FIRST STEPS FOR CREATING AN ONTOLOGY FOR COGNITIVE FUNCTION DEFECTS FOR REGULATORY APPLICATION

Conference Paper · October 2022

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chemicals to be tested for DNT, a DNT in vitro testing battery (DNT IVB) has been assembled under the guidance of the European Food Safety Authority (EFSA) in collaboration with the Danish- and US-Environmental Protection Agency and under the umbrella of the Organisation for Economic Cooperation (OECD). The DNT IVB consists of test methods based on primary human neural progenitor cells (hNPC), human induced pluripotent stem cell (hiPSC)-derived neural crest cells and neurons, as well as LUHMES cells and model the key neurodevelopmental processes hNPC proliferation, migration and differentiation into neurons and oligodendrocytes, neurite morphology, neural crest cell migration and neurite outgrowth. This IVB was challenged with 120 chemicals. In addition, a hiPSC-based test method for human neuronal network formation was set up and challenged with 28 pesticides. Concentration-response curves reveal benchmark concentrations (BMCs) for the 120 compounds in the individual test methods. Classification models for data interpretation were applied. For interpretation of compound results across the whole battery, respective most sensitive endpoints (MSEs) were determined. Battery results were used in two case studies, i.e. hazard characterization of deltamethrin and flufenacet in an Adverse Outcome Pathway-informed Integrated Approach for Testing and Assessment (by EFSA) and flame retardant prioritization (by the US-National Toxicology Program). These data demonstrate the successful set-up of a DNT-IVB for fit-for-purpose regulatory problem formulations. An OECD guidance document has been prepared (Crofton & Mundy 2021) that informs on use and interpretation of the DNT-IVB for regulatory application. Increasing trust in battery performance by testing more chemicals and lab-to-lab transfer will aid its implementation into regulation.

O-7A-2

FIRST STEPS FOR CREATING AN ONTOLOGY FOR COGNITIVE FUNCTION DEFECTS FOR REGULATORY APPLICATION

ABSTRACT #416

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Cognitive functions such as learning, thinking, reasoning, remembering, problem-solving, and attention are critical for day-to-day life. They are developed in a series of complex and sensitive brain developmental processes (differentiation, synaptogenesis, etc.). These processes can be disturbed by various environmental cues and lead to neurodevelopmental disorders such as cognitive function defects (CFD). This study aims to review the known links between prenatal exposure to chemicals, disturbed neurodevelopmental processes, and CFDs. The final goal of this initial approach is to create an ontology – a framework quantitatively and qualitatively integrating biological, toxicological, kinetic, and chemical data – as a new innovative strategy to predict repeated-dose developmental neurotoxic (DNT) effects of chemicals within the ONTOX project [1]. First, a literature study on CFDs was carried out. Second, a physiological map (PM) of the developing brain was created and CFD-relevant adverse outcome pathways (AOP) were identified. Finally, a tailored in vitro battery with human primary and iPSC-derived cell lines (2D and 3D) was proposed based on [2] and [3]. The created PM shows the neurodevelopmental processes and physiological mechanisms underlying neurodevelopmental disorders and enables the derivation of new CFD-relevant AOPs. Collected existing AOPs were mapped into an AOP network containing information about available in vitro assays for assessing compound effects on relevant molecular initiating events (MIE) and key events (KE) in the network. The described results are the first steps for the generation of a DNT ontology related to CFDs. The proposed ONTOX in vitro battery or an in silico approach will be used for filling artificial intelligence-identified data gaps in the ontology. Ultimately, the combination of these methods serves to create a new approach methodology that can, in combination with exposure assessment, advance human risk assessment in line with Next Generation Risk Assessment principles and

without the use of animals.

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O-7A-3

Evaluation of a human iPSC-derived BBB model for repeated dose toxicity testing
ABSTRACT #286

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Background and Objectives : The blood-brain barrier (BBB) is a highly restrictive barrier that preserves central nervous system homeostasis and ensures optimal brain functioning. Using BBB cell assays makes it possible to investigate whether a compound is likely to compromise BBBs functionality, thereby probably resulting in neurotoxicity. Recently, several protocols to obtain human brain-like endothelial cells (BLECs) from induced pluripotent stem cells (iPSCs) have been reported. Within the framework of the European MSCA-ITN in3 project, we explored the possibility to use an iPSC-derived BBB model to assess the effects of repeated dose treatment with chemicals. Methods: Our first objective was to evaluate different published protocols to differentiate iPSCs into BBB like endothelial cells regarding their expression of endothelial markers, formation of tight barrier and the presence of functional efflux pumps (e.g. ABCB1, ABCG2, ABCC1). After some protocol optimizations, the iPSCs derived BBB cells were found to exhibit important BBB characteristics up to 15 days after the end of the differentiation and could be used to assess the effects of repeated dose treatment, using Cyclosporine A (CsA) as a model compound. Results: Although iPSCs derived BBB cells were still undergoing transcriptional changes over time, a targeted transcriptome analysis (TempO-Seq) indicated a time and concentration dependent activation of ATF4, XBP1, Nrf2 and p53 stress response pathways under CsA treatment. Conclusion: Taken together, these results demonstrate that this iPSC-derived BBB model and iPSC-derived models in general hold great potential to study the effects of repeated dose exposure with chemicals, allowing personalized and patient-specific studies in the future.

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Comparative developmental neurotoxicity of NSAIDs in the zebrafish
ABSTRACT #353

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Background: Nonsteroidal anti-inflammatory drugs (NSAIDs) are the most frequently prescribed medications worldwide. NSAID have been shown to alter the development of the central nervous system and behaviour alterations have been observed in zebrafish embryos (1). Although their pharmacological mechanism of action is well-known, information about their adverse effects on neurological development is still unclear. The aim of this study was to compare the ability of NSAID to induce behavioral alterations in zebrafish embryos. Methods: Zebrafish embryos were exposed to increasing concentrations of various NSAIDs non-selective and selective cyclooxygenase, COX-1 and COX-2, inhibitors