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Towards a mechanistic approach in toxicology: Retinoic acid balance disturbance leading to neural tube closure defects.

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Retinoid signaling plays an important role in vertebrate embryo-fetal development and its disruption is teratogenic. The retinoic acid (RA) pathway controls retinoid homeostasis and regulates embryonic cell fate via nuclear receptor (RAR, RXR) activation. The RA pathway thus serves as an excellent prototype for adverse outcome pathway (AOP) elucidation associated with developmental defects. The disruption of the RA pathway, leading to defects in neural tube closure, was the basis for the construction of a developmental toxicity ontology. The prototype ontology describes retinoid homeostasis and putative molecular initiating events in chemical teratogenesis. Basic elements in the ontology are subjects (enzymes, receptors, cell types) and their quantitative relationships (response-response relationships), together forming a network of biological interactions that can be mapped to a vulnerable window for teratogen-induced neural tube defects such as spina bifida. We have searched literature using text-mining tools that allowed rapid identification of relevant information. We collected known molecular interactions, genetic signals and responses that: (a) play a crucial role in neural tube cellular differentiation; (b) establish anterior-posterior gradients (FGF and RA signaling) and dorsal-ventral gradients (zinc factors (Zic) and BMP signaling) for regional specification. Molecular initiating events important for RA balance (like CYP26 enzymes and RALDH2) potentially affected by xenobiotic compounds (using high-through-put screening data), were connected with toxicological data on the development of posterior neural tube defects. Ultimately, this network can be dynamically modeled in silico, providing an integrated computational systems model with which toxicity predictions can be made at the level of adverse outcomes in the intact individual. *This work does not reflect EPA policy.*