U.S. FOOD & DRUG ADMINISTRATION

National Center for Toxicological Research

Genetic & Molecular Toxicology

The mission of NCTR's Division of Genetic & Molecular Toxicology (DGMT) is to improve public health by providing FDA with the expertise, tools, and approaches necessary for the comprehensive assessment of genetic risk.

2023 Select DGMT Accomplishments

Evaluation of Nitrosamine Genotoxicity Using In Vitro and In Vivo Models

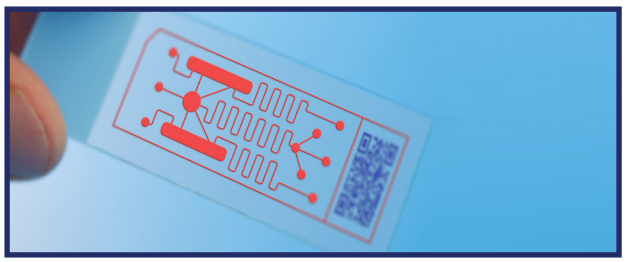
N-Nitrosamine drug impurities are a major concern for FDA, especially nitrosamine impurities formed by the drug substance itself, termed *N*-nitrosamine drug substance-related impurities or NDSRIs. Impurities can form at any time during the drug life cycle, for example, as by-products of synthesis, during storage, and as NDSRIs generated in the treated patient. *N*-Nitrosamine impurities that are likely to increase the risk of cancer are identified using mutation assays; *N*-nitrosamines that are mutagenic are assumed to be carcinogenic and are controlled at very low levels in drugs. Therefore, it is important for FDA to develop test models that can identify mutagenic *N*-nitrosamines. DGMT scientists have collaborated with the Center for Drug Evaluation and Research (CDER) Nitrosamine Drug Impurity Task Force to evaluate the mutagenicity and genotoxicity of a series of small-molecule *N*-nitrosamines and NDSRIs using in vitro bacterial and human cell mutation assays. Also, eight different *N*-nitrosamines were tested for their genotoxicity using 2-dimensional (2D) and 3-dimensional (3D) human hepatic (HepaRG) cell models. Finally, different *N*-nitrosamines are being evaluated for their mutagenicity in transgenic rodents. The objective of these studies is to develop screening and follow-up assays that determine the cancer risk of *N*-nitrosamine drug impurities with a high degree of confidence. The following publications describe the results from these studies: *Regul Toxicol Pharm* and *Arch Toxicol*.

Quantification of Genomic Damage by Next Generation Sequencing of Whole Genomes

DGMT scientists quantified in vivo genomic damage by whole genome clone analysis and high-fidelity (HiFi) error-corrected next generation sequencing (ecNGS). HiFi ecNGS was used to evaluate ultrarare off-target mutations in genome-edited cell populations. These ultrarare off-target mutations could lead to cancer and their analysis provides important information to FDA for regulation of therapies based on gene editing. This work was described in *Environ Mol Mutagen*.

A New Approach Methodology for Evaluating Germ Cell Mutation

DGMT scientists have established a *Caenorhabditis elegans* (worm) model to evaluate mutagenicity in germ cells. Using known mutagens, they evaluated mutagenic susceptibility of different stages of germ cell development in *C. elegans* using whole genome sequencing. These results suggest that *C. elegans* can be a less expensive and animal-friendly new approach method alternative to traditional rodent models for studying germ line mutations. A publication in *Arch Toxicol* describes this work in detail.



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Division Goals:

- Responding to Agency needs for genetic toxicology expertise and chemical-specific data
- Maintaining DGMT's tradition of leadership in regulatory genetic toxicology assay development and validation
- Developing better methods for carcinogenicity testing and translation of rodent studies to human cancer risk
- Developing advanced in vitro toxicological models that incorporate genotoxicity endpoints

By the Numbers

36	external working groups
18	scientific reports published
17	FDA/NCTR awards
16	collaborations with FDA centers
15	FDA working groups
7	competitive intramural-funding awards

Collaborations and Outreach

- FDA's CDER, along with NCTR's Division of Biochemical Toxicology and DGMT, used CarcSeq to detect DNA sequence alterations caused by the non-genotoxic carcinogen, lorcaserin, in treated rats. CarcSeq is an ecNGS technique developed in house to quantify expansions of Cancer Driver gene Mutations (CDMs).
- DGMT and the Center for Tobacco Products scientists validated Vitrocell exposure systems to investigate the in vitro toxicity of aerosols from electronic nicotine delivery systems and whole tobacco smoke from conventional cigarettes through exposures at the air-liquid interface of human airway-tissue models.
- DGMT researchers and University of Arkansas for Medical Sciences clinicians evaluated mutation in the *PIG-A* gene of blood cells from cancer patients who were treated with antineoplastic drugs.
- DGMT scientists collaborated with scientists from academia, industry, and other regulatory agencies in international consensus-building efforts to improve the science of genetic toxicology by publishing white papers on:
  - » the use of historical control data for evaluating genetic toxicology assay responses (*Environ Mol Mutagen*)
  - » using in vitro genotoxicity assays for tobacco product toxicity assessments (*Altern Lab Anim*)
  - » conducting the Comet assay (*Nat Protoc*)
  - » performing in vitro to in vivo extrapolation with genetic toxicology data (*Environ Mol Mutagen*)
  - » the promise of ecNGS for revolutionizing regulatory mutation assessments (*Mutat Res Rev Mutat Res*)