Harnessing Toxicity Testing in the 21st Century to Help Train Chemists

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Science to Inform, (US EPA, ret’d)

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Harnessing Toxicity Testing in the 21st Century to Help Train Chemists: A Regulatory Perspective

Focus on training about the use of science to inform decisions
Presentation Outline

• Problem facing decision makers about chemical safety
• What is Tox 21
• “Fit for Purpose”
  – Launching Tox 21 and how used now
  – Next - expand Tox 21 to inform decisions
• Key role of AOPs and IATA
• Application to “green chemistry”
• Role of Alternative Tests
• Work in Teams
• “Science Informs Policy Decides”
• International Harmonization and Stakeholder Engagement
Approach for this Talk

- Key points that I think are important to convey
  - Teachers
  - Students
- Undergraduate Level
- Belief that it is important to place knowledge in context
- Perspective of a regulatory decision maker and science manager
Acknowledgements

- EPA
  - Vicki Dellarco, ret’d
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  - Pat Schmieder
  - Bob Kavlock
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- FDA
  - Suzanne Fitzpatrick

- NIEHS
  - Ray Tice
  - Warren Casey

- JHU CAAT
  - Tomas Hartung
  - Marty Stephens

- Many, many others
• Problem facing decision makers about chemical safety

• What is Tox 21

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1. Problem Facing Decision Makers About Chemical Safety Around Y2K

• About 70,000 chemicals in commerce
• Some data on about 5,000
• Good data on less than 500
• EXPENSIVE in more ways than one
  – e.g., Pesticide active ingredient registration
    • About $20 Million
    • More than 10,000 animals sacrificed
    • More than 2 years to conduct testing
Good News

• Current testing paradigm time tested strong basis for risk management decisions
  – Animal testing first developed in the 1940’s
  – Widely used
    • Thousand of decisions
    • Hundreds of court cases
    • History of success
Bad News and “Reality Check”

- “Can’t test our way out”
  - Over 200 years to test all chemicals in commerce with traditional animal based testing approaches
  - Would bankrupt the country

- Evidence becoming increasingly available that animal tests are not good predictors of human toxicity
Needed to “Think Outside the Box”

What Are Possible Alternatives?

- Realized predictive Biology Becoming A Possibility
  - Advances in high speed computing
  - Advances in chemistry related to SAR
  - Advances molecular biology
- Federal agencies began to develop strategies to harness the advances
  - EPA “Framework for Computational Toxicology” 2003
  - NIEHS “Roadmap for a 21st Century National Toxicology Program” 2004
- EPA asked the National Academy of Sciences for advice
• Problem facing decision makers about chemical safety

• **What is Tox 21**
  • “Fit for Purpose”
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2. What is Tox21?

- Bottom line

  - In 2007 National Academy of Science Published “Toxicity Testing in the 21st Century” A Vision and A Strategy”

  - Tox21 = acronym for “Toxicity Testing in the 21st Century”

  - Tox21 refers to the evolving suite of methods, models, data and capabilities being developed to implement NRC’s vision and strategy

KEY RECOMMENDATIONS

• Use cell-based (high throughput) assays to understand how chemicals perturb normal cellular functions (i.e., toxicity pathway)
• Establish relationships of perturbations with “adverse outcomes”
• Develop in vitro to in vivo extrapolation methods
• Integrate results to predict hazard/risk

GOAL

Broader coverage of chemicals & endpoints
Reduce cost & time of testing
Use fewer animals
NRC Logic

• Life operates through a finite set of normal biological processes that exist from conception through death
• Act through normal cellular-response pathways
• Chemical exposures can disrupt normal cellular-response pathway and result in early cellular change
  • Early cellular change doesn’t necessarily lead to disease – some changes can be repaired
  • Those not repaired lead to adverse outcomes
• Key to the Tox21 is to:
  • define the cellular-response pathways and adverse outcome pathways
  • Learn to distinguish between them
  • Map in silico, in vitro and other approaches against these pathways to define coverage
  • Combine to assess exposure, hazard and risk efficiently
“Homeostasis” – Refers to the body possesses many adaptive response mechanisms to correct early cellular-response changes and return them to normal function.

Irreversible changes occur when the normal biological processes are overwhelmed.

What might lead to irreversible cellular response pathway changes?

- If the dose is sufficiently high
- If the exposure occurs over a long period of time
- If the damage occurs:  
  - at the wrong place or  
  - at the wrong time
NAS Model: Outcome Pathways – Definition and Example

Exposure

Uptake-Delivery to Target Tissues

Perturbation

Cellular response pathway

Biologic inputs

“Normal” Biological Function

Early cellular changes

Adaptive Responses

Molecular initiating event

Perturbed cellular response pathway

Adverse outcome relevant to risk assessment

Toxicity Pathway

Adverse Outcome Pathway

Adverse Outcomes (e.g., mortality, Reproductive Impairment)

Cell injury, Inability to regulate

Biologic inputs

Normal Biological Function

Adverse Outcomes

Early cellular changes

Adaptive Responses

Molecular initiating event

Perturbed cellular response pathway

Adverse outcome relevant to risk assessment

Toxicity Pathway

Adverse Outcome Pathway

Adverse Outcomes (e.g., mortality, Reproductive Impairment)
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3. “Fit for Purpose”

• NRC Tox21 Concept Is Being Applied by EPA and Others for example:
  • June 2015 Endocrine Disruptor Screening Program FR notice
  • May 2011 “Integrated Approaches to Testing and Assessment Strategies: Use of New Computational and Molecular Tools”
• Launching Tox21 applications to screen large inventories of previously untested chemicals
  • Identify those with biological activity that may be associated with an adverse response
  • Use this information to decide what to test them for next
  • Use this information to decide in what order to test
The “Art of the Possible”

- The current social contract is to use animal test results to inform decisions.
- Remember many thousands of regulatory decisions, hundred of court cases, consent agreements and more have been informed by traditional animal tests.
- They have proven to be “health protective”.
- Before we can switch over completely to Tox21 approaches need to show that they are at least as informative if not better than traditional animal based approaches.
- At this time it is not possible to completely switch over to Tox21 – **MAJOR PARADIGM SHIFT**.
- BUT we can phase it in over time and in a way that demonstrates it’s utility, effectiveness and use to inform safety decisions.
Tailor Depth of Understanding About Tests to the Need

- If applying for “green chemical design” or screening to prioritize need some indication of inherent relevant biological activity (don’t need to know as much)

- If testing to inform decisions need enhanced interpretation of data (need to know more)
  - Depending populations exposed
  - Cost of remedy, etc.
Partnerships Are Critical

• 2008 Federal government formed Tox21 Consortium
  – Environmental Protection Agency (EPA)
  – NIH
    • National Institute of Environmental Health Sciences (NIEHS)
  – NIH Chemical Genomics Center (NCGC)
  – Food and Drug Administration (FDA)

• Each applies expertise and mission focus
Transition New Predictive Methods

Near Term Goal: 1-5 years

- Phase 1 - Strengthen priority-setting and screening for data-poor compounds
- Phase 2 - Use new predictive methods to fill data gaps
- Phase 3 - Use these to guide targeted in vivo testing

Challenge: Informing Risk Assessments

Long Term—Establish Validity (5-15 years)

- Develop means to move in a credible and transparent manner to hypothesis, mechanism-driven, and risk-based approaches that focus on effects most relevant to risk assessment and risk management
Phase 1

- Proof of concept to show that Tox21 was feasible
  - Used well characterized compounds of known toxicity
  - Compared hundreds of high throughput screening tests
  - Used results to optimize test battery and discard non-predictive tests

- EPA ToxCast I Program
  - Screened 320 compounds, primarily pesticide active ingredients
  - In 550 high throughput assays

- NCGC/NCATs Phase 1 Program
  - Screened 2,870 compounds
  - In 140 quantitative high throughput assays
**Phase II**

- **Purpose** – work out the logistics for large scale testing
  - Develop approaches to screen large inventories of a diverse set of chemicals
  - Refine the approach developed under Phase I for a variety of toxic responses
  - Focus on endocrine disruption responses
- **Approach**
  - Screened chemicals to identify biological activity
  - Evaluate how this information can be used to identify what specific and limited follow up testing might be appropriate
- **EPA screened**
  - 1,800 chemicals (industrial and consumer products, food additives, touted "green" products, nanomaterials and drugs that never made it to the market)
  - Employed more than 800 *in vitro* high-throughput screening assays.
- **NCGC screened a 10,000 compound library in 30 assays**
  - Generated 14-point dose response curves for each chemical/each assay
  - Conducted 7,000 LC/MS analyses during testing with follow up after 4 months
High-throughput testing refers to the application of in vitro robotic testing plus bioinformatics and biocomputational tools.
Phase III

• Goal – help build the basis to use Tox21 approaches in risk assessment
  – Improve biological coverage
  – Improve human relevance
  – Build on Phases I and II
    • Understand how results relate to effects in the human body
    • Use Tox21 information to inform decisions

• Roadblock
  – Need to show the results are predictive and as protective if not more so than traditional animal based testing approaches
Drawbacks to Tox21 Methods

• As currently configured not well suited to evaluate
  – Volatile compounds
  – Compounds that require metabolism

• Not yet able to model complex interactions occurring in multicellular organisms or between organisms, e.g.
  – Immune system function
  – Behavior
  – Cognitive effects
  – Cancer
  – Altered Reproduction
  – Developmental effects
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4. Key Role of AOPs and IATA

- Organization for Economic Cooperation and Development (OECD) Adverse Outcome Pathway Development Program
  
  - Purpose: to adopt Tox21 approaches to inform risk decisions
  
  - Goal: Make decision making more efficient and reduce non-tariff trade barriers that result when different countries use different standards for regulation
OECD Approach to Establish Validity of Tox21

• Integrated Approach to Testing and Assessment (IATA)

• Adverse Outcome Pathways (AOP)
Integrated Approach to Testing and Assessment (IATA) Definition

IATA is “a narrative which delineates the documented, plausible, and testable processes by which a chemical induces molecular perturbations and the associated biological responses which describe how the molecular perturbations cause effects at the subcellular, cellular, tissue, organ, whole animal and (if required) population levels of observation”
Why an “Integrated Approach to Testing and Assessment?”

• Because it is a process that integrates existing information about what is known about a chemical, its chemical properties and impacts on biological systems with estimates of exposure to predict risk.

• It is a systematic process involving the formulation of plausible and testable hypotheses, and

• It is also used to identify what is not known to target subsequent testing on chemicals and endpoints of concern.
**Integrated Approaches to Testing & Assessment (IATA)**

- **INTEGRATE** existing information
  - Use information from new technologies with combined estimates of exposure in a manner that leads to better predictions of risk for regulatory endpoints

- **FORMULATE** plausible & testable hypotheses

- **TARGET** *in vivo* testing on chemicals & endpoints of concern
IATA is About Change & Improvement - Learn as You Go

• Designed to evolve as knowledge is gained so that future assessments will be better than those conducted now,

• At each iteration rely more and more on efficient, informative and cost-effective biologically based alternative non-animal approaches

• At each iteration rely less and less on animal testing
**IATA Process**

Goal: Enhance integrated testing & assessment with new technologies & toxicity pathway knowledge

- Exposure information
- (Q)SAR, *in vitro* screens
- Chemical groupings & read across

Prioritize for further testing

- Targeted *in vivo* testing
- Hazard Information

Make toxicity predictions by combining different types of existing information on a similar chemical or group of similar compounds

Risk Assessment & Risk Management

Adapted from US EPA 2011 SAP
**NAS Model: Outcome Pathways – Definition and Example**

- **Exposure**
- **Uptake-Delivery to Target Tissues**
- **Perturbation**

**Cellular response pathway**

**Biologic inputs**

**Early cellular changes**

**Adaptive Responses**

**“Normal” Biological Function**

**Adverse Outcomes**
(e.g., mortality, Reproductive Impairment)

**Toxicity Pathway**

**Adverse Outcome Pathway**

- **Molecular initiating event**
- **Perturbed cellular response pathway**
- **Adverse outcome relevant to risk assessment**
Adverse Outcome Pathway (AOP)

- Key to any IATA
- Formalizes the NRC Tox 21 concept of perturbations of normal cellular response pathways leading to adverse outcomes if the damage is not corrected by normal adaptive responses.
- There are two anchors of the AOP, beginning and end, respectively
  - Initial damage to the cellular response pathway is referred to as a molecular initiating event (mie)
  - The toxic endpoint is referred to the adverse outcome
- The anchors are linked by Key events
  - measurable biological responses that occur along the pathway between the mie and the adverse outcome
  - not necessarily fully defined mechanistic steps
- It must be shown that the mie and key events must occur for an adverse outcome to result
Schematic Representation of an AOP

Adapted from OECD Guidance Document for Developing AOPs, 2013
Mapping Methods, Models, Test Results and Data Streams Against AOPs Essential for Use to Inform Decisions

• AOPs
  • Provide a basis to identify what part of an AOP each method, model, data stream or test result covers
  • Provide a means to link predictive models and test results together to cover the full range of events leading from an mie to an adverse outcome.
• AOPs provide a basis to predict risk for other purposes
• AOPs provide a basis to help design of “safer” and “greener” chemicals
Map Methods, Models, Test Results and Data Streams to Adverse Outcome Pathways

Connections Necessary to Achieve the Vision

Published in: Shana J. Sturla; Alan R. Boobis; Rex E. FitzGerald; Julia Hoeng; Robert J. Kavlock; Kristin Schirmer; Maurice Whelan; Martin F. Wilks; Manuel C. Peitsch; *Chem. Res. Toxicol.* 2014, 27, 314-329.
AOPs Can Be Used for A Variety of Applications

Published in: Shana J. Sturla; Alan R. Boobis; Rex E. FitzGerald; Julia Hoeng; Robert J. Kavlock; Kristin Schirmer; Maurice Whelan; Martin F. Wilks; Manuel C. Peitsch; Chem. Res. Toxicol. 2014, 27, 314-329.
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5. Tox21 Applications to “Green Chemistry”

- Tox 21 has enabled the field of “green toxicology”
- Many Tox 21 tools are available now that can be used from the beginning of, as well as throughout, the design process to select less risky and more sustainable chemical options
- Harness
  - Chemicophysical properties of a substance that determine its biological activity,
  - Biological properties of related chemicals that share the same chemical structure space to target screening level efforts to separate the “greener” chemistries from less “green” ones
12 Principles of Green Chemistry” Provide Basis to Define Tox21 Role

1. Prevent Waste  
2. Atom Economy  
3. Less Hazardous Synthesis  
4. Design Benign Chemicals  
5. Benign Solvents & Auxiliaries  
6. Design for Energy Efficiency  
7. Use of Renewable Feedstocks  
8. Reduce Derivatives  
9. Catalysis (vs. Stoichiometric)  
10. Design for Degradation  
11. Real-Time Analysis for Pollution Prevention  
12. Inherently Benign Chemistry for Accident Prevention  

Those in red provide a framework for application of Tox21 tools and identification where Tox21 tools need to be augmented  

From Maertens et al. ALTEX 2013
Key Point - Includes but extends regulatory toxicology
OECD Substitution and Alternatives Assessment Toolbox

• Purpose
  • Help guide the development of “greener” chemicals
  • Help select safer alternatives
• Apply throughout the entire chemical enterprise
  • From design
  • Through use
  • To reuse/disposal
• Highlights the need to work in teams

New Paradigm for Risk Assessment

Prediction of adverse outcome

Detailed mechanistic understanding of toxicity

Scientific Integration

Multidisciplinary

Computational Models
Apical Measurements
Molecular Measurements
Enabling Technologies

Physics
Chemistry
Biology
Engineering
Toxicology

Mathematics

Systems Toxicology
Must Consider Exposure

• Risk assessment evaluates
  – Whether a chemical substance has properties that can alter biological processes (hazard)
  – In combination with the potential for the organism to contact the substance under various scenarios (exposure)
  – To evaluate the potential and probability of harm (risk)

• Risk Characterization is the culmination of this process by describing the potential for harm in terms of
  – Strength of the evidence
  – Uncertainties and variability
  – Provides context for risk managers and others
Chemicophysical Properties Determine Internal Dose and Toxicity

• Chemicophysical properties of a chemical are key to risk assessment
  – Determine where, how and how much will enter the body
  – Determine what the chemical will do to the body (pharmacokinetics) and
  – Determine what the body will do to the chemical (pharmacodynamics)
Chemico-physical Properties Are Key to Risk Assessment

- Critical to exposure assessment
  - Determine a chemical’s absorption
  - Determine distribution in the body
  - Determine how it will be metabolized and excreted

- Critical to hazard identification because determine what damage will be caused by
  - Parent Compound
  - Metabolites
And that may lead to an Adverse Outcome
Must Systematically Consider Exposure Through Entire Life Cycle

- Potential for exposure to substance, feedstock components, contaminants and break down products throughout life cycle
- Each step must be carefully identified and evaluated
- Consider every exposure scenario, from cradle to grave for each alternative being compared in context with their biological properties
- Requires partnership between chemists and toxicologists
NAS Framework for Chemical Selection

• EPA tasked NAS to “…identify the scientific information and tools required by regulatory agencies and industry to improve and increase consideration of potential health and environmental impacts early in the chemical design process.”

• Resulted in 2014 publication of “A Framework to Guide Selection of Chemical Alternatives”

• Describes a 13 step process
  – to help develop safer chemicals,
  – to avoid regrettable substitutes
  – other recommendations.
• Emphasized importance of planning & scoping to identify how and why the chemical will be used, what are its alternatives, how will they be evaluated, and how will uncertainty and variability be addressed
• Recommended determination of stakeholder engagement needs given that safety is as much an issue of social concern as it is of scientific assessment
• Identified subsequent steps to identify chemical function, application and performance requirements as well as identification of human and environmental health effects of concern to provide a baseline for comparison with potential alternatives
# Components of Green Toxicology

<table>
<thead>
<tr>
<th>Component</th>
<th>Description</th>
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<tbody>
<tr>
<td>Benign Design</td>
<td>Toxicologists partner with chemists to identify moieties with undesirable traits</td>
</tr>
<tr>
<td>Test early, produce safe</td>
<td>Front load inexpensive, predictive, fast screening level tests</td>
</tr>
<tr>
<td>Avoid exposure</td>
<td>Increase the efficiency of production process</td>
</tr>
<tr>
<td>Make testing sustainable</td>
<td>Reduce the number of animals used for testing</td>
</tr>
<tr>
<td>Use tests not yet mature for regulating</td>
<td>Provides biological activity information, can be targeted to particular chemistries, and builds capability and capacity</td>
</tr>
<tr>
<td>Green Toxicology as a driver for 21st Century Toxicity</td>
<td>Experience in green design provides basis for demonstrating utility of computational and other Tox 21 approaches</td>
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Alternative Whole Organism Testing to Supplement High

Adapted with permission from the National Academy of Sciences. Courtesy of the National Academies Press, Washington, D.C., 2014
Business Vision

• Integrate toxicity evaluation throughout the product development process from beginning to end
• Do it right the first time and minimizing waste
• Know what to test and when to stop development
  – Fail fast and cheaply - eliminate bad early
  – Succeed early
• Problem facing decision makers about chemical safety
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6. Role of Alternative Tests

- Tox21 tests cannot be used at this time to assess risk because they do not realistically model some effects of concern.
- Over time a variety of Tox21 approaches will be shown to produce data appropriate for risk assessment.
- Until then animal testing will be necessary*
  - Currently rats, mice and other mammals are employed despite cost, time and suffering.
  - Alternative animal tests are increasingly being applied.
  - Pioneering efforts to develop a “human on a chip” are underway.

* Note that the EU precludes animal testing for cosmetics under the REACH Cosmetics Directive.
Russell and Burch, 1958 – 3Rs

- Russell and Burch 1958 called for an end to the use of traditional animal species
  - Ethical reasons
  - Evidence that they didn’t mimic humans well
- 3Rs Concept
  - Refine the use of animals in testing
  - Reduce the number of animals used in testing
  - Replace the use of animals in testing
Bridging with Alternative Animal Test Methods

- Alternative whole animal tests include Zebrafish, Drosophila, and C. elegans
- Considered a refinement of animal testing
- Employ organisms in a lower taxa than mammals
- Can test for behavior, immune cancer, reproductive, developmental and other endpoints not available with Tox21 now
- They are more efficient and less costly than mammals
  - Shorter lifespans
  - Smaller size
  - Less costly husbandry and housing
Bridging with Alternative Animal Test Methods – cont’d

• Zebrafish example
  – Multicellular, multiorgan species
  – Exhibits behavior
  – Undergoes rapid development
  – Can test all life stages within weeks
  – Endpoints are conserved across species, including humans
Much Work is Needed to Build Links to Humans

• Before can routinely use alternative test species to inform risk decisions must build links showing how key events in alternative species AOPs compare to human AOPs
• But they serve as a critical link between Tox21 tests and traditional testing approaches to systematically compare AOPs to identify and diminish knowledge gaps
Build on the Past to Increase Confidence in the New Toxicity Testing Approaches

- Huge amount of traditional toxicity data
- Don’t sacrifice current levels of confidence trying to move from traditional design approaches to Tox 21 design approaches
  - Stepwise, iterative, learn as we go
  - Compare new with the old
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7. Work in Teams

• Use of AOPs through IATA will help build the necessary knowledge and understanding to apply Tox21 to inform decisions
• Partnerships between chemists, toxicologists, systems biologists and others is needed to provide a firm basis for sustainable chemistry
• To the extent that we build tools that are “fit for purpose” we can achieve a sustainable future more quickly and economically by:
  • proceeding efficiently in a directed way to harness knowledge about chemicophysical properties, and
  • Aplying this knowledge to conduct focused testing whose results progressively lead towards understanding the potential chemical impacts on environmental and human health.
Teamwork Needed to Identify and Diminish Gaps

• Move from data to information to knowledge to understanding
• Build tools that are “fit for purpose”
• Demonstrate that the new approaches are as good if not better than the old ones to achieve management and public acceptance
• Engage
  – Chemists need to think of toxicology as more than information on a MSDS
  – Toxicologists need to develop tools to help chemists understand toxicity and design better alternatives
  – All need to engage risk managers, other key decision makers and the public early and often to shift thinking beyond current regulatory frameworks
• Improve with each successive iteration
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8. Science is Used to Inform Decisions, Not Make Them

- Scientists sometimes wonder and occasionally get frustrated when others are not compelled by data.
- Important to note that many factors beyond science are important for decision making, especially on issues with potentially significant human and environmental health consequences.
  - Food and drug safety
  - Environmental Protection
- Bear in mind that while the risk assessment process is largely a scientific endeavor, the risk management process is largely a social endeavor - Remember
  - Science informs, policy decides
Risk Assessment/Risk Management Paradigm

1983 NRC Risk Assessment Paradigm

http://www.epa.gov/ttnatwo1/toxsourceparadigm.html
What Do I Need to do to Help Advance the Use of Toxicology to Inform Decisions?

• Develop an understanding of the political, legal, economic and other social factors considered by decision makers
• Apply this understanding to design studies that are “fit for purpose”
• Communicate the results in the most useful format, context and timeframe to inform decisions
• Realize that mistakes will be made in the move towards Tox21 implementation and that acceptance will proceed most effectively, quickly and efficiently if we:
  • Operate openly and transparently
  • Hear and value public concerns
  • Clearly and consistently demonstrate that we are trying to harness Tox21 to make the safety evaluation process more informative, more efficient and less costly
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• **International Harmonization and Stakeholder Engagement**
9. International Partnerships and Stakeholder Engagement Are Essential

- The NRC Tox21 Vision will only be realized to the extent it is adopted
- Given multifaceted nature of society stakeholder engagement within a country is required
- Given the global economy international harmonization of regulatory efforts is critically important and need to be aware of such requirements so that sustainable products are designed with global acceptance in mind
- No one organization or even country is able to achieve the Tox21 vision alone
  - Important to build on experiences of others
  - Develop worldwide
    - Information sharing
    - Common application tool boxes
    - Mutually accepted test guidelines
    - Harmonized testing frameworks and
    - Harmonized assessment guidance
International Partnerships and Stakeholder Engagement Are Essential – cont’d

- Global acceptance
- Information sharing
- Common application tool boxes
- Mutually accepted test guidelines
- Harmonize frameworks & guidance

Stakeholder Engagement

OECD
NAFTA
IPCS
EFSA
& others
In Summary

Harnessing Toxicity Testing in the 21st Century to Help Train Chemists: A Regulatory Perspective

- EPA et al. realized “Cant test our way out”
- NRC provided roadmap to know what to test, when to test, & how
- OECD extended approach through IATA and AOP
- IATA and AOPS help guide green chemistry
- Chemists and toxicologists in partnership can develop the means to require tests only when necessary because of green design
- Testing in animals will only be when absolutely necessary and a rare event; the ultimate goal is that most decisions informed by the inherent structure and properties of the chemical
- Initial focus on priority setting and capacity building
- Long-term use for risk assessment/risk management

Achievable with strong scientific & stakeholder support through a transparent process
Questions?

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