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In silico prediction of skin metabolism and its implication in toxicity assessment

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ABSTRACT

Skin, being the largest organ of the body, represents an important route of exposure, not only for the abundance of chemicals present in the environment, but also for products designed for topical application such as drugs and personal care products. Determining whether such incidental or intentional exposure poses a risk to human health requires consideration of temporal concentration, both externally and internally, 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. The majority of information on metabolic processes, however, has generally been acquired via studies performed on the liver. This paper outlines strategies that may be used to leverage current knowledge, gained from liver metabolism studies, to inform predictions for skin metabolism through understanding the differences in the enzymatic landscapes between skin and liver. The strategies outlined demonstrate how an array of *in silico* tools may be used in concert to resolve a significant challenge in predicting toxicity following dermal exposure. The use of *in vitro* methods for determining skin metabolism, both to provide further experimental data for modelling and to verify predictions is also discussed. Herein, information on skin metabolism is placed within the context of toxicity prediction for risk assessment, which requires consideration of both exposure and hazard of parent chemicals and their metabolites.

1. Introduction

Human skin is continually exposed to an abundance of diverse chemicals present in the environment, home, workplace or in products directly applied to the skin surface. Chemicals responsible for incidental exposure include industrial chemicals, pollutants, household or industrial cleaning and fragrancing products. Intentional exposure via skin occurs as a result of the application of personal care products, cosmetics or topical drug formulations. The ability of a chemical to elicit toxicity in humans, or indeed in any organism, is governed by three factors: (i) the intrinsic hazard of the chemical (or transformation product thereof); (ii) the potential for external exposure i.e. the presence of the chemical in the environment or in a topically applied product; and (iii) the ability of the chemical (or its transformation products) to reach its site of action in the body at adequate concentration. Knowledge of these three factors is essential in performing risk assessment, however, to obtain such information for all chemicals of interest via empirical testing would not be economically or practicably feasible nor would it be ethically responsible in terms of animal use. The application of alternative methods in evaluation of chemicals, or in risk assessment, is therefore essential. Whilst predictive toxicology has been used to address these issues for many years, metabolism has

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often proved to be a confounding factor that requires specific or inherent incorporation into the modelling process. Complications can arise in model building where it is the transformation product, rather than the parent molecule, that is responsible for the activity. Problems arising from metabolic activation and the presence of reactive metabolites, particularly following oral drug administration, are now well recognised and this has led to greater interest in predicting the identity of metabolites and their rate and extent of formation. Although it is known that the majority of organs possess metabolic capability, metabolism studies have predominantly focused on the liver - the main organ of metabolism and of key importance following oral exposure. As the skin is one of the most important routes of exposure, it is now recognised that predicting metabolism in skin is essential to obtaining accurate predictions of potential toxicity or activity (e.g. in the case of topical drug administration). There are several differences to consider between oral and dermal routes and incidental versus intentional exposure to chemicals. These factors include: frequency and duration of application or ingestion; concentration of the chemical; enzyme expression at the site of exposure or site of distribution; and the ease of uptake or distribution from the site. Notably, skin has evolved to provide a barrier function whereas the gastro-intestinal tract is designed for the uptake of essential nutrients. Also, toxicity testing has traditionally involved (relatively) high concentration, acute, oral dosing, whereas use of personal care products is generally a low dose, long term application. A wealth of information now exists relating to oral absorption and liver metabolism, this includes information on uptake, rate and extent of metabolite formation, metabolite identity, enzymes responsible and their expression. It is now possible to leverage this important data and apply it to predictions of skin uptake and metabolism, providing appropriate adjustments are made. Such adjustments need to take account of differences in exposure scenarios, uptake potential and enzyme expression / activity levels. This paper identifies various sources of information and *in silico* tools that may be applied to predicting skin metabolism and potential toxicity following dermal exposure. How the knowledge acquired from the application of these *in silico* tools can be put together in an overall predictive strategy is discussed, as well as the importance of incorporating further data from *in vitro* studies for modelling and verification purposes.

2. Skin metabolism in the context of toxicity prediction

Many factors determine the likelihood of a chemical eliciting local or systemic toxicity following dermal exposure. The significance of skin metabolism has increasingly been recognised and whilst this forms the focus of this paper, other aspects must also be considered in order to place the role of metabolism in context. Fig. 1 shows the numerous elements governing the potential to elicit toxicity and where skin metabolism fits within this overall scheme.

As illustrated in Fig. 1, a wide range of data types are required in order to reach an informed decision. Fortunately, there are many *in silico* tools, and other data sources, that may be leveraged to fill the gaps in knowledge relating to uptake, metabolism and potential toxicity of chemicals following dermal exposure. Leveraging such information can also lead to the development of more robust models, particularly where experimental data can be used to develop improved models and verify predictions in an iterative process.

Historically, data have predominantly been accumulated following oral administration to test subjects or obtained from *in vitro* liver assays. This has led to a wealth of information being generated, albeit for an alternative exposure scenario. Table 1 lists the potential data sources that could be used to fill gaps in

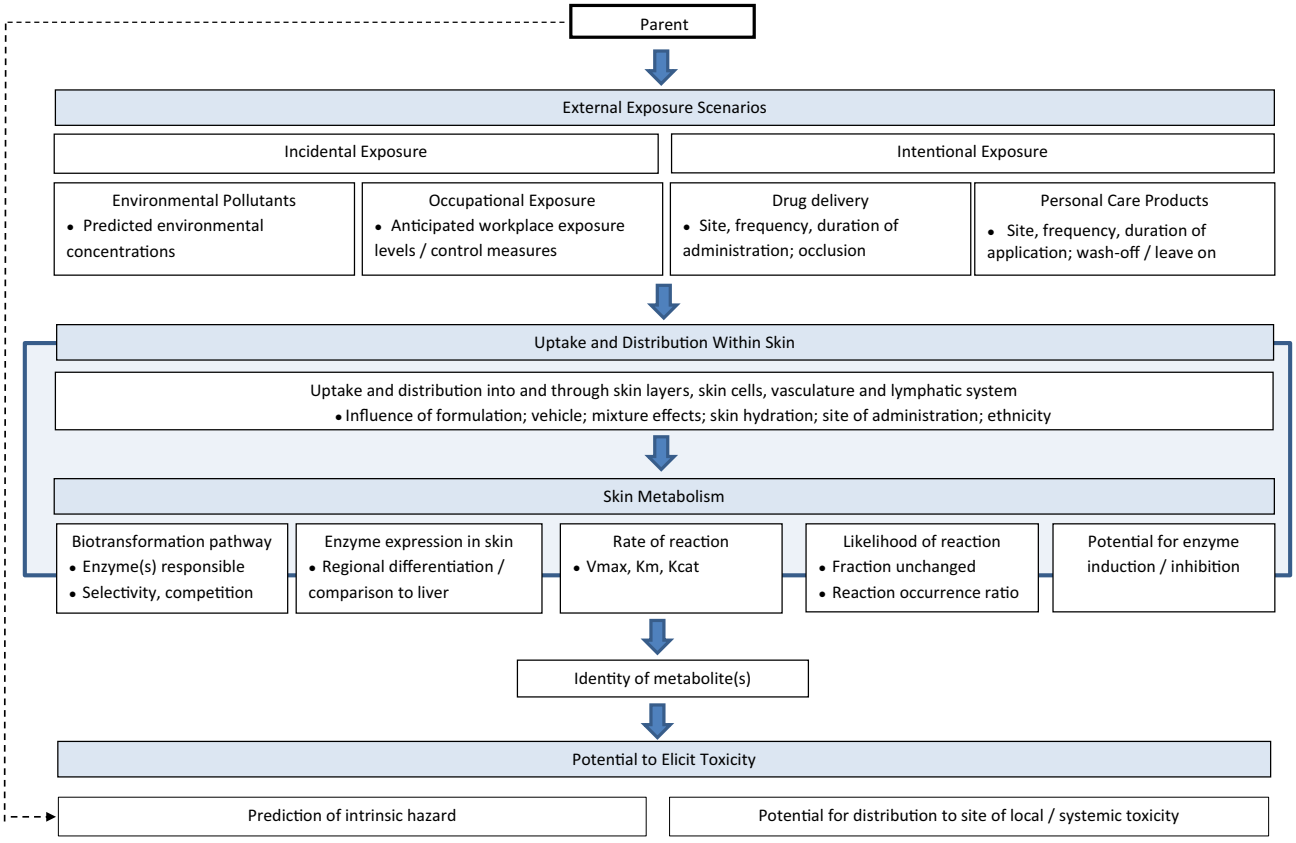

Fig. 1. Factors that govern the potential for a parent or metabolite to elicit toxicity and types of data required to aid prediction.