

Evaluation of the Carcinogenic Mode of Action for Tetrachloroethylene and Proposal for an Occupational Exposure Limit

Tetrachloroethylene (PCE) is classified by the United States Environmental Agency (US EPA) as "likely to be carcinogenic in humans," based primarily on evidence of increased liver tumors in mice. Evidence of an association between PCE exposure and cancer in humans is inadequate or limited at best, with few studies showing positive associations, and for those studies that do, exposure estimates are lacking and/or confounded by exposure to other potential carcinogens. The metabolism of PCE yields multiple metabolites through two main pathways: (1) the "oxidative pathway" *via* cytochrome P450 metabolism, and (2) the "glutathione (GSH) conjugation pathway" *via* GSH transferase activity. PCE and its main oxidative metabolite (trichloroacetic acid [TCA]) exhibit little, if any, genotoxicity. The GSH metabolites (trichlorovinyl glutathione [TCVG] and *S*-trichlorovinyl-L-cysteine [TCVC]), however, have been shown to be genotoxic. In 2012, US EPA derived a cancer toxicity value for PCE human health risk assessment based on liver tumors in mice and an assumption that oxidative metabolism is the primary pathway for PCE metabolism in mice. In this analysis, the basis of the US EPA-derived PCE toxicity value was evaluated, including the associated scientific literature describing toxicity, epidemiology, and possible modes of action for PCE carcinogenesis in mice and relevance to humans, and the dose-response assessment conducted by US EPA. The bases of several state (Massachusetts, Minnesota, and California) and international (Canada and Denmark) agency PCE cancer toxicity values were also evaluated. Based on this analysis, a carcinogenic mode of action for PCE is proposed that involves a non-genotoxic threshold associated with oxidative metabolism of PCE to TCA. An occupational exposure limit (OEL) for PCE that is consistent with the proposed mode of action is also recommended and compared to several agency-derived OELs for PCE. The results of this evaluation provide support for the application of several existing PCE OELs (*i.e.*, American Conference of Governmental Industrial Hygienists [ACGIH] threshold limit value [TLV], and the European Commission Scientific Committee on Occupational Exposure Limits [SCOEL] OEL) for cancer risk evaluation of workers exposed to PCE. This analysis should provide useful information for consideration by US EPA as it conducts its risk evaluation of PCE under the new Toxic Substances and Control Act (TSCA).