Samenvatting proefschrift

Dermal absorption of chemicals through normal and compromised skin

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Understanding and quantifying dermal absorption of chemicals and identifying factors which govern this process is necessary for assessment of human health risk.
The project described in this thesis aimed at *(1)* generating *in vivo* human data by using different methodology and *(2)* investigating factors which govern absorption processes.

Dermal absorption was assessed for the following model chemicals: 2-butoxyethanol (BE), sodium lauryl sulphate (SLS) and polyethylene glycol oligomers (PEG) ranging in molecular weight from 150 to 590 Da. Due to its excellent lipophilic and hydrophilic properties, BE is a frequently used solvent in industry and household, and information on the percutaneous absorption of this chemical in humans *in vivo* is limited. SLS is an anionic surfactant which is a common constituent of detergents and soaps and dermal exposure to this chemical in everyday life is frequent. SLS is a potent skin irritant, and the extent of absorption might therefore contribute to the extent of irritation. PEG is a polymer frequently used in intestinal and corneal permeability research. The advantages of PEG as a model compound include its availability in a wide range of molecular weights and the fact that the solubility of individual oligomers is not confounded by the molecular weight.
Among factors which may affect the extent and rate of dermal absorption we investigated *(1)* the influence of water as a vehicle on dermal absorption of BE, *(2)* the influence of molecular size of PEGs on dermal absorption and *(3)* the role of skin condition in the absorption of SLS and PEGs in the skin of atopic dermatitis (AD) patients and in the absorption of PEGs in the skin compromised by SLS.

Dermal absorption of 2-butoxyethanol

One study describes the assessment of dermal absorption of BE by using two different methods: biological monitoring (BM) and microdialysis (for explanation see further). Using BM method, dermal absorption of neat BE, 90 % and 50 % aqueous solution of BE was determined by measuring the concentration of BE in blood and of its major metabolite 2-butoxyacetic acid (BAA) in urine after dermal exposure and after inhalation exposure, the latter serving as a reference dosage. The average dermal absorption rates of neat, 90 % and 50 % aqueous solutions of BE as determined from the 24-hour excretion of BAA in urine amounted to 0.26 ± 0.17, 0.92 ± 0.60 and 1.34 ± 0.49 mg cm^{-2} h^{-1}. More detailed dermal kinetics could be deduced from the time course of BE concentration in blood. Using the linear system dynamics method based on mathematical (de)convolution, the dermal absorption rate as a function of time was obtained. This enabled us to calculate the maximal absorption rate and the permeability coefficient. These two parameters are important because they are used for comparison with *in vitro* assays. In addition, mathematical predictive models are based on permeability coefficients. The permeability coefficients of 50% and 90% aqueous solutions of BE were 1.75 ± 0.53 x 10^{-3} cm h^{-1} and 0.88 ± 0.42 x 10^{-3} cm h^{-1}, respectively. The permeability coefficient of neat BE could not be determined because the concentrations of BE in blood were under the detection limit of the analytical method.
Microdialysis showed to be a useful technique for determination of dermal absorption kinetics. In this study, semi permeable microdialysis probe was inserted in the dermis under the exposed skin site, in parallel to the skin surface. This probe was continuously perfused with physiological solution and dialysate was collected at regular intervals for the analysis of BE. Although the respective permeability coefficients for 50% and 90% aqueous solutions of BE of 6.1 ± 2.2 x 10^{-3} cm h^{-1} and 2.5 ± 2.3 x 10^{-3} cm h^{-1} were higher than the values obtained by BM method, the enhancing effect of water was consistent in both studies. The microdialysis technique showed to be suitable for studying skin metabolism without interference from the systemic compartment. The dermal metabolism seemed to be low, the amount of BAA was approximately 1 % of the amount of BE in the same dialysate.
BE is readily absorbed through the skin and the results showed that dermal absorption of BE from water solution is increased markedly compared to neat BE. Even water addition as low as 10% led to an approximate four-fold increase in absorption rates. *These findings are important for health risk assessment of occupational exposure to BE, since BE is commonly used in mixtures containing water. The dermal uptake of aqueous solutions of BE was substantial: assuming a 60- minute skin contact of an area of 1000 cm2, the dermal uptake would be four times higher than the pulmonary uptake of an 8-hour exposure at the occupational limit value for BE. The results clearly justify the introduction*

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of a skin notation for BE.
To explore the applicability of BAA as a biological indicator of exposure to BE we studied the excretion pattern of free and conjugated BAA after both inhalation and dermal exposure to BE. The results revealed high intra- and inter-individual variation in conjugation of BAA varying from 2-100% of total excretion. The use of only free BAA as indicator of exposure in present BM programs will therefore lead to erroneous estimation of the internal dose. Since conjugation changes with time, the time and duration of sampling would influence the outcome. The result of our study indicated total BAA, due to lower inter-individual variability, as a superior biomarker of exposure over free BAA.

Dermal absorption of chemicals through compromised skin

The absorption of model chemicals was determined in normal and compromised skin by means of the tape stripping technique. After end of exposure the whole SC was removed subsequently by adhesive tapes on which the amount of the chemical was determined. The penetration parameters, i.e. diffusion coefficient and partition coefficient, were determined by best-fit regression of the concentration of SLS or PEGs as a function of relative SC depth using an approach based on Fick's second law of diffusion. In healthy subjects the diffusion coefficient for SLS was 6.2 ± 3.0 x 10^{-9} cm2 h^{-1} and for PEGs it ranged from 1.9 ± x 10^{-9} (590 Da) to 8.4 ±x 10^{-9} cm^2 h^{-1} (150 Da). The partition coefficient was 196 for SLS and it ranged from 1.66 (150 Da) to 1.87 (590 Da) for PEGs. Patients with atopic dermatitis (AD) showed increased trans-epidermal water loss (TEWL): 8.4 ± 4.3 g m^{-2} h^{-1} compared to 6.3 ± 2.0 g m^{-2} h^{-1} in controls. Given the similar SC thickness in both groups this implicates a less effective barrier for water. The diffusion of both SLS and PEGs through uninvolved AD skin was enhanced, being twice as high as through normal skin, while the partition coefficient between the SC and water was 30 % and 50 % lower, respectively. The observed enhanced diffusion and lower partitioning tended to be more pronounced in patients with active AD compared to those with inactive AD. This indicates that state of disease influences permeability of the skin which is visibly not affected by AD.

Absorption of PEGs into the SC was also investigated in the skin compromised by SLS. The SLS pre-treatment caused moderate barrier impairment: the TEWL increased from 6.3 to 17.9 g m^{-2} h^{-1}. The skin compromised by SLS showed both an increased diffusion and partitioning of PEGs into the SC.
As expected, the diffusion of PEGs decreased with the MW in normal skin, skin of AD patients and in SLS-compromised skin. The gradual decrease of diffusion with increasing molecular weight is in agreement with recent findings that hydrophilic chemicals show less strong dependence of diffusion on the molecular weight than lipophilic chemicals. This might support existence of two different transport pathways through the SC for hydrophilic and lipophilic chemicals.
The partition coefficient showed no MW dependence in normal and AD skin; however, in the skin compromised by SLS the partitioning showed an unexplained increase with increasing MW.
These studies, are the first to have experimentally shown in vivo that the barrier for chemicals other than water is altered in the visibly not affected skin of AD patients.

(opmerking van de redactie: de samenvatting van het proefschrift is door de redactie iets ingekort)