

Sapphire News

Ethyl Acrylate Risk Assessment with a Hybrid Computational Fluid Dynamics and Physiologically Based Nasal Dosimetry Model.

Lisa M. Sweeney¹, Melvin E. Andersen², and Michael L. Gargas¹

¹ The Sapphire Group, Dayton, OH

² CIIT Centers for Health Research, Research Triangle Park, NC

Cytotoxicity in the nasal epithelium is frequently observed in rodents exposed to volatile organic acids and esters by inhalation. An interspecies, hybrid computational fluid dynamics and physiologically based pharmacokinetic (CFD-PBPK) dosimetry model for inhaled ethyl acrylate (EA) is available (Frederick et al., *Toxicol. Appl. Pharmacol.* 152:211-231, 2002) for estimating internal dose measures for EA, its metabolite acrylic acid (AA), and EA-mediated reductions in tissue glutathione (GSH). Nasal tissue concentrations of AA were previously used as the dose metric for a chronic Reference Concentration (RfC) calculation with this compound. However, EA was more toxic than expected based on calculated tissue AA concentrations. Unlike AA, EA causes depletion of tissue GSH. We have developed an RfC for EA using tissue GSH depletion in the olfactory epithelium as the primary measure of nasal tissue dose. The hybrid CFD-PBPK model was refined to improve the accuracy of simulations for GSH in rat olfactory tissues. This refined model was used to determine the concentration for continuous human exposures to EA predicted to reduce nasal GSH levels to the same extent as seen in rats exposed to EA at the no-observed-effect level (NOEL). Importantly, AA concentrations in the human nasal olfactory epithelium at the proposed chronic RfC were predicted to be lower than the AA concentrations estimated in the rat at the NOEL. Thus, a chronic RfC based on maintaining GSH in the human nasal olfactory epithelium at levels equivalent to the rat NOEL would also provide an adequate margin of safety with respect to AA concentrations in nasal tissues.