NTP
National Toxicology Program

Background on NTP's Proposed Approach to Genomic Dose-Response Modeling and Panel Charge

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Expert Panel Meeting on the Peer Review of Draft NTP Approach to Genomic Dose-Response Modeling
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Acknowledgments – NTP Proposed Approach

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National Toxicology Program
U.S. Department of Health and Human Services

Fred Parham
Mary Wolfe

A Method to Integrate Benchmark Dose Estimates with Genomic Data to Assess the Functional Effects of Chemical Exposure

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Software

Open Access

BMDExpress: a software tool for the benchmark dose analyses of genomic data

Longlong Yang[1], Bruce C Allen[2] and Russell S Thomas*[1]

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Jason Pirone

Hepatic transcriptomic alterations for *N*,*N*-dimethyl-*p*-toluidine (DMPT) and *p*-toluidine after 5-day exposure in rats

June K. Dunnick[1] · Keith R. Shockley[2] · Daniel L. Morgan[3] · Amy Brix[4] · Gregory S. Travlos[5] · Kevin Gerrish[6] · J. Michael Sanders[7] · T. V. Ton[5] · Arun R. Pandiri[5]

Ginkgo Biloba Extract 5 Day Genomics Studies

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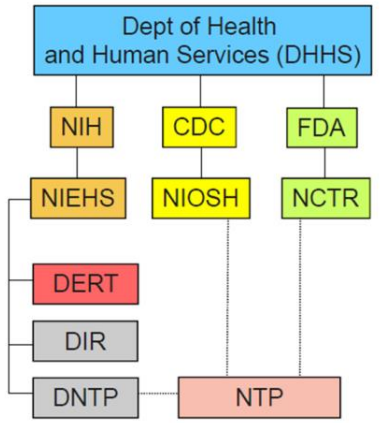
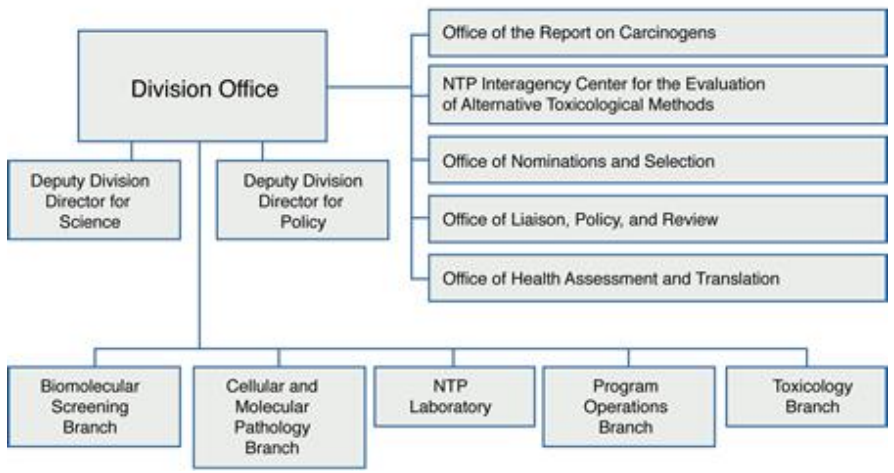
Bruce Allen

National Toxicology Program

- Interagency program
  - Established in 1978 to coordinate toxicology research in DHHS
  - Headquartered at NIEHS, part of NIH
- Research on submitted "nominations"
  - Thousands of agents evaluated in comprehensive toxicology studies
  - GLP compliant testing through government contracts
- Analysis activities
  - Report on Carcinogens (RoC)
  - Office of Health Assessment and Translation (OHAT)
  - NTP Interagency Center for the Evaluation of Alternative Toxicological Methods (NICEATM)

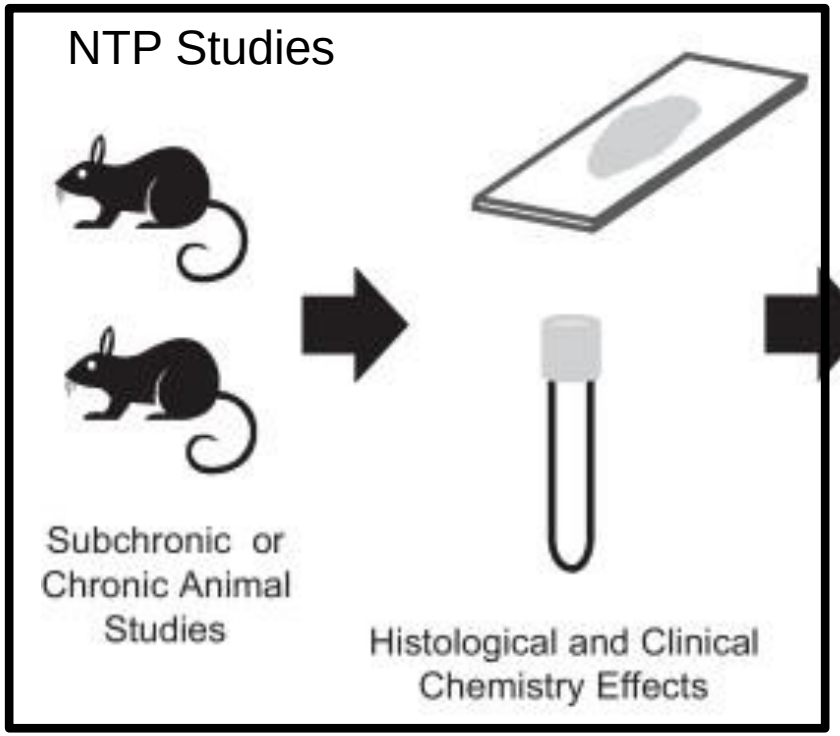
ntp.niehs.nih.gov

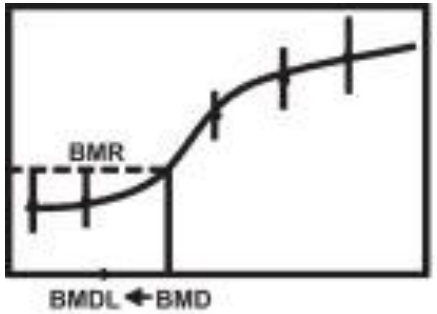




Use of NTP Data

Adapted from Thomas et.al., Mut. Res., 2012





$$\frac{BMD_{L=POD}}{\text{Uncertainty Factors}}$$

Reference Dose

Human Exposure Limits (e.g., food, water, air)

- BMR = Benchmark Response = Pre-defined level of effect (e.g., 20% decrease testosterone levels)
- BMD = Benchmark Dose = Dose that produces pre-defined level of effect based on D-R model

Testing Challenge

- Guideline toxicity assessments can take a significant amount of time and resources and NTP wants to be more responsive
- Need more efficient means of approximating apical BMDs of test articles – Get to a number faster!

Addressing the Testing Challenge

- Short-duration: Tox21
  - Phase 1 and 2: Targeted high throughput screening on a large set of chemicals (~10,000)
  - Phase 3: In vitro, genomic (transcriptomics) dose-response studies (GDRS) in organotypic testing systems
  - Coupled to IVIVe to estimate external dose potency
- Intermediate Duration: In vivo GDRS in target tissues (rodents)
- Why GDRS?
  - Massive parallel screening of biological space
  - Direct measurement of biological systems
  - Cross-species comparability
  - Relatively inexpensive

How do we design, analyze, and interpret GDRS?

NTP's Goal and Key Criteria GDRS

Overall Goal:

A biologically **comprehensive**, **efficient** assessment of test articles that can be used to estimate **biological potency** and **highlight associations** between **transcriptomic changes** and potential **toxicological effects**

- Employ trusted model systems (e.g., rats, HepaRG)
- Study design should support accurate biological potency estimates
- Potency estimates should be on a gene set level
- Ease of translation
  - Consider target audience….toxicology testing and regulatory community
  - As much as possible the analysis approach should be aligned with current regulatory practice
  - An attempt at association of transcriptomic findings with effects of toxicological concern

How do we envision GDRS results being used?

- Primary Use
  - Developing biological potency estimates that can be used to identify screening level exposure limits
  - Margin of exposure prioritization
    - **Incorporating new technologies into toxicity testing and risk assessment: moving from 21st century vision to a data-driven framework**
      - Thomas et. al., Toxicological Sciences, 2013
- Secondary Use
  - Identification of **potential** toxicological effects
  - Not intended for traditional hazard identification
    - Intention is to grow into this area
    - For more complicated endpoints (e.g., Cancer, Development) there remains much work to be done and data to be generated

Charge

- The expert panel is charged to:
  - (1) Review the proposed approach
  - (2) Recommend whether NTP should use the approach
  - (3) If recommended for use, identify any needed modifications or additional studies that would improve the approach.
- If the expert panel does not recommend use of the proposed approach, they are asked to
  - (1) Propose an alternative approach, if readily available
  - (2) Identify the elements that should be included in an alternative approach.