# Interagency Agreement: U.S. Food & Drug Administration National Center for Toxicological Research

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## Background and Rationale

An Interagency Agreement (IAA) was established in 1992 between the National Institute of Environmental Health Sciences (NIEHS) and the National Center for Toxicological Research (NCTR) of the U.S. Food & Drug Administration (FDA). The purpose of the IAA is to support toxicology studies on FDA-regulated chemicals that have been nominated to the National Toxicology Program, or that have been identified having mutual interest. These studies are designed to provide the FDA and other regulatory agencies with hazard identification and dose-response data to support risk assessment and risk management decisions that will affect public health.

## Goals and Objectives

The primary goals of the IAA are to: (1) Support the design and execution of toxicological studies that are consistent with the goals and needs of the FDA, NIEHS and NTP; (2) Obtain input from regulatory scientists at FDA, and where appropriate, other government agencies; (3) Provide oversight to ensure that the studies are conducted in the most rigorous scientific manner; (4) Ensure the data resulting from the studies are available to agencies to enable science-based, safety assessment and risk management decisions.

The goals of the IAA are met through the following objectives for each of the studies that are conducted under the IAA: (1) Implementation of validated toxicology studies (*e.g.* OECD or NTP guidelines); (2) When appropriate conduct studies with innovative designs to meet the needs of the FDA and/or NTP; (3) Incorporate appropriate mechanistic studies to assist in study interpretation, identification of potential translational biomarkers, and safety and risk assessments; (4) Provide the study data to the FDA regulatory and scientific community in a timely manner to provide the basis for risk assessments.

## Organization

The IAA is organized and managed by the NIEHS Project Officer, with an FDA Project Officer at NCTR for on-site management. The conduct and progress of the studies conducted under the IAA are monitored by the IAA Toxicology Study Selection and Review Committee (TSSRC). The TSSRC is composed of the NCTR Project Officer (TSSRC Chair), NIEHS Project Officer, NCTR Director, DNTP Toxicology Branch Chief, project leaders from NCTR, scientists from NIEHS, scientists from each of the FDA product centers (CBER, CDER, CDRH, CFSAN, CVM), and invited subject matter experts from government, academic, or industry.

The TSSRC meets twice yearly with the following objectives/tasks: (1) Review the toxicology research plan developed by the NCTR principal investigator for a specific chemical or substance in response to the nomination; (2) Recommend modifications to the research project plans or alternative studies that will enhance the regulatory utility of the studies that will be conducted under the IAA, taking into consideration that multiple toxicological endpoints may be required for

risk assessments (*e.g,.* carcinogenicity, reproductive/developmental toxicity, neurotoxicity, behavior alterations, immunotoxicity, mechanistic studies); (3) Consider and recommend alternative test systems that may meet the data needs of the regulatory agencies, such as the use of genetically modified mice or *in vitro* test systems; (4) Review the study protocols for appropriateness of the doses and study design and dose-selection to maximize the information for hazard identification and dose-response determination; (5) Monitor the progress of each project through reviewing the preliminary and final data; (6) Provide input into alternative endpoints or studies that may strengthen risk assessment and regulatory policy decisions that will affect public health.

## Project Outcomes

The IAA to date (1992-2016) has support projects on over 37 different chemicals or test articles that are of regulatory or scientific interest to the FDA and NTP. This IAA-based effort has resulted in the publication of 16 NTP Technical Reports, 3 NTP Toxicity Reports, 2 Genetically Modified Model Reports, and 263 scientific publications (as of December 2015).

The program areas that have been studied under the IAA for the past 24 years are listed below. Technical Reports or publications can be consulted for more information. The extent of contribution of the IAA-supported activities differed based on the specific data-gap needs, ranging from mechanistic support (*i.e.* riddelliine), specific assay support (*i.e.* cellular telephone radiation), analytical capabilities (*e.g.* NIEHS/FDA Phototoxicology Research and Testing Facility, Nanotechnology Core Facility), to subchronic and chronic bioassays.

### Dietary Supplement Program

- Aloe vera
- Bitter Orange (Citrus aurantium)
- Glucosamine and Chrondroitin Sulfate
- Riddelliine
- Usnea Lichen
- Usnic Acid

### Food Contamination Program

- Acrylamide
- Bisphenol A
- Fumonisin B1
- Furan
- Glycidamide
- Malachite Green
- Melamine plus Cyanuric Acid
- Urethane combined with Ethanol

### Endocrine Active Agents Program

- Ethinyl Estradiol
- Genistein
- Nonylphenol
- Vinclozolin and Methoxychlor

### Enhancing Toxicology Program

- Microbiome

**Drugs and Devices Program**

AIDS Therapeutics (Zidovudine, Nevirapine, Lamivudine, Nelfinavir, Efavirenz)
Cellular Telephone Radiation
Chloral Hydrate
Di(2-ethylhexyl)phthalate
Ketamine
Oxybenzone
Triclosan

**Nanoscale Materials Program**

Nanoscale Silver
Nanoscale Quantum Dots and Titanium Dioxide

**Phototoxicology Program**

Aloe Vera
Alpha Hydroxy Acid (glycolic acid)
Beta Hydroxy Acid (salicylic acid)
Retinyl Palmitate
Permanent Make-up Inks

## Significance and Public Health Impact of IAG

The studies that have been completed under the IAA have resulted in regulatory decisions by several agencies that may affect public health. Some of the data from the IAA-supported studies have led to increased understanding of the pharmacokinetics, mechanism of action, or dose-response of a chemical or substance. Other data has led to refinement of risk assessment models, while the results of some studies indicated that the chemical or substance was not toxic or carcinogenic to animals and did not pose a risk to humans.