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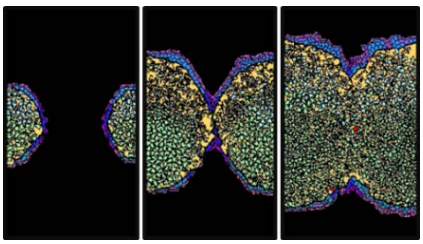
INNOVATIVE RESEARCH FOR A SUSTAINABLE FUTURE

Virtual Tissue Models: Predicting How Chemicals Impact Human Development

Human embryonic development is susceptible to chemical exposure, and predicting how chemicals may impact development is challenging. Traditionally, the predicted impact of chemical exposure on the human fetus is based upon experiments using laboratory animals. These experiments provide useful information; however, with tens of thousands of chemicals in commerce, and hundreds more introduced every year, animal studies are too costly and too slow to provide the data needed to assess effects on human development.



Cellular agent-based model simulating palatal shelf fusion.

U.S. EPA Chemical Safety for Sustainability (CSS) research adopts a systems-based approach to examine complex chemical-biological interactions and predict potential for adverse outcomes resulting from exposures to chemicals.

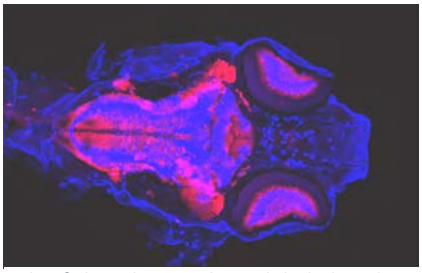
The Virtual Embryo and Virtual Thyroid projects use new computational methods to construct advanced *in silico* computer models capable of simulating how chemicals may affect human development. These computer models will help reduce dependence on animal study data, and provide much faster risk assessments.

Virtual Embryo Project

New types of *in vitro* (molecules, cells), *in vivo* (small model organisms), and *in silico* (computer-based) data are integrated into computer models that simulate critical steps in fetal development. These computer models are referred to as Virtual Tissue Models (VTMs).

VTMs simulate biological interactions observed during development and predict key events in the pathways that chemicals might disrupt, and that are thought to lead to adverse effects (called adverse outcome pathways, AOPs). Computational dosimetry models are used to convert the dose that leads to the effects seen in *in vitro* high-throughput assays to a level that would be comparable if given to a human. VTMs will use the results of dosimetry models and in vitro data to predict how a dose for a chemical might be harmful to the developing organism.

Virtual Thyroid Project



Zebrafish embryonic brain labeled to show neurons(red) and synaptic junctions (blue).

The thyroid gland regulates circulating levels of hormones critical for human nervous system development. Disruption of thyroid function during development leads to reduced IQ in children. Modeling the potential impact of chemical disruption of thyroid function and subsequent adverse impacts on brain development, is the goal of the Virtual Thyroid project.

The Virtual Thyroid project is developing *in vitro* models of

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the human fetal physiome and developing neurovascular unit (NVU). These models represent the complex relationships among fetal organs that regulate thyroid function during brain-liver-thyroid development, and among cell-cell interactions in organotypic culture models (OCMs) representative of various organ systems. For example, an *in vitro* assay for human brain effects or 'minibrains' may be used to critically evaluate patterns of neural growth, differentiation and migration in response to varying thyroid hormone levels. Another OCM application is modeling the dynamics of local thyroid hormone transport, metabolism, and signaling in the NVU.

Toxicological Tipping Points

A key question in modeling the effects of chemical exposure is distinguishing between adaptive responses those hat result in adverse outcomes. Biological systems have compensatory processes that protect organisms from stressors like chemicals exposures. Determining when systems are unable to recover from chemical exposure is addressed by the Tipping Points project. This project is developing mathematical models that predict perturbation of biological systems and determine when cellular systems are no longer able to recover, leading to adverse outcomes such as cancer.

An Intersection of Disciplines

VTMs are some of the most advanced methods being developed today to replace animal studies and provide the data needed to protect human health and the environment. The models are being developed by an interdisciplinary team that draws on knowledge from toxicology, computer science, bioinformatics, engineering, systems biology, mathematics, and statistics.

Collaboration Opportunities

Collaboration is essential to success in addressing the many challenges ahead. The Virtual Embryo and Virtual Thyroid Projects are collaborating with many other organizations interested in revolutionizing the current approach to assessing risk. Through these partnerships, the Virtual Tissues Project researchers share ideas, data and study results to collectively advance complex systems understanding to build predictive models to inform public health protective decisions.

For more information go to:
http://www.epa.gov/ncct/v-Embryo/

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