NTP
National Toxicology Program

Conduct of Studies to Evaluate the Toxicologic Potential of Selected Test Agents for the NTP

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Background and Significance

- NTP has a long history of conducting toxicity and carcinogenicity studies in laboratory animals as part of its mandate to characterize the toxicity of agents of public health concern
- Toxicology studies are typically conducted according to the following NTP Specifications
  - toxicity and carcinogenicity studies

    https://ntp.niehs.nih.gov/ntp/Test_Info/FinalNTP_ToxCarSpecsJan2011.pdf
  - reproductive and developmental toxicology studies

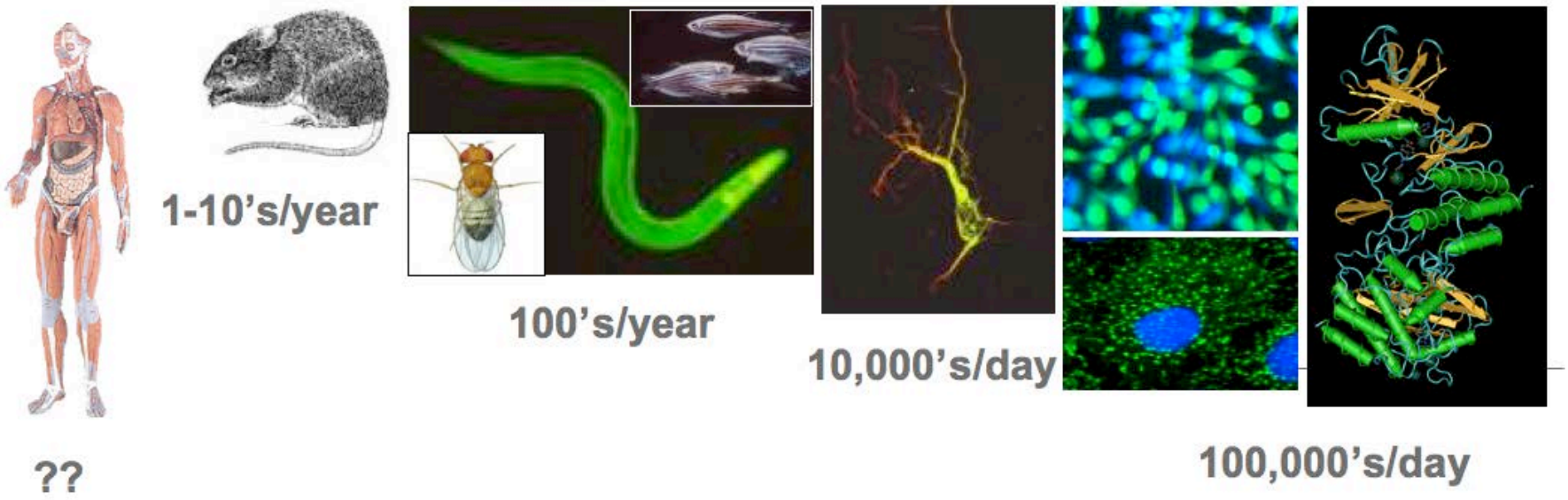
    https://ntp.niehs.nih.gov/ntp/test_info/finalntp_reprospecsmay2011_508.pdf

Existing Contract Activities

- In vivo Toxicology studies
  - Exposure paradigms: perinatal and adult
  - Durations: acute → chronic
  - Routes: Oral, dermal, intra-peritoneal, sub-mandibular cannulation, inhalation
  - Species: rats, mice, hamsters, guinea pigs, dogs
  - Endpoints:
    - In life toxicity evaluations and histopathology
    - Biochemical and molecular assays
    - Functional assessments – cardiac/pulmonary toxicity, reproductive/developmental toxicity, neurotoxicity

Evolving NTP Testing Paradigm

Biological levels and hazard evaluation strategies



Purpose of the Contract

- To conduct *in vitro* and *in vivo* studies with special emphasis on novel approaches and methodologies along with alternative animal models to facilitate NTP's efforts to characterize the potential adverse effects of test agents
  - *In vitro* studies using tissues, cells or cell components on groups/classes of chemicals
  - In vivo toxicology studies with an emphasis on functional and molecular endpoints
  - Incorporation of alternative animal models

Anticipated in vitro assays/alternative animal models

- In vitro assays
  - cellular stress pathways
  - cell death
  - receptor signaling pathways
  - transcriptomics
  - cellular communication
  - active transport
  - metabolism and disposition
  - cell differentiation
  - cell and tissue culture models
  - epigenetics
- Alternative animal models
  - C. elegans
  - Zebrafish

Anticipated Biochemical and Molecular Endpoints

- Biochemical assays
  - (e.g. Cytochrome p450, Cholinesterase Inhibition)
- “Omics” Platforms
  - Toxicogenomics – whole transcriptome microarrays
  - miRNA microarrays to capture small RNA species for microarray or qPCR applications
  - Nexgen Sequencing for Gene expression profiling by RNAseq (e.g. mRNA or miRNA)
  - Genomic sequencing (e.g. whole genome, exome sequencing) by DNAseq
  - Multiplexing of many transcripts and several samples at once such as Nanostring™ nCounter system

Anticipated Functional Assessments

- Neurotoxicity endpoints
  - detailed clinical observations, functional observation battery, motor activity, Morris water maze, prepulse startle inhibition
- Newer technologies for gait analysis
  - e.g. DigiGait, Motorater, or Catwalk
- Reproductive and developmental assessments
  - e.g. fertility, developmental landmarks, etc.
- Cardiac and pulmonary assessments
  - cardiac function using radio telemetry,
  - Pulmonary function using Flexivent or plethysmography

Proposed Changes to the Current SOW

- Expansion of current capabilities with an emphasis on:
  - *In vitro* studies
  - Use of alternative animal models
  - Developmental exposures
  - Evaluations of functional and molecular endpoints using current and advanced technologies

The BSC members are asked to review the concept for overall value and scientific relevance, as well as for fulfilling the program goal of protecting public health.

The NTP seeks approval from the BSC to continue this type of activity using a contract mechanism.