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Proposed Occupational Exposure Limits for Select Ethylene Glycol Ethers Using PBPK Models and Monte Carlo Simulations

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Methoxyethanol (ethylene glycol monomethyl ether, EGME), ethoxyethanol (ethylene glycol monoethyl ether, EGEE), and ethoxyethyl acetate (ethylene glycol monoethyl ether acetate, EGEEA) are all developmental toxicants in laboratory animals. Due to the imprecise nature of the exposure data in epidemiology studies of these chemicals, we relied on human and animal pharmacokinetic data, as well as animal toxicity data, to derive 3 occupational exposure limits (OELs). Physiologically based pharmacokinetic (PBPK) models for EGME, EGEE, and EGEEA in pregnant rats and humans have been developed (M. L. Gargas *et al.*, 2000, *Toxicol. Appl. Pharmacol.* 165, 53–62; M. L. Gargas *et al.*, 2000, *Toxicol. Appl. Pharmacol.* 165, 63–73). These models were used to calculate estimated human-equivalent no adverse effect levels (NAELs), based upon internal concentrations in rats exposed to no observed effect levels (NOELs) for developmental toxicity. Estimated NAEL values of 25 ppm for EGEEA and EGEE and 12 ppm for EGME were derived using average values for physiological, thermodynamic, and metabolic parameters in the PBPK model. The uncertainties in the point estimates for the NOELs and NAELs were estimated from the distribution of internal dose estimates obtained by varying key parameter values over expected ranges and probability distributions. Key parameters were identified through sensitivity analysis. Distributions of the values of these parameters were sampled using Monte Carlo techniques and appropriate dose metrics calculated for 1600 parameter sets. The 95th percentile values were used to calculate interindividual pharmacokinetic uncertainty factors (UFs) to account for variability among humans ($UF_{h,pk}$). These values of 1.8 for EGEEA/EGEE and 1.7 for EGME are less than the default value of 3 for this area of uncertainty. The estimated human equivalent NAELs were divided by $UF_{h,pk}$ and the default UFs for pharmacodynamic variability among animals and among humans to calculate the proposed OELs. This methodology indicates that OELs (8-h time-weighted average) that should protect workers from the most sensitive adverse effects of these chemicals are 2 ppm EGEEA and EGEE (11 mg/m^3 EGEEA, 7 mg/m^3 EGEE) and 0.9 ppm (3 mg/m^3) EGME. These recommendations assume that dermal exposure will be minimal or nonexistent.

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