

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
October 23, 2017



Fred Parham
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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 Yang¹, Bruce C Allen² and Russell S Thomas*¹



Acknowledgements: Meeting and Webinars



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Acknowledgements: Data

S1500+ **HepaRG** **Data**



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

Bio:Spyder

Sciome

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

June K. Dunnick¹ · Keith R. Shockley² · Daniel L. Morgan³ · Amy Brix⁴ ·
Gregory S. Travlos⁵ · Kevin Gerrish⁶ · J. Michael Sanders⁷ · T. V. Ton⁵ ·
Arun R. Pandiri⁵

Ginkgo Biloba Extract 5 Day **Genomics Studies**

Cynthia Rider
Molly Vallant



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Sciome

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National Toxicology Program

- Interagency program

- Established in 1978 to coordinate toxicology research in DHHS
- Headquartered at NIEHS, part of NIH

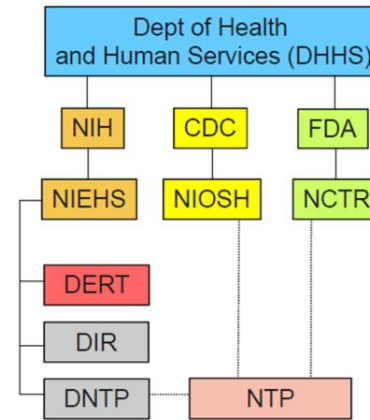
- Research on submitted “nominations”

- Thousands of agents evaluated in comprehensive toxicology studies
- GLP compliant testing through government contracts

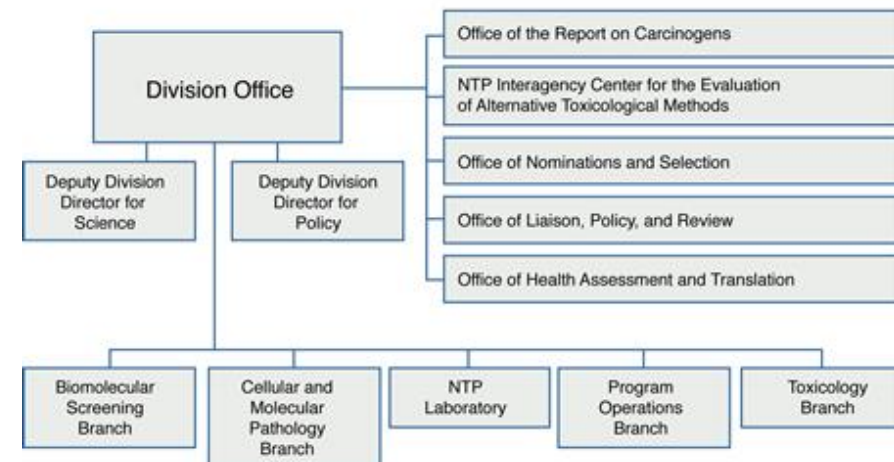
- Analysis activities

- 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

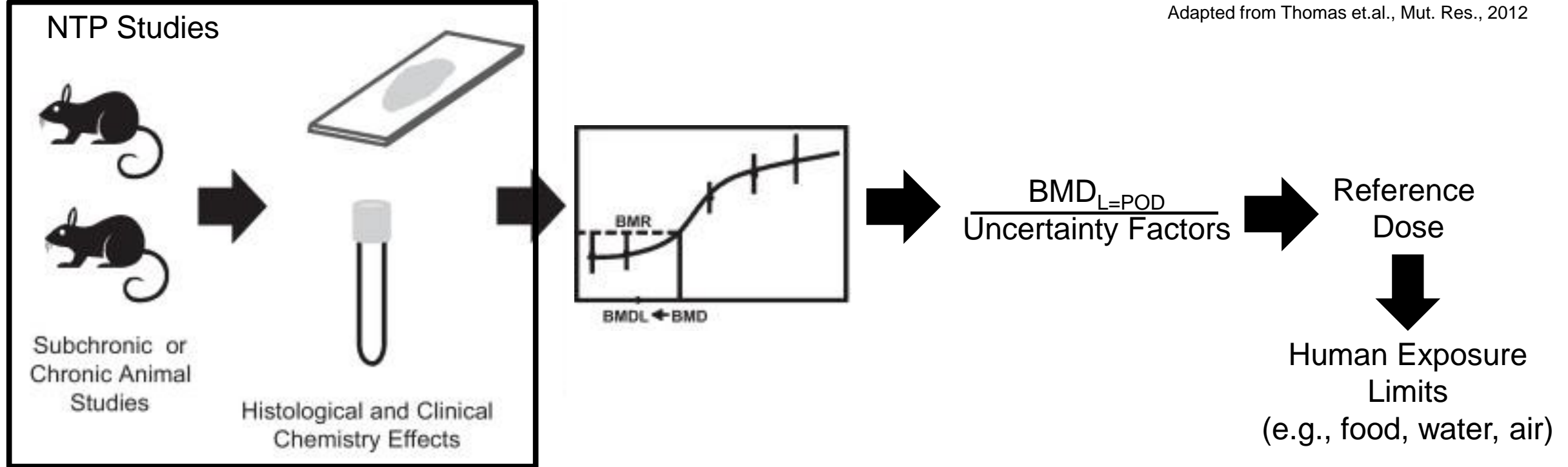


NIEHS Division of the National Toxicology Program





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



- 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?



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



- 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.