

Sapphire News

Quantitative Risk Analysis for N-Methyl Pyrrolidone using Physiologically Based Pharmacokinetic and Benchmark Dose Modeling.

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Establishing an occupational exposure limit (OEL) for N-methyl pyrrolidone (NMP) is important due to its widespread use as a solvent. Based on studies in rodents, the most sensitive toxic endpoint is a decrease in fetal/pup bodyweights observed after oral, dermal, and inhalation exposures of dams to NMP. Evidence indicates the parent compound is the causative agent. To reduce the uncertainty in rat to human extrapolations, physiologically based pharmacokinetic (PBPK) models were developed to describe the pharmacokinetics of NMP in both species. Since in utero exposures are of concern, the models considered major physiological changes occurring in the dam or mother over the course of gestation. The rat PBPK model was used to determine the relationship between NMP concentrations in maternal blood and decrements in fetal/pup body weights following exposures to NMP vapor. Body weight decrements seen after vapor exposures occurred at lower NMP blood levels than those observed after oral and dermal exposures. Benchmark dose (BMD) modeling was used to better define a point of departure (POD) for fetal/pup body weight changes based on dose-response information from two inhalation studies in rats. The POD and human PBPK model were then used to estimate the human equivalent concentrations (HEC) that could be used to derive an OEL value for NMP. The geometric mean of the PODs derived from the rat studies was estimated to be 350 mg*hr/L (expressed in terms of internal dose), a value which corresponds to a HEC of 480 ppm (occupational exposure of 8 hours/day, 5 days/week). The HEC is much higher than recently-developed internationally-recognized OELs for NMP of 10 ppm to 20 ppm, suggesting that these OELs adequately protect workers exposed to NMP vapor.