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Solid-phase microextraction as a universal tool for quantitative in vitro-to-in vivo extrapolation studies

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Reducing and eventually replacing animal tests by *in vitro* bioassays requires the quantitative extrapolation of effect data generated with *in vitro* test systems to whole organisms (quantitative in vitro-to-in vivo extrapolation, QIVIVE). QIVIVE models usually compare the nominal effect concentrations of the chemicals in the *in vitro* bioassays with total plasma concentrations *in vivo*. However, other dose metrics have been suggested that account for differences in bioavailability of the chemicals *in vitro* and *in vivo* due to different composition of e.g., cell culture media and human plasma. A better comparison is possible if freely dissolved concentrations in the assay medium ($C_{free,medium}$) and in plasma ($C_{free,plasma}$) are used. In this study we want to demonstrate that solid-phase microextraction (SPME), a widely used sample preparation technique, can support QIVIVE studies in many different aspects. SPME has been applied in previous studies to determine partitioning in diverse biological phases from bovine serum albumin and phospholipid liposomes to complex matrices like cell culture media and plasma. In two recent studies from our group, we could demonstrate that SPME cannot only generate partitioning data that are required as input parameters for prediction models for $C_{free,medium}$ and $C_{free,plasma}$ but can also be used for the time-resolved experimental determination of $C_{free,medium}$ in cell-based *in vitro* bioassays and to the determine $C_{free,plasma}$ in plasma samples from different species. We found that $C_{free,medium}$ in *in vitro* test systems can be several orders of magnitude lower than the nominal concentration (C_{nom}) and was not necessarily linearly related to C_{nom}. In human plasma $C_{free,plasma}$ was lower than $C_{free,medium}$ at the same C_{nom}, which can be explained by the fact that human plasma has more proteins and lipids than commonly used cell culture media. By comparing $C_{free,plasma}$ determined in human and trout plasma we found similar values for neutral and basic chemicals, but differences of several orders of magnitude for several acidic chemicals. The results of these two studies emphasise again the need to account for bioavailability for successful QIVIVE and that SPME may be used as a universal experimental tool that improves our understanding on how chemicals distribute *in vitro* and *in vivo*.