EXPLORATION OF DRUG-INDUCED MITOCHONDRIAL TOXICITY MECHANISMS ON HEPATIC MITOCHONDRIA AND CULTURED CELLS

INTRODUCTION
The ability to predict systemic toxicity is becoming increasingly important for the Cosmetic Industry, particularly in the context of the ban on animal testing. The screening of legacy data showed that the liver was the organ potentially affected by such ingredients upon systemic exposure (Vinken et al. 2012).

Assuming that mitochondrial dysfunction plays a key role in this toxicological outcome, we initiated a study with Mitologics to check whether their MiToxView® platform could be helpful for assessing general toxicity (acute and/or chronic).

OBJECTIVE OF THE STUDY
• To explore mitochondrial toxicity potential of 6 reference compounds, known hepatotoxics covering different mechanisms of actions (Table 1, Jennings et al. 2014)
• To evaluate at which extent such data can be helpful for the early assessment of general toxicity associated with new cosmetic ingredients
• Part A: evaluation of acute mitochondrial toxicity using HepaRG mitochondria
• Part B: evaluation of long term/metabolites mitochondrial toxicity using HepaRG cell line

REFERENCES
• P Jennings et al, SEURAT-1 liver gold reference compounds: a mechanism-based review, Arch Toxicol (2014) 88:2099–2133
• P Rustin et al, Biochemical and molecular investigations in respiratory chain deficiencies, Clin Chim Acta (1994) 228: 35-51

MATERIAL AND METHODS

RESULTS

CONCLUSION
• Full profiling performed for 6 reference compounds
• Promising results obtained:
  • Possibility of getting mechanistic information
  • Possibility of anticipating long term effect
  • Frationale by Porceddu et al. (ie, mitochondria-toxic drug when EC20 ≤ 100xCmax for at least 1 parameter), good correlation with reported human effect

FUTURE DIRECTIONS
Towards a more cost-biased model to extend both cost economy & test events
Towards a testing strategy for screening purposes