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Emerging E-Cigarette Science: Key Scientific Questions

E-Cig Europe Conference

Moira Gilchrist PhD
Philip Morris International R&D
October 8th 2015

PMI's Interests in the Category

- Purchased Nicocigs in 2014
- Commercialized an e-vapor product in Spain in 2015
- Entered into an agreement to develop the next generation of e-vapor products with Altria in 2015
- Commercialized *iQOS* (heat-not-burn technology) in Japan, Italy and Switzerland in 2014 and 2015

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The Objective is Harm Reduction

Offering adult smokers satisfying products that reduce risk

- Smoking is addictive and causes a number of serious diseases
- Worldwide it is estimated that more than one billion people will continue to smoke in the foreseeable future*

- Successful harm reduction requires that current adult smokers be offered a range of Reduced Risk Products so that consumer acceptance can be best fulfilled

*The Tobacco Atlas 3rd Edition. American Cancer Society, 2009
Figure adapted from Clive Bates presentation to E-Cigarette Summit (19 Nov 2013)
Note: Reduced-Risk Products ("RRPs") is the term we use to refer to products that have the potential to reduce individual risk and population harm in comparison to smoking combustible cigarettes

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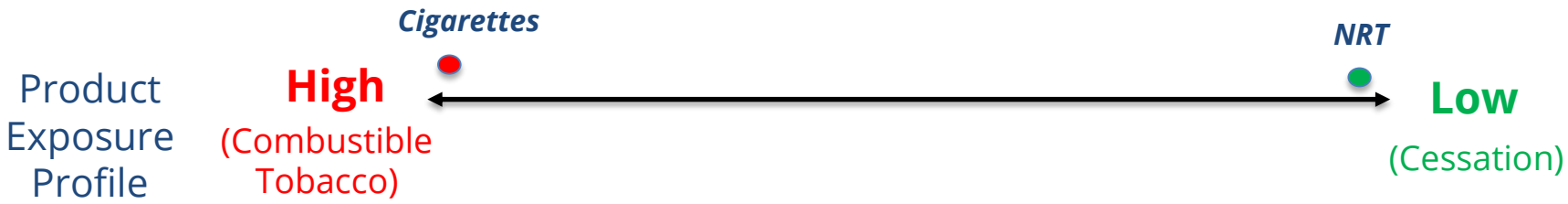
Reducing Harm: The Continuum of Risk



Developing less harmful products is more than wishful thinking; today's advancements in science and technology combined with consumer demand make it a concrete possibility

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Note: for illustrative purposes only

Reducing Harm: The Continuum of Risk

e-cigarettes, heat-not-burn tobacco products, and other innovations are examples of an emerging category of products that are potentially less harmful alternatives to cigarettes

Placement of individual products on the continuum must be supported by robust and product-specific scientific evidence

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Note: for illustrative purposes only

E-Cigarettes and Harm Reduction

- **There is growing consensus in the public health and scientific community that e-cigarettes are a reduced risk alternative to cigarettes**
  - The recent Public Health England (PHE) Report provided strong support and findings on risk and consumer use
  - Many public health advocates welcomed the report
  - The negative reaction of others was disappointing

- **Proactive steps required to address scientific questions and further support the category**

➔ **Harmful and potentially harmful constituents**

➔ **Long term use**

➔ **Standards**

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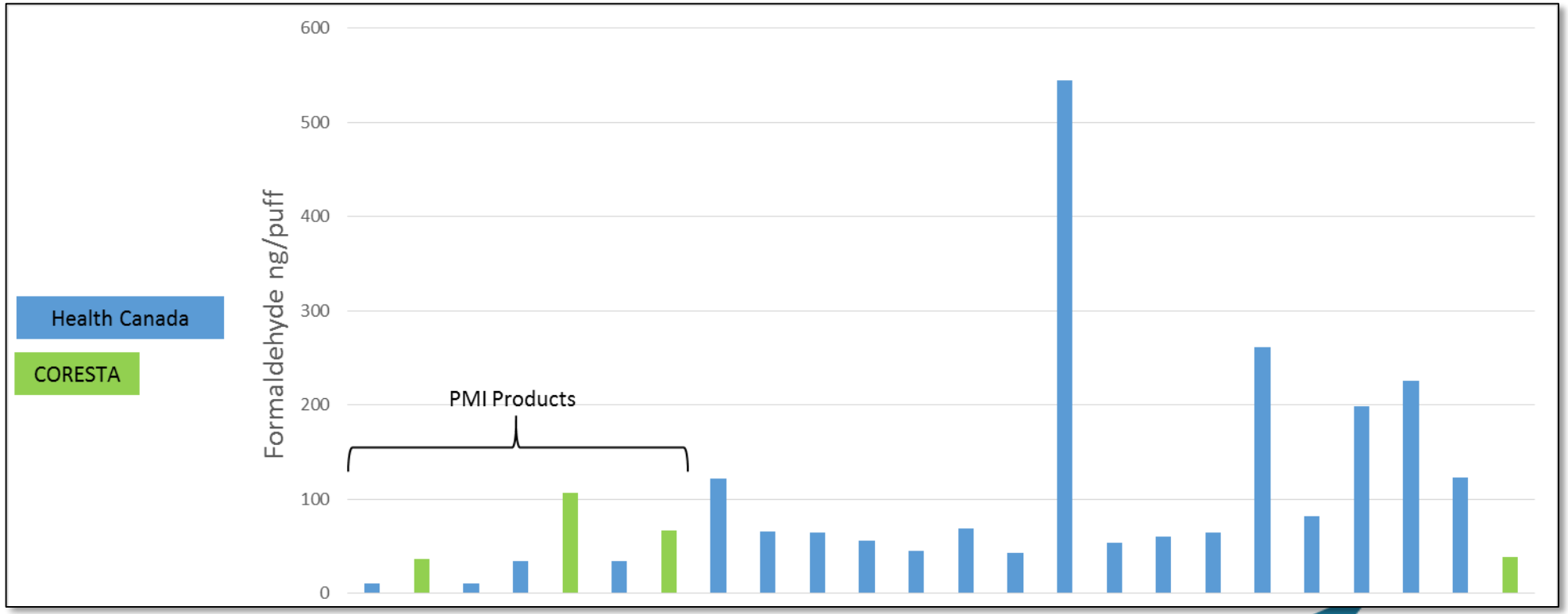
Harmful and Potentially Harmful Constituents

- **e-cigarette aerosols have been shown to contain significantly lower levels of Harmful and Potentially Harmful Constituents (HPHCs)**
  - Reduction compared to cigarette smoke is substantial according to the Public Health England report

- **Some reports of individual HPHCs have been highlighted**
  - This is aggravated under 'dry-puff' conditions (e.g., formaldehyde can be generated)
  - Under conditions of normal use the levels of HPHCs are far less than the amount found in cigarette smoke
  - Standards can address concerns about HPHCs

Formaldehyde – is this an issue?

We tested a total of 21 different marketed e-cigarette products under different puffing regimes (we excluded dry puff scenarios) and using validated analytical methods in accredited laboratories



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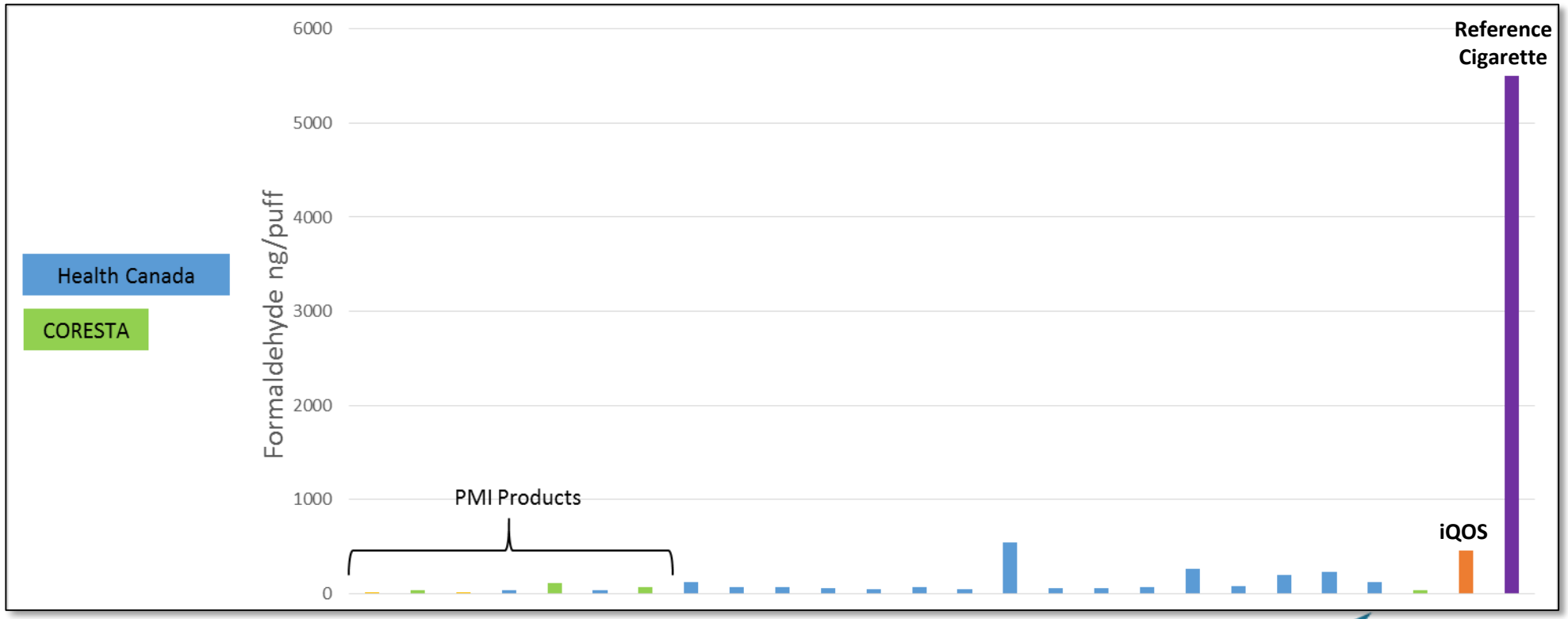
Formaldehyde – is this an issue?

All e-cigarettes tested had a <u>>90% reduction in formaldehyde/per puff</u> compared to the reference cigarette – the same is true for PMI's *iQOS* heat-not-burn tobacco product. These levels are not of toxicological concern.



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Effect of Long Term Use

- **Critics say that long term health effects of e-cigarettes are unknown**

- **Although there is not yet any epidemiological evidence, concerns can be addressed by:**
  - **Toxicological studies**
  - **Clinical studies**
  - **Consumer use data**

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Toxicology Studies

PMI R&D is conducting a sophisticated systems toxicology study on a range of aerosol formers looking at:

	Group	Propylene glycol (PG) (mg/l)	Glycerin (G) (mg/l)	Nicotine (mg/L)
1	Sham	0	0	0
2	Saline vehicle	0	0	0
3	Low PG+G	0.17	0.21	0
4	Medium PG+G	0.52	0.63	0
5	High PG+G	1.52	1.89	0
6	Low PG+G + Nicotine	0.17	0.21	23
7	Medium PG+G + Nicotine	0.52	0.63	23
8	High PG+G + Nicotine	1.52	1.89	23

- Pathology / Histopathology
- Clinical chemistry
- Hematology
- Inflammatory cells
- Transcriptomics
- Proteomics

Results will be presented at the American College of Toxicologists in November 2015 and published in a peer reviewed paper

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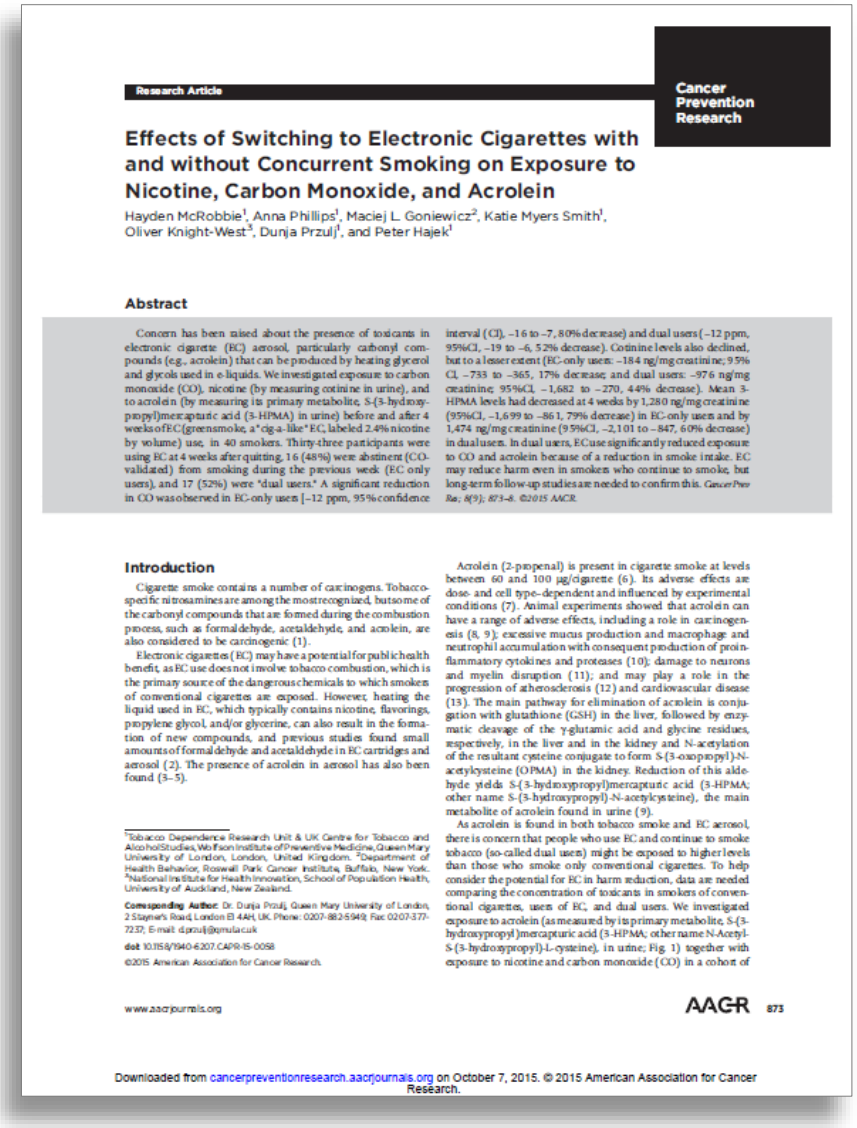
Clinical Studies



Research Article

Cancer Prevention Research

Effects of Switching to Electronic Cigarettes with and without Concurrent Smoking on Exposure to Nicotine, Carbon Monoxide, and Acrolein

Hayden McRobbie[1], Anna Phillips[1], Maciej L. Goniewicz[2], Katie Myers Smith[1], Oliver Knight-West[3], Dunja Przulj[1], and Peter Hajek[1]

Abstract

Concern has been raised about the presence of toxicants in electronic cigarette (EC) aerosol, particularly carbonyl compounds (e.g., acrolein) that can be produced by heating glycerol and glycols used in e-liquids. We investigated exposure to carbon monoxide (CO), nicotine (by measuring cotinine in urine), and to acrolein (by measuring its primary metabolite, S-(3-hydroxypropyl)mercapturic acid (3-HPMA) in urine) before and after 4 weeks of EC (greensmoke, a "cig-a-like" EC, labeled 2.4% nicotine by volume) use, in 40 smokers. Thirty-three participants were using EC at 4 weeks after quitting, 16 (48%) were abstinent (CO-validated) from smoking during the previous week (EC only users), and 17 (52%) were "dual users." A significant reduction in CO was observed in EC-only users [−12 ppm, 95% confidence interval (CI), −16 to −7, 80% decrease) and dual users (−12 ppm, 95%CI, −19 to −6, 52% decrease). Cotinine levels also declined, but to a lesser extent (EC-only users: −184 ng/mg creatinine; 95% CI, −733 to −365, 17% decrease; and dual users: −976 ng/mg creatinine; 95%CI, −1,682 to −270, 44% decrease). Mean 3-HPMA levels had decreased at 4 weeks by 1,280 ng/mg creatinine (95%CI, −1,699 to −861, 79% decrease) in EC-only users and by 1,474 ng/mg creatinine (95%CI, −2,101 to −847, 60% decrease) in dual users. In dual users, EC use significantly reduced exposure to CO and acrolein because of a reduction in smoke intake. EC may reduce harm even in smokers who continue to smoke, but long-term follow-up studies are needed to confirm this. *Cancer Prev Res; 8(9); 873–8. ©2015 AACR.*

Introduction

Cigarette smoke contains a number of carcinogens. Tobacco-specific nitrosamines are among the most recognized, but some of the carbonyl compounds that are formed during the combustion process, such as formaldehyde, acetaldehyde, and acrolein, are also considered to be carcinogenic (1).

Electronic cigarettes (EC) may have a potential for public health benefit, as EC use does not involve tobacco combustion, which is the primary source of the dangerous chemicals to which smokers of conventional cigarettes are exposed. However, heating the liquid used in EC, which typically contains nicotine, flavorings, propylene glycol, and/or glycerine, can also result in the formation of new compounds, and previous studies found small amounts of formaldehyde and acetaldehyde in EC cartridges and aerosol (2). The presence of acrolein in aerosol has also been found (3–5).

Acrolein (2-propenal) is present in cigarette smoke at levels between 60 and 100 μg/cigarette (6). Its adverse effects are dose- and cell type–dependent and influenced by experimental conditions (7). Animal experiments showed that acrolein can have a range of adverse effects, including a role in carcinogenesis (8, 9); excessive mucus production and macrophage and neutrophil accumulation with consequent production of proinflammatory cytokines and proteases (10); damage to neurons and myelin disruption (11); and may play a role in the progression of atherosclerosis (12) and cardiovascular disease (13). The main pathway for elimination of acrolein is conjugation with glutathione (GSH) in the liver, followed by enzymatic cleavage of the γ-glutamic acid and glycine residues, respectively, in the liver and in the kidney and N-acetylation of the resultant cysteine conjugate to form S-(3-oxopropyl)-N-acetylcysteine (OPMA) in the kidney. Reduction of this aldehyde yields S-(3-hydroxypropyl)mercapturic acid (3-HPMA; other name S-(3-hydroxypropyl)-N-acetylcysteine), the main metabolite of acrolein found in urine (9).

As acrolein is found in both tobacco smoke and EC aerosol, there is concern that people who use EC and continue to smoke tobacco (so-called dual users) might be exposed to higher levels than those who smoke only conventional cigarettes. To help consider the potential for EC in harm reduction, data are needed comparing the concentration of toxicants in smokers of conventional cigarettes, users of EC, and dual users. We investigated exposure to acrolein (as measured by its primary metabolite, S-(3-hydroxypropyl)mercapturic acid (3-HPMA; other name N-Acetyl-S-(3-hydroxypropyl)-L-cysteine), in urine; Fig. 1) together with exposure to nicotine and carbon monoxide (CO) in a cohort of

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doi: 10.1158/1940-6207.CAPR-15-0058

- Most studies have focused on nicotine pharmacokinetics and smoking cessation
- McRobbie *et al* studied the effect of switching on exposure to Nicotine, Carbon monoxide and Acrolein – published in June 2015
- **Significant decrease in tobacco smoke toxicant exposure, including in dual users**

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Consumer Use Data

- Cochrane report concluded that there is no evidence of health risks from short-term e-cigarette use

- PHE report concluded:
  - No impact on long-term decline of smoking rates
  - No evidence that e-cigarettes are acting as a route into smoking for children or non-smokers
  - Smokers "who cannot or do not want to stop smoking" should be encouraged to switch
  - No identified health risks to bystanders and any health risks of passive exposure likely extremely low

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Credible Standards

- Standard(s) for device, liquid, combinations and testing can help address many known challenges
- Process is underway:
  - CORESTA Recommended Method Nº 81 – Routine analytical machine for e-cigarette aerosol generation and collection published in June 2015
  - Draft e-cigarette standards published in France and UK earlier in 2015
  - New Technical Committee - CEN/TC 437 'Electronic cigarettes and e-liquids‘ - created under CEN (European Committee for Standardization)
    - Terminology and definitions
    - Requirements and test methods for e-cigarette devices
    - Requirements and test methods for e-liquids
    - Requirements and test methods for emissions

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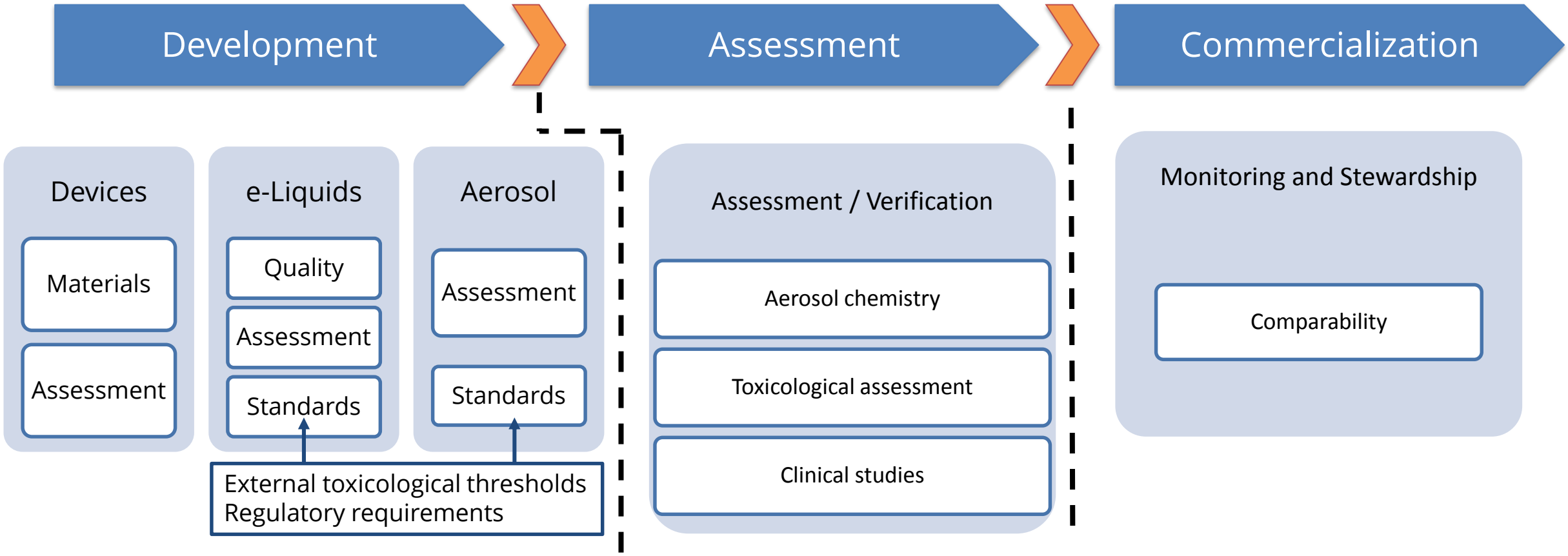
Credible Standards



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Indoor Air Quality

- **Data on the impact on indoor air quality of use of e-cigarettes indoors can be helpful in supporting the category**
- **PMI has conducted a pilot study using validated methods in an accredited facility to study the effect of using e-cigarettes on indoor air quality**
- **A full study is currently being completed and will be published**

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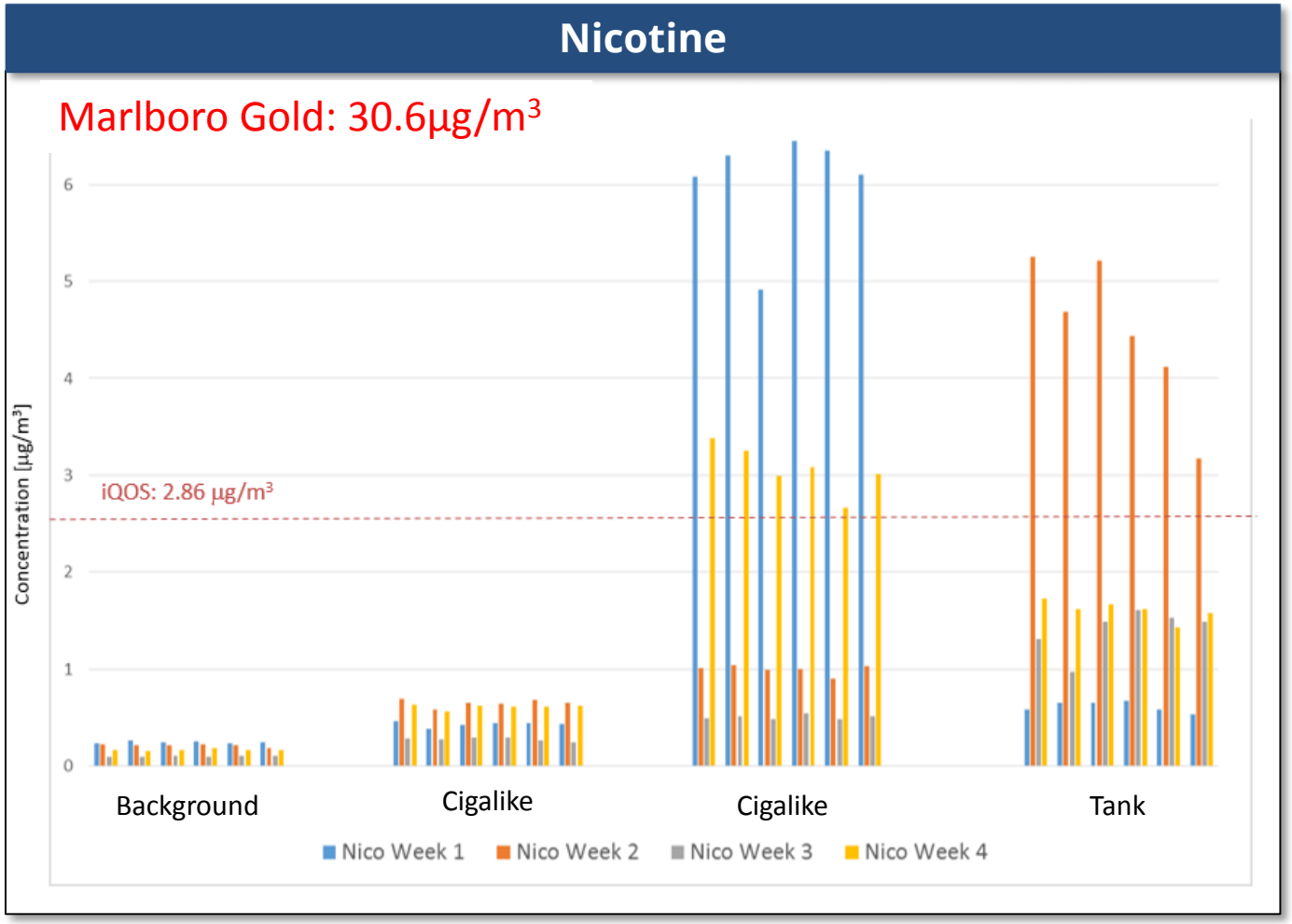
What is the Effect on Indoor Air Quality?



Pilot study

- Nicotine is detectable up to a <u>maximum</u> of around 6 µg/m^3
- This level is almost 100-fold lower that the European Agency for Safety and Health at Work[1] exposure limit of 500 µg/m^3 (over 8 hours) and 5 times less than a combustible cigarette
- Quantity of nicotine measured in air was much more influenced by vaping behavior than by base composition of e-liquid

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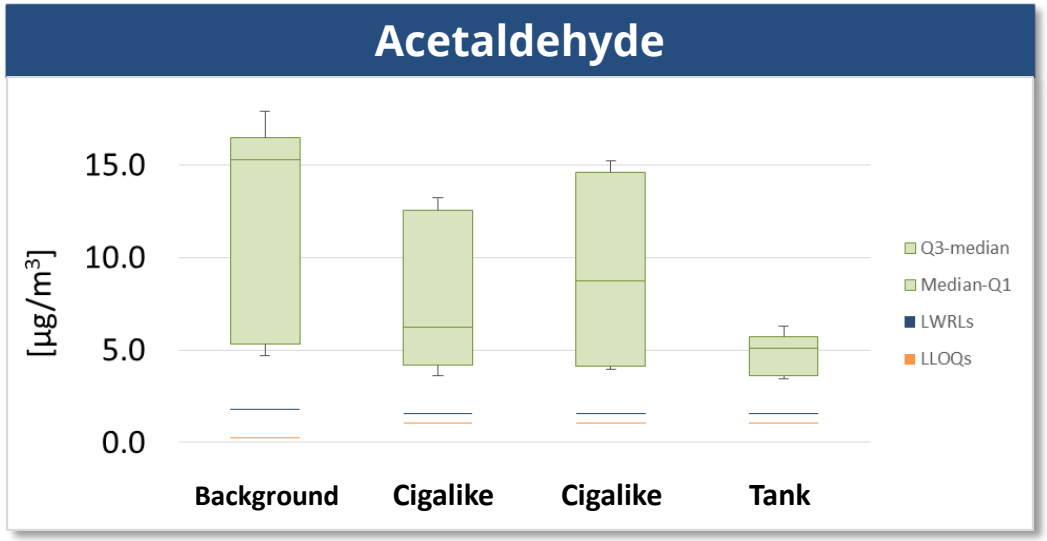
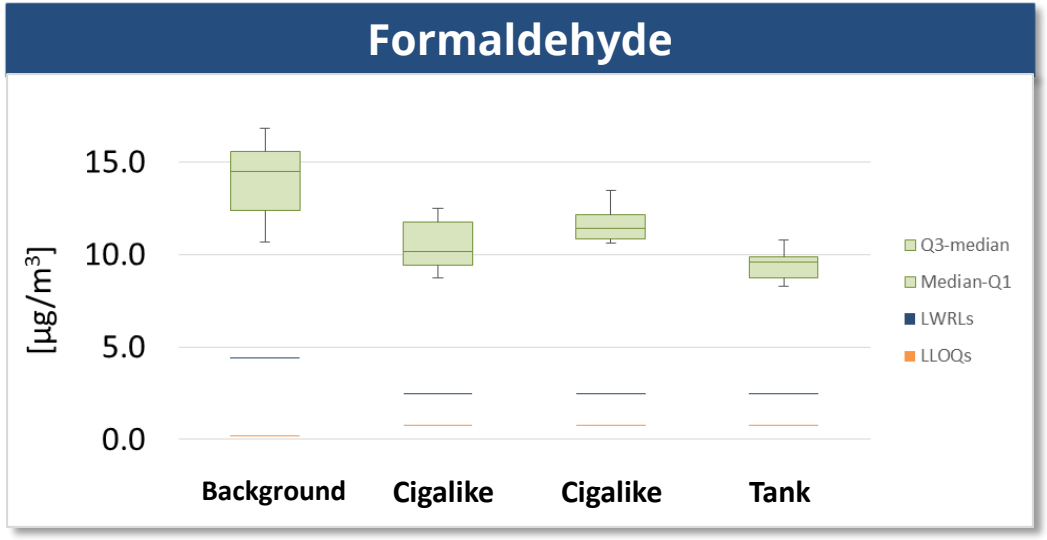
[1] European Agency for Safety and Health at Work: Directive 2006/15/EC

What is the Effect on Indoor Air Quality?





The same pilot study showed:

- Acetaldehyde and Formaldehyde are detectable in the background air (i.e. without product use)
- Levels detected when products were used were similar to background levels
- Vaping behavior did not influence the detected levels of either compound

A further full study is being conducted currently and results will be published

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Addressing Scientific Concerns

- **PMI has a comprehensive set of studies in place to address emerging scientific concerns around e-cigarettes**
- **We will share our data by submitting for peer review and publishing in scientific journals**
- **We also welcome independent studies by competent scientists to address these concerns**

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Voice of the Consumer

What do UK Consumers Tell Us?

Sampling universe: Adults aged 18+ nationwide who are current smokers of cigarettes or current users of e-cigarettes

Sample size: N=1,083 nationwide

- The survey also included an oversample to bring the total number of Scottish interviews to n=200

Data collection method: Online

Margin of error: ± 3.1%

Fielding dates: 24 - 28 July 2015

Local research supplier: Populus

This research is supported by Philip Morris Limited

- **Awareness**
- **Benefits**
- **Regulation**
- **Encouraging adult smokers to switch**

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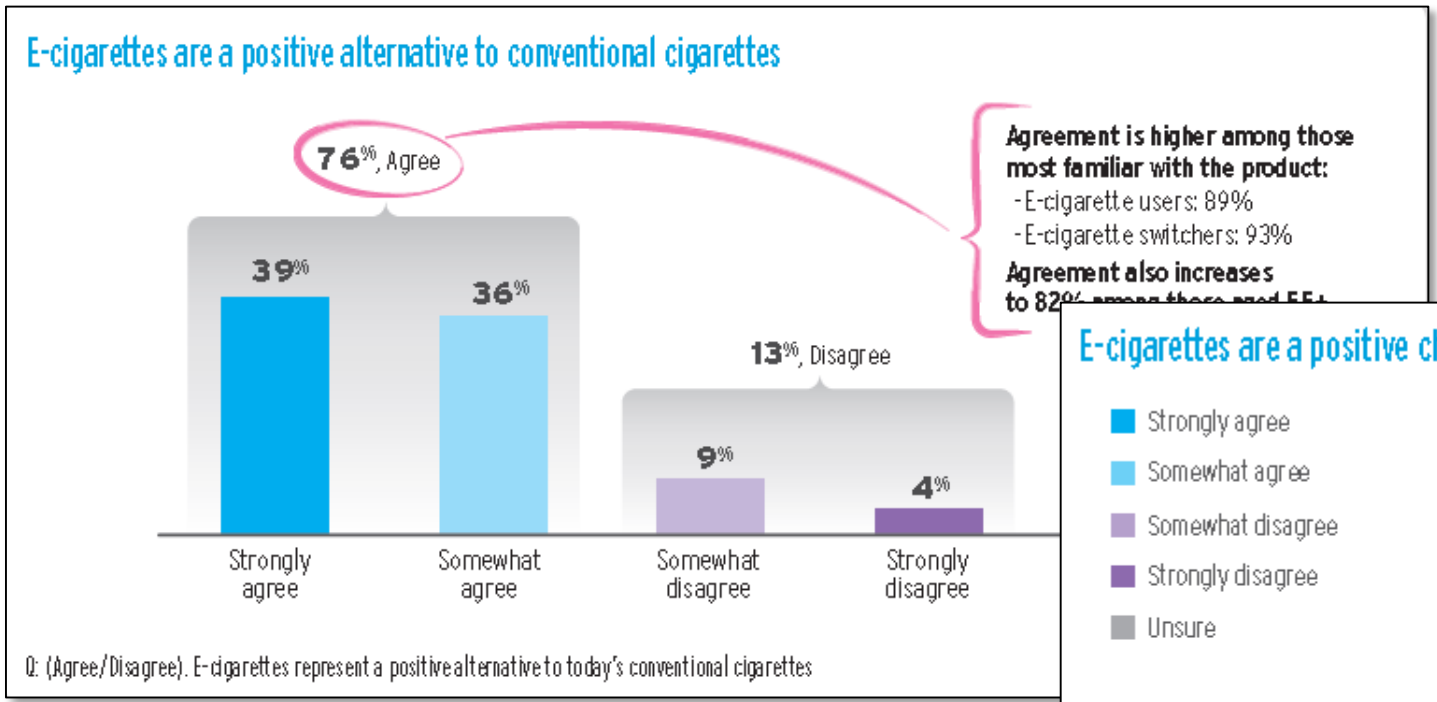
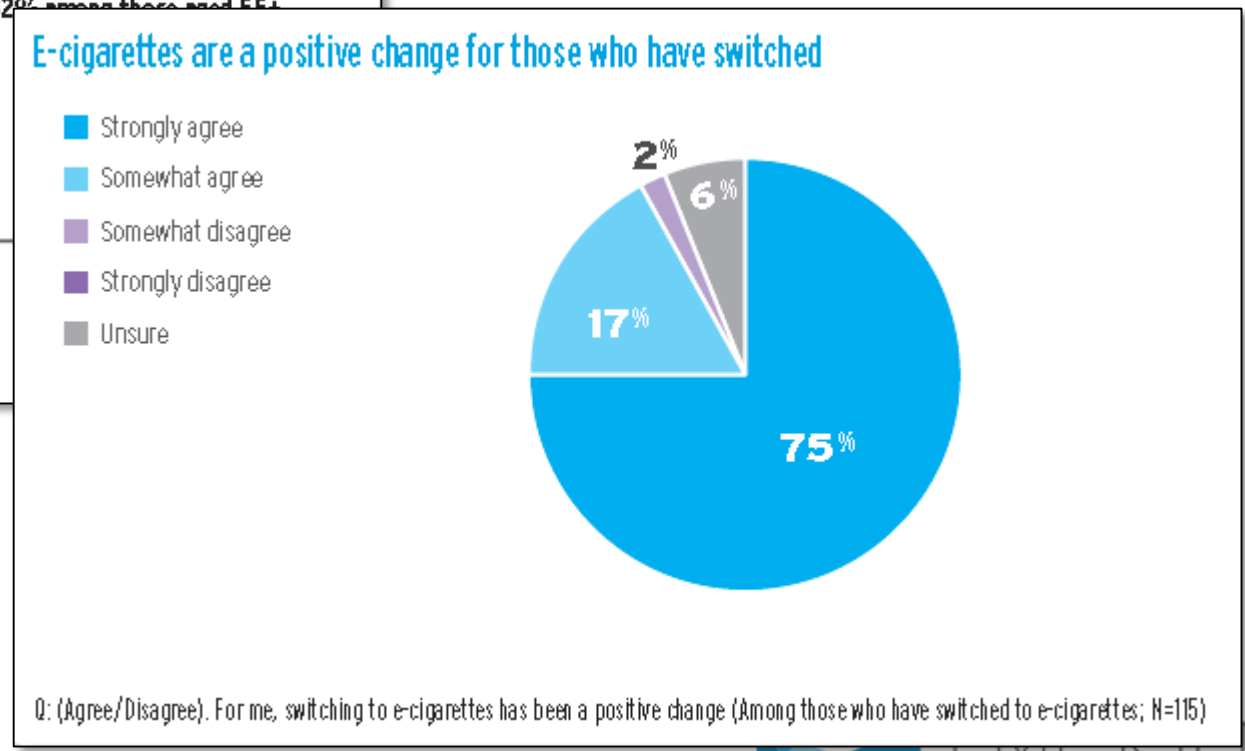
What do UK Consumers Tell Us?
Benefits of Switching are Recognized





What do UK Consumers Tell Us?
Consumers Demand Reasonable Regulation

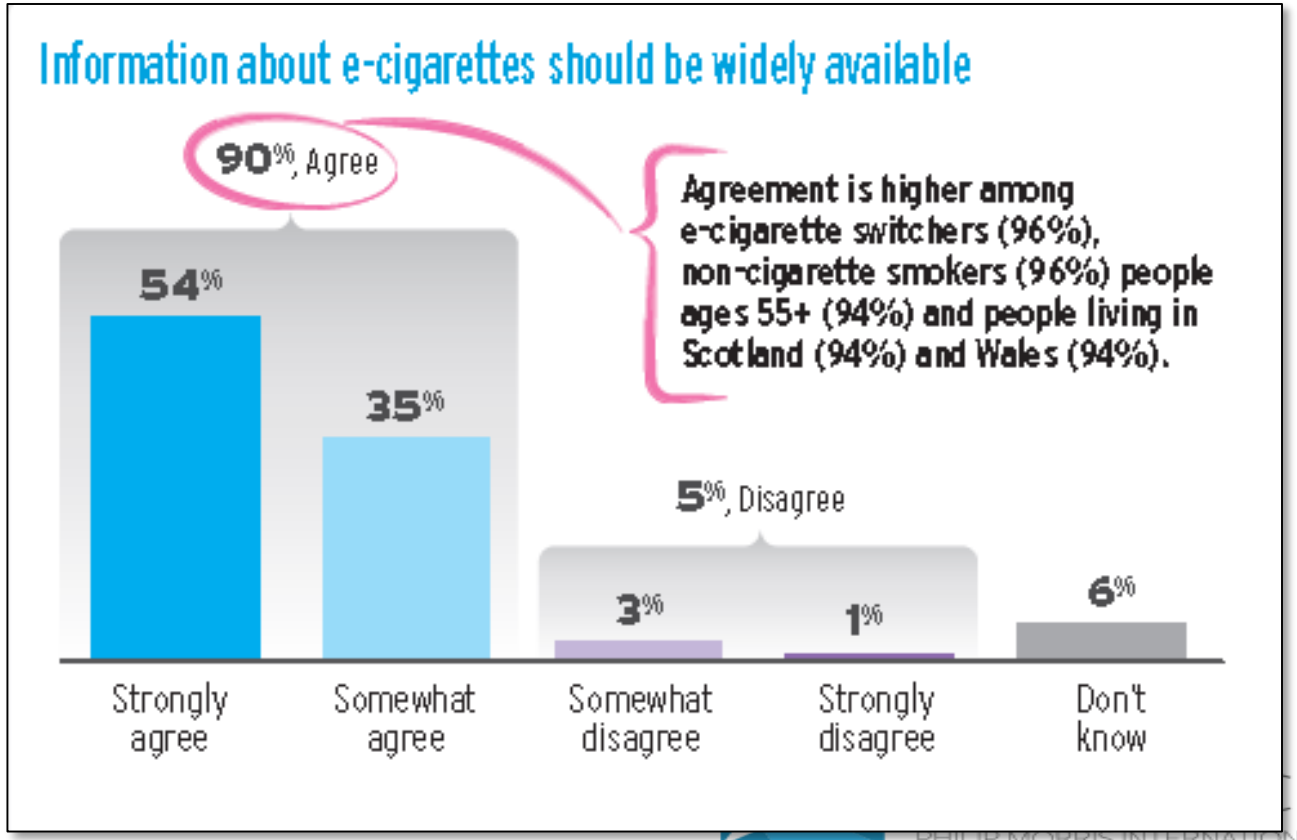
Government should ensure e-cigarettes are only used by those over 18

82%

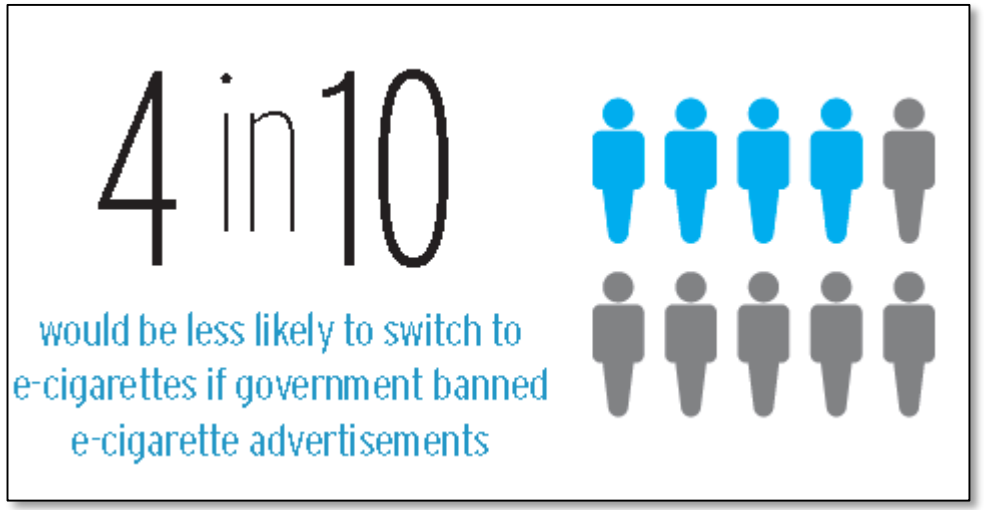
agree the Government should enact appropriate regulations to ensure e-cigarettes are not used by minors under 18

Q: (Agree/Disagree)

Information about e-cigarettes and their potential to reduce the risk of smoking as compared to conventional cigarettes should be widely available provided reliable scientific evidence is available

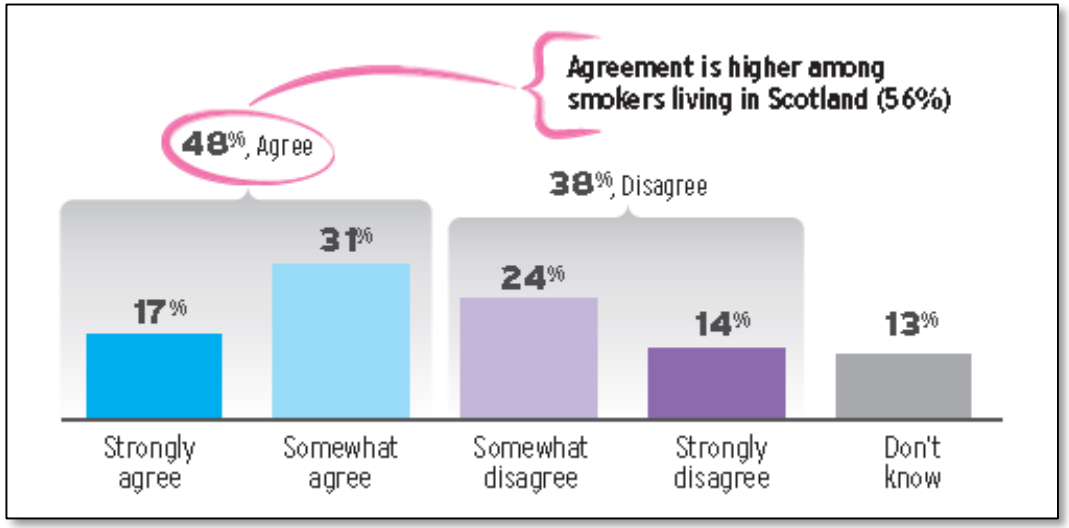


What do UK Consumers Tell Us?
Communication Can Encourage Adult Smokers to Switch



Q: (Agree/Disagree)

As an adult smoker, it is important to me to see advertisements for e-cigarettes [...] this is the best way for me to gather information [...]



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E-Cigarettes can Contribute to Tobacco Harm Reduction

A portfolio of reduced risk alternatives to cigarettes that are appealing to adult smokers is needed in order to reduce population harm

Adult smokers should be informed on the different risk profiles of products, provided that these differences **are substantiated by robust, product-specific scientific evidence**

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Reduced-Risk Products ("RRPs") is the term the company uses to refer to products with the potential to reduce individual risk and population harm in comparison to smoking combustible cigarettes. PMI's RRPs are in various stages of development and commercialization, and we are conducting extensive and rigorous scientific studies to determine whether we can support claims for such products of reduced exposure to harmful and potentially harmful constituents in smoke, and ultimately claims of reduced disease risk, when compared to smoking combustible cigarettes.

Before making any such claims, we will rigorously evaluate the full set of data from the relevant scientific studies to determine whether they substantiate reduced exposure or risk. Any such claims may also be subject to government review and approval, as is the case in the US today.

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Source: Philip Morris International R&D