

# Advancing the Next Generation of Risk Assessment

**Nex**  **Gen**



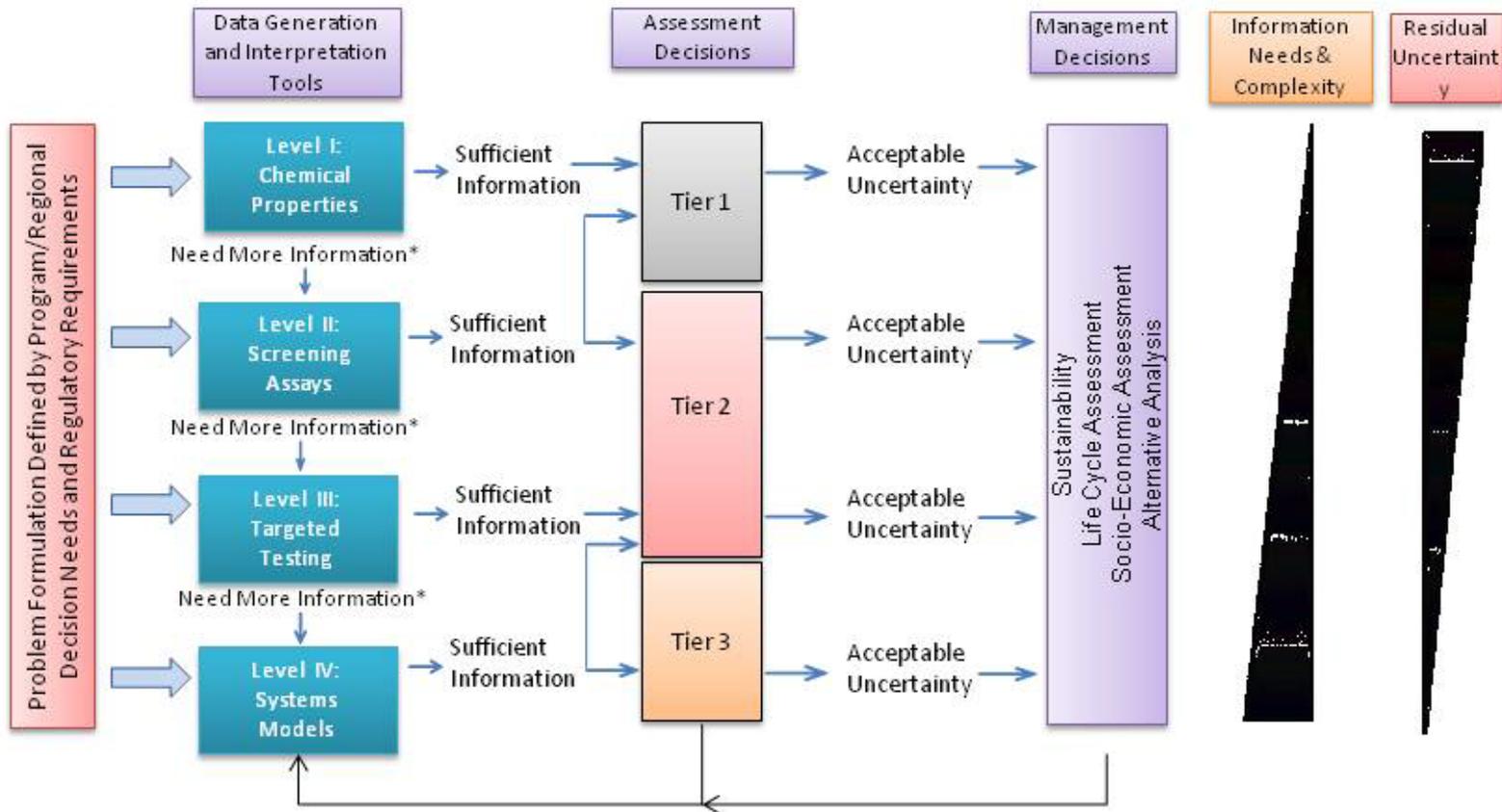
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***Sr. Science Advisor***

*National Center for Environmental Assessment*  
*Office of Research and Development*

# Outline

- Background
- Risk Context & Approaches
- Specific Examples
- Summary

**Figure 3. The CSS Research Program's Perspective on an Integrated Evaluation Strategy for Environmental Data Development and Decision Making**



\* Needed at all levels is information on inherent properties, hazard, exposure, and those management options deemed feasible by decision makers.

# Background

- **What is NexGen?**
  - ✓ Program to create a cheaper, faster and more robust system for chemical risk assessment by incorporating new knowledge about system biology
  
- **What are the goals of NexGen?**
  - ✓ Create prototypes
  - ✓ Develop decision rules for use of new information
  - ✓ Incorporate advances into risk assessment
  
- **Why is NexGen important?**
  - ✓ Agency must conduct credible, science-based assessments
  - ✓ New data can improve assessments
  - ✓ Translates research, including CSS, into application

# Background

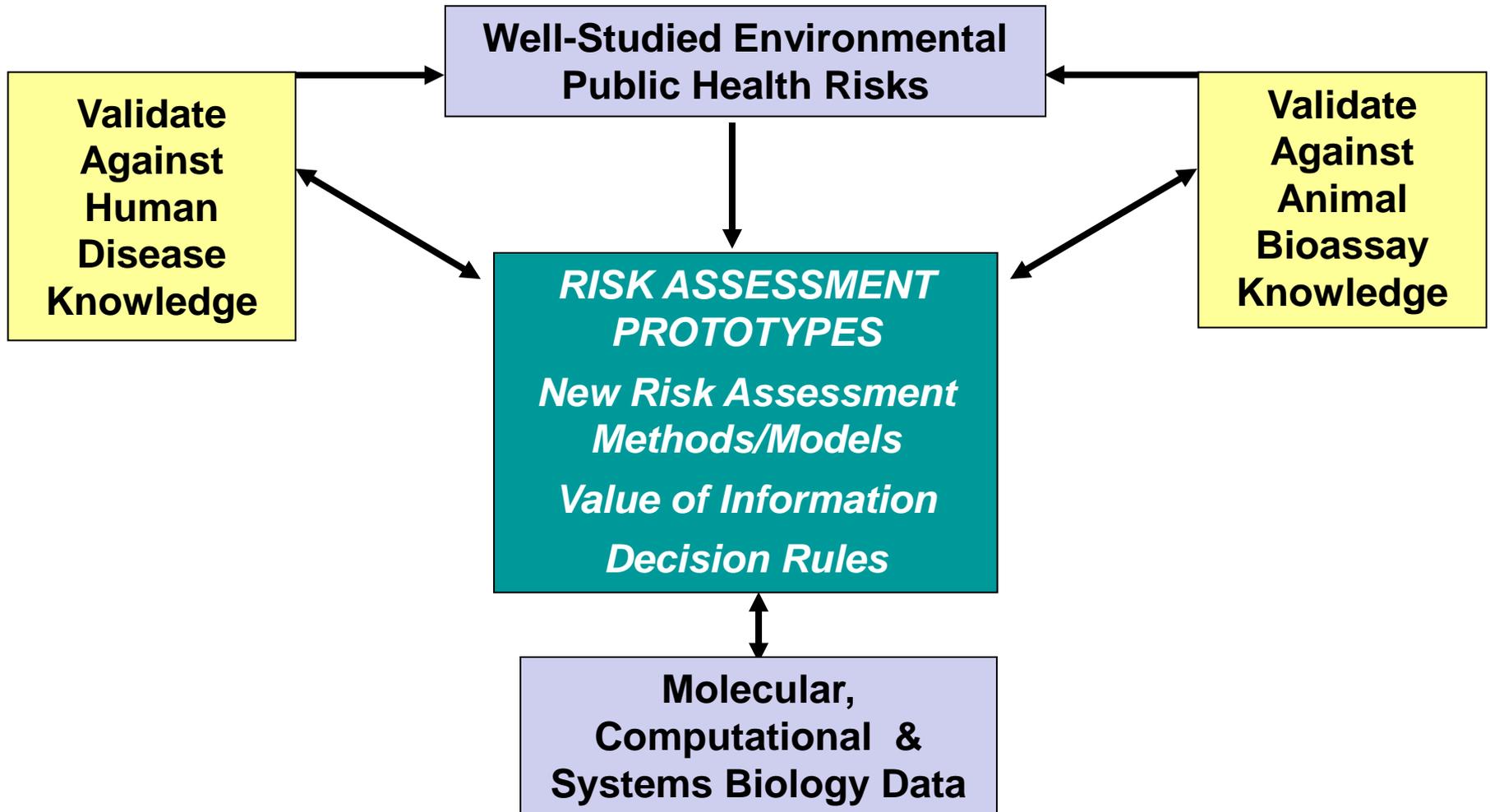
## *Who is involved?*

### **NexGen Partners' are providing advice and data on NCEA's implementation efforts**

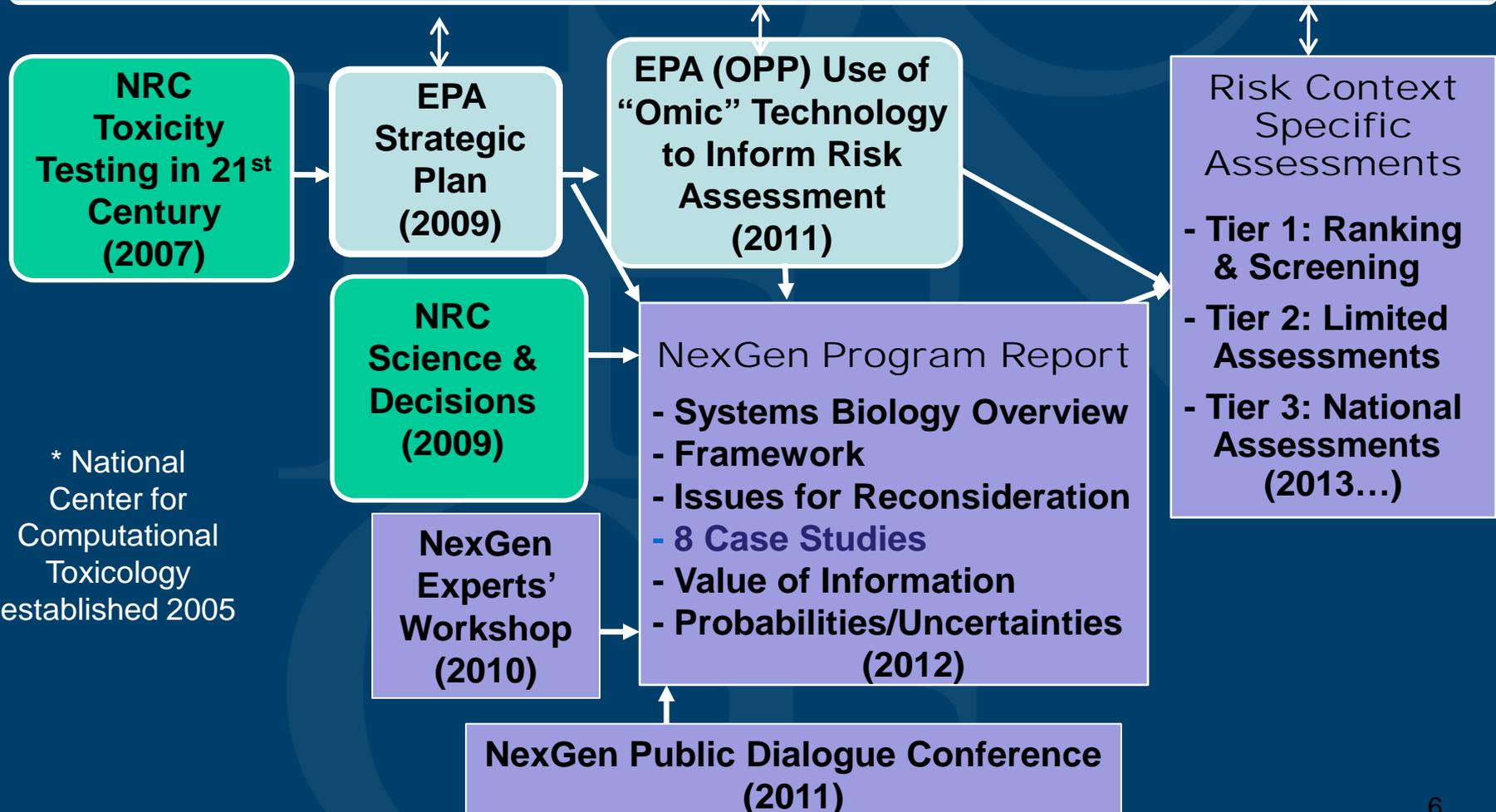
- EPA's Labs and Centers, and program offices
- National Institute of Environmental Health Sciences & National Toxicology Program
- Centers for Disease Control & Agency for Toxic Substances and Disease Registry
- National Institute of Occupational Health and Safety
- NIH Center for Translational Therapeutics
- FDA's National Center for Toxicological Research
- State of California's Environmental Protection Agency
- Health Canada
- European Joint Research Commission

# *What are we doing?*

## *Reverse Engineering Prototypes*



### Research: Chemical Safety for Sustainability, Human Health Assessment Reserach, Tox21 etc.\*



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- **Risk Context & Approaches**
- Specific Examples
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# Risk Context

*Potential Applications*

**Tier 1**  
10,000s of chemicals

**Tier 2**  
1000s of chemicals

**Tier 3**  
100s of chemicals

## Ranking & Screening

- New assessment queuing
- Greener chemicals & processes evaluations
- Urgent response
- Research priorities development

## Limited decisionmaking

- Limited exposure IRIS & PPRTV assessments
- Possible water contaminants queuing
- National Air Toxic Assessment support
- Urgent response
- Research priorities development

## Major decisionmaking

- High profile IRIS and ISAs chemicals
- Community assessments
- Special issues evaluations
  - ✓ Susceptible subpops
  - ✓ Mixtures & other stressors

Increasing Need for Confidence in the Decision

# Risk Context

## Types of Data Matched to Risk Context

<b>Tier 1</b> 10,000s of chemicals	<b>Tier 2</b> 1000s of chemicals	<b>Tier 3</b> 100s of chemicals
<i>High Throughput Only</i>	<i>Adds Med Throughput, High Content</i>	<i>Adds Low Throughput</i>
<b>Molecular Mechanisms, In Vitro Exposures</b>	<b>In Vivo/Situ/Silico Exposure, Tissue/Organism Integration</b>	<b>Most Realistic Scenarios</b>

- QSAR
- Test system - *in vitro*, robotic only
  - ✓ Cytotoxicity
  - ✓ Validated assay batteries~600
- No traditional data

- Test systems:
  - ✓ Short-term *in vivo* exposures – mammalian & alternative species
  - ✓ Tissue constructs
- Improved metabolism
- Different types of assays
- Some traditional data

- Test systems:
  - ✓ Molecular epidemiology
  - ✓ Molecular clinical
  - ✓ Molecular animal
  - ✓ All w phenotypic data
- ~ Environmental exposures
- All policy relevant data

Increasing Evidence



# Approaches Overview

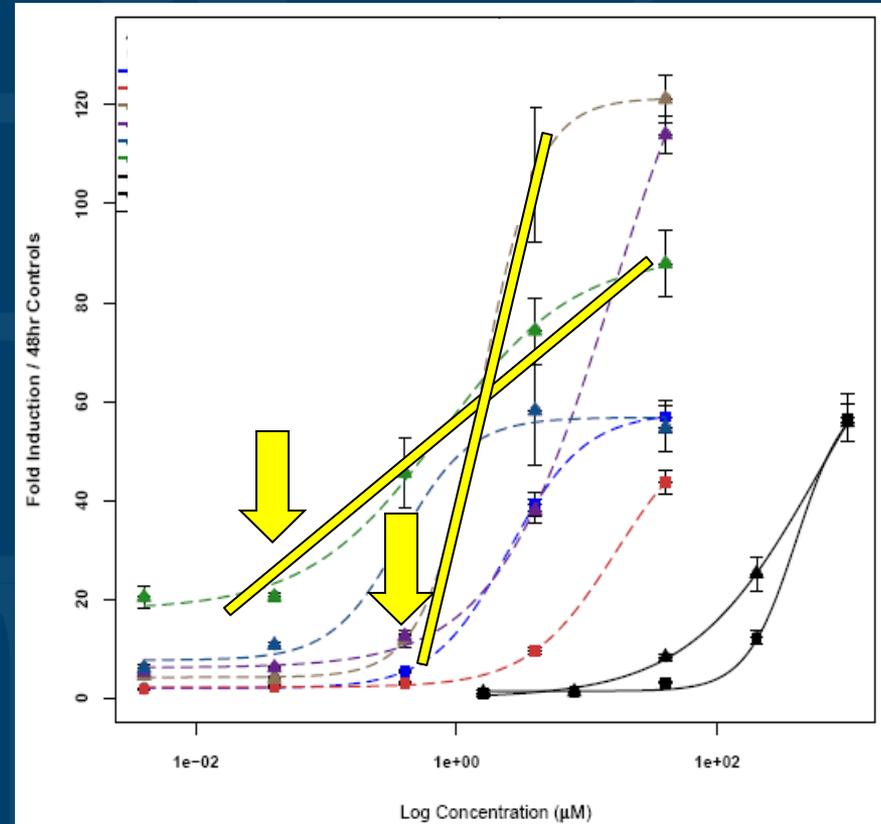
## *Hazard Id*

- Apply explicit **inclusion/exclusion criteria** for data
- Identify causal molecular **patterns** that make one chemical more likely to produce a specific effect than another
- Knowledge of single events or linear MOAs is general not sufficient (although can be suggestive of hazard); must consider **adverse outcome pathways**
- Apply Bradford-Hill criteria to judge **weight of evidence**
- Defines **new types** of critical effects for hazard id and dose-response assessment

# Approaches Overview

## *Exposure/Dose-Response*

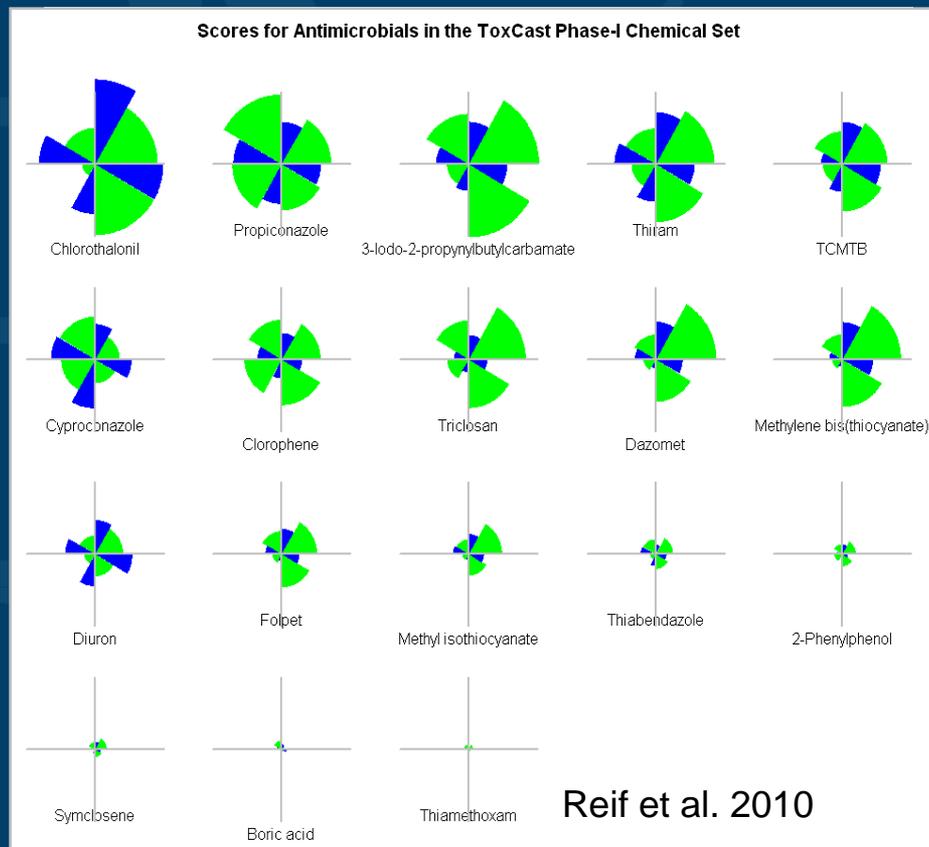
- Various approaches exist applied to these new types of critical effects
  - ✓ LOEL(s), LOAEL(s) or BMD
  - ✓ Slope(s) within experimental range



# Approaches Overview

## *Exposure/Dose-Response*

- Various approaches exist applied to these new types of critical effects
  - ✓ LOEL(s), LOAEL(s) or BMD
  - ✓ Slope(s) within experimental range
  - ✓ Integration across assay results

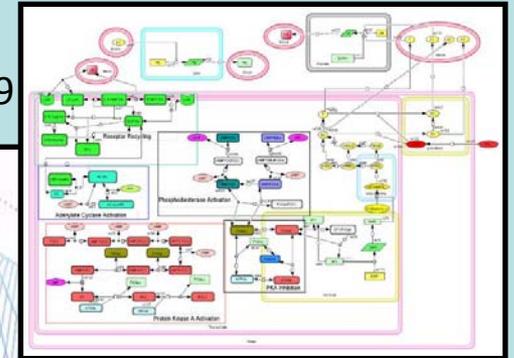
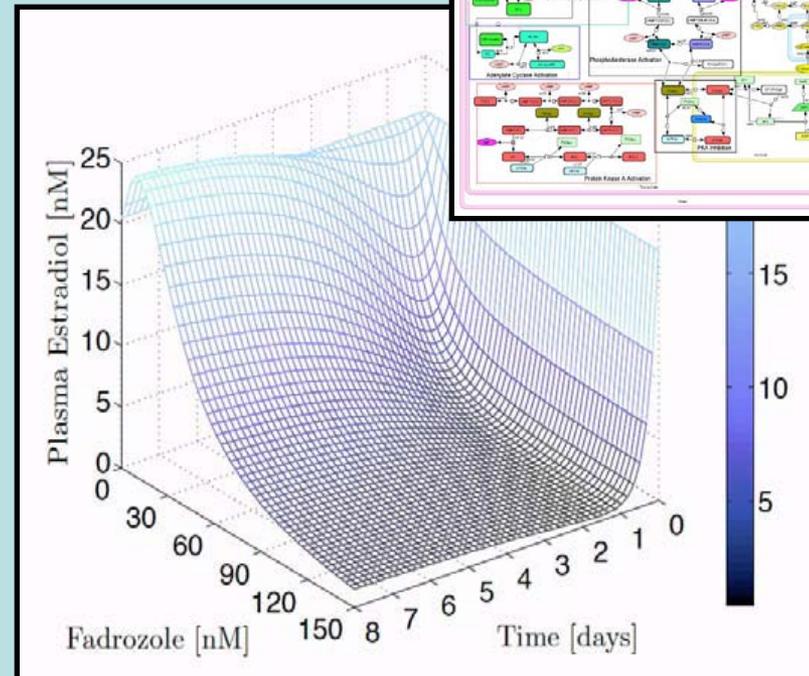


# Approaches Overview

## *Exposure/Dose-Response*

- Various approaches exist applied to these new types of critical effects
  - ✓ LOEL(s), LOAEL(s) or BMD
  - ✓ Slope(s) within experimental range
  - ✓ Integration across assay results
  - ✓ Systems biology modeling

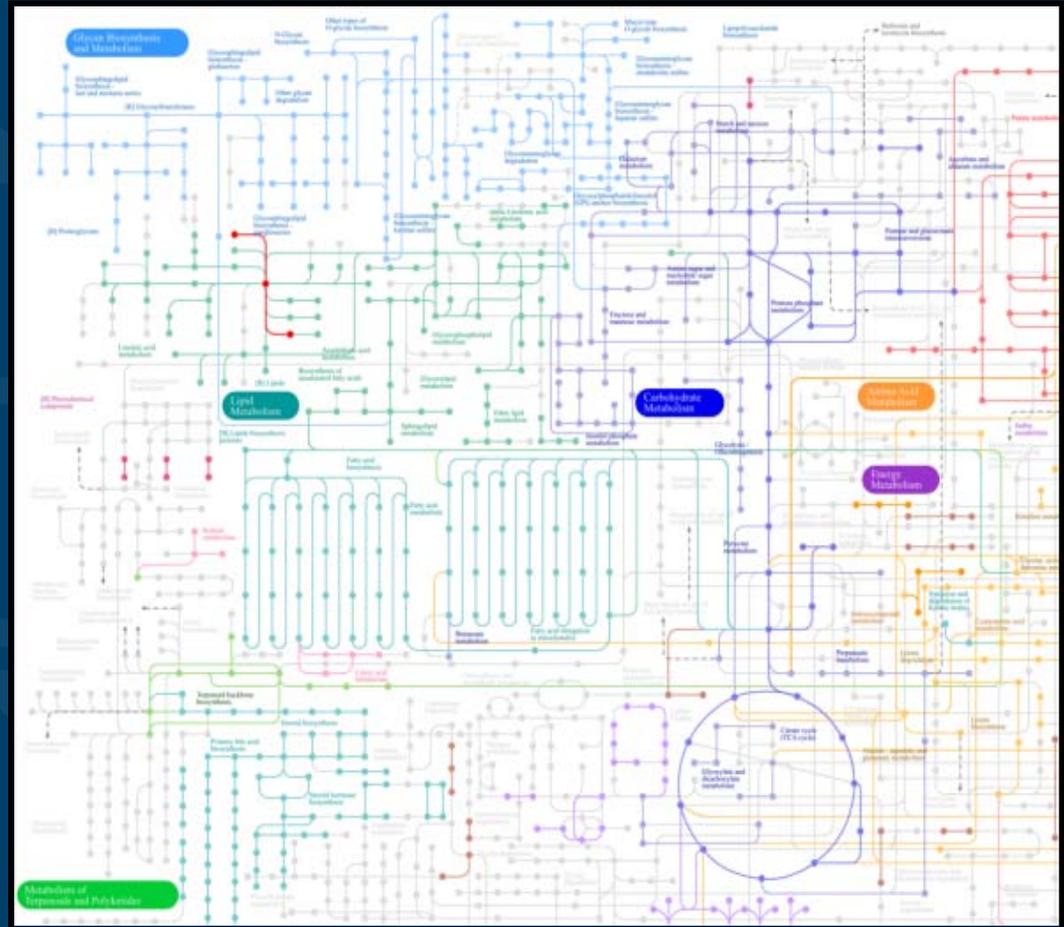
Villeneuve et al, EHP 2009



# Approaches Overview

## *Exposure/Dose-Response*

- Various approaches exist applied to these new types of critical effects
  - ✓ LOEL(s), LOAEL(s) or BMD
  - ✓ Slope(s) within experimental range
  - ✓ Integration across results
  - ✓ Systems biology modeling
  - ✓ Network or AOP information flow models
- Biologically, no reason to use different approaches for cancer and noncancer



# Other Steps

- Estimate equivalent human exposure and/or dose
  - Reverse dosimetry modeling
  - Monitored exposure & dosimetry/ PK modeling
  - Biomarkers
- Consider species relevance, if applicable
- Characterize variability among humans to the extent possible
- Consider background of response/adaptation
- Estimate population risks, including variability and uncertainty

**Goal is to replace assumptions with data, thus reducing the need for extrapolation or uncertainty factors**

CSS efforts to identify targets/pathways linked to toxicity & predictive of in vivo outcomes is a key component of NexGen across all Tiers.

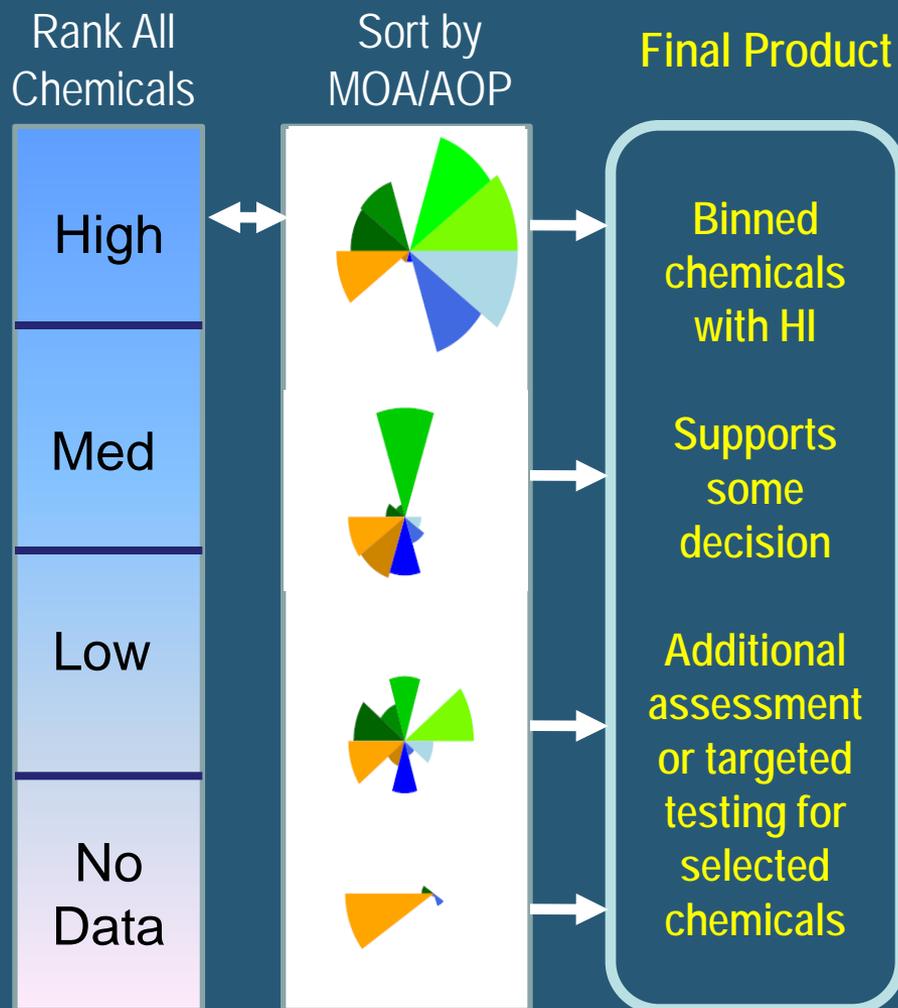
# Outline

- Background
- Risk Context & Approaches
- **Specific Examples**
  - Ranking and Screening
  - Limited Assessments
  - National Assessments
- Summary

# Tier 1: HT Ranking and Screening

# Tier 1: HT Ranking and Screening

- Common relative ranking for all chemicals with QSAR & HTS
- Benchmark ranking against known toxicants
- Adjust rankings using exposure surrogates & population variability
- Bin into high, medium, low risk or no data
- Sort high concern chemicals into MOA or AOP



# Tier 1: HT Ranking and Screening

*Assessments In Progress*

- Hydrofracking chemicals and **methods peer review** (2013)
- Pilot comprehensive environmental assessments (2014)
- Bin existing, new and emerging chemicals of concern, as data become available

**Tier 1 is primarily applied CSS methods as described in previous talk**

# Tier 2: Limited Assessments

# Tier 2: Limited Assessments

- High concern Tier 1 chemicals advance to limited scope assessments
- Aim is to generate a reference value as opposed to category of concern bin
- Differs from Tier 1 in the following:
  - In vivo, in situ, in silico exposures
  - More intact metabolism
  - Higher level of biologic integration
  - Additional endpoints e.g. neurobehavioral
- Information provided by these systems often reflects the omics of various cell types
- Three examples follow

# CSS Systems Models: Virtual Tissues

Systems modeling is a major CSS research theme

Virtual Tissues - Predictive models of chemical-induced disruption of normal functions

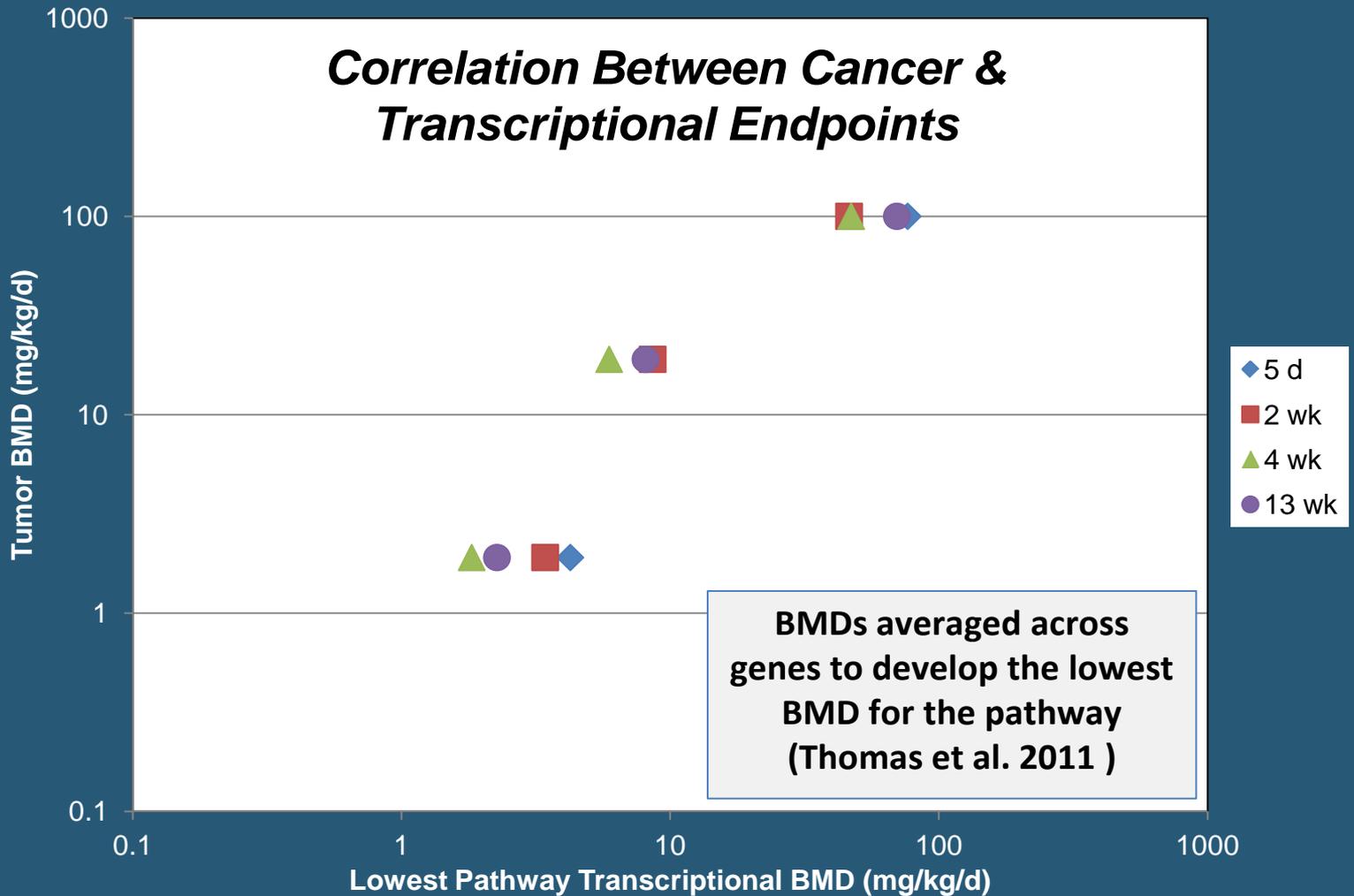
- Virtual Liver
- Virtual Embryo
- Virtual Endocrine System

## Virtual Tissues Goals

- Elucidate adverse outcome pathways (AOPs) – leverage *in vitro* data
- AOP-driven data collection - toxicokinetics and dynamics
- Quantitative computational predictive models of AOPs

# Tier 2: Limited Assessments

Short Duration In Vivo Exposures - *Rodent*



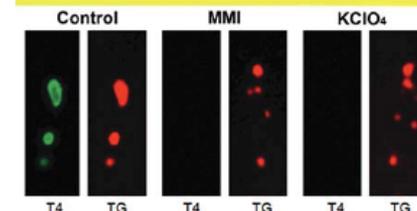
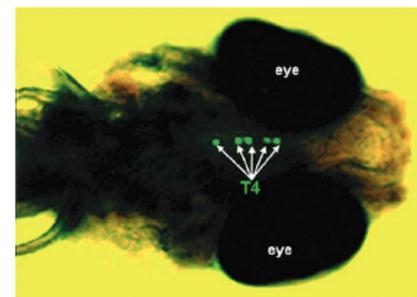
# Tier 2: Limited Assessments

## Short Duration In Vivo Exposures – *Alternative Species*

- Alternative species data can be used to determine hazard and dose response
- Species differences need to be characterized
- Understanding dose equivalents in various test systems is a challenge

Zebrafish eleutheroembryos in comparison to mammals

	Chemical	Mammals	Zebrafish (TIQDT)	In vitro
Direct effect	KClO <sub>4</sub>	Red	Red	Red
	KSCN	Red	Red	Red
	NaBr	Red	Red	Red
	NaNO <sub>3</sub>	Red	Green	Red
	MMI	Red	Red	Red
	PTU	Red	Red	Red
	BP2	Red	Red	Red
	Resorcinol	Red	Red	Red
	Phoroglucinol	Red	Red	Red
	SMX	Red	Red	White
	Amitrole	Red	Red	Red
	ETU	Red	Red	Red
	Mancozeb	Red	Red	White
	Pyrazole	Red	Red	White
	Genistein	Red	Red	Red
Indirect effect	BPA	White	Green	Red
	BP3	White	Green	Red
	Linuron	Green	Green	Red
	PFOS	Green	Green	White
	PFOA	White	Green	White
	BDE-47	White	Green	White
	BDE-209	Red	Green	White
	HBBD	Red	Green	White
	TBBPA	Green	Green	White
	DDT	Red	Green	White



Short-term exposure to direct TGFD induced a strong decrease in IT4C the thyroid follicles of zebrafish eleutheroembryos.

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Thienpont et al 2011 ET&C

# Tier 2: Limited Assessments

## *Provisional Values Development Underway*

- 6 in vivo transcriptomics-based assessments (2013)
- 6 high concern hydrofracking chemical (2014)
- Endocrine disruptors and mixtures (2014)
- High concern chemicals from Tier 1 (as available)

**Methods and products will be peer reviewed**

# Tier 3: Major Assessments

The intent is 3 fold:

1. Develop robust proofs of concept
2. Extend what is learned to chemicals with less data
3. Inform issues not well resolved by traditional data

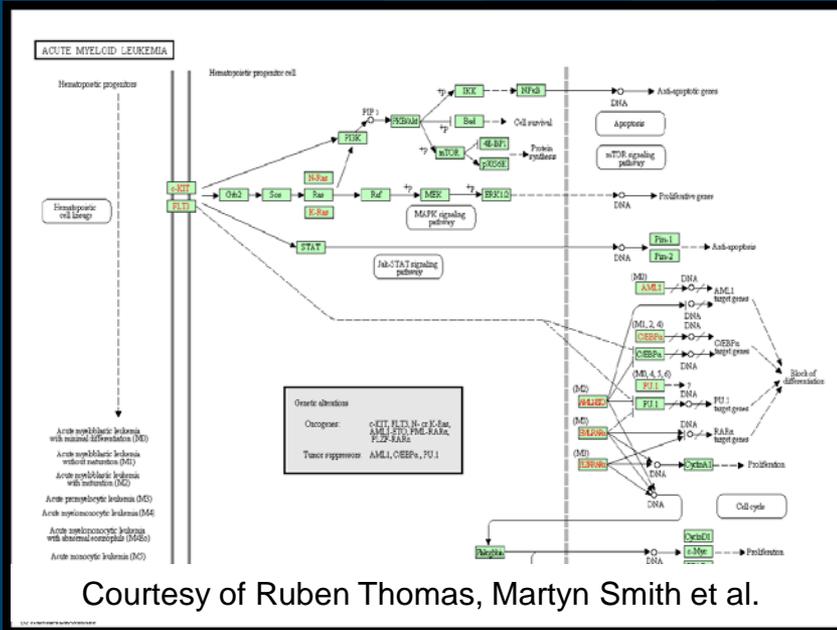
# Tier 3: Major Assessments

## Prototypes (ozone, benzene and PAHs) involve:

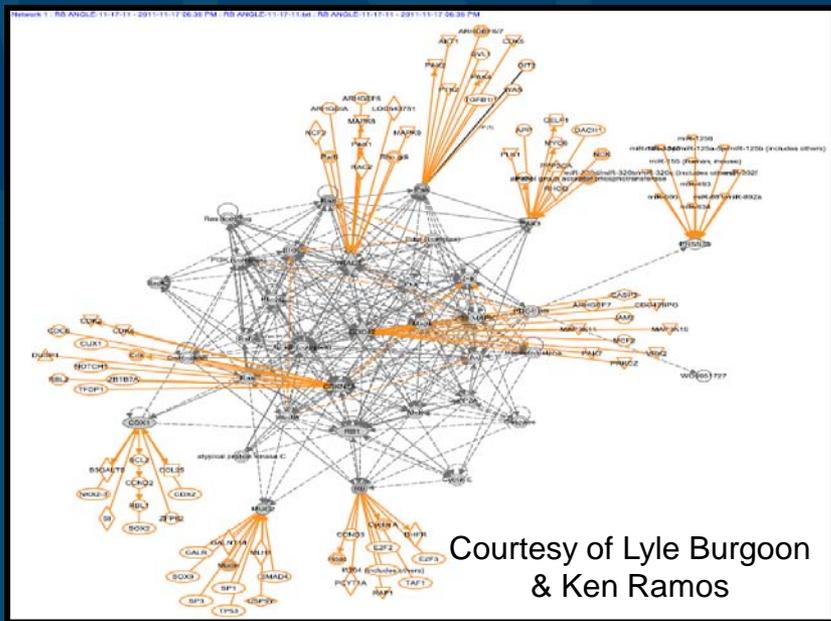
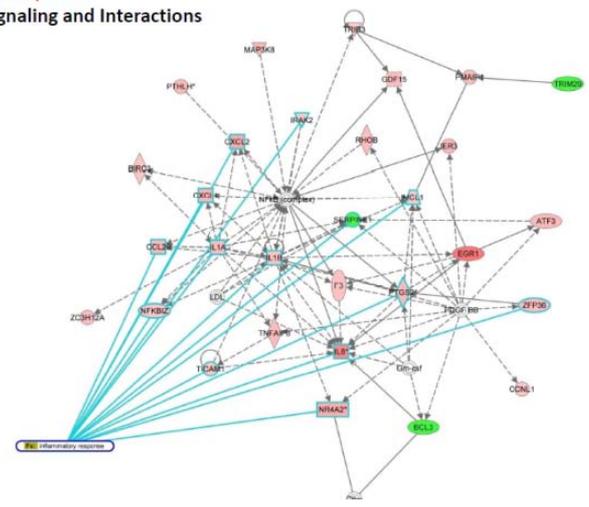
- Well understood human environmental exposures
- Known causal associations among exposure, traditional upstream events, and phenotypic outcomes
- Omics data from cells of phenotypically affected tissues
- “If you can’t do it with this data, it can’t be done”  
(Dan Costa, 2010)

# Ozone and Lung Inflammation/Injury

## Benzene and Hematotoxicity/Leukemia



- Top Functions:**
- Inflammatory Response
  - Cell-to-Cell Signaling and Interactions
  - Cell Stress



## PAHs and Lung Cancer

# Tier 3: Major Assessments

- Specific alterations in gene profiles are **consistent, coherent** and **biologically plausible indicators** of both traditional upstream and phenotypic events
- Induced alterations in gene transcription profiles are **both dose and time dependent**
- Relevance of animal data being addressed
- Susceptibility can be better characterized using omics
- Adds weight of evidence for effects suggested by epidemiology
- Furthers our understanding of biomarker of exposure & effect

**Argues that not-well-studied chemicals with the same signatures are of concern for the same health effects**

# Tier 3: Major Assessments

## *Chemicals Assessment & Topics Underway*

### IRIS

- ✓ BaP – role in mixtures (2013)
- ✓ Chloroform – mode of action (2013)
- ✓ Formaldehyde – mode of action (2013)
- ✓ Chromium – mode of action, route & species relevance (2013)
- ✓ Arsenic – mode of action and prenatal exposures (2014)

### ISAs

- ✓ Multipollutant ISA – mixtures (1 year)
- ✓ Ozone ISA – human studies, susceptible populations (2017)

### Cross-cutting issues

- ✓ Mouse lung tumors - mode of action & human relevance (2013)
- ✓ Hormone disruption – extrapolation from data rich to data limited chemicals and mixtures (2014)

# Outline

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- Specific Examples
- **Summary**

# Summary

- ✓ Assessment are being developed based on current state of the science, targeted to risk context
- ✓ Product will start becoming available in workshops, papers and for external peer review next year
- ✓ This has been made possible by the research in CSS and HSS and other research programs
- ✓ Other federal agencies have also contribute critical information
- ✓ Research continues to improve our state of knowledge and will be reflected in evolving risk assessments

## NexGen Implementation Agenda

### Ranking/Screening

- ✓ ~1000 HF chemicals
- ✓ Pilot comprehensive environmental assessments
- ✓ Bin existing, new and emerging chemicals of concern, as data become available

### Preliminary reference values

- ✓ 6 HF chemicals
- ✓ 6 in vivo transcriptomics-based assessments
- ✓ Hormone disruptors
- ✓ High concern Tox21/ToxCast chemicals

### IRIS assessments

- ✓ BaP
- ✓ Chloroform
- ✓ Chromium VI
- ✓ Formaldehyde
- ✓ Arsenic

### ISAs

- ✓ Multipollutant ISA
- ✓ Ozone ISA

### Cross-cutting issues

- ✓ Mouse lung tumors
- ✓ Hormone disruption

## **EPA**

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<http://www.epa.gov/risk/nexgen/>

# 2011 Advancing the Next Generation (NexGen) of Risk Assessment

## Public Dialogue Conference Agenda

### [Public Dialogue Conference Summary](#)

#### **Welcome and Introduction - Ms. Becki Clark**

**Vision for Safer Chemicals, Sustainable World - Dr. Paul Anastas:** [Video](#) – (includes both the Welcome, Introduction & Vision for Safer Chemicals content)

**Linking Research to Risk Assessment, Dr. Linda Birnbaum:** [Video](#) | [Presentation](#)

**The Next Generation of Risk Assessment (NexGen) Program: Overview and Invitation to Engage - Dr. Ila Cote:** [Video](#) | [Presentation](#)

**The Next Generation of Risk Assessment (NexGen): A Proposed Framework Dr. Daniel Krewski:** [Video](#) | [Presentation](#)

#### **Three Example Approaches to Understanding Human Health Risks Associated with Environmental Exposures**

- **Ozone - Dr. Robert Devlin:** [Video](#) | [Presentation](#)
- **Benzene - Dr. Martyn Smith:** [Video](#) | [Presentation](#)
- **Approaches for Chemicals with Limited Data - Dr. David Dix:** [Video](#) | [Presentation](#)

**Question and Answer Session with Speaker Panel:** [Video](#)

**Common Themes Heard - Dr Doug Crawford-Brown:** [Video](#) | [Presentation](#)

# Weight of Evidence for Causal Determination

Causal	<ul style="list-style-type: none"> <li>• Experimental evidence of a causal relationship among relevant chemical exposure, a specific pattern of molecular/cellular events and disease outcomes in humans.</li> <li>• Association has been observed between the pollutant and the outcomes in studies in which chance, bias, and confounding could be ruled out with reasonable confidence.</li> </ul>
Likely Causal	<ul style="list-style-type: none"> <li>• Experimental evidence and/or consistent associations in well conducted epidemiology studies of causal relationship among chemical exposure, specific molecular/cellular events and disease outcomes in humans or animals.</li> <li>• Association has been observed between the pollutant and the outcome in studies in which chance, bias, and confounding could be ruled out with reasonable confidence, but uncertainties remain.</li> </ul>
Suggestive	<ul style="list-style-type: none"> <li>• Evidence is suggestive of an association between relevant pollutant exposures, a specific pattern of molecular/cellular events and disease outcomes, but is limited because chance, bias and confounding cannot be ruled out.</li> </ul>

# Dose-Response

## *Criteria & Principles*

1. Key drivers within pathways must be identified and dose-response modeling performed on these key drivers whenever possible
2. These key drivers are the criteria genes, proteins, and metabolites that are associated with the key pathway.
3. The criteria genes, proteins, metabolites, or pathways must demonstrate a statistically significant difference compared to control.
4. The point of departure and ED<sub>50</sub> for criteria genes, proteins, metabolites, or pathways must not be greater than that for the key end-point.
5. The criteria pathway must be consistent across multiple studies (when multiple studies are present). Specific genes, proteins, or metabolites do not need to be consistent across multiple studies.
6. The criteria pathway must be involved in the key end-point, and must be part of the MOA/AOP.

# Key Steps in Assessment

1. Apply selection criteria for studies and data
2. Identify critical effects & evaluate overall causal weight of evidence
3. Apply optimal approach for dose-response evaluation
4. Estimate equivalent human exposure and/or dose
5. Consider species relevance, if applicable
6. Characterize variability among humans to the extent possible
7. Consider background of response/adaptation
8. Estimate population risks, including variability and uncertainty

# Ongoing NAS Emerging Science for Environmental Health Decisions Workshops

## Previous Workshops

[Computational Toxicology](#)

[Early Indicators of Disease](#)

[Epigenetics](#)

[The Exposome](#)

[Green Chemistry](#)

[Individual Exposomes](#)

[The Microbiome](#)

[Mixtures and Cumulative Risk Assessment](#)

[Stem Cells](#)

[Individual Variability](#)

## Upcoming Workshops

[Systems Biology Informed Risk Assessment](#)