2024 SOT Annual Meeting & ToxExpo
Session: Medical Devices
Poster: P484
Monday, March 11, 2024
9:15 AM – 11: 15 AM

Application of a 3D QSAR Approach for the Re-Evaluation of Organophosphorus Compounds for Cohort of Concern Identification

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Toxicological risk assessment within a risk management framework (ISO 10993-17:2023) of medical device chemical characterization data permits the use of a threshold of toxicological concern (TTC) limit for non-cohort of concern (CoC) compounds as defined by ISO/TS 21726:2019. Organophosphorus (OP) compounds (OPCs) are identified as a CoC per ISO/TS 21726, which can be broadly defined by any chemical with phosphorus containing groups bound to an organic backbone. Broadly defined OPCs were included in the CoC list based on known organophosphate neurotoxicity related to acetylcholinesterase (AChE) inhibition (AChEi) *via* irreversible phosphorylation at the catalytic site. To determine if this broadly defined OPC structural-alert system appropriately predicts AChEi, a two-tiered computational screening approach was utilized on a chemical test set selected from an exaggerated extractable chemical characterization study using an indirect blood path contacting medical device. The test set OPCs were analyzed for predicted probability for ligand bioactivity to AchE using SwissTargetPrediction *via* comparison to 370,000 known bioactive molecules and their physicochemical properties and Tanimoto coefficient similarity. A subset of OPCs, which generally contained phosphate moieties, were also identified to have low probability to have bioactivity with AChE. These compounds were then subjected to a validated three-dimensional (3D) decision framework to analyze docked conformations as described by Lee *et al.* (2016). AutoDock Vina 4 docking simulations were conducted with the predicted subset of OPs against AChE (PDBD: 5HF5), which identified favorable binding affinity interactions at the esteric site (-4 to –5.5 kcal/mol), oxyanion hole (-4.1 to -6.1 kcal/mol), and acyl pocket (-4.4 kcal/mol). Accordingly, the oxyanion hole and hydrogen bonding are a critical interaction for AChE and later inhibition at the esteric site, which was confirmed using paraoxon as a positive control that predicted esteric and oxyanion hole interactions with highly favorable binding affinities (-7.4 to -6.1 kcal/mol). Non-phosphate OPCs, such as triphenylphoshine oxide, also demonstrated favorable binding affinity to AChE, but not at locations with known bioactivity. Based on these data and literature, groups prone to hydrolysis reactions, such as phosphate, are most probably to have relevant AChEi activity. Therefore, these data suggest that refinement to the ISO/TS 21726 CoC assignment for OPCs should be considered with respect to specific structural alerts relevant to AChEi or the establishment of separate TTCs for OPCs based on structural features.