PPDC Work Group on 21st Century Toxicology/New Integrated Testing Strategies

Office of Pesticide Programs
US Environmental Protection Agency

September 4, 2008

Topics

- Introductions
- Workgroup Charter & Committee Activities
- Presentation
  - OPP Strategic Direction
    - NAS Report – Testing In the 21st Century
  - Current, near term, & future activities
- Agenda for Our Next Meeting
- Workgroup Report for the Oct PPDC Meeting

Moving Forward

- PPDC Workgroup on New Toxicology Testing Paradigm
  - **Work Group Objective**
    - *This work group will focus on communication and transition issues as EPA phases in new predictive and testing methods over the next three to five years. This workgroup will help to focus EPA's efforts on the key activities needed for successful communication and transition, including identifying ways to improve understanding and how to best communicate complex science to all stakeholders, and providing process recommendations to ensure smooth transition of the new testing paradigm.*

Our Strategic Direction: Integrative Testing Strategies

- What does this mean?
  - Integrative
    - use existing data, predictive computer-based models, & in vitro data, combined with estimates of exposure
  - Hypothesis-Driven
    - establish plausible hypothesis about toxicological potential of a pesticide or group of pesticides for causing adverse outcomes and determine what specific in vivo tests are required
- Is it a paradigm shift?
  - May be a modest change to existing approaches
    - Priority setting
    - Antimicrobials or inerts
  - May be a major revamp of overall approach to information requirements
    - Conventional pesticides

Testing Paradigms

- **Test Battery**
  - standard set of toxicity studies
    - conventional pesticide actives
- **Tiered Testing (Results-Driven)**
  - a sequential approach where results at one tier of testing is used to determine the next step in testing, if any
    - endocrine Tier 1 screening results to trigger Tier 2 testing
- **Integrated Testing Strategy (Hypothesis-Driven)**
  - Integration of different types of hazard & exposure information to guide priority & the type of testing
    - May be based on a tiered approach or results from a battery of assays

Integrative Testing Strategies

Less expensive predictive methods used to focus & identify potential data needs for chemicals/endpoints

Prioritization

Consider existing data - *QSAR* Exposure

Screening

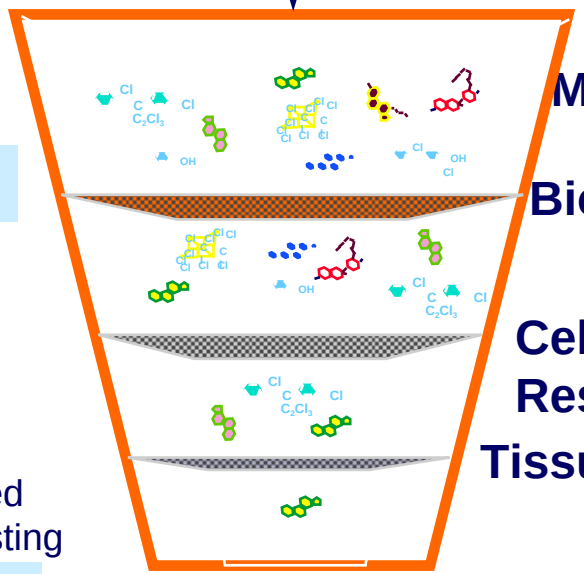
In vitro HTS omics

Efficient, Focused *In vivo* Animal Testing

Basis of safety findings (e.g., RfDs, MoEs, cancer slope values, FQPA safety factors)

Risk Assessment

Chemical Inventories



Molecular Interactions

Biochemical Responses

Cellular Responses

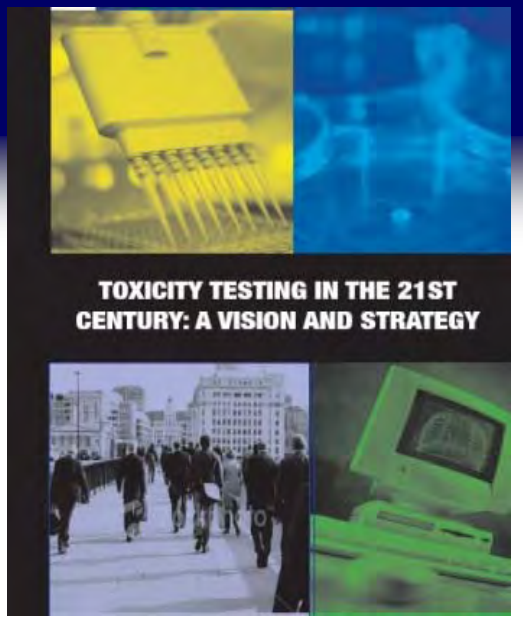
Tissue/Organ Function

Adverse Outcomes

Why Change the Current Paradigm?

- Improve ability to carry out mission of protecting public health & the environment
- Increase efficiency & reliability in assessing & managing risks appropriately by focusing on a pesticide's most likely hazards of concern for a given exposure situation
- Eliminate need for extensive animal testing (3Rs)
- Reduce cost & time in data development, review and processing

2007 NAS Report
Toxicity Testing in the 21st Century



Sponsored by US EPA

Broader coverage of chemicals, end points, life stages

Use fewer animals; least suffering for those used

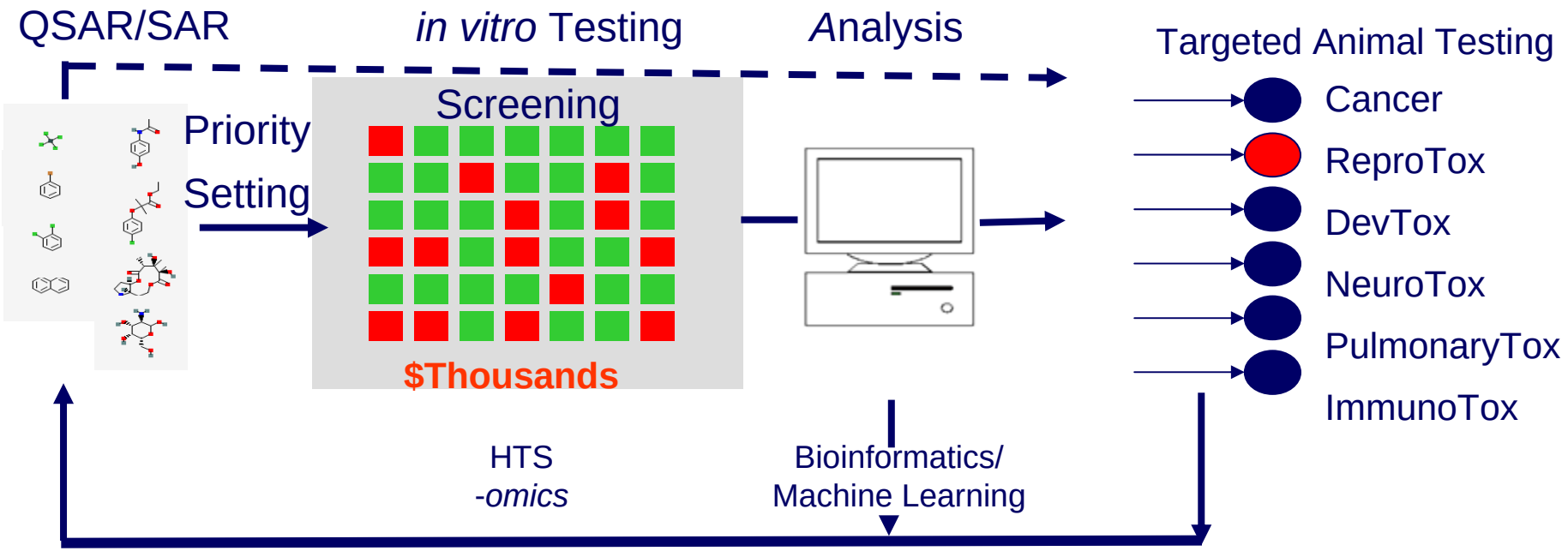
Consider New Technologies

Reduce cost & time of testing, increase efficiency & flexibility

More robust scientific basis by providing mode of action & dosimetry information

2007 NAS Report Transforming Toxicology

Combine in vitro testing & computational models to make predictions for In vivo outcomes & guide more targeted animal testing

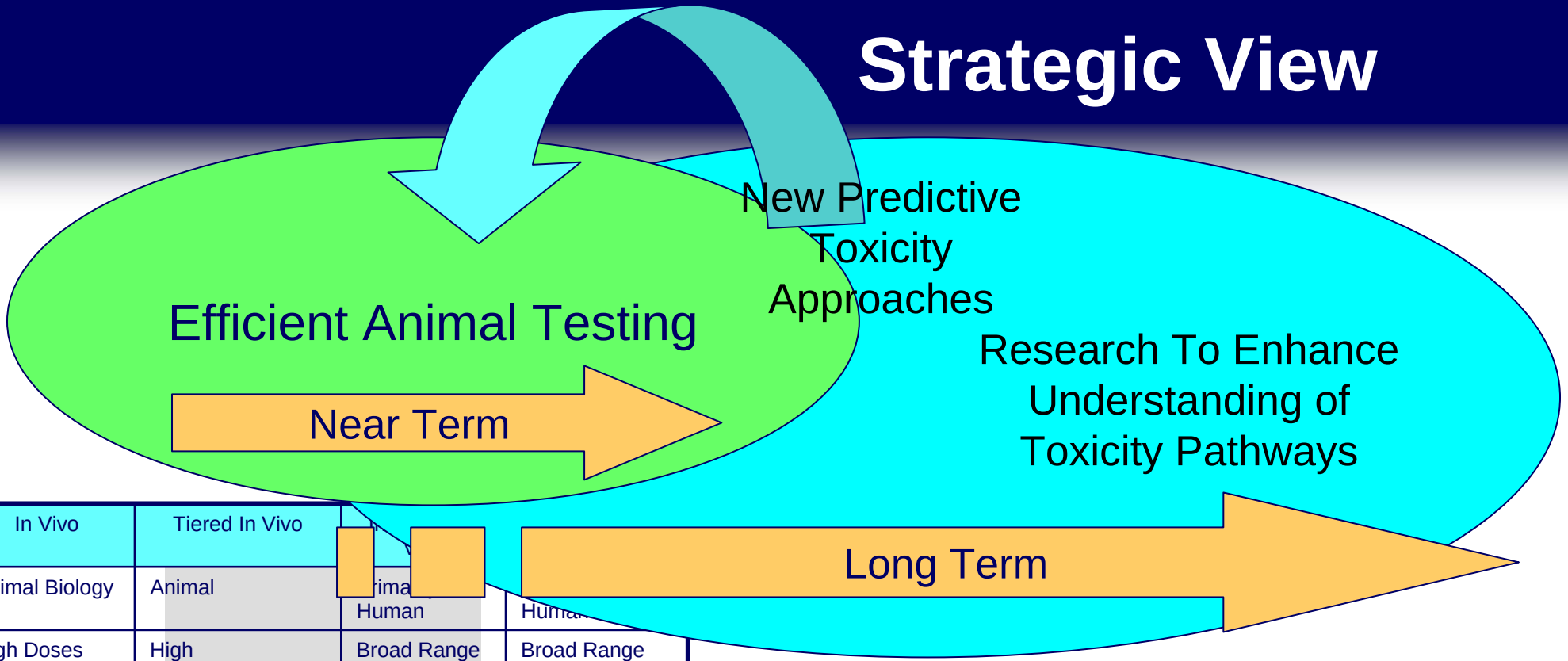


Research: Learn & Refine

NAS: Toxicity Testing Strategies

In Vivo	Tiered In Vivo	In Vitro & In Vivo	In Vitro
Animal Biology	Animal	Primarily Human	Primarily Human
High Doses	High	Broad Range	Broad Range
Low Throughput	Improved	High & Medium Thoughput	High Throughput
Expensive	Less	Less	Less
Time Consuming	Less	Less	Less
Large Animal Usage	Fewer	Substantially fewer	Virtually no animal usage
Based on Apical Endpoints	Apical Endpoints	Critical Cellular Perturbations	Critical Cellular Perturbations
	Some Screening (in vitro, in silico)	Screening (in vitro, in silico) & studies focused on mechanism	In vitro & in silico

Strategic View



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Moving Toward A New Paradigm Building From What We Learn

- Use of existing Agency's QSAR & expert system tools
  - Current OPP Activities
    - Inerts
    - SAR/QSAR in upcoming proposed data requirements for Antimicrobial Pesticides (Part 158W).

Moving Toward A New Paradigm Building From What We Learn

- Near Term Activities
  - Predictive models under evaluation
    - New QSAR Computer-Based Model for Potential Estrogenic Activity
  - Predictive models under development
    - ToxCast™
      - Toxicity predictions based on biological activity profiling using high through put assays
    - Metabolic Simulator
      - Predictions of metabolites/degradates

OPP Strategic View of Computer-Based & In Vitro Methods

- *Where we need to be* in the Near Term (<5 years) – Accelerated priority setting and screening & focused animal testing
- *Where we would like to be* in the Long Term (>15 years) - Virtually no animal usage
- *What needs to happen for g*reater reliance on emerging tools of computational tox **-** develop scientific basis & consensus to ensure management decisions are sound

Advance Research Agenda

>Improve link between fundamental research & regulatory application for computational toxicology

>Partner with EPA's Office of Research & Development, other Federal & International Agencies

Moving Forward

Discussion of topics/issues of interest to workgroup