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Comparative risk assessment of heated tobacco product (HTP) and electronic cigarette (EC) aerosols with cigarette smoke based on cancer potency and margin of exposure

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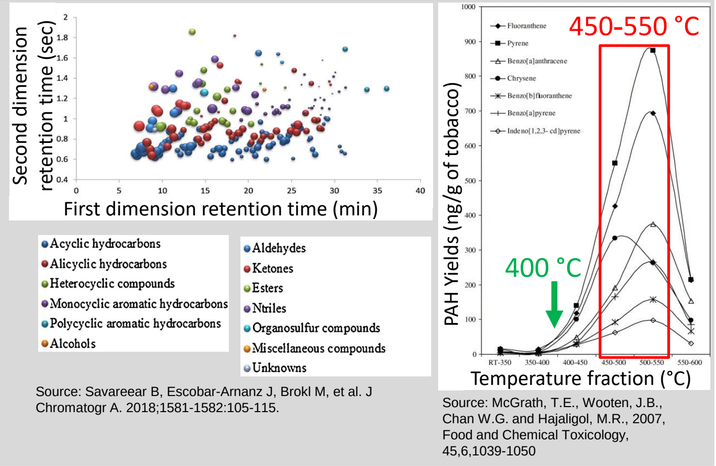
Outline

- Impact of smoking on health
- Specificity of non-combusted alternatives
- Estimate of the health risk with non-combusted alternatives
- Our model-based approach
- Results
- Limitations of the developed model
- Conclusions

Cigarette smoke and health impact

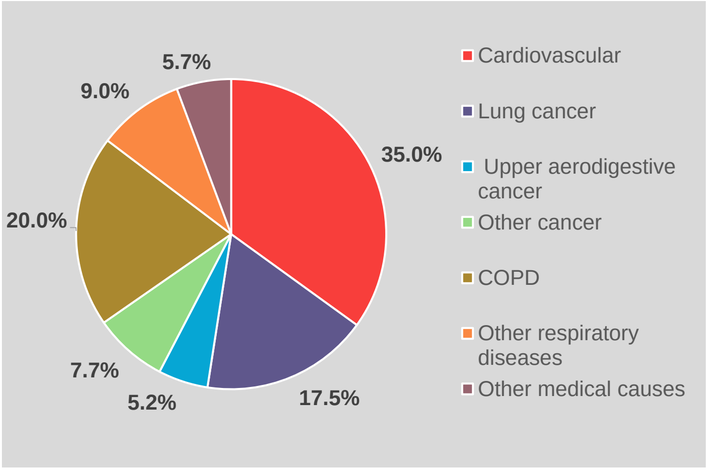


Source: Savareear B, Escobar-Arnanz J, Brokl M, et al. J Chromatogr A. 2018;1581-1582:105-115.

Source: McGrath, T.E., Wooten, J.B., Chan W.G. and Hajaligol, M.R., 2007, Food and Chemical Toxicology, 45,6,1039-1050

Smoke: A complex aerosol

- More than 7000 constituents
- About 100 recognized as harmful or potentially harmful
- Harmful or potentially harmful constituents (HPHC) responsible for smoking-related diseases
- Mainly formed during tobacco combustion



Reproduced from Ezzati, M., & Lopez, A. D. (2004). Chapter 11: Smoking and oral tobacco use. In: Ezzati, M., Lopez, A. D., Rodgers, A., & Murray, C. J. (2004). Comparative quantification of health risks. Global and regional burden of disease attributable to selected major risk factors. Vol 1:883-957. Geneva: World Health Organization.
COPD: Chronic Obstructive Pulmonary Disease

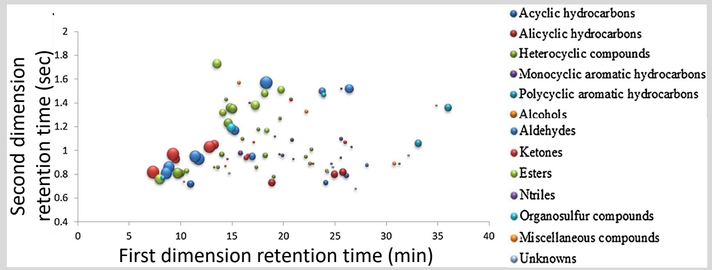
Health impact

- Cardiovascular diseases (35%)
  - Stroke
  - Ischemic heart disease
  - Other cardiovascular diseases
- Cancer (30.4%)
  - Lungs
  - Upper aerodigestive organs
  - Other organs
- Respiratory diseases (29%)
  - COPD
  - Emphysema
- Others (5.7%)

Non-combusted alternatives

Reduced Emissions

Aerosol Chemistry



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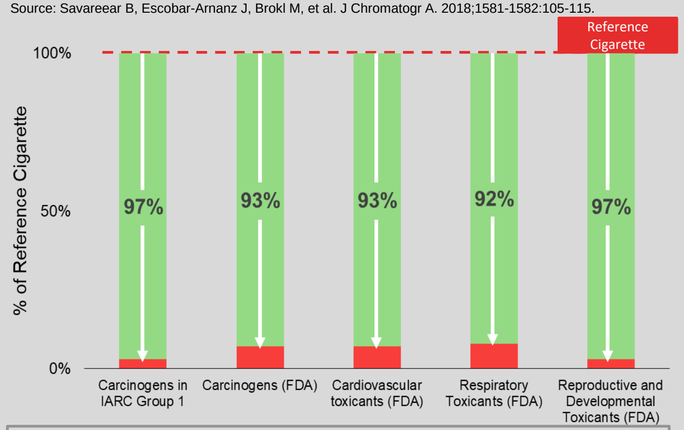

Source: PMI Science

Reduced Exposure

***In vitro* studies**
***In vivo* studies**
Clinical studies

Reduced Adverse Health Effects

***In vivo* studies**
Clinical studies
Epidemiological studies

Reduced emissions in HTPs and ECs

- A less complex aerosol
- Average reduction in formation of HPHCs with THS 2.2 relative to the levels measured in smoke from the reference cigarette on the basis of all compounds included in the FDA-93 list of HPHCs.

Health impact ?

- Long-term effects remain unknown
- Epidemiological studies not compatible with innovative product development
- Surrogate(s) to characterize associated potential health risks

THS 2.2 stands for Tobacco Heating System version 2.2 and refers to a commercialized version of IQOS.

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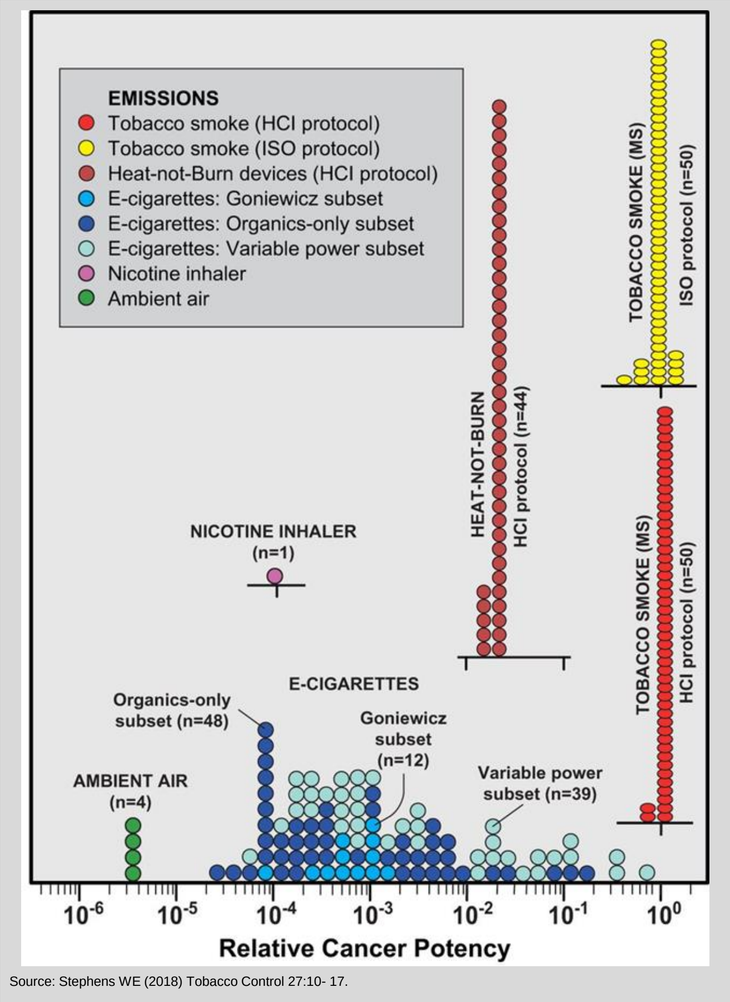
HTP, EC, and health risk estimates (1)



Source: Stephens WE (2018) Tobacco Control 27:10- 17.

Cancer risk

- Surrogate: Cancer potencies modeled with HPHC yields and their respective Inhalation Unit Risks (IUR, OEHHA)
- Comparative assessment of cancer potencies:
  - HTPs ~50-times reduction
  - ECs ~500-times reduction
- Comparative assessment of mean lifetime cancer risk:
  - HTPs ~40-times reduction
  - ECs ~250-times reduction

☛ HTPs and ECs: risk reduction relative to cigarettes

HCI: Health Canada Intense smoking regime
ISO: International Organization for Standardization
OEHHA: Office of Environmental Health Hazard Assessment

HTP, EC, and health risk estimates (2)

Cancer risk

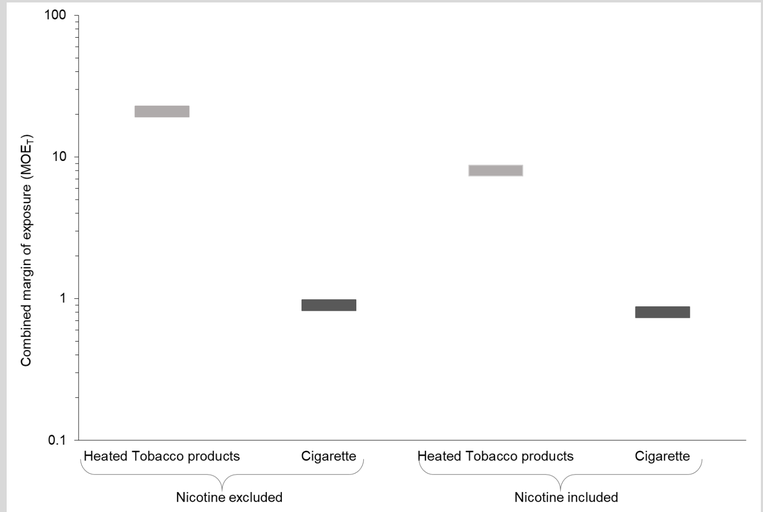
- Surrogate: Change in Cumulative Emission (CCE) modeled with HPHC emission yields and their respective relative potency factor (RPF, see Slob W. et al., Risk Analysis, 40: 1355-1366)

- Translation of the CCE into an health impact estimate:
  - CCE<1: increase in harm
  - CCE=1: health impact not modified
  - CCE≥10: Substantial reduction in harm may be expected

- Comparative assessment of IQOS with cigarette:
  - 8 compounds considered (acrylonitrile, acetaldehyde, benzo[a]pyrene, 1,3-butadiene, ethylene oxide, formaldehyde, nitrobenzene, and propylene oxide)
  - Calculated uncertainty range of CCE: 9.6 - 26
  - Cumulative emission from HTP exposure estimated about 10 to 25 times lower compared to cigarette exposure on the basis of the eight compounds

☛ Reduction in expected life span substantially smaller for HTP users than smokers

HTP, EC, and health risk estimates (3)



Adapted from Lachenmeier DW, Anderson P, Rehm J (2018) International Journal of Alcohol and Drug Research 7(2): 8-112018 7:4.

Non-cancer risk

- Surrogate: Combined margin of exposure (MOE_T) modeled with the margin of exposure (MOE) from selected compounds. MOE determined for the selected compounds by using their respective HPHC yields and corresponding toxicological thresholds, typically the BMDL (benchmark dose lower bound)

- Comparative assessment of MOE_T:
  - HTPs ~23-times increase (nicotine excluded)
  - HTPs ~10-times increase (nicotine included)

☛ HTPs: non-negligible risk reduction relative to cigarettes

Our approach

$$Cancer\ Potency = \sum_{j=1}^{n} IUR_j C_j$$

$$DAI = Puff\ volume \times Puff\ number \times DC$$

$$DAI = 0.001 \times DC$$

$$Lifetime\ Cancer\ Risk = \frac{DAI}{DBV} \times Cancer\ Potency$$

j refers to the jth compound
IUR: Inhalation unit risk
C: HPHC yield
DAI: Daily aerosol intake
DC: Daily consumption (20 cigarettes, 20 sticks for HTPs, or 20 L of inhaled aerosol for ECs)
Puff volume: 55 mL (aerosols generated under ISO 20778 and ISO 20768)
DBV: Daily breathed volume (20 m^3)

Cancer risk

- Surrogate: Cancer potencies modeled with HPHC yields and their respective IURs (US EPA or OEHHA)
- Lifetime cancer risk (LCR) estimates
- Conservative: highest IUR considered

$$MOE = \frac{Toxicological\ threshold}{Human\ estimated\ exposure\ dose}$$

$$MOE_j = \frac{IEL_j \times DBV}{DAI \times C_j}$$

$$MOE_T = \frac{1}{\sum_{j=1}^{n} \frac{1}{MOE_j}}$$

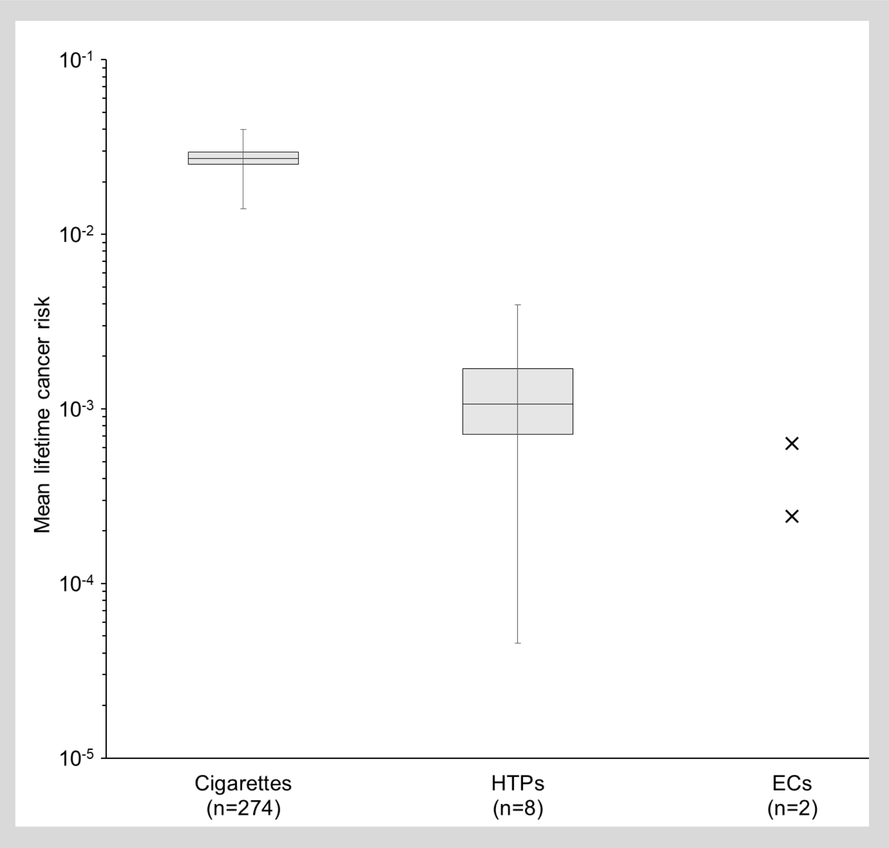
j refers to the jth compound
IEL: Inhalation exposure limit
C: HPHC yield
DAI: Daily aerosol intake
DBV: Daily breathed volume (20 m^3)

Non-cancer risk

- Surrogate: MOE_T modeled with HPHC yields and their respective MOE
- MOE based on inhalation exposure limits (IELs): DNELs (ECHA), RELs (OEHHA), and RfCs (US EPA)
- Conservative: lowest IEL considered

US EPA: United States Environmental Protection Agency
DNEL: derived no effect level
ECHA: European Chemicals Agency
REL: reference exposure limit
RfC: reference concentration

Cancer risk: HTPs and ECs vs. cigarette



Reduced mean LCR of non-combusted products relative to cigarettes

- $1.40x10^{-2}$ to $3.97x10^{-2}$ for cigarettes, with $2.73x10^{-2}$ as median
- $4.53x10^{-5}$ to $3.95x10^{-3}$ for HTPs, with $1.06x10^{-3}$ as median
- $2.42x10^{-4}$ and $3.95x10^{-4}$ for ECs

Significant decrease in cancer risk, as suggested by the model

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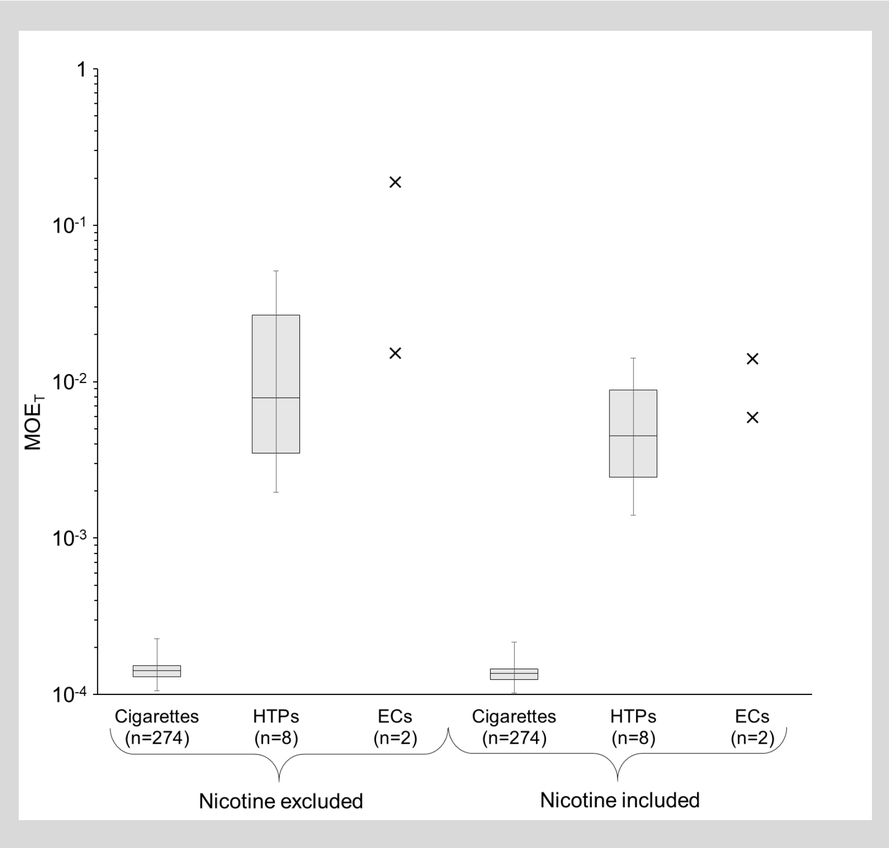
Non-cancer risk: HTPs and ECs vs. cigarette



Increased MOE_T of non-combusted products relative to cigarettes

- Excluding MOE for nicotine
  - $1.06x10^{-4}$ to $2.28x10^{-4}$ for cigarettes, with $1.42x10^{-4}$ as median
  - $1.96x10^{-3}$ to $5.10x10^{-2}$ for HTPs, with $7.86x10^{-3}$ as median
  - $1.53x10^{-2}$ and $1.73x10^{-1}$ for ECs

- Including MOE for nicotine
  - $1.03x10^{-4}$ to $2.16x10^{-4}$ for cigarettes, with $1.36x10^{-4}$ as median
  - $1.40x10^{-3}$ to $1.42x10^{-2}$ for HTPs, with $4.49x10^{-3}$ as median
  - $5.92x10^{-3}$ and $8.10x10^{-3}$ for ECs

☛ **Significant decrease in non-cancer risk, as suggested by the model**

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Limitations

- Only a global health risk description allowed

- No risk prediction in absence of
  - IUR/IEL
  - Yield data for the constituent of interest

- Inappropriate to evaluate synergistic effects

- Predicted risk affected by uncertainties
  - Animal studies used to derive toxicological thresholds
  - Study quality and reliability
  - Precision of the analytical methods

Conclusions

- Development of a health risk assessment model driven by the need to characterize both cancer and non-cancer risk associated with exposure to HTP and EC aerosols.
  - Mean lifetime cancer risk index used as an indicator of cancer risk
  - Combined MOE_T used as an indicator of non-cancer risk

- Main limitations:
  - Reliable analytical methods to determine chemical yields
  - Availability of IURs/IELs
  - Selection process among available thresholds

- Significant cancer and non-cancer risk reductions are suggested for HTPs and ECs relative to cigarettes, according to the developed model. This is consistent with published results.