

Poster: 0192

## **Development of Dermal Uptake Pharmacokinetic Models for Solvents in Rats**

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Dermal exposures and subsequent percutaneous absorption of solvents and other chemicals can be a critical exposure route in occupational settings. However, in silico predictive methods do not generally provide an accurate estimate of absorption when compared to dermal studies which have demonstrated that dermal exposures can be a significant contributor to total absorbed dose. Physiologically based pharmacokinetic (PBPK) models allow both the estimation of internal dose from a dermal exposure and the calculation of equivalent dose levels across dosing routes, since many chemicals have more significant oral or iv data sets. Dermal exposures to both lipophilic and hydrophilic chemicals were conducted in F344 rats with uptake measured via exhaled breath to allow detection of rapid concentration changes. Exposures were conducted by placing a set amount of test compound, either neat or in an aqueous formulation, into a sealed chamber secured to the back of the rat and monitoring exhaled breath concentrations from the animal in a gas uptake chamber for approximately three hours. Exposures were conducted for acetone, ethyl benzene, styrene, methyl ethyl ketone (MEK) and methyl n-butyl ketone (MnBK). Exposures were run with neat test material, in aqueous vehicle, or both neat and aqueous depending on solubility. All exposures were repeated at least three times and experiments with leaking test chambers were discarded.

The concentration of acetone peaked at approximately 10-20 minutes while styrene and ethylbenzene were still increasing at the end of the three hour exposures. Total dermal absorption was found to increase with styrene>ethyl benzene>MEK>MnBK>acetone. Dermal exposure routes were added to existing pharmacokinetic models for acetone, ethyl benzene, styrene and MEK. Additional exposures (oral, intraperitoneal and gas uptake) were conducted as the basis for constructing a model for MnBK. In addition, a single standardized model structure was constructed to allow for simple direct comparison of the test chemicals. The percutaneous absorption data and the PBPK model constructs allow a quantitative assessment of the risk from dermal exposures and an improvement in the occupational safety assessments of solvents.

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