2025 SOT Annual Meeting & ToxExpo
Session: Risk Assessment II
Poster: P751
Tuesday, March 18, 2025
9:15 AM – 11:45 AM

GRADIENT

Evaluation of US EPA's Proposed Rule for the Occupational Use of Carbon Tetrachloride and Proposal for a Revised Occupational Exposure Value

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Background and Purpose: Carbon tetrachloride (CTC) is classified by the United States Environmental Protection Agency (US EPA) as "likely to be carcinogenic to humans," based on evidence of increased liver and adrenal tumors in mice. In 2021, under the Toxic Substances Control Act (TSCA), US EPA derived a proposed chronic cancer occupational exposure value (OEV) for CTC (0.03 ppm), applying CTC toxicity reference values determined from mouse liver and adrenal tumor data as described in the final risk evaluation for CTC. Subsequently, in 2023, US EPA released its Proposed Rule for CTC that incorporated the proposed chronic cancer OEV. However, US EPA's proposed cancer OEV was not derived using methodology recommended in its own technical and methodological guidance or used in its prior derivations of CTC toxicity reference values (*e.g.*, physiologically based pharmacokinetic [PBPK] and benchmark dose [BMD] modeling); therefore, the proposed OEV is arguably not consistent with the best available science, as is mandated by TSCA. In its derivation of the CTC OEV based on liver tumors, US EPA applied the lowest observed adverse effect concentration (LOAEC)/no observed adverse effect concentration (NOAEC) approach, rather than PBPK and BMD modeling approaches, and also did not consider total liver tumors (*i.e.*, adenomas and carcinomas combined). In addition, US EPA derived an OEV based on mouse adrenal tumors; the relevance of rodent adrenal tumors to humans is considered highly uncertain. In this analysis, a revised cancer OEV for CTC was derived based on mouse liver tumors, using BMD and CTC-specific PBPK modeling approaches, and in conjunction with US EPA's technical guidance for derivation of toxicity reference values. Using these PBPK and BMD modeling approaches, a revised non-cancer OEV for CTC was also derived.

Methods: Using the total female mouse liver tumor data from the same study as US EPA (Nagano *et al.*, 2007), CTC-specific mouse PBPK models were used to estimate the internal dose of CTC in the liver based on the mean rate of CTC metabolism. BMD modeling of the internal dose metrics was then used to derive $BMDL_{10}$ values, which were converted to human equivalent concentrations (HECs) using interspecies conversion factors derived from CTC-specific human PBPK models. A total uncertainty factor (UF) of 30 was applied to the resulting liver tumor point of departure (POD) to account for differences between animals and humans (UF_A of 3) and for variation in sensitivity within human populations (UF_H of 10), with the subsequent value converted to account for human occupational exposure, resulting in a proposed revised liver cancer OEV for CTC. The use of PBPK and BMD modeling eliminated the need for additional uncertainty factors. Modified UFs were also considered, based on a healthy worker population (UF_H of 5) and an adjusted pharmacodynamic UF_A of 1.5. The UF_A adjustment is based on the fact that the CTC-specific PBPK models account for liver metabolism across species, and liver metabolism is a key step in the mode of action for CTC liver toxicity and tumor formation. Applying a similar approach to liver toxicity data from the same study (Nagano *et al.*, 2007), a non-cancer OEV for CTC was also derived.

Results: The proposed revised OEV for CTC, based on application of BMD and CTC-specific PBPK modeling approaches, is 50-fold higher than that proposed by US EPA. In comparison to other agency values, the proposed revised OEV for CTC is generally consistent with the National Institute for Occupational Safety and Health (NIOSH) recommended exposure limit (REL) for CTC of 2 ppm, but still

below the Occupational Safety and Health Administration (OSHA) permissible exposure limit (PEL) for CTC of 10 ppm and the American Conference of Governmental Industrial Hygienists (ACGIH) threshold limit value (TLV) for CTC of 5 ppm.

Conclusions: Based on the overall application of the best available science for CTC, including CTC-specific PBPK and BMD modeling, a proposed revised CTC OEV was derived that is more consistent with the current NIOSH REL and more achievable for worker compliance. This analysis should be considered by US EPA as it seeks to finalize the Proposed Rule for CTC under TSCA.