



UNDERSTANDING THE RELATIVE RISK SCALE



IMPERIAL
BRANDS

SCIENCE



KEY TAKEAWAYS FROM THIS DOCUMENT

- Burning tobacco and inhaling the smoke is the primary cause of smoking-related diseases.
- Nicotine is addictive and not risk free; however, it's not the primary cause of smoking-related diseases. Nicotine can be delivered in less harmful ways without burning tobacco.
- Not all nicotine-containing products are equally as harmful as combustible cigarettes.
- As Next Generation Products (NGPs) do not burn tobacco or produce smoke, they deliver nicotine alongside fewer and substantially lower levels of toxicants compared to cigarettes.
- Nicotine-containing products sit on a scale of risk. Cigarettes sit at one end, pharmaceutical Nicotine Replacement Therapies (NRTs) at the other, and non-combustible NGPs sitting in-between. Collectively, all NGPs sit closer to NRTs, indicating their significant harm reduction potential.
- The position of nicotine-containing products on this risk scale, relative to combustible cigarettes, is informed by three criteria in the following order of importance:



Combustion
(burning) of
tobacco



Presence of
tobacco leaf



Inhalation to
the lung

→ INTRODUCTION

Smoking is a cause of serious disease in smokers, including lung cancer, heart disease and emphysema. The primary cause of these smoking-related diseases originates from tobacco combustion (burning) and inhaling the smoke that's produced. This smoke contains high levels of harmful chemicals (referred to subsequently as 'toxicants'). Public health experts have concluded that whilst nicotine is an addictive substance and not risk free, it's not the primary of smoking-related diseases – inhaling tobacco smoke is. Combustible cigarettes are therefore the most harmful way to consume nicotine.

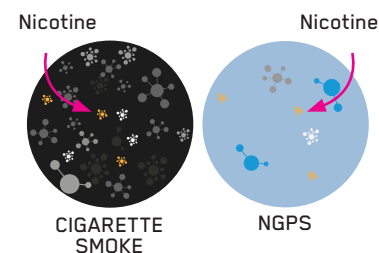
The best action adult smokers can take to improve their health is to stop all tobacco and nicotine use completely. However, despite the known risks of smoking, many adult smokers are uninterested or unwilling to take this step. With this in mind, a growing number of regulators and public health bodies advocate transitioning to nicotine products that are substantially less harmful than inhaled tobacco smoke is the next best option for adult smokers.

Not all nicotine-containing products carry the same level of risk. Science demonstrates the way in which nicotine is delivered to the consumer (i.e. the delivery mechanism) plays an important

role in determining the level of risk associated with a particular product. The most harmful form of nicotine delivery involves burning tobacco and inhaling smoke particles into the lung. By contrast, while medicinal nicotine products (Nicotine Replacement Therapies [NRTs] including nicotine patches, inhalers and gums) contain the same tobacco-derived nicotine as cigarettes, their delivery mechanisms don't involve the burning of tobacco and inhalation of smoke. These products therefore contain fewer and lower levels of toxicants found in tobacco smoke. This form of nicotine delivery has been deemed 'safe' by regulators and public health bodies and is recommended to help adult smokers quit smoking.

In recent years, other product categories have emerged that more efficiently deliver nicotine without burning tobacco, meaning they can more closely compete in terms of adult smoker acceptability with combustible cigarettes. Next Generation Products (NGPs) – like vapes, heated tobacco and tobacco-free oral nicotine pouches – are recent innovations designed to provide those adult smokers, who would otherwise continue to smoke, with less harmful but satisfying alternatives to help them transition away from smoking combustible cigarettes.

Though NGP categories vary, they share some key similarities:



All contain the same tobacco-derived nicotine that's also present in combustible cigarettes and NRTs



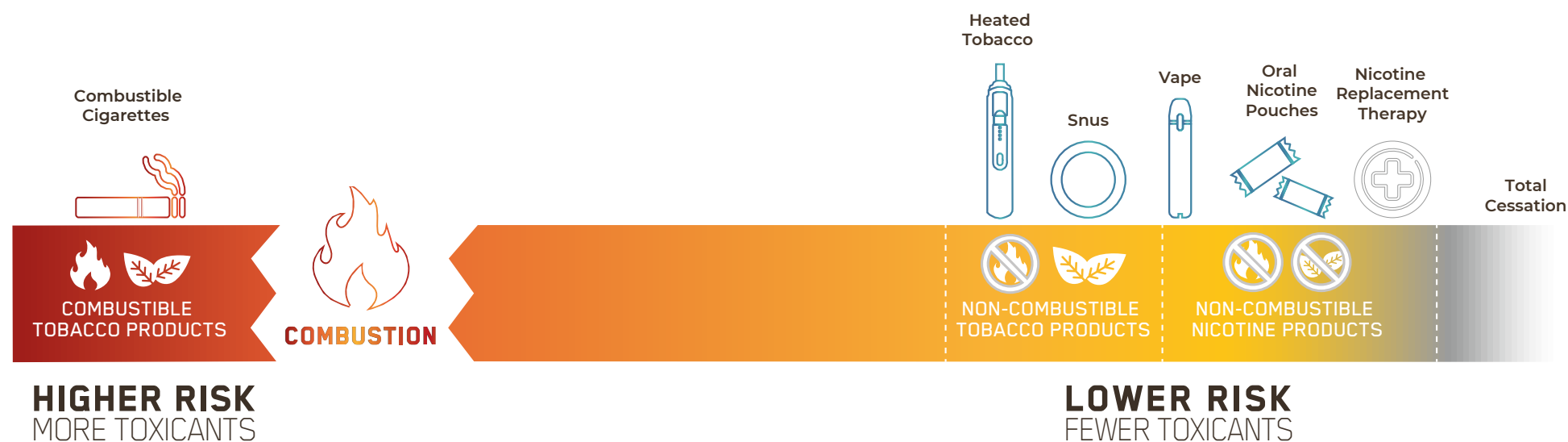
All deliver nicotine without combusting (burning) tobacco; they don't generate smoke either.

Not all nicotine-containing products are equally as harmful as combustible cigarettes. Given the range of different nicotine-containing products now available, there's a growing recognition that nicotine-containing products exist on a scale of risk (sometimes referred to as a 'continuum of risk', or similar terminology, by other organisations). Whilst burning tobacco to release nicotine and inhaling the smoke is the most crucial element determining a product's risk profile, consideration must also be given to whether products also contain tobacco leaf (even if it's not combusted/burnt) and whether the nicotine is delivered via inhalation to the lungs, or some other method.

Based on the current scientific evidence, Imperial Brands has developed a **relative risk scale** to illustrate the harm reduction potential of each nicotine-containing product relative to combustible cigarettes. Combustible cigarettes sit at one end of the scale (they are the most harmful nicotine delivery product with the highest risk of developing smoking-related diseases) and medicinal NRTs at the other, with the various non-combustible NGPs in between. Critically, there's a substantial reduction in potential smoking-related disease risk between combustible cigarettes and all NGPs. NGPs are therefore collectively grouped closer to NRTs on the scale, as they possess similar harm reduction profiles to one another.

→ THE RELATIVE RISK SCALE

An illustrative representation of the current scientific evidence:



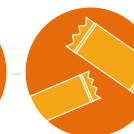
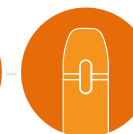


THE RELATIVE RISK SCALE

The relative risk scale provides an illustrative summary of the current scientific evidence base around all nicotine-containing products. Rather than focusing on any specific brand or product type, it instead presents the totality of the current scientific evidence base that underpins the broader categories for high-quality products. Critically, the relative risk scale demonstrates a clear distinction between high-risk combustible cigarettes and other, significantly less harmful nicotine-containing products – including NGPs and NRTs – that don't involve tobacco combustion.

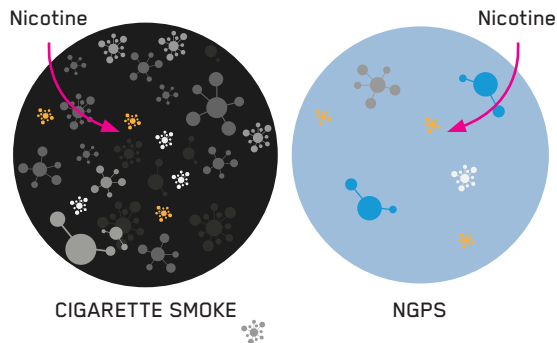


Combustible cigarettes sit as the far left of the relative risk scale; they possess the highest risk profile since they produce numerous toxicants at high levels. NRTs reside at the opposite end of the scale; they don't contain or burn tobacco, the majority don't require inhalation, and owing to their regulated status as medicines.



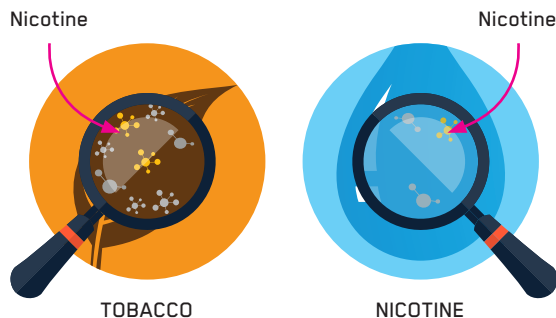
Since NGPs don't burn tobacco – the most critical element in determining a product's position on the relative risk scale – they are grouped more closely to NRTs. This is indicative of their significant potential to reduce smoking-related disease risk and harm, compared to combustible cigarettes. Additionally, the substantial difference in relative risk between combustible cigarettes and all NGPs is far greater than the risk profiles between different NGPs.

Overall, the harm reduction potential of NGPs – and therefore their position on the scale relative to combustible cigarettes – is based on the three criteria overleaf, listed in ranking order. Note that the distance between products on the scale is illustrative based on these criteria; however, it's important to reiterate all NGPs have favourable harm reduction profiles relative to continued combustible cigarette smoking.



1. TOBACCO COMBUSTION VS. THE ABSENCE OF COMBUSTION¹

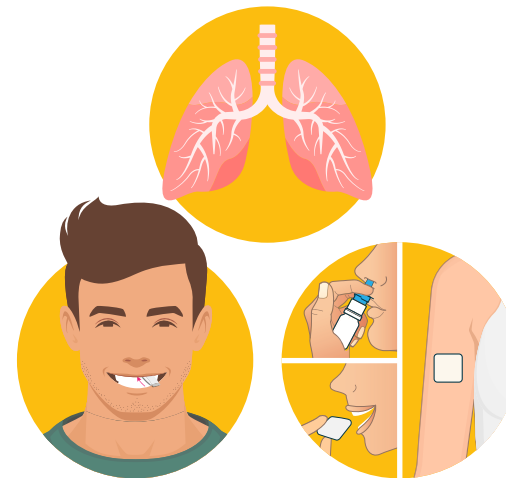
This is the most important differentiator between all nicotine-containing products and chiefly informs where each product sits on the scale. Combusting (burning) tobacco produces smoke containing over 7000 chemicals, around 100 of which are classified by public health experts as causes or potential causes of smoking-related diseases. Combustible tobacco products like cigarettes contain by far the highest levels of toxicants in their smoke, and therefore sit furthest to the left of the scale denoting the highest risk of developing smoking-related diseases². For this reason, there's a significant gap between combustible cigarettes and all non-combustible nicotine-containing products.



2. PRESENCE OF TOBACCO LEAF VS. ABSENCE OF TOBACCO LEAF

Some NGPs contain tobacco, albeit not combusted; others contain only nicotine, and no tobacco leaf. Tobacco-containing NGPs (e.g. heated tobacco) contain nicotine which is naturally present in tobacco leaf. For tobacco-free NGPs (e.g. vape e-liquids and tobacco-free oral nicotine pouches), nicotine is extracted from tobacco leaf and added to products. In high-quality products, including Imperial Brands' portfolio, nicotine is purified to 99.9% pharmaceutical grade standards. Tobacco, in its unburnt form, naturally contains some toxicants – albeit at substantially lower levels than those found in tobacco smoke – and so carries more risk than a product that does not contain tobacco. NGPs that contain tobacco leaf therefore sit slightly further to the left on the scale compared to NGPs that don't contain tobacco. However, this risk differential must be considered within the context of tobacco combustion, the primary cause of smoking-related disease. This is why all NGPs sit closely together on the risk scale.

INHALATION



ORAL / NASAL / DERMAL METHODS OF DELIVERY

3. METHOD OF NICOTINE DELIVERY
























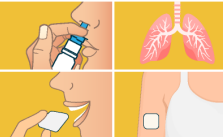




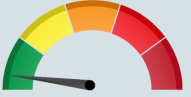
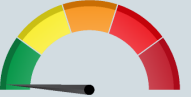
Human lungs contain a network of delicate structures called alveoli, used to exchange air. These alveoli are sensitive to injury from any external environmental exposures. As a result, inhalation of any material into the lung (other than fresh air) is likely to cause some biological effects. This means if an NGP delivers nicotine via inhalation through the lungs, it likely poses more risk than one used orally (where the lungs are not exposed to any foreign material). However, again this risk differential must be considered within the context of tobacco combustion, the primary cause of smoking-related disease. This is why all NGPs sit closely together on the risk scale.

¹ Combustion is the scientific word for burning. Three elements are necessary to create the chemical process of combustion: heat, fuel and oxygen. In a cigarette, tobacco acts as a fuel which ignites using a high-temperature heat source (usually from a lighter). The tobacco relies on oxygen in the air to burn, creating the by-products heat, light, smoke and ash. See the this explanatory blog post for further information on the science of combustion: <https://imperialbrandscience.com/blog/pulse-the-science-of-heat-not-burn/>.

² <https://www.fda.gov/tobacco-products/products-ingredients-components/harmful-and-potentially-harmful-constituents-hphcs>

→ THE RELATIVE RISK SCALE RATIONALE

To further help explain the position of each nicotine-containing product on the relative risk scale, we've developed a relative risk scale rationale which considers each product in turn.

	 COMBUSTIBLE CIGARETTES	 HEATED TOBACCO	 SNUS	 VAPE	 ORAL NICOTINE POUCHES	 NICOTINE REPLACEMENT THERAPY
COMBUSTION						
TOBACCO						
METHOD OF USE						
TOXICANTS (RELATIVE TO COMBUSTIBLE CIGARETTES)						



→ COMBUSTIBLE CIGARETTES

Combustible cigarettes sit on the far left of the relative risk scale with the highest risk profile; they contain the most toxicants – and at the highest levels – as a result of burning of tobacco and the

inhaling of smoke directly into the lung. Combustible products therefore pose by far the highest risk of smoking-related disease to adult smokers.



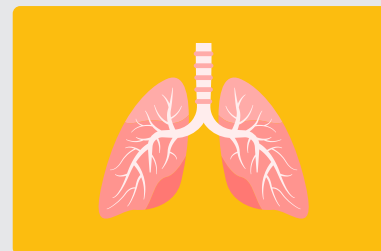
1. TOBACCO COMBUSTION VS. THE ABSENCE OF COMBUSTION

Usage involves the burning of tobacco and generation of numerous toxicants at high levels to release nicotine from the tobacco leaf.



2. PRESENCE OF TOBACCO LEAF VS. ABSENCE OF TOBACCO LEAF

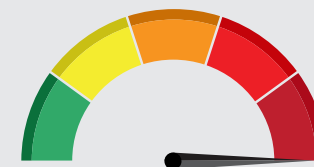
Contains tobacco leaf which naturally contains some toxicants.



3. METHOD OF NICOTINE DELIVERY

Smoke, which contains nicotine among many toxicants, is inhaled into the deep lung where the nicotine is absorbed quickly.

OVERALL LEVELS OF TOXICANTS AND SUBSEQUENT RISK:





→ NICOTINE REPLACEMENT THERAPIES (NRTS):

At the opposite end of the scale to combustible cigarettes sit NRTs. NRTs are tobacco-free, non-combustible pharmaceutical nicotine products, available as gums, inhalers and patches, and regulated as medically licensed smoking cessation products. They contain the same nicotine as combustible cigarettes but with fewer and substantially lower levels

of the other toxicants found in tobacco smoke. These medicinal nicotine-containing products have been deemed as 'safe' by regulators and are recommended to help adult smokers quit smoking. The available scientific evidence, including years of research by the pharmaceutical industry, shows nicotine – when decoupled from tobacco smoke – has a favourable safety

profile. NRTs subsequently sit on the far right of the scale with the lowest relative risk profile relative to combustible cigarettes.



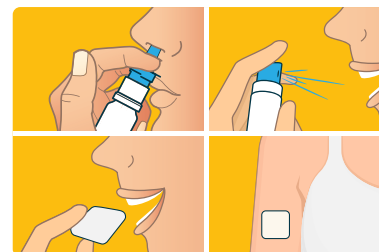
1. TOBACCO COMBUSTION VS. THE ABSENCE OF COMBUSTION

Usage doesn't involve the burning of tobacco. As such, there are fewer and lower levels of toxicants produced compared to cigarette smoke.



2. PRESENCE OF TOBACCO LEAF VS. ABSENCE OF TOBACCO LEAF

Is tobacco-free, meaning products contain lower levels of the toxicants naturally found in the tobacco plant.



3. METHOD OF NICOTINE DELIVERY

Nicotine isn't absorbed via the deep lung, meaning lung-related toxicity and disease risks are not to be expected. However, nicotine delivery is lower and much slower compared to combustible cigarettes and all NGPs.

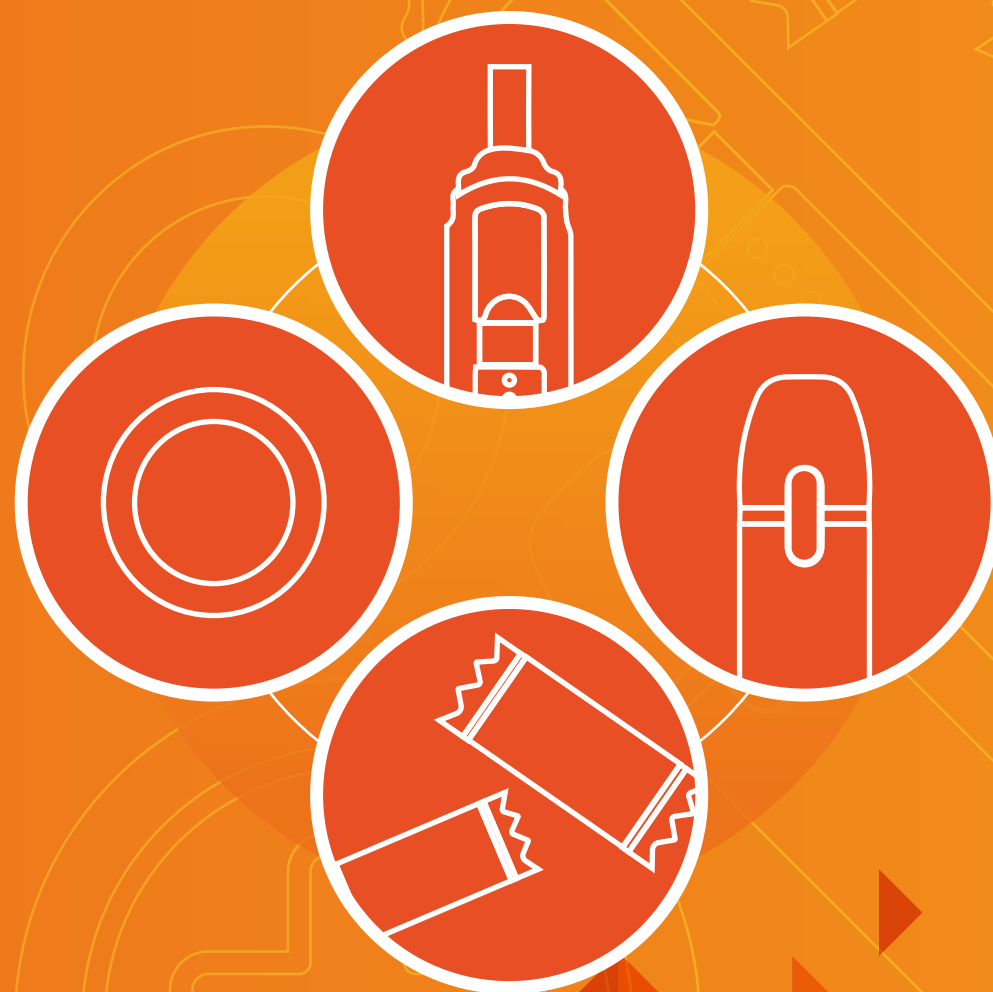
OVERALL LEVELS OF TOXICANTS AND SUBSEQUENT RISK RELATIVE TO COMBUSTIBLE CIGARETTES:



→ NEXT GENERATION PRODUCTS:

NGPs are non-combustible, nicotine-containing products. Free from burning tobacco and the generation of harmful tobacco smoke, NGPs contain far fewer and lower levels of toxicants. As such, their harm reduction potential compared to combustible tobacco is substantial.

Collectively, these products sit much further towards the right of the scale, closer to NRTs, with a significant gap – representative of substantial reductions in smoking-related disease risk – from combustible cigarettes. NGPs share comparable risk reduction profiles to one another and are subsequently grouped closely together on the scale. While there's a small variation in the risks between individual NGPs, there's a large reduction in risk for all NGPs as a group when compared to combustible cigarettes. Based on the three criteria outlined earlier, the position of each NGP relative to combustible cigarettes on the risk scale can be substantiated.





NEXT GENERATION PRODUCTS: HEATED TOBACCO (HT)

Although HTs contain tobacco leaf, critically they don't burn tobacco – the most crucial element in determining a product's risk profile. By heating – and not burning – tobacco, an inhalable aerosol (vapour) is produced which contains nicotine and flavour aromas from the

tobacco. As tobacco is not burnt, the vapour contains fewer and substantially lower levels of toxicants compared to combustible cigarette smoke. HTs contain tobacco, which naturally contains some toxicants, while vapour is inhaled into the lung for nicotine to be absorbed. This

carries slightly more risk than products that don't contain tobacco leaf, or products that don't require inhalation to deliver nicotine.



1. TOBACCO COMBUSTION VS. THE ABSENCE OF COMBUSTION

Usage doesn't involve the burning of tobacco: tobacco is heated to a temperature well below that of combustion to release nicotine from the tobacco leaf. As such, HTs don't produce smoke and the resulting vapour contains significantly fewer and lower levels of toxicants.



2. PRESENCE OF TOBACCO LEAF VS. ABSENCE OF TOBACCO LEAF

Contains tobacco leaf which naturally contains some toxicants.



3. METHOD OF NICOTINE DELIVERY

Inhaled into the deep lung where nicotine is absorbed quickly, similar to the delivery speed of a combustible cigarette.

OVERALL LEVELS OF TOXICANTS AND SUBSEQUENT RISK RELATIVE TO COMBUSTIBLE CIGARETTES:



→ TRADITIONAL SWEDISH-STYLE SNUS

Traditional Swedish-style snus is not technically classed as an NGR; it's been available for centuries in Scandinavia. However, the product has demonstrable harm reduction potential relative to continued combustible cigarette smoking

and as such it's considered an important part of the tobacco harm reduction story. Snus contains tobacco leaf. However as a smokeless product, tobacco is not burnt (the most crucial element determining a product's risk profile) and therefore

many of the toxicants present in cigarette smoke are not produced. Snus contains tobacco leaf, which naturally contains some toxicants, and so carries slightly more risk than a product that does not contain tobacco leaf. Nicotine is delivered

orally via the gum membranes, meaning lung-related toxicity and disease risks are not to be expected. The product's harm reduction potential relative to smoking is significant, as demonstrated by long-term epidemiological studies⁴.



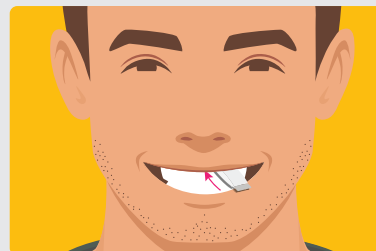
1. TOBACCO COMBUSTION VS. THE ABSENCE OF COMBUSTION

Usage doesn't involve the burning of tobacco and does not produce smoke. As such, there are significantly fewer and lower levels of toxicants produced compared to combustible cigarette smoke.



2. PRESENCE OF TOBACCO LEAF VS. ABSENCE OF TOBACCO LEAF

Contains tobacco leaf which naturally contain some toxicants.



3. METHOD OF NICOTINE DELIVERY

Nicotine is delivered and absorbed orally via the gum membranes, meaning lung-related toxicity and disease risks aren't to be expected. However, this method of nicotine delivery is slower than via the lungs.

OVERALL LEVELS OF TOXICANTS AND SUBSEQUENT RISK RELATIVE TO COMBUSTIBLE CIGARETTES



⁴ Clarke E et al., (2019) Snus: a compelling harm reduction alternative to cigarettes. Harm Reduct J. 2019; 16: 62



→ NEXT GENERATION PRODUCTS: **VAPES**

Vapes are non-combustible NGPs which can contain nicotine but, crucially, no tobacco leaf. High quality vapes use e-liquids which contain pharmaceutical grade high purity nicotine derived from tobacco leaf (the same nicotine as in NRTs), propylene glycol and vegetable glycerol alongside various flavourings. As

they do not combust tobacco – the most crucial element determining a product's risk profile – vapes produce significantly fewer and lower levels of toxicants compared to combustible cigarette smoke. In addition, as vapes are tobacco-free, they contain lower levels of the toxicants naturally found in the tobacco

plant and in tobacco-containing NGPs. Nicotine is delivered via inhalation into the lung, which carries slightly more risk than a product that doesn't require inhalation to deliver nicotine.



1. TOBACCO COMBUSTION VS. THE ABSENCE OF COMBUSTION

Usage doesn't involve the burning of tobacco. As such, there are significantly fewer and lower levels of toxicants produced compared to combustible cigarette smoke.



2. PRESENCE OF TOBACCO LEAF VS. ABSENCE OF TOBACCO LEAF

Doesn't contain tobacco leaf, meaning products contain lower levels of the toxicants naturally found in the tobacco plant.

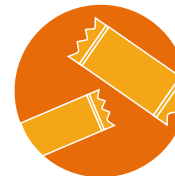


3. METHOD OF NICOTINE DELIVERY

Inhaled into the lung where nicotine is absorbed quickly, closer to the speed of a combustible cigarette than NRTs.

OVERALL LEVELS OF TOXICANTS AND SUBSEQUENT RISK RELATIVE TO COMBUSTIBLE CIGARETTES:





→ NEXT GENERATION PRODUCTS: TOBACCO-FREE ORAL NICOTINE POUCHES

Tobacco-free oral nicotine pouches use pharmaceutical grade high purity nicotine derived from tobacco leaf (the same nicotine used in NRTs) that's either combined with a plant fibre-based substrate (e.g. wheat or bamboo) or in a

dry powder format. Oral nicotine pouches do not burn tobacco and do not contain any tobacco leaf. In addition, they deliver nicotine orally via the gum membranes, meaning lung-related toxicity and disease risks are not to be expected. Assessment

based on the three criteria outlined (non-combustion, non-tobacco and no-inhalation) places oral nicotine pouches closest to NRTs on the relative risk scale.



1. TOBACCO COMBUSTION VS. THE ABSENCE OF COMBUSTION

Usage doesn't involve the burning of tobacco and doesn't produce smoke. As such, there are significantly fewer and lower levels of toxicants produced compared to combustible cigarettes.



2. PRESENCE OF TOBACCO LEAF VS. ABSENCE OF TOBACCO LEAF

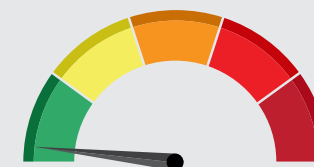
Is tobacco-free, meaning products contain lower levels of the toxicants naturally found in the tobacco plant.



3. METHOD OF NICOTINE DELIVERY




Nicotine is delivered and absorbed orally via the gum membranes, meaning lung-related toxicity and disease risks aren't to be expected. However, this method of nicotine delivery is slower than via the lungs.

OVERALL LEVELS
OF TOXICANTS AND
SUBSEQUENT RISK
RELATIVE TO COMBUSTIBLE
CIGARETTES:





IN SUMMARY

- Burning tobacco and inhaling the smoke is the primary cause of smoking-related diseases.
 - Though addictive and not risk free, nicotine isn't the primary cause of smoking-related disease. Nicotine can be delivered in less harmful ways without burning tobacco, meaning not all nicotine products are equally as harmful as combustible cigarettes
 - As Next Generation Products (NGPs) don't burn tobacco or produce smoke, they deliver nicotine alongside fewer and substantially lower levels of toxicants compared to cigarettes.
 - Nicotine products reside on a scale of risk. Cigarettes sit at one end, pharmaceutical nicotine products (NRTs) at the other, with non-combustible NGPs sitting in between. Collectively all NGPs sit closer to NRTs, which is indicative of their significant harm reduction potential.
 - Imperial Brands' relative risk scale communicates this range in risk, providing an illustrative summary of the current scientific evidence base around high-quality, nicotine-containing product categories.
- The position of nicotine-containing products on this risk scale, relative to combustible cigarettes, is informed by three criteria in ranking order:
 - 
Combustion (burning) of tobacco
 - 
Presence of tobacco leaf
 - 
Inhalation to the lung
 - While there are minor variations in risk between individual NGPs, there's a large reduction in risk for all NGPs as a group when compared to combustible cigarettes.
 - The reasoning behind each NGP's positioning is further explained in the relative risk scale rationale. This graphic summarises how each criteria is applied to each product category, relative to combustible cigarettes.



IMPERIAL
BRANDS

SCIENCE

WWW.IMPERIALBRANDSSCIENCE.COM