

The Science of Smoke-Free Products & Nicotine

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Vice President Global Scientific Engagement

May 7th, 2024
2024 Jefferies Virtual Reduced Risk Seminar



PMI SCIENCE
PHILIP MORRIS INTERNATIONAL

PMI Science: 2024 Jefferies Virtual Reduced Risk Seminar (May 7, 2024)

Designing a Smoke-Free Future

Our Mission is to Make Cigarettes Obsolete



Our stated ambition is to convince all current adult smokers that intend to continue smoking to switch to **[smoke-free products]** as soon as possible.



André Calantzopoulos
Executive Chairman

— February 2016



By 2030, our ambition is to be a substantially **smoke-free company**, with over two-thirds of our total net revenues coming from smoke-free products. We see a realistic path to becoming a **smoke-free company** over time, and this will be achieved market-by-market—as we are already demonstrating today.



Jacek Olczak
CEO

— October 2023



Best-in-Class R&D Capabilities in the Industry

Information Since the Altria Spin-Off in 2008 Through 2023



Published over

+530

publications & book chapters



Invested^(a)

\$12.5

Billion



287

Toxicological Assessments

29

Clinical Assessments

69

Perception & Behavior Studies

(a) To develop, scientifically substantiate and commercialize innovative smoke-free products

Source: PMI Integrated Report 2023 (Status as of December 2023). Note: all figures 2008 - 2023



Despite Reduced Prevalence There are Still +1 Billion Smokers

Tobacco Harm Reduction can Help Reduce the Number of Smokers Faster



Spatial, temporal, and demographic patterns in prevalence of smoking tobacco use and attributable disease burden in 204 countries and territories, 1990–2019: a systematic analysis from the Global Burden of Disease Study 2019

GBD 2019 Tobacco Collaborators*

Summary
Background: Ending the global tobacco epidemic is a defining challenge in global health. Timely and comprehensive estimates of the prevalence of smoking tobacco use and attributable disease burden are needed to guide tobacco control efforts nationally and globally.

January 2023, 997, 3334-66
doi:10.1016/S0140-6736(23)01169-7
May 17, 2023
ISSN: 1473-3099 (print)
ISSN: 1473-3107 (online)

Number of smokers has reached all-time high of 1.1 billion, study finds

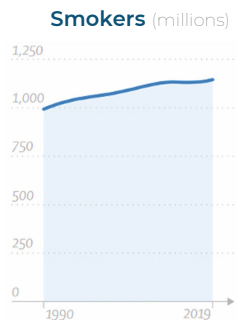
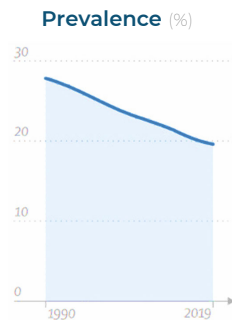
Governments told to focus on stopping young from taking up habit that killed 8 million people in 2019

Smoking killed almost 8 million people in 2019 and the number of smokers rose as the habit was picked up by young people around the world, according to new research.

A study published in the Lancet on Thursday said efforts to curb the habit had been outstripped by population growth with 150 million more people smoking in the nine years from 1990, reaching an all-time high of 1.1 billion.

... efforts to curb the habit [smoking] had been outstripped by population growth with 150 million more people smoking in the [twenty]-nine years from 1990, reaching an all-time high of 1.1 billion.”^[1]

Without intervention, deaths attributable to smoking will increase over the coming decades.^[2]



Sources: [1] The Guardian (Link – Accessed May 2023); [2] Global Burden of Disease 2019 Tobacco Collaborators (DOI: 10.1016/S0140-6736(23)01169-7)



Population Harm Reduction

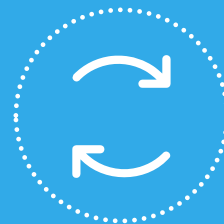
A Complement to Current Tobacco Control Approaches



Population Harm Reduction



Individual Risk Reduction



Smokers Switching

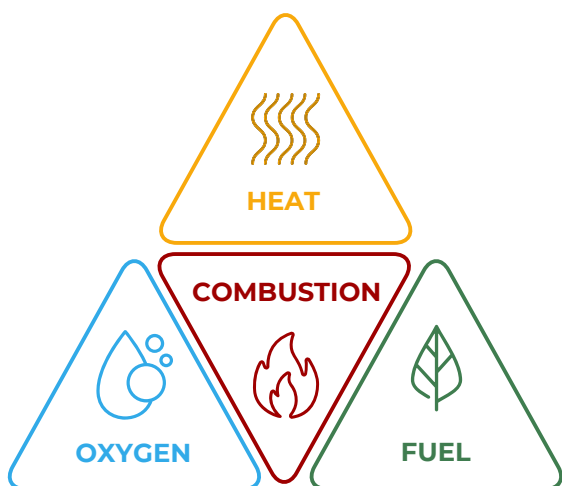
Successful Harm Reduction... requires that current adult smokers be offered a range of reduced-risk products so that consumer acceptance can be best fulfilled

Source: Adapted from Clive Bates' presentation to E-Cigarette Summit (19 November 2013)



Understanding Combustion

Specifically, Tobacco Combustion



Cigarettes: Tobacco Combustion



Identified over

+6000

chemicals in cigarettes smoke ^[1]



Approximately

100

are harmful or potentially harmful constituents ("HPHCs") ^[2]

Source: [1] Rodgman and Perfetti 2013 (DOI: [10.1201/b13973](https://doi.org/10.1201/b13973)); [2] U.S. FDA "Harmful & Potentially Harmful Constituents in Tobacco Products & Tobacco Smoke"

Nicotine and Health

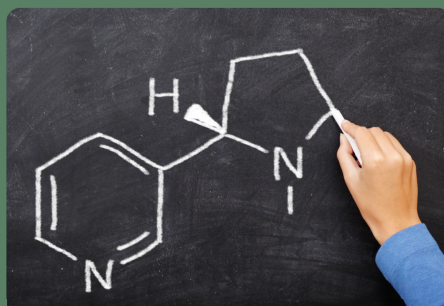
Not The Primary Cause of Smoking-Related Diseases



... it's the thousands of chemicals contained in tobacco and tobacco smoke that make tobacco use so deadly.

... This toxic mix of chemicals—not nicotine—cause the serious health effects among those who use tobacco products, including fatal lung diseases, like chronic obstructive pulmonary disease (COPD) and cancer. [1]

U.S. FDA Website
(Accessed: 10 April 2021)



Nicotine, though addictive and not risk-free, **is not the primary cause of smoking-related disease**

NHS Website [3]
"Vaping Myths and the Facts"

Source: [1] U.S. FDA Link www.fda.gov; [2] Royal College of Physicians Link www.rcp.ac.uk; [3] National Health Service Link www.nhs.uk;



Current evidence suggests **nicotine itself confers little risk to health**, though acute exposure at typical levels from consumer nicotine products can result in addiction, short-term enhanced cognitive effects, elevated heart rate and blood pressure. [2]

Royal College of Physicians
(Accessed: April 2024)

Myth 2: Nicotine is very harmful to health

Fact

Although nicotine is addictive, it is relatively harmless to health.

It is the many other toxic chemicals contained in tobacco smoke that cause almost all the harm from smoking.

Nicotine itself does not cause cancer, lung disease, heart disease or stroke and has been used safely for many years in medicines to help people stop smoking.



Nicotine is Not a Carcinogen

Based on the Assessment and Categorization of the Constituents in Smoke by Public Health Organizations

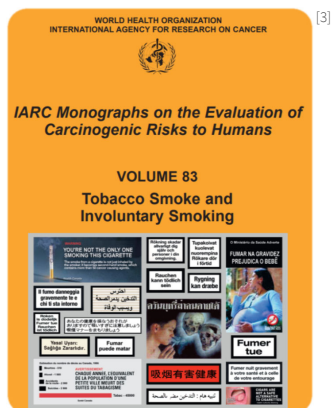
Original Investigation

Does nicotine replacement therapy cause cancer? Evidence from the Lung Health Study

Robert P. Murray, John E. Connett, & Lisa M. Zazawa

In the U.S. FDA's List of Harmful and Potentially Harmful Constituents [2] they Classifies **Nicotine** as a Reproductive and Developmental Toxicant and Addictive—**not a Carcinogen**

Constituent:	Carcinogen (CA), Respiratory Toxicant (RT), Cardiovascular Toxicant (CT) Reproductive or Developmental Toxicant (RDT), Addictive (AD)
Nicotine	RDT, AD



Extracted from IARC Monograph 83 "Table 1.14. Carcinogens in Cigarette Smoke"

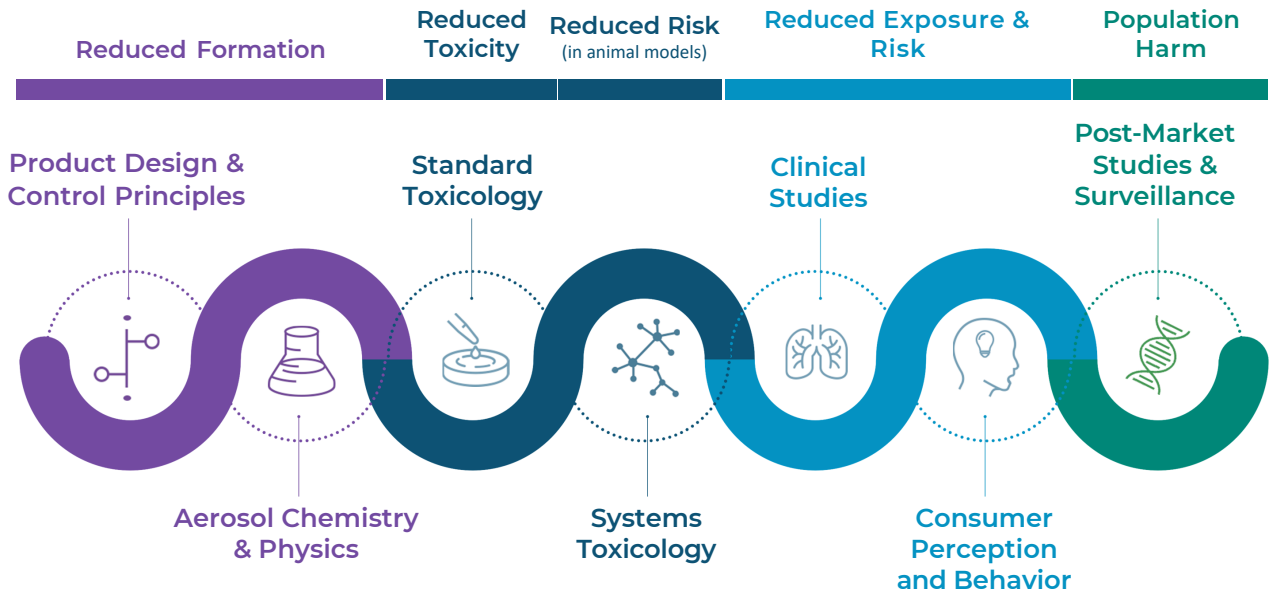
Chemical Class	Number of Carcinogens	Representative Carcinogens	
Polycyclic aromatic hydrocarbons (PAHs) and heterocyclic hydrocarbons	15	Benzo[a]pyrene Benz[a]anthracene	Dibenz[a,h]anthracene Furan
N-Nitrosamines	8	4-(Methylnitrosamino)-1-(3-pyridyl)-1-butanone (NNK) N'-Nitrosornicotine (NNN)	
Aromatic amines and Heterocyclic amines	12	4-Aminobiphenyl	2-Naphthylamine
Aldehydes	2	Formaldehyde	Acetaldehyde
Phenolic compounds	2	Catechol	Caffeic acid
Volatile hydrocarbons	7	Benzene Isoprene	1,3 Butadiene
Other organic compounds	12	Ethylene oxide	Acrylonitrile
Metals and metal compounds	8	Cadmium	Polonium-210

Source: [1] Murray 2009 (DOI: 10.1093/ntr/ntp104); [2] U.S. FDA "Harmful & Potentially Harmful Constituents in Tobacco Products & Tobacco Smoke"; [3] IARC Monograph 83: "Tobacco Smoke & Involuntary Smoking"



Totality of the Evidence

PMI's Scientific Assessment Approach (includes following elements)



Source: Adapted from Smith 2016 (DOI: [10.1016/j.yrtph.2016.07.006](https://doi.org/10.1016/j.yrtph.2016.07.006))



IQOS Aerosol is Fundamentally Different From Cigarette Smoke

Aerosol Chemistry & Physics



Cigarette Smoke and IQOS Aerosol

Were Collected on a Cambridge Filter Pad in Accordance with the Health Canada Intense Smoking Regimen

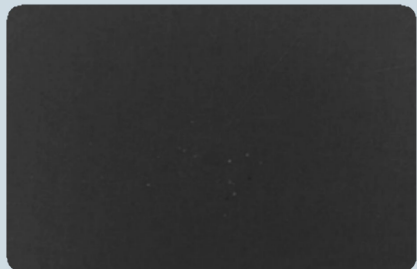
Conducted under Health Canada's Intense Smoking Regime x 5 sticks; Cigarette Smoke = 3R4F Reference Cigarette; IQOS Aerosol = IQOS version 2.2; 90-95% reduction in toxicants (excluding nicotine).
Source: Ghosh 2014 (DOI: [10.2478/cttr-2014-0008](https://doi.org/10.2478/cttr-2014-0008))



Absence of Solid Particles in the IQOS Aerosol

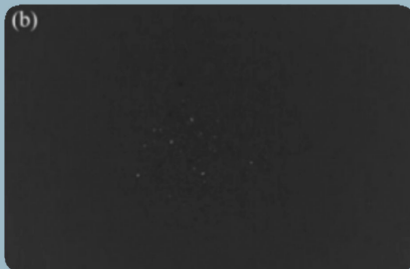
Aerosol Chemistry & Physics

Scanning Electron Microscopy Images
After Collected Samples are Passed Through a Thermodenuder



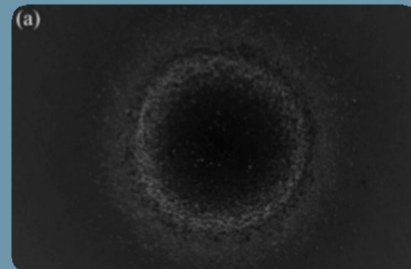
AIR

No solid particles



IQOS AEROSOL

No Solid Particles
(IQOS aerosol does not contain solid particles from combustion)



CIGARETTE SMOKE

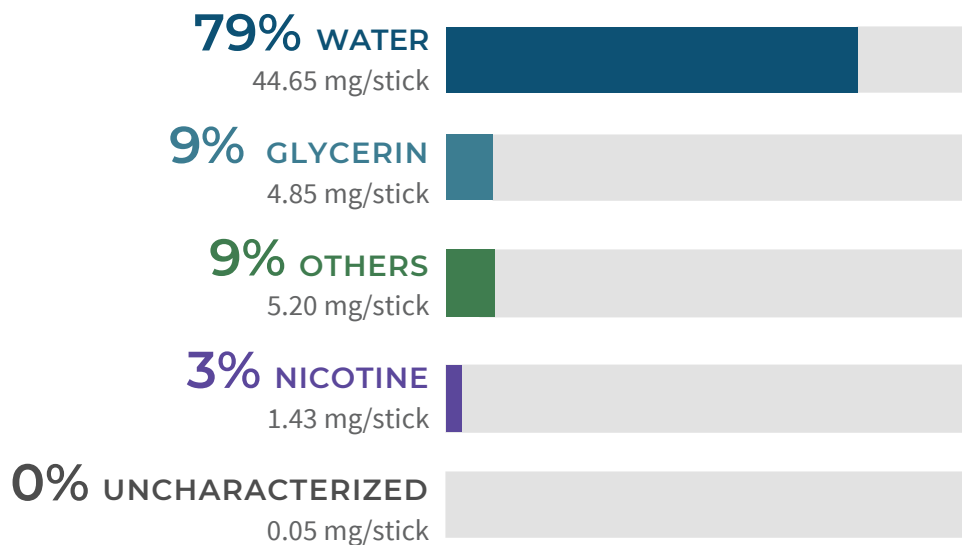
Carbon-Based Particles
Median diameter = 75 nm
Amount: 6×10^{11} particles \cong 0.7 mg^{+c}

Conducted under Health Canada's Intense Smoking Regime; Cigarette Smoke = 3R4F Reference Cigarette; IQOS Aerosol = IQOS version 2.2
Source: Pratte 2017 (DOI:10.1177/0960327116681653)



Composition of IQOS Aerosol is Well Characterized

Aerosol Chemistry & Physics



The majority (91%) of IQOS aerosol is comprised of **water, glycerin, and nicotine**

Other compounds contribute about **5.25 mg/stick** of which only 0.05 mg (0%) are uncharacterized

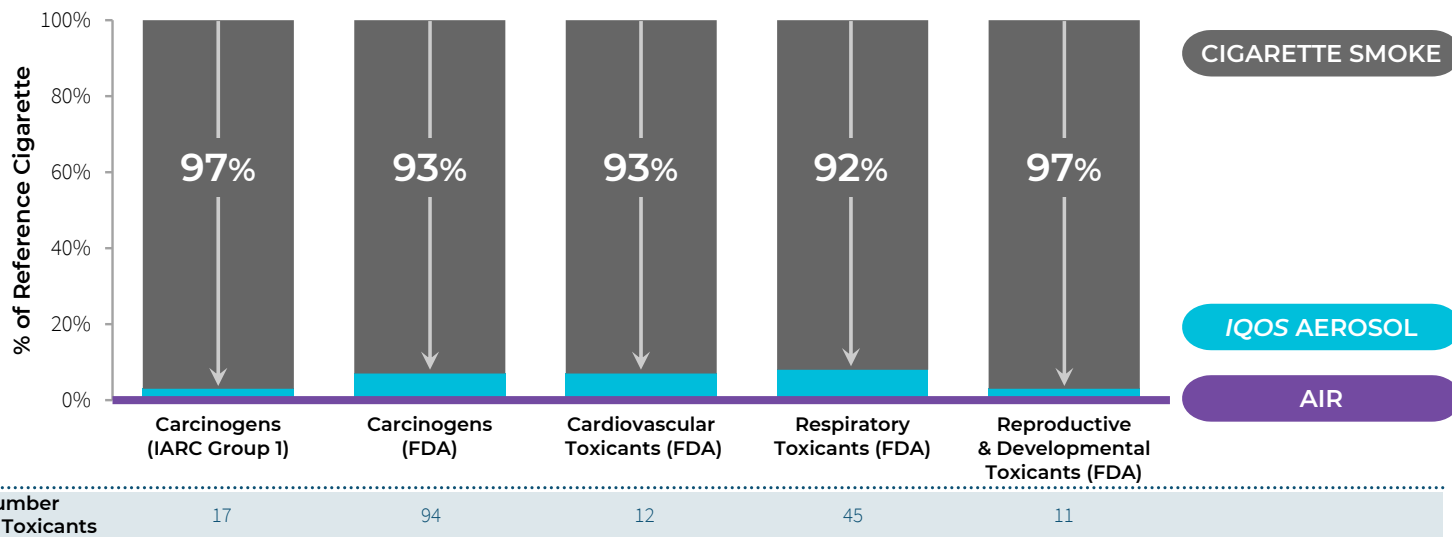
Conducted under Health Canada's Intense Smoking Regime; IQOS Aerosol = IQOS version 2.2
Source: U.S. FDA PMTA TPL Review Document p 42; raw data on file.



Reduced Emission of Toxicants

Aerosol Chemistry and Physics

Average Reduction Harmful & Potentially Harmful Constituent Formation IQOS Relative to the 3R4F Reference Cigarette, by Disease Category



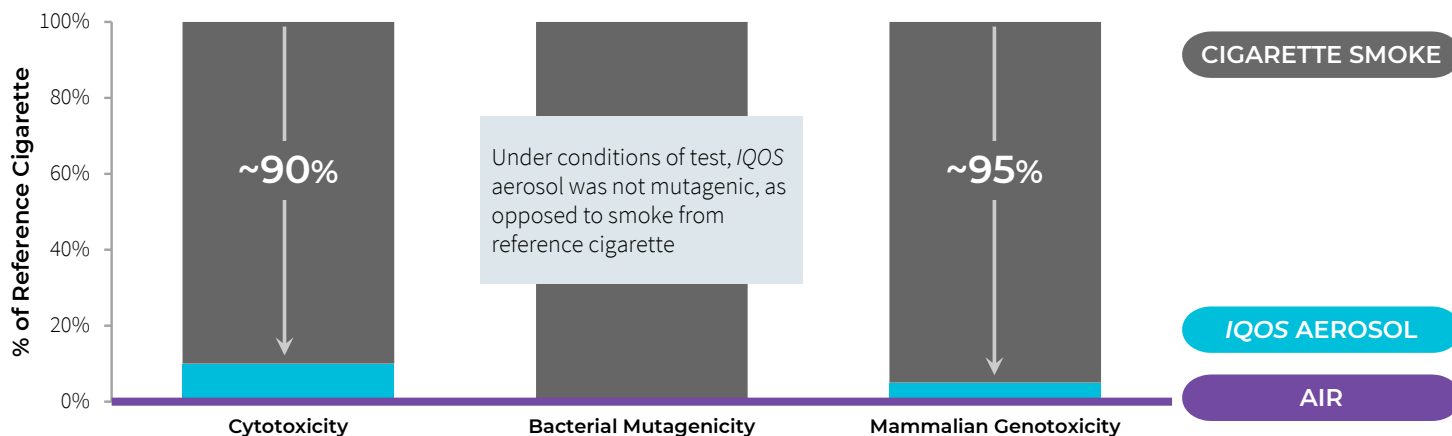
Conducted under Health Canada's Intense Smoking Regime; Comparison on a per-stick basis (excluding nicotine); Cigarette Smoke = 3R4F Reference Cigarette; IQOS Aerosol = IQOS version 2.2; Disease categories as defined in U.S. FDA "Harmful & Potentially Harmful Constituents in Tobacco Products & Tobacco Smoke" (includes +93 constituents because some are classes or isomers)



Reduced Toxicity

in vitro Toxicological Assessments

Average Reduction in Toxicity IQOS Relative to the 3R4F Reference Cigarette



Based on Neutral Red Uptake (Cytotoxicity), Ames (Mutagenicity), and Mouse Lymphoma Assay (Genotoxicity)

Cigarette Smoke = 3R4F Reference Cigarette; IQOS Aerosol = IQOS version 2.2
Source: April 26, 2018 Amendment: Submission of P1 Characterization Study Available @www.fda.gov

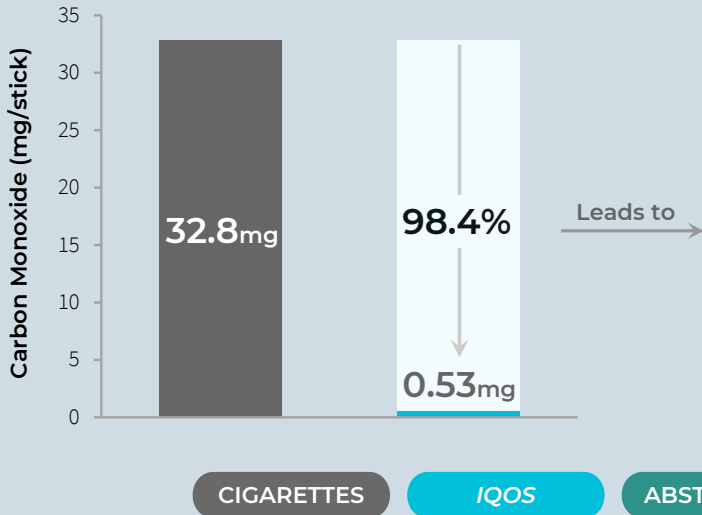
Reduced Carbon Monoxide Exposure

Clinical Assessment (In Smokers Who Would Have Otherwise Continued to Smoke Cigarettes)



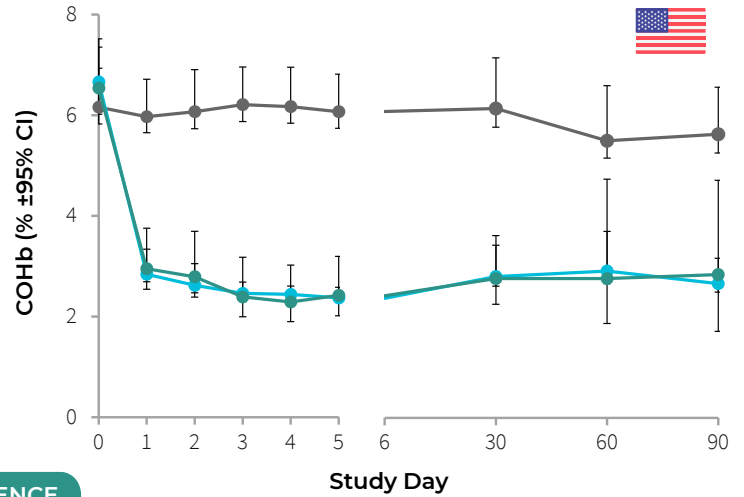
Emission Substantially Reduced [1]

Carbon Monoxide in IQOS Relative to 3R4F Reference Cigarette



Exposure Substantially Reduced [2]

Carboxyhemoglobin After Switching Completely to IQOS

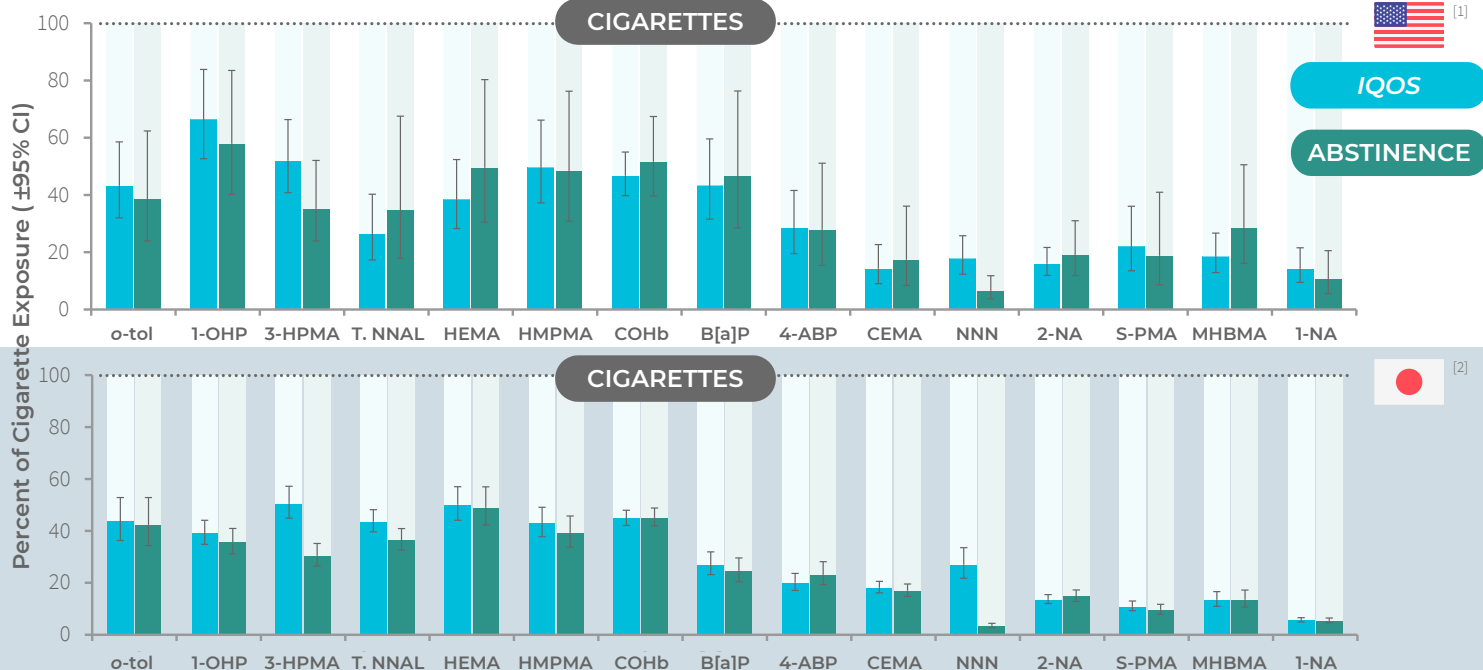


Aerosol chemistry conducted under Health Canada's Intense Smoking Regime; Cigarette = 3R4F Reference Cigarette (aerosol chemistry); IQOS = IQOS version 2.2

Source: [1] Aerosol Chemistry - Schaller 2016 (DOI: [10.1016/j.yrtph.2016.10.001](https://doi.org/10.1016/j.yrtph.2016.10.001)); [2] U.S. Randomized Reduced Exposure Study (n=120) — Haziza 2019 (DOI: [10.1093/ntr/ntz013](https://doi.org/10.1093/ntr/ntz013))

Smokers Who Switched Completely Reduced Their Exposure

Clinical Assessment (In Smokers Who Would Have Otherwise Continued to Smoke Cigarettes)



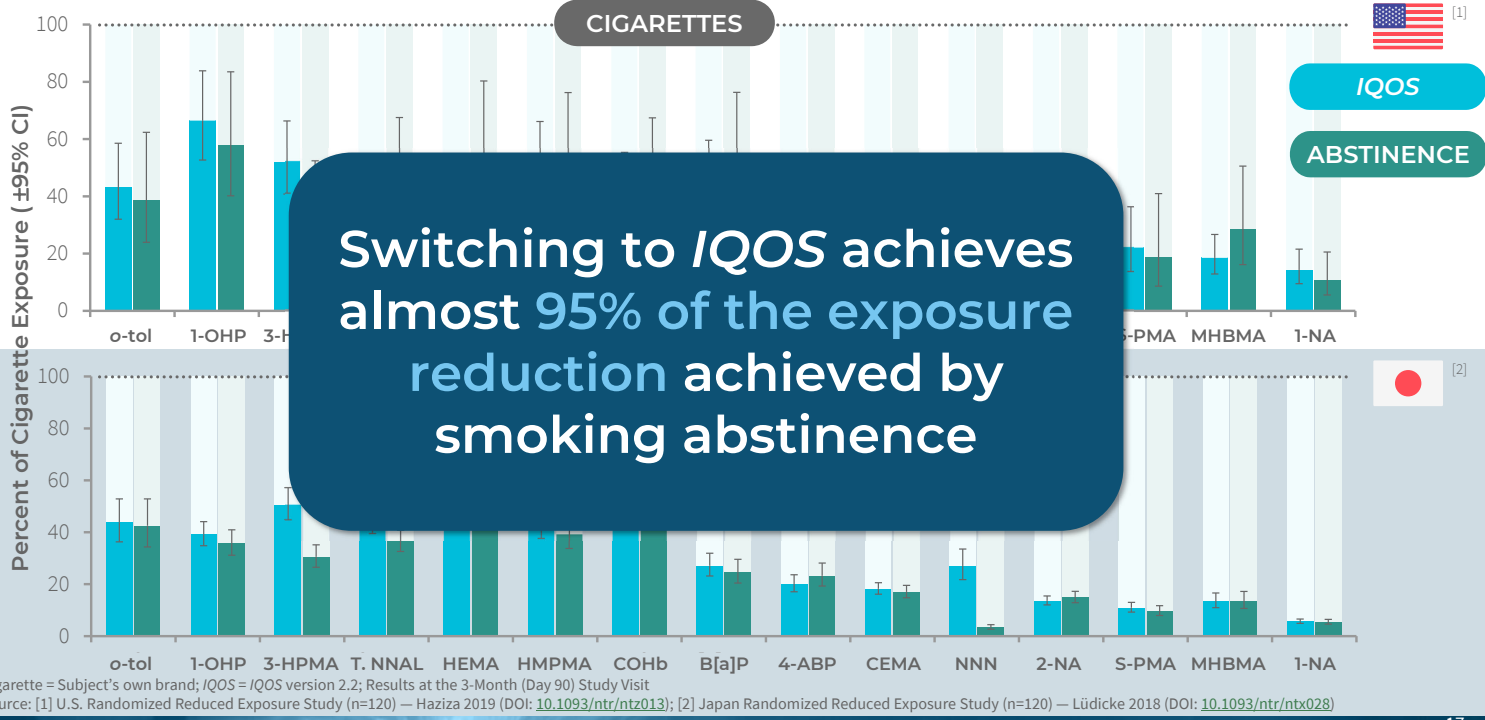
Cigarette = Subject's own brand; IQOS = IQOS version 2.2; Results at the 3-Month (Day 90) Study Visit

Source: [1] U.S. Randomized Reduced Exposure Study (n=120) — Haziza 2019 (DOI: [10.1093/ntr/ntz013](https://doi.org/10.1093/ntr/ntz013)); [2] Japan Randomized Reduced Exposure Study (n=120) — Lüdicke 2018 (DOI: [10.1093/ntr/ntx028](https://doi.org/10.1093/ntr/ntx028))



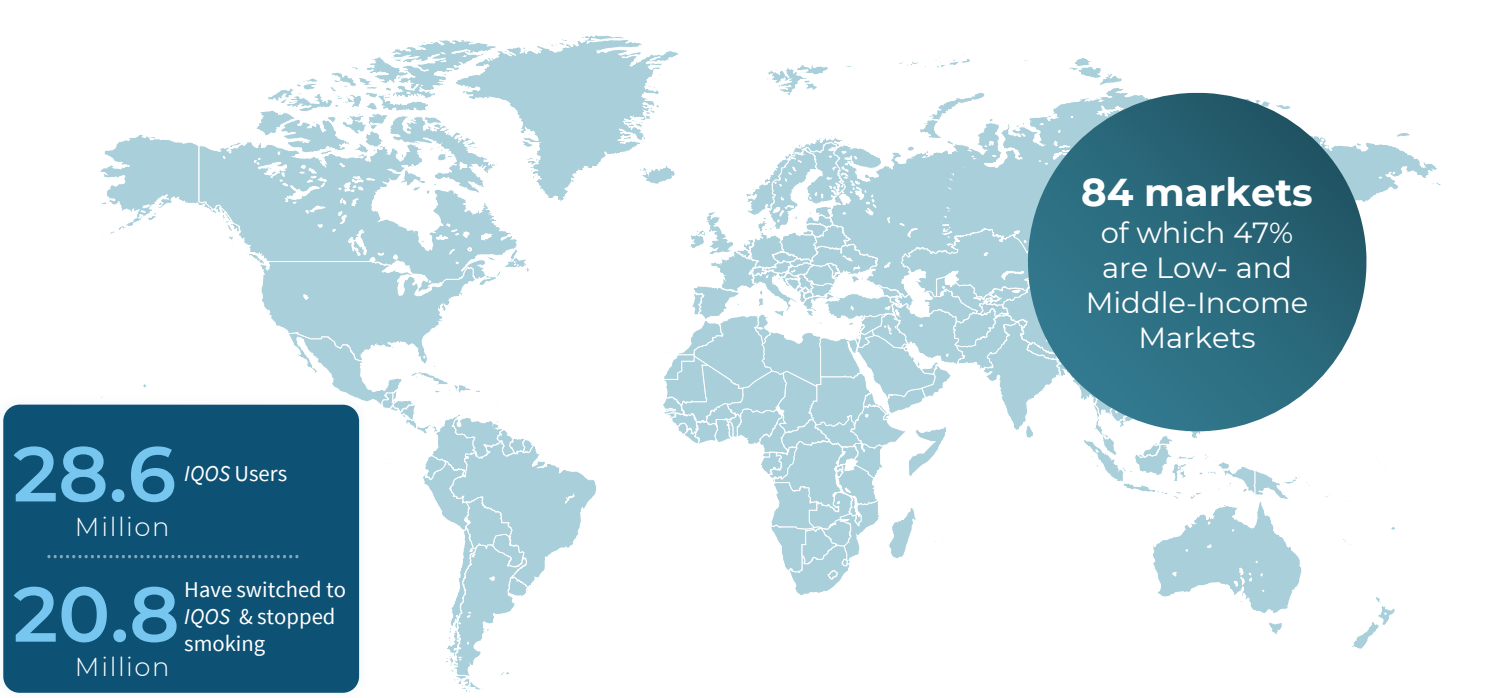
Smokers Who Switched Completely Reduced Their Exposure

Clinical Assessment (In Smokers Who Would Have Otherwise Continued to Smoke Cigarettes)



Progress In Commercialization of Smoke-Free Products

Commercialized in Key Cities or Nation-wide in 84 markets of which 47% are Low- and Middle-Income Markets



Source: [1] FY 2023 Earnings Release



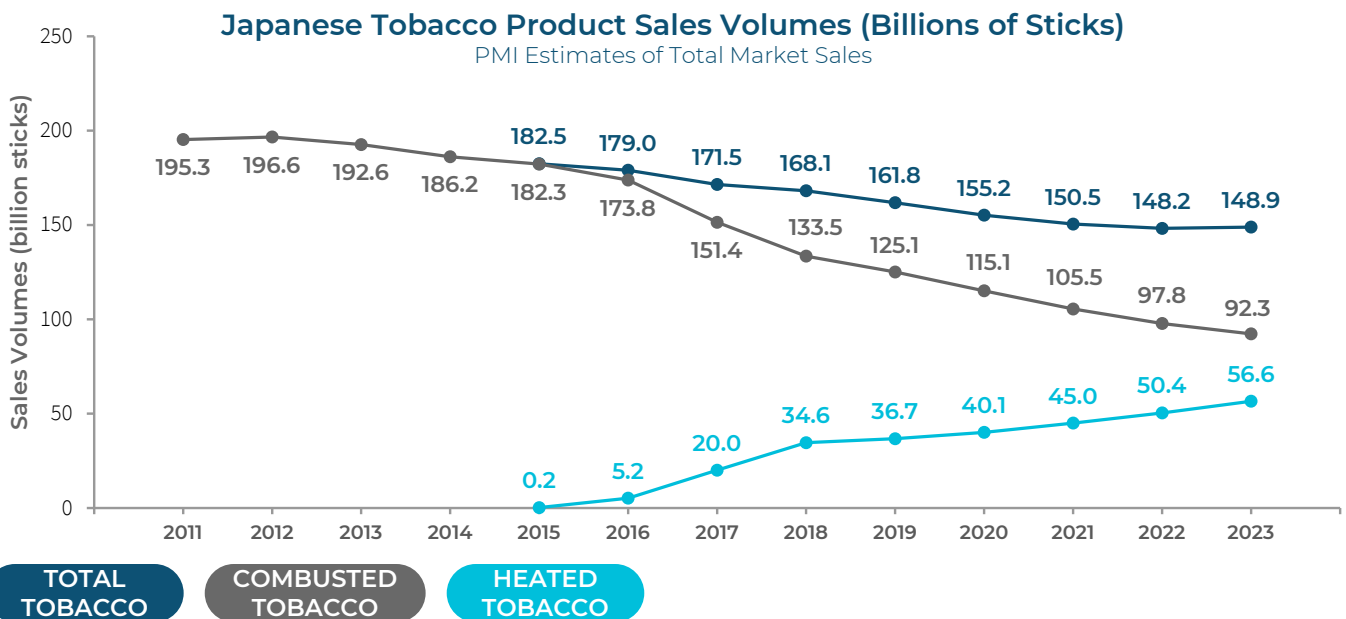
Japanese Experience

Impact of HTP Introduction in Japan



Heated Tobacco is Replacing Cigarettes in Japan

Rapid Decrease in Cigarette Volumes Following the Introduction of Heated Tobacco Products



Note: Total tobacco volumes include cigarillos. Source: PMI Financials or estimates

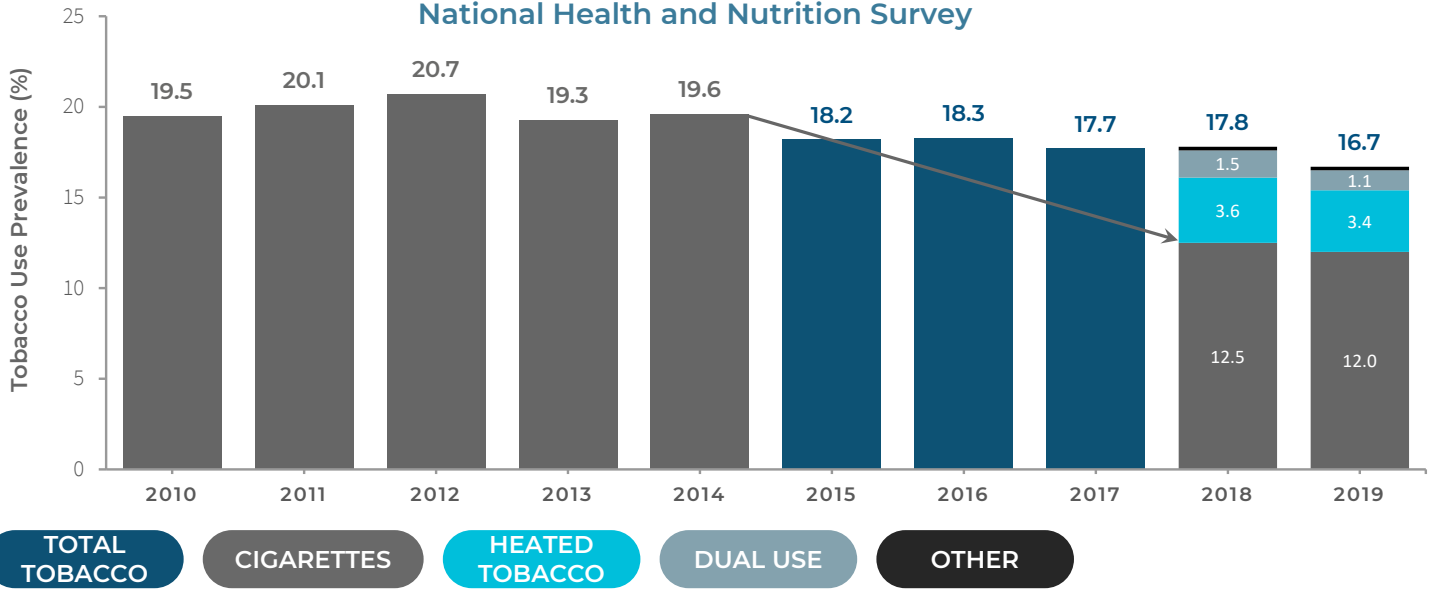


Prevalence Declines With Introduction of Heated Tobacco

Smoking Prevalence Reached 13.1% in 2019 — Approaching the Japanese Target of 12% by 2025



Japanese Adult (≥ 20 years) Tobacco Use Prevalence National Health and Nutrition Survey



Source: National Health and Nutrition Survey, Japan (2020) (Accessed: May 2023)



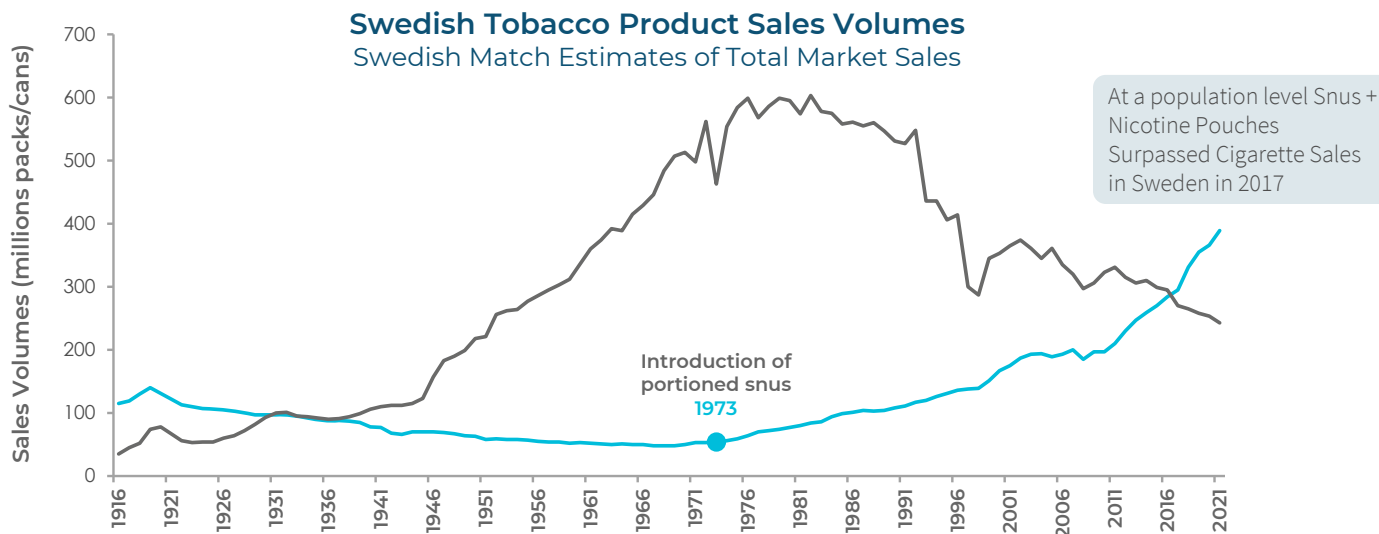
Swedish Experience

Impact of Snus & Nicotine Pouches Uptake in Sweden



Increase in Snus Sales Correlates with Decrease in Cigarettes Sales

The Scientific Literature Attributes the Decrease in Cigarette Sales in Sweden to the Availability of Snus



CIGARETTES

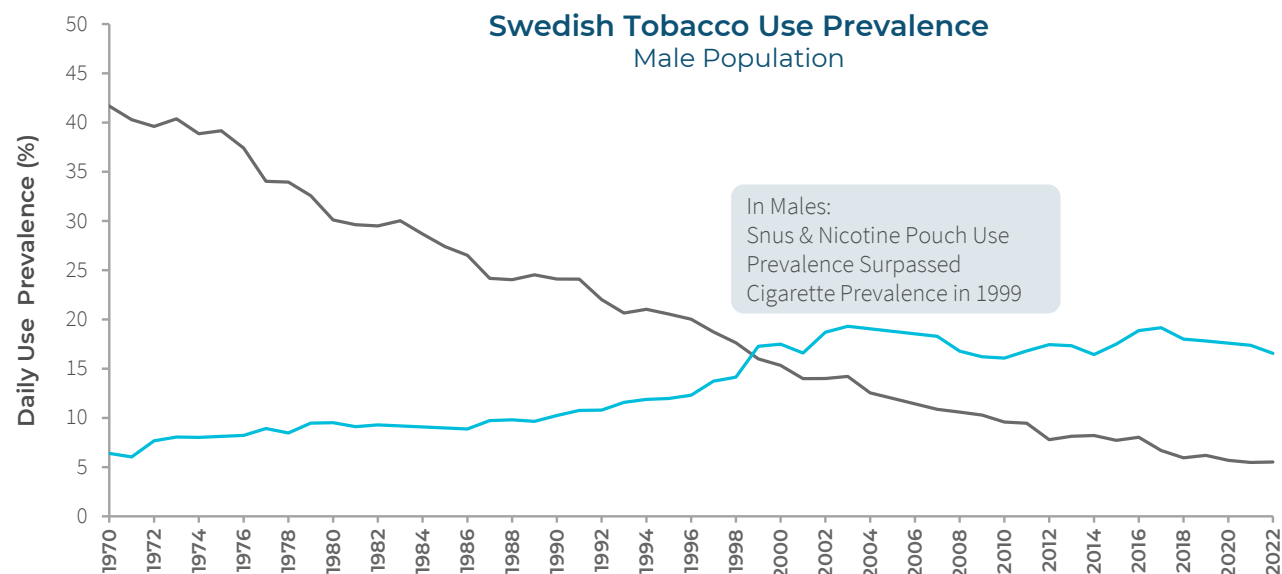
SNUS & NICOTINE POUCHES

Note: Temporal associations do not demonstrate cause and effect and are subject to inherent limitations. Specific factors associated with changing cigarette sales volumes over time have not been fully analyzed. 20 cigarettes per pack; 21 estimated average pouches in can for snus and nicotine pouches. Source: [1] Swedish Match estimates; Scientific Literature [2] Ramström 2016 (DOI: 10.3390/tjrrph13111110); [3] Clarke 2019 (DOI: 10.1186/s12954-019-0335-1); [4] Furberg 2005 (DOI: 10.1136/tc.2005.012476); [5] Ramström 2006 (DOI: 10.1136/tc.2005.014969); [6] Rodu 2002 (DOI: 10.1046/j.1365-2796.2002.01057.x)



Male Tobacco Use Prevalence in Sweden Over Time

Overall, Tobacco Use Continued to Decline — Snus & Nicotine Pouch Use Growing as Cigarettes Decline



CIGARETTES

SNUS & NICOTINE POUCHES

Note: Temporal associations do not demonstrate cause and effect and are subject to inherent limitations. Specific factors associated with changing cigarette sales volumes over time have not been fully analyzed. Source: Swedish Match Annual Market Reports carried out by Testologen AB (1970-1974), Svenska Testhuset AB (1975-1987), TEMO (1988-2004), and IPSOS (2007-2022)

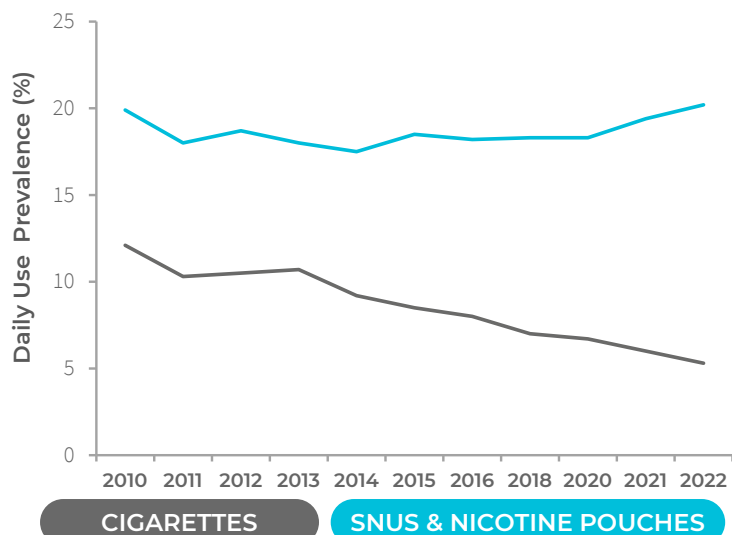


In Sweden Men Switched Away from Cigarettes Before Women

Change in Prevalence of Snus and Nicotine Pouches in Women Has Been Much More Recent

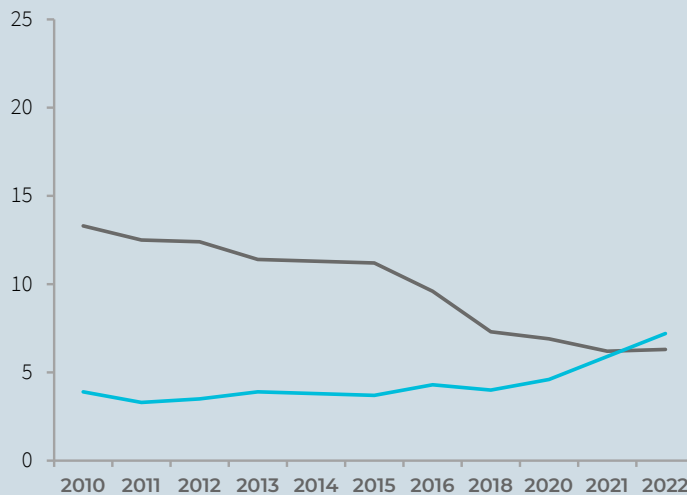
Prevalence in Males Ages 16-84 years

Snus & Nicotine Pouches Surpassed Cigarettes in 1999



Prevalence in Females Ages 16-84 years

Snus & Nicotine Pouches only Recently Surpassed Cigarettes



Note: Temporal associations do not demonstrate cause and effect and are subject to inherent limitations. Specific factors associated with changing cigarette sales volumes over time have not been fully analyzed. Source: Adapted from Nationella Folkhälsoenkäten. FoHM Användning av tobaks- och nikotinprodukter (själrapporterat) efter ålder, kön och år. Andel (procent). PxWeb (folkhalsomyndigheten.se)

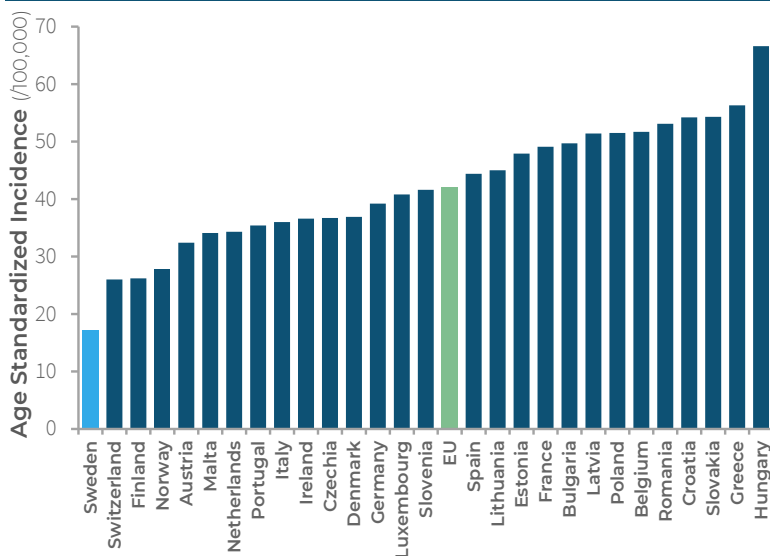


Lung Cancer in Sweden Compared to Other EU Countries

Male Lung Cancer Incidence is the Lowest In EU—Female Lung Cancer Approximates the EU Average

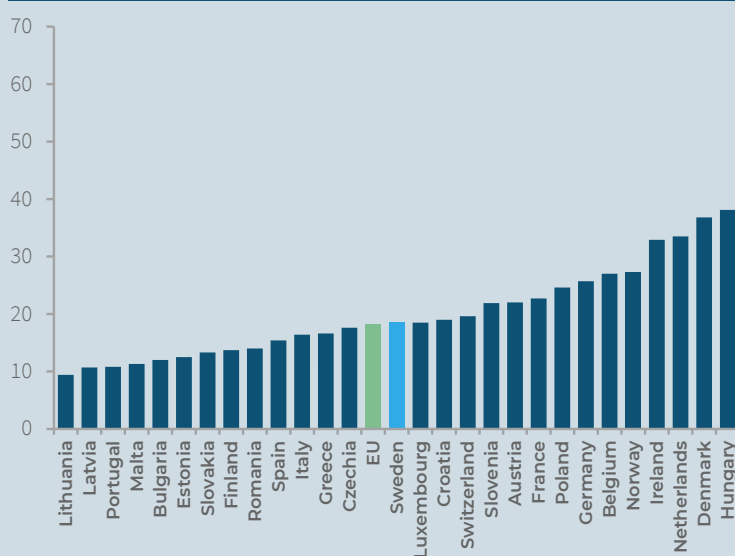
Lung Cancer Incidence (per 100,000)

Male Populations by Country



Lung Cancer Incidence (per 100,000)

Female Populations by Country



Source: [1] International Agency for the Research on Cancer: Global Cancer Observatory (<https://gco.iarc.fr/today/online-analysis-map?v=2020>)



Independent Studies on Youth Use of Heated Tobacco

Studies Indicate Low Youth Use — both Lifetime and Past 30-day Use

Orth B & Merkel C (2020) [1]

- 2019 Drug Affinity Study from the German Federal Centre for Health Education. Among youths (ages 12-17) and young adults (ages 18-25)
- Computer-aided telephone interviews; dual-frame: landline & mobile
- Sample size: 7,000 youths and young adults (April 15 to June 20, 2019)

Use prevalence	Heat-not-Burn		E-cigarettes	
	Ever use in lifetime	Ever use in past 30 days	Ever use in lifetime	Ever use in past 30 days
Youths (12-17 years old)	0.5%	0.1%	14.5%	4.1%

Gentzke et al. (2022) [2]

- Annual National Youth Tobacco Survey cross-sectional, nationally representative, school-based, self-administered survey of U.S. middle school (grades 6-8) and high school (grades 9-12) students
- Sample size: 20,413 youth from 279 schools (January 18 to May 21, 2021)

Use prevalence	Heat-not-Burn		E-cigarettes	
	Ever use in lifetime	Ever use in past 30 days	Ever use in lifetime	Ever use in past 30 days
Middle and High School Students	1.8%	0.7%	19.4%	7.6%

Delgrande et al. (2019) [3]

- National Health Behavior in School-aged Children » (HBSC) survey 2018
- On 715 randomly selected public-school classes
- Sample size of survey: 11,121 youth (ages 11-15)

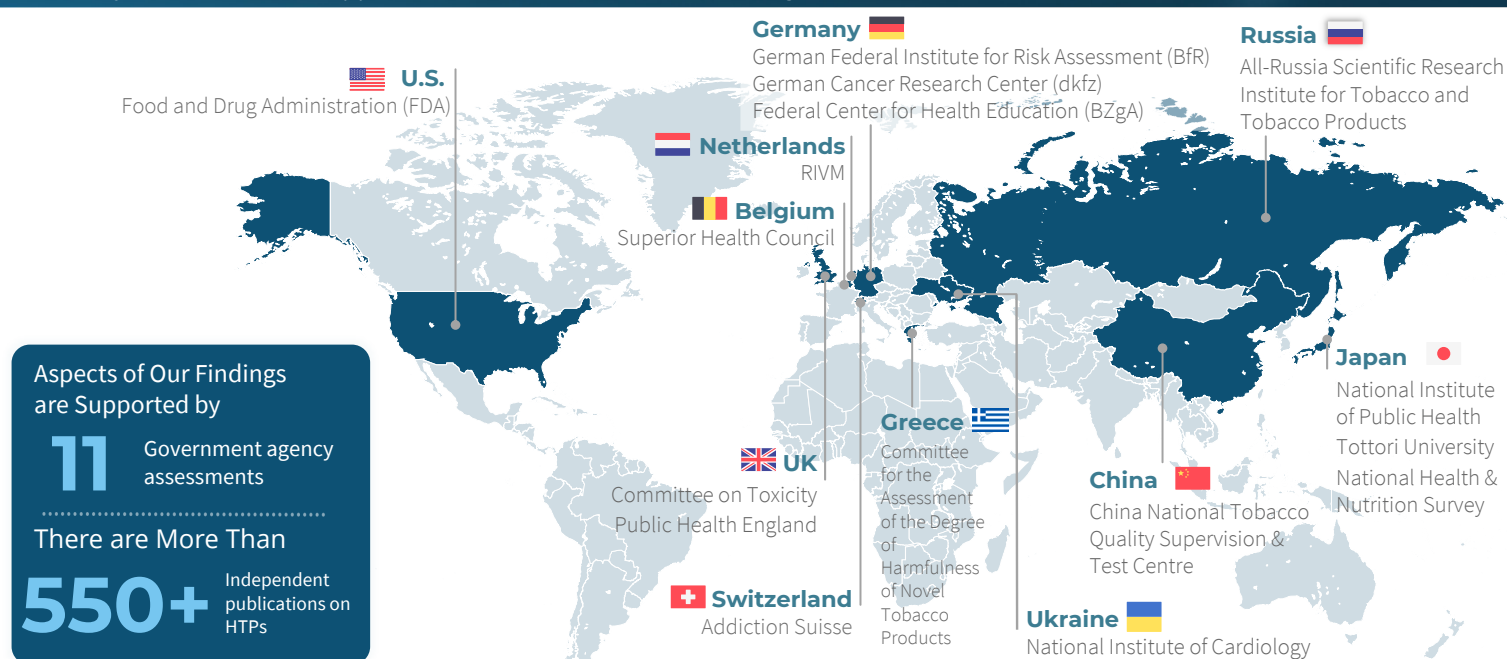
Use prevalence	Heat-not-Burn		E-cigarettes	
	Ever use in lifetime	Ever use in past 30 days	Ever use in lifetime	Ever use in past 30 days
15 years old	1.7%	1.1%	43.0%	16.8%

Sources: [1] Orth 2020 (DOI:10.17623/BZGA:225-DAS19-DE-1.0); [2] Gentzke 2022 MMWR Surveillance Summaries 2022 71(5); [3] Delgrande 2019 Rapport de recherche N°100, Addiction Suisse



Increasing Number of Third-Party Studies

Totality of the Evidence Supports Harm Reduction Potential vs. Cigarettes



Source: PMI Science.com Note: There were less than 20 independent papers published by the end of 2017, today there are more than 100 independent papers published per year that contain original data, analysis, methodology, case reports, and reviews on the heated tobacco products (does not include published commentaries and opinion pieces)



U.S. FDA—Overall Conclusion on IQOS

Orders Granted Pre-Market Tobacco Application (2019) and Modified Risk Tobacco Product Application (2020)



The applicant has demonstrated that the products sold or distributed with the proposed modified risk information meet the standard under section 911(g)(2) of the FD&C Act, including that a **measurable and substantial reduction in morbidity or mortality among individual tobacco users is reasonably likely in subsequent studies**, and issuance of an order is **expected to benefit the health of the population as a whole** taking into account both users of tobacco products and persons who do not currently use tobacco products.”^[1]

Source: <https://www.fda.gov/media/139796/download?attachment> (Accessed: May 2024)

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Questions & Answers

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