NTP’s New Effort to Modernize the Assessment of Carcinogenic Potential of Environmental Chemicals

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Director, NICEATM

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NTP – A program of partnerships

National Toxicology Program, HHS
(Headquartered at the NIEHS)

Assistant Secretary for Health

Policy Oversight
NTP Executive Committee
- CFSC
- EPA
- FDA
- NCEH/ATSDR
- DoD

Director
NIEHS and NTP

Science Oversight (External)
- NTP Board of Scientific Counselors
- Scientific Advisory Committee on Alternative Toxicological Methods

FDA
NCTR

NIH
NIEHS

CDC
NIOSH

DNTP

• Vision
  – To improve public health through the development of data and knowledge that is translatable, predictive and timely.

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• **Mission**
  
  – Identify and address public health issues through collaboration with public stakeholders and global partners.
  
  – Generate and communicate trusted scientific information to support decision making on environmental hazards of public interest.
  
  – Lead the transformation of toxicology through the development and application of innovative tools and strategies.
Translational Toxicology Pipeline

Applying our capabilities in deliberate, integrated and complementary ways.
Types of Programs

- **Single Agent**
  - Agent-specific health assessments

- **Agent Classes** - e.g. RFR, PAHs, Herbals, Mixtures
  - Agent class-specific health assessments

- **REACT** - e.g. PFAS, Elk River, Deepwater Horizon
  - ‘Rapid’ response agent/class-specific health assessments

- **Health Effects Innovation (HEI) areas**
Move towards a model where deep understanding of human pathobiology informs the evaluation of risk
Health Effect Innovation Program Management Team (PMT)
The 14th Report on Carcinogens contains information on **248 substances** — **62** known to be a human carcinogen and **186** reasonably anticipated to be a human carcinogen — including some classes of related chemicals or substances.
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
• 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.
Key Challenge – Predictive Toxicology Conundrum

ER pathway to breast cancer

From Morgan et al., 2016, Pharmacology & Therapeutics 165: 79-92

Appreciation to Cynthia Rider for introducing me to this.
Key Challenges – Predictive Toxicology Conundrum

ER pathway to breast cancer

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

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## Methods for Identifying Human Carcinogens

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We are just starting, but here is what we know.....
• Animal models will continue to be a critical component of the process
  
  – Invest in new in vivo technologies and approaches (e.g., duplex sequencing, in vivo imaging, genetic variability, etc.)
  
  – Develop expertise in comparative physiology
• Key New Approach Methodologies (NAMs)
  – In Vitro to In Vivo Extrapolation (IVIVE)
  – Incorporation of Metabolism
  – High Content Platforms (e.g., cell painting, transcriptomics)
  – In Silico Predictions and Computational modeling
  – Genetic Diversity
  – Repeat Dose / Chronic Exposure
  – Mixtures
Scientists rise up against statistical significance

Valentin Amrhein, Sander Greenland, Blake McShane and more than 800 signatories call for an end to hyped claims and the dismissal of possibly crucial effects.

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**Wrong Interpretations**

An analysis of 791 articles across 5 journals* found that around half mistakenly assume non-significance means no effect.


**Wrongly interpreted 51%**

** Appropriately interpreted 49%**

**ARTICLES 791**

World Beyond p < 0.05

Moving to a World Beyond “p < 0.05”

Ronald L. Wasserstein, Allen L. Schirm & Nicole A. Lazar
Exposure, Exposure, Exposure!
U.S. agencies and stakeholders will work together to build a new framework to develop, establish confidence in, and encourage use of new approaches to toxicity testing that improve human health relevance and reduce or eliminate testing in animals.

- Published Jan 30, 2018
- https://ntp.niehs.nih.gov/go/natl-strategy
MUST Start Here
Problem Formulation
Converging on Cancer Workshop
April 29, 30 – Washington DC

2:50 – 3:10 p.m.  A Modern Approach for Evaluating Human Cancer Risk From Exposure to Chemicals
Doug Wolf – Syngenta

3:10 – 3:25 p.m.  Instructions for the Breakout Groups

3:25 – 5:00 p.m.  Breakout Groups

5:00 – 6:30 p.m.  Poster Reception With Independently Sponsored Refreshments

Day Two, Tuesday, April 30

9:00 – 9:15 a.m.  Regulatory Questions That Mixture Science Can Help Address
Lauren Zeise – OEHHA

9:15 – 9:35 a.m.  Developing Rational Hypotheses for Testing Mixtures of Chemicals That Target Pathways of Carcinogenesis
Cynthia Rider – NIEHS/NTP

9:35 – 9:55 a.m.  AOP Based Approach for Mixture Testing and Risk Assessment by the EuroMix Project
Johanna Zilliacus – Karolinska Institutet

9:55 – 10:15 a.m.  Cancer Risk Assessment for Environmental Chemical Mixtures and Combined Chemical and Nonchemical Stressors
Glenn Rice – U.S. Environmental Protection Agency

10:15 – 10:45 a.m.  Break and Transition to Breakout Groups

10:45 a.m. – noon  Breakout Groups

Noon – 1:30 p.m.  Lunch on Your Own

1:30 – 3:00 p.m.  Breakout Groups

3:00 – 3:30 p.m.  Break and Preparation for Report Back

3:30 – 4:30 p.m.  Report Back From Breakout Groups

4:30 – 4:45 p.m.  Wrapup
Questions?

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