U.S. FOOD & DRUG ADMINISTRATION
NATIONAL CENTER FOR TOXICOLOGICAL RESEARCH

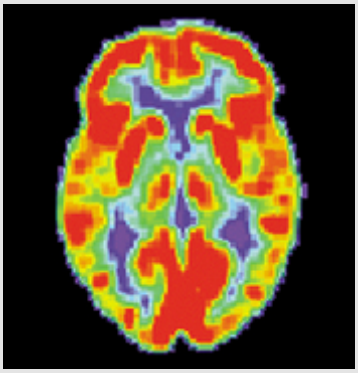
NCTR Quarter Page

Research Highlights, Activities, and Publications
Oct 2016-Dec 2016

Safety Evaluation of Veterinary Antimicrobial Drug Residues in Food

Scientists from FDA's NCTR and Center For Veterinary Medicine, and industry (Zoetis) have published a review on the safety evaluation of veterinary antimicrobial drug residues in food with regard to the human intestinal microbiome. The article describes the globally harmonized guideline, VICH GL36(R), which was issued by the International Cooperation on Harmonization of Technical Requirements for Veterinary Medicinal Products (VICH). The guideline is used by national and international regulatory agencies to assess the effects of animal drug residues in animal-derived food on human intestinal bacteria. The review:

- describes the steps in the VICH GL36(R) guideline to derive a microbiological acceptable daily intake (mADI)
- provides insights on the microbiological endpoints of



Minimally Invasive Biomarkers of Anesthetic-Induced Neurotoxicity

NCTR scientists have published a review article on the use of positron emission tomography (PET) to repeatedly monitor anesthetic-induced neurotoxicity during brain development. PET technology offers the advantage of a minimally invasive approach that can accurately target known molecular and cellular events using specific tracers in longitudinal studies. PET approaches are also translational in nature as they, theoretically, can be used in pediatric populations.

This review further discusses general anesthetic-induced neurotoxicity in the developing brain as tested using microPET-imaging techniques in preclinical studies. The article is available online at *Neurotoxicology and Teratology*.

For more information, please contact Xuan Zhang, Ph.D., Division of Neurotoxicology, FDA/NCTR.

Model for Prediction of Estrogenic Activity in Sunscreen Product Ingredients

Scientists from FDA's NCTR and CDER developed a computational model to predict the estrogen receptor binding activity of sunscreen-product ingredients. As proof of principle, the consensus model was applied to 32 chemicals used in sunscreen products. The model, which consists of two NCTR-developed Decision Forest models built on two different training sets, predicted estrogenic activity for seven of the 32 chemicals — five of which were confirmed by

human health concern used to determine the mADI
- describes research issues related to the potential development of antimicrobial resistance due to exposure to residual levels of antimicrobial drugs in food
- identifies current research gaps in the relationship between animal-drug residue levels, the human intestinal microbiome, and human health.

This publication is now available online at *Drug Testing and Analysis*.

For more information, please contact Carl Cerniglia, Director, Ph.D., Division of Microbiology, FDA/NCTR.

Intrinsic Resistance of *Burkholderia cepacia* Complex to Antiseptics

Scientists from FDA's NCTR and Center for Drug Evaluation and Research, and the University of Michigan have shown that resistance of *Burkholderia cepacia* complex (BCC) bacteria to benzalkonium chloride (BZK) is due to intrinsic resistance mechanisms. These mechanisms include removal of BZK by efflux pumps and the metabolic inactivation of BZK by catabolic enzymes. The study evaluated the susceptibility of 20 BCC strains to BZK and used metabolic and proteomic approaches to determine the mechanisms responsible for the antiseptic resistance of BCC, which was not well understood until now.

BZK is a commonly used antiseptic in pharmaceutical formulations in the United States, and a number of microbial outbreaks have been linked to antiseptics contaminated with BCC bacteria, which are opportunistic pathogens. The article is available online at *mBio*.

GLOBAL SUMMIT ON REGULATORY SCIENCE 2017

THEME:
Emerging Technologies for Drug and Food Safety
DATE:
September 18-20, 2017
LOCATION:
Brasilia, Brazil

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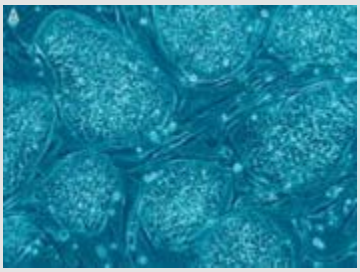


miRNA-Mediated Maturation of Stem Cell-Derived Cardiomyocytes

NCTR scientists have published a review that explores the potential role of microRNAs (miRNAs) for improving the *in vitro* maturation of cardiomyocytes (heart cells) from human induced pluripotent stem cells (hiPSC-CMs). Derived cardiomyocytes are a promising *in vitro* model for studying the effects of drugs on the heart. However, hiPSC-CMs derived with current procedures lack various functions of fully adult human heart cells, and thus are limited in their utility. This review discusses key miRNAs associated with heart development and function, as well as potential strategies to enhance cardiomyocyte maturation. The combination of miRNAs with other maturation factors may improve the *in vitro* maturation process of hiPSC-CMs, resulting in a more relevant human-cardiac model. The review is available previously published data. The model has potential for use as a risk-assessment tool when available scientific data is inadequate and represents advancement in the characterization of estrogenic activity in widely used consumer products, such as sunscreens. This publication is now available online at *International Journal of Environmental Research and Public Health*.

For more information, please contact Huixiao Hong, Ph.D., Division of Bioinformatics and Biostatistics, FDA/NCTR or Diego Rua, Ph.D., Division of Nonprescription Drug Products, FDA/CDER.

Dr. Daniel Acosta, NCTR Deputy Director of Research

2016 Univ. of Texas, William J. Sheffield Outstanding Alumnus Honoree

The Sheffield award, named to honor former Associate

For more information, please contact Carl Cerniglia, Ph.D., Director, Division of Microbiology, FDA/NCTR.

Sex Differences in Doxorubicin-Induced Cardiotoxicity

Scientists from NCTR, the National Cancer Institute, the Arkansas Heart Hospital, and Korea University have demonstrated an increased susceptibility to doxorubicin (DOX)-induced cardiac toxicity in adult male mice as compared to adult female mice. This reflects the difference in toxicity noted in male and female cancer patients treated with DOX. Male mice exhibited greater myocardial damage than their female counterparts as evidenced by:

- increases in cardiac troponin T levels in plasma
- the development of cytoplasmic vacuolization in cardiomyocytes
- increases in apoptosis and DNA damage in the myocardium, particularly in the left atrium.

This new mouse model has the potential to address biological mechanisms of DOX-induced cardiac injury and to identify sex-specific early biomarkers of DOX-induced cardiotoxicity. This may open avenues for reducing the toxicity of this highly effective anti-cancer drug. This publication is now available online at *Toxicology and Applied Pharmacology*.

online at *Food and Chemical Toxicology*.

For more information, please contact Xi Yang, Ph.D., Innovative Safety and Technologies Branch, Division of Systems Biology, FDA/NCTR.

NCTR Science Advisory Board Meeting

The annual NCTR Science Advisory Board (SAB) meeting was held November 1-2, 2016, in Little Rock, Arkansas. The Board heard presentations on the current research priorities and future goals from Dr. William Slikker, NCTR Director, and the six NCTR research divisions; including the Division of Bioinformatics and Biostatistics response to the SAB subcommittee site-visit report. Representatives from FDA's Centers for Drug Evaluation and Research, Devices and Radiological Health, Biologics Evaluation and Research, Veterinary Medicine, and the Office of Regulatory Affairs gave presentations on their Center's priorities and areas of current and potential future collaboration.

The SAB meets yearly to provide objective advice to the NCTR Director, researchers, and senior staff on 1) strengths of NCTR's research program to build upon and 2) data gaps that need to be addressed to meet FDA regulatory-science needs.

The full SAB meeting was followed by a two-day meeting of an SAB subcommittee. The subcommittee was comprised of two members of the SAB and three subject-matter experts who were tasked with conducting an in-depth review of the current research program and future plans of NCTR's Division of Systems Biology. The subcommittee will present its findings to the full SAB at the next yearly meeting. Each NCTR research division undergoes periodic evaluation by these subject-matter experts.

Dean William J. Sheffield, is the highest honor awarded each year to recognize a particularly outstanding alumnus of The University of Texas College of Pharmacy.

Daniel Acosta, Jr., Ph.D. graduated first in his class at the University of Texas College of Pharmacy. He decided to pursue a graduate degree in pharmacology and toxicology at the University of Kansas and was awarded a four-year National Science Foundation Traineeship — at the time, one of the most nationally competitive graduate fellowships available to first-year graduate students. Before he could begin graduate school he was drafted into the U.S. Army and served in South Korea. He received his Ph.D. in Pharmacology and Toxicology from the University of Kansas School of Pharmacy.

He was the 4th dean of the University of Cincinnati's James L. Winkle College of Pharmacy from 1996 to 2011 and a member of the faculty from 2012 through 2013. He was a member of the University of Texas College of Pharmacy faculty (1974-1996) where he helped develop a nationally ranked program in toxicology as the founding Director of the Graduate Toxicology Training Program. Dr. Acosta

For more information, please contact Varsha Desai, Ph.D., Division of Systems Biology, FDA/NCTR.

PBPK Model for Oral Extended-Release Methylphenidate

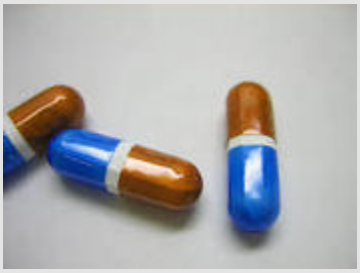
Scientists from FDA's NCTR and CDER have developed a physiologically based pharmacokinetic (PBPK) model to characterize the pharmacokinetic behaviors of oral extended-release methylphenidate (MPH) formulations in adults. A previously developed PBPK model for immediate-release MPH was modified by integrating information on the:

- anatomy and physiology of the gastrointestinal tract
- MPH physicochemical properties
- extended-release formulation information.

This model has potential application in evaluating extended-release MPH kinetics in children and could offer assistance in optimizing dose regimens for individualized treatment. MPH is a commonly prescribed medication for attention-deficit/hyperactivity disorder (ADHD) which is one of the most common neurobehavioral disorders in childhood, with effects that can persist into adolescence and adulthood. This publication is now available online at *PLoS ONE*.

For more information, please contact Xiaoxia Yang, Ph.D., or Jeffrey Fisher, Ph.D., Division of Biochemical Toxicology, FDA/NCTR.

For more information, please contact Donna Mendrick, Ph.D., Associate Director for Regulatory Activities, FDA/NCTR or William Slikker, Jr., Ph.D., Director, FDA/NCTR.



Serum Phospholipid Biomarkers of Acetaminophen

Scientists from NCTR, the University of Arkansas for Medical Sciences, Arkansas Children's Hospital, and the Medical College of Wisconsin demonstrated that specific serum phospholipids (phosphatidylcholine [PCs] and lysophosphatidylcholine [lysoPCs] with very long chain fatty acids) are significantly decreased in pediatric acetaminophen-overdose patients as compared to therapeutic dose groups and healthy controls; and correlate with current clinical indicators of liver injury.

A single phospholipid was shown to discriminate between the overdose and control groups with 100 percent sensitivity and specificity. The results of this proof-of-concept study suggest not only mechanisms by which acetaminophen causes toxicity, but also that these phospholipids could be used for diagnosis of acetaminophen overdose. The article is now available online at *Toxicology Reports*.

For more information, please contact Richard Beger, Ph.D., Director, Biomarkers and Alternative Models Branch, Division of Systems Biology, FDA/NCTR.

was selected as the Deputy Director for Research at the FDA's National Center for Toxicological Research in 2014.

Read more about Dr. Daniel Acosta.

NCTR Research Scientist, Dr. Rick Beger Delivers Engaging FDA Grand Rounds Presentation

Dr. Rick Begar presented "Metabolomics and Proteomics Biomarkers Discovery and Validation in Toxicity Studies" at the FDA Grand Rounds on November 1, 2016. Metabolomics and proteomics technologies are being used in nonclinical and clinical studies to discover translational biomarkers in biofluids that would enable us to diagnose and predict toxicity before it occurs.

The FDA Grand Rounds is webcast

View NCTR's Recent Scientific Publications

NCTR Animal Care Receives Top AAALAC Accreditation Rating

The Association for Assessment and Accreditation of Laboratory Animal Care (AAALAC) granted continued “Full Accreditation” for the NCTR Animal Care Program with no additional suggestions or requirements in their accreditation review letter. The letter informed, "the [NCTR] program conforms to AAALAC International standards as set forth by the Guide for the Care and Use of Laboratory Animals, NRC 2011. Therefore, FULL ACCREDITATION shall continue."

Progress on FDA Studies Reviewed

The 47th meeting of the Toxicology Study Selection and Review Committee (TSSRC) was held November 8-9, 2016, at FDA’s White Oak facility. The TSSRC met to discuss ongoing studies that are part of the Interagency Agreement between FDA/NCTR and the National Institute of Environmental Health Sciences/National Toxicology Program (NIEHS/NTP). This partnership between FDA/NCTR and NIEHS/NTP supports toxicology studies at NCTR that provide data for the FDA risk-assessment process.

Ongoing studies at NCTR in the following areas were discussed:

- Food constituents or contaminants (bisphenol A; arsenic; melamine+cyanuric acid; brominated vegetable oil)
- Dietary supplement component (aloin, black cohosh)
- Role of the microbiome in toxicology studies
- *In vitro* air-liquid interface inhalation model.

The TSSRC is comprised of:

- NCTR leadership
- NCTR research scientists

every other month to highlight cutting-edge research underway across FDA, and its impact on protecting and advancing public health. Each session features an FDA scientist presenting on a key public-health challenge and how FDA is applying science to its regulatory activities. The Translational Impact Award is presented to a scientist whose recent (last 10 years) outstanding clinical, environmental health, or translational research has improved human and/or public health in an area of toxicological concern.

	• NTP leadership • Subject-matter experts from NTP • Regulatory scientist and subject-matter experts from the FDA Product Centers • Subject-matter experts from National Institutes of Health (NIH). The committee meets twice each year and is responsible for scientific oversight of study design and progress of ongoing work under this Interagency Agreement. The next meeting of the TSSRC will be held May 3-4, 2017, at FDA's White Oak facility. For more information, please contact Gonçalo Gamboa da Costa, Ph.D., Division of Biochemical Toxicology, FDA/NCTR or Nigel Walker, Deputy Program Director For Science, NIH/NIEHS.	