The Changing Toxicology Landscape: Challenges and the Future of Risk Assessment

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Evolving Needs

Growing Opportunity
21st Century Vision

To support the evolution of toxicology from a predominately observational science at the level of disease-specific models to a predominately predictive science focused upon a broad inclusion of target-specific, mechanism-based, biological observations.

A National Toxicology Program for the 21st Century, November 2004
• We have a need to address a rapidly increasing list of concerns.

• We have a need to respond to a broad stakeholder group with changing expectations.

• We have a need to bring more human relevance and individual precision to our hazard characterizations.

• We have a need to build confidence in a different approach to assessing hazards.

• We have a need to decrease our dependence on animals as a primary modeling platform.
Opportunity

- Aspiration
- Advances in technology
  - Machine learning/Artificial intelligence
  - iPSC
  - Complex in vitro microphysiological systems
  - Computer vision and holistic physiologic monitoring in animal studies
  - Biomonitoring patients/people
- Willingness to innovate
- An ability to leverage our experiences
  - NTP
  - Tox21
• What is NTP’s unique value?
  – Ability to focus on complex challenges for prolonged periods of time
  – Impactful science supporting policy and regulation
  – Opportunity to address chronic health effects
  – Build predictive capabilities

• What does it mean to be human-relevant?
  – Studying things of contemporary human concern/importance
  – Studying things in a relevant human context
    • Modeling human exposure context- quantity, route
    • Demonstrating exposure/outcomes relationships
  – Addressing public confusion
• How do we build confidence in non-traditional evidence?
  – Demonstrating human relevance
  – Understanding mechanisms
    • Toxicologists and pathologists working together
Hypothesis-driven Research

Data / Knowledge Mining

QSAR Profiling

Bioactivity Screening

In vitro Studies

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

Chronic in vivo Studies

Short term in vivo Studies

Knowledge Integration

Iterative learning

Human Health Effects

Bespoke and human-relevant animal studies

Communicate

Machine/Deep learning capabilities

Fully leveraging ‘pre-animal’ capabilities

Innovating the Paradigm
Evolving Our Portfolio

**Goals**
- Increase impact
- Improve sustainability
- Increase visibility
- Improve complementarity
Carcinogenicity Testing for the 21\textsuperscript{st} Century

Developmental Neurotoxicity Modeling

Cardiovascular Hazard Assessment in Environmental Toxicology

Aims

- Fill a gap in current capabilities
- Build on existing effort
- Align to NIH model
- Leverage our key strengths and value
X lbs./yr. commercial production
• In 2018, an estimated 1,735,350 new cases of cancer will be diagnosed in the United States and 609,640 people will die from the disease.

• Approximately 38.4% of men and women will be diagnosed with cancer at some point during their lifetimes (based on 2013–2015 data).

• In 2017, an estimated 15,270 children and adolescents ages 0 to 19 were diagnosed with cancer and 1,790 died of the disease.

• The number of cancer deaths (cancer mortality) is 163.5 per 100,000 men and women per year (based on 2011–2015 deaths).

Neurodevelopmental Disorders

Autism Spectrum Disorder

Estimated Autism Prevalence 2018

* Centers for Disease Control and Prevention (CDC) prevalence estimates are for 4 years prior to the report date (e.g. 2018 figures are from 2014)

Source: autismspeaks.org, “CDC increases estimate of autism’s prevalence by 15 percent, to 1 in 59 children"

Courtesy of Robert Sills, Mamta Behl
CV Morbidity and Mortality

Mortality
Selected Causes of Death

Figure 2. Age-adjusted death rates for selected causes of death for all ages, by sex: United States, 2004–2014


Chart 27-2. The 23 leading diagnoses for direct health expenditures, United States, average annual 2012 to 2013 (in billions of dollars).
COPD indicates chronic obstructive pulmonary disease; and GI, gastrointestinal (tract).
Source: National Heart, Lung, and Blood Institute; estimates are from the Medical Expenditure Panel Survey, Agency for Healthcare Research and Quality, and exclude nursing home costs.

Circulation. 2017;135:00-00. DOI: 10.1161/CIRC.0000000000000485
Other Fundamental Shifts

- **Contextualizing hazard**
  - How do you make hazards relevant?
  - Where/when does hazard characterization become risk assessment?

- **Enabling stakeholders**
  - Which stakeholders?
    - Regulatory/Policy
    - Scientific
    - Public
    - Industry
• How might potential challenges of the future affect the NTP mission?

• How should the NTP position itself to be impactful in the toxicology and risk assessment communities?
Thank You!