Generating Screening Level Developmental Neurotoxicity (DNT) Information of Chemicals in a New Approach Methods (NAMs) Battery

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Today 15-20% of children are diagnosed with a neurodevelopmental disorder. Evidence indicate that chemical exposure contributes to these disorders. However, majority of chemicals have not been tested for developmental neurotoxicity (DNT) as current test guidelines are based on traditional in vivo animal studies that are costly, time consuming and require large numbers of animals. Within the Division of Translational Toxicology, the DNT Health Effects Innovation (HEI) program was developed in 2019, to evaluate the risks of chemical exposure to the developing nervous system. One aim was to implement a DNT screening battery that covers key neurodevelopmental events to provide timely data for decision making and to prioritize compounds with potential for DNT. The battery includes 2D and 3D human and rodent in vitro assays that measure proliferation, cell migration, neurite growth, neural network formation and function, and a zebrafish embryo neurobehavior assay. Based on nominations from various stakeholders the DNT HEI program selected and distributed 115 chemicals for testing in the battery and additional 100+ chemicals currently undergoing testing. Moreover, the program developed a unified data analysis pipeline to combine data from the individual assays and DNT-DIVER, a web application tool. Combined with PBPK and IVIVE modeling, this approach was applied in the development of an IATA case study for the OECD DNT guidance document. It demonstrates applicability of the DNT battery for prioritization and how human exposure data can be used to interpret this data and support the contextualization of these studies in potential future risk assessment.