A Next Generation Risk Assessment Case Study for Coumarin in Hypothetical Cosmetic Products


1. Introduction

Next Generation Risk Assessment (NGRA) is an exposure-led, hypothesis-driven risk assessment approach that integrates New Approach Methodologies (NAMs) to assure safety without the use of animal testing. Over recent years several theoretical frameworks depicting a tiered and iterative approach to conducting a NGRA have been published [Berggren et al, 2017; Dent et al, 2018], although there is a lack of examples of implementation of these frameworks.

In this study we conducted a hypothetical safety assessment of 0.1% coumarin in a face cream and body lotion using only NAMs to inform a safety decision, focusing on the potential for systemic toxicity.

2. Exposure Estimation

Exposure estimates can be calculated using representative usage amounts for each product type and typical physiological data for consumers. However to facilitate comparison in vitro points of departure (PoDs) on internal consumer exposure can be estimated using Physiologically Based Pharmacokinetics (PBK) Modelling. ADME parameters were identified either from literature or from experimental data to support the creation of a PBK model for coumarin.

In this case, distributions of Cmax values were determined for both face cream and body lotion use scenarios and can be seen in Fig.2. The final output for coumarin shows possible distributions at two different clearance rates (in silico and in vitro) to visualise the impact this parameter can have on the predicted Cmax and standard deviation.

In silico tools predicted:
- Protein binding
- DNA binding
- Reactive metabolites (e.g. epoxides) predicted to be formed.
- No binding alerts for the 39 targets in MIT ellipsoid (pharmacologically relevant receptor binding predictions).

Pushchm and ToxCast databases showed:
- Coumarin was only ‘Active’ in very few assays of the ~5000 present
- Coumarin inhibited both Monamine oxidases and carbonic anhydrases at concentrations between 3 µM - 40 µM
- The AC50 values from the dose response curves of the ‘Active’ assays were used as PoDs for the MoC calculation.

3. In Vitro Biological Activity Characterisation

In vitro genotoxicity screening using 6 CFP reporter mouse embryonic fibroblasts cells spanning DNA damage, p53 activation, oxidative stress and protein damage biomarkers.

Coomassie was negative in ToxTracker, but reactive metabolite(s) could induce DNA lesions secondary to oxidative stress.

In vitro activity characterisation showed no genotoxic, no binding DNA adduct formation, no protein damage.

4. Conclusions

From the data presented above it can be concluded that Coumarin is not genotoxic, does not bind to any of the 44 SafetyScreen targets, shows low bioactivity in the test systems and does not show any immunomodulatory effects at consumer relevant exposures.

Whilst there is not yet agreement on how large a BEI should be to assure human safety, the predicted Cmax values for face cream and body lotion were at all 100 times lower than all the recorded PoDs. In conclusion, the weight of evidence suggests that the inclusion of 0.1% coumarin in these products would be low risk to a consumer.

References

Berggren et al. 2017, Computational Toxicology 4:31-44.