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Metabolism studies of the Phenion[®] full thickness skin model as compared to other *in vitro* models and human native skin

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The understanding of organ and species specific metabolism is essential for safety assessment to achieve biological relevant results. Skin metabolism can significantly alter the activity of topically administered substances, e.g., by converting them into harmless metabolites or genotoxic compounds. The biotransformation of a wide range of exogenous compounds is affected by several phase I and phase II enzymes. Similar to the situation in the liver the cytochrome p450 oxidases are the most important phase I enzymes in skin. In addition, a range of flavin-containing monooxygenases (FMOs) seem to play an important role in skin metabolism. However, much less is known about their regulation or substrate specificity in the dermal compartment.

As an alternative to animal testing we have developed a three-dimensional human skin model to investigate the xenobiotic metabolism of epidermis and dermis separately. Our Phenion[®] Full Thickness Skin Model consists of a dermal and an epidermal layer and thereby provides a higher physiological complexity than existing *in vitro* models. The interaction of both compartments is essential for cell differentiation and regeneration as well as xenobiotic metabolism.

To investigate the suitability of *in vitro* models with regard to human native skin we compared *in vitro* skin models with different physiological complexities, (1) the commercially available Phenion[®] Full Thickness Skin Model, (2) an alternative epidermis model, (3) monolayer cultures of fibroblasts, (4) monolayer cultures of keratinocytes and (5) human native skin. To exclude possible donor variabilities all four *in vitro* models were constructed with cells from the same donor. In addition we compared *in vitro* models from various donors to assess individual variabilities. Basal gene expression of phase I and phase II enzymes as well as the inducibility by typical model substances were evaluated with quantitative RT-PCR.

Further approaches will comprise the analysis of phase I and II enzymes on protein expression level and enzyme activity as measured by analyzing biotransformation reactions with known model compounds.

Our results demonstrate that *in vitro* skin models with rising physiological complexity mirror the native situation more realistically. This makes them an ideal tool to study questions of toxicology related to skin *in vitro*.

Keywords: human skin metabolism, skin model, cytochrome P450, flavin monooxygenase