

Towards Building an AOP-based Prenatal Developmental Toxicity Ontology

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Retinoid signaling plays an important role in embryo-fetal development and its disruption is broadly teratogenic. The retinoic acid (RA) pathway includes elements in retinoid metabolism and nuclear receptor (RAR, RXR) activation and thus serves as an excellent prototype for adverse outcome pathway (AOP) elucidation associated with developmental defects such as caudal regression. Based on available data in the literature, interactions on the molecular level were mapped, starting at RA metabolism leading to caudal regression at both the anterior-posterior axis and the dorsal-ventral axis. We expanded an earlier AOP relating RA perturbation to neural tube and axial malformations in mammalian development through the use of text mining tools that allowed rapid identification of relevant literature related to human developmental biology. Important aspects are for example the RA balance and WNT and FGF signaling. Extracted information on RA related molecular regulators and biomarkers was structured in an ontology software environment. Gradients of expression on the anterior-posterior and dorsal-ventral axis, which are critical for normal development, were visualized. This prototype serves as an initial framework for a broader ontology of AOPs based, at least initially, on chemical structure, using data from approximately 900 published developmental toxicity studies that contains information on putative molecular initiating events responsible for each AOP and downstream key events.

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