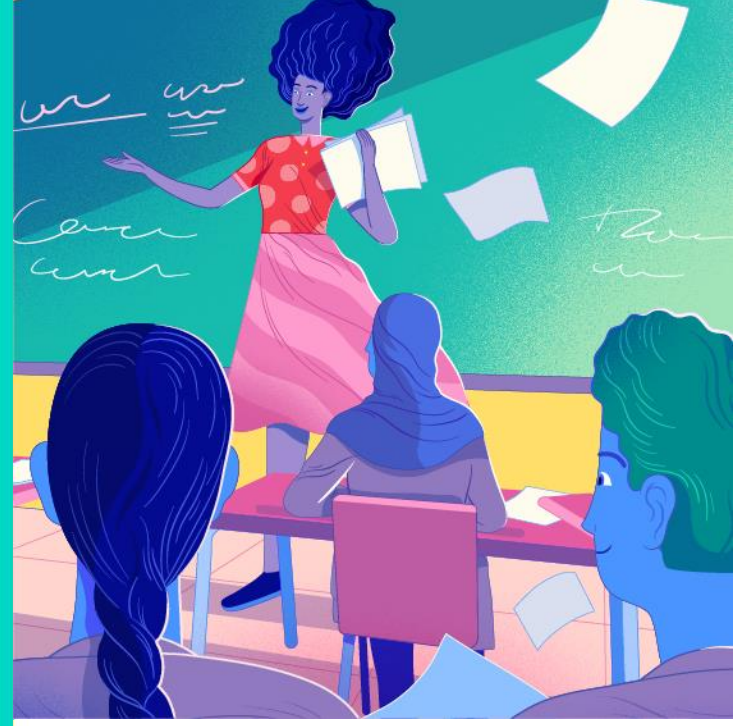
Assuring safety without the use of animals

History of Safe Use



Paul Russell

2.5bn consumers reached

48k suppliers

190 countries

60% sales in emerging markets

12 billion euro brands

1.3bn people helped to improve health and hygiene

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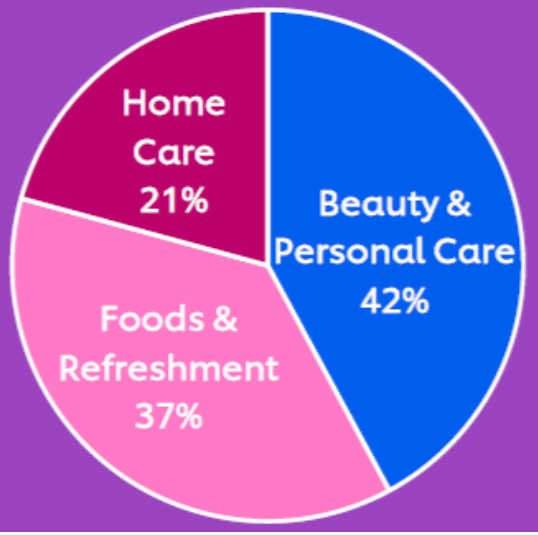

90% local leaders

14 of the top 50 global consumer brands

Lifebuoy, sunsilk, Dove, Knorr, LUX, vim, Brooke Bond, Sunlight, Rexona, closeup, Comfort, Lipton, POND'S, Pepsodent

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Safety & Environmental Assurance Centre (SEAC)

PROTECTING CONSUMERS, WORKERS & OUR ENVIRONMENT BY ENSURING UNILEVER'S PRODUCTS & PROCESSES ARE SAFE & SUSTAINABLE BY DESIGN

CENTRE OF EXCELLENCE – SAFETY & ENVIRONMENTAL SUSTAINABILITY SCIENCES

APPLYING SCIENCE

GOVERNANCE
We provide scientific evidence to manage safety risks & environmental impacts for new technologies

ADVANCING SCIENCE

NEW CAPABILITY
We harness the latest science to create new tools to assess innovations of the future

SHARING SCIENCE

COLLABORATION
We partner with leading scientists from around the globe

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Can we use a new ingredient safely?

- **Can we safely use x% of ingredient y in product z?**

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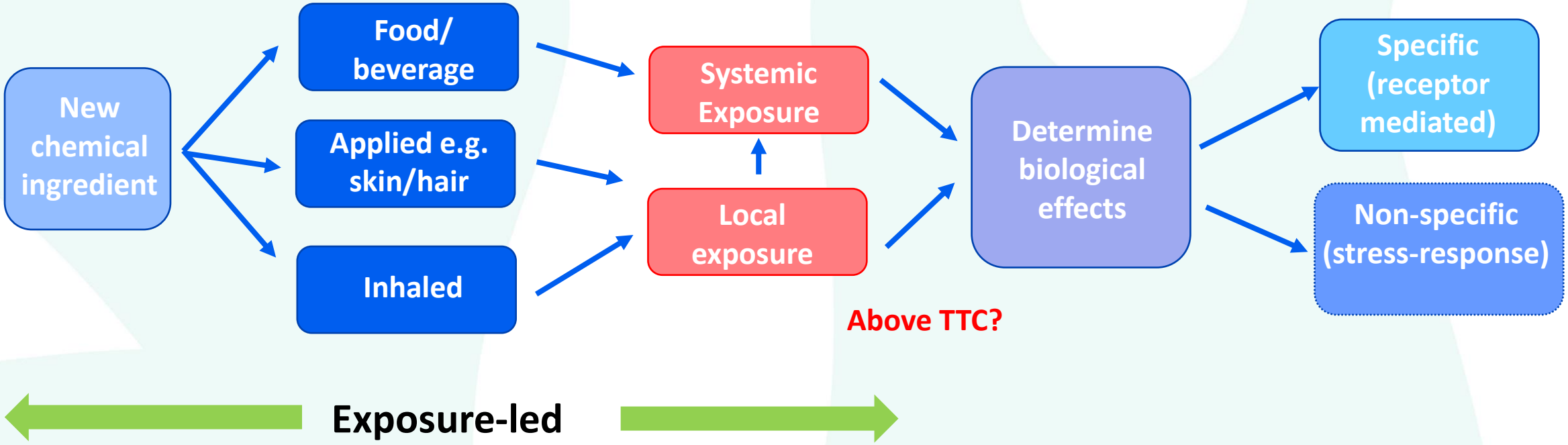
Exposure-led risk assessments



Do you have a favourite?

'Everything is poison, there is poison in everything. Only the dose makes a thing not a poison.' Paracelsus

Amygdalin
(0.6g/kg seeds)

1.1 kg apple seeds

Formaldehyde
(0.06g/kg)

116 kg pears

Solanine
(0.2g/kg)

79 kg potatoes

Cucurbitacin E
(0.25-7 g/kg,
high in bitter courgettes)

119 kg courgettes

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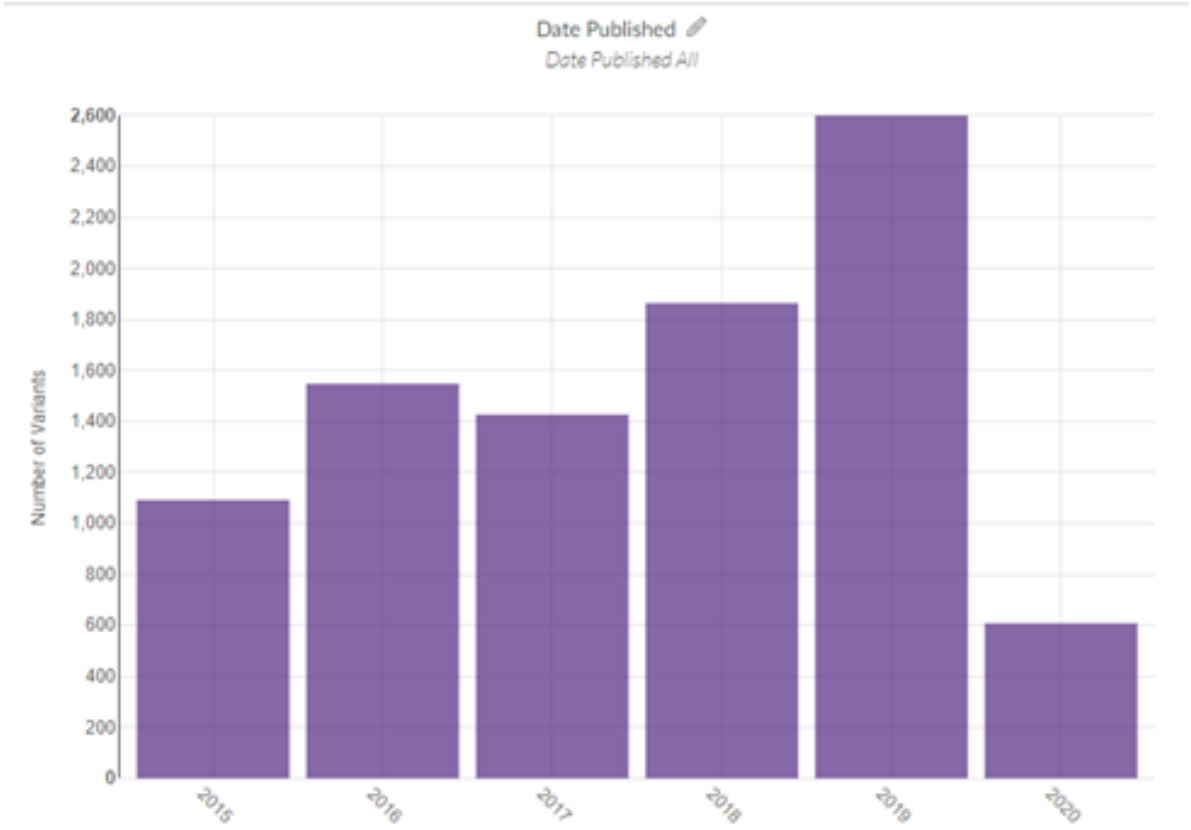
Naturals in cosmetics

- There is now a growing consumer demand for cosmetic products which contain botanical derived ingredients with established or perceived functional benefit.
- Sales volumes have therefore increased for natural or organic cosmetics.
- Public believe that natural ingredients are safer than synthetic ingredients.



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‘It’s natural so it must be safe…..’

Aristolochic acid

- *Aristolochia* spp
- Renal failure in ~300 patients worldwide
- Mis-identification of similar herbs

Poison Ivy

- *Toxicodendron radicans*
- Urushiol resins
- Also found in mango skin & cashew tree

Stinging nettle

- Urtica dioica
- Needle-like spines (histamine)

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‘History of Safe Use’ Risk Assessment

- Risk assessment of botanical materials (herbals, traditional Chinese medicines, Ayurvedics etc) which have a long history of use in certain parts of world.

- ‘History of Safe Use’ (HoSU) is widely used for safety assessment of food ingredients (e.g. novel foods and foods derived from genetically modified organisms) and the principles can be extended for cosmetic products.

- History of safe use assessments need to be robust, transparent and evidence based.
  - Identification of suitable comparator with a history of prior use
  - Evidence for toxicological concern of the comparator.
  - The similarity of the botanical of interest with the comparator.

Useful references:

History of safe use as applied to the safety assessment of novel foods and foods derived from genetically modified organisms; Constable, A et al, Food and Chemical Toxicology; 45 (12) (2007); 2513-2525.

A multi-criteria decision analysis model to assess the safety of botanicals utilizing data on history of use; Neely, T *et al;* Toxicology International; 18 (2011); 20-29.

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Evidence of History of Use (Exposure)

- Origin of ingredient
- Similarity of ingredient specification
- Preparation and processing similarity
- Similarity of population to be exposed especially products aimed at babies/children - comparator should have similar history of exposure
- Number of people exposed
- Pattern of use/frequency of application
- Bioavailability/Skin penetration

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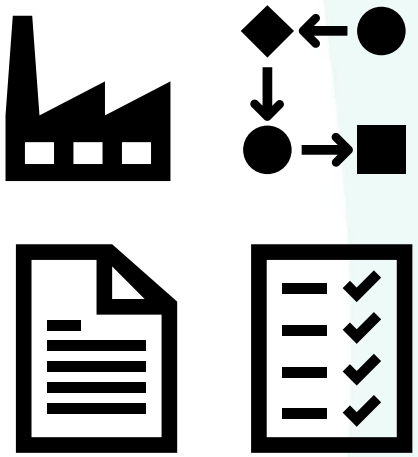
Naturally challenging

Raw Material Identification

e.g. Which Ginseng?
American, Korean,
Chinese, Indian….

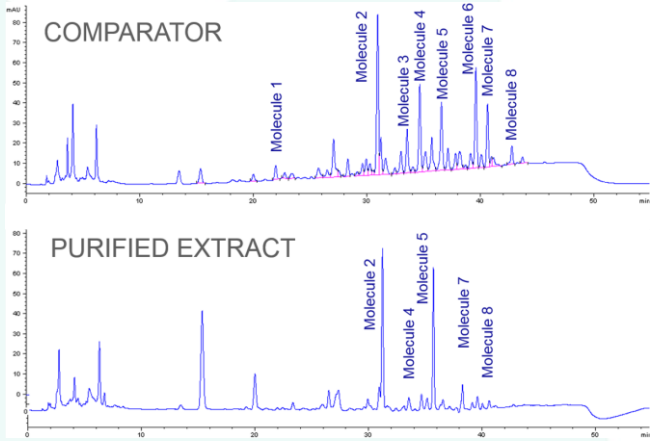
Specification control

- Processing
- Marker compounds
- Mass balance?



Chemical analysis

- Fingerprinting
- Targeted quantitation



Control of sample variation: Natural plant variation, Geographical, Seasonal, Age…

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Evidence for Concern (Hazard)

- Toxicology data
- High Concern: Reproductive or developmental toxicity, mutagenicity, neurotoxicity or any organ toxicity, data showing skin sensitization (type IV allergy), type I allergy, skin carcinogenicity, phototoxicity effects
- Chemical components of concern
- High concern: known skin sensitisers, photoallergens, proteins….
- Biological effects/mechanism of action
- Evidence of adverse effects in man (Information from literature review or existing clinical data)

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Case Study: Green tea in skin cream

Green tea in skin cream

- Green tea (Camelia sinensis)
- Traditionally drunk as a hot beverage – some history of topical use
- Large amount of historical oral consumption information
- The primary chemical components are polyphenols
- Request was for green tea extract to be included in a leave on skin product
- History of Safe Use approach used

Information Gathering

Criteria	Response for green tea	Evidence
Origin of ingredient	Identical to traditional/comparator	*Camelia sinensis* leaves used. Harvested in SA Asia for tea production
Similarity of specification	Almost the same	Fingerprint and quantitative assessment of components confirms similar specification
Preparation and processing	Almost the same	Aqueous extract – prepared by boiling dried leaves
Populations	Use encompasses population intended to expose e.g. healthy adult females	Evidence of topical use of green and black tea
No. of people exposed	Thousands	Evidence of topical use reported in open literature
Duration of exposure	20 years +	Evidence of topical use reported in open literature
Pattern/frequency of use	Ingested and topically applied on a daily basis	Evidence from Natural Medicines Database
Bioavailability	Not known	-
Toxicological data	Some data showing green tea extracts to cause skin sensitisation when applied topically	Literature search (numerous references)
Chemical components of concern	Catechins	Literature search (numerous references)
Biological effects/mechanism of action	Catechins may have anti-inflammatory activity	Evidence from Natural Medicines Database
Evidence of adverse effects in man	Some evidence of irritation when used at high concentrations in topical applications	Literature search (numerous references)

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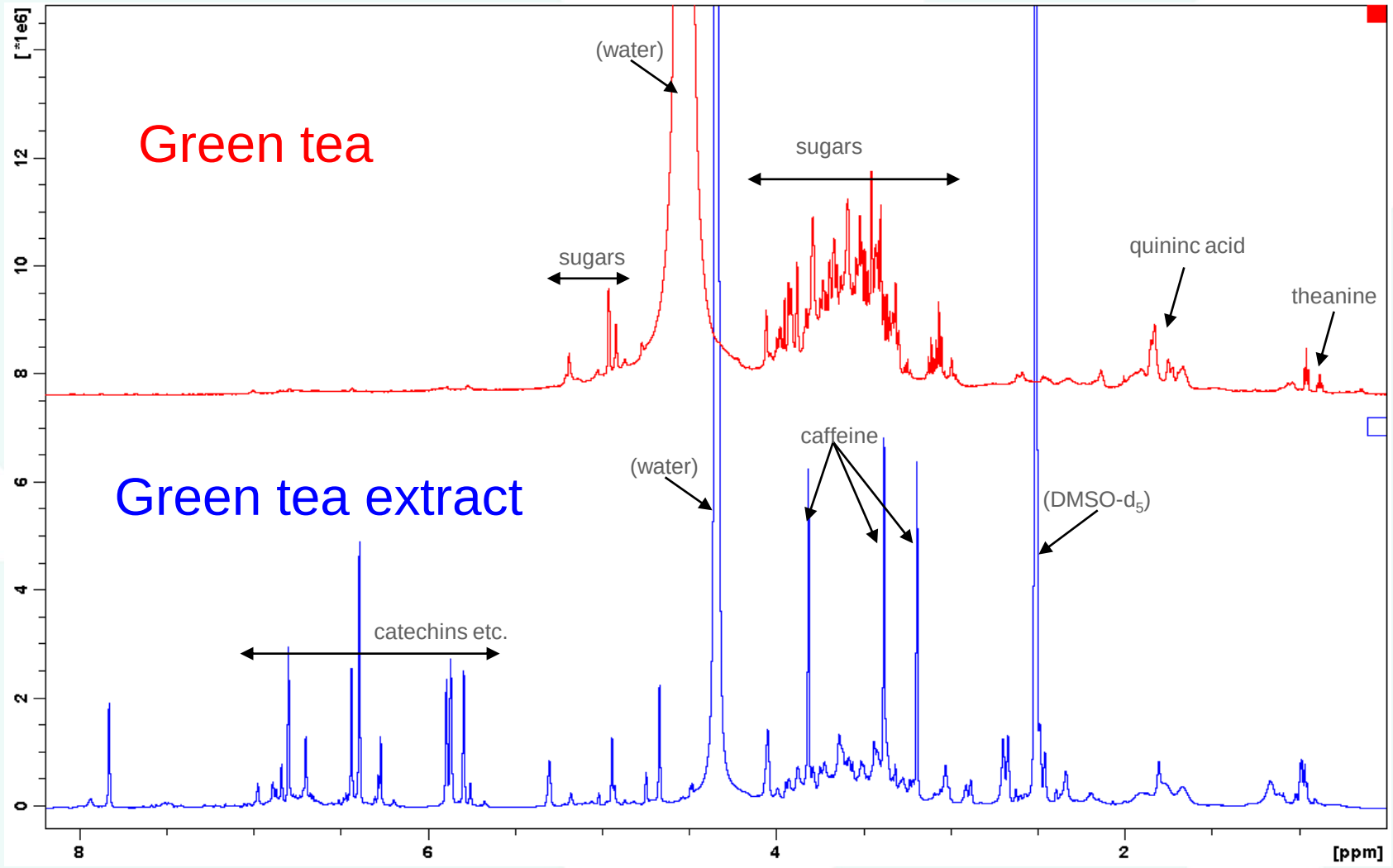
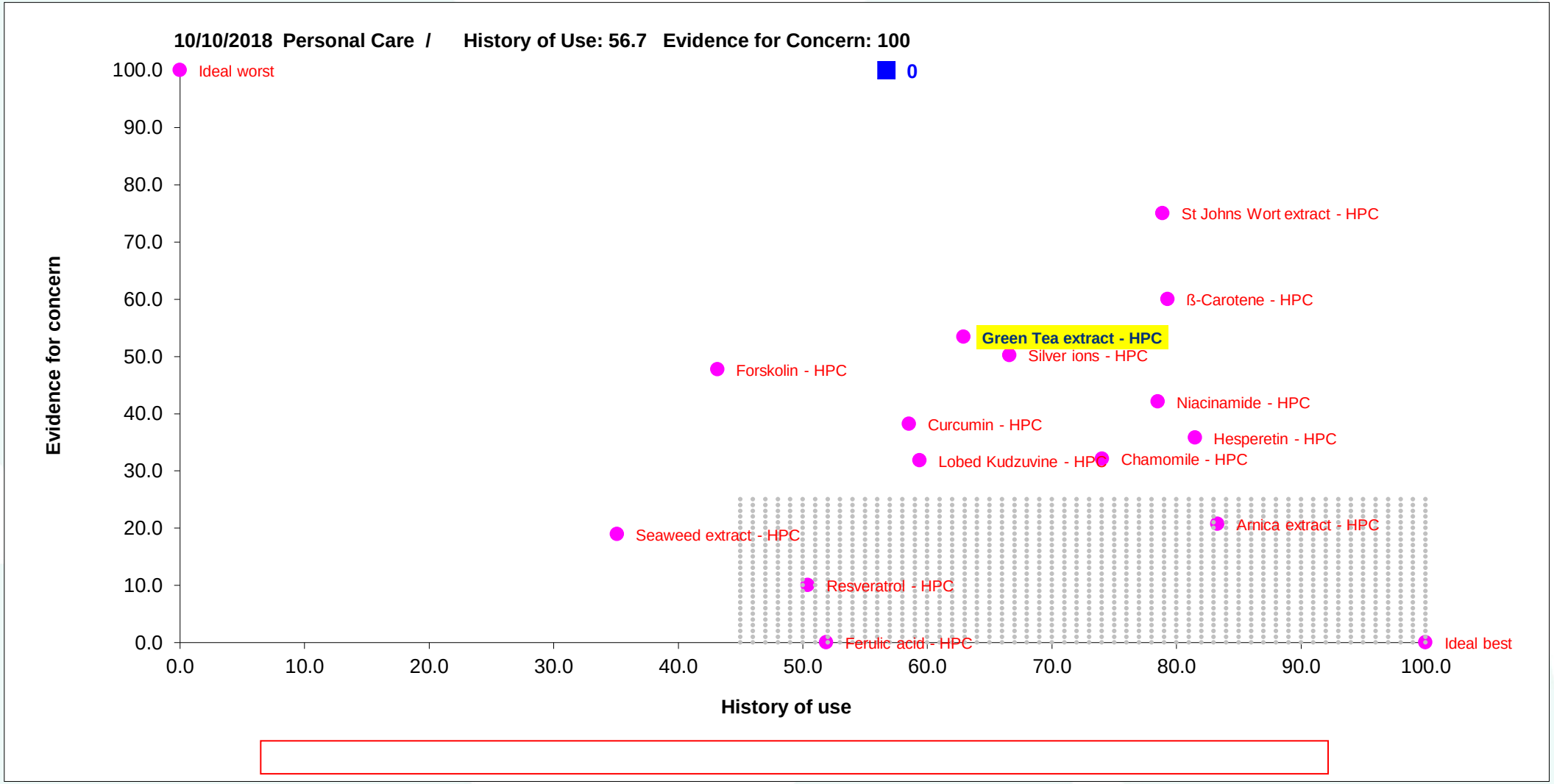
Green Tea – Composition analysis



Benchmarking the output – Unilever HoSU model



Risk assessment outcome

- Not supported for the desired use scenario based on high evidence of concern using the software tool

- Further hazard and exposure data would be required to refine the assessment
  - In vitro assays to assess sensitisation hazard
  - Skin penetration measurement/prediction

Summary

- Exposure led risk assessment is essential to confidently assess the safety of an ingredient for specific use scenarios
- History of safe use assessments use available data to inform decision making or identify next steps for refinement

For more information on Unilever's ongoing research to develop non-animal approaches to safety assessment visit www.tt21c.org

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