

ENVIRONMENTAL DEFENSE FUND

**EPA B.O.S.C.
Computational Toxicology
Subcommittee Meeting**

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Environmental Defense Fund Comments

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Finding the ways that work

Policy Relevance of Computational Toxicology

- Need: Address huge legacy of unassessed chemicals
 - Screen and prioritize thousands of chemicals
 - Identify hazard endpoints that require more scrutiny
- Need: Address emerging endpoints and science
 - Low dose effects, endocrine disruption, autism
 - Risks to sensitive subpopulations, life stages
- Need: Identify intrinsically “safer” chemicals
 - Rapid screening capability for new chemicals
- Need: Ensure safety of complex, new technologies
 - Potentially infinite variations
 - Combination materials, e.g., nano-bio complexes

Some NGO Concerns

- Insufficient attention to:
 - Pathways leading to chronic disease
 - Emerging endpoints/science
- Basis for assay validation too limited
- Assay interpretation is a black box
 - How will risks to sensitive subpopulations, life stages be characterized?
 - Is in vitro dose-response in vivo-relevant?
 - What is a “significant” perturbation?

Is Comp Tox Relevant to Public Health Concerns?

- Incorporate critical public health concerns
 - Increasing rates of chronic disease
 - Neurological: autism, Alzheimer's, Parkinson's
 - Metabolic: diabetes, obesity
 - Autoimmune disease: Lupus, MS
 - Reproductive: decreased fertility
 - Pathways and endpoints must capture disease pathways
 - Targeted testing to protect sensitive & susceptible populations
 - Environmental exposures as component of multi-factorial causes

Can Comp Tox Integrate Emerging Endpoints/Science?

- Emerging science and complex endpoints
 - Endocrine disruption
 - Epigenetics
 - Neurotoxicity
 - Immunotoxicity
- Low dose effects
- Skepticism of leading scientists in these fields
 - Need to engage scientists, NGOs in assay development, interpretation

Validation Concerns

- Current approach: compare ToxCast results with OPP whole animal data
- Doesn't compare "like" endpoints
- Recommendation: compare in vivo and in vitro assays that cover the same endpoints
 - Especially important for complex pathways
 - Compare HTS EDC results to both in vivo bioassays and the EDSP test battery

Interpretation: Caution Ahead!

- Accounting for risks to sensitive subpopulations, life stages
 - Include assays that capture variability
 - Incorporate variability via uncertainty factor(s)
- Recognizing that perturbation occurs along a continuum
 - Adversity depends on context
 - Small perturbations can have significant biological impacts
 - How to define “significant” perturbation?
- Considering in vivo relevance of dose response
 - In vitro D-R informative but not necessarily definitive
 - Interpretation may require specific proof-of-concept studies
- Recommendation: institute dialogue that leads to guidance on interpretation

New Opportunities

- Think beyond traditional risk assessment application
- Advancing green chemistry
 - Provides additional data for informed substitution
 - Identify chemicals with lower biological perturbation profile
- Addressing the mixtures challenge
 - HTS offers greater capacity to test mixtures
 - Whole product testing

Nanotechnology, etc.

- Potentially infinite variations to assess
- Balancing safety assessment vs rapid commercialization is a challenge
- Development of rapid, inexpensive, effective test methods will help provide early answers
- Technical challenges to overcome:
 - Delivery of nanomaterial to cells

Criticality of NCCT

- Continued funding NCCT will help to advance alternative testing methods and analysis
- Resources are needed to foster dialogue on the interpretation of assays for decision-making
 - Target experts in Neurological, Developmental, Immunological and Reproductive Toxicology
 - Dialogue will give NGO scientists an entry point to participate in developing interpretive framework
- NCCT should collaborate with EPA experts in Pollution Prevention, Green Chemistry and Design for the Environment for maximum benefit