The Cosmetics Europe Systemic Toxicity Task Force has led the Pharmacology Profiling project, which aims to provide a screening approach using in vitro binding and enzymatic assays to identify potential bioactivities of cosmetic-relevant chemicals. This approach is based on the knowledge that several targets of pharmacological interest have been linked to human adverse drug reactions (ADRs), and the screening of these has helped the Pharma industry in identifying drug candidates, as well as off-target and potential adverse effects. In a feasibility study, a set of 100 cosmetics relevant chemicals will be profiled in the assays to develop a benchmark dataset. The aim of this work is to contribute to a practical, initial resource for Next Generation Risk Assessment (NGRA) to inform a possibly relevant systemic toxicity Mode of Action (MoA) of the cosmetic ingredient. Here, we describe the selection of chemicals and targets.

1. Target candidates with possible safety liabilities
   - Set reactions systemic genotype hepatic
   - Chemicals producing only local effects (off CMR)
   - Filter according to time/dose response
   - Select a set of 100 target chemicals

2. Literature curation based on in vivo and clinical evidence
   - Mechanism-based linkages of targets to established toxicities
     - Tissue expression
     - Pharmacological promiscuity, evidence from Eurofins
     - Cross-reactivity within

3a. Mechanism-based linkages of targets to established toxicities (AOPs)
   - How is the tissue expression profile related to frequently reported adverse reactions and pathological effects?
   - Toxicity pathways - are there any well-established AOPs associated with the target?
   - Is there high homology and reported cross-reactivity within the subfamily (e.g. Carbamoyl Ashbyhase, Dopamine receptors 62, 63, Q1, kinases, etc.)

3b. Questions to quality target
   - How is the function expression profile related to frequently reported adverse reactions and pathological effects?
   - Toxicity pathways - are there any well-established AOPs associated with the target?
   - Is there high homology and reported cross-reactivity within the subfamily (e.g. Carbamoyl Ashbyhase, Dopamine receptors 62, 63, Q1, kinases, etc.)

4.-250 cosmetic-relevant chemicals
   - Preparations, fragrances, hair dye, UV Filters, masking agents, conditioners, buffers, antioxidants
   - Wide range of physiological properties and organ toxicities

5. Benchmark chemical selection criteria
   - Include:
   - Chemicals with NOAEL and LOAEL values
   - Study duration >34 days, unless no data available otherwise
   - Preference for 50-day studies over a cancer bioscore
   - First preferred but in e.g. not: if available
   - Near-normal data preferred over in-vitro cases
   - Include chemicals with ToxCast data
   - Include e.g. hair dye included for the systemic, not local effects
   - Positive controls (drugs) used in toxicogenomics assays
   - Only chemicals (previously in skin assays) considered

6. Benchmark chemical safety tests
   - Initial test at 10 ml normal concentration
   - When activity observed, potency quantified in follow-up dose-response testing

8. Testing of benchmark chemicals in target assays
   - The ideal of 83 target assays will be used to complement other data streams used in NGRA. These include in silico MoA tools to assess Structure Activity Relationships and support real work, as well high Throughput Transcriptional (HTT) to assess biological effects in cells in vitro.

9. Next Steps
   - The result of 83 target assays will be to complement other data streams used in NGRA. These include in silico MoA tools to assess Structure Activity Relationships and support real work, as well high Throughput Transcriptional (HTT) to assess biological effects in cells in vitro.