U.S. FOOD & DRUG ADMINISTRATION

National Center for Toxicological Research (NCTR)

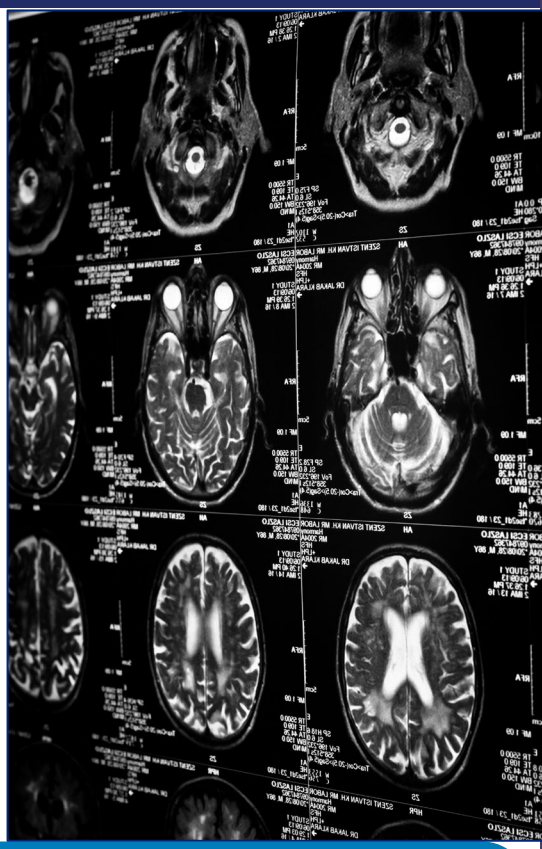
Neurotoxicology

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 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 FDA product centers and 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 2022

Cannabidiol (CBD) Exposure and Its Effects

In collaboration with FDA's Office of the Chief Scientist, Center for Food Safety and Nutrition (CFSAN), and Center for Drug Evaluation and Research (CDER), DNT researchers completed a multiple-year assessment of CBD effects 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. Data from these studies are being analyzed and will fill data gaps and guide future regulatory decisions.

The Acute Neurotoxic Effects of Ketamine During Adolescence

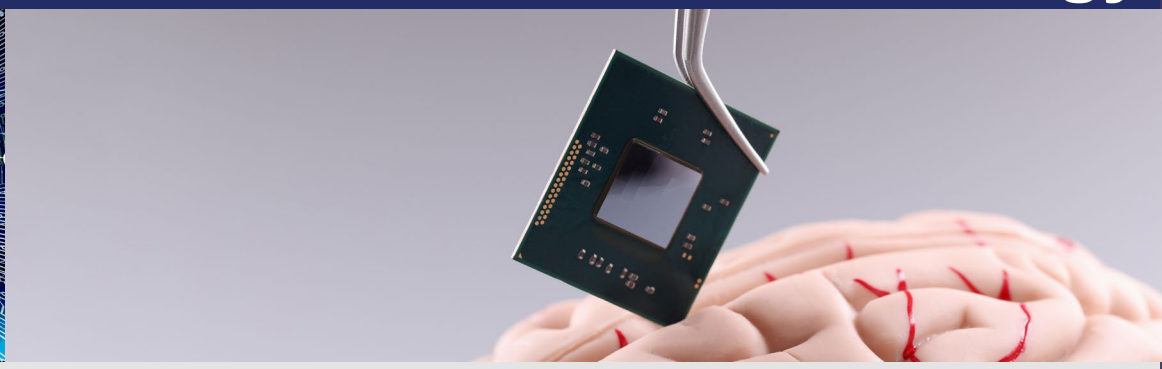
Clinical trials show ketamine can quickly alleviate the acute symptoms of depression. The research community wants to test the effects of ketamine for treatment of different indications and in an adolescent population. However, comprehensive safety data for ketamine in children does not exist. In collaboration with CDER, we tested ketamine in adolescent and adult rats. Our data show that adolescent rats do not have an increased sensitivity to the neurotoxic effects of ketamine. These data will impact future guidelines on the acceptable doses of ketamine in future clinical trials.

NCTR Division of Neurotoxicology
John Talpos, Ph.D., Division Director
Jefferson, AR
www.fda.gov/NCTR

U.S. FOOD & DRUG ADMINISTRATION

National Center for Toxicological Research (NCTR)

Neurotoxicology



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, DNT researchers used zebrafish to explore how arsenic causes neurotoxicity. Results from this work were presented at various meetings in 2022 and were published in *Neuroscience Letters*. Expanding on the results, DNT plans to use zebrafish to study arsenic and cadmium exposure in combination. Ultimately, zebrafish may allow researchers to study toxicity faster and at a lower cost. This is particularly useful when studying the toxicity of co-exposure, as frequently occurs with heavy metals.

2023 Ongoing Projects

Blood-Brain Barrier-Related Neurotoxicity

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. Division scientists are currently investigating changes to BBB-related proteins in a rat model of Alzheimer's disease and are preparing for a study to investigate the interaction between hyperglycemia and Alzheimer's disease on brain vasculature. To complement these animal studies, "brain-on-a-chip" technology is being used to better understand the mechanisms behind BBB dysfunction with the goal of better modelling Alzheimer's Disease.

T_2 Magnetic Resonance Imaging (MRI) as a Biomarker of Neurotoxicity

Unlike the heart or lungs, the brain cannot be directly observed at work. Most tools to study neurotoxicity require destruction of the brain. Neurotoxicity can only be assessed once in each study animal. Advanced imaging methods like MRI are an exception to this. When using MRI, tissue is exposed to a strong magnetic field. This causes the protons in water molecules to align to this magnetic field and oscillate at a specific resonant frequency. When this brief external pulse of electromagnetic radiation is applied, these protons absorb the energy and then radiate it, producing a brief signal. This signal is used to construct a picture of the brain. NCTR scientists are studying if this picture can act as a biomarker of neurotoxicity. If so, neurotoxicity can be assessed multiple times in one animal. Ultimately this means more comprehensive toxicity assessments can be performed with fewer animals. Such an approach could improve the safety of future drugs while reducing the number of animals used in biomedical research.

NCTR Division of Neurotoxicology
John Talpos, Ph.D., Division Director
Jefferson, AR
www.fda.gov/NCTR