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SCIENCE

Scientific Substantiation of Imperial Brands Nicotine Pouches: A Promising Tobacco Harm Reduction Product for Adult Smokers

May 2021

Imperial Brands Nicotine Pouches Have Significant Tobacco Harm Reduction Potential For Adult Smokers

The strength of Imperial Brands scientific assessment programme resides in the totality of the nine lines of scientific evidence provided, as follows:

Line of Evidence I: Imperial Brands nicotine pouches contain substantially lower levels of select toxicants of notable public health interest compared to combustible cigarette smoke.

Line of Evidence II: The reduced levels of toxicants in Imperial Brands nicotine pouches translates directly into substantially reduced *in vitro* biological responses (mutagenicity, genotoxicity, and cytotoxicity) compared to combustible cigarette smoke condensate: on average >99% reduction in cytotoxicity with no mutagenic or genotoxic responses under the conditions of test.

Line of Evidence III: In laboratory models, Imperial Brands nicotine pouches do not elicit skin sensitisation properties.

Line of Evidence IV: Imperial Brands nicotine pouches deliver nicotine to the blood of adult smokers via the oral mucosa (not swallowed), which on average have a lower and slower nicotine delivery compared to combustible cigarettes. As such, Imperial Brands nicotine pouches likely have a lower abuse liability compared to combustible cigarettes, but this should not be interpreted as evidence that these products are not addictive.

Line of Evidence V: Imperial Brands nicotine pouches offer a satisfying alternative to combustible cigarettes and reduce adult smokers' desire to smoke.

Line of Evidence VI: Imperial Brands nicotine pouches have a favourable short-term safety and tolerability profile during the observation period with no serious adverse events related to the product observed.

Line of Evidence VII: Adult smokers and non-smokers properly understand that Imperial Brands nicotine pouches contain nicotine and are not risk-free but are likely to be less harmful than combustible cigarettes.

Line of Evidence VIII: Imperial Brands nicotine pouches appeal overwhelmingly to adult smokers with very low interest amongst never smokers and former smokers. There is little evidence that Imperial Brands nicotine pouches would serve as a gateway to regular nicotine use amongst nicotine naïve populations.

Line of Evidence IX: The main reason for adult smokers' interest and intent to purchase Imperial Brands nicotine pouches is for tobacco harm reduction and to reduce the health risks associated with combustible cigarette smoking.

In summary, the totality of the scientific evidence generated by Imperial Brands above, coupled with the company's commitment to robust product quality, stewardship, and manufacturing standards, as well as implementation of effective youth access prevention programmes, convincingly demonstrates that Imperial Brands #2 and #3 nicotine pouches are an effective tobacco harm reduction tool beneficial to population-level health.

Introduction

Tobacco harm reduction represents one of the most promising global public health policies available with the potential to save many lives if fully embraced. The concept of tobacco harm reduction is simple and compelling: to encourage adult smokers who would otherwise continue to smoke to transition to less harmful products that deliver nicotine, but with fewer and substantially lower levels of toxicants associated with burning tobacco¹. Adult smokers are more likely to transition to less harmful products if the product provides a satisfying experience. This is why continued product innovations are crucial to making harm reduction a reality and thereby benefiting public health. A recent tobacco harm reduction innovation is nicotine pouches. High quality nicotine pouches deliver nicotine via the oral mucosa; since they are not combusted and contain no tobacco leaf, they have the potential to be significantly less harmful than continued combustible cigarette smoking.

Nicotine pouches are available in a growing number of countries, adding to the repertoire of reduced harm alternatives for adult smokers. Typically, these small pouches contain high purity pharmaceutical grade nicotine sprayed onto dry powder or a plant fibre-based substrate, and other high-quality ingredients including flavourings, humectants to retain moisture, and additives to ensure product stability. Pouches are placed under users' lips for up to an hour, steadily releasing nicotine which is absorbed into the bloodstream through the oral mucosa². This way of consuming nicotine is in complete contrast with smoking tobacco, and even the inhalation of heated tobacco and e-vapour aerosols, where nicotine is predominately absorbed through the airways and lungs³.

As nicotine pouches neither contain any tobacco leaf nor require combustion, it is to be expected that levels of toxicants of notable public health interest such as tobacco-specific nitrosamines (TSNAs), polycyclic aromatic hydrocarbons (PAHs) and carbon monoxide will be substantially lower compared to tobacco smoke and other non-combustible tobacco and tobacco-free products, if at all present at detectable levels. Moreover, as the use of nicotine pouches does not involve any inhalation into the lung, lung-related toxicity and disease risks are not to be expected. By extension therefore, nicotine pouches also do not pose any risk to bystanders.

Imperial Brands nicotine pouches are currently marketed as zoneX and SKRUF. These nicotine pouches are produced according to robust quality, stewardship and manufacturing standards.

Imperial Brands has conducted a comprehensive scientific assessment⁴ of its innovative wheat fibre-based #2 and #3 nicotine pouch products in comparison to combustible cigarettes. A summary of the broad evidence-base obtained from these studies is presented here and convincingly demonstrates that these scientifically substantiated nicotine pouch products have significant tobacco harm reduction potential for adult smokers who may choose to use these products to reduce or replace combustible cigarette smoking.

¹ O'Leary, R., & Polosa, R. (2020). Tobacco harm reduction in the 21st century. *Drugs and Alcohol Today*, ahead-of-print(ahead-of-print). doi: 10.1108/DAT-02-2020-0007

² Lunell, E., Fagerström, K., Hughes, J., & Pendrill, R. (2020). Pharmacokinetic Comparison of a Novel Non-tobacco-Based Nicotine Pouch (ZYN) With Conventional, Tobacco-Based Swedish Snus and American Moist Snuff. *Nicotine & Tobacco Research*. doi: 10.1093/ntr/ntaa068

³ O'Connell G, Pritchard JD, Prue C, Thompson J, Verron T, Graff D, Walele T. A randomised, open-label, cross-over clinical study to evaluate the pharmacokinetic profiles of cigarettes and e-cigarettes with nicotine salt formulations in US adult smokers. *Intern Emerg Med*. 2019 Sep;14(6):853-861. doi: 10.1007/s11739-019-02025-3. Epub 2019 Feb 2. PMID: 30712148; PMCID: PMC6722145.

⁴ For more details on Imperial Brands Scientific Assessment Framework: <https://imperialbrandsscience.com/our-research/>

Summary of Key Scientific Results on Imperial Brands #2 and #3 Nicotine Pouches

1. Imperial Brands nicotine pouches contain substantially lower levels of select toxicants of notable public health interest compared to combustible cigarette smoke.

- Given Imperial Brands nicotine pouches contain high purity pharmaceutical grade nicotine derived from tobacco leaf and the fact that the maximum public health benefit that nicotine pouches offer is likely to be derived from understanding these products in the context of smoking tobacco, it is important to compare levels of toxicants of public health interest to levels in combustible cigarette smoke.
- Levels of 16 toxicants of notable public health interest including NNN, NNK, formaldehyde, acetaldehyde, and benzo[a]pyrene were analysed in Imperial Brands nicotine pouches and compared to levels in combustible cigarette smoke.
- Of the 16 toxicants assessed, only four were quantifiable in Imperial Brands nicotine pouches: acetaldehyde, formaldehyde, nickel and chromium. Compared to combustible cigarette smoke, levels of acetaldehyde and formaldehyde were reduced by >94% in Imperial Brands nicotine pouches. By way of context, levels of nickel and chromium were substantially below permissible levels set for medicinal products.
- No microbial activity was detected in Imperial Brands nicotine pouches and levels of mycotoxins (i.e., naturally occurring toxins produced by certain moulds [fungi]), including Ochratoxin A and Aflatoxins B1, B2, G1 and G2, were not quantifiable.

Reduced Levels of Select Toxicants of Notable Public Health Interest in Imperial Brands Nicotine Pouches Compared to Combustible Cigarette Smoke...

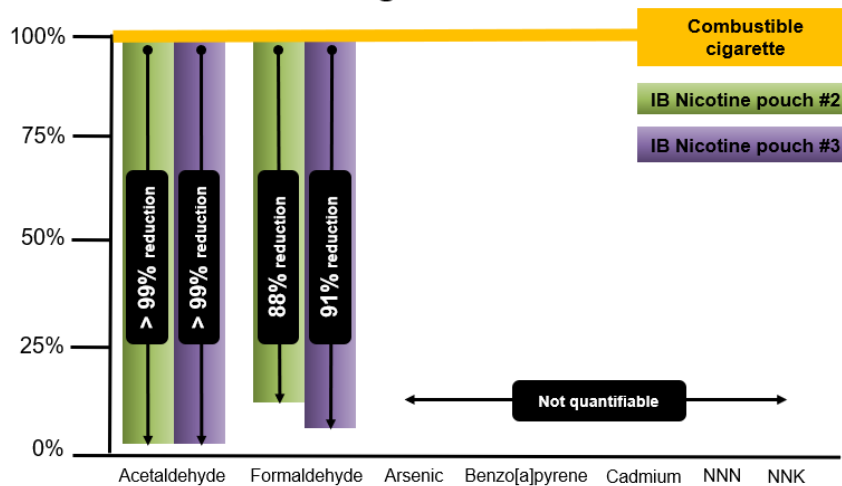


Figure 1. Representative average reductions in levels of select toxicants in Imperial Brands (IB) nicotine pouches compared to levels measured in combustible cigarette smoke.

Line of Evidence I: Imperial Brands nicotine pouches contain substantially lower levels of select toxicants of notable public health interest compared to combustible

2. The reduced levels of toxicants in Imperial Brands nicotine pouches translates directly into substantially reduced *in vitro* biological activity compared to combustible cigarettes.

- In standardized laboratory models, cells were exposed to nicotine pouch extracts or combustible cigarette smoke condensate and the responses compared.
- **Cytotoxicity** is considered a potential step in several chronic disease processes associated with smoking, including cancer, cardiovascular disease, and emphysema. In the assay for cytotoxicity assessment with human-derived cells, Imperial Brands nicotine pouches demonstrated a >99% reduction in cytotoxic response compared to combustible cigarette smoke condensate.
- **Mutagenicity** is a measure of the ability of a substance to cause changes in the genetic material of a cell. In the assay for assessing mutagenic potential, Imperial Brands nicotine pouches did not elicit a mutagenic response under the conditions of test. By contrast, combustible cigarette smoke condensate was mutagenic.
- **Genotoxicity** is damage to the structure or function of genetic material. Genotoxicity has been mechanistically linked with the development of cancer. In the assay for genotoxicity assessments, Imperial Brands nicotine pouches did not elicit a genotoxic response under the conditions of test. By contrast, combustible cigarette smoke condensate was significantly genotoxic.

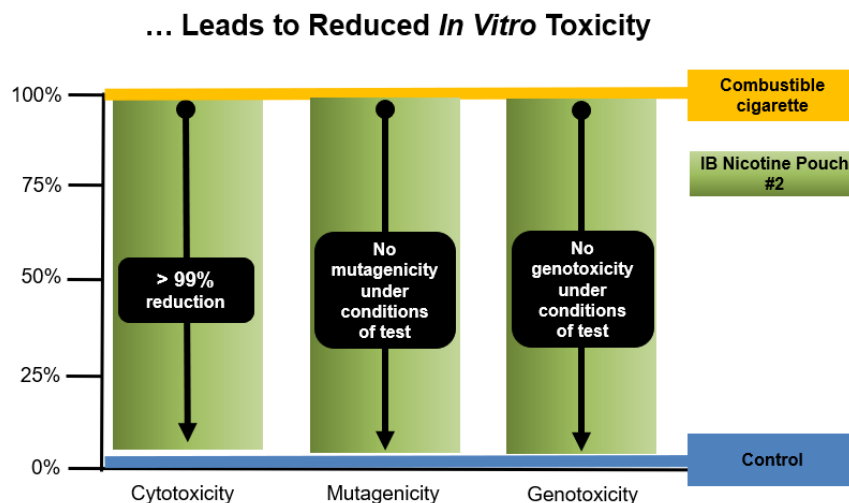


Figure 2. Representative average reductions in *in vitro* toxicity for Imperial Brands (IB) nicotine pouches compared to levels measured for combustible cigarette smoke condensate.

Line of Evidence II: The reduced levels of toxicants in Imperial Brands nicotine pouches translates directly into substantially reduced *in vitro* biological responses (mutagenicity, genotoxicity, and cytotoxicity) compared to combustible cigarette smoke condensate: on average >99% reduction in cytotoxicity with no mutagenic or genotoxic responses under the conditions of test.

3. In laboratory models, Imperial Brands nicotine pouches do not elicit skin sensitisation properties

- Imperial Brands nicotine pouches undergo rigorous risk assessments by in-house professional toxicologists and other specialists to determine the suitability of ingredients and materials used in the products.
- A key aspect of a robust product risk assessment is to ensure the ingredients used will not cause rashes or an allergic response in consumers at the levels used in the product.
- In a laboratory skin sensitisation assay that uses human cell lines and assesses the gene expression profile of 200 markers to predict whether a test item is classified as a skin sensitiser (capable of causing an allergic response) or a non-sensitiser, Imperial Brands nicotine pouches were not predicted to cause an allergic reaction or skin rashes under the conditions of test.

Line of Evidence III: In laboratory models, Imperial Brands nicotine pouches do not elicit skin sensitisation properties.

4. Imperial Brands nicotine pouches deliver nicotine efficiently to the blood of adult smokers via the oral mucosa, which on average have a lower and slower nicotine delivery compared to combustible cigarettes.

- To understand how adult smokers' bodies absorb the nicotine that is delivered by Imperial Brands nicotine pouches, how long it is present in the body following use of the product, and how this compares to the blood nicotine delivery of a combustible cigarette, a single use pharmacokinetic study with 24 adult users of oral nicotine products and combustible cigarettes was conducted in a controlled clinical setting.
- Imperial Brands nicotine pouches provide peak (C_{\max}) and overall nicotine exposures (AUC_{0-90}) which are lower compared to combustible cigarettes. The speed of nicotine absorption from Imperial Brands nicotine pouches is also much slower than for cigarette smoke (T_{\max} minutes vs. seconds).
- As the blood nicotine delivery from Imperial Brands nicotine pouches on average is lower and slower compared to combustible cigarettes, this indicates these products likely have a lower abuse liability compared to combustible cigarettes, with a low potential for increased addictiveness relative to combustible cigarettes among current adult smokers.
- The blood nicotine delivery profile of Imperial Brands nicotine pouches also shows unequivocally that the nicotine is absorbed via the oral mucosa (buccal absorption) with limited (if any) gastrointestinal absorption of nicotine. The obtained clear pharmacokinetic profiles and parameters for Imperial Brands nicotine pouches show there are no secondary nicotine peaks, which may be detected after 2-4 hours⁵, which would be indicative of nicotine absorption via swallowing.

⁵ Dautzenberg B, Nides M, Kienzler JL, Callens A. Pharmacokinetics, safety and efficacy from randomized controlled trials of 1 and 2 mg nicotine bitartrate lozenges (Nicotinell). BMC Clin Pharmacol. 2007 Oct 8;7:11. doi: 10.1186/1472-6904-7-11. PMID: 17922899; PMCID: PMC2194660.

Mean Blood Nicotine Concentration vs. Time for Imperial Brands Nicotine Pouches vs. Combustible Cigarette

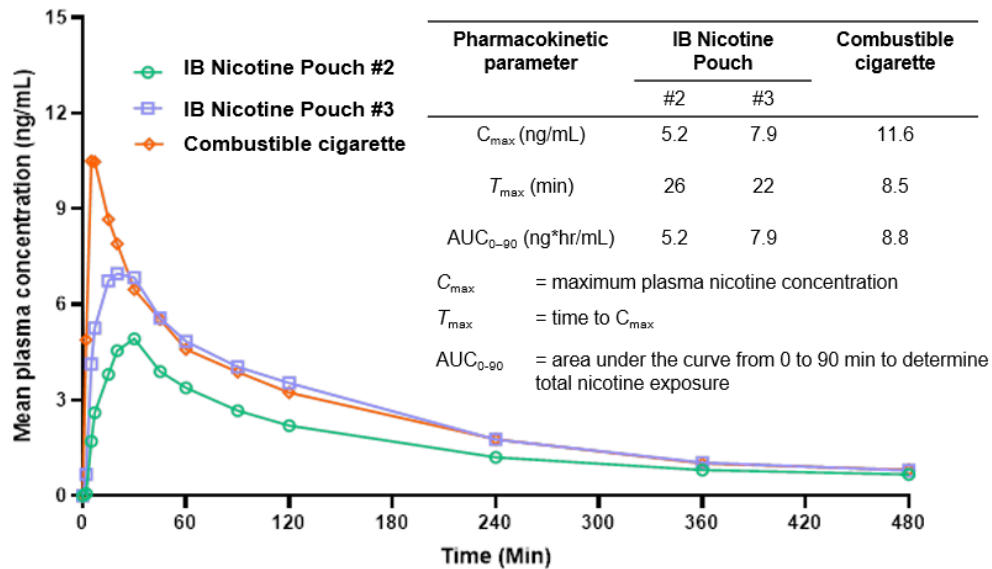


Figure 3. Average blood nicotine delivery pharmacokinetic profiles for Imperial Brands (IB) nicotine pouches vs. combustible cigarette (linear scale) over 480 mins.

Line of Evidence IV: Imperial Brands nicotine pouches deliver nicotine to the blood of adult smokers via the oral mucosa (not swallowed), which on average have a lower and slower nicotine delivery compared to combustible cigarettes. As such, Imperial Brands nicotine pouches likely have a lower abuse liability compared to combustible cigarettes, but this should not be interpreted as evidence that these products are not addictive.

5. Imperial Brands nicotine pouches offer a satisfying alternative to combustible cigarettes and reduce adult smokers' desire to smoke

- To understand how adult smokers feel after having used Imperial Brands nicotine pouches, in particular their desire to smoke combustible cigarettes again, and whether these products are likely to be an acceptable alternative to adult smokers, a pharmacodynamic study was conducted in parallel to the pharmacokinetic blood nicotine delivery study above.
- After a period of overnight abstinence, changes in desire to smoke combustible cigarettes and satisfaction levels were measured on a Visual Analogue Scale during product use and for eight hours thereafter.
- Following initial use of Imperial Brands nicotine pouches and combustible cigarettes, there was a significant reduction in desire to smoke combustible cigarettes compared to baseline (i.e., prior to any product use).
- Imperial Brands nicotine pouches offered sustained reductions in desire to smoke combustible cigarettes for up to four hours before returning to baseline levels whereas for combustible cigarettes desire to smoke again returned to baseline much sooner.
- During the usage period, Imperial Brands nicotine pouches provided similar levels of satisfaction to combustible cigarettes, indicating these products are a satisfying alternative to combustible cigarettes for adult smokers.

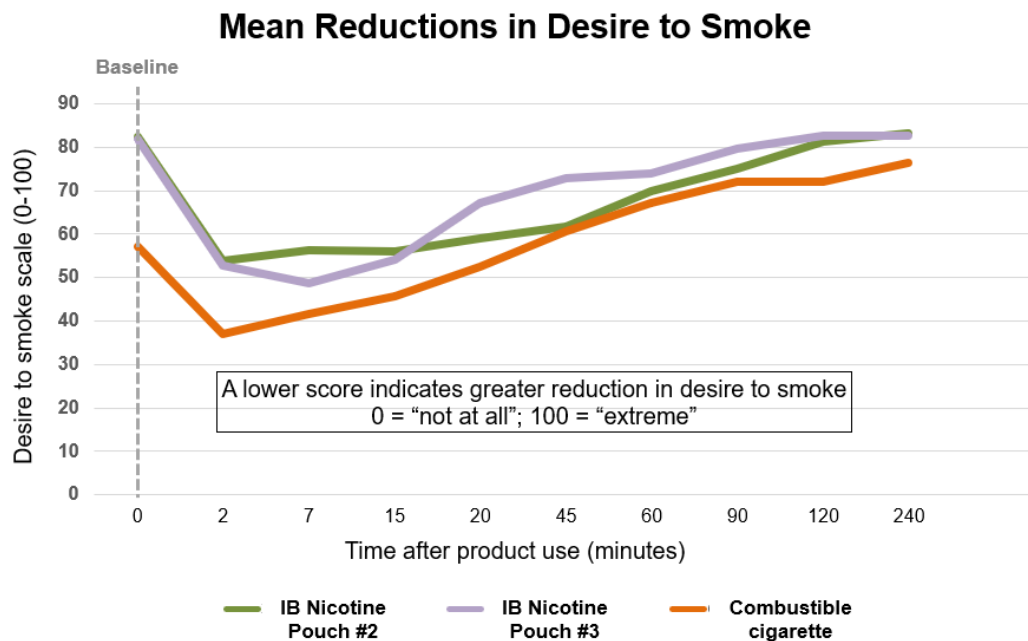


Figure 4. Average reductions in desire to smoke for Imperial Brands (IB) nicotine pouches vs. combustible cigarette (VAS scale) over 240 mins.

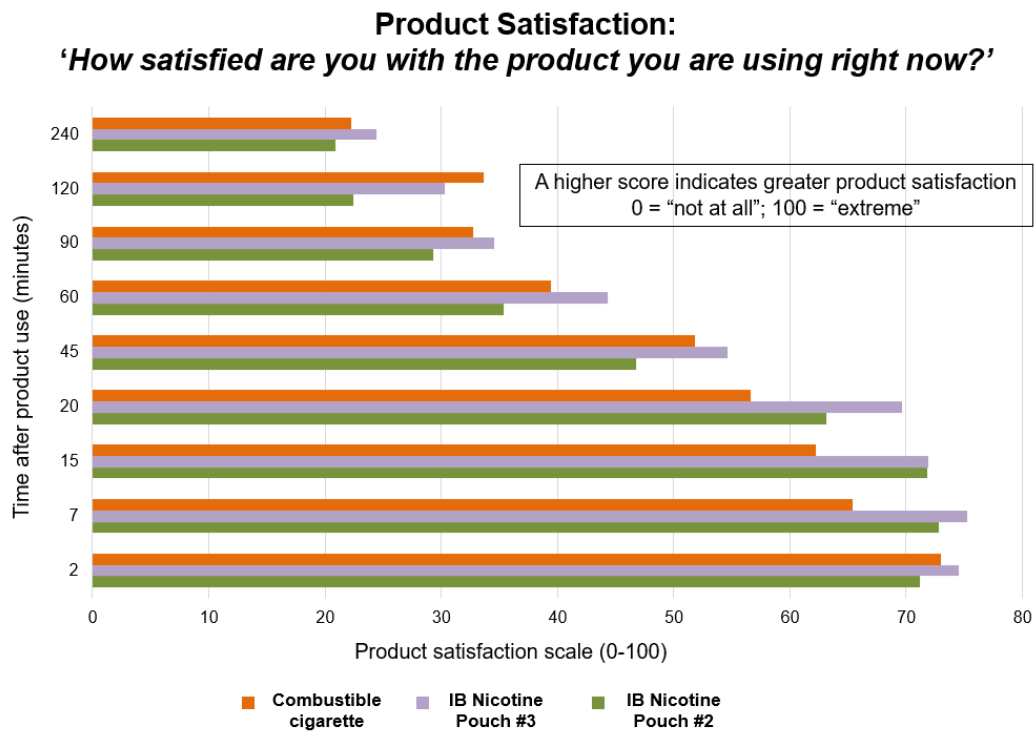


Figure 5. Average product satisfaction scores for Imperial Brands (IB) nicotine pouches vs. combustible cigarette (VAS scale) over 240 mins.

Line of Evidence V: Imperial Brands nicotine pouches offer a satisfying alternative to combustible cigarettes and reduce adult smokers' desire to smoke.

6. Imperial Brands nicotine pouches have a favourable short-term safety and tolerability profile

- Imperial Brands nicotine pouches were well tolerated by adult smokers with a favourable short-term safety profile during the period of the study.
- There were no serious adverse events during the clinical study. There was one incidence of a mild adverse event: one case of hiccups considered probably related to use of Imperial Brands nicotine pouches. Hiccups is a common, temporary and self-resolving event frequently reported in other nicotine product clinical studies.
- No clinically significant changes in laboratory safety samples, physical examinations, and cardiovascular measures were observed following Imperial Brands nicotine pouch product use.

Line of Evidence VI: Imperial Brands nicotine pouches have a favourable short-term safety and tolerability profile during the observation period with no serious adverse events related to the product observed.

7. Adult smokers and non-smokers properly understand that Imperial Brands nicotine pouches are not risk-free but are likely to be less harmful than continued combustible cigarette smoking.

- In a study of 250 adult tobacco and nicotine product users in both lower literacy and higher literacy groups, over 90% understood and formed accurate perceptions about the potential health risks and hazards of Imperial Brands nicotine pouches from the product labels and packaging. This included understanding the product contains nicotine and is an addictive chemical; that the product is not for those under the legal age to purchase and should not be used if pregnant; and that the product should not be swallowed, nor multiple pouches used at the same time.
- Importantly, the information provided did not promote any misconceptions that Imperial Brands pouches are risk-free, which may lead to inappropriate use of the products. Lower literacy level respondents also showed a consistent understanding of the information provided.
- In a study of 1532 adult tobacco and nicotine product users and non-users, Imperial Brands nicotine pouches were understood to be not risk-free and contain nicotine which is an addictive chemical. This was correctly understood across adult current, former and never users of tobacco and nicotine products.
- Imperial Brands nicotine pouches were also perceived as likely having a lower risk than continued combustible cigarette smoking with lower risks for developing lung cancer, mouth cancer, and cardiovascular disease.

Line of Evidence VII: Adult smokers and non-smokers properly understand that Imperial Brands nicotine pouches contain nicotine and are not risk-free but are likely to be less harmful than combustible cigarettes.

8. Imperial Brands nicotine pouches have appeal to adult smokers with very low interest amongst never and former smokers.

- In a study of 1532 adult tobacco and nicotine product users and non-users, curiosity in using Imperial Brands nicotine pouches was very low amongst never smokers and former tobacco and nicotine-containing product users and largely limited to the target audience of current adult smokers.
- Intentions to purchase Imperial Brands nicotine pouches was very low among never smokers and largely limited to current adult smokers.
- Given curiosity and possible intent to initiate and purchase Imperial Brands nicotine pouches is very low among never-smokers, there is little evidence that these products would serve as a ‘gateway’ to regular nicotine use or combustible cigarette smoking in nicotine naïve populations.

Curiosity and intent to purchase Imperial Brands nicotine pouches amongst UK adult tobacco and nicotine product users and non-users

	Likely to try Imperial Brands nicotine pouches	Likely to purchase Imperial Brands nicotine pouches
Smokers with intentions to quit (25-60 years)	16%*	11%*
Smokers without intentions to quit (25-60 years)	16%*	15%*
Younger adult smokers (18-24 years)	22%	17%
Recent quitters (18-60 years)	3%	3%
Long-term quitters (18-60 years)	0%	0.5%
Never nicotine/tobacco product users (25-60 years)	4%	4%
Younger never nicotine/tobacco product users (18-24 years)	2%	3%

Statistical significance * $P < 0.0001$

Table 1: Curiosity and intent to purchase Imperial Brands nicotine pouches.

Line of Evidence VIII: Imperial Brands nicotine pouches appeal overwhelmingly to adult smokers with very low interest amongst never smokers and former smokers. There is little evidence that Imperial Brands nicotine pouches would serve as a gateway to regular nicotine use amongst nicotine naïve populations.

9. Adult smokers’ interest and intent to purchase Imperial Brands nicotine pouches is mainly for tobacco harm reduction reasons.

- Amongst adult smokers who stated a positive intention to purchase Imperial Brands nicotine pouches, the motivations were underpinned by tobacco harm reduction. The main reason for interest and intent to purchase Imperial Brands nicotine pouches for adult smokers was that they perceived Imperial Brands nicotine pouches to be less harmful than combustible cigarettes (42%). The second most common reason was to use as an aid to stop smoking (29%).

	n (%)	N
Most important reason		
Imperial Brands nicotine pouches might be less harmful to me than combustible cigarettes.	90 (41.9%)	215
Second most important reason		
Imperial Brands nicotine pouches can help me quit smoking.	51 (29.1%)	174
Imperial Brands nicotine pouches might be less harmful to people around me than combustible cigarettes.	37 (23.7%)	156
Imperial Brands nicotine pouches might help me to cope with stress and to relax.	22 (22.0%)	100
Imperial Brands nicotine pouches might help me deal with cravings to smoke.	21 (21.0%)	100
Third most important reason		
Imperial Brands nicotine pouches can help me cut back on smoking combustible cigarettes.	19 (19.0%)	100
Imperial Brands nicotine pouches might help me deal with cravings to smoke.	16 (16.0%)	100
Imperial Brands nicotine pouches might be less harmful to people around me than combustible cigarettes.	24 (15.4%)	156
I can use Imperial Brands nicotine pouches in places where smoking combustible cigarettes isn’t allowed	23 (15.2%)	151
Imperial Brands nicotine pouches might help me to cope with stress and to relax.	15 (15.0%)	100

Table 2: Main reasons to purchase and use Imperial Brands nicotine pouches.

Line of Evidence IX: The main reason for adult smokers' interest and intent to purchase Imperial Brands nicotine pouches is for tobacco harm reduction and to reduce the health risks associated with combustible cigarette smoking.

Imperial Brands Nicotine Pouches Have Significant Tobacco Harm Reduction Potential For Adult Smokers

The strength of Imperial Brands' scientific assessment programme resides in the totality of the nine lines of scientific evidence provided, as follows:

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