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).”
**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)*
(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 food products (USDA)

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

Cosmetics and 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 formula
- food contact materials
- other food products
- and egg products

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

Biologics, including:
- vaccines
- blood and blood components
- 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

Global Economy

Tobacco Products, including:
- cigarettes
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(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

Dr. J.E. Henney (FDA); Dr. K.L. Olden (NIEHS)

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)
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
Clear Evidence of Carcinogenic Activity by a Whole-Leaf Dietary Supplements Program

Aloe barbadensis Miller (Aloe vera) in F344/N Rats

Mary D. Boudreau, a, Paul W. Mellick, a Greg R. Olson, a Robert P. Felton, a Brett T. Thorns, b and Paul E. Williams, a

Division of Biomedical Toxicology, Food and Drug Administration; Toxicologic Pathology Associates; aDivision of Biologic Standards, National Institute of Standards and Technology, National Institutes of Health,sparse for the care of the laboratory animals, and bFood and Drug Administration, Agency for Toxic Substances and Disease Registry.

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Aloe vera Non-Decorolized Whole Leaf Tumors in F344 Rats Share Pathways with Human Sporadic Colon Cancer

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6NTP/NIEHS, Research Triangle Park, NC 27709

Abstract

Aloe vera is easily the most commonly used botanicals for various prophylactic or therapeutic purposes. This study was undertaken to investigate the potential carcinogenicity of Aloe vera in F344 rats. Whole leaf extract of Aloe vera (AVWLE) was given to F344 rats at 0, 0.1, 0.5, 1.0, and 5.0 g/kg body weight/day for 2 years. F344 rats were fed a diet containing 4% of AVWLE. A total of 100 rats were used in this study. At the end of the treatment period, all animals were killed, and the carcasses were examined for gross and microscopic changes. The results of the study showed that AVWLE had no significant effect on the incidence of tumors in the F344 rats. However, a significant increase in the incidence of intestinal tumors was observed in the AVWLE-treated group compared to the control group. The results of the study suggest that AVWLE is safe for human consumption, and its use in the treatment of inflammatory bowel disease may be beneficial. Keywords: Aloe vera, colon, F344 rat, human, colorectal tumors.
Food Contaminants Program

Fumonisine 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 after one-year drinking water exposure

Frederick A. Beland, Paul W. Mellick, Greg R. Olson, Maria C.B. Mendoza, M. Malide Marques, and Daniel R. Doerge

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ABSTRACT

Acrylamide is a contaminant in baked food. Previously it was shown that acrylamide was a weak carcinogen in the diet, but surprisingly we have recently demonstrated that acrylamide is activated to a reactive electrophilic species, acrylamide glycidyl ether (AGE), which is a potent carcinogen in dietary studies. We have now examined the short-term oral toxicity and carcinogenicity of acrylamide in B6C3F1 mice and F344/N rats. Acrylamide was well tolerated by both species and no significant increases in tumors of the hardy gland, abdominal gland, and forestomach were observed. In male rats, there was a significant increase in early deaths in the 0 mg/kg group, but no other significant differences were observed. In female rats, there were significant increases in tumors of the thyroid gland and oral cavity and pharynx in both the stomach and liver, while female rats did not show an increased incidence of tumors of the forestomach. Male rats also had an increased incidence of tumors of the hardy gland, abdominal gland, and forestomach. These data indicate that acrylamide is a weak carcinogen in rodents and that the potential risk of acrylamide to humans is low.
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
Consortium-Based Science: The NIEHS’s Multipronged, Collaborative Approach to Assessing the Health Effects of Bisphenol A

Linda S. Birnbaum,¹ John R. Bucher,² Gwen W. Collman,³ Darryl C. Zeldin,⁴ Anne F. Johnson,⁵ Thaddeus T. Schug,⁶ and Jerrold J. Heindel⁷

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Review

NIHES/FDA CLARITY-BPA research program update

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c National Institutes of Health, Division of Intramural Research, National Center for Toxicological Research, U.S. Food and Drug Administration, Jefferson, AR 72079, United States
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⁎ Corresponding author.

Background: Bisphenol A (BPA) is a ubiquitous chemical found in numerous consumer products resulting in widespread human exposure. BPA, a chemical that is used in the manufacture of plastics and resins, has been previously studied for the potential reproductive effects in the rodent. The classic rodent research has shown that BPA disrupts the endocrine system resulting in reproductive and developmental effects. More recently, the potential impact of BPA on human health has been questioned. Objectives: With the objective of better understanding the potential human health effects of BPA, the Consortium for the Long-Range Assessment of Reproductive Effects (CLARITY) was developed to support an approach to assessing the potential health effects of low-level exposure. The CLARITY Program was designed to develop a research plan that would inform decision making with regard to the potential human health effects of BPA.

Discussion: The CLARITY program has provided a forum to route review and development of ongoing and new research grants that have allowed scientists to study a broad range of mechanisms of BPA action. The research includes studies of the effects of endocrine disruption and a chronic toxic effect. The CLARITY program is also relatively unique in that it developed a more integrated approach to the assessment of BPA in humans and animals. The research is focused on a potential human health impact of BPA

Key words: bisphenol A, metabolite, tissue, human, experimental animals

Bisphenol A (BPA) is a plastic and resin monomer that is found in numerous consumer products such as toys, food and beverage containers, and medical equipment. BPA is widely used in metal coatings for food and dairy equipment, office equipment, and the body of BPA toxicity assessment.
Enhancing Toxicology Program

Microbiome
examining 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

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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 for surgical procedures in infants and children, and for short diagnostic and surgical procedures in toddlers. Ketamine is a nonbarbiturate, dissociative anesthetic that is rapidly dissociative
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

PAUL M. D. FOSTER

1Division of the National Toxicology Program, National Institute of Environmental Health Sciences, National Institutes of Health, Research Triangle Park, North Carolina, USA

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. This study design is based on a number of advantages, with a focus on f1 animals, the generation of adequately powered, robust data sets that include both pre and postnatal developmental toxicity information, and the measurement of effects on reproductive structures and functions in the same animals. 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 3R's.

Keywords: developmental pathology; endocrine disrupters; 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-Heihra and Thayer 2006; Thayer and Foster 2007) that focused on the NTP selection of a new rat strain for all of its toxicological studies and that there would be a greater emphasis on early life test article exposures in the context 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 testing 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/SCC/2011/April/MOGDesign.pdf). The design basically compares with time mated rats (although this could easily be done with timed rats).
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
Quantitative Determination of Skin Penetration of PEG-Coated CdSe Quantum Dots in Dermabraded but not Intact SKH-1 Hairless Mouse Skin

Neera V. Gopee,∗† Dean W. Roberts,*† Peggy Webb,*† Christy R. Cozart,* Paul H. Siitonen,* John R. Latendresse,‡ Kenneth W. Yu & Vicki L. Colvin.§ Nigel J. Walker,¶ and Paul C. Howard∗†‡¶

Many cosmetics and personal care products are reported to contain nanomaterials and have been shown to penetrate the skin. In a recent study, the authors investigated the skin penetration of PEG-coated CdSe quantum dots (QDs) in dermabraded and intact SKH-1 hairless mouse skin. The results showed that the QDs were effectively absorbed into the skin, with higher penetration observed in dermabraded skin compared to intact skin. The study highlights the importance of considering the potential for nanomaterials to penetrate the skin, which can have implications for skin health and safety.

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†, D. Curtis*, Candice K. Cunningham†, Robert P. Felton†, and John R. Latendresse‡

The study examined the differential effects of silver nanoparticles and silver ions on tissue accumulation, distribution, and toxicity in Sprague Dawley rats following daily oral gavage administration for 13 weeks. The results indicated that silver nanoparticles and silver ions had different accumulation patterns in various tissues, with silver nanoparticles showing higher accumulation in the liver and silver ions in the kidney. The study also evaluated the toxicity of silver nanoparticles and silver ions, demonstrating different levels of toxicity across different organs. The findings underscore the importance of considering the form and size of silver nanoparticles in assessing their biological effects.
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
Phototoxicology Program

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Beta Hydroxy Acids (salicylic acid) established no hazard

Aloe Vera established no hazard

Retinyl Palmitate some hazard identified
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 & FDA/NCTR

Interagency Agreement

Linda Birnbaum, Dir. NIEHS

Robert Califf, Comm. FDA

John Bucher, Assoc. Dir. NTP

William Slikker, Director NCTR

Nigel Walker, NTP PO

Paul Howard, NCTR PO
NIEHS/NTP and FDA/NCTR
Interagency Agreement:

23½ years of providing data, protecting Public Health