Interagency Agreement (IAA) between NIEHS/National Toxicology Program (NIEHS/NTP) and FDA/National Center for Toxicological Research (FDA/NCTR)

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Disclaimer

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Purpose of Presentation

“... to update the NTP Board of Scientific Counselors regarding the 23½ year history, (and some perspectives of the future) of the Interagency Agreement (IAA) between the NIEHS/National Toxicology Program (NIEHS/NTP) and FDA/National Center for Toxicological Research (FDA/NCTR).”
U.S. Food & Drug Administration

MISSION: FDA is responsible for protecting the public health by assuring the safety, efficacy and security of human and veterinary drugs, biological products, medical devices, our nation’s food supply, cosmetics, and products that emit radiation.

FDA is also responsible for advancing the public health by helping to speed innovations that make medicines more effective, safer, and more affordable and by helping the public get the accurate, science-based information they need to use medicines and foods to maintain and improve their health. FDA also has responsibility for regulating the manufacturing, marketing and distribution of tobacco products to protect the public health and to reduce tobacco use by minors. (bold and color for emphasis by presenter)
U.S. Food & Drug Administration (list is not exhaustive)

**Foods, including:**
- dietary supplements (including vitamins)
- bottled water
- food additives (including colorants)
- infant formulas
- food contact materials
- other food products (USDA \(\rightarrow\) some meat, poultry, and egg products)

**Drugs (human), including:**
- prescription drugs (both brand-name and generic)
- non-prescription (over-the-counter) drugs

**Biologics, including:**
- vaccines
- blood and blood products
- cellular and gene therapy products
- tissue and tissue products
- allergenics

**Medical Devices, including:**
- simple items (eg tongue depressors and bedpans)
- complex technologies (eg heart pacemakers, diagnostic devices)
- dental devices
- surgical implants and prosthetics

**Electronic Products emitting radiation, including:**
- microwave ovens
- x-ray equipment
- laser products
- ultrasonic therapy equipment
- mercury vapor lamps
- sunlamps

**Cosmetics, including:**
- color additives found in makeup and other personal care products
- skin moisturizers and cleansers
- nail polish and perfume

**Veterinary Products, including:**
- veterinary drugs and devices
- livestock feeds
- pet foods

**Tobacco Products, including:**
- cigarettes
- tobacco for cigarettes, pipes, cigars, etc.
- roll-your-own tobacco
- smokeless tobacco
- tobacco ‘devices’

(May 2016 ; Deeming Rule for other products)
U.S. Food & Drug Administration

(list is not exhaustive)

**Foods, including:**
- dietary supplements (including vitamins)
- bottled water
- food additives (including colorants)
- infant formulas
- food contact materials
- other foods

**Drugs, including:**
- prescription drugs (both brand-name and generic)
- non-prescription (over-the-counter) drugs

**Biologics, including:**
- vaccines
- blood and blood products
- cellular and gene therapy products
- tissue and tissue products
- allergens

**Medical Devices, including:**
- simple items (e.g. tongue depressors and bedpans)
- complex technologies (e.g. heart pacemakers, diagnostic devices)
- dental devices
- surgical implants and prosthetics

**Electronic Products emitting radiation, including:**
- microwave ovens
- x-ray equipment
- laser products
- ultrasonic therapy equipment
- mercury vapor lamps

**Cosmetic color additive personal care products**

**Veterinary Products, including:**
- livestock feeds
- pet foods
- veterinary drugs and devices

**Tobacco Products, including:**
- cigarettes
- tobacco for cigarettes, pipes, cigars, etc.
- roll-your-own tobacco
- smokeless tobacco
- tobacco ‘devices’

(May 2016; Deeming Rule for other products)
Electronic Products emitting radiation, including:
- microwave ovens
- x-ray equipment

Foods, including:
- dietary supplements (including vitamins)
- bottled water
- food additives
- infant formulas
- food contact materials
- other food products
- and egg products

Drugs, including:
- prescription drugs
- non-prescription drugs

Biologics:
- vaccines
- blood and blood products
- cellular and gene therapy products
- tissue and tissue products
- allergenics

Medical Devices, including:
- simple items (e.g., tongue depressors and bedpans)
- complex technologies (e.g., heart pacemakers, diagnostic devices)
- dental devices
- surgical implants and prosthetics

Global Economy
- Tobacco Products, including:
  - cigarettes
  - tobacco for cigarettes, pipes, cigars, etc.
  - roll-your-own tobacco
  - smokeless tobacco
  - tobacco ‘devices’
  (May 2016; Deeming Rule for other products)
National Center for Toxicological Research: 
FDA Research Resource

- Established January 1971
- Non-regulatory national resource owned and managed within DHHS by FDA
- Conduct integrated, toxicological research
- Foster interagency, academic, and industrial collaboration in support of risk-assessment needs related to public health.
National Center for Toxicological Research

Mission –
... conduct toxicological studies, and scientific research to develop and support innovative tools and evaluation of approaches that FDA uses to protect and promote individual and public health.

FDA Jefferson Arkansas Campus; homes of FDA/NCTR and FDA/Office of Regulatory Affairs/Arkansas Regional Laboratory
NCTR Research Strategy

Hazard Quantification
   (hazard identification/quantification, mechanism of action, etc.)
Biomarkers (exposure or effect; genomics, proteomics, metabolomics)
Bio-imaging (MRI, CT, microPET, SEM, histopathology)
Organotypic models (3D & stem cells)
Microbiome (preclinical studies)
Precision/Personalized Medicine
Nanotoxicology (hazard identification/quantification; standards)
Inhalation Toxicology (tobacco constituents)
Modeling (PK, PBPK, PD, QSAR)
Bioinformatics (preclinical hazard identification; data mining)
Regulatory Science Training
Interagency Agreement (IAA) between FDA/NCTR and NIEHS/NTP

The missions of NTP and NCTR sometimes overlap when an FDA-regulated product (or contaminant) is nominated to (considered by) NTP for toxicology studies.
Interagency Agreement (IAA) between FDA/NCTR and NIEHS/NTP

Interagency Agreement (IAA) established December 1992 to facilitate cooperation between FDA/NCTR and NIEHS/NTP: (1) on compounds of interest to FDA and NIEHS/NTP; (2) to facilitate FDA regulatory decisions.

Initiated 10 Dec 1992

Nigel J. Walker, PhD, NTP Project Officer
Paul C. Howard, PhD, FDA Project Officer
Goals of IAA

(1) **Conduct toxicological studies** at NCTR on FDA-regulated or FDA-interest chemicals/compounds.

(2) **Ensure design** and conduct of toxicological studies are consistent with **regulatory needs** and goals of FDA and NIEHS/NTP.

(3) **Provide oversight** and ensure studies are conducted in the most rigorous scientific manner.

(4) **Ensure communication** of study data from the studies are available to enable regulatory agencies (U.S. and worldwide) to make science-based, safety assessment and risk management decisions.
Interagency Agreement (IAA):
How do we accomplish study design that meets regulatory needs, best science & design practices, etc.?

Toxicology Study Selection and Review Committee:
semi-annual; NTP, FDA/NCTR, FDA-regulatory centers.
(goal: best science; maximum information for regulators)

(Example of good communication)
Interagency Agreement (IAA):
How do we accomplish study design that meets regulatory needs, best science & design practices, etc.?

Toxicology Study Selection and Review Committee:  
semi-annual; NTP, FDA/NCTR, FDA-centers ... well ... sometimes we end up in a scrum!
Goals of IAA

(1) **Conduct toxicological studies** at NCTR on FDA-regulated or FDA-interest chemicals/compounds.

(2) **Ensure** design and conduct of toxicological studies are consistent with *regulatory needs* and goals of FDA and NIEHS/NTP.

(3) **Provide oversight** and ensure studies are conducted in the most rigorous scientific manner.

(4) **Ensure communication** of study data from the studies are available to enable regulatory agencies (U.S. and worldwide) to make science-based, safety assessment and risk management decisions.
Interagency Agreement:

Public Health impact by providing hazard identification and dose response data for accurate risk assessment.

Technical Reports (GLP) or other reports (n=19)
- Fumonisin B₁ (TR496)
- Chloral hydrate (TR502, TR503)
- Riddelliine (TR 508)
- Urethane ± ethanol (TR510)
- α-Hydroxy (glycolate) and β-Hydroxy (salicylate) acids (TR524)
- Malachite Green (TR527)
- Genestein (TR539, TR545)
- Ethinyl Estradiol (TR547, TR548)
- Aloe Vera (TR553, TR547)
- Retinyl Palmitate (TR568)
- AIDS Therapeutics (AZT +/- combinations; TR569, GMM14, GMM16)
- Acrylamide (TR575)
- Glycidamide (TR588)

Peer-reviewed scientific publications since 1992 (n>260)
Programs of Study under IAA

- Dietary Supplements Program
- Food Contaminants Program
- Enhancing Toxicology Program
- Endocrine Active Agents Program
- Drug & Device Program
- AIDS Therapeutics Program
- Nanoscale Materials Program
- Phototoxicology Program
Dietary Supplements Program

Bitter Orange, *Citrus aurantium* combination with caffeine and exercise

Usnea lichen, Usnic Acid *hepatotoxic in rats and mice*

Glucosamine, Chondroitin *biochemical alterations in diabetic rats*

Aloe vera *gastrointestinal carcinogen, rats*

Currently under study
Aloe vera Non-Decolorized Whole Leaf Intestinal Tumors in F344 Rats Share Pathways with Human Sporadic Cases

Arun R. Pandir1,2, Robert C. Sils1, Mark J. Hornerby1, Supya Hua Hua L. Hon1, Gordon P. Flack1, David E. Maloney1, C. Nigel J. Walker6, and Mary D. Brown1

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Abstract

Aloe vera is one of the most commonly used botanicals for various prophylactic indications. We demonstrate a dose-dependent increase in large intestinal tumors in F344 rats given non-decolorized whole leaf extract (AVWLE) in drinking water. The morphological analysis of tumors in the F344 rats were compared to human colorectal cancer (CRC) literature. Large adenomas with hyperplastic elements were found in AVWLE-exposed rats. The k-ras oncogene was found in tumors from AVWLE-exposed rats, but not in control rats. The k-ras mutations were also found in AAVNLE-exposed rats. In conclusion, the AVWLE is a carcinogen in F344 rats and may share pathways with human colorectal cancer.

Keywords: Aloe vera, colon, F344 rat, human, colorectal cancer.
Food Contaminants Program

Fumonisin B1

*led to worldwide regulatory levels*

Malachite Green

*reinforced US ban on imports*

Urethane ± Ethanol

*no synergism, no regulatory action required*

Acrylamide, Glycidamide

*critical study for Risk Assessment, worldwide*
Carcinogenicity of acrylamide in B6C3F1 mice and F344/N rats: drinking water exposure

Frederick A. Beland a,*, Paul W. Mellick b, Greg R. Olson b, Maria C.B. Mendosa c, M. Matilde Marques d, Daniel R. Doerge a

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c Research Center for Biodiversity and Environmental Toxicology, University of Lisbon, 1049-001 Lisbon, Portugal

ABSTRACT

Acrylamide is a contaminant in baked goods, and we have previously shown that acrylamide is a bladder carcinogen in male rats. We have also shown that acrylamide is activated by S-adenosyl-L-homocysteine to glycidamide. We have further demonstrated that acrylamide and glycidamide cause bladder tumors in male rats. In this study, we examined the carcinogenicity of acrylamide in male and female B6C3F1 mice and F344/N rats. Male and female B6C3F1 mice and F344/N rats were fed drinking water containing acrylamide at concentrations of 0, 50, 150, and 500 ppm for 2 years. There were no significant differences in body weight gain, food consumption, or survival between the control and acrylamide-treated groups. There were no macroscopic or microscopic changes in any organ that could be attributed to acrylamide treatment. These results suggest that acrylamide is not a carcinogen in mice and rats.
Food Contaminants Program (continued)

Furan

extending dose-response data

Melamine + Cyanuric Acid

establishing the dose-recovery LOAEL

Bisphenol A (CLARITY)

extensive 2-yr bioassay, tissues to NIEHS collaborators (U01)

Arsenic

PK, PBPK, and bioassay for low levels of As

Currently under study
Food Contaminants Program

Furan extending dose-response data

Melamine + Cyanuric Acid establishing the dose-recovery LOAEL

Bisphenol A (CLARITY) extensive 2-yr bioassay, tissues to NIEHS collaborators (U01)

Arsenic PK, PBPK, and bioassay for low levels of As Currently under study

Reproductive Toxicology

Concepts that are emerging at the molecular level

Addressing reproductive health effects of BPA: Collaborative, multi-angle scientific approach

Approach to assessing the health effects of BPA: Collaborative, multi-angle, scientific approach

Consensus-Based Science: The NEHS, Multipronged, Collaborative Approach to Assessing the Health Effects of BPA

Review

Journal homepage: www Elsevier com/journals/reproduction

Elsevier
Enhancing Toxicology Program

Microbiome
examing the role of microbiome in rodent bioassay

Nanotechnology Standards
developing standards and standard approaches for nanomaterial toxicological evaluation

Currently under study
Endocrine Active Agents Program

Genistein
multigeneration study; established effects

Ethinyl Estradiol
multigeneration study; established effects

Nonylphenol
renal toxicity
Drug & Device Program

Ketamine
established brain apoptosis rat, behavior changes in rodents, NHP

Chloral Hydrate
none to equivocal hazard

AIDS Therapeutics (AZT, 3TC, NVP)
some and equivocal evidence of carcinogenesis
THE ROLE OF THE N-METHYL-D-ASPARTATE RECEPTOR IN KETAMINE-INDUCED APOPTOSIS IN RAT FOREBRAIN CULTURE

C. WANG, C. SADOVOVA, X. FU, L. SCHMUEDEL, A. SCALLET, J. HANIG AND W. SIKKERS

Key words: NMDA receptor, ketamine, antagonist, antisense oligonucleotide, neurodegeneration, apoptosis.

Ketamine, a noncompetitive N-methyl-d-aspartate (NMDA) receptor ion channel blocker, has been used as a general anesthetic and for short diagnostic and surgical procedures in infants and children. Ketamine is a non-barbiturate, dissociative anesthetic agent that provides rapid dissociative and amnestic effects. It also offers analgesia and ameliorates acute postoperative pain. This study investigated the role of the NMDA receptor in ketamine-induced apoptosis in rat forebrain culture.
Drug & Device Program (continued)

Oxybenzone
established reproductive/developmental toxicity with two assays (NTP & NCTR)

Cellular Telephone Radiation
NTP – chronic bioassay
NCTR – neuro-immunohistochemistry; in vitro

Triclosan
topical PK and carcinogenesis
Regulatory Forum Opinion Piece*: New Testing Paradigms for Reproductive and Developmental Toxicity—The NTP Modified One Generation Study and OECD 443

PALL M. D. FOSTER

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ABSTRACT

The National Toxicology Program (NTP) has developed a new flexible study design, termed the modified one generation (MOG) reproduction study. The MOG study will encompass measurements of developmental and reproductive toxicity parameters as well as enable the setting of appropriate dose levels for a cancer bioassay through evaluation of target organ toxicity that is based on test article exposure that starts during gestation. This study design is compared and contrasted with the new Organization for Economic Co-operation and Development (OECD) 443 test guideline. The MOG study has a number of advantages, with a focus on postnatal developmental toxicity information, and the measurement of effect on reproductive structures and function in the same animal. This new study design does not employ the use of internal triggers in the design structure for the use of animals already on test and is also consistent with the principles of the 3Rs.

Keywords: developmental pathology; endocrine disruptors; female reproduction; male reproduction; reproductive system; safety assessment.

One of the major roles of the National Toxicology Program (NTP) has been in the development of new toxicology test methods. Following 2 workshops (King-Herbert and Thayer 2006; Thayer and Foster 2007) that focused on the NTP selection of a new rat strain for all of its toxico logical studies and that there would be a greater emphasis on early life test article exposures in the conduct of its cancer bioassays, it became apparent that there was a need for some dose range finding studies that involved early life test article exposure (gestation, lactation, and continuing exposure through adulthood). At the same time, NTP also showed that they could markedly increase the power to detect postnatal developmental effects (including those consequent to in utero exposure) in their developmental and reproductive toxicity (DART) studies by simply retaining more of the offspring from each litter post weaning (on most DART littering studies, only 1 male and female from each litter is retained) that would normally be culled or only given a cursory examination (Blystone et al. 2010).

Taken together, the program realized that in performing the necessary setting of dose levels and identification of target organ toxicity in order to undertake a perinatal cancer bioassay, it was possible at the same time to use animals already produced following exposure during gestation and lactation to develop additional, high-quality DART information in a single design, which we have termed the modified one generation (MOG) study (http://ntp.nichs.nih.gov/ntp/About_NTP/psc/ 2011/April/MOGDesign.pdf). The design basically compares 1 month old rats with time mated rats (although this could easily be expanded to 6 weeks)
Nanoscale Materials Program

Nanotechnology Core Facility
valuable resource to FDA and NIEHS

Nanoscale Silver
definitive 90-day toxicity study

Nanoscale Quantum Dots and TiO2
defined lack of dermal penetration
Differential Effects of Silver Nanoparticles and Silver Ions on Tissue Accumulation, Distribution, and Toxicity in the Sprague Dawley Rat Following Daily Oral Gavage Administration for 13 Weeks

Mary D. Boudreau*,1, Mohammed S. Imam*, Angel M. Paredes†, Erin L. Stavert*, Candice K. Cunningham†, Robert P. Felton†,
Phototoxicology Program

Alpha Hydroxy Acids (glycolic acid) 
*established no hazard*

Beta Hydroxy Acids (salicylic acid) 
*established no hazard*

Aloe Vera 
*established no hazard*

Retinyl Palmitate 
*some hazard identified*
NTP TECHNICAL REPORT
ON THE
PHOTOCARCINOGENESIS
STUDY OF
RETINOIC ACID AND RETINYL PALMITATE
[CAS Nos. 302-79-4 (All-trans-retinoic acid)
and 79-81-2 (All-trans-retinyl palmitate)]
IN SKH-1 MICE
(SIMULATED SOLAR LIGHT
AND TOPICAL APPLICATION STUDY)

NATIONAL TOXICOLOGY PROGRAM
P.O. Box 12233
Research Triangle Park, NC 27709

August 2012

NTP TR 568
IAA: Taking Advantage of Unique Resources at FDA/NCTR

- High density imaging (SEM)
- Sequential imaging efforts
- Rodent (and higher-order) learning
IAA: Impact on FDA and Future Direction

IMPACT
• Results used for regulatory decisions (e.g. acrylamide)
• Study results generating debate regarding public risk (e.g. BPA, retinyl palmitate, aloe vera)

FUTURE DIRECTION
• Continue with studies of high interest/concern to FDA and NTP (e.g. arsenic, botanicals/dietary supplements, food contaminants, endocrine active compounds)
• Examine new methods/approaches for utility to inform NTP and FDA regarding hazard and risk [e.g. microbiome, advanced sequential imaging (electron microscopy; neuropathology), organotypic models, nanotechnology]
NIEHS/NTP and FDA/NCTR

Interagency Agreement:

23½ years of providing data, protecting Public Health