

Interpretation of results from *in vitro* dermal penetration studies

Extract from: Technical Guidance Document in Support of Risk Assessment

In vitro dermal absorption studies

In vitro dermal absorption studies should preferably be performed according to OECD guideline 428 (OECD 2000c,d). Although *in vitro* studies using various methods with respect to e.g. the type of diffusion cell and the skin membrane used are increasingly being submitted, there is still debate over the way in which *in vitro* data could or should be used in risk assessment. Recently, an evaluation of available data on *in vitro* dermal absorption was performed under auspices of the OECD (OECD, 2000a). Because the available studies, comparing *in vitro* and *in vivo* test results, contained too many variables (different species, thickness and types of the skin, exposure duration, vehicles, etc.), evaluation of *in vitro* test methods by means of data available from public literature appeared to be difficult (OECD, 2000a). A major issue of concern relating to *in vitro* methods was the presence of test substance in the various skin layers, i.e., absorbed into the skin but not passed into the receptor fluid. It was noted that it is especially difficult to examine very lipophilic substances *in vitro*, because of their low solubility in most receptor fluids. By including the amount retained in the skin *in vitro*, a more acceptable (but probably conservative) estimation of skin absorption can be obtained. Alternatively, this issue can be addressed by conducting additional *in vitro* or *in vivo* studies. Water-soluble substances can be tested more accurately *in vitro* because they more readily diffuse into the receptor fluid (OECD, 2000a). At present, provided that skin levels are included in the overall percentage absorption figure, results from *in vitro* methods seem to adequately reflect those from *in vivo* experiments supporting their use as a replacement test to measure percutaneous absorption. Preferably, *in vitro* studies should include reference compounds to increase the confidence of the results (see OECD, 2000d).

Other measures of dermal absorption that can be derived from *in vitro* dermal absorption studies are the (maximum) flux and the permeability coefficient (K_p). The maximum flux (defined as the (maximum) mass of test chemical passing through a unit area of skin per unit of time (in $\mu\text{g}/\text{cm}^2/\text{h}$) and calculated from the linear part of the absorption vs. time curve) at relevant exposure levels can be used for semi-quantitative comparison of absorption of chemicals between species, between compounds within one species, and between different vehicles within one species. In this regard, it is important to realise that *in vitro* studies give relative results, i.e. that they should in first instance be compared with results generated within the same test system at comparable and relevant test conditions. If appropriate dermal penetration data are available for rats *in vivo*

and for rat and human skin *in vitro*, the *in vivo* dermal absorption in rats may be adjusted in light of the relative absorption through rat and human skin *in vitro*. The latter adjustment may be done because the permeability of human skin is often lower than that of animal skin (e.g., Howes et al., 1996). A generally applicable correction factor for extrapolation to humans can however not be derived, because the extent of overestimation appears to be dose, substance, and animal specific (Bronaugh and Maibach, 1987; ECETOC, 1993).

The permeability coefficient (K_p) is a value (in cm/h) that represents the rate at which a chemical penetrates the skin. This is calculated from the flux divided by the applied concentration (OECD, 2000d). Because, by definition, the permeation constant (K_p in cm/hr) is established at infinite dose levels, the usefulness of the K_p for dermal risk assessment is limited.