U.S. FOOD & DRUG ADMINISTRATION

National Center for Toxicological Research (NCTR)

Biochemical Toxicology

About the Division of Biochemical Toxicology (DBT)

Division Mission, Strategies, and Metrics

Mission: Conduct fundamental and applied research designed to define the biological mechanisms of action underlying the toxicity of FDA-regulated products as well as characterize the carcinogenic risks associated with chemicals of interest to FDA.

Strategies: Conduct bioassays, mechanistic studies, and computational modeling.

Metrics: Provide reports to FDA Product Centers and funding agencies and publish manuscripts.

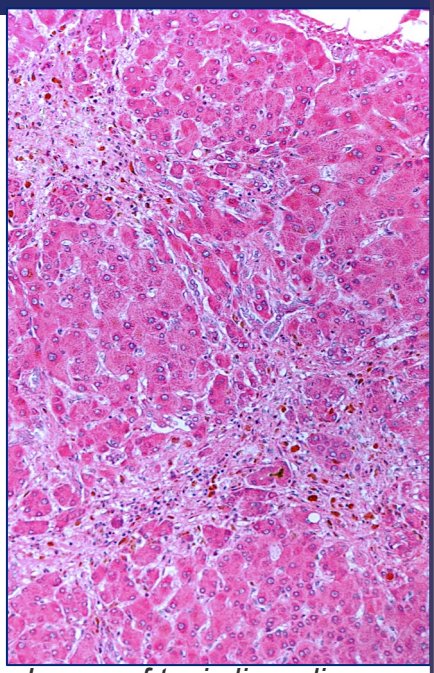

Image of toxic liver disease

Select DBT Accomplishments in 2021

Investigating Male Reproductive Toxicities Induced by Cannabidiol and Its Main Metabolites

Researchers at NCTR, in collaboration with scientists from the Center for Food Safety and Applied Nutrition, investigated potential male reproductive toxicities and their underlying mechanisms induced by cannabidiol (CBD) and its main metabolites — 7-carboxy-CBD and 7-hydroxy-CBD — using immortalized mouse Sertoli cells and primary human Sertoli cells. Study results showed that CBD inhibited cellular proliferation, disrupted the cell cycle, and altered the cytoskeleton organization. 7-carboxy-CBD and 7-hydroxy-CBD also inhibited cellular proliferation and decreased DNA synthesis during S-phase of the cell cycle. In summary, study results indicated that CBD and its main metabolites can inhibit cell proliferation in mouse and human Sertoli cells and the findings will help the FDA better define safety concerns regarding CBD. A paper reporting the study findings was published in *Food and Chemical Toxicology.*

Characterizing Metabolically Competent HepG2 Cells for Assessing Drug-Induced Liver Toxicity

In a previous study, NCTR scientists developed a battery of HepG2-derived stable cell lines that individually express 14 cytochrome P450s (CYP1A1, 1A2, 1B1, 2A6, 2B6, 2C8, 2C9, 2C18, 2C19, 2D6, 2E1, 3A4, 3A5, and 3A7). This work has now been expanded to characterize each cell line for its CYP expression and enzyme activity by measuring messenger RNA and protein levels and metabolite formation. The NCTR investigators demonstrated the metabolic stability and response robustness of each of the CYP-overexpressing HepG2 cell lines. These cells can provide a practical in vitro approach for 1) screening drug and chemical metabolism, 2) metabolism-associated drug toxicity investigations, and 3) drug-drug interaction studies. These data were reported in the *Journal of Environmental Science and Health, Part C, Toxicology and Carcinogenesis.*

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Investigating the Toxicokinetics and Toxicity of the Cigarette Smoke Carcinogen NNK

The Center for Tobacco Products (CTP)/NCTR Inhalation Toxicology Core Facility is a joint effort by NCTR and CTP to provide technical expertise in applied inhalation research. Using testing procedures that are compliant with international test guidelines (e.g., Organization for Economic Co-operation and Development), NCTR and CTP scientists have studied the biological responses in experimental animals following well-defined nose-only inhalation exposures. These data are used to quantify the adverse health risks associated with humans using tobacco products. Data from recently completed toxicokinetic, subacute toxicity, and subchronic toxicity studies of 4-(methylnitrosamino)-1-(3-pyridyl)-1-butanone (NNK) — a carcinogenic compound found in cigarette smoke — have been published in two papers in *Toxicological Sciences* and in a paper in *Food and Chemical Toxicology*.

Ongoing Research Projects in 2022

- Assessment of the developmental reproductive toxicity of metformin and glyburide
- Assessing epigenetic effects of nanoparticles in human cells
- Assessing epigenetic effects of the human food additive food-grade titanium dioxide in vitro
- Development of an artificially intelligent virtual pregnant woman modeling suite to support regulatory decisions
- Development of a first-generation in-house FDA pregnancy PBPK model-based tool to enhance the safety and efficacy of therapeutic agents in the perinatal period
- Effects of the fibrinolytic enzymes nattokinase and lumbrokinase alone or in combination with aspirin in blood parameters
- Evaluation of brominated vegetable oil in SD rats
- Fetal and neonatal toxicokinetics of C6-fluorotelomer alcohol
- Flow cytometry analysis of anti-SARS-CoV-2 antibodies in human plasma
- Genomic and genetic determinants of the susceptibility to non-alcoholic fatty liver disease (NAFLD) and NAFLD-related liver cancer
- High-throughput functional screens and mechanistic analysis of microRNAs that regulate chemotherapeutic resistance in ovarian cancer
- Identification of the structures and development of in silico models for predicting the levels of pyrrolizidine alkaloids-DNA adducts
- Percutaneous absorption of the cosmetic contaminant 1,4-dioxane
- Percutaneous absorption of the sunscreen component avobenzone
- Performance of 3D-bioprinted human skin equivalents for in vitro dermal absorption testing of FDA-regulated drugs and cosmetic ingredients used for dermal and transdermal applications
- Pharmacokinetic analysis of nicotine in Sprague-Dawley rats
- Pharmacokinetics of cannabidiol and its major metabolites in pregnant Sprague-Dawley rats and their pups exposed orally to cannabidiol
- Pharmacokinetics of cannabidiol upon dermal exposure in rats
- Relationship between liver epigenomic phenotype and susceptibility to nonalcoholic steatohepatitis
- Surveillance of SARS-CoV-2 in wastewater as a complementary tool to estimate the viral spread in Arkansas
- Stimulate innovation in clinical evaluations and personalized medicine to improve patient outcomes with triple negative breast cancer
- The biodistribution and placental transfer of tattoo pigments applied to the dorsal skin of pregnant female SKH-1 mice
- Toxicokinetic profile and toxicity of high-molecular-weight polyethylene glycols in Sprague Dawley rats

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