



The National Toxicology Program Today

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The NTP Today

- ◆ People
- ◆ Current Research Highlights
- ◆ Analysis and Policy Activities
- ◆ Expectations



NTP Organization

Policy Oversight

Executive Committee

ATSDR	NCI/NIH
CPSC	NIEHS/NIH
EPA	OD/NIH
FDA	NIOSH
NCEH/CDC	OSHA



Ken Olden
Director



External Science Oversight and Peer Review

NTP Board of
Scientific Counselors



NCTR

National Center for Toxicological Research
U.S. Food and Drug Administration



People

- ◆ **Scientific and Technical FTEs**
 - NIH/NIEHS ~ 75
 - FDA/NCTR ~ 33
 - CDC/NIOSH ~ 12
- ◆ **Agency Partners**
 - NTP Executive Committee
 - Interagency Committee for Chemical Evaluation and Coordination
 - Report on Carcinogens Review Group
 - Center for the Evaluation of Risks to Human Reproduction - Core Committee and Working Groups
 - Interagency Coordinating Committee on the Validation of Alternative Methods and Working Groups

NTP Research Program

Study Starts in 2004

- 10 Cancer studies
- 3 Reproductive tox studies
- 4 Immunotox studies
- 21 Sub-chronic tox studies
- 4 Transgenic studies
- > 50 Genetic tox studies

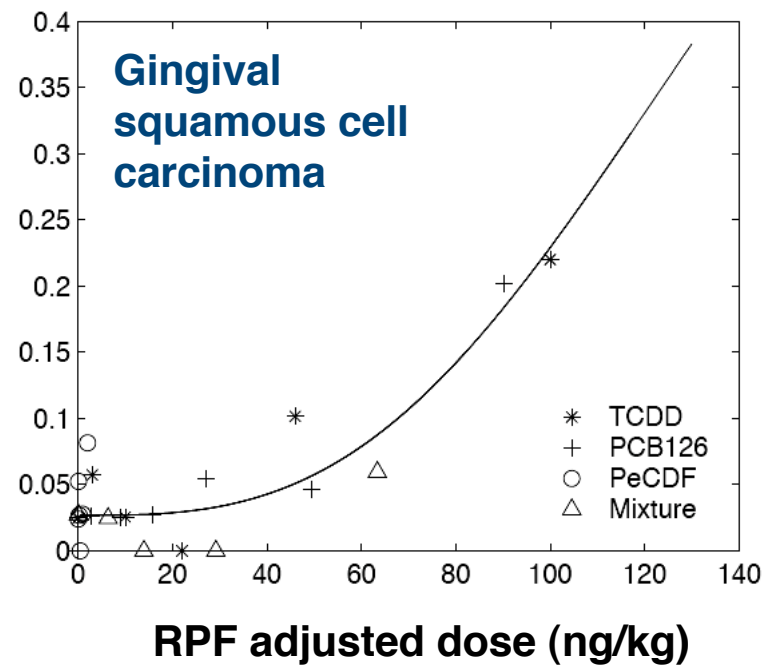
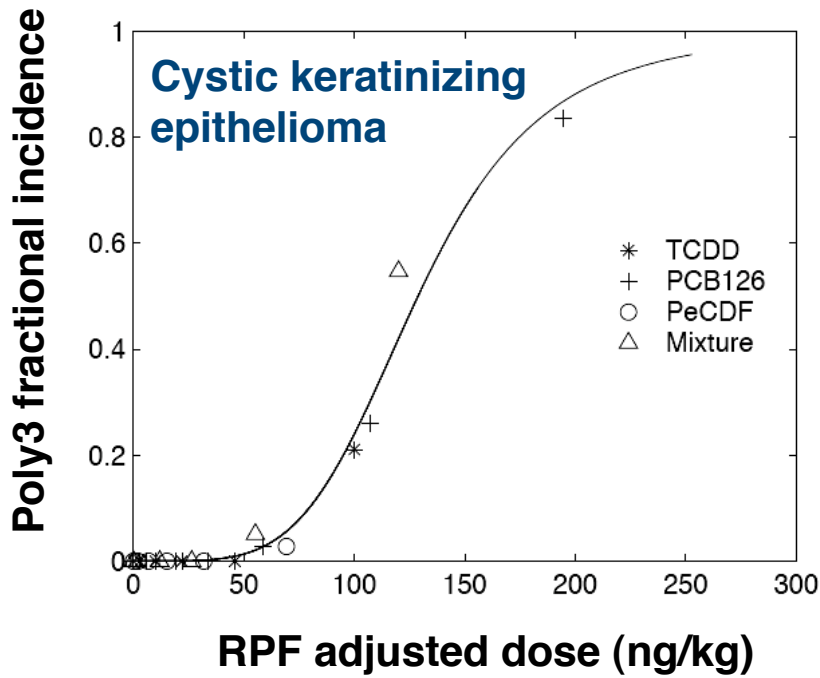
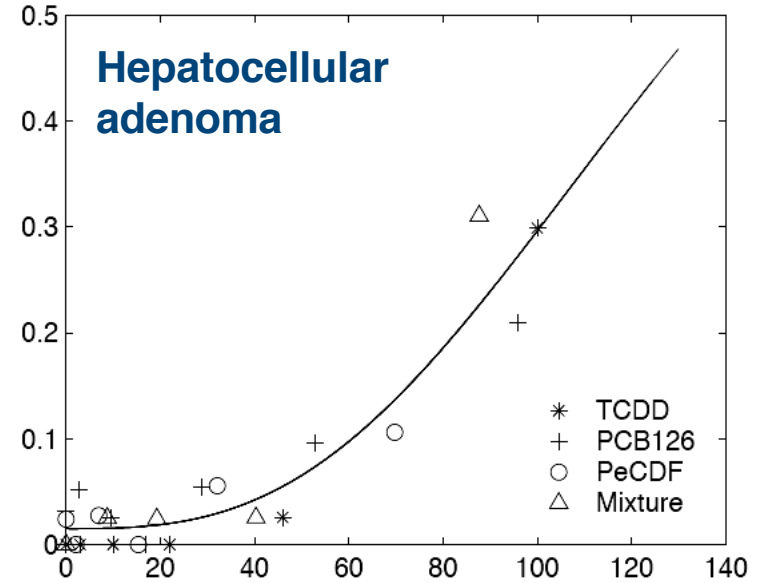
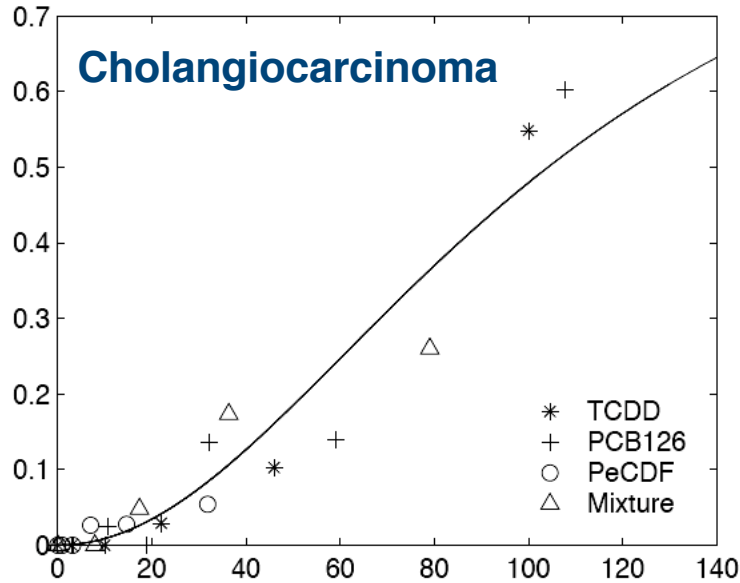
Ongoing '03-'04

- 76 Cancer studies
- 22 Reproductive tox studies
- 17 Immunotox studies
- 21 Sub-chronic tox studies
- 4 Transgenic studies
- > 100 Genetic tox studies

Research Highlights

Dioxin TEF Evaluation

- ◆ **Eight 2-year carcinogenicity studies**
 - Female Sprague Dawley rats
 - Multiple doses, times, CYPs, THs, tissue dosimetry
- ◆ **Phase I - Evaluating dose additivity and TEFs**
 - TCDD; TEF = 1.0
 - PeCDF; TEF = 0.5
 - PCB 126; TEF = 0.1
 - Ternary mixture of TCDD, PeCDF and PCB126
 - ◆ Represents approximately 48% of human TEQ
- ◆ **Phase II - Interactions between PCB classes**
 - Constant and varying ratio mixtures of PCB126 and PCB153
 - Constant ratio mixture of PCB126 and PCB118
 - PCB 118; TEF = 0.0001



Herbal Medicines



Herbs and herbal compounds under study by the NTP



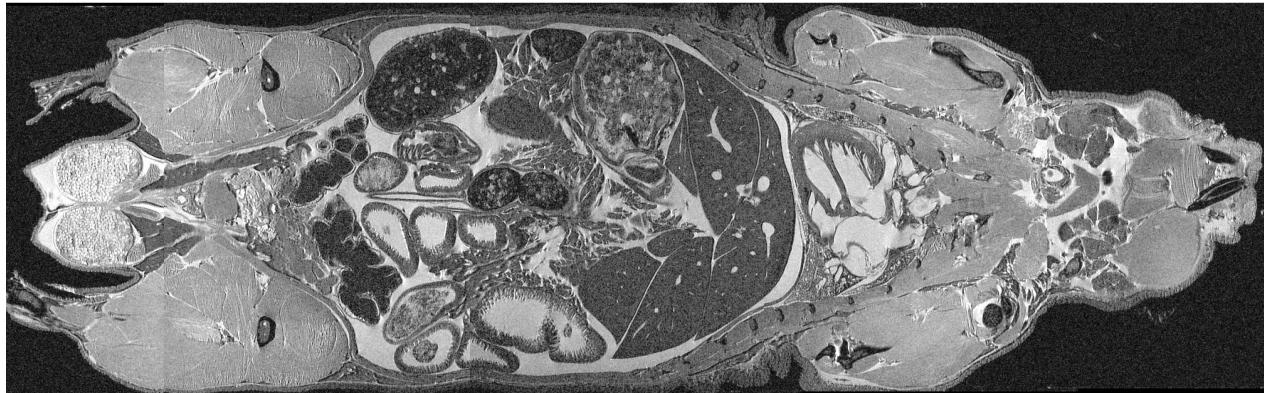
- Aloe vera gel
- Black cohosh
- Comfrey
- *Echinacea purpurea* extract
- Ephedra
- *Ginkgo biloba* extract
- Ginseng and ginsenosides
- Goldenseal
- Grape seed extract and pine bark extract
- Kava kava
- Milk thistle extract
- Pulegone
- Thujone

Cardiotoxicity

- **Histology, electrophysiology, telemetry and imaging**
 - Ephedra /caffeine
 - Bis (2-chloroethoxy) methane
 - AZT
- **Methods validation**
 - QT interval prolongation

Imaging Techniques

- ◆ **Magnetic resonance imaging (MRI)**
- ◆ **Micro computerized axial tomography (Micro CT)**
- ◆ **Ultrasound**
- ◆ **Digital pathology**



Safe Water

Water Disinfection By-Products

Effects of Algal Toxins

Toxicity of Chromium VI, Tungsten and Aluminum



RECREATION HAZARD

Blue-green algae hazard

All persons are warned that blue-green algae is present in this storage and may affect the health of persons coming into contact with the water.

The recreation hazard posed by blue-green algae varies according to the amount of algae present within the storage at any time. The current recreation hazard level should be checked before recreational activities are undertaken.

As the recreation hazard increases so does the risk of being adversely affected through these activities.

WARNING
警告

Current Recreation Hazard

medium

low high

- Swimming, sailing, water skiing, diving or any other activity involving body contact with the water may cause skin and eye irritation.
- Dangerous algal toxins can accumulate in the internal organs of fish. Remove all internal organs of fish before cooking or eating.
- Drinking or accidentally swallowing water directly from the dam may result in illness.

Hexavalent Chromium

- ◆ **Nominated by the California Congressional delegation because of widespread groundwater contamination by a known (respiratory) carcinogen**
- ◆ **NTP studies address hypothesis that hexavalent chromium is reduced to non toxic trivalent chromium prior to absorption from GI tract**
 - **Extensive kinetic studies in species with and lacking forestomach**
 - **Immunotoxicity studies**
 - **Prechronic and chronic toxicity and cancer studies by oral route**

Polybrominated Diphenyl Ethers

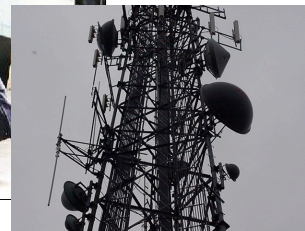
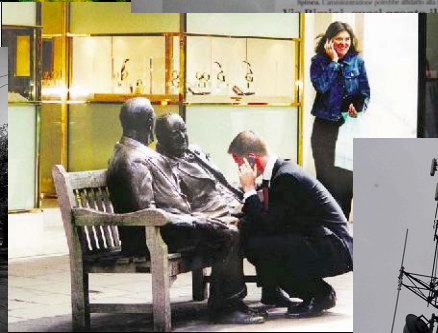
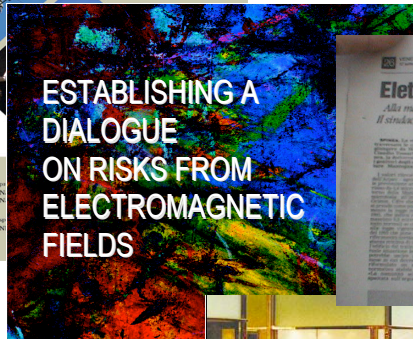
- ◆ **Components of flame retardants, nominated by Cal EPA because of human tissue burden data, possible link to human breast cancer**
- ◆ **Widespread environmental contaminants with long half lives**
- ◆ **Studies are underway with DE-71 (primarily tetrabromodiphenyl ether and pentabromodiphenyl ether) and isolated congeners**
 - **Metabolism/ toxicokinetics**
 - **Toxicological characterization**
 - **Genetic toxicity**
 - **Cancer studies in traditional models- commercial mixture DE-71**
 - **Individual congeners and DE-71 evaluated in transgenic mice (Hras2)**

Electromagnetic/Radiofrequency Radiation

Public outreach and communication

Research program on cell phones and towers

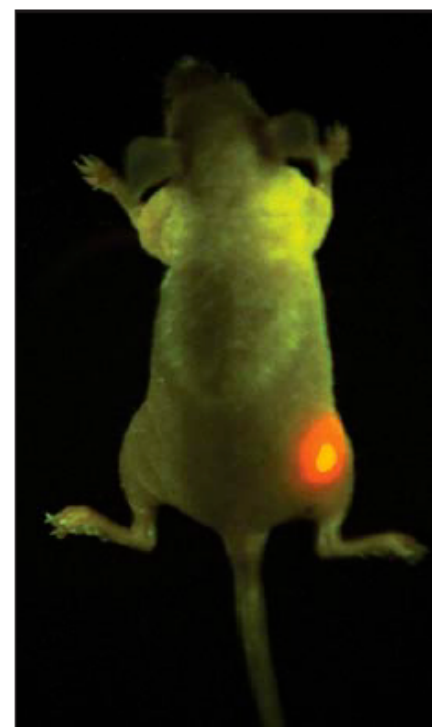
International coordination and cooperation



Nanotechnology Safety Initiative

Classes of manufactured Nanomaterials in the NTP Nanotechnology Nomination

- Ceramic, metal oxides such as TiO_2 , ZnO
- Nanocrystalline fluorescent semiconductor quantum dots
- Carbon systems - e.g. single- or multi-walled carbon nanotubes; fullerenes



Bull's-eye. Red quantum dots injected into a live mouse mark the location of a tumor.

Nanotechnology Safety Initiative

Scientific Approach

- 1) Evaluate physical and toxicological properties of major classes of manufactured nanomaterials representing a cross section of size, surface coatings and physicochemical properties and use these as model systems to study how nanomaterials interact with biological systems.
- 2) Determine appropriate methods of detection, characterization and quantification of nanoscale materials in tissues and study how materials are absorbed, distributed, taken up and eliminated by cells and organelles.

Gene Therapies

- ◆ **Current studies**
 - Evaluation of several retroviral vectors for insertional mutagenesis and leukemias, and adenoviral vectors encoding the human growth hormone gene
- ◆ **Potential risks**
 - Reproductive toxicities
 - Transmission of altered genetic material to future generations
 - Autoimmune disease or immune dysfunction
 - Allergenicity



Complex Occupational Exposures

Interagency Agreement: NIEHS/NIH and NIOSH/CDC

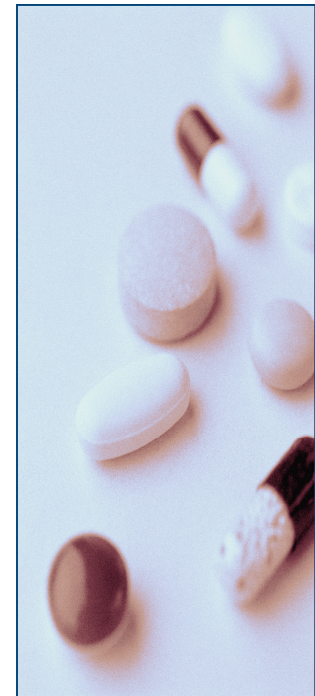
- Characterize worker exposure, identify health research gaps, and develop protocols for laboratory toxicology studies
- ◆ **Cellulose insulation**
 - Characterized cellulose insulation dust and worker exposure
- ◆ **Asphalt fumes**
 - Developed methods to characterize and reproduce fumes and monitor exposures for inhalation toxicity studies
- ◆ **1-Bromopropane**
 - Conducting industry-wide exposure assessment
 - Follow-up health and exposure evaluation of workers at major sites
- ◆ **Welding Fumes**
 - Developed methods to characterize and reproduce fumes and to monitor exposures for inhalation toxicity studies



FDA Priority Nominations

Interagency Agreement: NIEHS/NIH and FDA/NCTR

- Provide comprehensive toxicological evaluations on substances of high priority to the FDA
- ◆ **Acrylamide/glycidamide**
 - Developmental neurotoxicity, genotoxicity, carcinogenicity
- ◆ **Aloe Vera**
 - Oral studies assessing toxicity to colon
- ◆ **Ketamine**
 - Examining potential neurotoxicity to developing CNS
- ◆ **AIDS combination therapies**
 - Perinatal carcinogenicity of drugs used to prevent mother to child transmission of HIV
- ◆ **Bitter Orange**
 - Developmental toxicity and cardiac function for this ephedra replacement



Endocrine Disruptor Initiative

Interagency Agreement: NIH/NIEHS and FDA/NCTR to study estrogenic substances in multiple generations:

- Reproductive, developmental and carcinogenicity studies including neurotoxicity and immunotoxicity endpoints

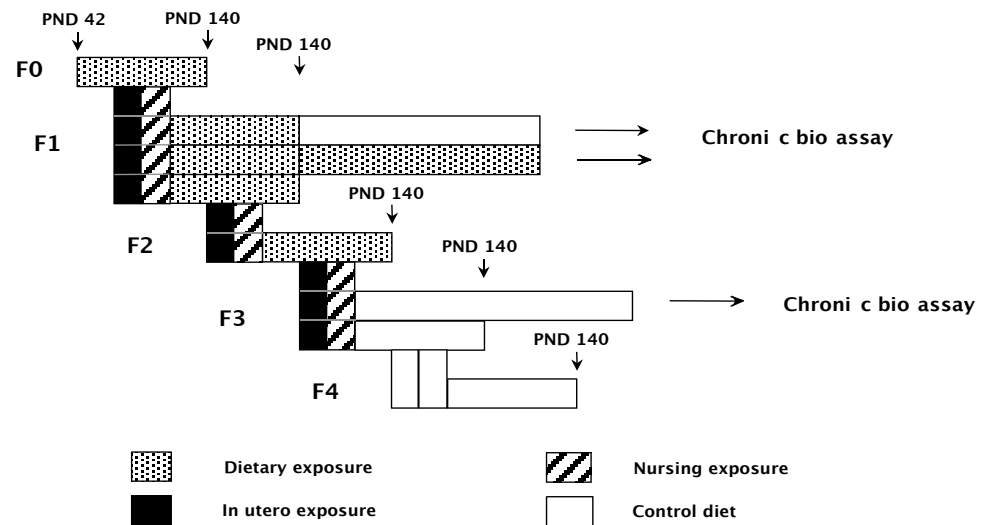
Nonylphenol

Genistein

Ethinyl estradiol

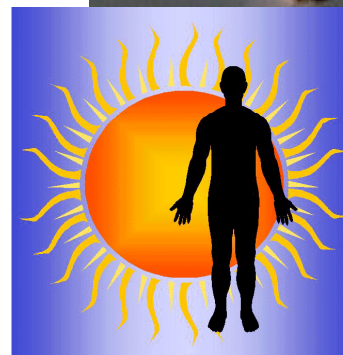
Vinclozolin

Multigeneration Dosing Schedule



NTP Center for Phototoxicology

- ◆ Located at NCTR
- ◆ Conducts mechanistic-based research and phototoxicology and photocarcinogenesis studies
- ◆ State-of-the-art laboratory
- ◆ Current research
 - Alpha- and beta- hydroxy acids
 - Aloe vera
 - Retinyl palmitate
 - Nanoscale materials



Transgenic Animals in Cancer Testing

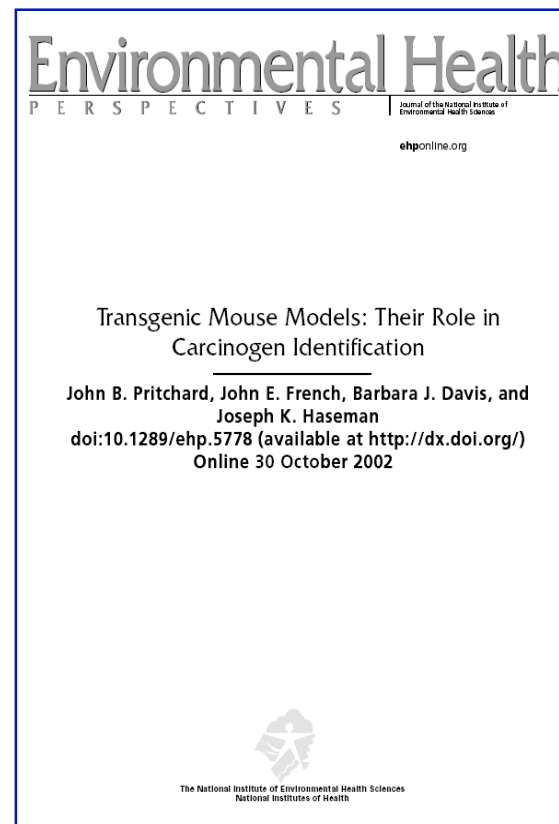
- ◆ **Goal**
 - Replace and reduce number of animals used
 - Reduce testing time
 - Increase use of mechanistic information
- ◆ **Evaluate effectiveness of existing transgenic testing results**
- ◆ **Develop guidelines for when to use specific models**



Transgenic Mouse Models

Pritchard et al. evaluation

- ◆ Concordance of selected model results with IARC and ROC carcinogen lists
- ◆ Design and analysis issues



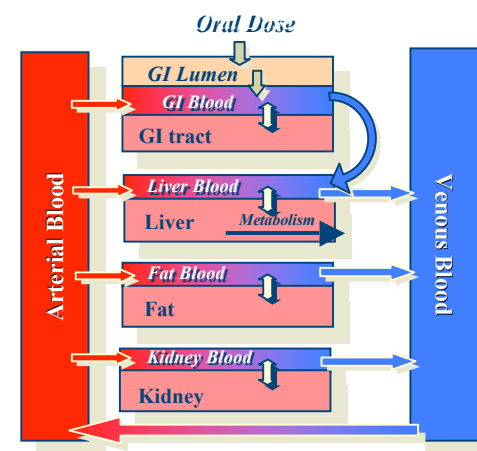
Toxicogenomic Research

- ◆ **With NCT, identify patterns of gene expression for**
 - **Common mechanisms**
 - **Common toxicities**
- ◆ **Ongoing genomics studies**
 - **Sentinel animal aging study**
 - **Aflatoxin B1 hepatocarcinogenesis**
 - **Allyl- propylbenzenes class study**
 - **Algal toxin hepatotoxicity**



Mechanism-Based Mathematical Modeling

- ◆ PBPK models to more fully develop exposure response relationships
- ◆ Further develop models of biochemical pathways and link these pathways to toxicogenomic information

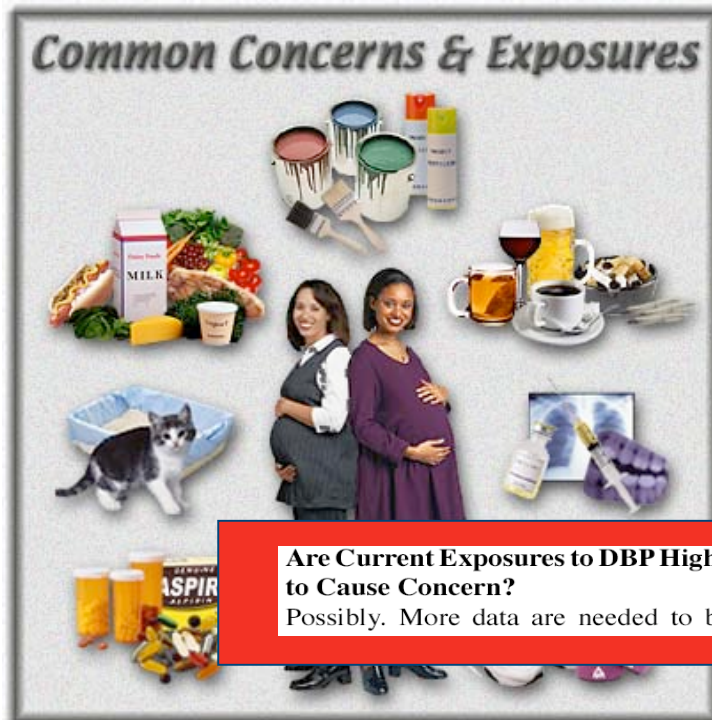


Center for the Evaluation of Risks to Human Reproduction

Provides assessments of adverse effects on reproduction and development caused by agents in the environment



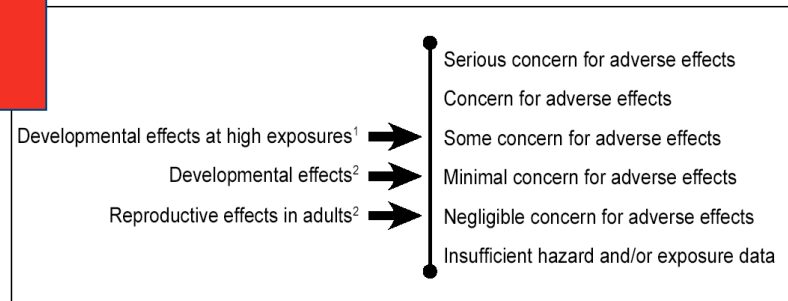
NTP-CERHR Monographs



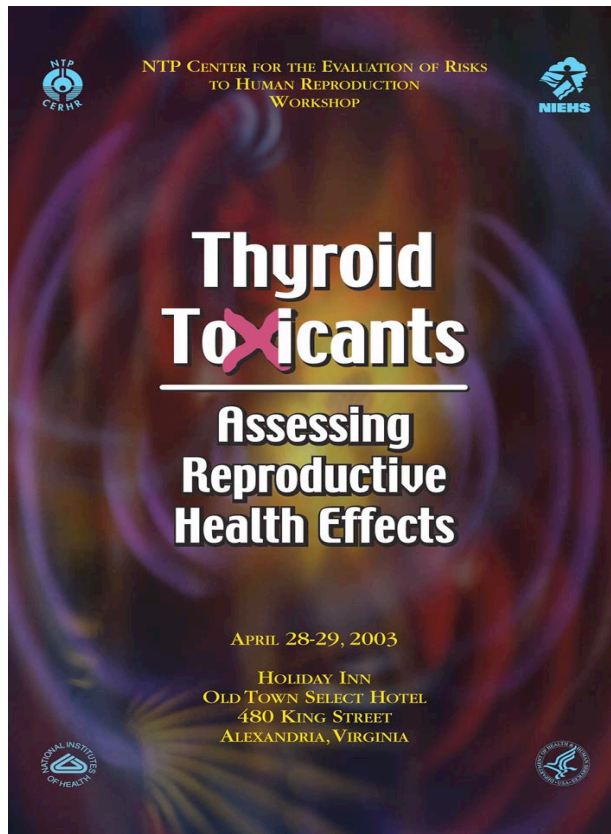
Are Current Exposures to DBP High Enough to Cause Concern?
Possibly. More data are needed to better un-

- ◆ 16 Working Groups
- ◆ 13 Monographs
- ◆ Recent: Prozac, Acrylamide, and Ritalin
- ◆ Upcoming: DEHP, Styrene

Figure 3. NTP conclusions regarding the possibilities that human development or reproduction might be adversely affected by exposure to DBP



CERHR/NTP Workshops



- ◆ Identify general mechanisms and chemical effects that are likely to impact on human health
- ◆ Lay a stronger foundation for mechanism-based toxicology

NTP Interagency Center for the Evaluation of Alternative Toxicological Methods

- ◆ Facilitates the development, scientific review, and validation of alternative toxicological test methods
- ◆ Interagency Coordinating Committee on the Validation of Alternative Methods (ICCVAM)
 - Established in 2000 as a permanent interagency committee under NICEATM
- ◆ Current activities
 - *In vitro* endocrine disruptor screening methods
 - Refinements to *in vitro* ocular toxicity methods
 - OECD guidance documents on *in vitro* GLPs and validation process
 - *In vitro* alternatives for testing vaccine efficacy



NTP Research Databases



- ◆ Available on the NTP website (<http://ntp.niehs.nih.gov/>)
- ◆ Expanding public accessibility to NTP data to include all study types
- ◆ Providing web-based applications for using data

Expectations

- ◆ Continue to provide basic toxicology information for public health protection
- ◆ Increase emphasis on understanding and explaining exposure-response relationships
- ◆ Integrate results from new “data rich” techniques, genomics, proteomics, etc.
- ◆ Develop new methodologies for toxicological assessments
- ◆ Provide guidance for the proper utilization of new types of information in hazard identification and characterization

The NTP Today

- ◆ **Leading the nation in research aimed at the prevention of environmental causes of disease**
- ◆ **Providing the science that supports public health decisions regarding environmental exposures**
- ◆ **Partnering with all stakeholders to improve risk characterization and assessment**
- ◆ **Developing the tools to move toxicology and risk assessment forward to meet the demands of the 21st century**