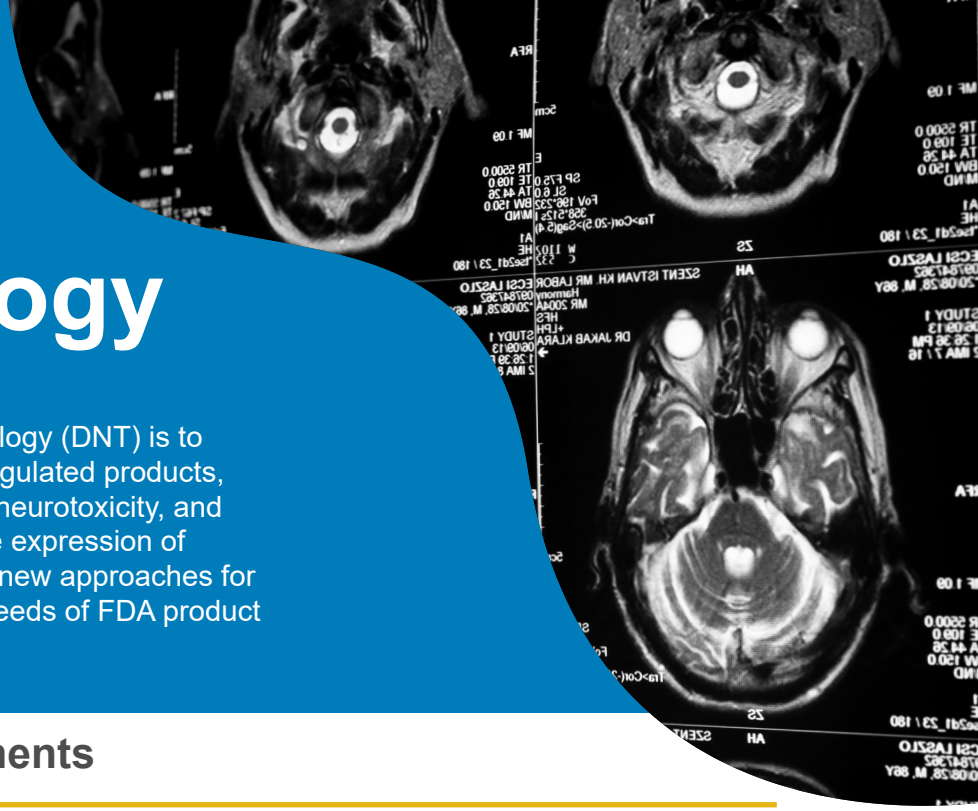
U.S. FOOD & DRUG ADMINISTRATION

National Center for Toxicological Research

Neurotoxicology



The mission of NCTR's Division of Neurotoxicology (DNT) is to 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.

2023 Select DNT Accomplishments

DNT Research Presented at Society of Toxicology Annual Meeting

- Division efforts to identify minimally invasive markers for central nervous system (CNS) toxicity led to development of an effective myelin-damage model. This project is in collaboration with an international consortium of leading scientists that represent regulatory bodies such as Center for Drug Evaluation and Research (CDER), other partner agencies like Centers for Disease Control and Prevention and Environmental Protection Agency, and various industry and pharmaceutical partners. Initial data from this project was presented by Division staff at the 2023 Society of Toxicology (SOT) annual meeting where sensitivity of T_2 Magnetic Resonance Imaging (MRI) was demonstrated in the early detection of grey matter damage in CNS in an oral rat model of cuprizone-induced neurotoxicity.
- Results from a study evaluating the mechanism of ketamine-induced neurotoxicity was also presented at the 2023 SOT annual meeting. Division staff presented results showing a potential sex and aged dependent effect of ketamine on the central nervous system. Young rats (21, 30, 35 days old) or adult rats (90 days old) were exposed to a single high dose of ketamine. Interestingly, neurotoxicity was only observed in female animals exposed to the highest dose of ketamine. This finding was unexpected since younger rats had higher blood levels of ketamine. However, adult female animals had significantly higher levels of norketamine, a primary metabolite of ketamine. These data suggest that adolescent rats are not at increased risk for ketamine-induced neurotoxicity and highlight the potential impact of norketamine on ketamine-induced neurotoxicity.

Advancing the Use of T_2 MRI to Assess Neurotoxicity

For over a decade, DNT researchers have explored how T_2 MRI can be used to study neurotoxicity. This noninvasive method allows real time assessment of toxicity, meaning multiple assessments can occur in the same animal. This approach may be faster and require fewer animals than traditional safety assessments.

Funding

- Secured funding from Perinatal Health Center of Excellence to study the long-term effects of neonatal opioid withdrawal syndrome in rats, as well as the interactions between opioids and cannabinoids on in vitro models of human brain development.
- Collaborated with NCTR's Division of Microbiology on a project designed to study the impact of diet and sex on the development of Parkinson's disease. The project has been short-listed for funding from FDA's Office of Women's Health.

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Accomplishments (Cont.)

Presentations

- Gave 4 lectures as part of the FDA-wide **Practical Neurotoxicology Course** organized by CDER's Neurotoxicity Assessment Subcommittee. Presentations highlighted ongoing Division research on complex animal behavior analysis, use of zebrafish as an alternate model for screening of neurotoxicity, and current advances in minimally invasive biomarkers of CNS toxicity.
- Participated in the 2-day public workshop, **State of the Science on Assessing Developmental Neurotoxicity Using New Approach Methods (NAMs)** at the Joint Institute for Food Safety and Applied Nutrition. Presentations included how NAMs are being used to enhance data gained from traditional animal models in regulatory settings, and what capabilities would be lost in transition to an in vitro-based assessment approach.

Collaborations

- DNT and FDA's Center for Food Safety and Applied Nutrition researchers showed that arsenic exposure to zebrafish eggs and larvae induced developmental neurotoxicity (*J Appl Toxicol*). While it is likely that multiple pathways are involved in arsenic toxicity, additional research is ongoing exploring how the Sonic Hedgehog (SHH) pathway may result in an overproduction of motor neurons in the zebrafish (*Neurosci Lett*). Additional work is aimed at developing an Organization of Economic Cooperation and Development adverse outcome pathway that can document how alterations to the SHH pathway may result in neurodevelopmental disorders.
- DNT continues its longstanding collaboration with The Icahn School of Medicine at Mount Sinai on evaluating neurobehavioral effects on heavy metal exposure in children. This collaboration, in conjunction with Mexico's National Institute of Perinatology, has resulted in multiple publications linking heavy metal exposures to changes in cognitive performance (*Environ Res*).
- DNT and Health and Environmental Sciences Institute continue to evaluate the development of minimally invasive biomarkers of neurotoxicity in preclinical models. A goal of this project is to link changes in MRI imaging with potential blood-born biomarkers for neurotoxicity.

By the Numbers

41	active protocols
11	posters presented
8	papers published
6	projects completed/closed
3	scientific conferences