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

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blood and blood products
acellular and gene therapy products
tissue and tissue products
allergens

**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

**Cosmetics, including:**
personal care products
skin moisturizers
hair products
nail polish and perfumes

**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)
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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.
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
Clear Evidence of Carcinogenic Activity by a Whole-Leaf
Dietary Supplement of Aloe barbadensis Miller (Aloe vera) in F344/N F<br>
Rats

Mary D. Boudreau,† Paul W. Mellick,‡ Greg R. Olson,§ Robert P. Felton,¶ and Pi

†Division of Biochemical Toxicology, Food and Drug Administration; Toxicologic Pathology Associates; and §Division of Bioi

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Aloe vera Non-Decolorized Whole Leaf Intestinal Tumors in F344 Rats Shar Pathways with Human Sporadic C

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Neil J. Walker6, and Mary D. Boudreau1

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5National Center for Toxicological Research (NCTR), Jefferson, Arkansas
6NTP/NIEHS, Research Triangle Park, North Carolina

ABSTRACT

Aloe vera is one of the most commonly used botanicals for various purposes and demonstrated a dose-dependent increase in large intestinal tumors in F344 rats with non-decolorized whole leaf extract (AVNWE) in drinking water. The morphological characteristics of tumors in the F344 rats treated with Aloe vera were compared to human colorectal cancer (CRC) literature. A large number of tumors were induced in CRC. The commonly mutated genes (K-ras, C-kit, and p53) and TGF-β pathway were evaluated in CRC and AVNWE-induced large intestinal tumors. The number of tumors indicated eight of twelve adenomas (Ad) and six of twelve adenomas (Ad) and mutations in exon 2 and 3 of the K-ras gene (two of eight Ad). The results of this study indicate that the AVNWE-induced large intestinal tumors are similar to human colorectal cancer in terms of molecular alterations. These results may have implications for the development of new therapeutic strategies for the treatment of colorectal cancer.

Keywords: Aloe vera; colon; F344 rat; human; colorectal cancer.

INTRODUCTION

In recent years, there has been an increasing interest in the use of dietary supplements as a means of promoting health and well-being. These supplements are marketed as natural remedies for various conditions, and there is a perception that they are safe and free of adverse effects. However, there is a growing body of evidence that suggests that some dietary supplements may have significant adverse effects, including carcinogenic activity.

Currently, there is a need for rigorous scientific research to evaluate the safety and efficacy of dietary supplements. This study was conducted to investigate the potential for carcinogenic activity of Aloe vera, a widely used dietary supplement. The results of this study provide valuable insights into the safety and efficacy of Aloe vera and may have important implications for public health.
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

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ABSTRACT

Acrylamide is a contaminant in baked food products. Previously we reported that acrylamide is activated to a genotoxic metabolite that is cytotoxic to the bladder cancer cell line, T24. We have now examined the genotoxic potential of acrylamide in drinking water for two years and in drinking water for 4 years. A total of 12 male and 12 female mice per group were exposed to acrylamide in drinking water and 12 male and 12 female rats per group were exposed to acrylamide in drinking water. Exposure to acrylamide caused an increased incidence of tumors of the bladder in male mice. Male mice also had an increased incidence of tumors of the mammary gland, thyroid gland, and oral cavity in acrylamide-exposed animals. In female rats, there was a significant increase in tumors of the mammary gland, oral cavity, and subcutaneous tissue. Male rats also had an increased incidence of tumors of the mammary gland, thyroid gland, and oral cavity. These data indicate that acrylamide is a genotoxic agent and that the genotoxic potential of acrylamide should be considered in the risk assessment for acrylamide exposure.
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. Heindel⁶

¹National Institute of Environmental Health Sciences (NIEHS), National Institutes of Health (NIH), Division of Extramural Research, Services (DHHS), Research Triangle Park, North Carolina, USA; ²Division of Intramural Research, NIEHS, NIH, DHHS, Research Triangle Park, North Carolina, USA; ³Division of Extramural Research, NIEHS, NIH, DHHS, Research Triangle Park, North Carolina, USA; ⁴Division of Intramural Research, NIEHS, NIH, DHHS, Research Triangle Park, North Carolina, USA; ⁵Division of Extramural Research, NIEHS, NIH, DHHS, Research Triangle Park, North Carolina, USA; ⁶Division of Extramural Research, NIEHS, NIH, DHHS, Research Triangle Park, North Carolina, USA.

Background: Bisphenol A (BPA) is a plastic and epoxy resin monomer that is used in the manufacture of numerous consumer products resulting in widespread human exposure. BPA was first identified as an endocrine disruptor in the 1990s. The US Environmental Protection Agency (US EPA) determined that BPA is a hazardous substance in 2008.

Objective: Study the role of Bisphenol A (BPA) & other endocrine disruptors (EDCS) in human health using a multipronged, collaborative, and transdisciplinary approach to inform decision-making.

Discussion: NIEHS has been promoting a round-robin approach to encourage collaborations amongst researchers. The Consortium of EDC Research (CER) is one of the most recent examples, which is a round-robin study that involves more research groups and is more integrated across the scientific and human health communities.

Keywords: bisphenol A, endocrine disruptor, environmental health, consortium-based science.
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 in pediatric surgical procedures in infants and toddlers. Ketamine is a nonbarbiturate, dissociative anesthetic providing short diagnostic and surgical procedures. Research into rapid dissociative

Who We Are

SmartTots is a collaborative effort of the IARS, the U.S. FDA and many others who are working to make anesthesia safer for infants and children.
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

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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. This study design has a number of advantages, with a focus on rats, the generation of adequately powered, robust data sets that include both per 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 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 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 toxicological 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.niehs.nih.gov/ntp/About_NTP/BSG/2011/April/MOGDesign.pdf). The design basically combines with time mated rats (although this could easily be expanded to include any strain of interest) to a conception day (GD) 6...
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. Goppe,*† Dean W. Roberts,*† Peggy Webb,*† Christy R. Cozart,* Paul H. Siti
ten,* John R. Latendresse,‡ N. X. V. Xu,§ and Paul C. Howard*†‡

Many cosmetics are reported to contain nanomaterials of which the absorption of these materials by the skin is of concern. The current study was designed to determine the dermal penetration of a 37 nm diameter CdSe quantum dot (QD) formulation coated with polyethylene glycol (PEG) into skin of SKH-1 Hairless mice. The CdSe QDs were dispersed in saline and applied to intact and dermabraded (keratinolytic) dorsal skin sites of male SKH-1 Hairless mice. The stratum corneum was monitored in situ using a confocal microscope to determine the time required for complete sloughing of the stratum corneum (SC) layer. The dermabraded skin sites were more permissive to the penetration of the CdSe QDs compared to intact skin sites. The fluorescence signal of the QDs was detected at the dermabraded skin sites but not the intact skin sites at 2 h after application. The signal intensity at the dermabraded skin site gradually increased over time and was still present at 48 h after application. The signal intensity at the intact skin site was not detected at 2 h after application and no signal was detected at 48 h after application. These results indicate that the dermabraded skin is more permissive to the penetration of nanomaterials compared to the intact skin site. Application of nanomaterials to intact skin may result in dermal penetration and absorption.

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†, Angel M. Paredes*, Candice K. Cunningham†, Robert P. Felton†,

1. The contents of this document are not complete and may be missing some parts or sections.
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 & FDA/NCTR
Interagency Agreement

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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