Phenomics and transcriptomics applied in mode-of-action analyses for developmental neurotoxicity of TBBPA in vitro resulting in two novel AOPs

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INTRODUCTION

The chemical group of flame retardants (FRs) comprises diverse classes of compounds, applied to furniture and consumer products, like plastics and textiles as well as to electrical devices and baby products to reduce the risk of fire. Within the past decades FRs like polybrominated diphenyl ethers have been identified as threats to human health, thus there was a clear need to replace these compounds by safe(r) and less persistent alternatives like other brominated flame retardants, e.g. Tetrabromobisphenyl A (TBBPA). Such alternatives have been released onto the market, however, information on kinetics and toxicities are sparse. Considering the fact that the nervous system, especially during development, is a sensitive target for conventional flame retardants, it is essential to assess the developmental neurotoxicity (DNT) potential of replacement compounds.

METHODOLOGY

We have developed 3D neurosphere in vitro test methods (NPC1-6) based on human primary neural stem/progenitor cells (NPCs), which represent distinct neurodevelopmental key events (KEs), including NPC proliferation, migration and differentiation into neural effector cells (neurons, astrocytes and oligodendrocytes (OLs)), as well as thyroid hormone (TH)-dependent oligodendrocyte maturation. Using these neurosphere test methods, i.e. NPC1-6, we evaluated the endophenotypic adverse effects of TBBPA on neurodevelopmental processes. Additionally, we performed microarray analyses to gain deeper mechanistic understanding and placed the data in an AOP-context.

RESULTS

The studied FR TBBPA altered distinct neurodevelopmental KEs, while its impact on the differentiation into OLs and their TH-dependent maturation was classified as DNT-specific and identified as the most sensitive endpoints. We identified two modes-of-action (MoA) in

terms of how TBBPA interferes with the establishment of a population of OLs, dependent and independent of TH signalling: (i) TBBPA as a TH disruptor impairing human OL maturation by dysregulation of oligodendrogenesis-associated genes. (ii) TBBPA disrupted genes regulating cholesterol homeostasis, reducing OL numbers independently of TH signalling. These two MoA converge in a novel putative adverse outcome pathway (AOP) network on the KE hypomyelination.

DISCUSSION

This study demonstrates the power of combining endophenotypic with transcriptomic analyses for better understanding MoA and building AOPs for DNT, a promising approach for future risk assessment procedures.