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Defining skin xenobiotic metabolism using a combined *in vitro /in silico* approach

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Skin represents an important route of exposure and determining whether such incidental or intentional exposure poses a risk to human health requires consideration of temporal concentration, in addition to assessing the chemical's intrinsic hazard. In order to elicit a toxic response in vivo the chemical must reach its site of action in sufficient concentration, as determined by its absorption, distribution, metabolism and elimination (ADME) profile. Whilst absorption and distribution into and through skin layers have been studied for decades, only more recently has skin metabolism become a subject of intense research, now recognised as playing a key role in both toxification and detoxification processes. EU directives on animal use for toxicity testing and the lack of human skin for research has prompted an increase in the use of tissue-engineered human skin models. These models are histologically similar to human skin and express metabolising enzymes making them ideal in vitro tools for toxicity testing. In this talk, I will discuss how the use of these models in combination with in silico tools may be used to resolve a significant challenge in predicting toxicity following dermal exposure. I will highlight how in vitro data can be used to drive novel multiscale mathematical models that predict the kinetics of xenobiotic metabolising enzymes, their transdermal distribution, spatiotemporal metabolite distributions and whole body systemic exposures for a wide range of chemical structures. The ability to predict metabolism in the skin would significantly aid risk assessment and shorten the length of time from discovery to patient benefit.