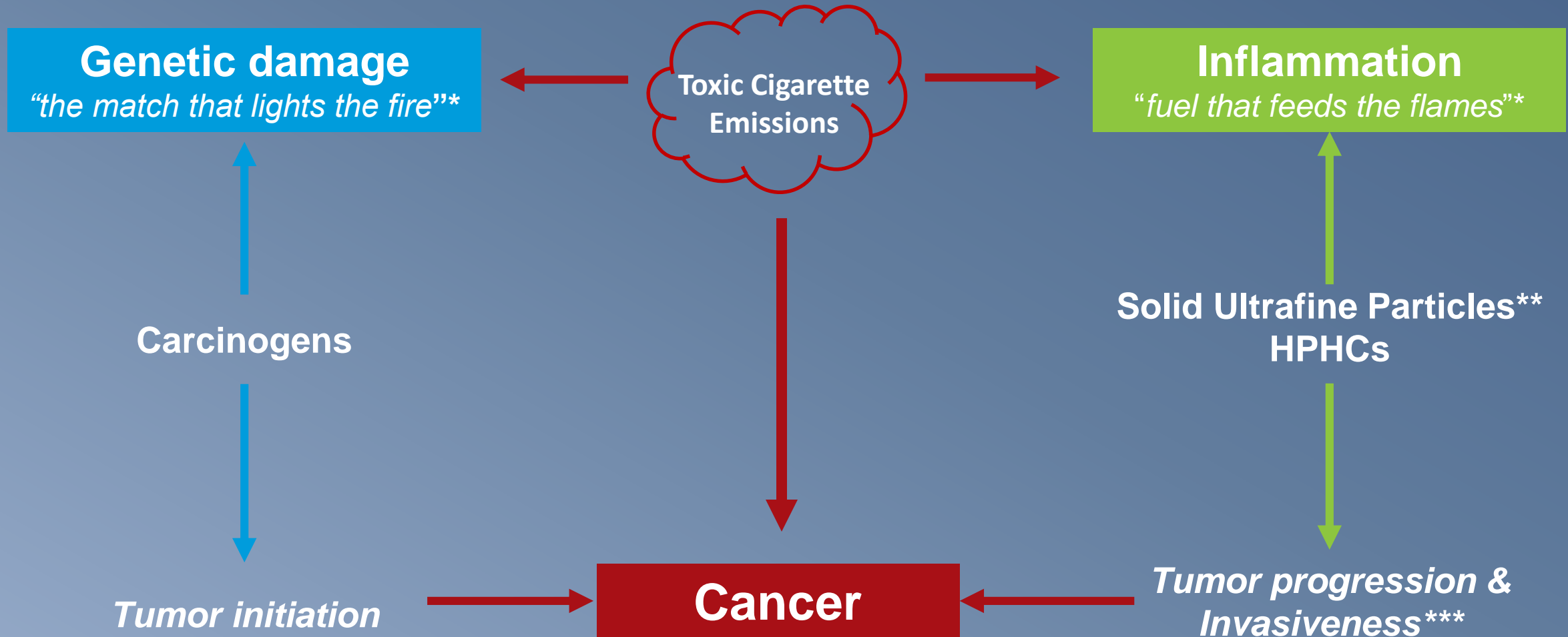
Note:
- Intense Health Canada's Smoking Regime;
- Comparison on a per-stick basis; Excludes Nicotine, Glycerin and Total Particulate Matter
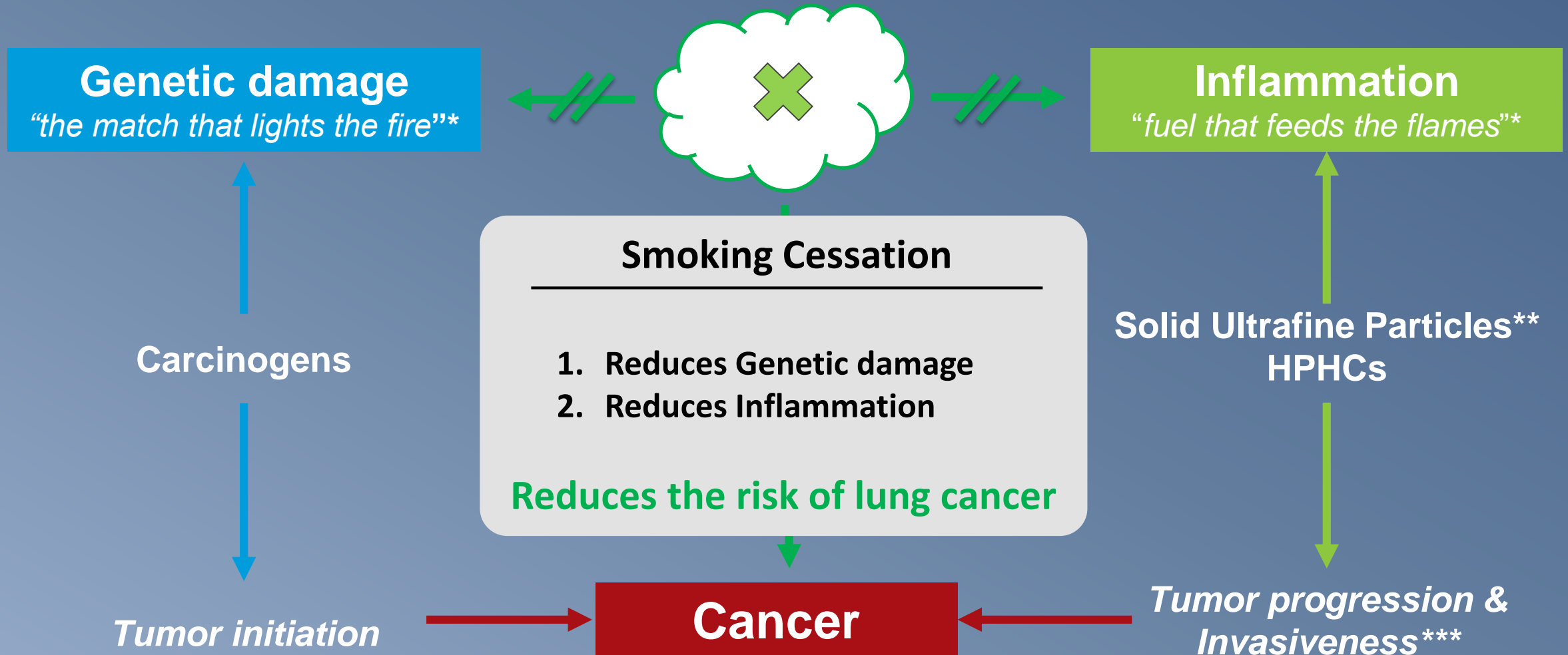
How Cigarette Smoke Causes Cancer?

Genetic damage
*"the match that lights the fire"**

Toxic Cigarette Emissions

Inflammation
*"fuel that feeds the flames"**

Carcinogens

Solid Ultrafine Particles**
HPHCs

Tumor initiation

Cancer

*Tumor progression & Invasiveness***

* Balkwill F and Mantovani A. Inflammation and cancer: back to Virchow? Lancet, 2001, 357:539–45.
** You *et al*. Nanoparticulate carbon black in cigarette smoke induces DNA cleavage and Th17-mediated emphysema. eLife 2015; 4:e09623
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How Smoking Cessation Decreases Cancer Risk

Genetic damage
*"the match that lights the fire"**

Inflammation
*"fuel that feeds the flames"**

Smoking Cessation

1. Reduces Genetic damage
2. Reduces Inflammation

Reduces the risk of lung cancer

Carcinogens

Solid Ultrafine Particles**
HPHCs

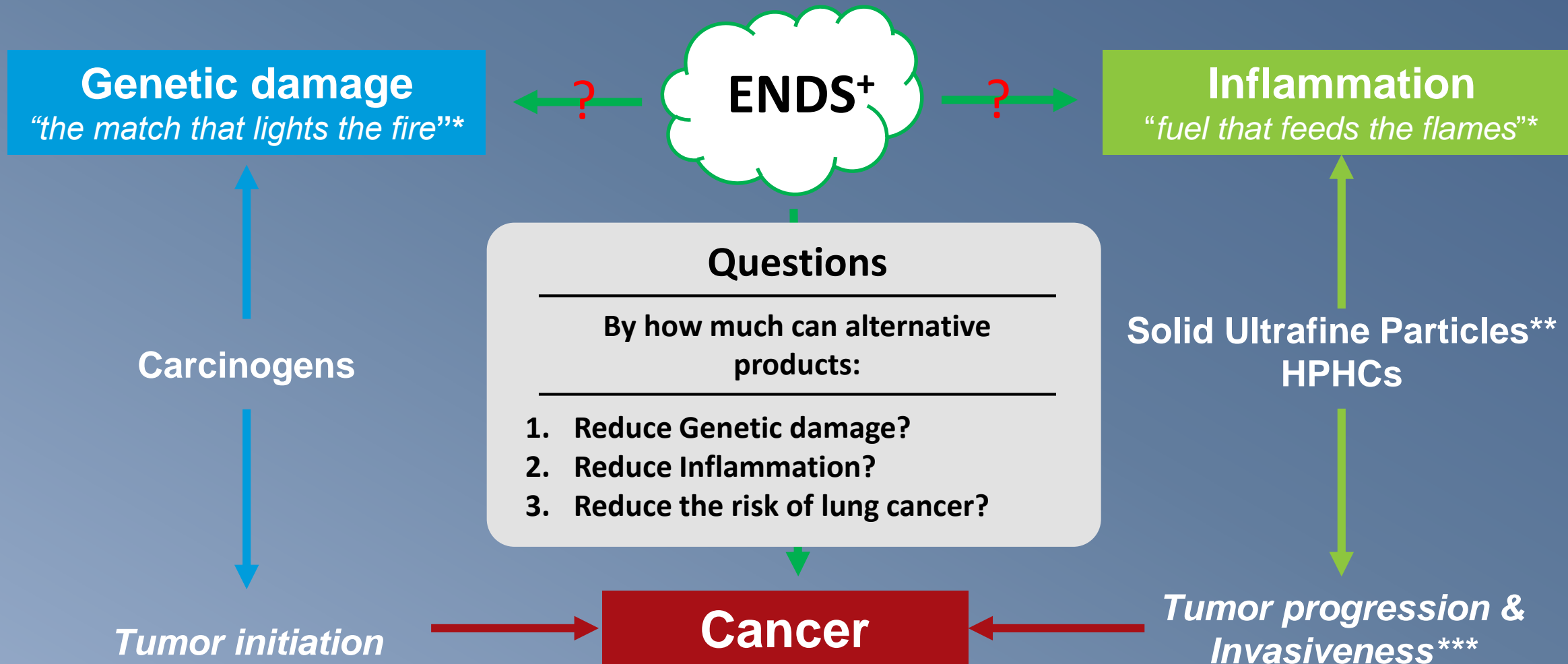*Tumor initiation*

Cancer

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** You *et al*. Nanoparticulate carbon black in cigarette smoke induces DNA cleavage and Th17-mediated emphysema. eLife 2015; 4:e09623
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How Much Can ENDS Reduce Cancer Risk?

Genetic damage
*"the match that lights the fire"**

ENDS+

Inflammation
*"fuel that feeds the flames"**

Carcinogens

Questions

By how much can alternative products:

1. Reduce Genetic damage?
2. Reduce Inflammation?
3. Reduce the risk of lung cancer?

Solid Ultrafine Particles**
HPHCs

Tumor initiation

Cancer

*Tumor progression & Invasiveness****

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+ Electronic Nicotine Delivery Systems.

25

Smoking Prevalence Globally and in Korea

–

Why less harmful alternatives are needed

People will continue to smoke

- Worldwide it is estimated that more than **1 billion people** will continue to smoke in the foreseeable future.[1]

- According to the ACS more than 46,700 death are attributable to smoking-related diseases every year in Korea.[2]

- More than 18% of the population (~33% of males) continue to smoke cigarettes in Korea.[3]

[1] http://www.who.int/tobacco/publications/surveillance/reportontrendstobaccosmoking/en/index4.html
[2] American Cancer Society: https://tobaccoatlas.org/country/south-korea/
3 OECD Health Statistic 2018, https://stats.oecd.org/index.aspx?DataSetCode=HEALTH_STAT#, as accessed on August 28th 2018

Emerging Smoke-Free Regulatory Trends

*"…**new product innovations** could make a lot of sense and **help people transfer off cigarettes**"*

- Scott Gottlieb, Commissioner Food & Drug Administration

*"help people to quit smoking by **permitting innovative technologies that minimise the risk of harm**" / "maximise the availability of safer alternatives to smoking"*

*"**heat-not-burn**, snus, moist snuff, dissolvable and inhaled nicotine **may be significantly safer than cigarettes**."*

- Nicky Wagner, Former Associate Health Minister

Growing number of countries are recognizing the benefit of novel smoke-free products

Scientific Update

PMI's Evidence on IQOS related to Cancer

Prof. Manuel C. Peitsch

PMI Chief Scientific Officer

Agenda

- Totality of Evidence on IQOS to date

- Can switching to IQOS reduce genetic damage, inflammation?

- Can switching to IQOS reduce the risk of lung cancer?

Reduced Formation: by Disease Category

Toxic Cigarette Emissions → Exposure → Molecular changes → Disruption of biological Mechanisms → Cell/Tissue Changes → Disease → Population Harm

PMI

Reduced Emissions → Reduced Exposure → Reduced Adverse Health Effects

- Reduced Emissions of Harmful Chemicals
- No solid ultrafine particles (PM 2.5)

- Exposure Reduction in IQOS users
- Effect on By-Standers

- Incidence of Lung Carcinomas in animal model significantly reduced

How Cigarette Smoke Causes Cancer?
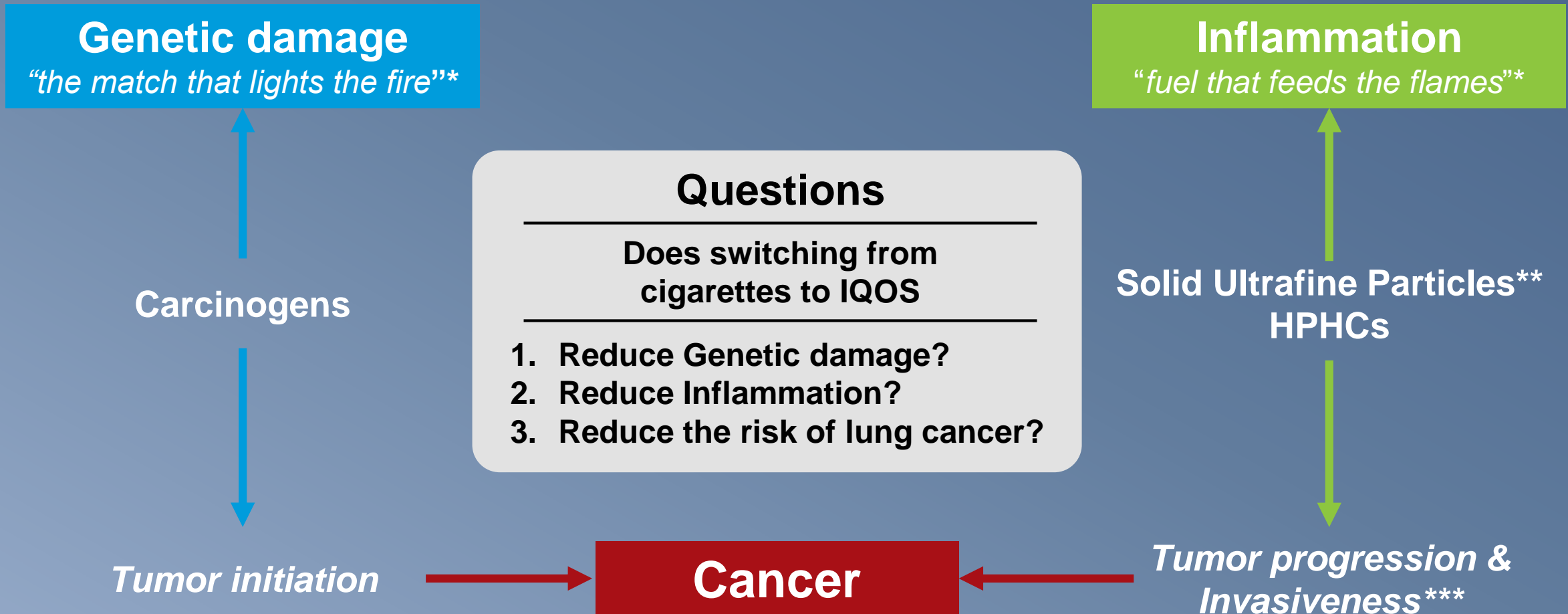
Genetic damage
"the match that lights the fire"*

Inflammation
"fuel that feeds the flames"*

Carcinogens

Solid Ultrafine Particles**
HPHCs

Questions

Does switching from cigarettes to IQOS

1. Reduce Genetic damage?
2. Reduce Inflammation?
3. Reduce the risk of lung cancer?

Tumor initiation

Cancer

Tumor progression & Invasiveness***

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Genetic Damage is Reduced by IQOS

Does Switching to IQOS Reduce Genetic damage?

Evidence from IQOS Assessment

Genetic damage
"the match that lights the fire"*

↕

Carcinogens

↓

Tumor initiation

Reduced Emission of Carcinogens 🔬

Reduced Exposure to Carcinogens	Reduced Genotoxicity	Reduced DNA Damage

Reduced Exposure Response

Reduced Genetic Damage
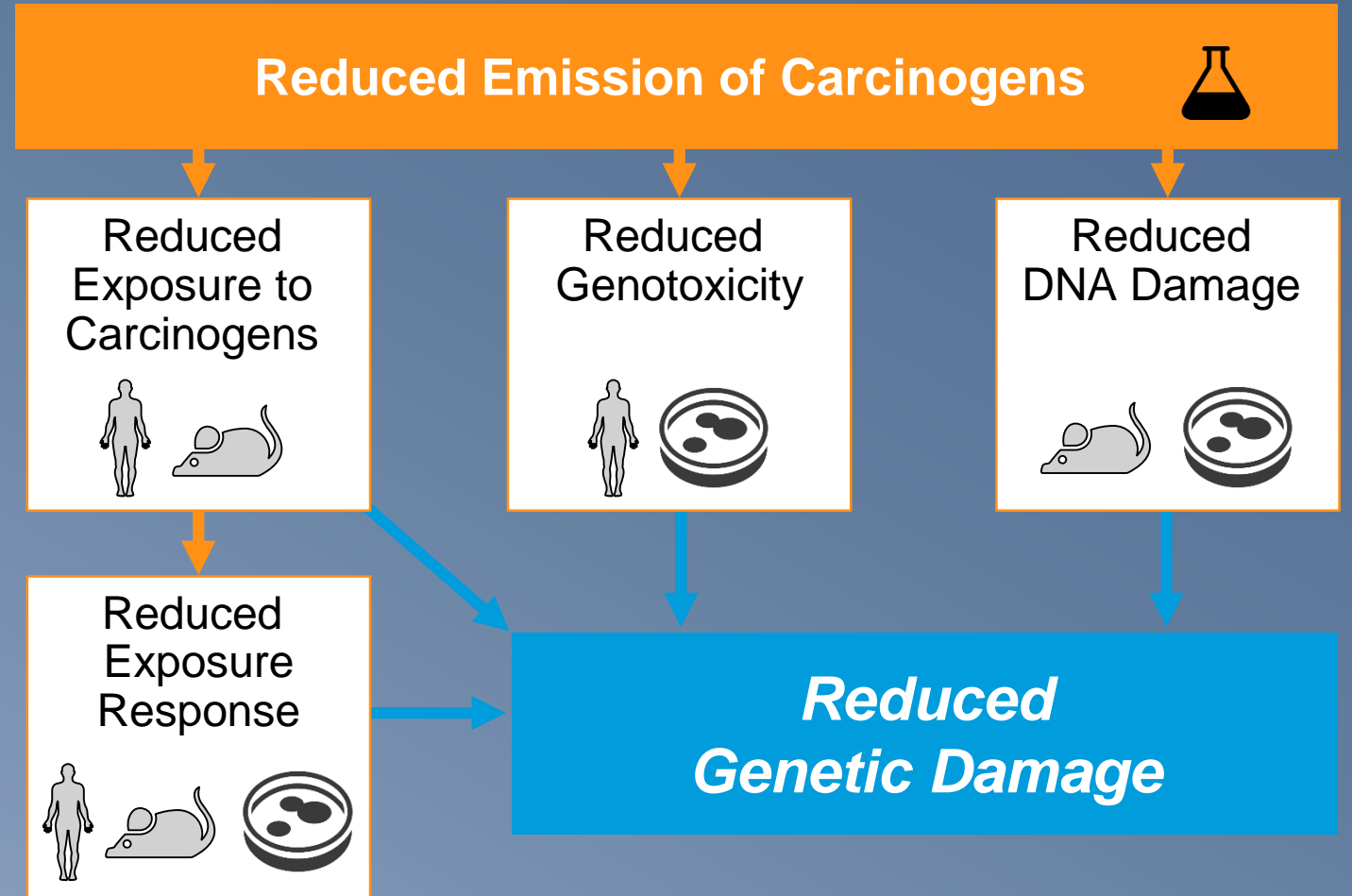
* Balkwill F and Mantovani A. Inflammation and cancer: back to Virchow? Lancet, 2001, 357:539–45.

Levels of Harmful Chemicals Significantly Reduced For IQOS

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

Reference Cigarette

% of Reference Cigarette

100%

75%

50%

25%

0%

WHO
(9 chemicals)

FDA
(18 chemicals)

Health Canada
(44 chemicals)

PMI
(58 chemicals)

Carcinogens
(15 chemicals)

IQOS

KFDA's analysis of the HNB aerosol also confirmed the on average 90% lower levels of harmful chemicals in the HNB aerosol compared to cigarette smoke.
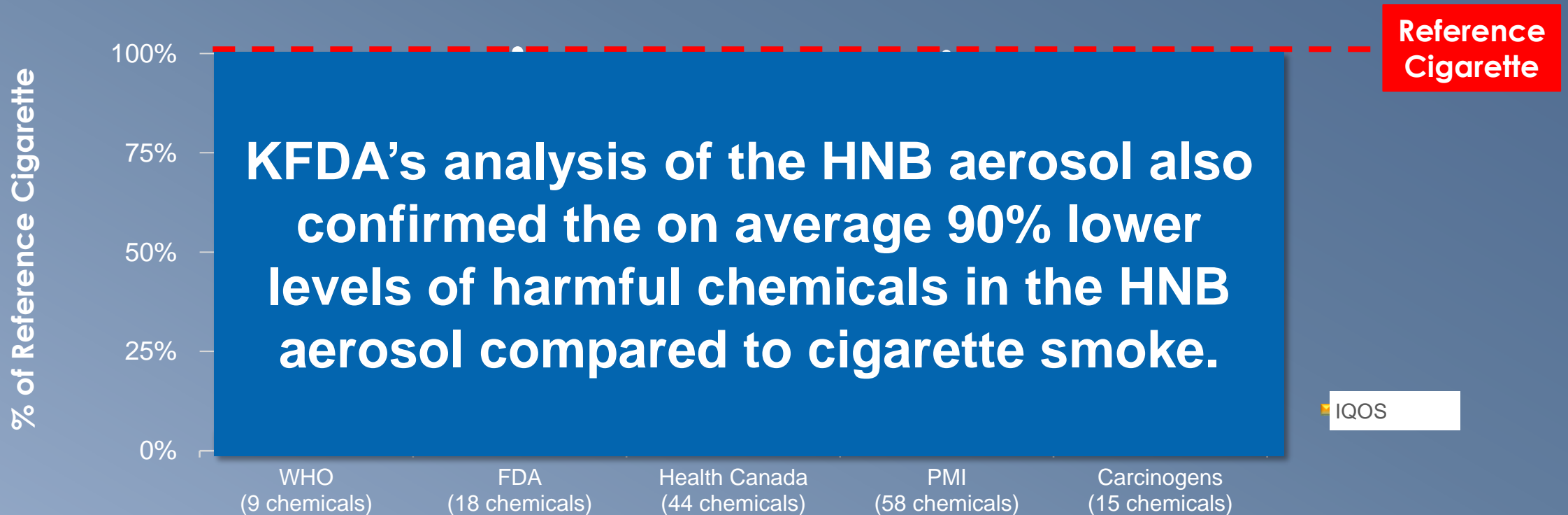
*Aerosol collection with Intense Health Canada's Smoking Regime (55 mL puff volume, 2 second puff duration, 30 second interval puff); Comparison on a per-stick basis Reduction calculations exclude Nicotine, Glycerin and Total Particulate Matter
The PMI 58 list includes the FDA 18,and the 15 carcinogens of the IARC Groups 1

Reduced Exposure To Carcinogens
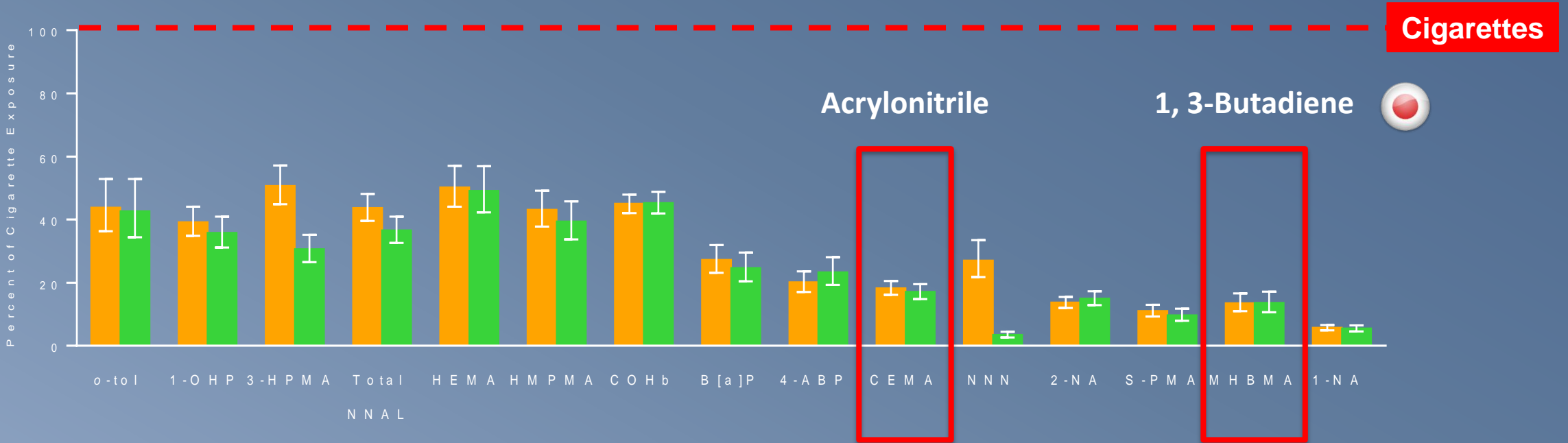
Genetic Damage is Reduced by IQOS

Note: the "switch to IQOS" and "Switch to cessation" study groups were exposed for 2 month to 3R4F cigarette smoke prior to being switched.
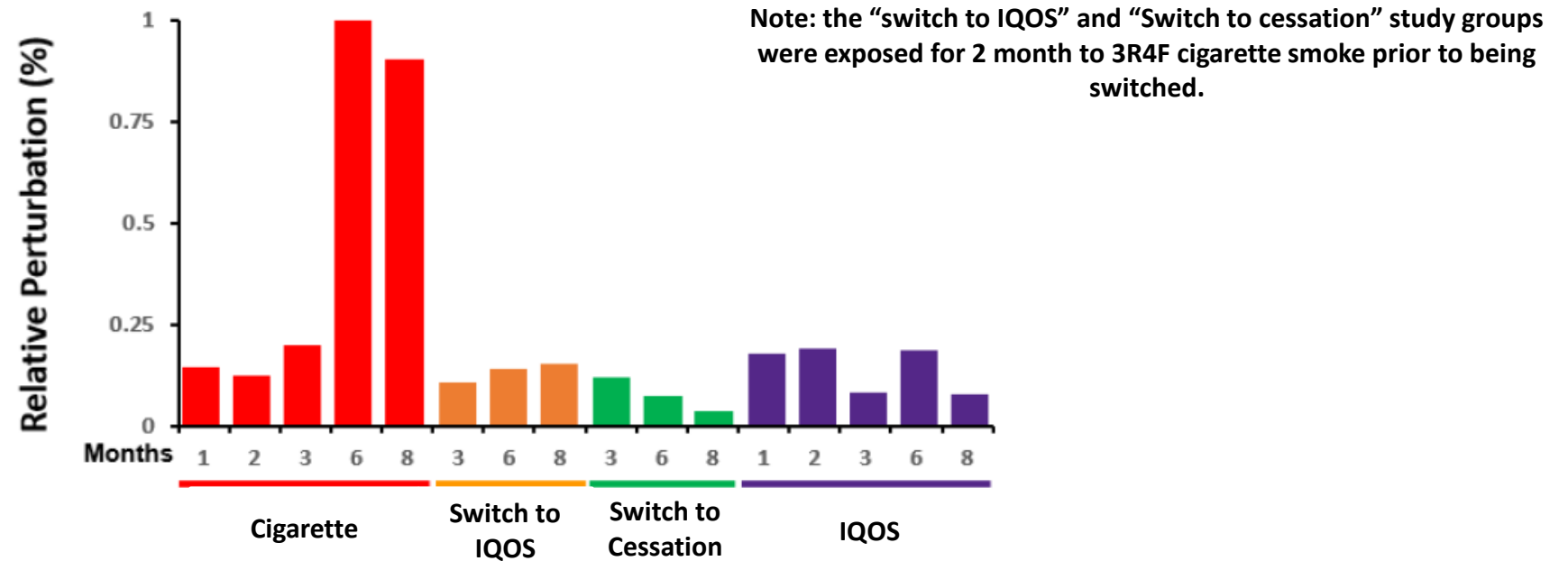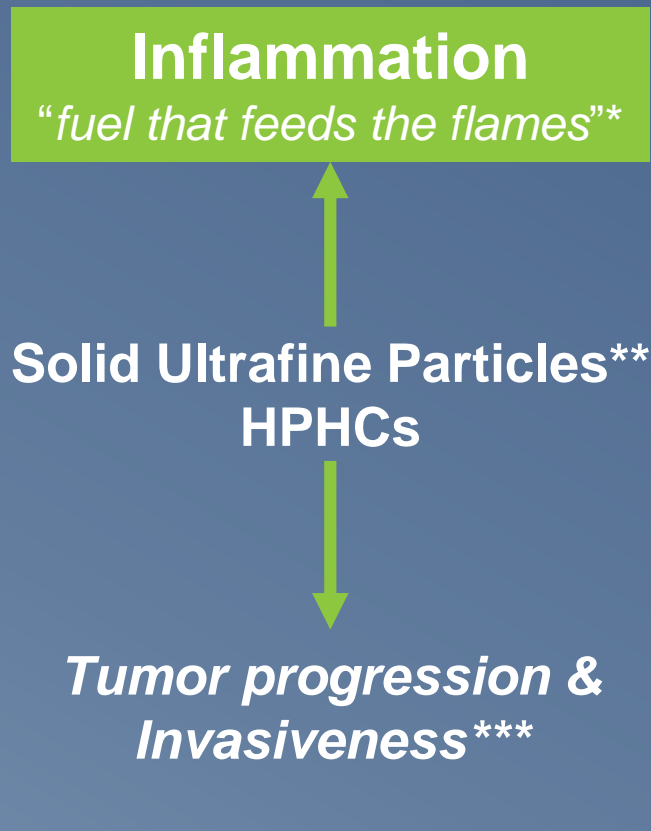
Perturbation of the DNA damage response network of the nasal epithelium in the Apoe$^{-/-}$ mouse switching study.

Inflammation is Reduced by IQOS

Evidence from IQOS Assessment
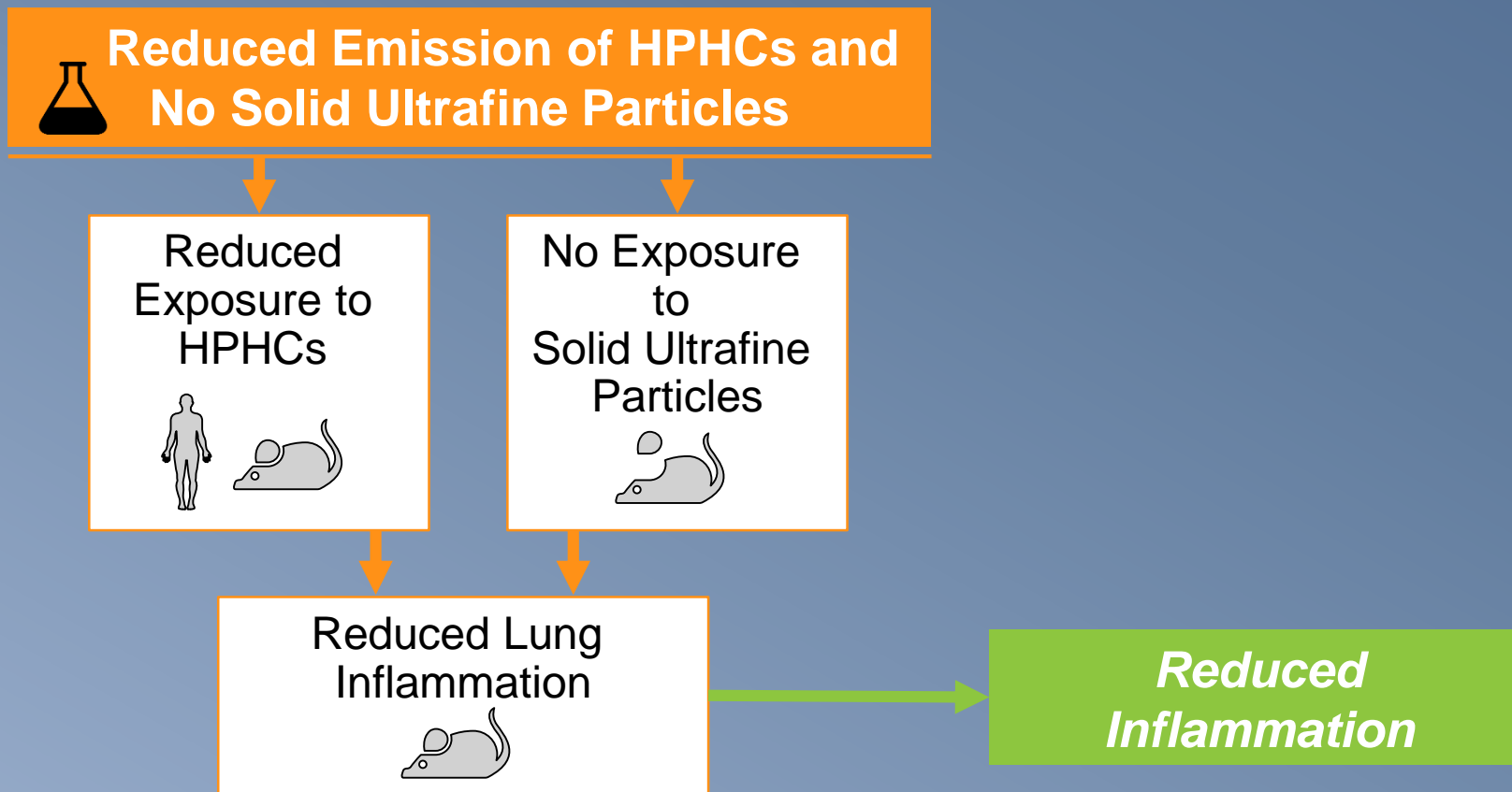
Does Switching to IQOS Reduce Inflammation?

Reduced Emission of HPHCs and No Solid Ultrafine Particles

Inflammation
*"fuel that feeds the flames"**

Reduced Exposure to HPHCs

No Exposure to Solid Ultrafine Particles

Solid Ultrafine Particles**
HPHCs

Reduced Lung Inflammation

Reduced Inflammation

Tumor progression & Invasiveness**

* Balkwill F and Mantovani A. Inflammation and cancer: back to Virchow? Lancet, 2001, 357:539–45.
** You *et al*. Nanoparticulate carbon black in cigarette smoke induces DNA cleavage and Th17-mediated emphysema. eLife 2015; 4:e09623
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Solid Ultrafine Particle Deposition in the Lung

Cigarette Smoke

Solid Ultrafine Particles
6×10^{11} particles $\sim= 0.7$ mg*
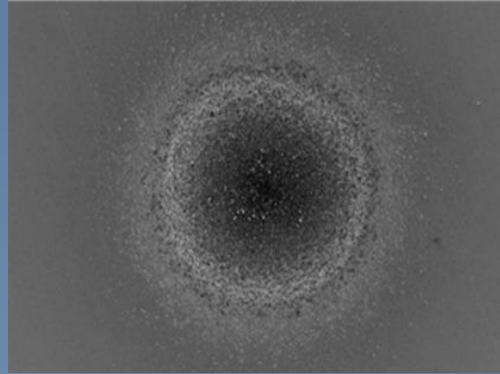
IQOS Aerosol

No Solid
Ultrafine Particles

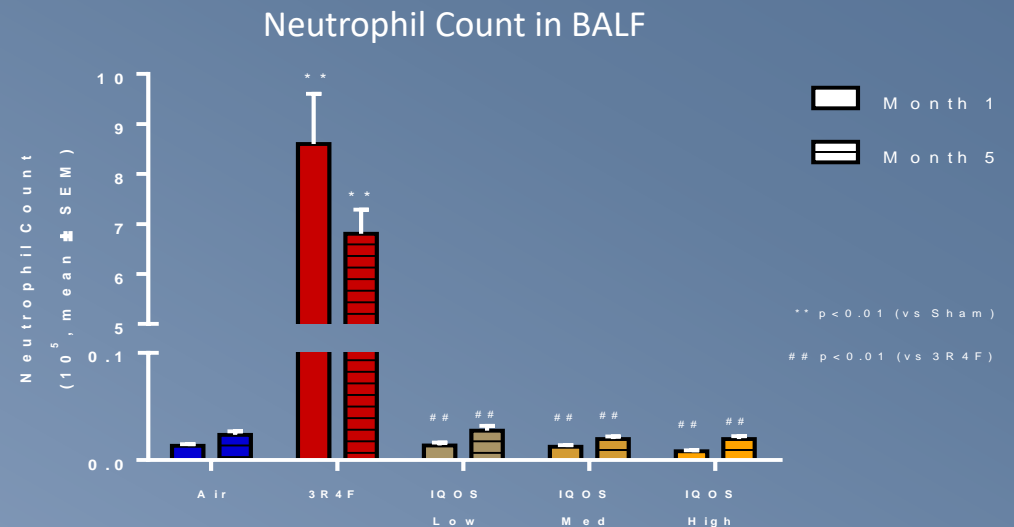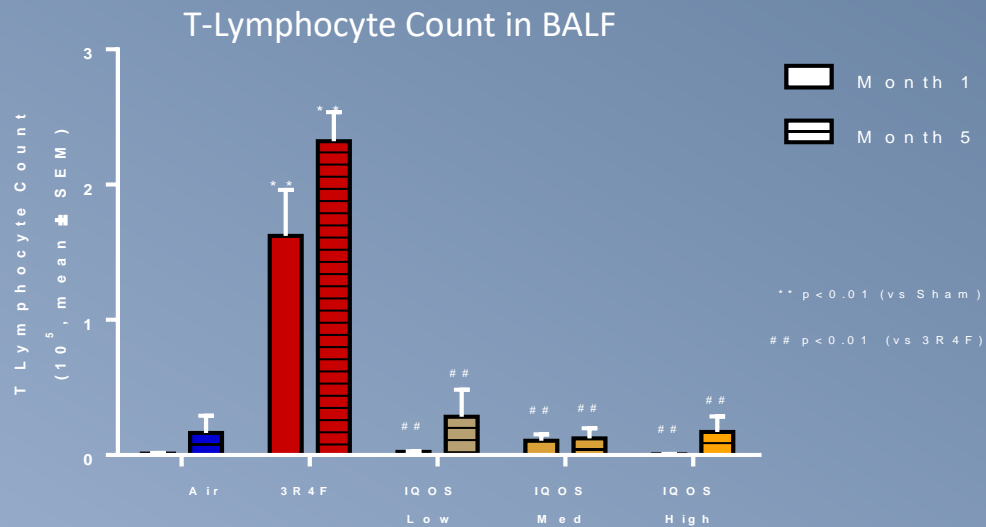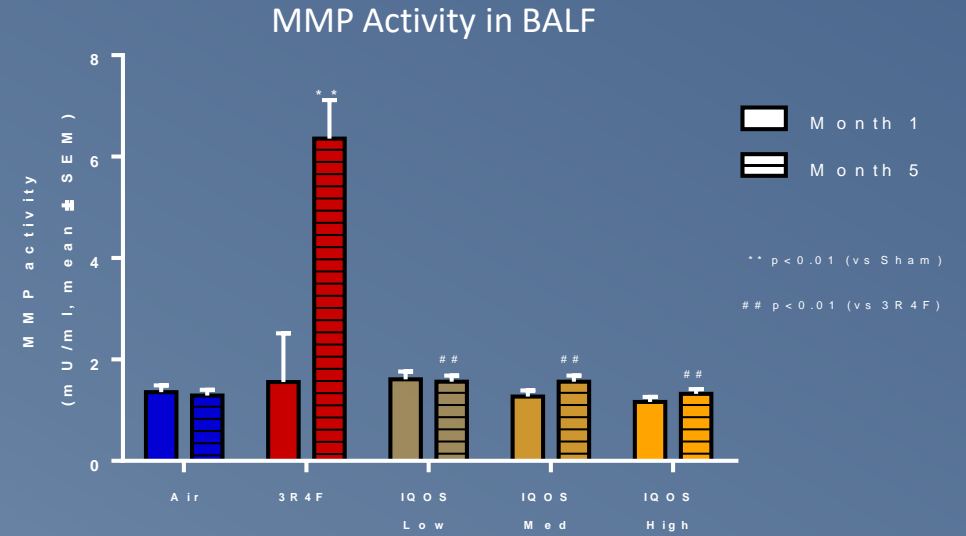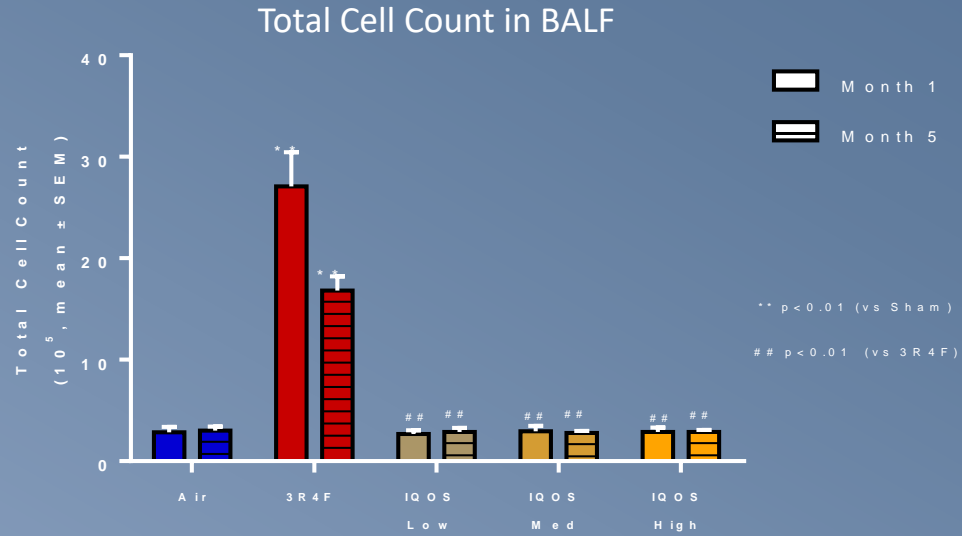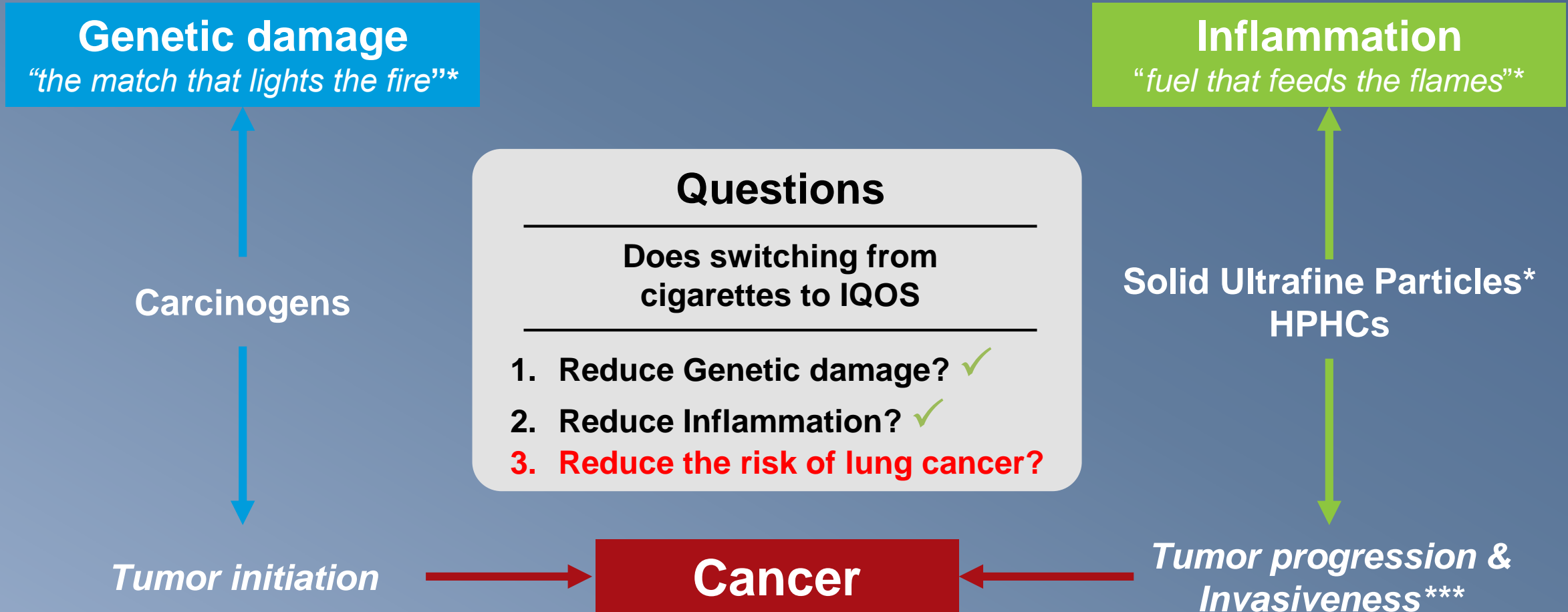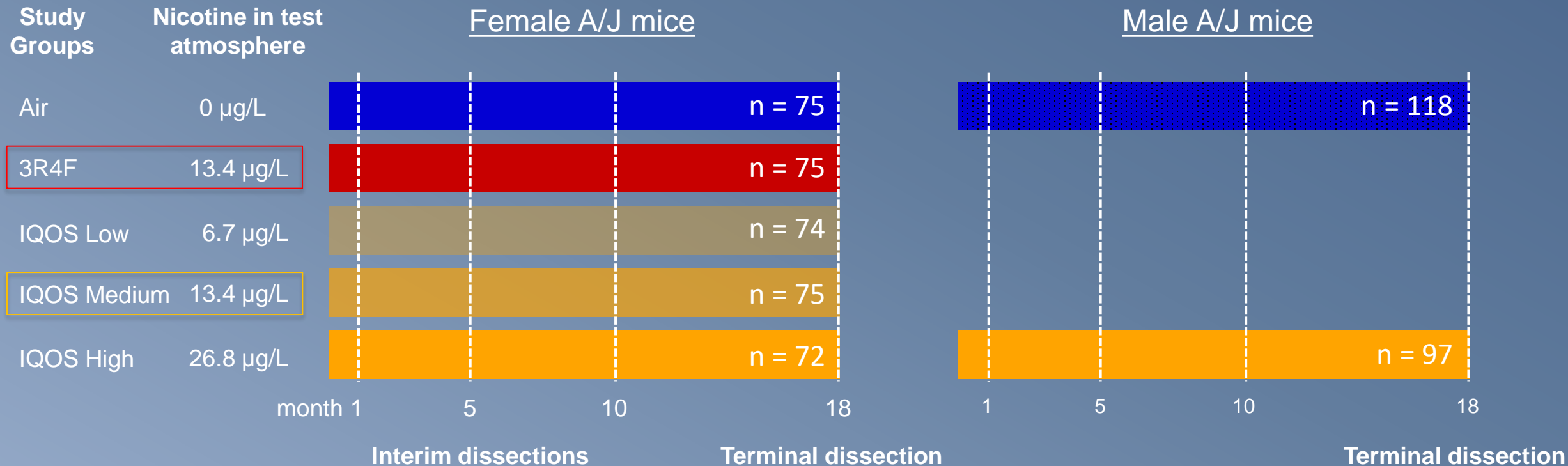**Lung Deposition after 6 months**

Cigarette smoke*
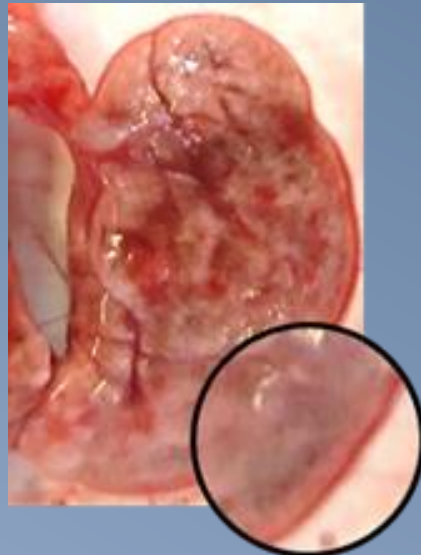
IQOS aerosol*

* Corresponding nicotine concentrations

No Lung Inflammation in IQOS Exposed Mice

Total Cell Count in BALF

MMP Activity in BALF

T-Lymphocyte Count in BALF

Neutrophil Count in BALF

** p<0.01 (vs Sham)

p<0.01 (vs 3R4F)

How Cigarette Smoke Causes Cancer?

Genetic damage
*"the match that lights the fire"**

Inflammation
*"fuel that feeds the flames"**

Carcinogens

Solid Ultrafine Particles*
HPHCs

Questions

Does switching from cigarettes to IQOS

1. **Reduce Genetic damage?** ✓
2. **Reduce Inflammation?** ✓
3. **Reduce the risk of lung cancer?**

Tumor initiation → **Cancer** ← *Tumor progression & Invasiveness****

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Lung Cancer Study - Design

26.8 µg/L nicotine concentration in IQOS aerosol represents 56 Sticks/day*

Study Groups	Nicotine in test atmosphere	Female A/J mice	Male A/J mice
Air	0 µg/L	n = 75	n = 118
3R4F	13.4 µg/L	n = 75	
IQOS Low	6.7 µg/L	n = 74	
IQOS Medium	13.4 µg/L	n = 75	
IQOS High	26.8 µg/L	n = 72	n = 97

Female A/J mice: month 1 5 10 18 — Interim dissections / Terminal dissection

Male A/J mice: 1 5 10 18 — Terminal dissection

n = Number of animals at months 18 assessable for carcinoma incidence.
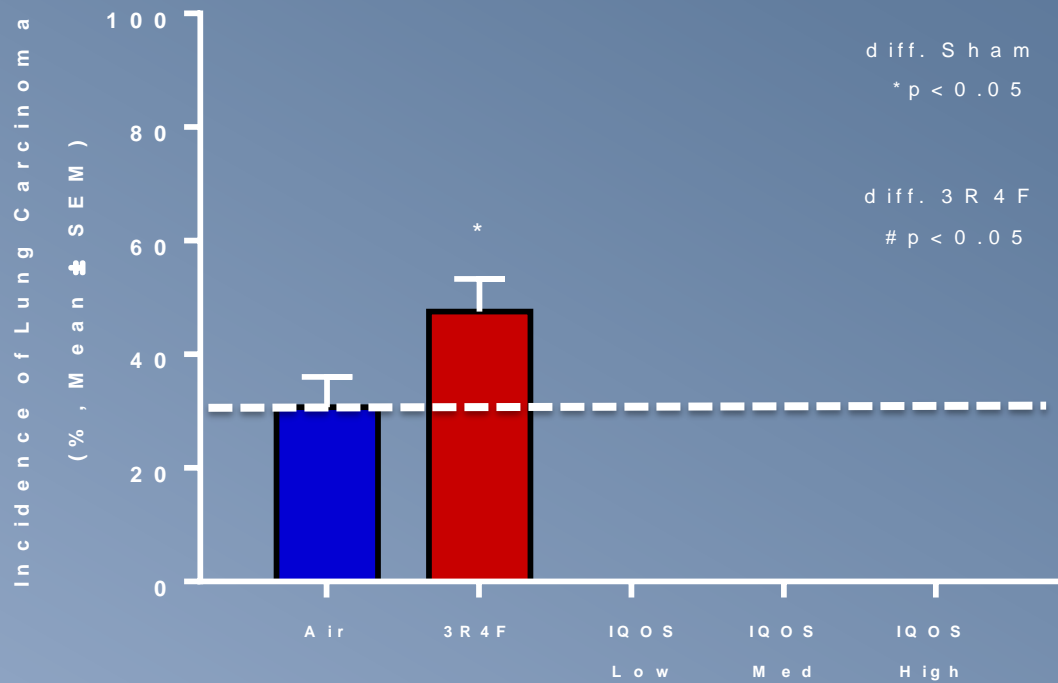
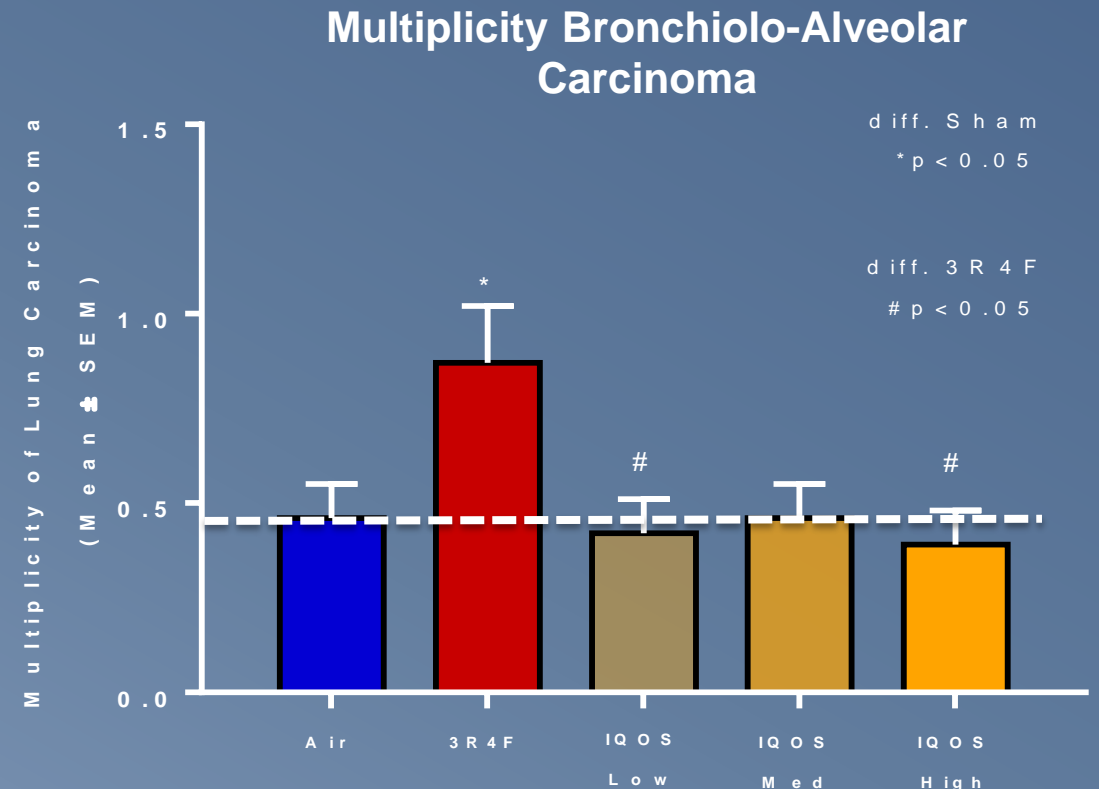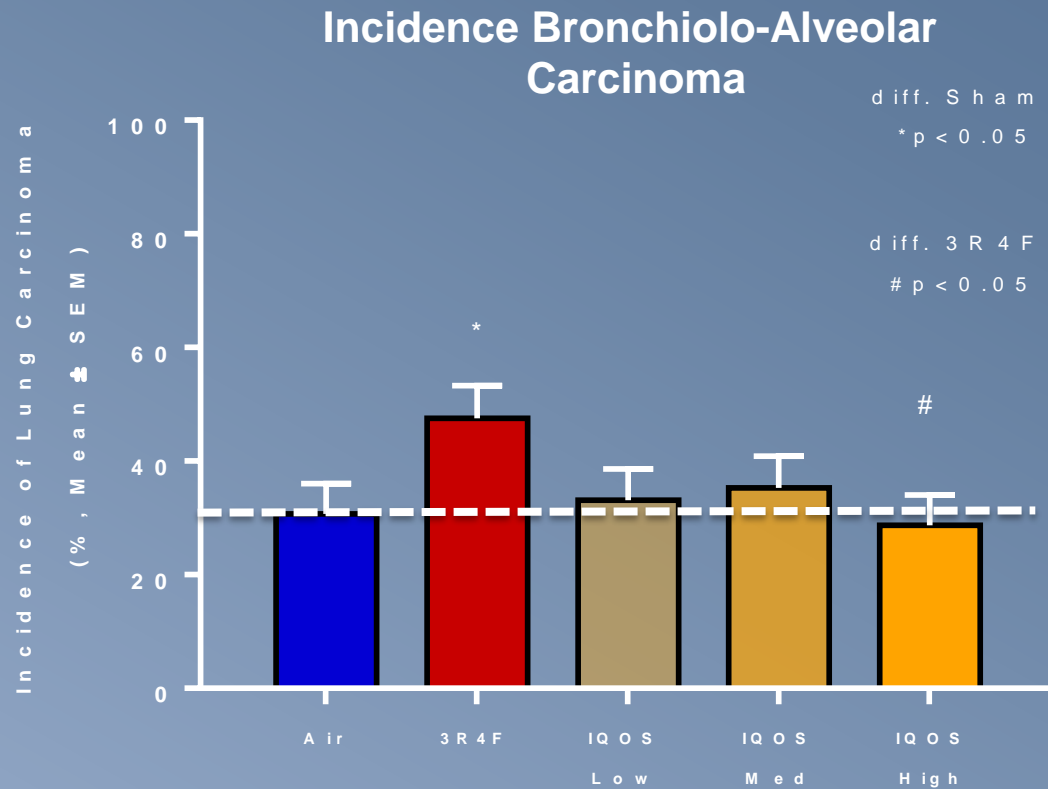# Incidence and Multiplicity of Lung Carcinoma
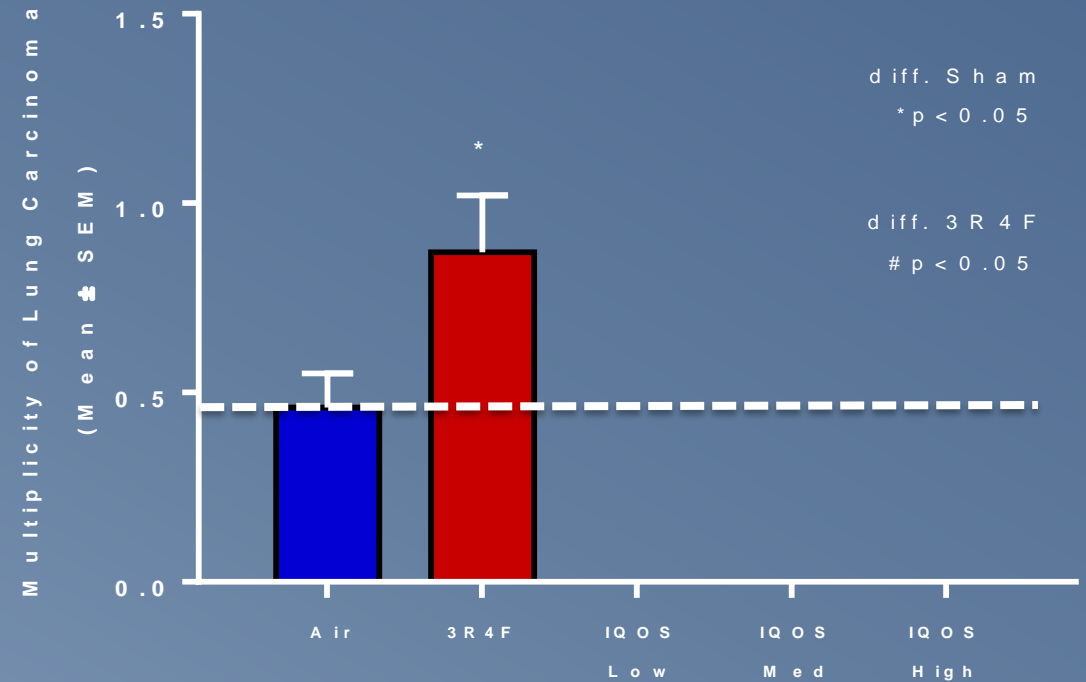
Incidence and multiplicity of Lung Carcinomas are significantly increased upon exposure to 3R4F smoke compared to air exposure.

Incidence and Multiplicity of Lung Carcinoma

Incidence and multiplicity of Lung Carcinomas in IQOS exposed mice was significantly lower compared to 3R4F smoke exposed mice and similar to air exposed mice.

Conclusions

- IQOS reduces genetic damage compared to continued smoking

- IQOS reduces inflammation compared to continued smoking

- IQOS reduces incidence and multiplicity lof lung adenomas and lung carcinomas in a validated cancer animal model

Risk Assessment Model

Toxic Cigarette Emissions

Exposure → Molecular changes → Disruption of biological Mechanisms → Cell/Tissue Changes → Disease → Population Harm

PMI

Reduced Emissions → Reduced Exposure → Reduced Adverse Health Effects

- Reduced Emissions of Harmful Chemicals
- No solid ultrafine particles (PM 2.5)

- Exposure Reduction in IQOS users
- Effect on By-Standers

- Incidence of Lung Carcinomas in animal model significantly reduced

What We Know Today

- IQOS is not risk free and is addictive and the best choice is to quit

- Smokers carry a time-dependent relative risk of disease based on their smoking history when they quit or switch to IQOS

- IQOS is a much better choice for smokers than to continue smoking cigarettes

- We all share the responsibility to provide accurate information based on sound science

- Consumers have the right to receive accurate and non-misleading information to make an informed, better choice for their health