MEETING ABSTRACT

Annual Meeting of the Society of Environmental Toxicology and Chemistry
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Boston, MA

Goal 4. Safe Pesticides/Safe Products

Platform Presentation -- Invited
Session: "The Use of Adverse Outcome Pathways in Ecotoxicological Hazard Assessment of Chemicals"
Chairs: Steven Enoch, Patricia Schmieder

Establishing Adverse Outcome Pathways of Thyroid Hormone Disruption in an Amphibian Model

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The Adverse Outcome Pathway (AOP) provides a framework for understanding the relevance of toxicology data in ecotoxicological hazard assessments. The AOP concept can be applied to many toxicological pathways including thyroid hormone disruption. Thyroid hormones play a critical role in vertebrate morphological and neural development, and are important for maintenance of multiple physiological functions. Control of thyroid hormones is conserved across vertebrates via regulation by the hypothalamic-pituitary-thyroid axis (HPT). It has been well-established that disruption of the ability of the HPT axis to maintain normal levels of thyroid hormones can occur through exposure to various anthropogenic chemicals in the environment. Understanding the capacity of these chemicals to disrupt thyroid hormone levels and produce an adverse effect in the organism is critical for making sound risk assessment decisions. Furthermore, linking the initial molecular event in which a chemical interacts with the biological target to the processes leading to the adverse outcome, can provide a basis for developing predictive chemical structure activity relationships for thyroid hormone disruption. The molecular initiating events that can lead to decreased circulating thyroid hormone include inhibition of iodide uptake by the thyroid via the sodium-iodide symporter, inhibition of thyroid peroxidase which directly catalyzes the production of hormone, and induction of thyroid hormone metabolizing enzymes, including the thyroid hormone deiodinases. The amphibian provides an excellent model for developing AOPs that cover the various potential pathways to thyroid hormone disruption because amphibian metamorphosis is dependent upon thyroid hormone and is an easily quantified apical endpoint. The development and application of in vitro, ex vivo, and in vivo assays as they are applied to understanding disruption of thyroid hormone regulation in vertebrates will be presented. These assays include in vitro enzyme assays that measure the ability of a chemical to directly inhibit thyroid hormone synthesis, ex vivo assays that may be used to assess thyroid hormone release and metabolism, and final confirmation of an adverse effect with an in vivo metamorphosis assay. Developing a suite of AOPs for thyroid hormone disruption can provide an integrated set of mechanistic tools for identifying and verifying potentially active chemicals. This abstract does not necessarily reflect EPA policy.

Impact Statement: As the Agency is faced with greater numbers of chemicals and limited toxicological data for these chemicals, there will be a greater need to rely on predictive models to relate in vitro and/or in silico information to likely outcomes in organisms. This presentation demonstrates how the Adverse Outcome Pathway approach can be used to develop a framework in which to think about and develop assays for generating data that can be understood and utilized in the context of hazard assessment of chemicals, specifically those that disrupt normal thyroid hormone function. This effort addresses work toward addressing the needs of the Program Offices for tools to prioritize and assess the potential risk of chemicals for endocrine disrupting effects.