Integrated Approach for Testing and Assessment for Developmental Neurotoxicity (DNT) to Prioritize Aromatic Organophosphorus Flame Retardants

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Organophosphorus flame retardants (OPFRs), used as replacements for brominated flame retardants (BFRs), have become compounds of concern over their developmental neurotoxic (DNT) potential. This concern is due to their structural similarities to organophosphate pesticides, which have known harmful DNT outcomes, and their abundance in the environment. However, limited toxicity testing exists on the DNT potential of OPFRs due to the challenges associated with the traditional in vivo DNT guideline testing. Recently, an in vitro battery (IVB) consisting of assays that evaluate cellular processes in neurodevelopment and function was developed to enhance DNT assessment. We supplemented this DNT-IVB by including additional DNT endpoints and mechanisms not covered in the battery. To translate in vitro bioactivity into human exposure-relevant metrics, we performed physiologically based toxicokinetic (PBTK) modeling to relate human exposure to plasma concentration. We collected additional data from the Integrated Chemical Environment (ICE; https://ice.ntp.niehs.nih.gov/) and literature to determine if these DNT-IVB assays provide sufficient mechanistic coverage to prioritize chemicals for further testing. We evaluated eight aromatic and halogenated OPFRs and benchmarked them against two BFRs with known DNT potential. DNT battery data revealed that the aromatic OPFRs had similar concentrations and potency to the BFRs. Additional in vitro data suggested potential mechanisms involving endocrine disruption that warrant further investigation. Furthermore, results from PBTK modeling revealed that human exposure to some OPFRs could result in plasma concentrations comparable to in vitro bioactivity concentration, suggesting safety concerns for human health. Project was funded by the NIEHS under Contract No. HHSN273201500010C.