INNOVATION OF REDUCED RISK ALTERNATIVES: ORAL TOBACCO AND NICOTINE PRODUCTS

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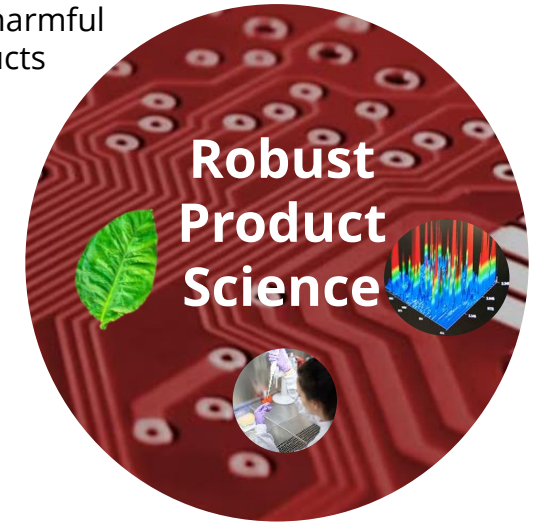
PMI SCIENCE
PHILIP MORRIS INTERNATIONAL

Innovation and Tobacco Harm Reduction

Our main goal is to design a smoke-free future and provide a portfolio of product options helping adult smokers, who would otherwise continue to smoke, to switch to less harmful alternative nicotine products



Innovation
Integration of new technologies to satisfy consumer needs and help adult smokers switch to less harmful alternative nicotine products

Multi product categories
HTPs, ENDS, nicotine pouches etc.

Monitors and controls
to minimize unintended events

Harm reduction
Acceptance and usage of scientifically substantiated smoke free products

Dialog with regulators
for science-based regulatory framework

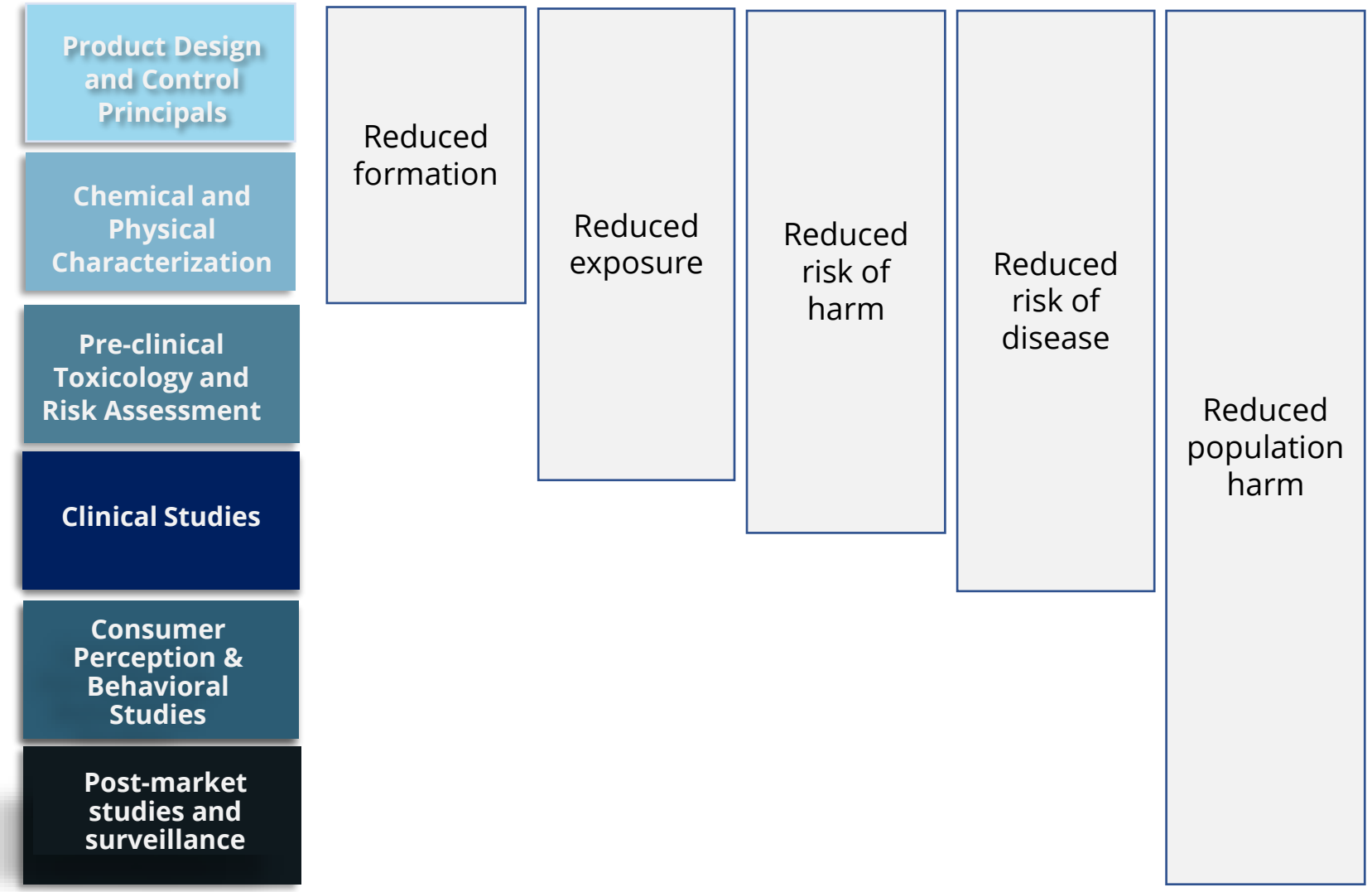
ENDS, electronic nicotine delivery system;
HTP, heated tobacco product

Population Harm Reduction

Successful Harm Reduction Requires Current Adult Smokers to be Offered a Range of Reduced-risk Products that are acceptable by Adult Tobacco and Nicotine Users while Minimizing Unintended Use

Source: Figure adapted from Clive Bates presentation to E-Cigarette Summit (19 Nov 2013)

Balance between Speed of Innovation & Robust Product Science

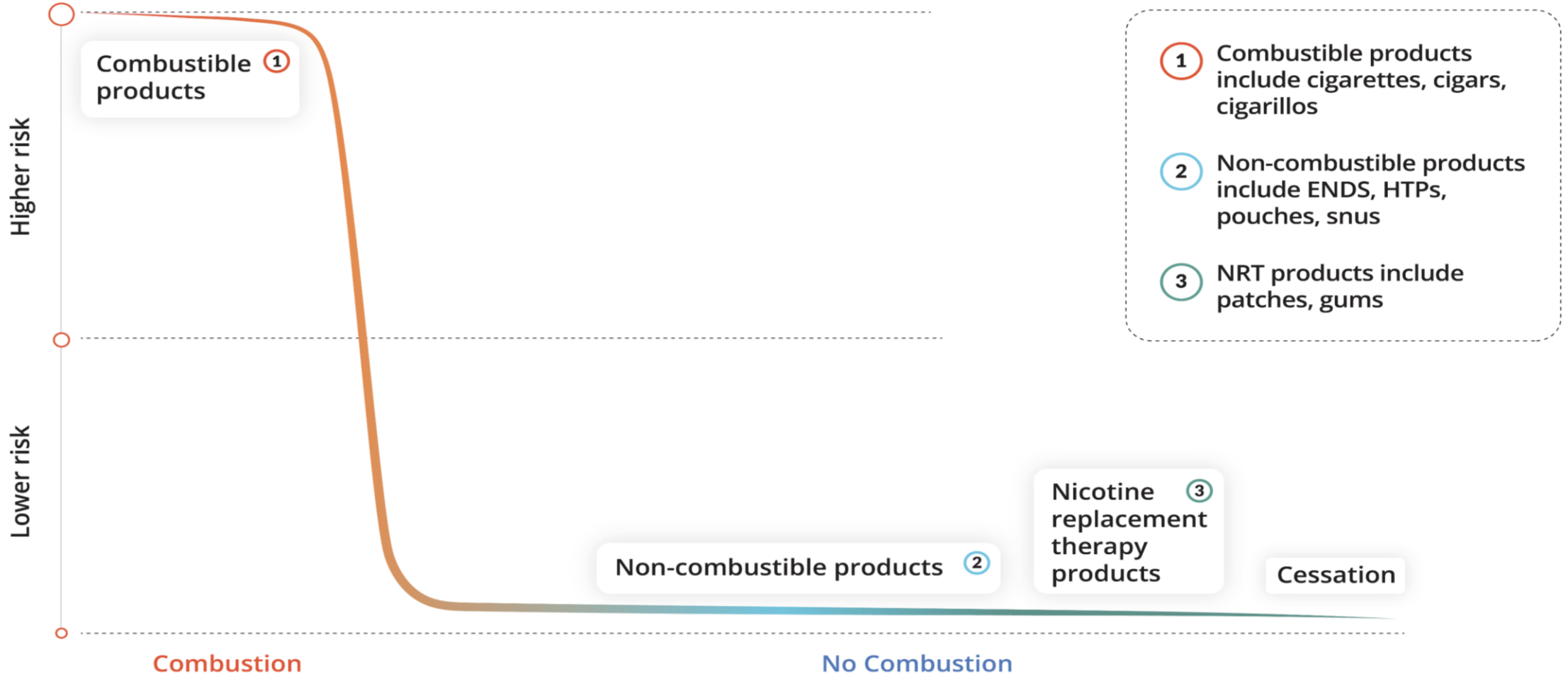


Balance between Speed of Innovation & Robust Product Science

Product Design and Control Principals **Chemical and Physical Characterization** **Non-clinical Toxicology and Risk Assessment**	• Product design using QbD principles • Manufactured to appropriate quality standards and sufficiently characterized to document product performance parameters • All components and ingredients are appropriate for use and will not present new or increased toxicity • Adherence to Swedish Institute of Standards on Nicotine Pouches • No combustion; reduced HPHC levels compared to cigarettes • Reduced toxicity in *in vitro* systems compared to cigarettes • Oral safety – pre-clinical and clinical
Clinical Studies	• Pharmacokinetic studies do not raise additional questions about nicotine uptake • Reduced HPHC formation leads to reduced exposure in humans • Reduced risk and harm
Consumer Perception & Behavioral Studies	• Product use behavior among adult smokers and non-smokers • Product design and messaging is appropriate for adult smokers but not attractive to youth and non-smokers
Post-market studies and surveillance	• Consumer perception and tobacco use behavior • Longer-term assessment of exposure and health outcomes • Adverse events related to product use

HPHC, harmful and potentially harmful constituent; QbD, quality by design

Risk Cliff between Combustible and Non-combustible Products



Graph for illustrative purpose only.
ENDS, electronic nicotine delivery systems; HTP, heated tobacco product; NRT, nicotine replacement therapy

Nicotine Pouches vs. Traditional Snus

Traditional Snus

- **Contains tobacco and commercialized for decades**
- Different flavors, but tobacco dominates
- Swedish Match snus product authorized by the U.S. FDA to be commercialized with the claim: **"Using General Snus instead of cigarettes puts you at a lower risk of mouth cancer, heart disease, lung cancer, stroke, emphysema, and chronic bronchitis"[1]**
- Usage leads to **tooth discoloration**

VS.

Nicotine Pouches

- **Commercialized since 2017**
- No tobacco
- Predominantly non-tobacco flavors
- Epidemiological data on snus indicates that this tobacco-free product has high potential to be significantly less harmful than continuing to smoke and/or using snus
- White pouches **do not stain teeth**

[1] FDA grants first-ever modified risk orders to eight smokeless tobacco product (https://www.fda.gov/news-events/press-announcements/fda-grants-first-ever-modified-risk-orders-eight-smokeless-tobacco-products)

General Snus

FDA NEWS RELEASE

FDA grants first-ever modified risk orders to eight smokeless tobacco products

FDA concludes completely switching from cigarettes to these authorized products lowers certain health risks

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For Immediate Release: October 22, 2019

The U.S. Food and Drug Administration announced today that, for the first time, it has authorized the marketing of products through the modified risk tobacco product (MRTP) pathway. The authorizations are for eight Swedish Match USA, Inc. snus smokeless tobacco products sold under the "General" brand name.

GRANTED DUE TO:

- Significantly lower levels of HPHCs (TSNAs) than traditional smokeless tobacco*
- Low likelihood of nonuser uptake or decreases in cessation

"Using General Snus instead of cigarettes puts you at a lower risk of mouth cancer, heart disease, lung cancer, stroke, emphysema, and chronic bronchitis"[1]

*Tobacco-specific nitrosamines comprise one of the most important groups of carcinogens in tobacco products, particularly cigarettes and fermented dipping snuff.
Source: https://www.acs.org/pressroom/newsreleases/2012/august/first-identification-of-a-strong-oral-carcinogen-in-smokeless-tobacco.html

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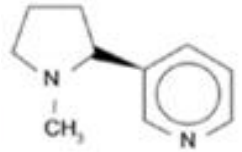
Typical Nicotine Pouch Composition

Pouch

- Composed of
  - Organic cellulose compounds
  - Polyethylene
  - Thermosealable resins
- The thickness and proliferation affect nicotine release dynamics

Nicotine base

- Nicotine salt
- Nicotine resinate



Binder and/or filler

- Microcrystalline cellulose/cellulose powder
- Water for moist products
- Humectants (glycerol)
- Binder (alginate)

Sweetener or flavor

- Sweeteners
  - Magnasweet
  - Xylitol
  - Acesulfame K
  - Sucralose
- E-numbered food-grade flavors such as:
  - Mint
  - Citrus
  - Berries
- Sodium chloride
- Salmiak

pH buffer

- Sodium bicarbonate
- Sodium carbonate

Chemical and Physical Characterization

Example: Swedish Institute of Standards for Nicotine Pouches[1]

- Supply chain requirements
  - Ingredients are food or pharma grade
  - Negative list (prohibited ingredients)
  - Ingredient quality
  - Toxicological risk assessment
- Final product
  - Constituent limits: pH (≤9.1) ; Nicotine (20 mg/pouch)
  - Water activity (<0.7; if above, toxicological risk assessment
  - Shelf life
- Packaging
  - Approved for food packaging
  - Product information and labeling
  - Disclosure of consumable/flavoring formulation

GOTHIATEK standard for snus[2]

GOTHIATEK® limits for undesired substances in nus production

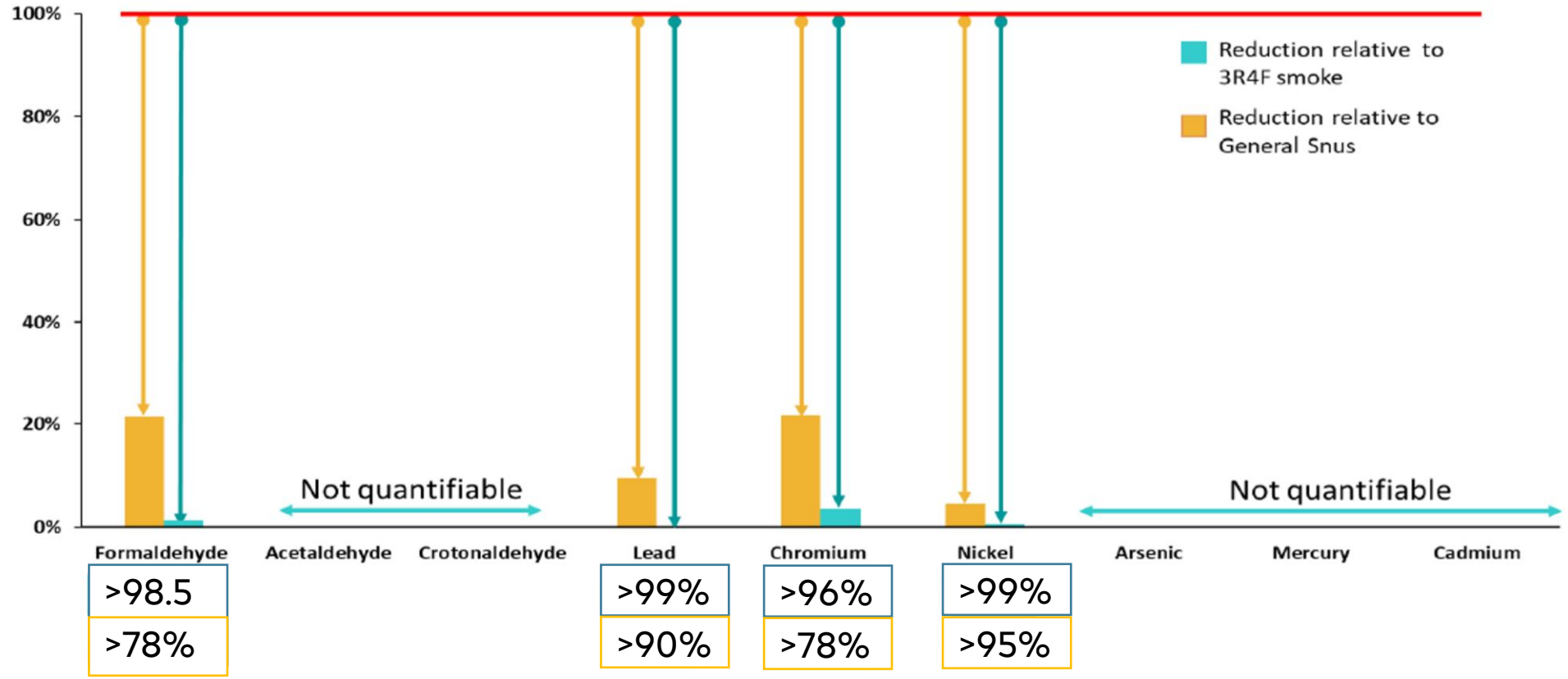
- TSNA
- B[a]P
- Ochratoxins and aflatoxins
- Aldehydes
- Metals
- Agrochemicals
- Declaration of contents in accordance with food labeling
- Manufacturing controls

1 Swedish Institute for Standards (SIS) for Nicotine-containing, tobacco-free oral products– Safety and quality related requirements (SIS/ftTS 72SIS/TK 442/N107)

2 Swedish Match - GOTHIATEK® standard

B[a]P, benzo(a)pyrene; TSNA, tobacco-specific nitrosamine

Reduced Harmful Toxicants



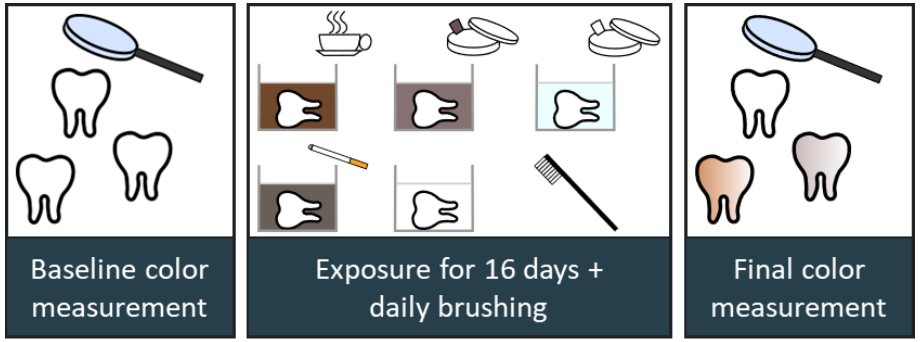
Representative percent average reduction in selected HPHC levels for nicotine pouch (Shiro) compared to General Snus* and reference 3R4F cigarette smoke

PMI Nicotine pouches have a >99% reduction in toxicants vs. cigarettes and far lower levels of HPHCs than General Snus

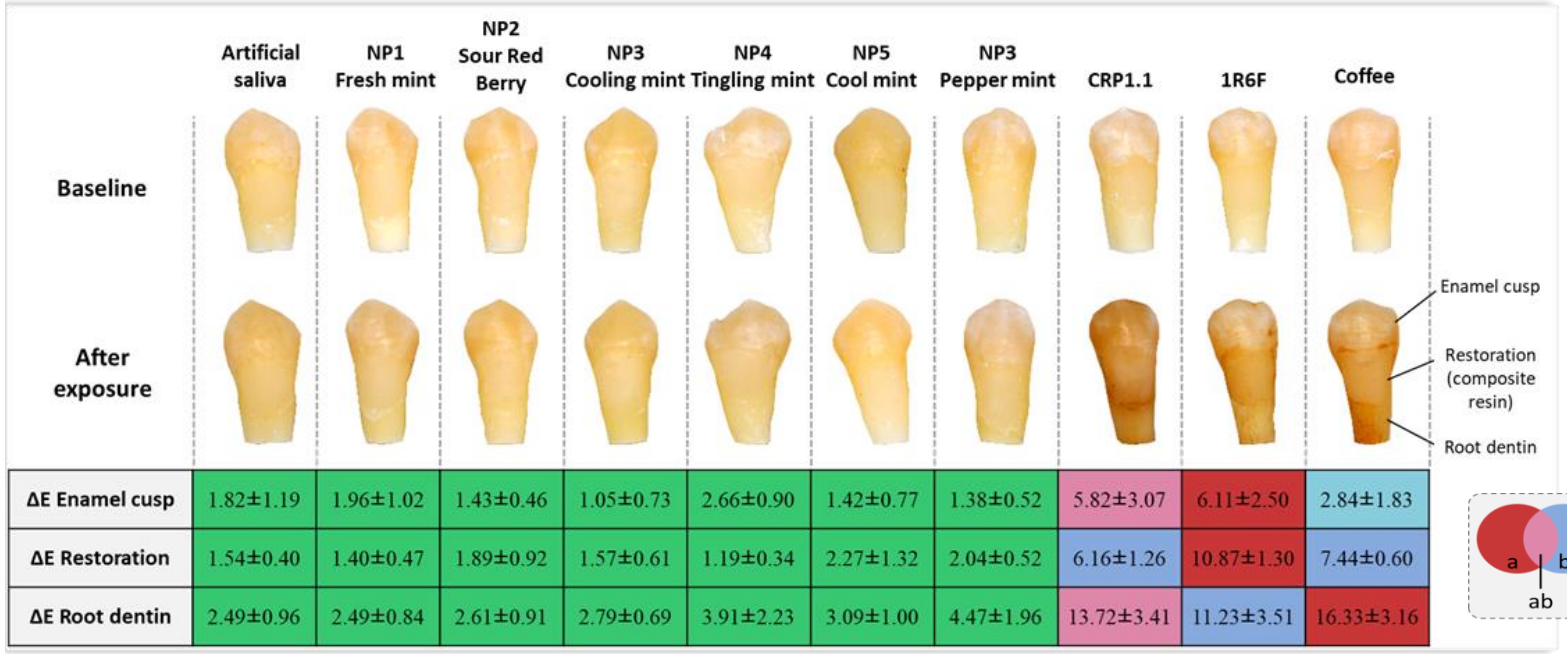
* General Snus data extracted from MRTP application

Tooth Discoloration

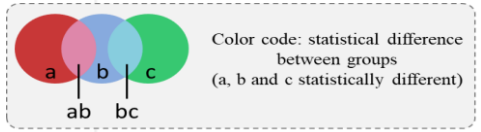
Study Design:



Results:



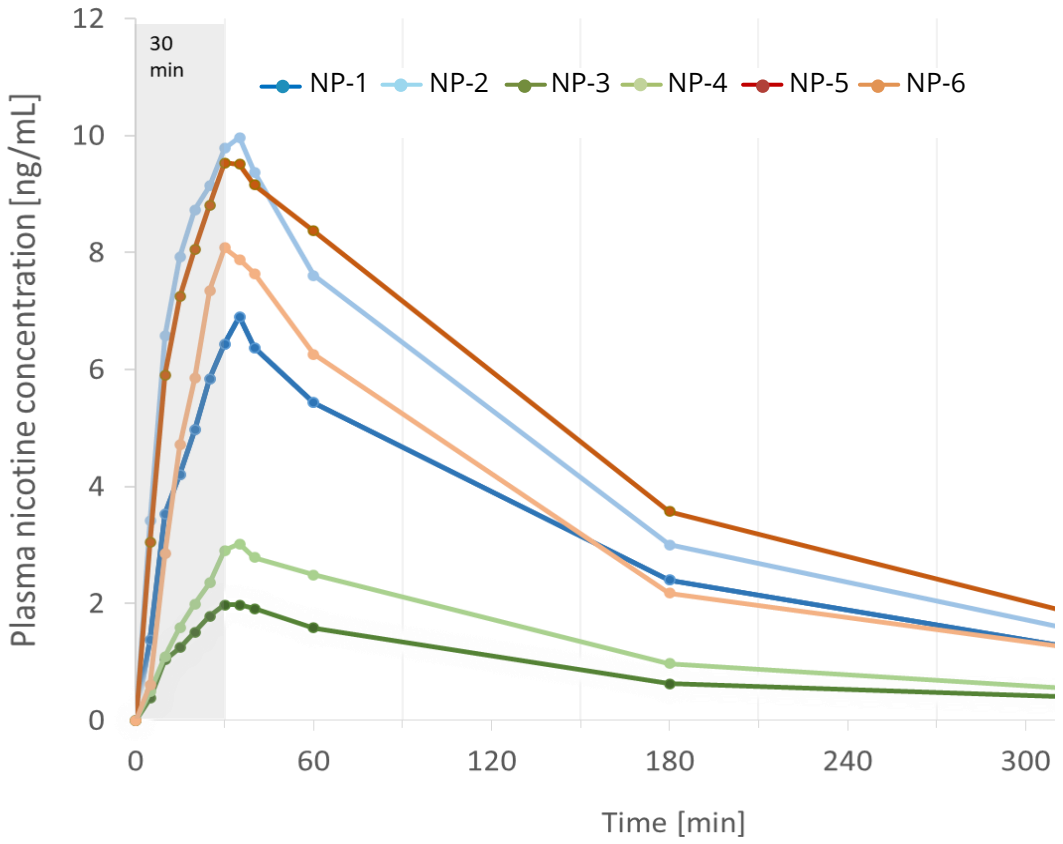
	Artificial saliva	NP1 Fresh mint	NP2 Sour Red Berry	NP3 Cooling mint	NP4 Tingling mint	NP5 Cool mint	NP3 Pepper mint	CRP1.1	1R6F	Coffee
ΔE Enamel cusp	1.82±1.19	1.96±1.02	1.43±0.46	1.05±0.73	2.66±0.90	1.42±0.77	1.38±0.52	5.82±3.07	6.11±2.50	2.84±1.83
ΔE Restoration	1.54±0.40	1.40±0.47	1.89±0.92	1.57±0.61	1.19±0.34	2.27±1.32	2.04±0.52	6.16±1.26	10.87±1.30	7.44±0.60
ΔE Root dentin	2.49±0.96	2.49±0.84	2.61±0.91	2.79±0.69	3.91±2.23	3.09±1.00	4.47±1.96	13.72±3.41	11.23±3.51	16.33±3.16



PMI Nicotine Pouches do not cause tooth discoloration

Nicotine Pouches Exploratory Study:

Nicotine Uptake Pharmacokinetics/Pharmacodynamics (PK/PD)



AUC, area under the curve; Cmax, maximum concentration; Tmax, time to reach Cmax
https://www.clinicaltrials.gov/ct2/show/NCT05317195

Product	Parameters
NP-1	Nicotine Moisture pH Pouch format
NP-2	
NP-3	
NP-4	
NP-5	
NP-6	

Study to investigate:

- 24 healthy, smoking subjects
- Fixed product-use duration (30 min)
- Nicotine PK profiles
- Subjective effects: Craving, Liking, Satisfaction
- Safety and tolerability
- Uptake: Analysis of residual nicotine

Results:

- Cmax driven by formulation, not exceeding cigarette smoking
- Tmax driven by duration of product use
- All subjects reported reduced craving after the start of product use
- Liking and product evaluation differ between products
- No safety signals
- Not all nicotine extracted

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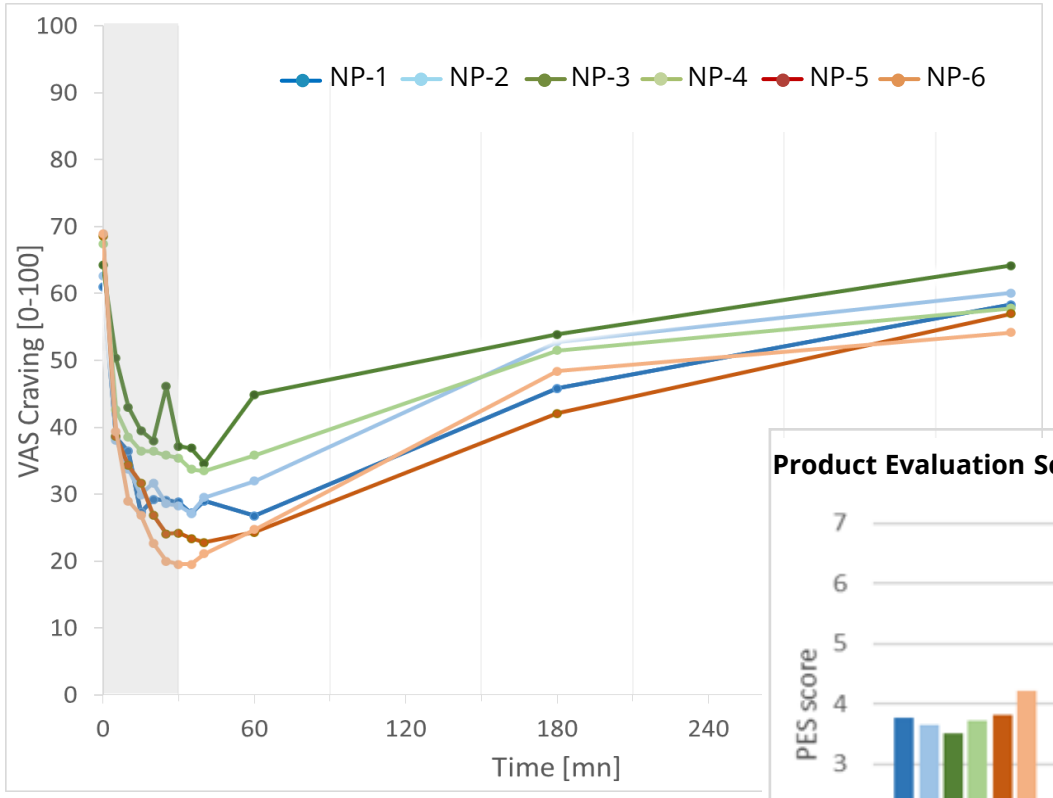

VAS, visual analog scale

https://www.clinicaltrials.gov/ct2/show/NCT05317195

Results:

- Consumers respond differently to nicotine strength
- Differences in PK absorption profiles do not necessarily induce similar differences in PD profiles (Liking and Satisfaction), although craving is reduced for all products tested
- Lower strength products do address craving for cigarettes and deliver satisfaction – albeit at reduced rates
- Subjective effects are self-reported and weakly associated with nicotine absorption

Summary

- PMI's main goal is to design a smoke-free future and provide a portfolio of product options that help adult smokers who otherwise continue to smoke switch to less harmful alternative nicotine products

- Robust product science is key to developing and assessing those products and demonstrate their harm reduction potential

- Not all tobacco and nicotine products present the same health risks: Tobacco-free nicotine pouches are relatively new products that may serve as a low-risk alternative to cigarettes or conventional tobacco-based oral products among current tobacco users

- Our assessment program was designed to collect multiple types of scientific data to validate the hypothesis that nicotine pouches carry less risk than continued smoking, with a focus on nicotine pharmacokinetics, product use behavior, and long-term use health risks

THANK YOU