# NCTR Quarter Page

***Research Highlights, Activities, and Publications***
***(April 2017-June 2017)***

## Developmental Neurotoxicity Associated With Pediatric General Anesthesia

NCTR scientists have published a review article that focuses on preclinical studies of general anesthesia-induced effects on brain and behavioral development. The authors address multiple anesthetic agents and their effects on various aspects of neurotoxicity and functional outcomes, potential protective compounds, and potential areas of future research. This review was published in a special issue of *Neurotoxicity and Teratology* devoted to "Developmental Neurotoxicity Associated with Pediatric General Anesthesia: Preclinical Findings," also co-edited by an NCTR scientist.

For more information, please contact Merle Paule, Ph.D., Division Director, Division of Neurotoxicology.

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## Save the Date: 2017 Global Summit for Regulatory Science

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

FDA/NCTR will be co-hosting the 2017 Global Summit for Regulatory Science with the Brazilian Health Regulatory Agency — ANVISA — to be held in Brasilia, BRAZIL on September 18-20, 2017. The Global Summit on Regulatory Science (GSRS) is an international conference for discussion of innovative technologies and partnerships to enhance translation of basic science into regulatory applications within the global context. To engage the global community to address regulatory-science research and training needs, GSRS is held in different countries on an annual basis.

The conference provides an opportunity for scientists from government, industry, and academic-research communities to objectively assess the utility of emerging technologies for addressing regulatory-research questions and to discuss the best way to translate these technologies into real-world applications. It provides a platform where regulators, policy makers, and bench scientists from various countries can exchange views on how to develop, apply, and implement innovative methodologies into regulatory assessments in their respective countries, as well as harmonizing strategy via global collaboration. The theme for this year's GSRS is "Emerging Technologies for Drug and Food Safety" and in addition to panel discussions and poster sessions, the agenda will include the following scientific topics:

- Global Regulatory Landscape
- Emerging Fields and Methodologies
- Drug and Food Safety
- Towards Acceptance of New Approaches to Safety Assessment: Standards and Reproducibility
- Science-Based Regulatory Practice.

There is no registration fee; however, registration is required to attend the conference. For recurring updates, visit www.fda.gov/globalsummit.

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## Risk Evaluation of Perchlorate Exposure in Pregnant Women Using Probabilistic Biologically Based Dose-Response (BBDR) Modeling

NCTR scientists developed a probabilistic biologically based dose-response (BBDR) model to predict thyroid effects (as indicated by reductions in maternal serum free thyroxin, fT4) of perchlorate exposure in late-gestation pregnant women. The model predicted a decrease in fT4 levels from perchlorate exposure only when drinking water exposures were combined with food for a total daily intake of 0.45 to 0.50 µg/kg/day of perchlorate. Based on the model, drinking water concentrations of perchlorate less than 7.6-9.2 µg/L were not found to cause a statistically significant reduction in maternal fT4 levels.

The U.S. population is ubiquitously exposed to perchlorate through food and drinking water. Perchlorate inhibits the uptake of iodide in the thyroid, which decreases thyroid hormone production. Pregnant women are particularly sensitive since decreases in maternal thyroid hormones have been associated with fetal neurodevelopmental defects. This study demonstrated the potential application of a probabilistic BBDR model for perchlorate risk assessment in a sensitive life-stage at a population level. This work was supported in part by the FDA Office of Women's Health. A manuscript describing the study is available online at *Toxicology and Applied Pharmacology*.

For more information, please contact Annie Lumen, Ph.D., Division of Biochemical Toxicology or Nysia George, Ph.D., Division of Bioinformatics and Biostatistics.

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## Nanotechnology Training

The NCTR/ORA Nanotechnology Core Facility — located on the Jefferson Laboratories campus in Arkansas — conducted a "Nanotechnology Hands-on Training" course from June 27-29, 2017. In attendance were 12 FDA

reviewers and research staff from different FDA product centers and offices. This annual training was sponsored by the FDA Nanotechnology Task Force/Office of Chief Scientist with instructors from across FDA from NCTR, Office of Regulatory Affairs, Center for Drug Evaluation and Research, and Center for Devices and Radiological Health. The lecture topics included:

- basic tools and instrumentation used for nanomaterial characterization (Transmission and Scanning Electron Microscopy, Atomic Force Microscopy, Dynamic Light Scattering and Asymmetric, and Centrifugal Flow Field Flow Fractionation)
- regulatory considerations for generic and new drug products and devices containing nanomaterial
- nanomaterial characterization
- evaluation of data
- nanomaterial and product specific issues to be considered when reviewing submissions.

For additional information, please contact Anil Patri, Ph.D., Director, NCTR/ORA Nanotechnology Core Facility.

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## Neuro-degenerative Markers are Increased in Postmortem BA21 Tissue from African Americans with Alzheimer's Disease

NCTR scientists conducted a research study that identified significant differences in Alzheimer's disease (AD) brain proteins that are related to ethnicity or race. The research community has known that African Americans and Hispanics develop AD at an earlier age and that their symptoms are often more severe, but have not understood why. Although the prevalence of the characteristic plaques and tangles may not exhibit ethnicity-related differences, differences in levels of neurodegenerative proteins have not been described. Because the symptoms of AD are worse in African Americans, understanding the differences in the brain may help explain this.

The NCTR scientists looked at levels of neurodegenerative proteins in the brain tissue of African American men and women, and Caucasian men and women with AD. Some proteins in the brain are associated with AD. For example, levels of the S100B protein are typically increased in the brains of people with AD and brain injuries. Five proteins associated with neurodegenerative diseases were measured (S100B, sRAGE, GDNF, Aβ40, Aβ42 and the Aβ42/Aβ40 ratio). The tissue samples came from the BA21 region (a ridge on the cerebral cortex of the brain) which is involved in language generation and processing and is known to be affected by AD. A multiplex assay was used to determine the levels of these proteins. There were no significant differences between men and women and no significant ethnicity with sex interactions on any protein. Effect size calculations indicated "medium" to "very large" effects. The statistically significant levels of the proteins studied include:

- S100B levels were increased 17% in African Americans. S100B is typically elevated in AD cases; however, the increased levels in African Americans here may be indicative of increased severity in specific populations.
- Aβ42 levels were increased 121% in African Americans, leading to a 493% increase in the Aβ42/Aβ40 ratio. Increased Aβ42/Aβ40 ratios in this study are compatible with increased disease severity and might indicate increased AD pathogenesis in African Americans.

While many brain proteins are altered in AD patients, these NCTR study results indicate that some of those AD-associated proteins are different between African Americans and Caucasians. The results are compatible with the hypothesis of increased neuroinflammation in African Americans with AD. The next step in this series of studies is to understand what other differences occur in the brains of African Americans and Caucasians with AD, such as:

1. different levels of neuroinflammation
2. differences in chemokines and cytokines in the brain

3. genetic differences that might explain the protein level changes.

This comprehensive study could potentially lead to targeted pharmacotherapies for specific populations which could better treat AD symptoms and perhaps slow the disease progression. A manuscript describing the study is available online at *Journal of Alzheimer's Disease*.

For additional information, please contact Sherry Ferguson, Ph.D., Division of Neurotoxicology. This study was an NCTR collaboration with:

- Dr. John Panos, *formerly in the Division of Neurotoxicology
- Dr. Vijayalakshmi Varma, Division of Systems Biology
- Daniel Sloper, Division of Systems Biology

## Effects of Mucous-Penetrating Nanoparticles in a Cultured Vaginal Epithelial-Cell Model

FDA scientists from NCTR, Center for Drug Evaluation and Research, and Office of Regulatory Affairs published a study to demonstrate that mucous-penetrating nanoparticles consisting of poly lactic acid-co-glycolic acid (PLGA)-polyethylene glycol (PEG) nanospheres and PEG-functionalized graphene-oxide sheets were cytotoxic (toxic to cells) and exacerbated the oxidative stress from *Candida albicans* (yeast) infection in human vaginal epithelial cells *in vitro*. The representative mucous-penetrating nanoparticles for intravaginal drug delivery had varying effects on autophagy and endoplasmic reticulum stress, and also induced:

- cytotoxicity
- cell death
- DNA damage

These results suggest that drug-delivery nanoparticles may cause intracellular damage to vaginal pithelial cells by multiple mechanisms. Additional *in vivo* studies will be necessary to determine the potential effects of these nanoparticles in women with active vaginal yeast infections.

Biodegradable and non-toxic nanoparticles have attracted attention as potential carriers for drugs. This work was supported in part by FDA's Office of Women's Health. A manuscript describing the study is available online at *PLoS ONE.*

For more information, please contact Robert D. Wagner, Ph.D., Division of Microbiology.

## Evaluating Toxicity of Tobacco Smoke Solutions in an *In Vitro* Air-Liquid-Interface Airway Model

FDA scientists from NCTR and the Center for Tobacco Products have developed an *in vitro* toxicity testing system. The system consists of an air-liquid-interface (ALI) human-airway tissue model and a panel of toxicity endpoints associated with human respiratory diseases. The ALI culture system was used to evaluate the toxicity of whole smoke solutions (WSS) prepared from two commercial cigarettes that differ in smoke constituents and showed time- and dose-dependent differences in mucin secretion, matrix metalloproteinase secretion, and protein carbonylation between the two WSSs.

Overall, these preliminary results suggest that using human ALI airway models to quantify disease-relevant endpoints is a potential tool for generating toxicity data that may inform tobacco regulatory activities. This study was funded by FDA's Center for Tobacco Products. A manuscript describing the study is available online at *Toxicological Sciences*.

For more information, please contact Xuefei Cao, Ph.D., Division of Genetic and Molecular Toxicology.

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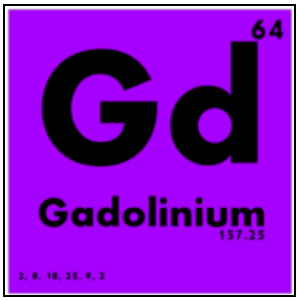


## NCTR Conducting Study as Part of FDA Research on Gadolinium-Based Contrast Agents (GBCAs) for Magnetic Resonance Imaging

**Excerpt from MedWatch Safety Alert dated May 22, 2017.*

An FDA review to date has not identified adverse health effects from gadolinium retained in the brain after the use of GBCAs for magnetic resonance imaging. All GBCAs may be associated with some gadolinium retention in the brain and other body tissues. However, because FDA identified no evidence to date that gadolinium retention in the brain from any of the GBCAs, including GBCAs associated with higher retention of gadolinium, is harmful, restricting GBCA use is not warranted at this time. FDA will continue to assess the safety of GBCAs and plans to have a public meeting to discuss this issue in the future.

FDA evaluated scientific publications and adverse event reports submitted to FDA. Some human and animal studies looked at GBCA use over periods longer than a year. These publications and reports show that gadolinium is retained in organs, such as the brain, bones, and skin. The publications show that linear GBCAs retain more gadolinium in the brain than macrocyclic GBCAs. However, the review did not identify adverse health effects related to this brain retention.

FDA continues to assess the safety of GBCAs. NCTR is conducting a study on brain retention of GBCAs in rats. Other research is also being conducted about how gadolinium is retained in the body. FDA will update the public when new information becomes available and we plan to have a public meeting to discuss this issue in the future.

Read the MedWatch Safety Alert.

Read the FDA Drug Safety Communication.

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## View NCTR's Recent Scientific Publications

**Review article related to "Developmental Neurotoxicity Associated with Pediatric General Anesthesia"**
http://www.sciencedirect.com/science/article/pii/S0892036216301386

**Special issue of *Neurotoxicity and Teratology* devoted to "Developmental Neurotoxicity Associated with Pediatric General Anesthesia: Preclinical Findings"**
http://www.sciencedirect.com/science/article/pii/S089203621730034X

**Global Summit Registration**
https://www.accessdata.fda.gov/scripts/email/NCTR/GSRSregform/GSRS_Registration.cfm

**"Risk Evaluation of Perchlorate Exposure in Pregnant Women Using Probabilistic Biologically Based Dose-Response (BBDR) Modeling" in *Toxicology and Applied Pharmacology***
http://dx.doi.org/10.1016/j.taap.2017.02.021

**"Neuro-degenerative Markers are Increased in Postmortem BA21 Tissue from African Americans with Alzheimer's Disease" in *Journal of Alzheimer's Disease***
http://content.iospress.com/articles/journal-of-alzheimers-disease/jad170204

***"*Effects of Mucous-Penetrating Nanoparticles in a Cultured Vaginal Epithelial-Cell Model" in *Plos ONE article***
http://dx.doi.org/10.1371/journal.pone.0175250

**"Evaluating Toxicity of Tobacco Smoke Solutions in an *In Vitro* Air-Liquid-Interface Airway Model" in *Toxicological Sciences***
http://dx.doi.org/10.1093/toxsci/kfw239

**Medwatch Safety Alert related to Gadolinium-Based Contrast Agents for Magnetic Resonance Imaging**
https://www.fda.gov/Drugs/DrugSafety/ucm559007.htm

**FDA Drug Safety Communication related to Gadolinium-Based Contrast Agents for Magnetic Resonance Imaging**
https://www.fda.gov/Drugs/DrugSafety/ucm559007.htm

**NCTR's Recent Scientific Publications**
http://www.accessdata.fda.gov/scripts/publications/more.cfm