Joel M. Cohen, Sc.D., DABT
Brad C. Hansen

2019 SOT Conference
Poster: Computational Toxicology II
Tuesday March 12, 2019
9:15AM-4:30PM

Looking Under the Hood – Expert Review of *in silico* Carcinogenicity Predictions.

Alternative testing strategies are seeing increased application in chemical safety assessments across a variety of contexts. However, predictive toxicology tools should not be used as a "black box," and limitations including "out of domain" results (i.e. no valid prediction can be made) require expert review to make informed hazard and risk conclusions. We evaluated the in silico carcinogenicity predictions for three perfluorinated compounds [Tetradecafluorohexane; CAS 355-42-0], [Hexacosafluorododecane; CAS 307-59-5], and [Perfluoro(1,3-dimethylcyclohexane); CAS 335-27-3] using the freely available Toxtree program as well as the expert-rule based program Derek Nexus. We then applied expert review to the Toxtree program's assessment of chemical structure and carcinogenic potential. The two perfluorinated alkane chemicals triggered an alert for perfluorooctanoic acid (PFOA), in spite of evidence indicating these compounds are relatively unreactive, and the fact these compounds lack any oxygen or hydroxyl functional groups typical of PFOA compounds. Furthermore, this alert was triggered for a series of six additional perfluorinated alkanes (C7-C10, C20 and C25) suggesting that these results are attributable to their common C6F11 substructure. The perfluorinated aryl compound triggered an alert as a polyhalogenated cycloalkane. This alert was triggered for any halogenated aryl with three or more halogens bonded directly to the ring. Yet, neither the supporting mechanistic justification for this specific alert nor the available training data set considered perfluorinated cycloalkanes. Evaluation of these same compounds with the expert-rule program Derek Nexus did not trigger any alerts for carcinogenicity. These findings support our conclusions that the Toxtree carcinogenicity predictions for these three perfluorinated compounds are inaccurate, and highlight the importance of expert review in the application of in silico toxicology tools. The structural alerts we considered for the in silico assessment of these three chemicals have the potential to overgeneralize perfluorinated compounds and propose unlikely toxicological mechanisms.