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Bridging the gap from external to internal exposure: use of *in silico*, PBPK and *in vitro* methods to predict the biokinetics of topically applied cosmetic ingredients

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Abstract

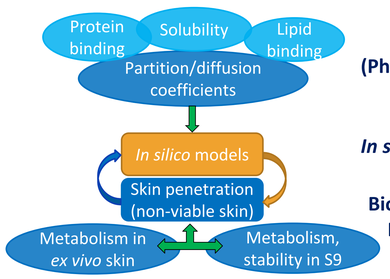
The estimation of internal exposure of a topically applied chemical from the skin surface across the skin layers and into the systemic circulation is a key step in the assessment of potential toxic effects. Input data from *in vitro* assays can be applied to physiological based pharmacokinetic (PBPK) models which are used to estimate the absorption, distribution, metabolism and excretion (ADME) of chemicals. Once an internal concentration is estimated, it can be related to known concentrations causing toxicity. Following on from this, the link between the internal exposure and the No Observed Adverse Effect Levels can then be used to develop the internal Threshold of Toxicological Concern (TTC) concept. The concept of predicting the internal exposure with only alternative methods, the development of the internal TTC concept and the aggregate exposure prediction are key parts of the CE Long Range Science Strategy that will feed into our systematic rational for safety assessment.

Introduction

Understanding the bioavailability of chemicals and fate of a chemical after exposure via different routes is key to the safety assessment of topically applied chemicals. The Cosmetics Europe ADME Task Force (TF) will therefore evaluate and develop *in silico*, *in vitro* and other alternative approaches to enable the transition from external exposure estimations to internal doses as part of the exposure assessment of cosmetic ingredients. The main route of exposure of cosmetic ingredients is via the skin; therefore, this is a priority, although alternative methods to address oral and inhalation are also being evaluated. Selected chemicals will be used in case studies in which *in vitro* and *in silico* data will be extrapolated to interpret *in vivo* exposure scenarios.

ADME LRSS Project overview

Skin bioavailability



(Physico-) chemical properties

***In silico* models**

Bioavailability & Metabolism

The "Skin Bioavailability and Metabolism" project is near to completion. In this project, up to 50 cosmetics-relevant chemicals have been tested in a number of skin relevant assays. An overview of this project is summarized in **POSTER 273**

In vitro ADME data generation

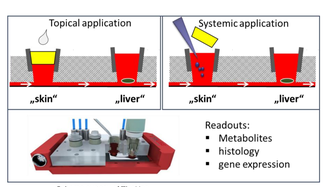
2D *in vitro* assays

An "*in vitro* ADME Toolbox" has been set up in order to generate human *in vitro* data for input into PBPK models. The Toolbox includes: solubility in different solvents, metabolic stability in human hepatic models (microsomes, S9 or hepatocytes), uptake into human hepatocytes, CYP induction, human plasma protein binding, Caco-2 permeability.

3D *in vitro* models

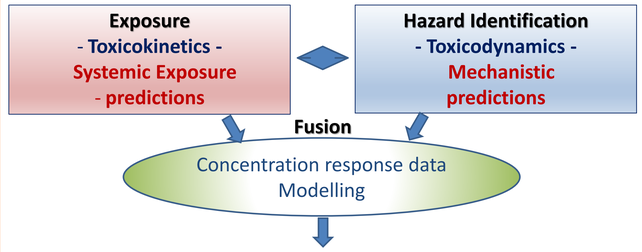
The TissUse multi-organ chip (MOC) is a dynamic, perfused tissue culture device, emulating the human biology at the smallest biologically acceptable scale. We are using the skin-liver-organ chip model to integrate important parameters such as skin penetration, skin metabolism and subsequent hepatic metabolism to help elucidate the metabolism of test chemicals after single and repeated topical and systemic application.

Schematic representation of organoid origin and their use in the MOC device Organoids are connected via microfluidic channels. The setting allows for comparative analyses of effects after topical and systemic application of compounds.



Scheme curtesy of TissUse

Our Systematic Rationale



Case Studies - as guiding principle:

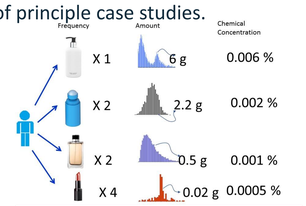
- **Concentration response data / modelling**
- **Quantitative *in vitro-in vivo* extrapolation (QIVIVE)**

Safety Assessment

Combined evaluation & extrapolation

Aggregate exposure assessment

Knowledge on realistic exposure of consumers is a key information when performing safety assessment. We will conduct a pilot study to model aggregate exposure to cosmetic-relevant chemicals using the Creme Care & Cosmetics probabilistic aggregate exposure model with detailed information collected from CE member companies. The information will be used in proof of principle case studies.

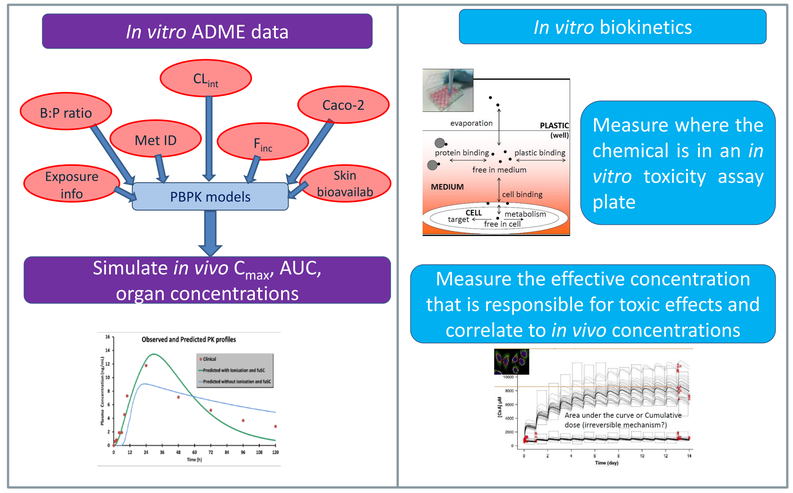


Total aggregate chemical exposure: 458 µg

Scheme curtesy of Creme Global

Predicting the internal exposure

Systemic exposure predictions (external to internal dose and route-to-route extrapolation) to facilitate safety assessment will be established using a cosmetic-relevant PBPK platform into which *in vitro/in silico* data from the ADME data repository will be integrated.



- **PBPK ADME Modeling**
- **Internal TTC: If an internal TTC can be defined by combining the internal exposure data from this work with historical NOAEL values, exposure-based waiving of toxicity data may be possible.**
- **Use in case studies: read across / *ab initio* concepts as part of safety assessment**

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