Re-Envisioning Toxicity Assessment @ NTP

Warren Casey, PhD, DABT
Director, NICEATM

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New DNTP Vision (2019)

“To improve public health through the development of data and knowledge that is translatable, predictive and timely.”

Brian R. Berridge, DVM, PhD, DACVP
Scientific Director, Division of NTP
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Human-Relevant  Impactful

Brian R. Berridge, DVM, PhD, DACVP
Scientific Director, Division of NTP
Applying our capabilities in deliberate, integrated and complementary ways.
Types of Programs at NTP

• Single Agents – e.g., Arsenic, Benzene

• Agent Classes - e.g. PAHs, PFAS
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• Health Effects Innovation (HEI) areas
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Move towards a model where deep understanding of human pathobiology informs the evaluation of risk
Key Challenge – Pathobiology Is Continuum

- Transition from normal to abnormal is generally not binomial.
- Thresholds of biological perturbation that represent ‘toxicity’ are difficult to define and not generally well understood mechanistically.
- Contextualizing those perturbations in a myriad of possible individual susceptibilities is even more difficult.
Health Effect Innovation Programs

• Cardiovascular Hazard Assessment in Environmental Toxicology

• Developmental Neurotoxicity Modeling

• Carcinogenicity Assessment
NTP Congressional Mandate (1978)

Section 301(b)(4) of the Public Health Service Act, as amended, requires that the Secretary of the Department of Health and Human Services (DHHS) publish an annual report on substance use and abuse. The Report on Carcinogens (RoC) lists:

• (A) All substances that are known to be human carcinogens or may reasonably be anticipated to be human carcinogens; and to which a significant number of US residents are exposed.

• (B) Information concerning the nature of such exposure and the estimated number of persons exposed to such substances
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NTP is not obligated to employ any specific approach to assessing carcinogenicity.
Does “Chemical X” cause cancer in rats/mice?
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What environmental factors are contributing to the increase in incidence / mortality of ”cancer x” in humans?
Cancer Incidence

NCI, Surveillance, Epidemiology, and End Results (SEER)
Cancer Incidence

NCI, Surveillance, Epidemiology, and End Results (SEER)
Cancer Mortality

Breast  Testicular  Lymphoma  Kidney

Mokdad et al. JAMA 2017

Slide provided by Alison Harrill, NTP
All Cancers

Mortality

Incidence

Merged
ER pathway to breast cancer

From Morgan et al., 2016, Pharmacology & Therapeutics 165: 79-92
ER pathway to breast cancer

This is the inflection point we need to model since it represents the bridge between observation and prediction.

From Morgan et al., 2016, Pharmacology & Therapeutics 165: 79-92
The Future of Carcinogenicity Assessment @ NTP will be...

• Human Relevant
• Mechanistic
• Exposure Driven
Problem Formulation
Problem Formulation