



PMI RESEARCH & DEVELOPMENT

Review of smoke chemistry methodology and reduction of selected harmful and potentially harmful constituents (HPHCs) in mainstream smoke

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Smoke chemistry methodology

- Conventional cigarette (CC) smoke is a complex mixture of > 6000 constituents identified in mainstream smoke
- The cigarette smoke is generated by smoking machines using specified smoking regimes
- A number of constituents are routinely measured:
 - To determine tar, nicotine and CO levels when required for pack information
 - To characterize the product in terms of its yield of aerosol constituents (may also be required by regulatory authorities, e.g., Health Canada)
- The aerosols from pMRTPs are analyzed to determine if the yield of constituents is reduced when compared to CC
- The comparator product can be a reference cigarette (e.g., as supplied by the University of Kentucky – 3R4F cigarette) or commercially available products





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PMI's Three Product Platforms^(a)

Platform 1



Platform 2

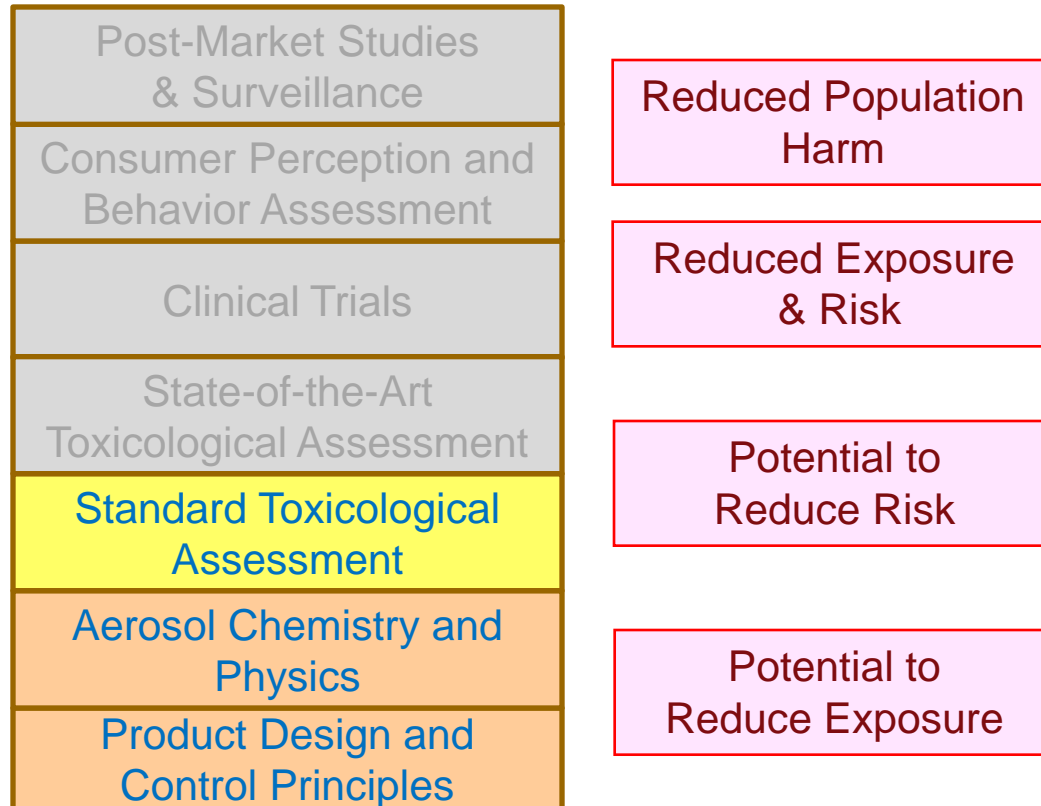
Platform 3

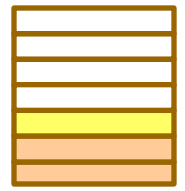


(a) The products described are subject to ongoing development and therefore the descriptions are illustrative and do not necessarily represent the latest stages of product development



PMI's assessment strategy





Nonclinical assessment

Product design, manufacturing and controls

- pMRTP production is under control, meets required quality standards and consistently delivers according to specifications. It is then ready to enter the formal product assessment phase

Non-clinical evidence:

- Chemical analysis – for known and novel aerosol constituents
- Toxicological assessment - in cell systems and laboratory animals

To do what?

- Determine if the product is acceptable for:
 - Use by internal/external volunteer panels in support of product development
 - Clinical studies
 - Market Launch



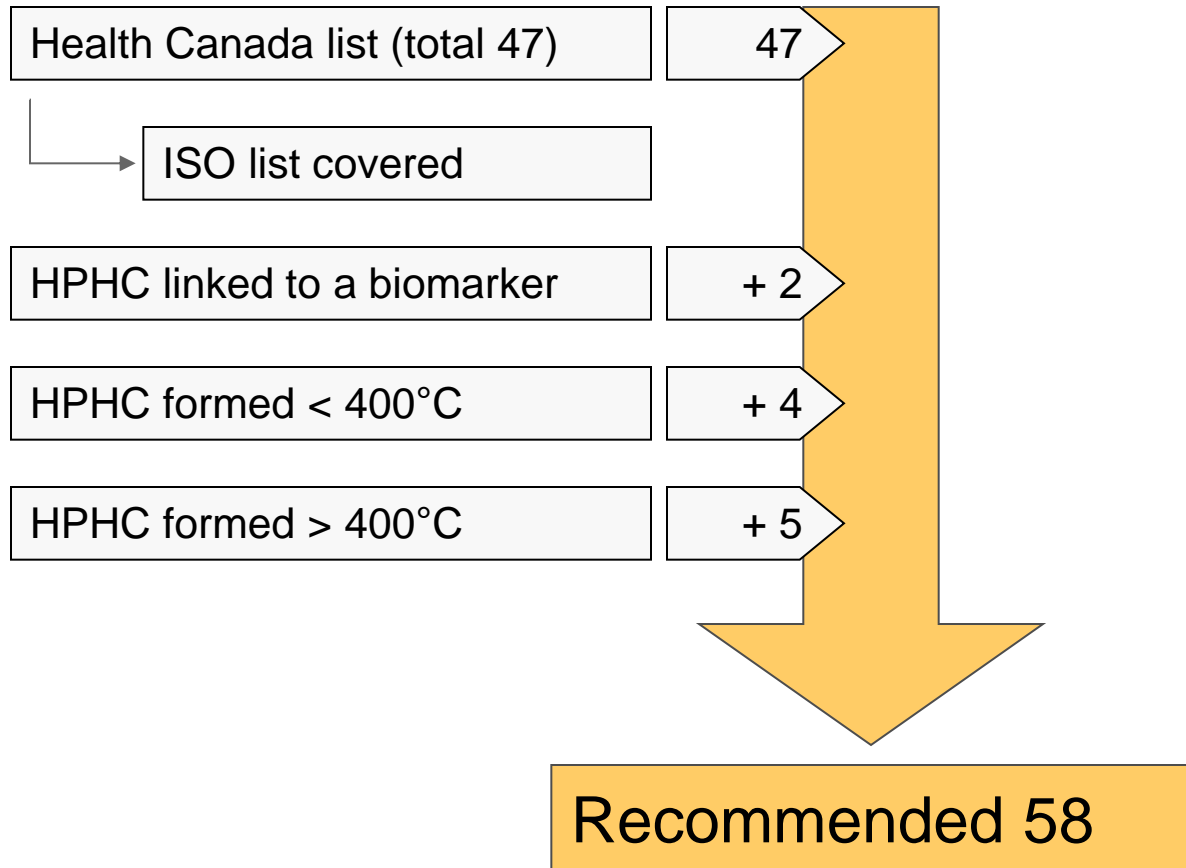
Harmful and Potentially Harmful tobacco smoke Constituents (HPHCs)

- HPHC includes any chemical or chemical compound in a tobacco product or in tobacco smoke:
 - That is or potentially is inhaled, ingested or absorbed
 - That has the potential to cause direct or indirect harm to users or non-users of tobacco products
 - For example, constituents that are toxicants, carcinogens and addictive chemicals
- Different regulatory authorities have different lists of HPHCs
- The existing FDA list contains 93 HPHCs*

We routinely measure 58 constituents based on our criteria and validated methods – but we intend to match the list required by regulatory authorities

* Food and Drug Administration, 2012. Harmful and Potentially Harmful Constituents in Tobacco Products and Tobacco Smoke; Established List. Federal Register Vol. 77, No. 64; pp. 20034-20037 (April 3, 2012). Available at <http://www.fda.gov/downloads/TobaccoProducts/GuidanceComplianceRegulatoryInformation/UCM297981.pdf>

Rationale for the list of PMI 58 HPHCs



PMI R&D laboratories quality system

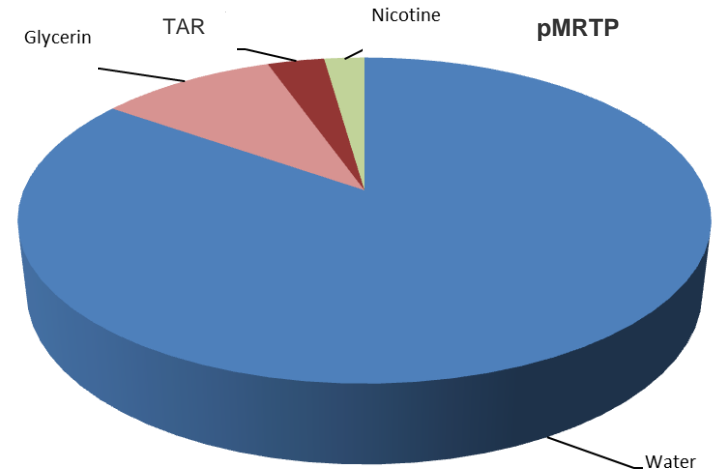
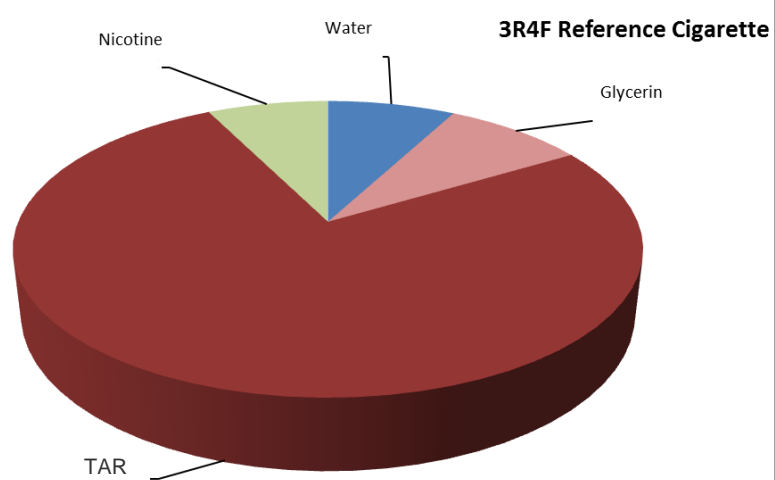
Aerosol Chemistry and
Physics
Product Design and
Control Principles

- PMI R&D performs analysis under appropriate quality standards
 - ISO 17025 accredited
 - GLP accredited
- Methods validated according to internal and external guidelines (ICH)
- Participation in industry ring trials and proficiency testing



Towards a Less Complex Aerosol

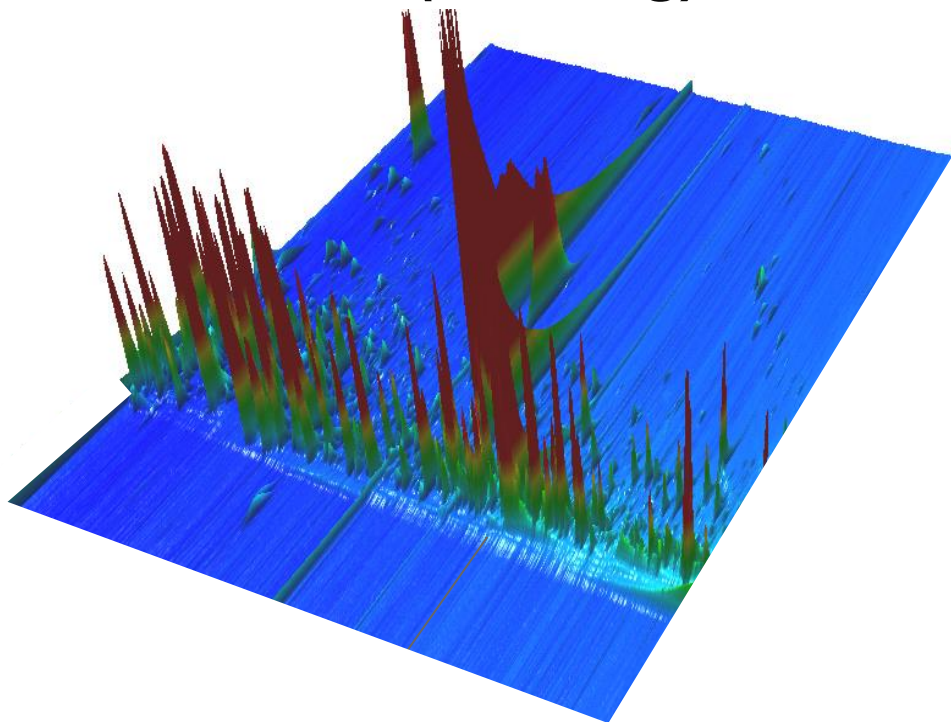
$$\text{TAR} = (\text{Total Particulate Matter} - \text{Water} - \text{Nicotine})$$



Smoke Chemistry Comparison: Conventional Cigarette vs. pMRTP

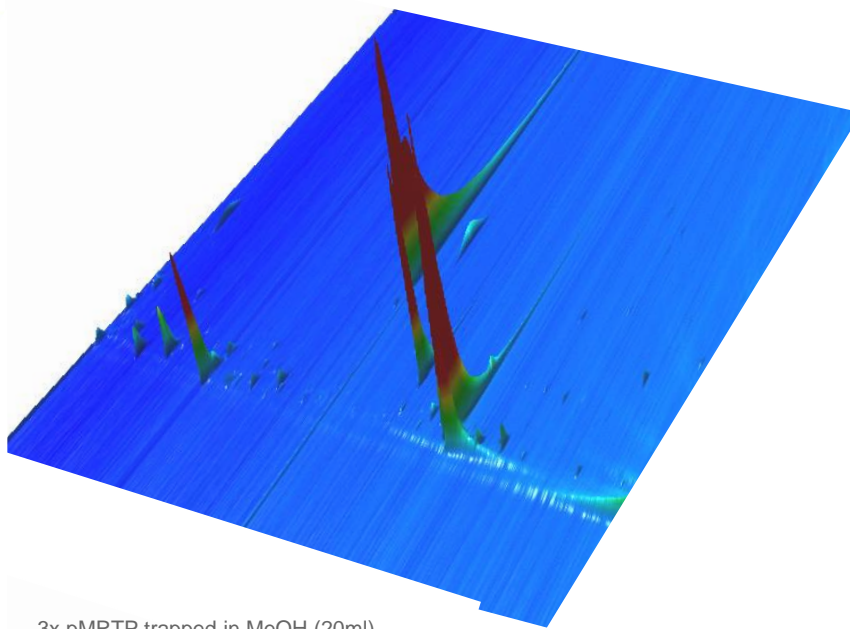
[2-Dimensional Gas Chromatography-Mass Spectrometry]

Conventional Cigarette (*Burning*)



3x CC trapped in MeOH (20ml)
1 Cambridge Pad + 2 Impingers (-78°C) in Series
Smoking Regime : **55 mL/2 s/30 s**
12 Sinusoidal Puffs

pMRTP (*Heating*)



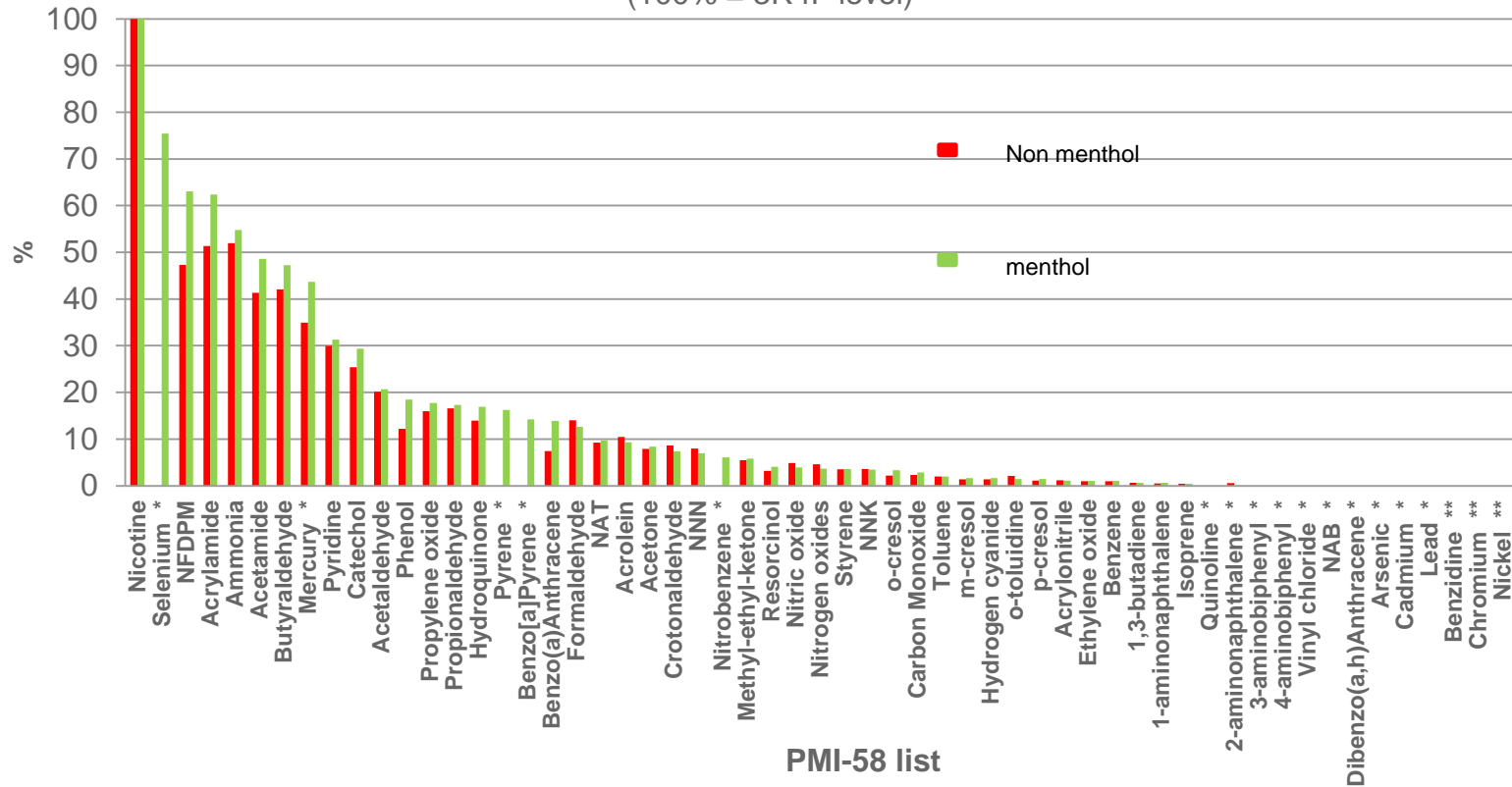
3x pMRTP trapped in MeOH (20ml)
1 Cambridge Pad + 2 Impingers (-78°C) in Series
Smoking Regime : **60 mL/2 s/30 s**
12 Sinusoidal Puffs



pMRTP Performance: Aerosol Chemistry

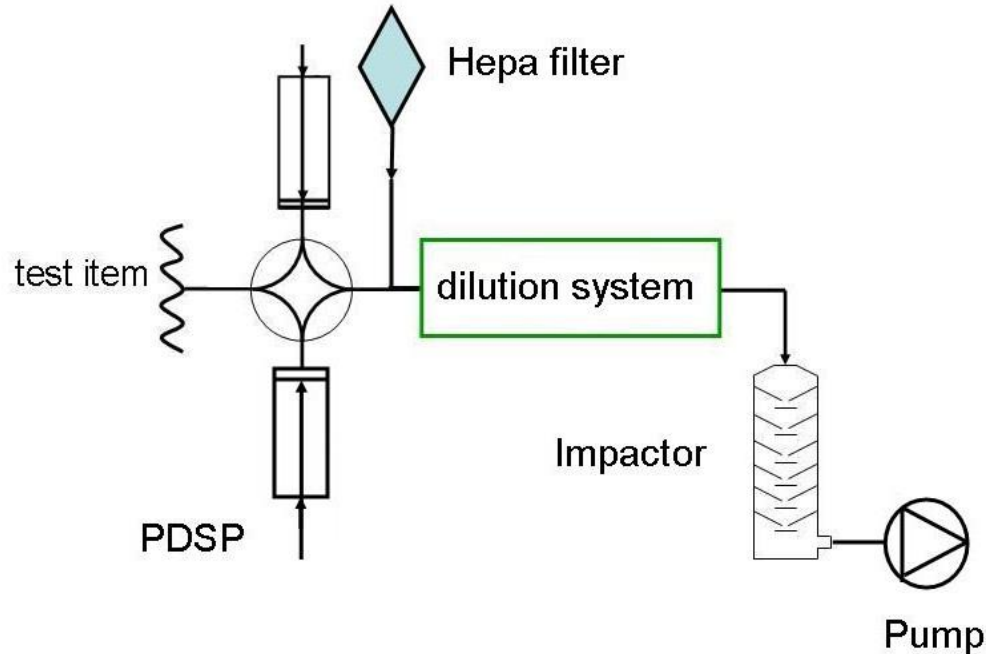
PMI set of 58 HPHC's:

Comparison relative to 3R4F on per mg nicotine basis
(100% = 3R4F level)



Relative deliveries of the PMI 58 HPHCs for pMRTP compared with the 3R4F cigarette (on a per mg nicotine basis).

Droplet Size Distribution (DSD)



Commercial 9-stage PIXE cascade impactor selectively fractionates the aerosol particles depending on their size dependent inertia

Determination of the particles' Mass Median Aerosol Diameter (MMAD) and Geometric Standard Deviation (GSD)

New constituents that may be found in pMRTP

- Important that not only is the exposure reduced to known HPHCs but also that exposure to new HPHCs is not generated by a pMRTP
- GC-MS fingerprint methods are applied to determine if new compounds are generated – when compared to CC
- Challenge to identify new compounds – largely because of the complexity of the CC aerosol
- When novel compounds are detected they are assessed for structural alerts and concentration found in the aerosol

Summary and conclusions

- Measurement of HPHCs in a pMRTP is important for:
 - Product characterization
 - Demonstration of potential to reduce exposure compared to CC
 - Part of the nonclinical assessment of the pMRTP to confirm no new or increased levels of HPHCs
 - Aerosol chemistry and physics is an essential step for hazard characterization
 - Subsequent steps in the assessment program will determine if the reduction in yield of HPHCs translates to a reduction in exposure and risk

