About the Division of Neurotoxicology (DNT)

Mission
Identify/quantify neurotoxicity related to FDA-regulated products, develop and qualify quantitative biomarkers of neurotoxicity, and identify biological pathways associated with the expression of neurotoxicity to improve risk assessments and new approaches for diagnosis, as well as supporting the evolving needs of FDA product centers.

Goals
Provide the data and expertise necessary for crucial regulatory decisions made by the product centers and to advance regulatory science research in neurotoxicology for FDA.

Strategies
Use and develop translationally valid imaging approaches, alternative preclinical models, and cross-species metrics of brain function to identify novel markers of neurotoxicity.

Select DNT Accomplishments in 2021

Cannabidiol (CBD) Exposure and Its Effects
An emerging focus within FDA is developmental toxicity associated with cannabidiol. In collaboration with FDA’s Office of the Chief Scientist, DNT researchers began a multiple-year assessment of the effects of CBD early in life on brain development and cognitive performance in the rat. Additionally, researchers studied the possibility of early-life exposure to CBD altering the immune response later in life. These studies are expected to determine if the brain’s “defense mechanisms” against infection and injury change in response to these exposures. Work will continue into 2022 and will fill data gaps and guide future regulatory decisions.

Developmental Toxicity of Inorganic Arsenic Exposure
Arsenic occurs naturally in groundwater and can find its way into various foods including rice, a popular ingredient in baby foods. NCTR researchers collaborated with Center for Food Safety and Applied Nutrition to complete a comprehensive assessment of the neurotoxic potential of early-life exposure to arsenic. In these studies, rats were used to model the human response to arsenic exposure. The effects of arsenic on behavior and brain development were assessed and will soon be published. These data will help inform the Agency on acceptable levels of arsenic exposure from food in children.
The brain is a sensitive organ and exists in a micro-environment maintained by the blood-brain barrier (BBB). Failure of the BBB will compromise this micro-environment and can lead to brain damage. In collaboration with the Office of Women’s Health and NCTR’s Nanocore, DNT scientists investigated sex-linked differences in inflammation changes in the BBB’s response to Alzheimer’s disease. Specifically, the impact of sex on BBB function, disease progression, and cognitive function were assessed. To complement these animal studies, “brain-on-a-chip” technology was used to better understand the mechanisms behind BBB dysfunction. The Division also took delivery of a new inverted live-cell imaging confocal microscope to enable assessments of BBB function and other neurotoxicity endpoints.

**Blood-Brain Barrier-Related Neurotoxicity**

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**Using Zebrafish Model to Explore Arsenic-Related Neurotoxicity**

The rat is a powerful and predictive research model but is slow compared to alternative research models. In collaboration with the NCTR-led Perinatal Health Center of Excellence, researchers in the Division used the zebrafish to explore how arsenic causes neurotoxicity. This work will also allow the Division to assess the effectiveness of zebrafish for future toxicity assessments of other heavy metals. Using zebrafish may allow researchers to perform toxicities faster and at a lower cost. Preliminary findings from this work were presented at governmental workshops in 2021.

**Anesthesia-Related Neurotoxicity**

The Division has been a leader in the field of developmental anesthesia-related neurotoxicity for over a decade. It is continuing this rich tradition by performing formal toxicity assessments, working to understand the conditions that lead to toxicity, and describing the mechanisms of toxicity. In collaboration with Center for Drug Evaluation and Research, DNT scientists completed the experimental phase of an assessment of the neurotoxic potential of ketamine in a pediatric population. Moreover, the Division is using alternative assays to study the comparative toxicity of different anesthetic regimens and will soon begin studies to assess the interactions between cannabinoids and opioids on brain development. Through this work, the Division’s goal is to understand the conditions needed for anesthesia-related neurotoxicity and to better define the risk associated with general anesthesia in a pediatric population.