National Institute for Public Health and the Environment
Ministry of Health, Welfare and Sport

Towards Building an AOP-based Prenatal Developmental Toxicity Ontology

Yvonne C.M. Staal[1], Nancy Baker[2], Lyle D. Burgoon[3], George Daston[4], Thomas B. Knudsen[5], Aldert H. Piersma[1]

[1] RIVM: National Institute of Public Health and the Environment, Bilthoven, The Netherlands; [2] Leidos, RTP, NC, United States; [3] US Army Engineer Research and Development Center, RTP, NC, United States; [4]Proctor & Gamble Company, Cincinnati OH, United States; [5] NCCT, US EPA/ORD, RTP, NC, United States

Background and Aim

Ontologies are a way to formalize domain-specific scientific knowledge. A **developmental ontology** would help researchers describe the pathways and processes critical to embryonic development and provide a way to link their chemical disruption to adverse outcomes. Designing one for developmental toxicology is scientific challenging, given the complexity of embryogenesis and the continuous changes at the molecular, cellular, tissue and organ levels occurring in time and location throughout gestation.

Our aim is to explore the construction of an ontology that integrates biological targets of toxicity with chemical structure-activity information and developmental trajectories by focusing on one important pathway as a prototype. We decided to start from the perspective of **retinoic acid (RA**), which is a morphogen that regulates embryonic growth and differentiation and a known human teratogen.

Retinoid signaling includes elements in retinoid metabolism (e.g., RALDH, CYP26) 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.

Focus: RA metabolism leading to caudal regression

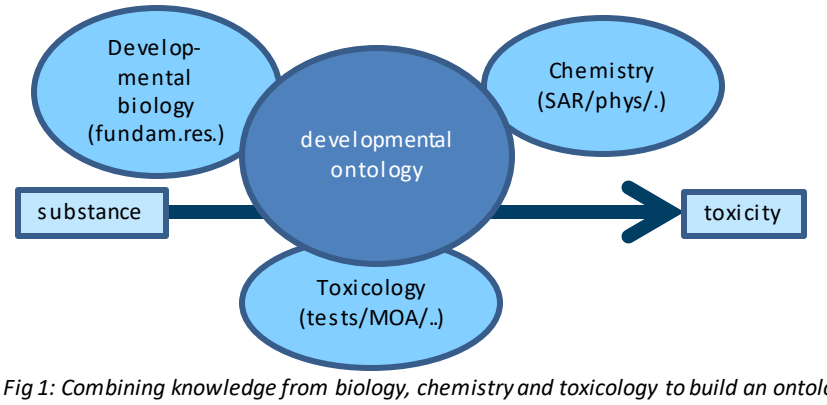

Fig 1: Combining knowledge from biology, chemistry and toxicology to build an ontology that will be used to assess prenatal developmental toxicity.

Methods

We will approach the ontology from two directions: biology and chemistry. The chemistry direction will focus on compounds that disrupt development through perturbation of the retinoic pathway. The biology direction will formalize the pathway players (genes, proteins, and endogenous chemicals) and the relationships to each other and their activity.

Chemistry: key steps

- Identify chemicals with known or predicted activity at retinoid pathway
- Define categories of chemical-biological interaction (mechanisms of action)
- Based on a decision tree for developmental toxicants (Wu et al., Chem. Res. Toxicol. 2013, 26, 1840–1861).
- Translate chemical activity into ontology entries

Biology & Toxicology: key steps

- Assess the available data in the literature using a HTP text mining tool
- Map interactions on the molecular level into ontology entries
- Focus on the **anterior-posterior axis** and the **dorsal-ventral axis**

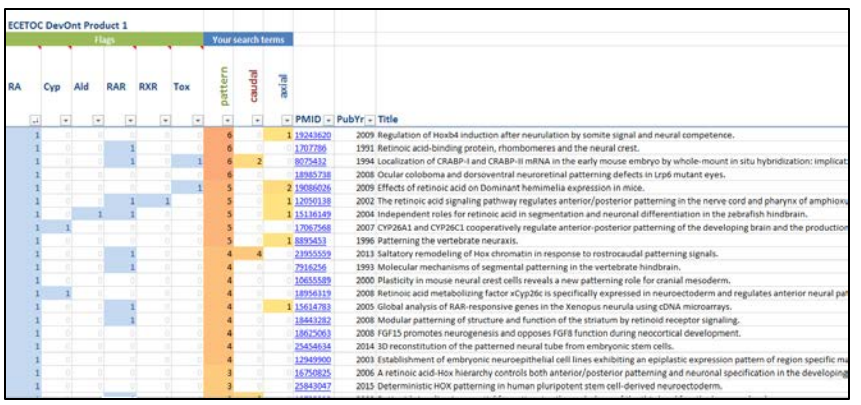

Fig 2: A sample of the literature mining output

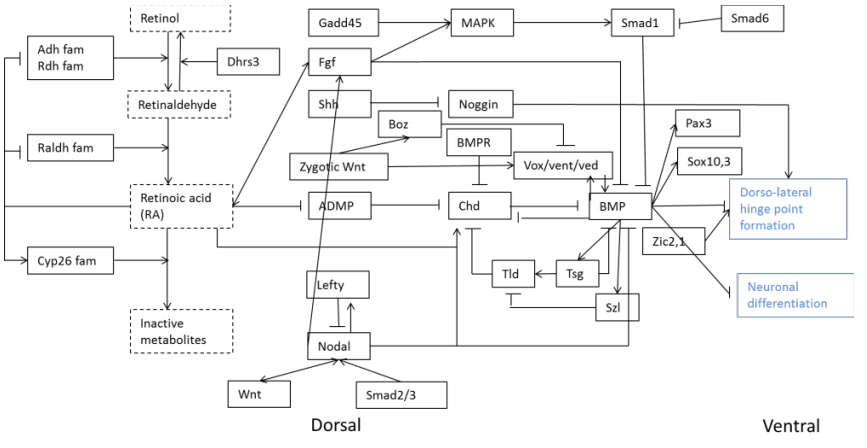

Fig 3: Gene and molecular interactions on the dorsal-ventral axis focusing on RA binding, and leading to caudal effects.

Extracted information from the chemistry and biology tasks will be structured in **an ontology software environment** in triple-store format. With this data and visualization tools, we will visualize perturbation of the caudal development by chemical disruptors of the retinoid system.

Summary:

This prototype of ontology construction serves as an initial framework for a broader ontology using data from approximately 900 published developmental toxicity studies that contains information on putative molecular initiating events and key events that play roles in a number of critical developmental adverse outcome pathways.

RIVM: National Institute for Public Health and the Environment; Antonie van Leeuwenhoeklaan 9, 3721 MA Bilthoven, The Netherlands
www.rivm.nl. *Disclaimer: does not necessarily represent U.S. EPA policy.*