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Dynamic skin and liver co-culture to assess the effect of application routes on the metabolism of AHT

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INTRODUCTION

This project is based on the HUMIMIC Chip2 – a Multi-Organ-Chip from TissUse enabling the co-culture of skin (eg. EpiDerm™ or Phenion) and liver models (consisting of HepaRG and stellate cells) – and aims to provide information about the influence of exposure scenarios on the bioavailability and metabolic fate of chemicals. The aromatic amine hair dye, 4-amino-2-hydroxytoluene (AHT), was selected as a case study chemical to recapitulate a pre-clinical rat pharmacokinetics study.

EXPERIMENTAL DESIGN PRINCIPLES

The skin models provided by either MatTek or Henkel and liver spheroids consisting of HepaRG cells and human stellate cells were co-cultured for 6 days in the Chip2. Half medium exchange was performed every day. AHT is an ingredient in hair dyes and was therefore applied one day after inoculation of the organ models in the chip once topically on top of the skin model (mimicking a real-life scenario) or systemically into the liver compartment, resulting in a concentration of 2.5 µM in the Chip2. The dynamic co-culture continued for 5 days. Samples of the medium were taken at various time points for analysis of LDH, glucose, lactate and albumin content, as well as for quantification of parent compound and metabolites.

RESULTS

The morphology and metabolic activity of the organ models were well maintained for 6 days in the Chip2. Topical exposure resulted in a marked lower systemic concentration of the parent chemical compared to systemic application (Fig. 3). The kinetics and quantitative profiles of several AHT metabolites were altered by topical application compared to systemic application, including N-acetyl-AHT and AHT-sulfate. Importantly, there was a higher peak concentration of N-acetyl-AHT after topical (712-1376 nM) compared to systemic (370-430 nM) application, indicating that a first-pass effect in all 3 skin models had occurred. The AUC for this metabolite was also increased by up to 275% after topical exposure. In contrast to N-acetyl-AHT, the peak concentration and AUC of AHT-sulfate was lower after topical compared to systemic application.

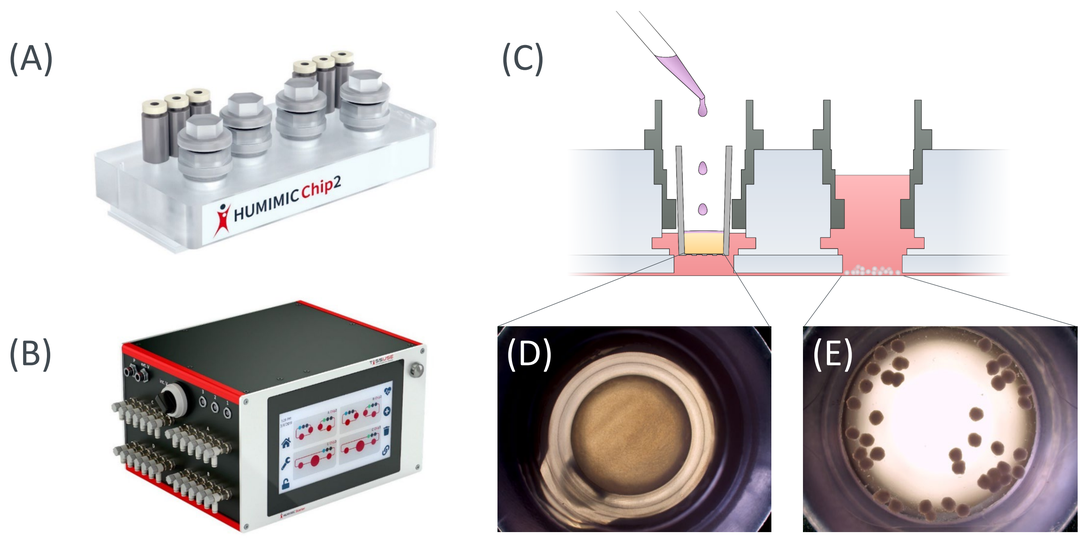

Fig. 1. (A) HUMIMIC Chip2 and (B) HUMIMIC Starter. All products are produced in-house and according to ISO EN 9001-2015 high standards **(C-E) HUMIMIC Chip2 set-up.** (C) Schematic overview of the multi-organ-combination in the Chip2. (D) EpiDermTM by MatTek in the skin compartment. (E) Liver spheroids (consisting of HepaRG cells and stellate cells) in the liver compartment.

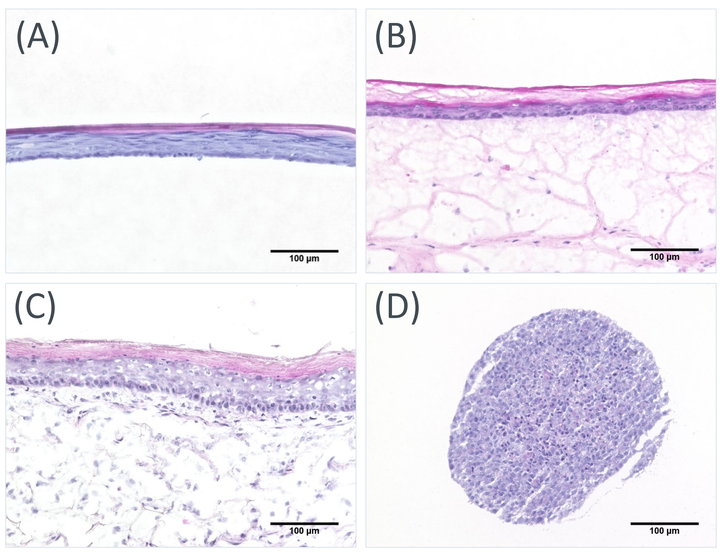

Fig. 2. Histology of the organ models used in the HUMIMIC Chip2. Hematoxylin stainings of (A) EpiDerm™ by MatTek, (B) **EpiDerm FT™ by MatTek**, (C) Phenion FT skin model by Henkel and (D) liver spheroids. Cryosections of 8 µM were used for all stainings.

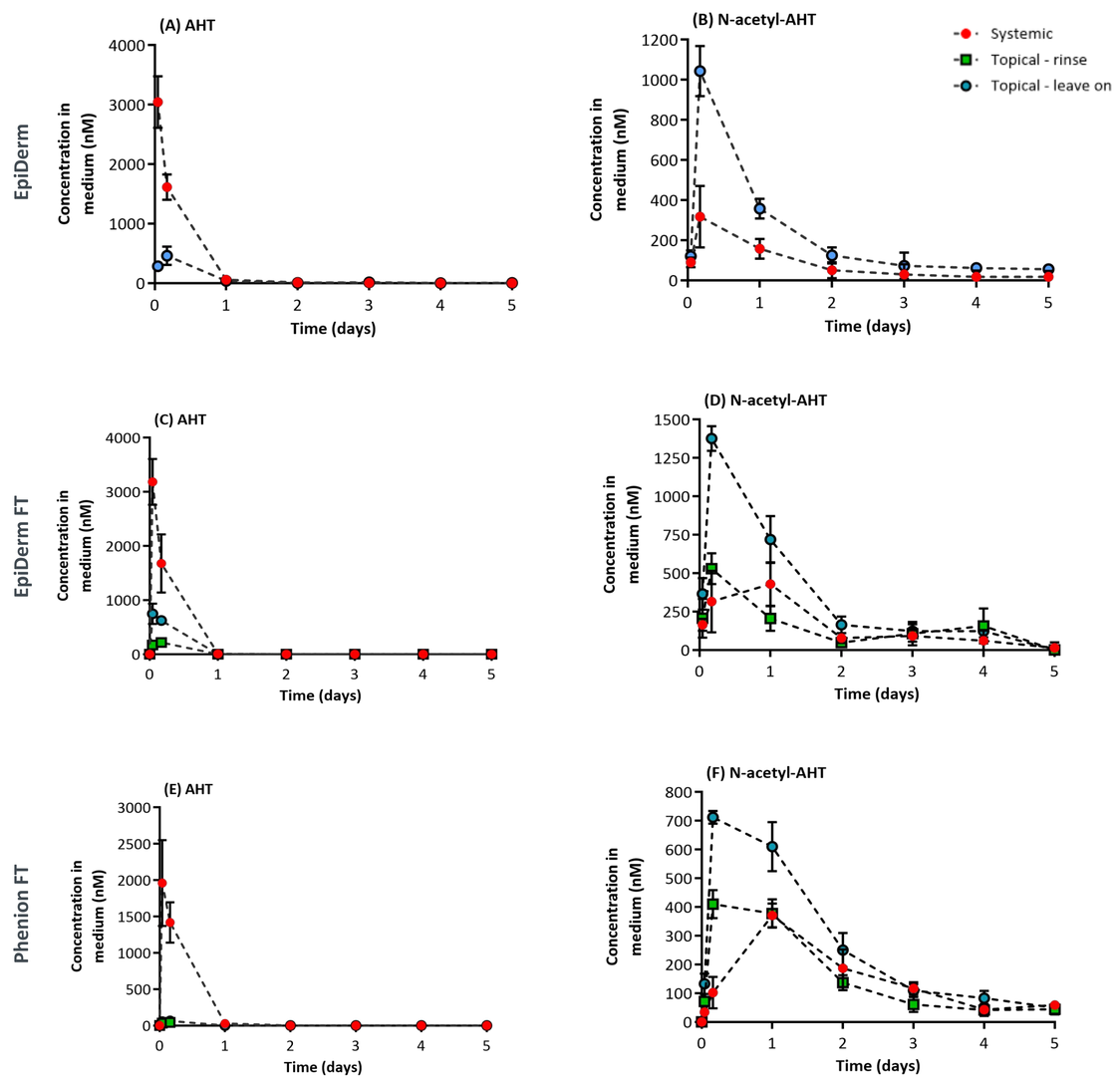

Fig. 3. Concentration of AHT (A, C, E) and N-acetylated AHT (B, D, F) in the Chip2 with 3 different skin models after systemic and topical application of 2.5 µM AHT. Values are a mean of 3 circuits ± SD starting from 1 h after application.

SUMMARY & OUTLOOK

We demonstrate that the Chip2 is able to sustain skin and liver organ models for several days and provide information about the influence of exposure scenarios on the bioavailability and metabolic fate of the cosmetics ingredient, AHT. Results of an *in vivo* rat study could be mimicked with the Chip2, indicating that this dynamic culture model can mimic *in vivo* findings.

An important aspect of the model is that consumer-relevant scenarios, such as rinsing of a hair dye after 30 minutes, can be incorporated into the experimental design.

This project is part of Cosmetics Europe´s Long Range Science Strategy (LRSS) and aims to establish biokinetic and toxicodynamic models addressing internal exposure via the dermal and systemic exposure routes. It is a promising model for inclusion in a toolbox of New Approach Methodologies (NAMs) for Next Generation Risk Assessments (NGRAs).

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