Evaluation of an adverse outcome pathway network for thyroid hormone system disruption across taxonomic groups

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INTRODUCTION

Thyroid hormone system disrupting chemicals (THSDCs) are widely regarded as potential threats to human and environmental health. Thus, efforts are under way within the human health and ecotoxicology communities to develop screening assays capable of identifying THSDCs and to describe adverse outcome pathways (AOPs) that link thyroid hormone system disruption (THSD) to adverse outcomes. The Horizon 2020 project EndocRine Guideline Optimisation (ERGO) aims to break down the wall between human and environmental health assessment of chemicals using an AOP network (AOPN) approach and promoting the use of non-mammalian assays for predicting effects in mammals, including humans, and vice versa.

METHODOLOGY

In recent years, a fish-specific AOPN, which consists of 5 AOPs linking the inhibition of enzymes which are important for the synthesis and activation of THs to impaired swim bladder inflation, has been developed. This network is currently being expanded to include AOPs leading to altered visual function. When further expanding the network to include all AOPs for THSD in different species (either endorsed or under development), a cross-species AOPN for THSD emerges. This broader AOPN, which includes AOPs currently applicable to fish, amphibians or mammals, provides a scientifically plausible and evidence-based foundation for the measurement of endpoints using fish and amphibian assays to predict outcomes in humans and vice versa. In the present work, we evaluated which AOPs have already been defined for more than one taxon, which AOPs are taxon-specific and thus irrelevant to other taxa, and which novel pathways linking molecular initiating events to adverse outcomes in a particular taxon are potential targets for dedicated AOP development. Based on this evaluation, we identified assays in fish and amphibians that are likely to predict effects in humans and vice versa.

RESULTS

By filtering the AOPN based on the currently described taxonomic domain of applicability of the AOPs (i.e. fish, amphibians or mammals), it was found that most AOPs have been developed with a focus on one specific taxonomic group and information on the taxonomic domain of applicability is often missing. The AOPN currently includes 14 molecular initiating events (MIEs) leading to THSD and the coverage of MIEs is highest in the AOPs applicable to amphibians. Furthermore, while mammalian AOPs largely focus on developmental toxicity (DNT) as the adverse outcome, fish and amphibian AOPs thus far mostly lead to impaired swim bladder inflation and altered amphibian metamorphosis – both taxon-specific adverse outcomes. Other adverse outcomes include thyroid carcinoma, kidney toxicity, altered visual function, hearing loss and reduced fertility.

DISCUSSION

Based on this evaluation, we identified data gaps and prioritised AOP development efforts. AOPs leading to altered visual function are currently being developed as a first explicit case of cross-species AOP development. Based on the evaluation of the AOP network, priority endpoints to be added to fish and/or amphibian tests include thyroid hormone levels, swim bladder inflation, impaired eye development, thyroid histopathology and expression of thyroid-related genes. Since developmental neurotoxicity (DNT) is often considered the most important outcome of THSD in humans, and no AOPs for DNT in fish and amphibians exist, DNT was highlighted as an additional priority for cross-species AOP development and a potential route to expedite the use of fish and amphibian assays for predicting effects in humans. Other than DNT, there are adverse health effects with the potential for cross-species extrapolation, including reduced fertility, hearing loss or neurosensory development in general, and kidney toxicity. Lastly, another significant omission is the lack of AOPs describing THSD in birds and reptiles. The content of this abstract neither constitutes US EPA policy nor necessarily reflects such policy.