

An Overview of ORD and It's Computational Toxicology Program

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Charge Questions

- As EPA prepares for the 21st-century toxicity testing to inform decision making, **what specific issues should it consider in areas of identifying sufficient and appropriate data for risk assessment and risk characterization.** How would these differ, or be the same, for such EPA applications as chemical screening, prioritization, risk assessment and green chemistry
- **What are the barriers** that prevent EPA from using outputs of the CompTox program, if any, in support of programmatic needs?
 - How might they be overcome?
 - What are the challenges of acceptance of 21st-century approaches as part of the weight of the evidence in decision making, what might EPA do to address these challenges?
- How well do the outputs of the CompTox program **align with EPA's programmatic needs?**
 - Are the outputs of the CompTox program currently being used in EPA, If not, why not?
- How should the use of the CompTox program outputs be **effectively communicated** to stakeholders? What additional research or other steps should be taken to enhance communication?

ORD's Role in Achieving EPA's Mission



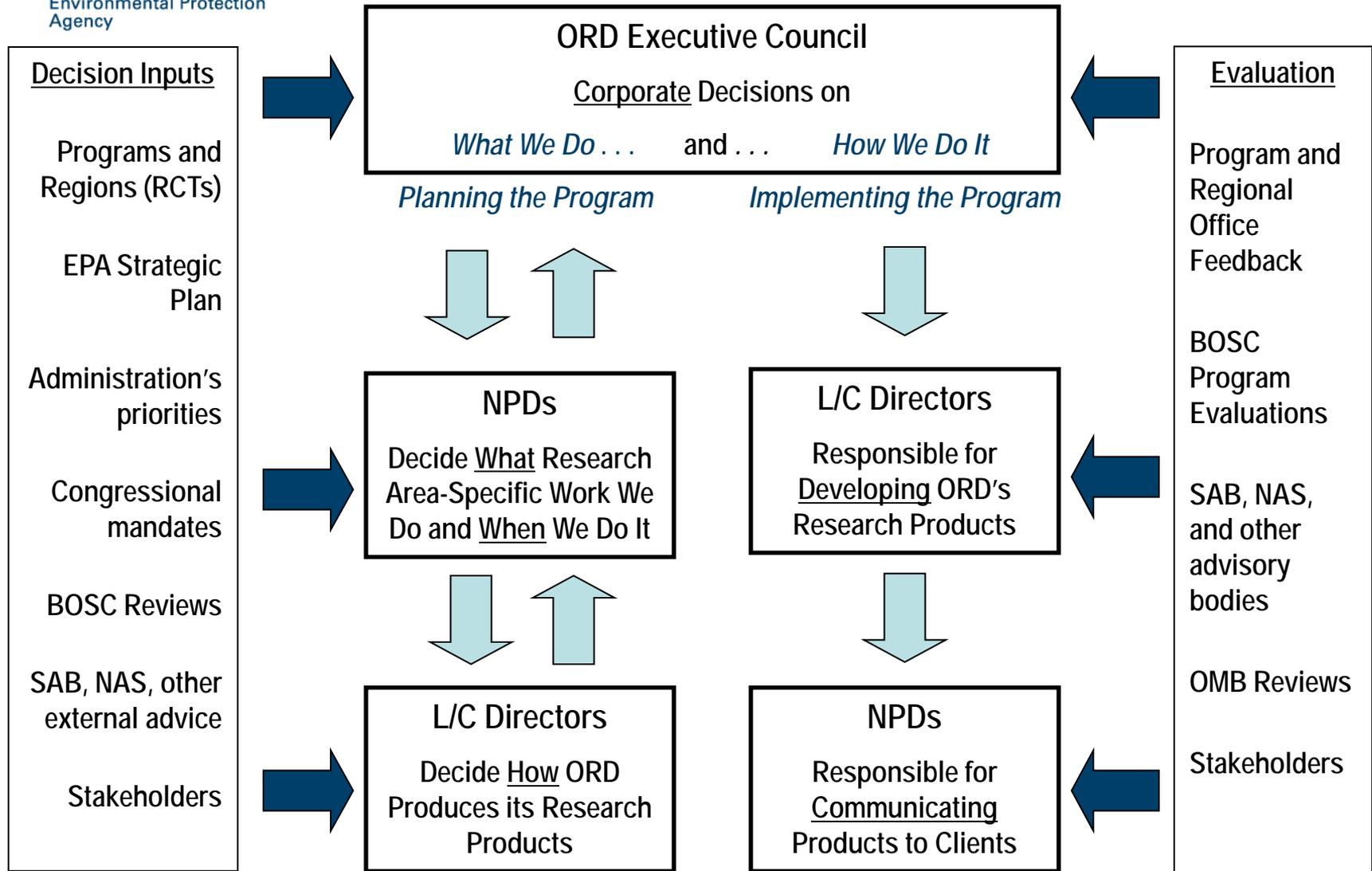
Mission of EPA's Office of Research and Development (ORD)

Provide the scientific foundation to support the EPA's mission by:

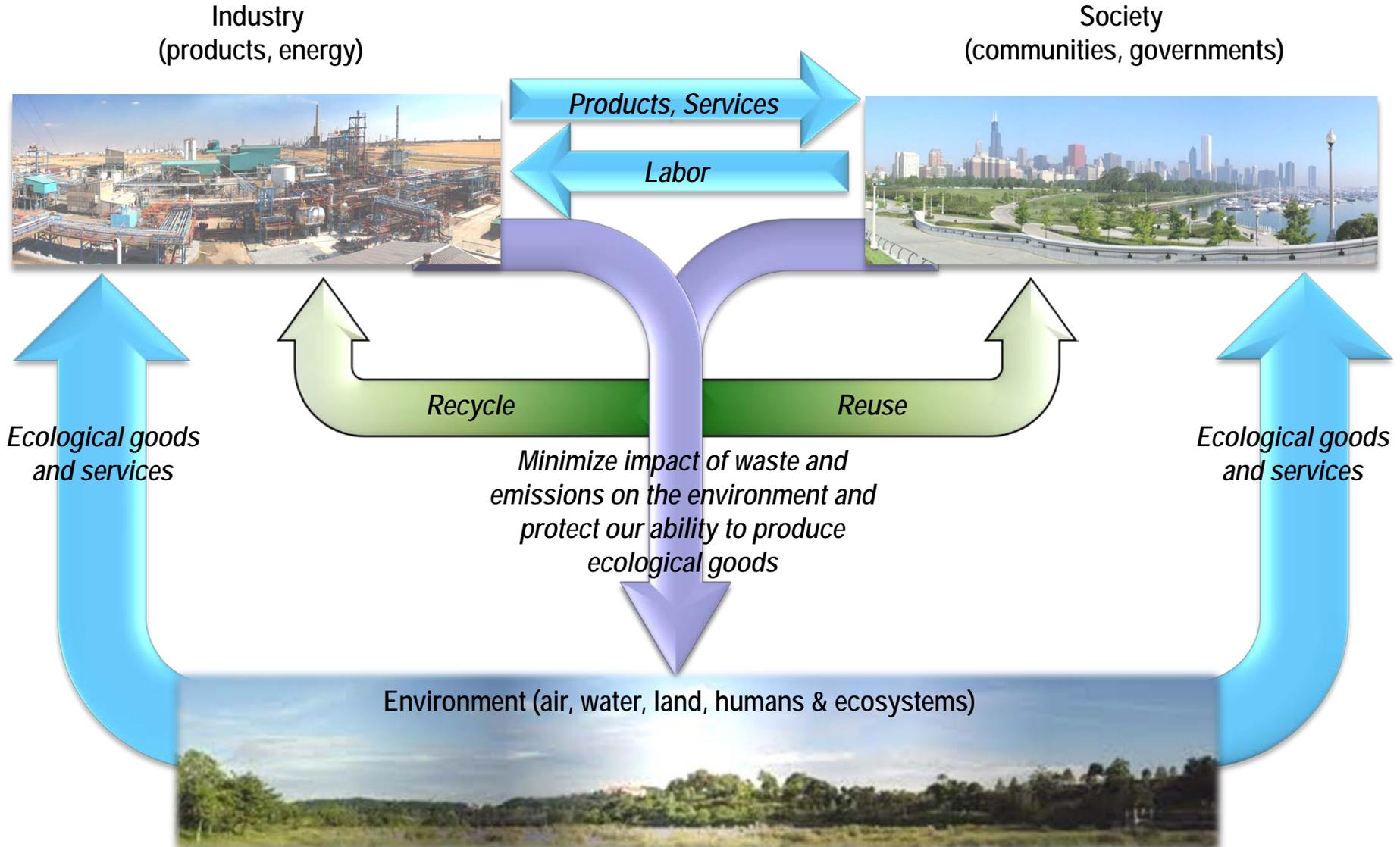
- **Conducting research and development** to identify, understand, and solve current and future environmental problems
- **Providing responsive technical support** to EPA's Programs and Regions
- **Collaborating with our scientific partners** in academia and other agencies, private-sector organizations, state and tribal governments, and other nations
- **Exercising leadership** in addressing emerging environmental issues and advancing the science and technology of risk assessment and risk management



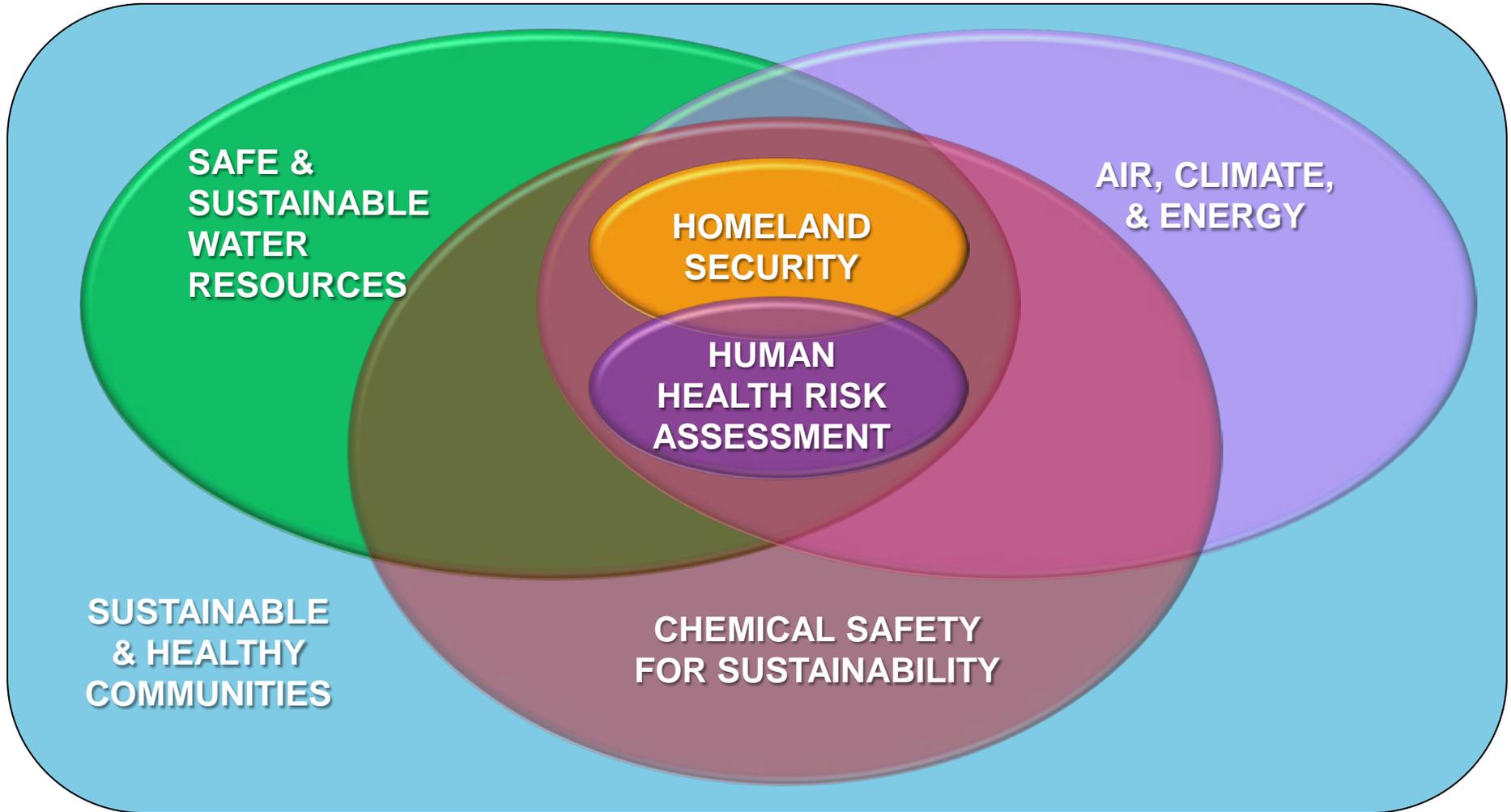
How ORD Develops its Research Programs



A Systems Approach to Sustainability



Integrated ORD Research Programs



Administrator Jackson's Priorities

- Reducing Greenhouse Gas Emissions
- Improving Air Quality
- Managing Chemical Risks
 - “More than 30 years after Congress enacted the Toxic Substances Control Act, it is clear that we are not doing an adequate job of assessing and managing risks of chemicals in consumer products, the workplace and the environment. It is now time to revise and strengthen EPA's chemicals management and risk assessment programs”
 - “...we must be sensitive to the burdens pollution has placed on vulnerable subpopulations, including children, the elderly, the poor and all others who are at particular risk to threats to health and the environment. We must seek their full partnership in the greater aim of identifying and eliminating the sources of pollution in their neighborhoods, schools and homes.”
- Cleaning up Hazardous Waste Sites
- Protecting America's Water



Existing Chemicals

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Endocrine Disruptor Screening Program (EDSP)

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Pesticides: Regulating Pesticides

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You are here: EPA Home » Pesticides » Regulating Pesticides

EPA and the states (usually that state's agriculture office) register or license pesticides for use in the United States. EPA receives its authority to register pesticides under the [Federal Insecticide, Fungicide, and Rodenticide Act \(FIFRA\)](#). States are authorized to

Quick Resources



United States Environmental Protection Agency

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ENVIRONMENT

European Commission > Environment > Chemicals > REACH

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Chemicals

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- REACH Review 2012
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- Links

REACH

REACH is the European Community Regulation on chemicals and their safe use ([EC 1907/2006](#)). It deals with the **Registration, Evaluation, Authorisation and Restriction of Chemical substances**. The law entered into force on 1 June 2007.

The aim of REACH is to improve the protection of human health and the environment through the better and earlier identification of the intrinsic properties of chemical substances. At the same time, REACH aims to enhance innovation and competitiveness of the EU chemicals industry. The benefits of the REACH system will come gradually, as more and more substances are phased into REACH.

The REACH Regulation places greater responsibility on industry to manage the risks from chemicals and to provide safety information on the substances. Manufacturers and importers are required to gather information on the properties of their chemical substances, which will allow their safe handling, and to register the information in a central database run by the [European Chemicals Agency \(ECHA\)](#) in Helsinki. The Agency acts as the central point in the REACH system: it manages the databases necessary to operate the system, co-ordinates the in-depth evaluation of suspicious chemicals and is building up a public database in which consumers and professionals can find hazard information.

The Regulation also calls for the progressive substitution of the most dangerous chemicals when suitable alternatives have been identified. For more information read: [REACH in Brief](#).

One of the main reasons for developing and adopting the REACH Regulation was that a large number of substances have been manufactured and placed on the market in Europe for many years, sometimes in very high amounts, and yet there is insufficient information on the hazards that they pose to human health and the environment. There is a need to fill these information gaps to ensure that industry is able to assess hazards and risks of the substances, and to identify and implement the risk

NEWS

- 22/09/2011: REACH Directors Contact Group F...
- 20/05/2011: EU to ban cadmium in jewellery, b...
[Read more \(IP/11/620\)](#)
- 17/02/2011: Six dangerous substances to be r...
[Read more \(IP/11/196\)](#)
- 01/12/2010: First REACH registration closes: a...
chemicals in the EU

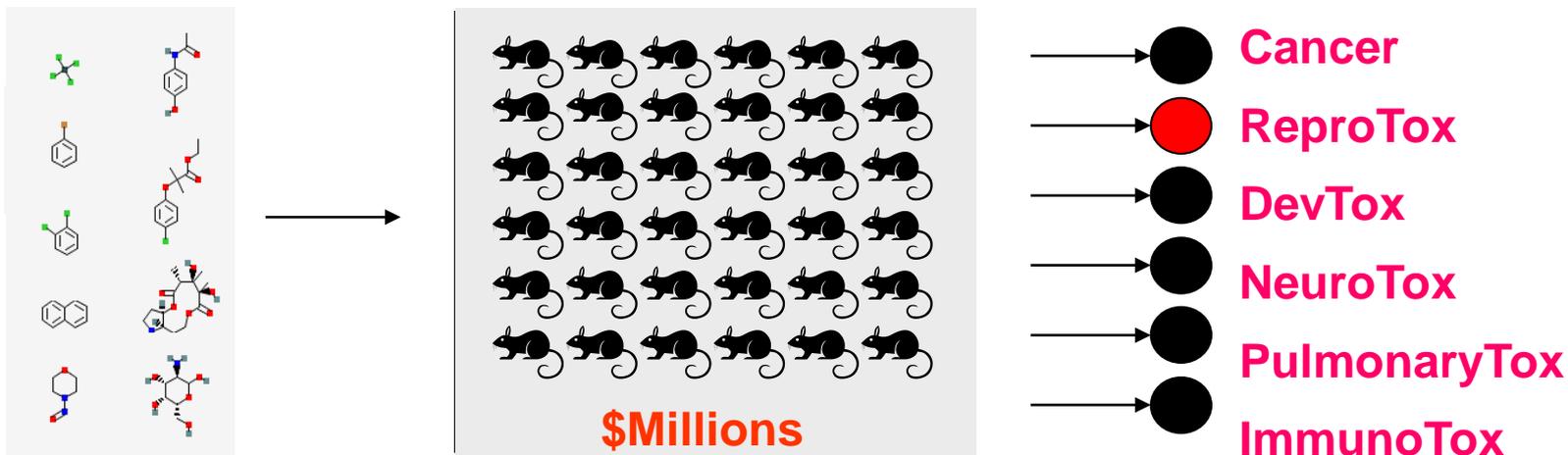
More news...

For detailed information on REACH: [European Chemicals Agency](#)



Current Approach to Toxicity Testing

in vivo testing

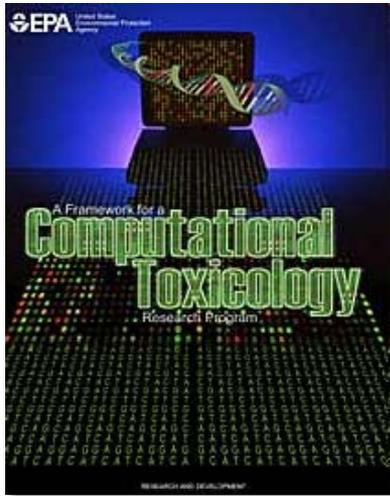


For a food use pesticide: up to \$10m in toxicology, \$1m to interpret, years to complete

21st Century Chemicals-Related Research Needs

- Understanding environmental **impacts throughout chemical life cycles**—from production, through use, to disposal/recycling
- **Enabling more, and more-timely, chemicals-related decisions** by developing integrated testing strategies and risk prediction approaches that are cheaper, faster, and more reliable, as well as more informative for risk management purposes
- Targeting key complex issues such as **characterizing mixtures of chemicals**, understanding the significance of intermittent chemical exposures, and assessing **individual susceptibilities** to chemical exposures **over life stages**
- Developing **virtual tools** (i.e., liver, embryo) for predicting human health impacts
- Combining recent advances in computational toxicology with **cumulative exposure information** to inform risk assessments
- Identifying opportunities to **apply green chemistry** principles

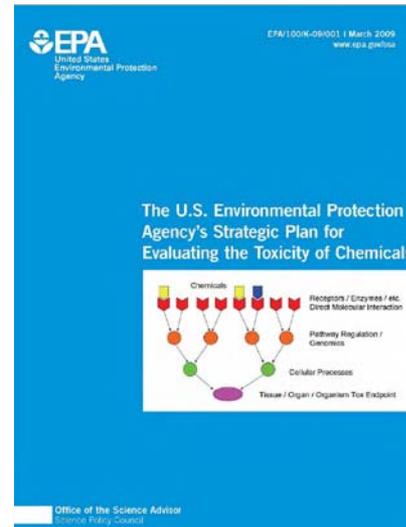
A Fast Moving Decade



2003



2007



2009

2005

2011

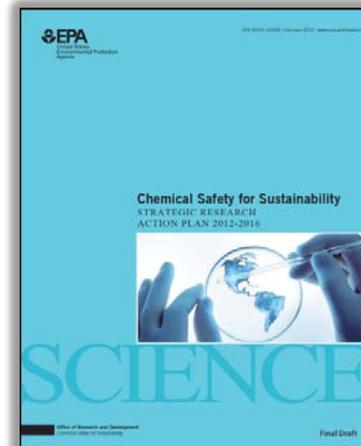
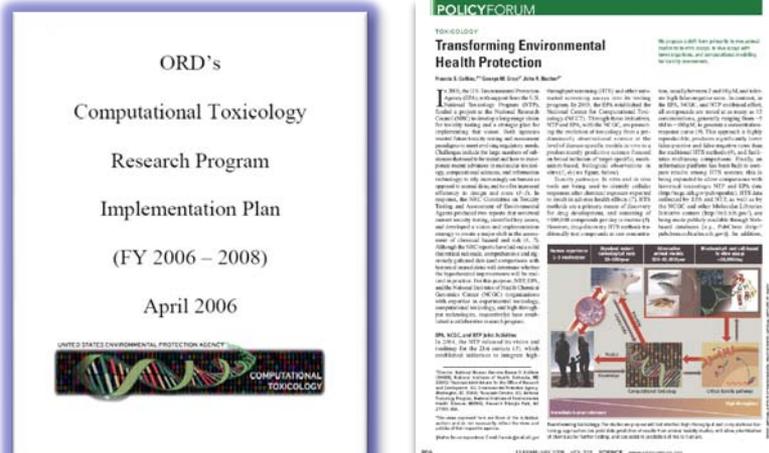
2004

2006

2008

2010

2012



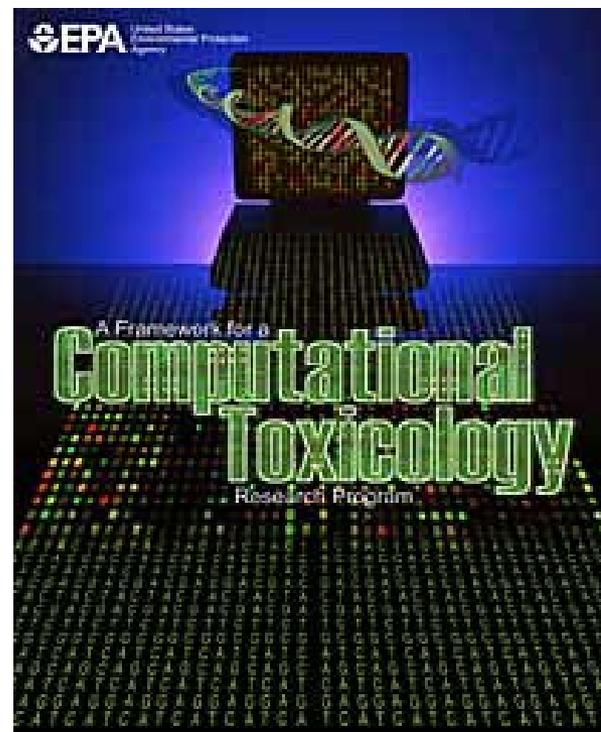
The Framework for a CompTox Program (2003)

Goals:

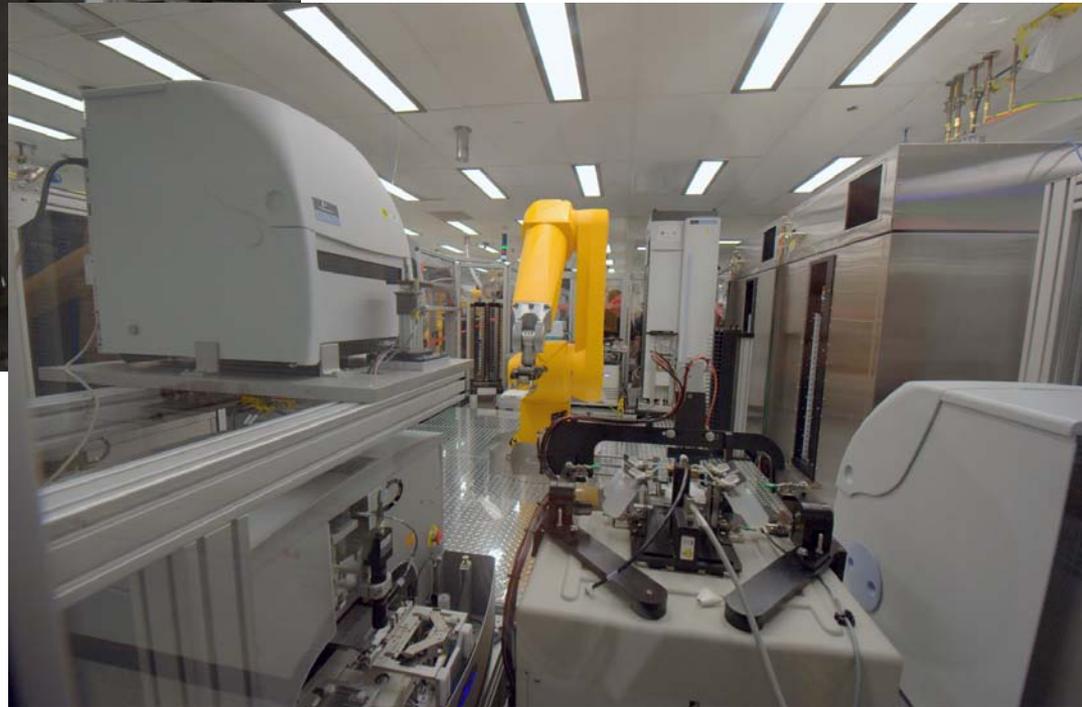
- Improve Linkages in the Source to Outcome Paradigm
- Provide Predictive Models for Hazard Identification
- Improve Quantitative Risk Assessment (Dose, Species, Chemical)

Success:

- Measured by ability to produce faster and more accurate risk assessments for less cost relative to traditional means and to classify chemicals by their potential to influence molecular and biochemical pathways of concern



Tox21 Robot Ribbon-Cutting (March 10, 2011)

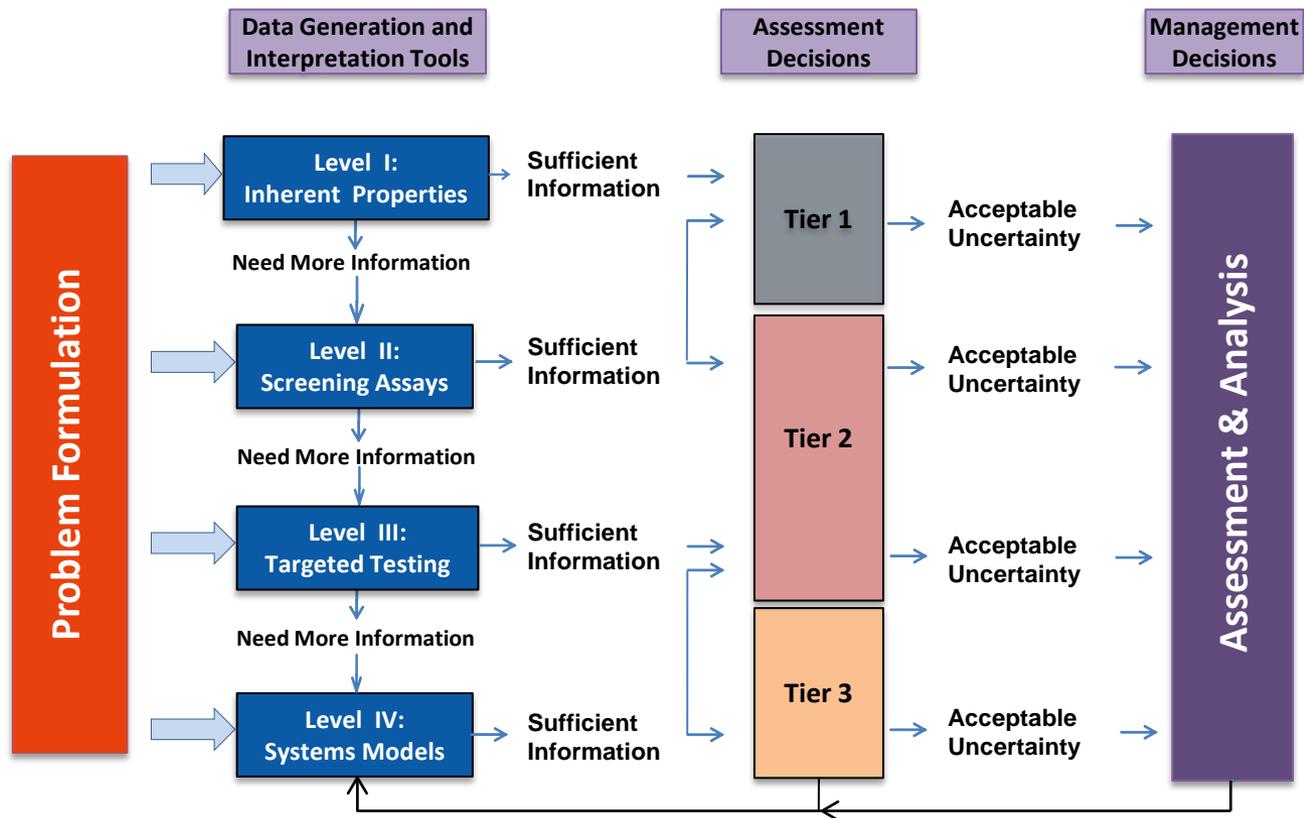


EPAs Chemical Safety for Sustainability Research Program



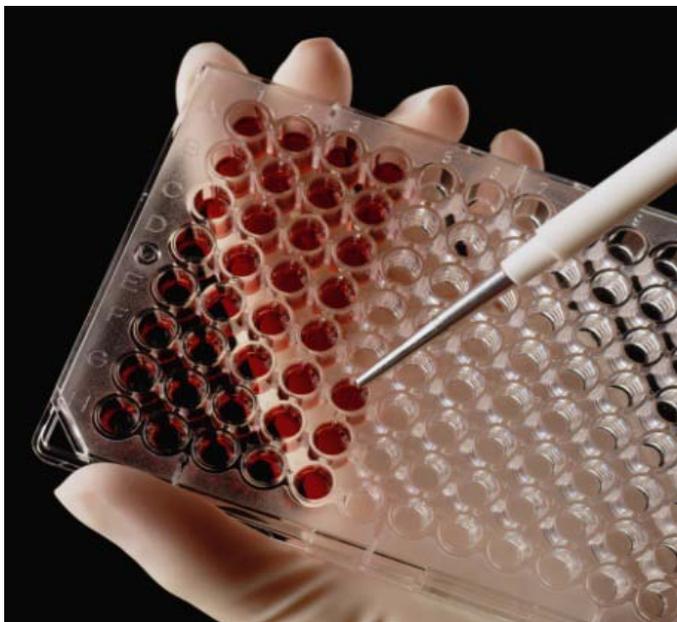
- Improve protection of human health and environment by evaluating chemicals for potential risks
- Assess potential risks of nanomaterials and endocrine disrupting chemicals
- Use advances in computational toxicology research to assess toxicity of chemicals
- Provide tools and guidance for “greener” chemical production to improve environmental sustainability

CSS Conceptual Model

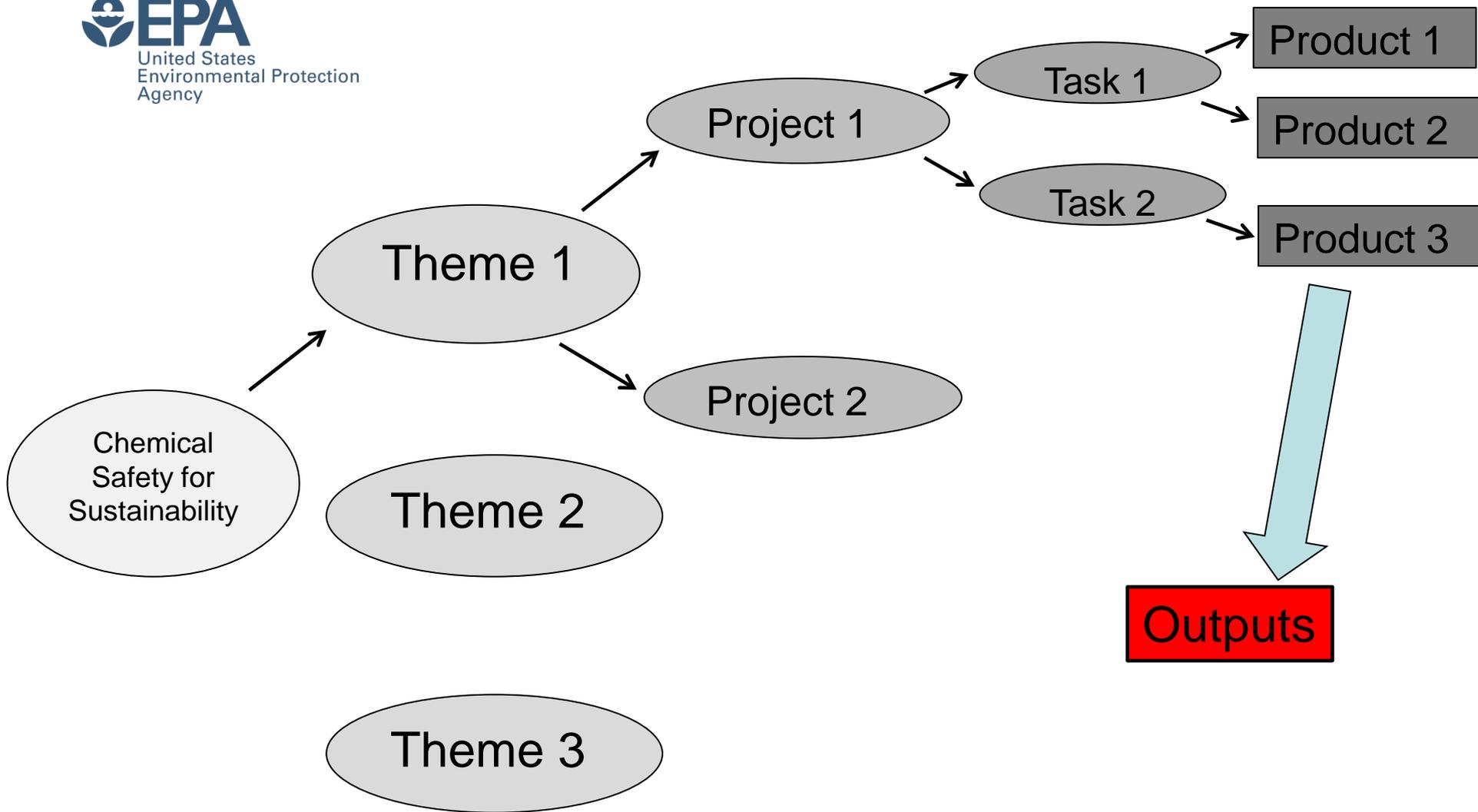


Chemical Safety for Sustainability (CSS) Research Program

8 Research Themes

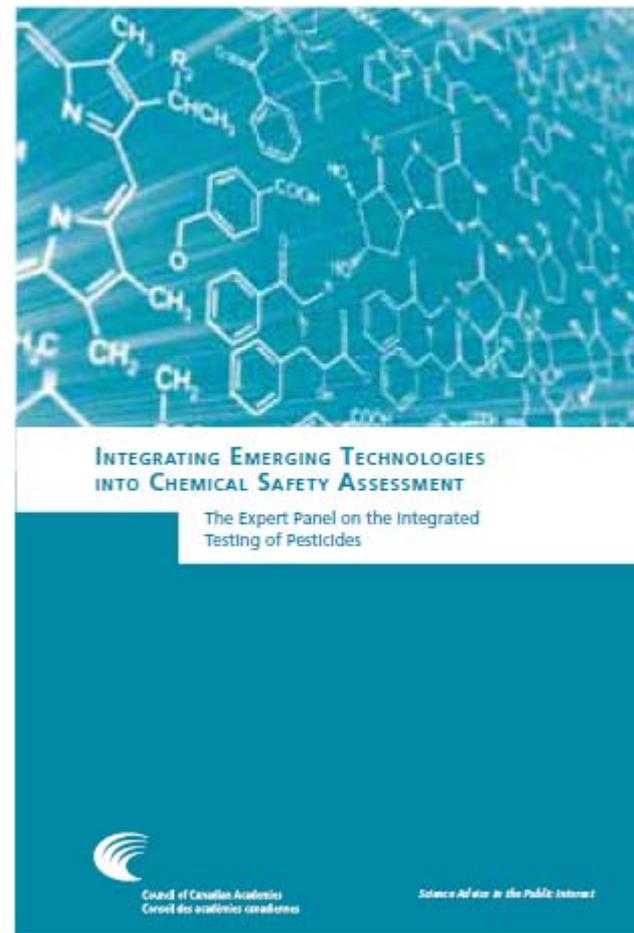


- Chemical Inherency
- Systems Models
- Biomarkers
- Cumulative Risk
- Life Cycle Considerations
- Extrapolation
- Dashboards
- Evaluation



"The issues inherent in the current approach to chemical testing are two-fold: to address the lack of toxicity data for the vast majority of industrial chemicals and to recognize that regulatory decisions must be based on the best available science. The Panel believes that these challenges can be best met by adopting an Integrated Approach to Testing and Assessment (IATA)."

– Leonard Ritter, Chair of the Expert Panel



Canadian Council of Academies, 2012

A Few Words on Communication

- Communications Specialist hired in 2009
- Active Website
- Monthly Webinars
 - Community of Practice (external)
 - CSS Theme Presentations (internal)
- Publications Fact Sheets
 - ToxCast Models
 - High Throughput Risk Assessment
- Partner Surveys
- Media events
 - Tox21 Robot dedication
 - Release of the 10k Library
 - L’Oreal CRADA signing



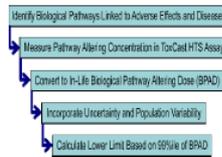
Estimating Toxicity-Related Biological Pathway Altering Doses for High-Throughput Chemical Risk Assessment
February 13, 2011

Impact Statement
Important inputs to chemical risk assessments are estimates of the highest allowable exposure levels that are protective of human health. Typical acceptable exposure values such as the Reference Dose (RfD) are based on exposure and time consuming animal toxicity tests. Non-animal based methods to estimate safe exposure levels would be beneficial because these tests of thousands of testing chemicals with limits or so animal testing data, and hundreds more chemicals introduced into commerce every year.

This paper presents an approach to use on data poor chemicals to derive screening-level estimates of allowable exposure levels. The method uses knowledge about how chemicals alter biological processes or pathways related to human disease. The proposed method for high-throughput chemical risk assessment (HTRA) uses data from rapid chemical screens to estimate exposures that would alter biological pathways in a way that could potentially lead to toxicity or disease.

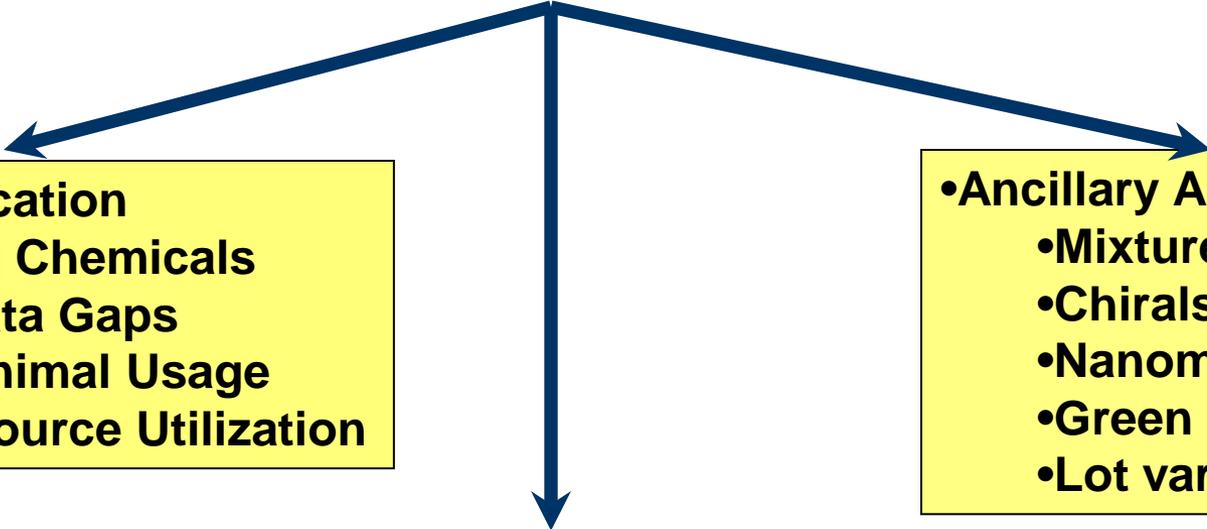
Study Description
A proposed HTRA approach for chemicals is presented that focuses on biological pathways linked to adversity and disease. The approach combines results from ToxCast and Tox21 High-Throughput Screening (HTS) assays with data on metabolism and pharmacokinetic modeling to estimate exposure levels reasonably expected to be without risk of chemically induced disease in human populations. The proposed HTRA approach is essentially a five-step process (FIGURE 1) that calculates a Biological Pathway Altering Dose (BPAD) useful in estimating acceptable exposure levels.

Figure 1-Proposed Five-Step Process for High-Throughput Risk Assessment (HTRA).



1. **Identify pathways linked to adverse outcomes:** Biological pathways are a key connection between mode of action based risk assessment and HTS. This approach starts by identifying known targets (genes, proteins) and pathways linked to disease.
2. **Measure chemical activity in concentration-response:** The next step is to use ToxCast HTS data to determine the concentration of a chemical that can perturb the biological pathway in cells. This is termed the Biological Pathway Altering Concentration (BPAC).
3. **Convert HTS concentration-response to human dose-response:** Using metabolic measurements and pharmacokinetic models, the BPAD is calculated.
4. **Incorporate population variability and uncertainty:** All measurements and estimates are subject to uncertainty and population variability. The HTRA model incorporates both of these in a manner analogous to traditional risk assessments.
5. **Estimate lower limit for pathway perturbation:** The final step is to estimate a lower limit from the BPAD below which there is minimal risk of the toxicity-related pathway being perturbed, the BPAD₉₅.

Implications for Success of Computational Toxicology



•Hazard Identification

- Prioritizing Chemicals
- Closing Data Gaps
- Efficient Animal Usage
- Better Resource Utilization

•Ancillary Applications

- Mixtures
- Chirals
- Nanomaterials
- Green Chemistry
- Lot variations

•Risk Assessment

- Focusing on highest priority chemicals
- Providing Mode(s) of Action
- Targeted/Intelligent Testing
- Identifying Susceptible Populations



“...to integrate modern computing and information technology with molecular biology to improve Agency prioritization of data requirements and risk assessment of chemicals”

***Providing Decision Support Tools for
High-Throughput Screening, Risk Assessment and Risk Management***

ORD's Organization

