



**NTP**  
National Toxicology Program

# National Toxicology Program Update

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## Outline

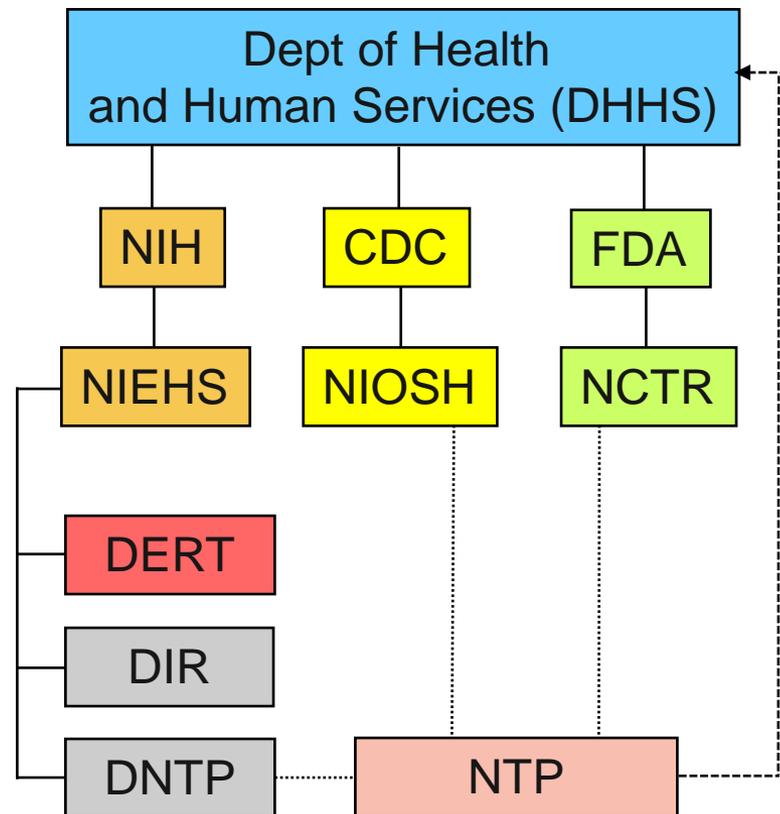
- NIEHS/NTP activities
- Toxicology in the 21st Century (Tox21)
- NCTR-NIEHS opportunities



## National Toxicology Program

- Interagency program established in 1978
- Thousands of agents evaluated in comprehensive toxicology studies and GLP compliant studies
- Report on Carcinogens (RoC)
- Office of Health Assessment and Translation (OHAT)
- NTP Interagency Center for the Evaluation of Alternative Toxicological Methods (NICEATM)

[ntp.niehs.nih.gov](http://ntp.niehs.nih.gov)





## **NIEHS/NTP research activities of interest in 2014/15**

- 2 NTP technical reports on rodent carcinogenicity
  - Green tea extract (Botanical ingredient)
    - No evidence of carcinogenicity
    - Clear toxic effects though in multiple tissues including liver, nose, GI, BM
  - Indole-3-carbinol (Dietary supplement)
    - Some evidence; female rats uterus/Clear evidence in male mouse liver
- New research
  - BPA alternatives, BPAF, BPS and derivatives
  - Triclocarban, Triclosan



## **NIEHS/NTP “analysis” activities of interest in 2015**

- New Report on Carcinogens Concepts (reviewed in 2014)
  - Selected Viruses
  - Goldenseal Root Powder
  - Cobalt
- Draft Office of Health Assessment and Translation Concepts
  - Inflammation-based Atherosclerosis Associated with Environmental Exposures
  - NIEHS-EPA Collaborative Project on Personal Care Product and Home Exposures
  - Immunotoxicity of Perflurooctanoic Acid (PFOA) and Perfluorooctane Sulfonate (PFOS)

## Systematic Review

- Developing a framework for integrating systematic review methodology into its literature-based analysis activities.
- Meetings with international groups about OHAT Approach for Systematic Review and Evidence Integration for Literature-based Health Assessments
- “Lessons learned” public webinar: July 2014
- Development of a systematic review approach for in vitro data in partnership with WHO
- Systematic review and evidence integration for literature-based environmental health science assessments. Rooney, AA, Boyles, AL, Wolfe, MS, Bucher, JR, Thayer, KA. (2014) Environ. Health Perspect.





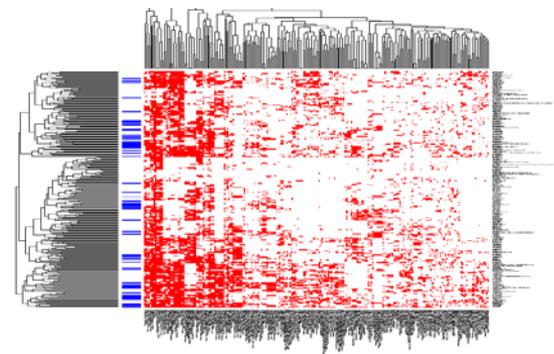
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## Toxicology in the 21st Century (Tox21)

- NTP Vision and Roadmap 2004 goal
  - “Develop a high throughput capability for mechanistic targets”
- Interagency collaboration
  - NIEHS/DNTP, US EPA, NIH/NCATS, FDA
- Main goals
  - Identify mechanisms of action
  - Prioritize substances for further in-depth toxicological evaluation
  - Develop predictive models for in vivo biological response
- Revised 5-year MoU to add FDA signed on July 19, 2010





## Tox21” - Phase II (2011-14)

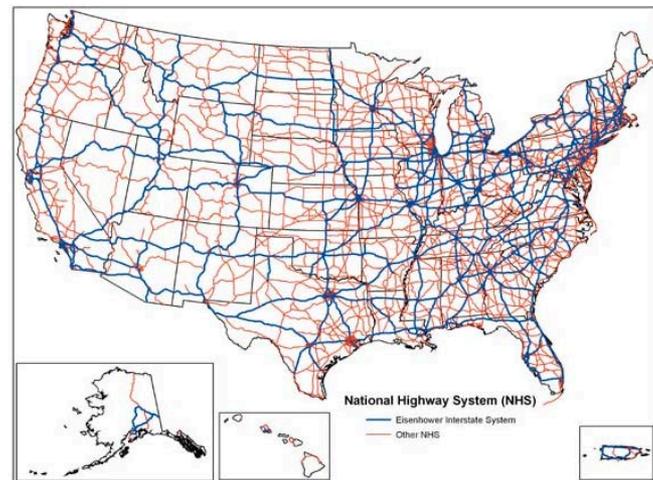
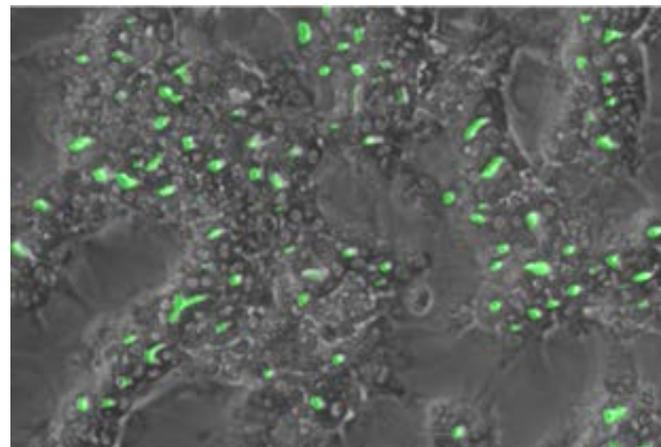
- "EPA's ToxCast™: ~700 compounds in ~700 assays, ~1000 compounds in endocrine activity assays
  - NCGC qHTS Phase II: 10K compound library: nuclear receptor activation or inhibition, induction of cellular stress response pathways, characterizing human variability in response
- Lessons learned paper
  - Tice RR , Austin CP et al EHP 2013
- Systematic study of mitochondrial toxicity of environmental chemicals using quantitative high throughput screening.
  - Attene-Ramos MS, Huang R et al 2013
- Profiling of the Tox21 10K compound library for agonists and antagonists of the estrogen receptor alpha signaling pathway.
  - Huang R, Sakamuru S et al 2014



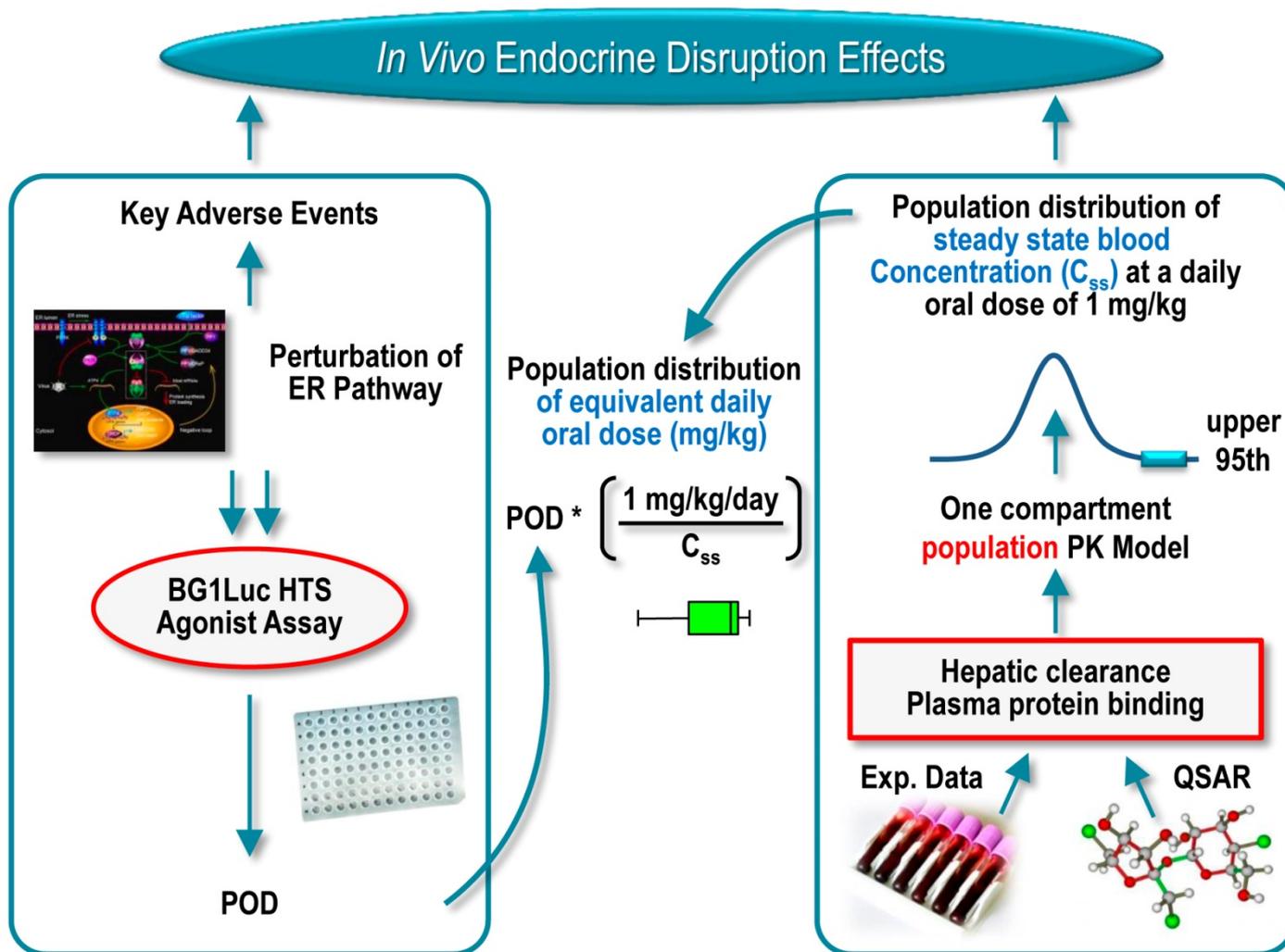
## Tox21 Phase III

- Increased focus on tools for in vitro concentration to in vivo extrapolation
- Different cells systems
  - capable of xenobiotic metabolism (primary hepatocytes, HepaRG, HepG2 3D)
  - ES/iPSC derived differentiated cell populations
- Expanded utilization of lower organisms (zebrafish, nematode)
  - High content screening
- High-throughput transcriptomics project
  - Selection of 1500 “sentinel” genes
  - Genes are included to ensure maximal biological pathway coverage.

HepaRG Cells



# Use of PK/PBPK Modeling for Reverse Dosimetry



Abbreviations:  $C_{ss}$  = steady-state blood concentration; POD = point of departure; QSAR = quantitative structure-activity relationship.



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## **NIEHS-NCTR interagency agreement (1993-present)**

- Ensure toxicology studies provide FDA regulatory scientists with appropriate data for regulatory decision making
- Oversight provided by twice year TSSRC meetings between NIEHS and NCTR staff and FDA center representatives
- Portfolio areas
  - Botanicals/Dietary Supplements (eg aloe vera)
  - Food contaminants (eg acrylamide)
  - Endocrine Active Agents (eg BPA)
  - Drugs and Devices (eg AIDS combination therapeutics)
  - Nanoscale materials
  - Phototoxicants/Photocarcinogens (eg retinyl palmitate)
- 19 NTP technical reports, >200 publications



## Needs and Opportunities

- Regulatory science
  - Improve interactions between academic, govt and regulatory scientists
  - Lessons learned from CLARITY-BPA
- Tox21
  - Targeted interrogation of relationships based on Tox21 data
  - Improve science base for In vitro- in vivo extrapolation (IVIVE)
  - Development of metabolically capable multicellular systems
- Application of alternate approaches
  - Botanical dietary supplements
  - Mixtures



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