Dermal absorption of chemicals through normal and compromised skin

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Conclusions and recommendations
The results presented in this thesis, considered in the context of those achieved within the EDETOX project, help in focusing the scope of needed investigations and in defining our recommendations.

**We strongly encourage performance of human volunteer studies**

The present studies showed that well designed human *in vivo* experiments are a valuable tool for assessment of dermal absorption. They use a physiologically and metabolically intact system, and no inter species extrapolation is needed. The preference for alternative methods, such as *in vitro* measurements, *in vivo* animal studies or predictive mathematical modelling, over human *in vivo* studies is usually argumented by ethical and practical considerations. However, recent methodology and sensitive measurement techniques allow for exposures at concentration levels which are far below current occupational exposure limits. Although we recognize that human volunteer studies are laborious, the value and necessity of *in vivo* human data more than compensates for it.

**In vivo studies should be designed in such a way that absorption kinetics rather than systemic dose is derived**

Most *in vivo* methods are based on measurement of total systemic absorption yielding only average dermal absorption rate into the skin. This might be sufficient for practical purposes, e.g. for biological monitoring (BM) of occupational exposure. Realising that skin absorption is a time dependent process, these data are poorly translatable to other exposure scenarios and are not suitable for evaluation of alternative methods, such as *in vitro* or mathematical predictive models. Determination of dermal absorption rate as a function of time by using, e.g. mathematical (de)convolution, should be preferred. As shown in the study on 2-butoxyethanol, this approach enables determination of detailed dermal kinetics including permeability coefficient, maximum skin flux and lag time. These absorption parameters are needed for human risk assessment and allow direct comparison with *in vitro* data and predictive mathematical models.
Conclusions and recommendations

Additional work is needed to enable reliable determination of recovery before the microdialysis technique becomes suitable for wider application

Although microdialysis is a complex and relatively invasive technique, it showed its potential in studying influence of the vehicle on dermal absorption of a chemical. Additionally, as demonstrated in the presented study on 2-butoxyethanol, metabolism occurring in the skin can be measured by this technique without interference from the systemic compartment. However, assessment of recovery i.e. the proportion of the chemical that was recovered in the dialysate relative to the amount penetrated through the skin, remains one of the main problems of this technique.

Further research is needed in evaluation of the tape stripping technique with emphasis on standardization and development of a valid and feasible method for measurement of stratum corneum thickness

Tape stripping is a relatively non-invasive and simple technique for determination of dermal absorption, and it is not surprising that the interest in this technique is growing in the area of cosmetics, pharmaceuticals, and risk assessment. The value of this technique is in the fact that it measures diffusion coefficient and partition coefficient separately, which showed to be advantageous in studying absorption mechanism. However, at present there are no approved guidelines and the used procedures are poorly standardised. In addition, the measurement of the stratum corneum thickness is very error prone, which is a problem as it is essential for proper data analysis.

There is a need for further investigations of the effect of vehicle formulation and mixtures on absorption

Data on dermal absorption are usually obtained from studies with neat chemicals. As demonstrated in the study on 2-butoxyethanol, even a small addition of water to the application solution enhanced absorption of 2-butoxyethanol dramatically. Since in occupational settings and everyday life the skin is usually exposed to chemical mixtures, further research is necessary to understand the mechanism by which chemical mixtures affect dermal absorption.
Conclusions and recommendations

There is a need for more in vivo data on dermal absorption of chemicals in damaged and diseased skin.

Data on dermal absorption through damaged skin in humans in vivo are missing. The studies on percutaneous penetration of two model chemicals demonstrated altered skin barrier in patients with atopic dermatitis even on the skin sites visibly not affected by disease. Higher dermal absorption was also demonstrated in the skin damaged by sodium lauryl sulphate. Compromised skin not only increases absorption, but would facilitate entrance of larger molecules such as proteins which normally would not be able to pass through the skin. This emphasizes the importance of continuous skin protection and maintenance of the skin barrier. Since a compromised skin barrier due to environmental damage or skin disease is not uncommon we would strongly encourage more studies on dermal absorption of compromised skin. The extent of dermal absorption is not only important for systemic effects, but as shown in this study, permeability of the skin plays an important role in the individual susceptibility to local skin effects of chemicals.

Due to lack of data on dermal absorption of chemicals and insufficient knowledge about the factors which influence this process, the setting up of quantitative exposure limits for dermal exposure is not possible yet.

For chemicals which are substantially absorbed through the skin, when possible, biological monitoring should be performed

The study on 2-butoxyethanol showed that systemic absorption due to dermal exposure can be substantial and may exceed the inhalation route which is traditionally seen as the most important entry route for chemicals in occupational setting. As long as there are no occupational exposure limits for skin exposure, when available, biological monitoring should be used. Sampling strategy by development and implementation of biological monitoring in occupational settings should take into account the differences between dermal and inhalation kinetics.