NIEHS/DNTP Portfolio in Support of NTP

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NTP Board of Scientific Counselors Meeting
June 17, 2019
• Some NTP basics
• Describing the DNTP portfolio
• Survey of current research
• Shift and alignment
• Structure and focus
• Planning for the future
Division of the National Toxicology Program (DNTP)
Funding

<table>
<thead>
<tr>
<th>Year</th>
<th>Amount</th>
<th>Percentage</th>
</tr>
</thead>
<tbody>
<tr>
<td>FY 2016</td>
<td>$130.9 million</td>
<td>104.5% (80%)</td>
</tr>
<tr>
<td>FY 2017</td>
<td>$133.5 million</td>
<td>$109.7 (82%)</td>
</tr>
<tr>
<td>FY 2018</td>
<td>$136.7 million</td>
<td>$112.1 (82%)</td>
</tr>
<tr>
<td>FY 2019</td>
<td>$134.3 million projected</td>
<td>$113.6 (85%)</td>
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</tbody>
</table>

Legend:
- NIEHS
- NIOSH
- NCTR
Capabilities and mechanisms

• NIEHS contracts
  – 30 contracts in FY2018

• In-house research
  – Experimental, computational, evaluative

• Interagency agreements
  – FDA/NCTR  – EPA/NCCT
  – CDC/NIOSH  – EPA/NCEA
  – NIH/NCATS  – DOE/ORNL
DNTP Operations

• Project and product centered research
• Shared resources, managed centrally
  – Individual projects/people are not "funded"
• Distributed governance
  – Internal decision-making largely consensus-based
• Teams assembled to include appropriate:
  – Disciplines, expertise, roles

Product

Process
Primary outputs

- Technical Reports
- Toxicity Reports
- Research Reports
- Monographs
- Report on Carcinogens
- Scientific journal articles

- Data (e.g. CEBS)
- Databases (e.g. ICE)
- Computational tools (e.g. DNT-DIVER)
- Research resources (e.g. Nonneoplastic Lesion Atlas)
- Presentations and posters

CEBS: https://manticore.niehs.nih.gov/cebssearch/
ICE: https://ice.ntp.niehs.nih.gov
DNT-DIVER: https://sandbox.ntp.niehs.nih.gov/neurotox/
NNL Atlas: https://ntp.niehs.nih.gov/nnl/
Examples of NTP products cited by health agencies

- Federal rulemakings
  - EPA dust-lead hazard standards
    - *OHAT Low-Level Lead Monograph* (2012)
- California EPA Proposition 65
  - Cancer hazard determinations
- Health guidance
  - NIOSH List of Hazardous Drugs in Healthcare Settings

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Broadly defined

- **Portfolio definition (Oxford)**
  - “A range of products or services offered by an organization”

- **Portfolio as a unifying concept**
  - All scientific activities

- **Tangible components**
  - Research products, programs, projects, studies

- **“Soft” components**
  - Advice, consultations, outreach, support, training
Structure and components

- Organized largely around capability and discipline
- Descriptors
  - Types of substances
  - Types of studies
  - Types of methods/approaches
  - Types of products
- Mammalian toxicology
  - Repeat dose toxicology
  - Carcinogenicity bioassays
  - Immunotoxicology
  - Developmental and reproductive toxicology
  - Neurotoxicology
  - Genetically modified models
- Alternative models
  - Zebrafish
  - HepaRG spheroids
- ADME/Toxicokinetics
- Analytical chemistry
- Bioinformatics
- Biological modeling
- Computational toxicology/QSAR
- Genotoxicity
- Literature scoping
- Molecular pathology
- Systematic review
- Transcriptomics
<table>
<thead>
<tr>
<th>Types of Substances Evaluated</th>
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</thead>
<tbody>
<tr>
<td>• Antimicrobials</td>
</tr>
<tr>
<td>• Biological agents</td>
</tr>
<tr>
<td>• Botanicals and dietary supplements</td>
</tr>
<tr>
<td>• Consumer products</td>
</tr>
<tr>
<td>• Cyanotoxins</td>
</tr>
<tr>
<td>• Dietary and drinking water exposures</td>
</tr>
<tr>
<td>• Endocrine active substances</td>
</tr>
<tr>
<td>• Flame retardants</td>
</tr>
<tr>
<td>• Food additives/contaminants</td>
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<tr>
<td>• Industrials</td>
</tr>
<tr>
<td>• High threat agents</td>
</tr>
<tr>
<td>• PAHs</td>
</tr>
<tr>
<td>• PFAS</td>
</tr>
<tr>
<td>• Metals</td>
</tr>
<tr>
<td>• Mixed exposures</td>
</tr>
<tr>
<td>• Molds and mycotoxins</td>
</tr>
<tr>
<td>• Nanomaterials</td>
</tr>
<tr>
<td>• Natural products</td>
</tr>
<tr>
<td>• Oil and gas chemicals</td>
</tr>
<tr>
<td>• Particles and fibers</td>
</tr>
<tr>
<td>• Pesticides</td>
</tr>
<tr>
<td>• Physical agents</td>
</tr>
<tr>
<td>• Safer alternatives</td>
</tr>
<tr>
<td>• Therapeutics</td>
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Current DNTP Research Portfolio

Project categories

• Research and Testing Activities
  – Toxicology studies
  – Tox21 and biomolecular screening
  – New, revised, or alternative test methods
  – Investigative studies

• Analysis Activities
  – Non-cancer health effects
  – Cancer hazards

Disposition, metabolism, and toxicokinetics

Genetic toxicity

Systems Toxicity
  - Immune, developmental, reproductive

General toxicology and carcinogenicity
  - 5 days → 2 years

Toxicogenomics

Research and Testing Activities

Toxicology studies

Research and Testing Activities

Tox21 and biomolecular screening

- Develop, apply, and evaluate innovative high-throughput and/or high-content approaches to characterize the impact of chemicals on key steps in toxicity pathways

- Ongoing projects
  - Assay development
  - Data analysis
  - Screening/testing

New, revised, or alternative test methods

- Development of non-animal approaches
  - Acute systemic toxicity
  - Botulinum neurotoxin testing
  - Cardiotoxicity
  - Developmental toxicity
  - Endocrine disruptor activity
  - Skin sensitization
  - Ocular irritation

- Test method evaluations
  - Electrophilic allergen screening assay
  - OptiSafe
  - EpiAirway™

Investigative studies

- Agent-specific, targeted research on specific substances of concern to NTP
  - Botanicals, crumb rubber, PFAS, PAHs
- Development of methods and capabilities to advance the NTP mission
  - Metabolomics
  - Complex in vitro systems
  - In vitro imaging and pathology
- Mechanisms of neurotoxicity and the developmental basis of adult disease

Evaluating non-cancer health effects

- Human health hazard assessments
- Scoping reviews
- Evidence maps
- State-of-the-science evaluations
- Improving systematic review and evidence integration methods

https://ntp.niehs.nih.gov/pubhealth/hat/selected/topic.html
Evaluating human cancer hazards

- Integrated cancer hazard evaluations
  - Consideration for new editions of the *Report on Carcinogens*

- 14th *Report* (2016): 248 listings

- Improving methods for evaluating mechanistic evidence to inform carcinogenicity assessments


*Monograph on Halocetic Acids Found as Water Disinfection By-Products*

March 2018

*Monograph on Helicobacter pylori (Chronic Infection)*

October 2018
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• All projects – Study Type Grouping

• Counts of test substance x study → not equivalent to level of effort

• N = too many!

• Dissatisfaction with transit time through conduct and reporting pipeline

• Working through prioritization and managed attrition
Substance-Focused

Programmatic Strategy

Testing Capability Investigation

- Focused
- Aligned
- Complementary

Strategic Shift

Testing Capability development
Mechanistic investigation

- Studies
- Projects
- Programs
Some things old, some things new

• Broad scientific areas
  – Substance-based hazard evaluations
  – Understanding environmental contribution to human disease
  – Targeted capability development

• Discrete scientific programs
  – Health Effects Innovation Programs
  – Exposure-Based Research Themes
  – Responsive Research
Targeted capability development

- Directly support/enable scientific initiatives
- Leverage and improve upon existing strengths
- Intentionally developed to fill in blind spots, clear path to application
Strategic Areas of Focus

**Health Effects Innovation Programs**
- Cardiovascular Health Effects Assessment
- Re-Envisioning Carcinogenicity Assessment
- Developmental Neurotoxicity Modeling

**Exposure-Based Research Themes**
- Combined Exposures and Mixtures
- Consumer Products and Therapeutics
- Occupational and Inhalation Exposures

**Responsive Research**
- Per- and Polyfluoroalkyl Substances (PFAS)
- Emerging Contaminants /Issues of Concern
- Safe and Sustainable Alternatives
Hypothesis-driven Research

Bioactivity Screening

CompTox

Data / Knowledge Mining

Evidence Evaluations

Informatics

Knowledge Integration

Iterative learning

Short term in vivo Studies

Chronic in vivo Studies

Predictive Toxicology

In vitro Studies

Machine/Deep learning capabilities

Fully leveraging ‘pre-animal’ capabilities

Human-relevant in vitro systems- e.g. 3D complex

DNTP Translational Toxicology Pipeline

Guideline Toxicology

Investigative Toxicology

Communicate

Human Health Effects

Bespoke and human-relevant animal studies

Evidence Evaluations

Hypothesis-driven Research

Informatics

Iterative learning

Predictive Toxicology

Guideline Toxicology

Evidence Evaluations

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Portfolio strategic aims

Structure and manage to increase:

• Impact – innovation, prediction, translation
• Integration – across DNTP, NIEHS, “Big NTP”
• Agility – seize opportunities
• Opportunity – build partnerships, leverage resources
• Efficiency – upgrade operations and systems
• Sustainability – effort toward delivering not fixing
• Long-term viability – prepared to tackle tomorrow’s problems
Commitments, concerns, challenges

- Delivering on current obligations
- Maintaining core capabilities and partnerships
- Fostering disciplined creativity
- Adopting novel mechanisms for engagement and coordination
- Broadening leadership and mentoring skills development
- Expanding range of products: knowledge > decision > action
Questions and Comments