Safety & Environmental Assurance Centre

Laura Price, Paul Barrett, Silvia Klamert, Aline Métris

Longitudinal studies to risk assess microbiome perturbations induced by the application of cosmetics which target the microbiome

Unilever, Safety & Environmental Assurance Centre, Colworth Science Park, Sharnbrook, Bedfordshire, MK44 1LQ, United Kingdom

Background

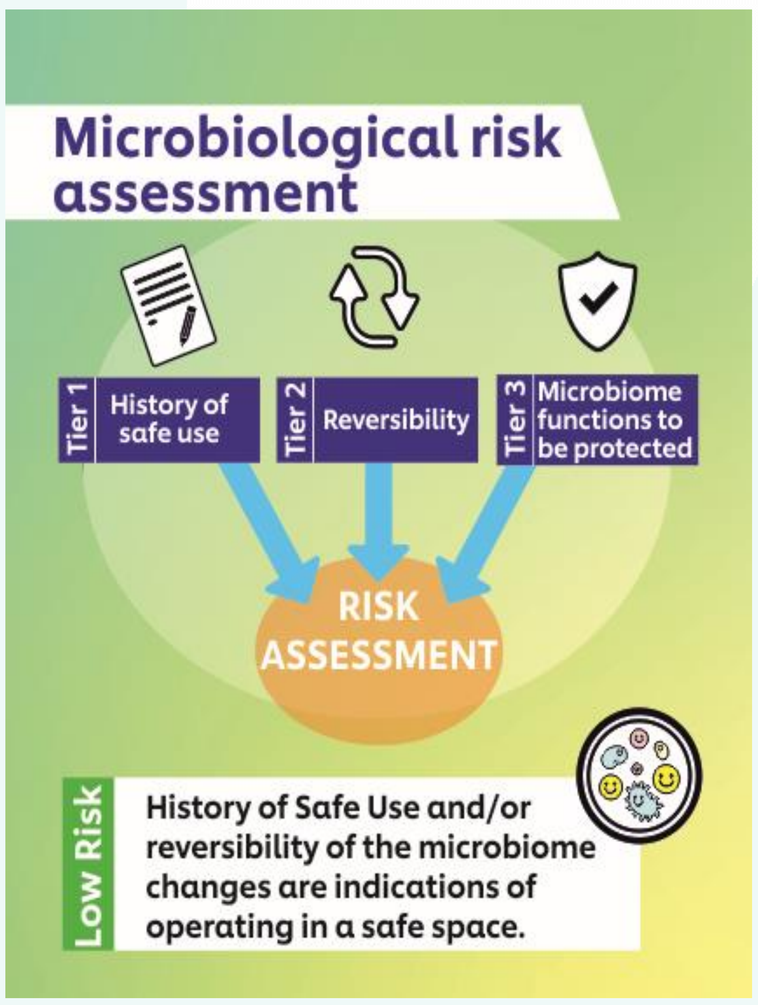
Microbiome perturbations by personal care products

- Daily intervention with personal care products can have an **impact on the skin and oral microbiomes**[1] via antimicrobials, phage and prebiotics / probiotics. These may have a broad spectrum of activity or be designed to impact a specific genus or species (e.g. anti-dandruff technologies).
- The microbiome has a function in **protecting the host** through immune modulation and preventing colonisation by pathogens etc.

Safety of microbiome perturbations: Microbiological Risk Assessment

- We propose a **3-tiered risk assessment decision framework** to assess the likelihood of a detrimental microbiome shift by application of a personnel care product targeting the microbiome[2].
- When no history of safe use is available, **longitudinal studies** are underpinning the science to assess the safety of microbiome shifts.

Framework



Tier 1 History of safe use

Can be used when there is a prolonged and safe history of exposure to an active, e.g. several years of market data, in a similar product, or as a benchmark for comparative assessment of novel products[2,3].

★ For novel products clinical data (exposure to levels at in use concentration) are required.

Tier 2 Reversibility

Can be used as a precautionary principle to test that short-term intervention does not permanently modify the microbiome[4,5,6].

★ Samples are taken before, during and after treatment in a longitudinal study and checked for microbiome returning to the pre-treatment state.

Tier 3 Microbiome functions to be protected

When no reversibility is seen in a Tier 2 clinical, Tier 3 may be used to characterise the nature of the change (taxa and/or functional capacity) to inform a safety decision. The health consequences of microbiome dysbiosis are currently not well characterised. There is a need to develop understanding of the key microbiome functions that need to be protected to ensure safety.

★ To investigate time-related notions, such as resistance to invasion and resilience to perturbations, longitudinal studies using Next Generation Sequencing and -omics data are required.

Future research & Conclusions

Longitudinal studies challenges

- Interpersonal variation
- Lack of publicly available data with quality metadata for large scale analysis
- Integration of different sequencing and analysis approaches e.g. meta-transcriptomics, metabolomics
- Characterisation of host-microbe interactions

For the first time, we propose incorporating microbiome data as part of a tiered approach for the risk assessment of these products.

Future Research

More research based on Next Generation Sequencing and -omics technologies is required to understand the endpoints of microbiome dybiosis (e.g. which functions are to be protected for resilience and resistance to colonisation with undesired species)

Metris et al., Microbial Risk Analysis, 2021

Proposed developments

- Functions rather than taxa for a more mechanistic understanding and potentially decrease interpersonal variability
- Metadata harmonisation between clinical studies to facilitate meta-analysis
- Development of in-silico methods to integrate functions from different sequencing and analysis approaches
- Use of in-vitro systems to benchmark technologies and characterisation of host-microbe interactions

See related Poster: Sangha, J., *et al.* *In vitro* model to study the effect of sugar on *S. mutans* in an oral community.

References
[1]McBain, A. J., O'Neil, C. A., Amezquita, A., Price, L. J., Faust, K., Tett, A., Segata, N., Swann, J. R., Smith, A. M., Murphy, B., Hoptroff, M., James, G., Reddy, Y., Dasgupta, A., Ross, T., Chapple, I. L., Wade, W. J and Fernandez-Piquer, J. Consumer Safety Considerations of Skin and Oral Microbiome Perturbations, *submitted*.
[2]Metris, A., Barrett, P., Price, L., Klamert, S., Fernandez-Piquer, J. (2021). A tiered approach to risk assess microbiome perturbations induced by application of beauty and personal care products. https://doi.org/10.1016/j.mran.2021.100188
[3]Neely, T., B. Walsh-Mason, P. Russell, A. V. Horst, S. O'Hagan and P. Lahorkar (2011). A multi-criteria decision analysis model to assess the safety of botanicals utilizing data on history of use *Toxicology International* 18(1): 20-29.
[4] SanMiguel, A. J., Meisel, J. S., Horwinski, J., Zheng, Q., Bradley, C. W., & Grice, E. A. (2018). Antiseptic Agents Elicit Short-Term, Personalized, and Body Site–Specific Shifts in Resident Skin Bacterial Communities. *Journal of Investigative Dermatology*, 138(10), 2234-2243.
[5]Oh, J., Byrd, A. L., Park, M., Kong, H. H., Segre, J. A., & NISC Comparative Sequencing Program. (2016). Temporal stability of the human skin microbiome. *Cell*, 165(4), 854-866.
[6] Saville, C. R., Metris, A., Humphreys, G. J., O'Neill, C., Barrett, P., Fernandez-Piquer, J., McBain, A. J., (submitted). Transitory Shifts in Skin Microbiota Composition and Reductions in Bacterial Load and Psoriasin following Ethanol Perturbation.