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Editorial

Editorial: Developmental neurotoxicity

The developing human brain is inherently more susceptible to damage caused by toxic agents than is the brain of an adult (Bondy and Campbell, 2005; Rodier, 1995). This is why many environmental chemicals, including heavy metals, pesticides, organic solvents, flame retardants and persistent organic pollutants, can cause neurodevelopmental damage (Grandjean and Landrigan, 2006; Martin et al., 2017). It is suggested that this damage is associated with the rise in children's learning disabilities, autism, and ADHD (Bennett et al., 2016; Grandjean et al., 2017). However, the number of chemicals with sufficient information on their developmental neurotoxicity (DNT) is sparse (Fritsche, 2017). Based primarily on this lack of data, a clear consensus was generated by scientists across the world (Bennett et al., 2016), including co-authors of this special issue (Fritsche et al., 2018), that current DNT testing based on the *in vivo* OECD 426 (OECD, 2007) or EPA OPPTS 870.630 (EPA, 1996) test guidelines are not sufficient to adequately screen and characterize compounds potentially toxic for the developing brain. Consequently, a new testing paradigm is urgently needed that uses time- and cost-efficient methods to screen large numbers of chemicals for their DNT potential, providing adequate experimental data that allow regulatory decisions.

As stated in this special issue, the DNT scientists recommend developing a standardised *in vitro* testing battery using mixed neuronal/glial cultures, preferably derived from human pluripotent stem cells (illustrated on the cover picture; Fig. 1 from Bal-Price et al., 2018) to generate data on the effects of chemicals on key neurodevelopmental processes that represent different stages of human brain development (Fritsche, 2017). In addition, the use of alternative species, such as zebrafish or *C. elegans* could complement such an *in vitro* battery with behavioural studies due to the organisms' intact developing nervous systems. The endpoints of these test methods should be anchored to key events identified in the existing DNT adverse outcome pathways (AOPs), increasing scientific confidence in the mechanistic understanding of the toxicity pathways involved (Bal-Price and Meek, 2017). Because the number of DNT AOPs is currently low, such data might also lead to new AOP development. Furthermore, *in silico* models are needed to provide rapid chemical structure-based screening. Finally, these test methods ought to be used in an integrated fashion using an IATA (Integrated Approaches to Testing and Assessment) platform. Such a platform allows designed fit-for-purpose data generation for various regulatory purposes with different problem formulations (Bal-Price et al., 2018). This joint effort that is currently performed under the coordinating roof of the OECD in collaboration with the European Food Safety Authority and the US as well as the Danish Environmental Protection Agency will result in an OECD DNT guidance document on the use and data interpretation of an alternative DNT testing battery (Bal-Price et al., 2018). Such a guidance will be extremely helpful for a faster evaluation of compounds regarding their DNT potential and thus aiding in the closure of data gaps.

Summing up, this special issue of *Toxicology and Applied Pharmacology* contains several articles outlining novel concepts (*i.e.*, AOP, IATA, ontology-driven animal-free testing) as well as a range of alternative approaches (*i.e.*, *in vitro*, zebrafish, *C. elegans*, *in silico*, a systems biology approach), which are the flagships for more effective DNT testing for better protection of pregnant women, infants and children exposed to environmental chemicals.

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