IMPERIAL BRANDS SCIENCE

NEXT GENERATION PRODUCTS

An approach to toxicological risk assessment for MOND* flavours

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*Modern oral nicotine delivery products

Talk overview

- Imperial Brands PLC approach to Product Stewardship
- Product introduction
- Product Stewardship Strategy
  - Quality of materials & ingredients
  - Desk-based risk assessment
  - *In vitro* testing
- Impact of flavours on the toxicological profile of MONDs

MOND: Modern oral nicotine delivery products

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Imperial Brands PLC approach to Product Stewardship

Imperial Brands as a responsible manufacturer has a duty to understand our products and their associated risks, including those related to consumer safety and regulatory compliance as well as any potential risks that may materialise.

Where no regulations exist, we ensure products meet our internal standards

Imperial Brands does not commission or conduct research involving animals.

PETA

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Imperial Brands' approach to Product stewardship and Tobacco Harm Reduction

Learn more about our SAF here:

Imperial scientists have developed a multi-stage, multi-discipline, Scientific Assessment Framework (SAF) to evaluate product safety and substantiate the harm reduction potential of our NGP relative to cigarettes

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MOND as an alternative nicotine delivery product

- Tobacco smoke contains around 7,000 chemicals.
- Modern oral nicotine delivery products (MOND) generally, do not contain or burn tobacco.
- Therefore, contain significantly fewer and lower levels of harmful chemicals compared to cigarette smoke.

Flavours & Humectants

Nicotine

Plant fibre-based substrate
(non-tobacco)

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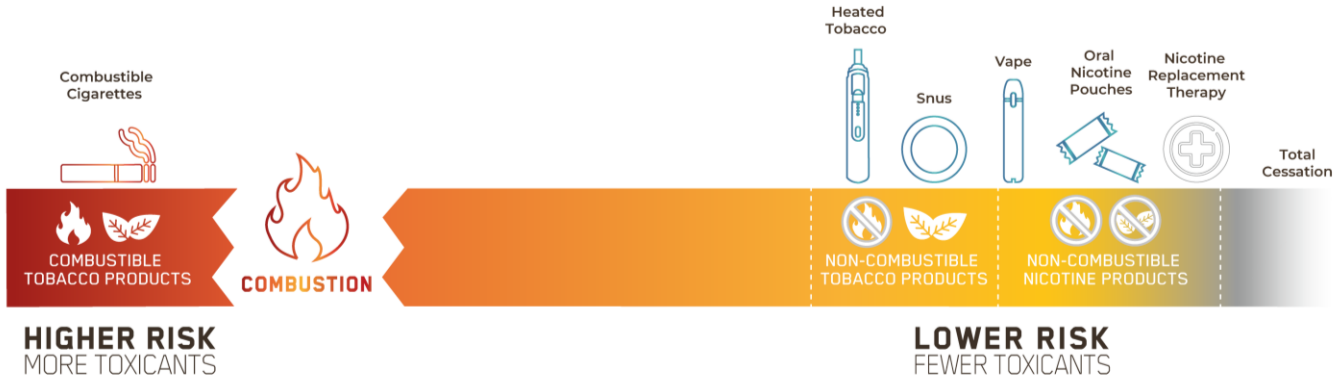
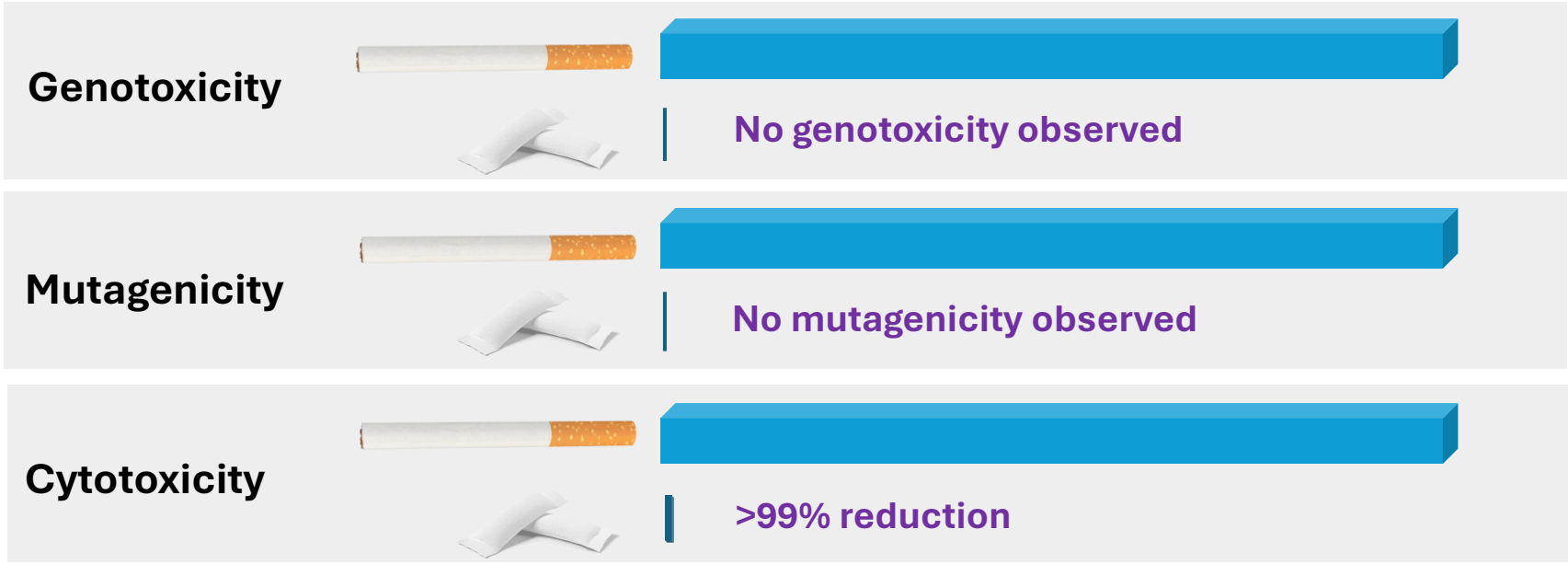
MOND have harm reduction potential compared to cigarettes

Imperial Brands Relative Risk Scale: Illustrative representation of the current scientific evidence

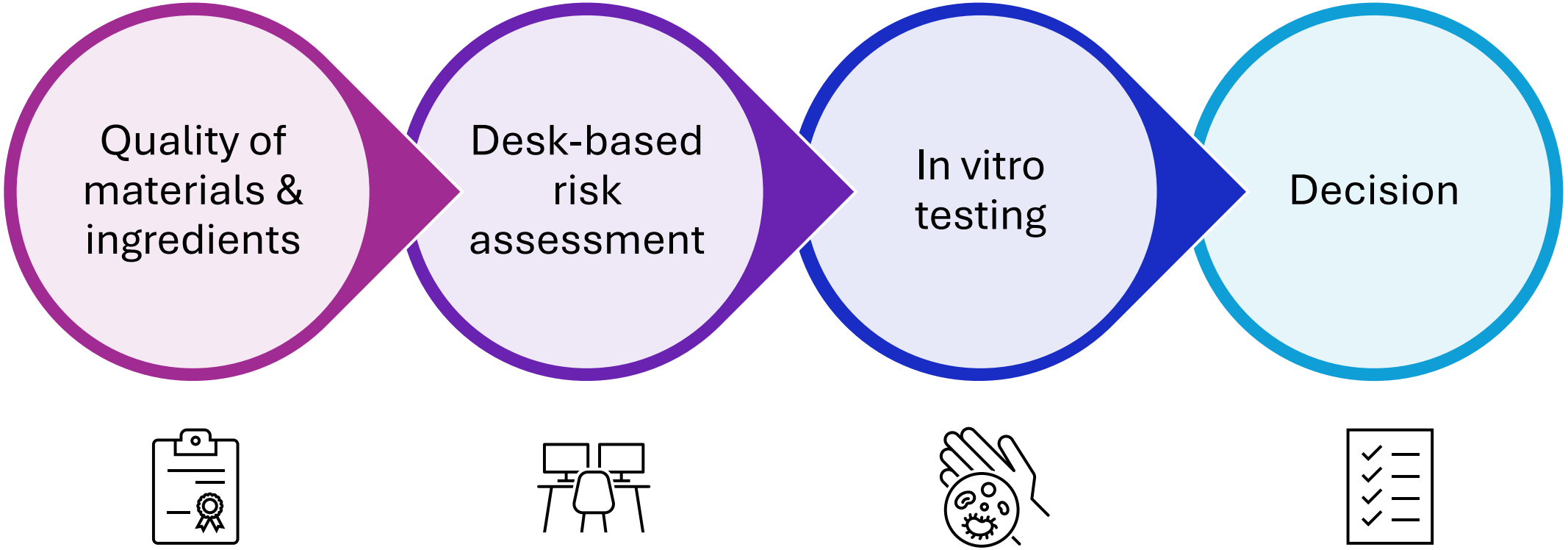


In vitro data: Based on a Zone X #2 product (5.8 mg/pouch) compared to a conventional cigarette



Preclinical Assessment of Tobacco-Free Nicotine Pouches Demonstrates Reduced *In Vitro* Toxicity Compared with Tobacco Snus and Combustible Cigarette Smoke *Yu et al.* Applied In Vitro Toxicology 2022 8:1, 24-35

Product Stewardship Strategy



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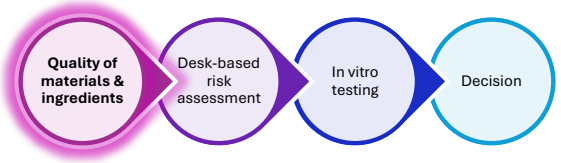
Quality of material & ingredients



Quality standards

Pharmaceutical grade nicotine
European Pharmacopoeia (Ph.Eur.) or US Pharmacopeia (USP)

Pharmaceutical and food grade humectants

Food grade:
- **Plant fibres**
- **Flavourings**
  (Regulation (EC) No 1334/2008)
- **Pouch material**
  (Regulation (EC) No 1935/2004)

Supporting evidence

- Full compositional disclosures
- Declarations of conformity against relevant regulations
- Certificates of Analysis (CoAs) and declarations of impurities
- Further analytical testing if required

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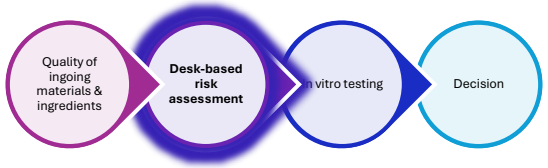
Ingredient Desk-based Risk assessment



Ingredient Hazard Charachterisation

Thorough literature review

Human health-related endpoints including but not limited to:

- Carcinogenicity
- Repeat dose toxicity
- Skin sensitisation

In silico tools

Identify potential hazards

- ToxTree
- DEREK Nexus by Lhasa
- OECD QSAR Toolbox, etc.

Review relevant regulatory limits

Including but not limited to:

- EFSA/JECFA ADI (Acceptable Daily Intake)
- DNEL (Derived No Effect Level) from publicly available high-quality studies

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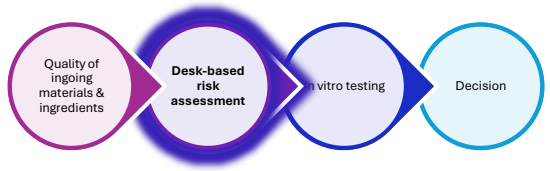
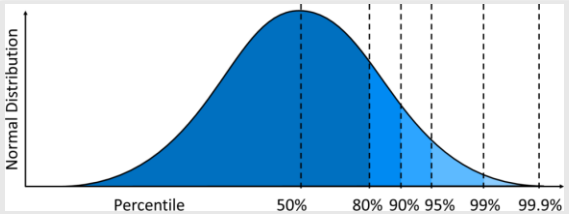
Desk-based risk assessment



Ingredient Exposure assessment



By Christoph Roser at AllAboutLean.com under the free CC-BY-SA 4.0 license.

Conservative consumption models protective of 95th percentile based on actual use data

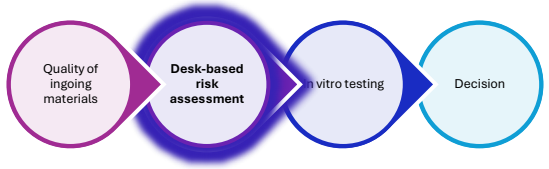
Our approach follows widely accepted methodologies such as those described by ECHA[1]

Use of appropriate factors to manage uncertainties where required:

- Intraspecies
- Interspecies
- Exposure duration
- Product specific rates etc.

[1]European Chemicals Agency. (2011). Guidance on information requirements and chemical safety assessment: Part B – Hazard assessment (Version 2.1).

Desk-based risk assessment



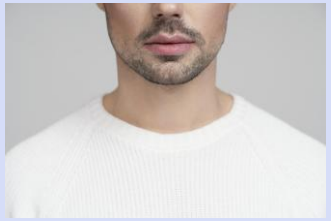
The results from the previous stages are combined along with regulatory checks where applicable

- Where the results are satisfactory *in vitro* testing is conducted on the finished product by our Lab Network team
- If the results are not acceptable then further actions may take place:

Rejection of the formulation

Reformulation

Ingredient-specific testing



Dissolution/ Mouth level exposure studies

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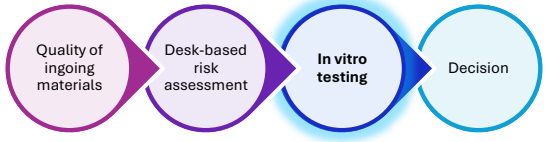
In vitro testing



- Ames (Bacterial reverse mutation)
- IVM (In vitro micronucleus)
- NRU (Neutral red uptake)

- The results are reviewed by our AGP Pre-market Stewardship team in combination with the desk-based assessment
- Further testing can be conducted with mechanistic assays such as High Content Screening (STPOST53; Abstract ID: 2728)

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Final Decision

Weekly Meetings

+

Results from *in vitro* testing

↓

Consensus decision
Based on all available data

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Flavours play a role in THR: Consumer acceptance

Evidence from behavioural science and population studies shows that flavours significantly increase consumer acceptance[1].

[1]*Grandolfo, E. et al. (2024). Tobacco-Free Nicotine Pouches and Their Potential Contribution to Tobacco Harm Reduction: A Scoping Review. Cureus, 16(2), e54228.* https://doi.org/10.7759/cureus.54228

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In vitro testing of 21 flavoured products

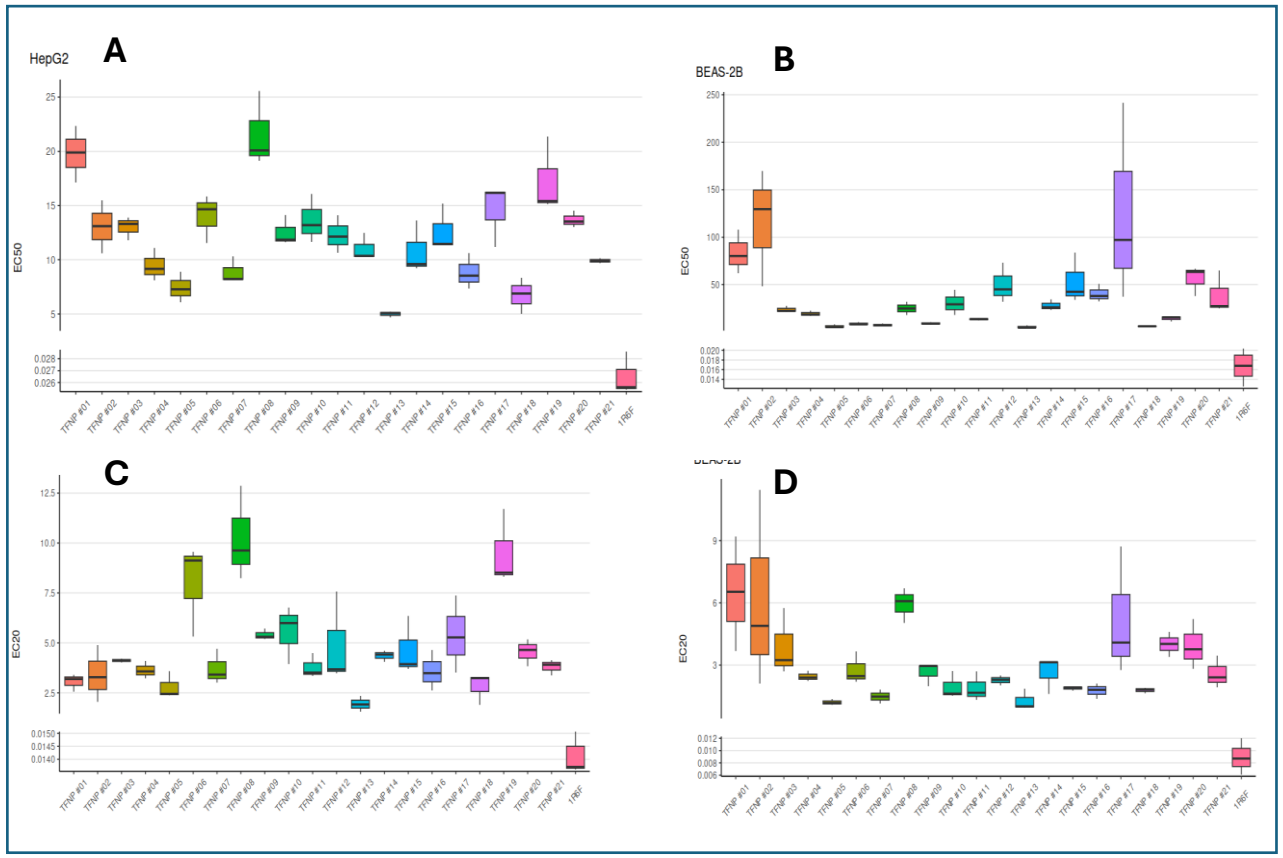

Figure 1 (A-D): Concentrations (mg extract/ml medium) required to induce 50% and 20% cytotoxicity in HepG2 and Beas-2B cells compared to negative control (EC20) for the test article extracts .

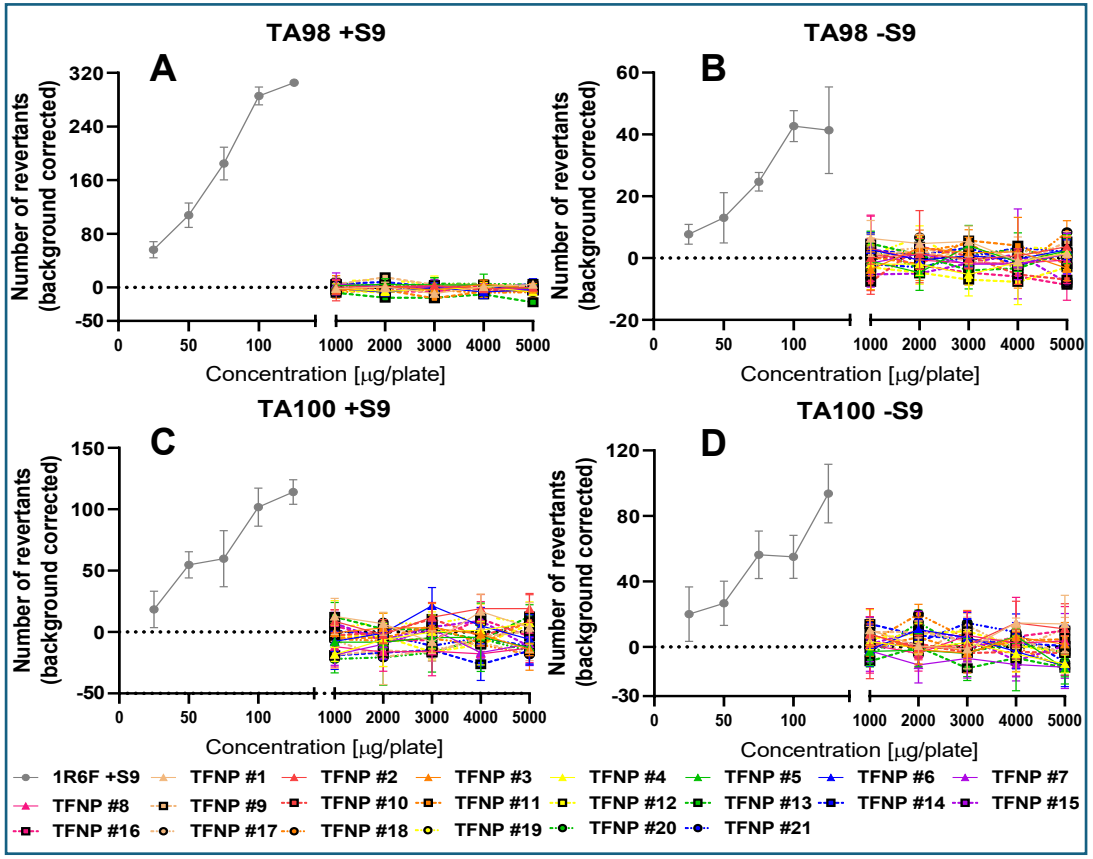

Figure 2 (A-D): Dose-specific mutagenicity in *Salmonella typhimurium* in TA98 and TA100 cell lines in the presence and absence of metabolic activation (S9) after exposure.

Bento, J., Wieczorek, R., Pour, S. J., Trelles-Sticken, E., Papikinos, K., & Chapman, F. (2024).In-vitro assessment of TFNP pouches reveals marked reductions in toxicity compared to cigarettes. September 2024. Available at: https://imperialbrandsscience.com/wp-content/uploads/2024/09/In-vitro-assessment-of-TFOND-pouches-reveals-marked-reductions-in-toxicity-compared-to-cigarettes.pdf

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Conclusions

- A framework regarding the toxicological risk assessment of ingredients is critical in offering consumers high quality products they can trust
- Our approach is based on widely recognised guidance
- Flavours are critical to the THR potential of MONDs and can be used without increasing the toxicological profile of the final product
  - Use of high-quality ingredients and approved based on rigorous testing and toxicological risk assessment
  - Responsibly marketed to intended audiences

THR: Tobacco Harm Reduction MONDs: Modern oral nicotine products

Acknowledgments

- AGP Pre-Market Stewardship team
- Harm Reduction and Engagement team
- Lab Network

And all of you for your attention!