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Implementing EPA's Chemical Safety for Sustainability Research Program

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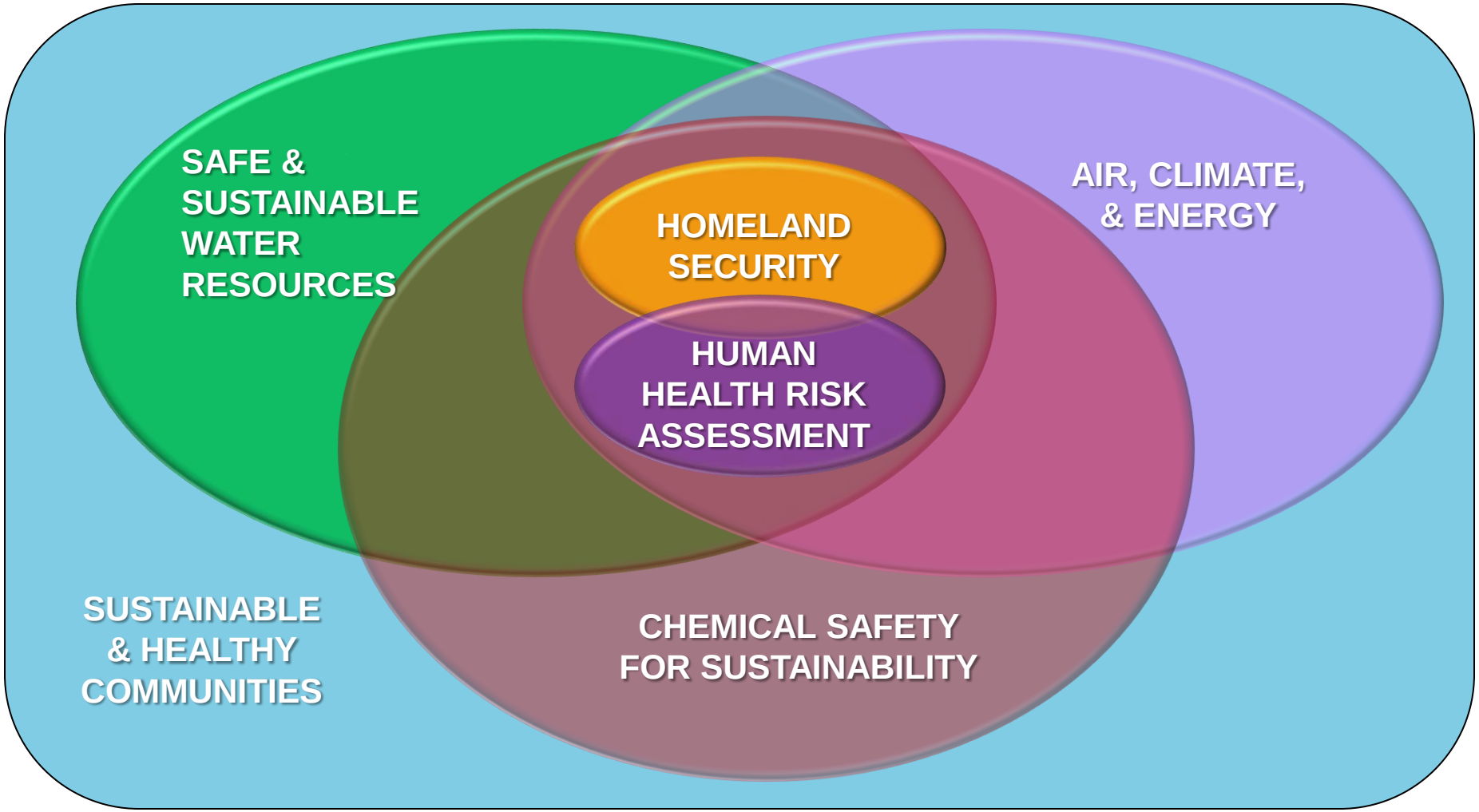
SAB/BOSC Briefing
July 10-11, 2012

Office of Research and Development
CSS

Outline

- Overview of CSS Program
- Information related to charge questions
  - CSS progress in first year of implementation
    - Program Development, Management, and Outreach
    - Scientific Contributions and Products
  - Sustainability – CSS contributions
  - Balancing immediate and emerging research priorities
  - Key areas – endocrine disrupting chemicals, nanotechnology, and computational toxicology research
  - Examples of CSS transformative exposure research

Integrated ORD Research Programs



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Environmental Complexity

- A host of emerging drivers - from climate change, to children's health, to green chemistry, to urbanization - demand better information for better environmental and public health decisions.
- Science of CSS needs to be agile, adaptive, responsive, and anticipatory/predictive, delivering knowledge that is impactful, timely, and relevant to current and future environmental health challenges.

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Capacity Building

- CSS research enhances EPA's scientific capacity to:
  - Quickly assess and mitigate impacts in the face of emerging environmental health threats and natural and human-caused disasters – *agile*;
  - Customize solutions that are scaled to the problem formulated – *adaptive*;
  - Engage and empower a broad set of audiences in developing solutions – *responsive*;
  - Anticipate and forecast human and ecological threats – *anticipatory/predictive*

Chemical Safety for Sustainability Research Program

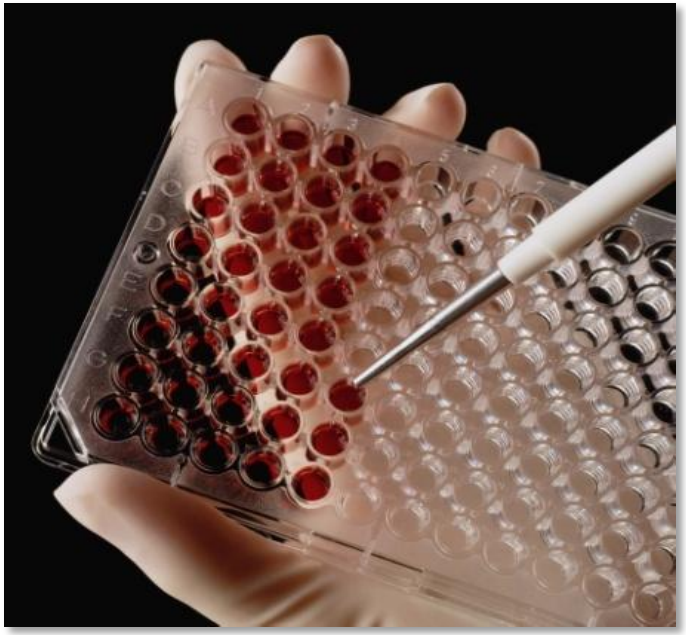
Problem Statement

Although chemicals are essential to modern life, we lack innovative, systematic, effective, and efficient approaches and tools to inform decisions that reduce negative environmental and societal impacts of chemicals.

Vision

EPA science will lead the sustainable development, use, and assessment of chemicals by developing and applying integrated chemical evaluation strategies and decision support tools.

CSS Research Program



8 Research Themes

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

21 projects, 55 task, 320 products
14 key deliverables in FY12

CSS Progress: Program Development, Management, and Outreach

- Established CSS Network
  - Research Topics/Projects/Tasks and Project Leads and Task Leads
- Hiring NPD (exposure expertise)
- Progress towards a 'balanced' matrix
- Engaging partner advocates in program and regional offices
- Planned CSS retreat (July 12, 2012) to refine strategic direction

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Highlights of Progress in Year 1

- Developing and operationalizing Strategic Research Action Plan (StRAP)
- Laying the groundwork for integration within CSS and across ORD/EPA (next generation RA, EDCs, nanomaterials)
- Incorporating innovation into CSS operations, products, and outputs
- Increasing focus on green chemistry
- Advancing computational exposure science through ExpoCast to enhance predictive capabilities for prioritization, sustainable design, green chemistry, and high throughput risk assessment

CSS FY12 Representative Products

1.2.1	Develop methods for characterizing the physical and chemical properties that influence the bioavailability of nano silver.
2.2.1	Computational model of the hepatic lobule that accounts for extrapolation from in vitro hepatoxicity data to in vivo. The product will utilize ToxCast data and knowledge-based tools to construct dynamic molecular networks, estimate cell level concentrations based on microvascular transport, and predict chronic hepatic effects on selected EDSP21/TSCA21/OW21 chemicals (chemicals selected in collaboration with OSCPP).
2.3.2	Revised version of SHEDS-Multimedia (v4) as recommended by 2010 FIFRA SAP to included output results for different scenarios, case-studies and sensitivity analyses addressing OPP needs including dietary and residential scenarios.
2.5.1	Completion of high-throughput screening data sets on first 1000 EDSP21 chemicals, and ToxCast Phase II chemical library.
2.5.3	ExpoCast high-throughput exposure predictions for prioritization of initial ToxCast, TSCA21 and EDSP21 chemicals including exposure metrics and fate and transport modeling of large chemical libraries.
3.3.1	Web-based software tool to conduct reverse dosimetry probability calculations for estimating exposure concentrations that are likely to have produced the observed biomarker concentrations.
4.2.2	Data, methods and science on understanding sources and exposures to PCBs in schools and mitigating risks to children to support EPA Regional and Program Office decisions.
4.2.2	Evaluation of PCB encapsulants.
5.2.1	Joint patent application with CRADA partner for butanol recovery from dilute solutions during manufacturing via membrane-based separation processes in response to the need of OTAQ (OAR) to assess biobutanol as a fuel substitute for bioethanol to potentially lessen greenhouse gas emissions.
5.2.3	Demonstration of how the GREENSCOPE sustainability indicator model can evaluate human health and environmental risks, for an example such as manufacturing of biodiesel.
5.2.4	Sign CRADA w/an industrial partner to research how to design supply chains to be as sustainable as possible.
7.1.3	Prototype dashboard for OPP to support ecological risk assessment.
7.1.4	Prototype version 1.0 of web-based dashboards followed by updates every six months including: EDSP21 (Endocrine Disruptor Screening Program for the 21st Century) dashboard for evaluating screening, testing, exposure and sustainability information relevant to potential endocrine disruption.
2.2.4	Awarded eight grants for the solicitation from the RFA entitled "Developing High-Throughput Assays for Predictive Modeling of Reproductive and Developmental Toxicity Modulated through the Endocrine System or Pertinent Pathways in Humans and Species Relevant to Ecological Risk Assessment."

= ecological health
= human health
= ecological and human health

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Sustainability: A Life Cycle Focus

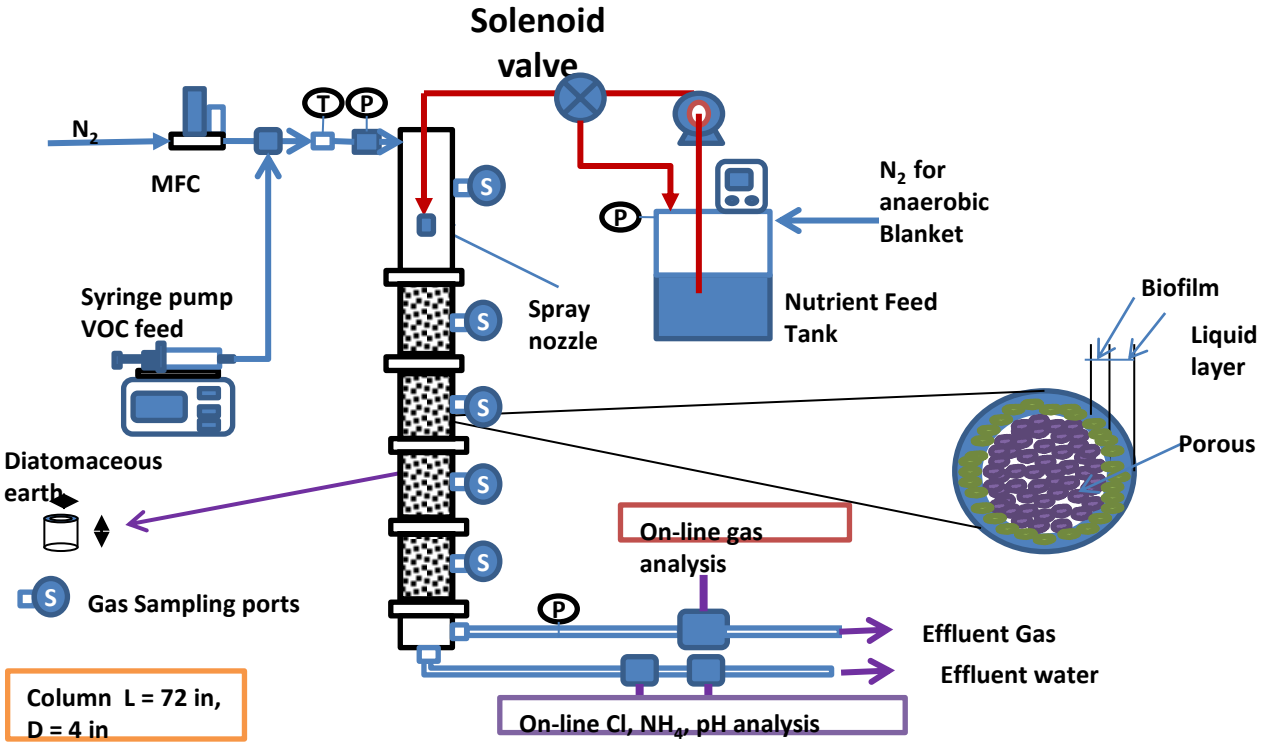
- Identification of key linkages in the continuum between the production of a chemical, its release, fate/transport of a chemical in the environment, the resulting exposures and adverse outcomes for humans and/or the environment so that sustainable risk management approaches can be scaled up and delivered to decision-makers.

Examples of Research that Contributes to EPA's Sustainability Framework

- Green Chemistry Research and Collaborations with California (5.2.1)
- Green Remediation, using Nanomaterials (5.2.1)
- Membrane for Efficient Biofuel Production (5.2.2)
- GREENSCOPE Sustainability Software (5.2.3)
- Innovation and Technology Management for Sustainability (5.2.4)
- Unified platforms for gathering data, enhanced modeling products such as QSARs for analysis of chemical substitutes (Task 1.3.1)
- Sustainable Replacements for HAPs (2.5.1)
- Two STAR RfAs

Innovation Project: Controlling Disinfection By-products with Biological Degradation

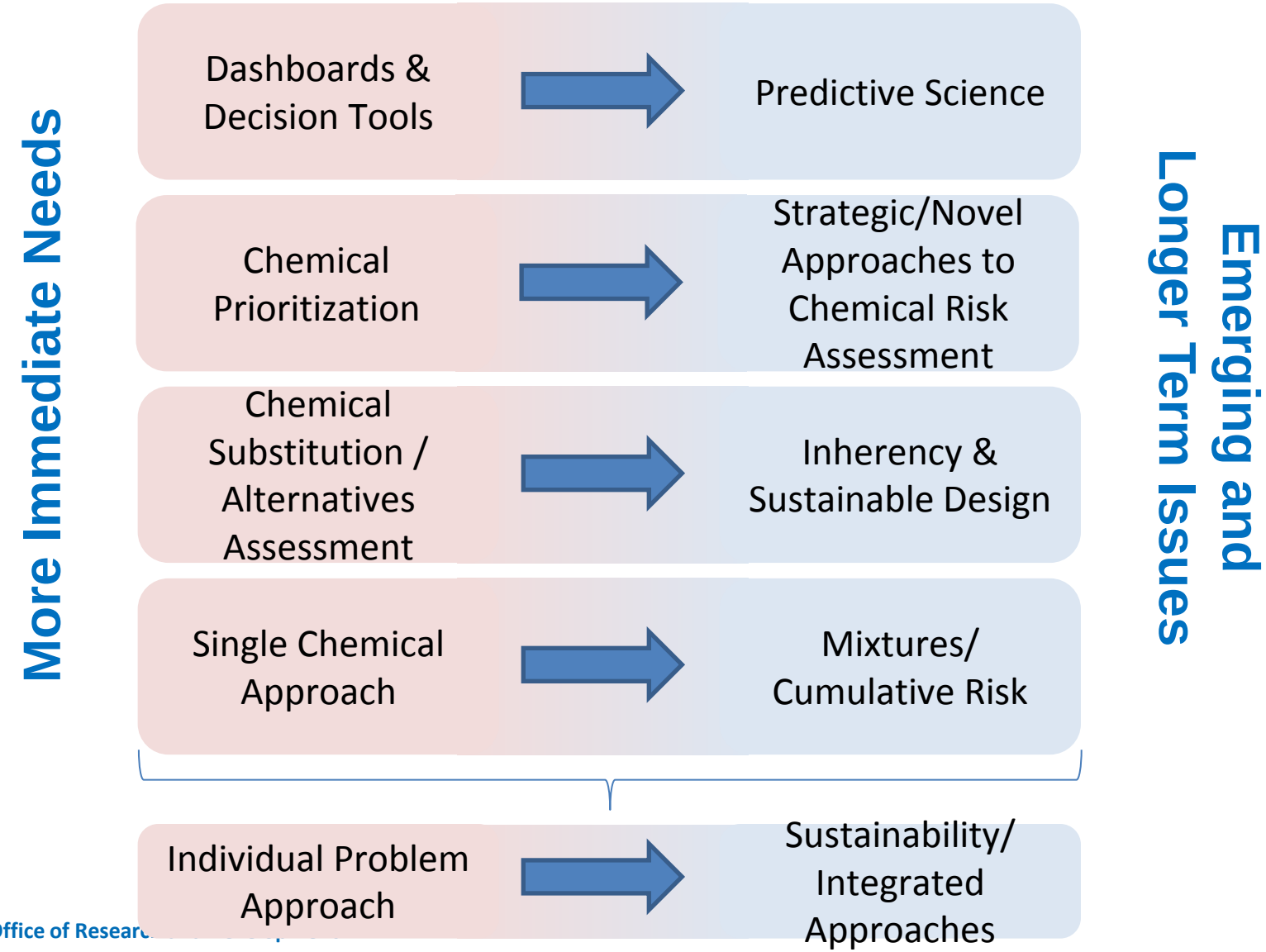
- Water treatment systems that use chlorinated disinfectants generate a range of Toxic Disinfection By-Products, such as trihalomethanes
- Primary objective is to encourage the growth of anoxic and anaerobic microorganisms for two purposes:
  - Degradation of water contaminants to biogas (methane) using a low-energy process
  - Methane can be recovered as a biofuel



Balancing Immediate Needs and Emerging Issues: Emerging CSS Research Objectives

- Protecting human and ecosystem health in an evolving chemical landscape
- Changing the paradigm for chemical safety assessments
- Developing and applying approaches to assess exposures and human and ecological effects of chemical mixtures
- Evaluating interactions among chemical exposures and between chemicals and other environmental stressors to address cumulative risk
- Providing tools and guidance for "greener" chemical production to enable and improve environmental sustainability

Balancing Immediate Needs and Emerging Issues: The Evolution of the CSS Program



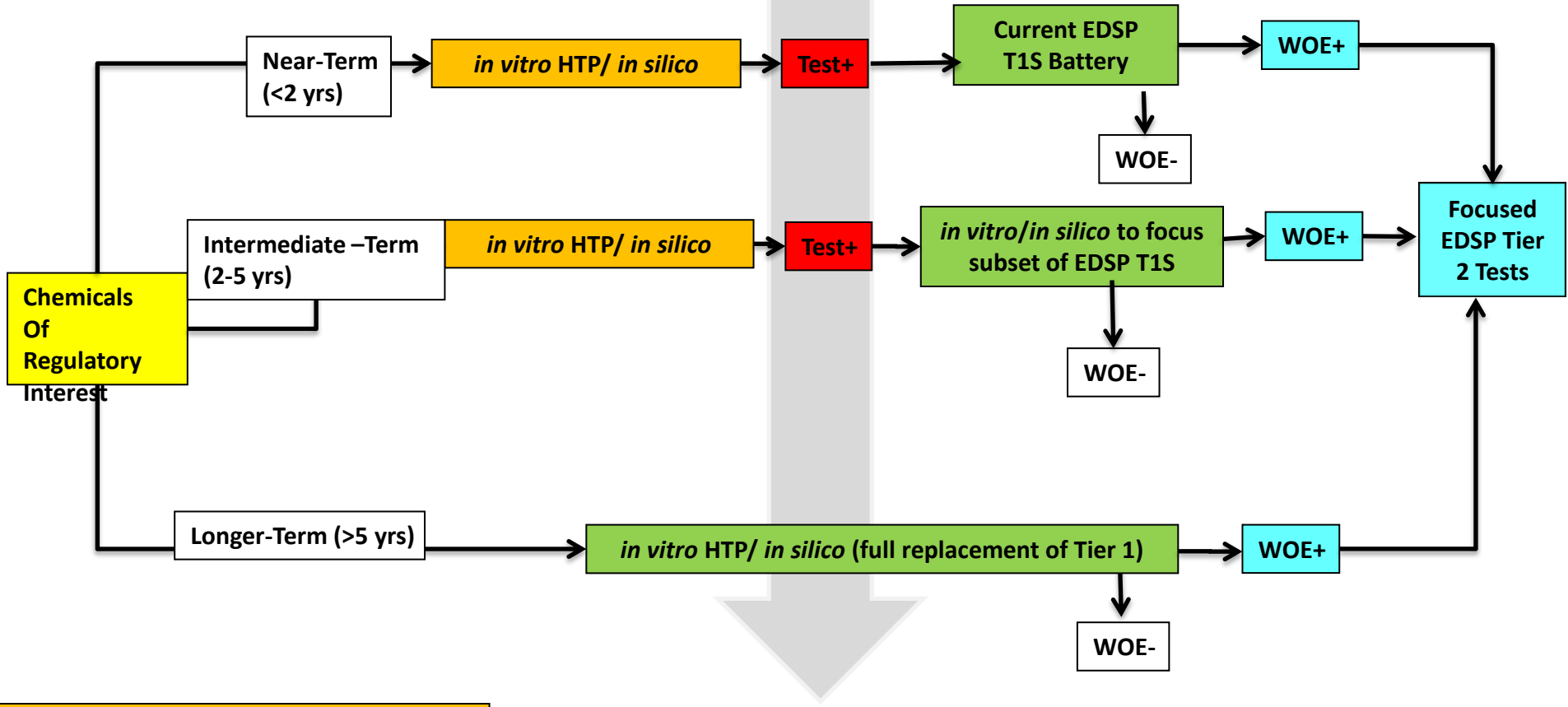
Endocrine Disrupting Chemicals (EDCs)

- Adverse Outcome Pathway concept and data streams that inform them in many EDC CSS products
- Application to levels of organization based on source to outcome
- CSS support to the Endocrine Disruptor Screening Program (EDSP) and responsive to EDSP 21 workplan

EDSP21 Work Plan: Timing and Approach

The universe of chemicals passes through each version of the HTP/*in silico* pipeline to evaluate chemicals in refined tests, for new pathways, to evaluate, improve, and validate methods.

EPA Research provides basis for improving the suite of assays and models to advance chemical prioritization and screening



Chemical Prioritization
Includes , registration review timeline, physico-chemical properties, exposure estimates, *in vitro* assays and computer models (QSAR, expert systems, systems biology models).

Screening Decisions
Near-Term: Incorporates HTP/*in silico* prioritization methods
Intermediate-Term: Run subset of current T1S assays indicated by HTP and *in silico* predictions
Longer-Term: Full replacement of EDSP T1S Battery

Source: http://www.epa.gov/endo/pubs/edsp21_work_plan_summary%20_overview_final.pdf

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CSS Products: Models

2.2.1. Virtual Liver:

- **Computational model** that accounts for extrapolation from *in vitro* to *in vivo* hepatotoxicity data. Utilizes ToxCast data and knowledge-based tools to construct dynamic molecular networks, estimate cell level concentrations based on microvascular transport, and predict chronic hepatic effects on selected EDSP21/TSCA21/OW21 chemicals. (FY12)
- **Data to assess the mechanisms and kinetics of xenobiotic transformations, transport, enzyme induction, enzyme inhibition, and pathway elucidation.** Supports development of computational (in silico) models linking exposure-to-effects via internal dose for characterizing and mitigating the effect of ADME on HTS liver assay results used in chemical prioritization and risk assessment. The product will initially focus on selected chemicals relevant to EDSP21 and TSCA21 *Dashboards (CSS Theme 7)* and will provide empirical data for models to predict the influence of transporters on hepatic clearance and microdosimetry. (FY13)
- **Data to assess the mechanisms and kinetics of xenobiotic transformations, transport, enzyme induction, enzyme inhibition, and pathway elucidation.** Supports development of computational (*in silico)* models linking exposure-to-effects via internal dose for characterizing and mitigating effect of ADME on HTS liver assay results used in chemical prioritization and risk assessment. ill initially focus on selected chemicals relevant to EDSP21 and TSCA21 Dashboards and will provide empirical data for models to predict the influence of transporters on hepatic clearance and microdosimetry. (FY13)

2.2.2. Virtual Embryo:

- **Integration of angiogenesis information:** A cell-agent based systems model developed from empirical data and biological knowledge of blood vessel development. Angiogenesis model trained with compounds showing anti-angiogenic properties, assessed in a forward validation for predictive developmental toxicity among 1,000+ ToxCast chemicals in pregnant rats/rabbits, and tested for vascular disruption in zebrafish embryos and embryonic stem cell assays for 30+ chemicals in EDSP21/TSCA21/OW21/OPP21. (FY13)
- **Implementation of cell-agent based models linked to complex embryological phenomena (limb-bud morphogenesis, reproductive tract development).** Deliver computer models imputing knowledge of signaling networks, tissue induction, spatial patterning, and molecular clocks to recapitulate morphogenesis and predict points of departure for dysmorphogenesis. Models trained with 20 reference compounds in ToxCast and applied to 20 data-poor chemicals in TSCA21. (FY13)

2.2.3. HPG Axis:

- **Development of a computational (*in silico*) systems model that simulates key aspects of a chemicals potential to disrupt normal HPG axis regulation,** linking changes in key events within adverse outcome pathways (chemicals selected from EDSP21). (FY13)
- **Improve AOP models by incorporating key events data for the hypothalamic-pituitary-gonadal (HPG) axis.** This product will inform the development of rapid test methods to define novel toxicity pathways in disruption of reproductive functions on selected chemicals from the EDSP21 case study (e.g., adrenal progesterone, neuropeptide regulation, steroid hormone metabolism). (FY13)

2.5.3. Exposure:

- **ExpoCast high-throughput exposure predictions** for prioritization of initial ToxCast, TSCA21 and EDSP21 chemicals including exposure metrics and fate and transport modeling of large chemical libraries. (FY12)

EDSP Support: FY12/13 cont.

CSS Products: Chemical Prioritization, Screening and Testing
2.1.1. • **A searchable AOP knowledgebase:** Step 1. A standardized template for identifying key contents and format of the AOP descriptions to populate a searchable AOP knowledgebase. Includes several example AOPs descriptions for reproductive toxicity and developmental neurotoxicity with relevance to EDSP21 and Priority Setting workplans developed with OCSPP and OW. (FY13)
2.2.3. • **PATHFINDER:** Proof-of-concept that the transgenic Xenopus tadpole is a useful bioindicator of a thyroid endocrine signal. This product will determine its effectiveness in detecting the presence of EDCs that impact the thyroid axis, including a limited validation via testing of positive controls, known mammalian responses, and identification of a suite of thyroid-responsive genes for screening purposes. (FY13)
2.5.1. **HTS Screening** • Completion of high-throughput screening data sets on first 1000 EDSP21 chemicals, and ToxCast Phase II chemical library. (FY12) • Accelerated ToxCast screening data on additional chemicals beyond the current EDSP21 library; access new endocrine-related assays for EDSP21 (especially thyroid and steroidogenesis-related); validation studies on EDSP21 assays including targeted in vitro data on EDSP21 chemicals; database to manage EDSP21 data as well as data from guideline EDSP Tier 1 and Tier 2 studies; prioritization/weight of evidence methods/models for using EDSP21 data by program partners. (FY13) • Validated medium-throughput assays to screen and prioritize chemicals for developmental neurotoxicity. (FY13) • Data sets for ToxCast chemicals in screening assays for AOPs identified in Task 2.1.1. (FY13)
2.5.2. **HTS Signatures:** • Prioritization and selection of ToxCast Phase-1 and Phase-II chemicals for the TSCA21, OW21, and OPP21 case studies based on endpoints for cancer, developmental and reproductive toxicity. (FY13) • Expansion of ToxCastDB pathway-models and predictive signatures for developmental toxicity, reproductive toxicity and chronic/cancer endpoints using data on ToxCast Phase-II chemicals. (FY13)

EDSP Support: FY12/13 cont.

CSS Products: Chemical Prioritization, Screening and Testing
6.1.1. **Expert Systems** • Enhanced Chemical Class-based Expert System to prioritize endocrine disruption (e.g., estrogen receptor (ER) mediated) potential of food/non-food use pesticide inerts and antimicrobials. Linked to *Dashboards (Theme 7).* (FY13) • An expert system based on human ER binding and transactivation for prioritizing chemicals with ED potential. Linked for delivery to Dashboards. (FY13)
6.1.2. **Effects and Exposure Extrapolation** • Integrated method linking endocrine active substance exposure in the environment with biological effects observed in *in vitro* and *in vivo* assays. (FY13)
6.2.3. **EDSP Tier 2** • EDSP Tier 2 test (T2T) guidances and protocols are delivered, including web-based guidance for diagnosing and scoring, and evaluating EDC-induced pathology in fish and amphibian. (FY13)
7.1.4. **Dashboards:** • Prototype version 1.0 of web-based dashboards followed by updates every six months including: EDSP21 Dashboard for evaluating screening, testing, exposure and sustainability information relevant to potential endocrine disruption. (FY12) • EDSP Data Evaluation Record Composers to capture of Tier 1 assay results to populate OPP database are delivered. (FY12)

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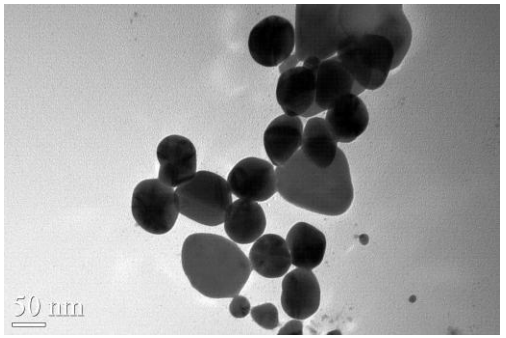
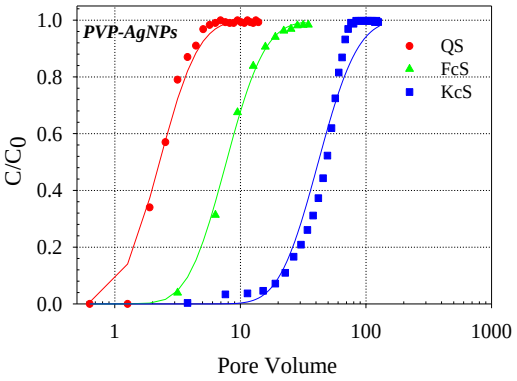
Nanomaterials Research

- Intramural work focused on key nanomaterials:
  - Representative of nanomaterial classes for trends' assessment:
    - metals, metal oxides, and carbon-based materials
  - Intended for commercialization after review under EPA Statutes
- Intramural research, and collaborations
- Extramural research, and collaborations

Integrated Research on Nano Silver

- ORD's unique integrated approach to evaluate the same AgNPs across the research continuum from characterization through fate & transport to eco and human toxicity resulted in the final conclusion that *cationic AgNPs are more toxic than anonic AgNPs*. This result is important for EPA's OCSPP
- Used commercially /Subject to FIFRA
- Work done in conjunction with SHC
  - Characterization in water, bioavailability in soils, leaching from clothing and other consumer products
- Collaborators: NIST, CPSC, Industry, CEIN/UCLA, Virginia Tech





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Alterations in physical state of silver nanoparticles exposed to synthetic human stomach fluid

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ABSTRACT

The bioavailability of ingested silver nanoparticles (AgNPs) depends in large part on initial particle size, shape and surface coating, properties which will influence aggregation, solubility and chemical composition during transit of the gastrointestinal tract. Citrate-stabilized AgNPs were exposed to synthetic human stomach fluid (SSF) (pH 1.5) and changes in size, shape, zeta potential, hydrodynamic diameter and chemical composition were determined during a 1 h exposure period using Surface Plasmon Resonance (SPR), High Resolution Transmission Electron Microscopy/Energy Dispersive X-ray Spectroscopy (TEM/EDS), Dynamic Light Scattering (DLS) and X-ray Powder Diffraction (XRD) combined with Rietveld analysis. Exposure of AgNPs to SSF produced a rapid decrease in the SPR peak at 414 nm and the appearance of a broad absorbance peak in the near infrared (NIR) spectral region. During exposure to SSF, changes in zeta potential, aggregation and morphology of the particles were also observed as well as production of silver chloride which appeared physically associated with particle aggregates.

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Integrated Research on Nano Copper

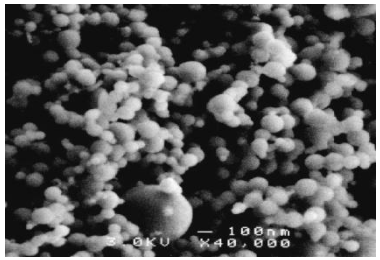
- Copper carbonate is used commercially as fungicide/herbicide in agricultural uses and the treatment of wood, and is currently subject to EPA review
- Research Areas:
  - Characterization of Nano Copper in the treatment solution
  - Develop method for the differentiation of ionic and micronized copper
  - Evaluation of the leachability of copper from MC treated lumber as a function of
    - Particle size, contact time, leaching solution, pH and ionic strength
- Collaborations:
  - Initiated a Cooperative Research and Development Agreement with Osmose Inc.
  - Initiated an Inter-Agency Agreement with Consumer Products Safety Commission (CPSC) to evaluate the safety of micronized copper
  - Working with Center of Environmental Implication of Nanotechnology CEIN UCLA to evaluate exposure and toxicity
- Expected Products:
  - Leaching of micronized copper from treated lumber
  - Bioavailability of micronized copper in treated wood
  - LCA case study

CSS Systems Models Project 2.6: An Integrated Systems Approach to Assess and Predict the Toxicity of Engineered Nanomaterials and Their Applications

Task 2.6.1: Integrated Multi-Tiered Systems Toxicology Approach to Determine and Predict the Health Effects of Nanomaterials

1. Physicochemical Characterization

Agency relevant NPs and interfacing with other efforts (NRMRL/NERL:CSS 1.1/1.2; OECD)



Well Characterized Engineered-Manufactured Nanomaterials (vertical and horizontal testing)

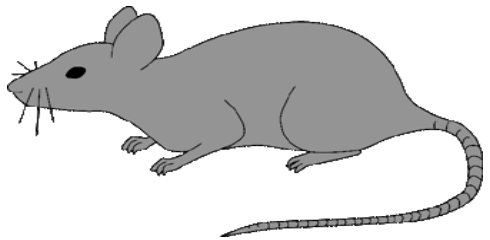
Collaborations (NCCT; NRMRL: CSS 1.2; NIEHS; OECD)

Collaborations (NCCT; NERL; OECD)

-Screen/Rank
-Design *In Vivo*
-Testing-Targeted Testing

Translational Capacity
-Qualify and "Validate" Alternative *In Vitro* Tests Predictive of *In Vivo* Toxicity

2. Alternative Test Methods ***(Non-Cell and Cell Based Assays)***



3. In Vivo Toxicology

ToxCast High Throughput Assays for Bioactivity Profiling of Engineered Nanomaterials

First Steps:

- Choose testing materials
- Develop handling protocol
- Determine testing concentrations
- Characterize materials
- Perform HTS
- Analyze data
  - determine compatibility of HTS assays for use with nanomaterials
  - determine if assays cover endpoints relevant to nanomaterials

Longer Term:

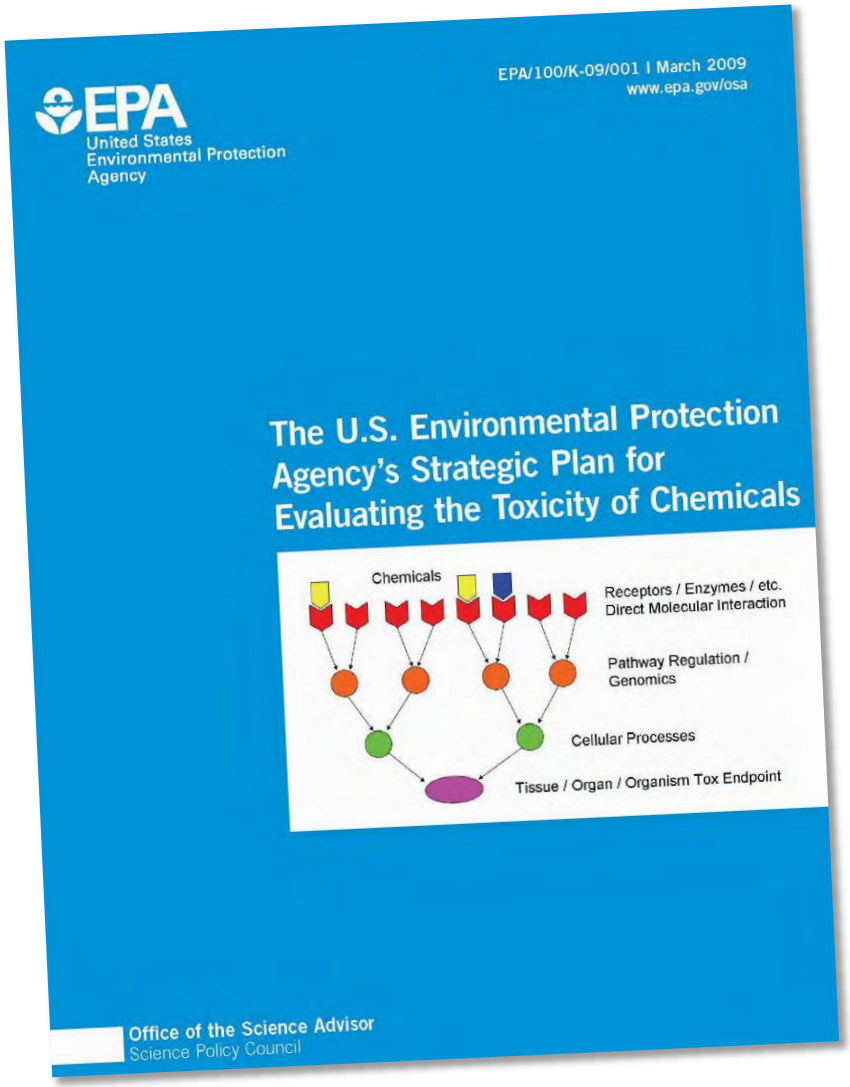
- Classify and prioritize NMs for further research/hazard identification
- Characterize biological pathway activity
- Identify key nanomaterial physicochemical characteristics influencing activities

Materials Tested

Nano	Other
• Ag • Cu • TiO2 • SiO2 • CeO2 • ZnO • SWCNT • MWCNT • Au	• AgNO3, Micro Ag • CuCl2 • Micro TiO2 • Micro SiO2 • CeCl3, micro Ce • ZnCl2, micro Zn

- **Sources:**
  - **ENPRA, OECD, PMNs, CEINT, Commercial**

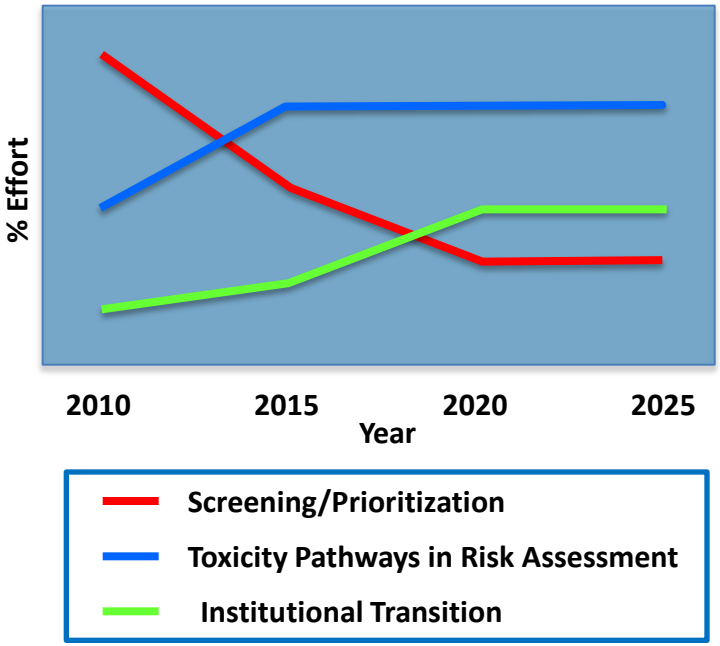
CSS Computational Toxicology Research



EPA Response to NAS 21st Century Testing Report

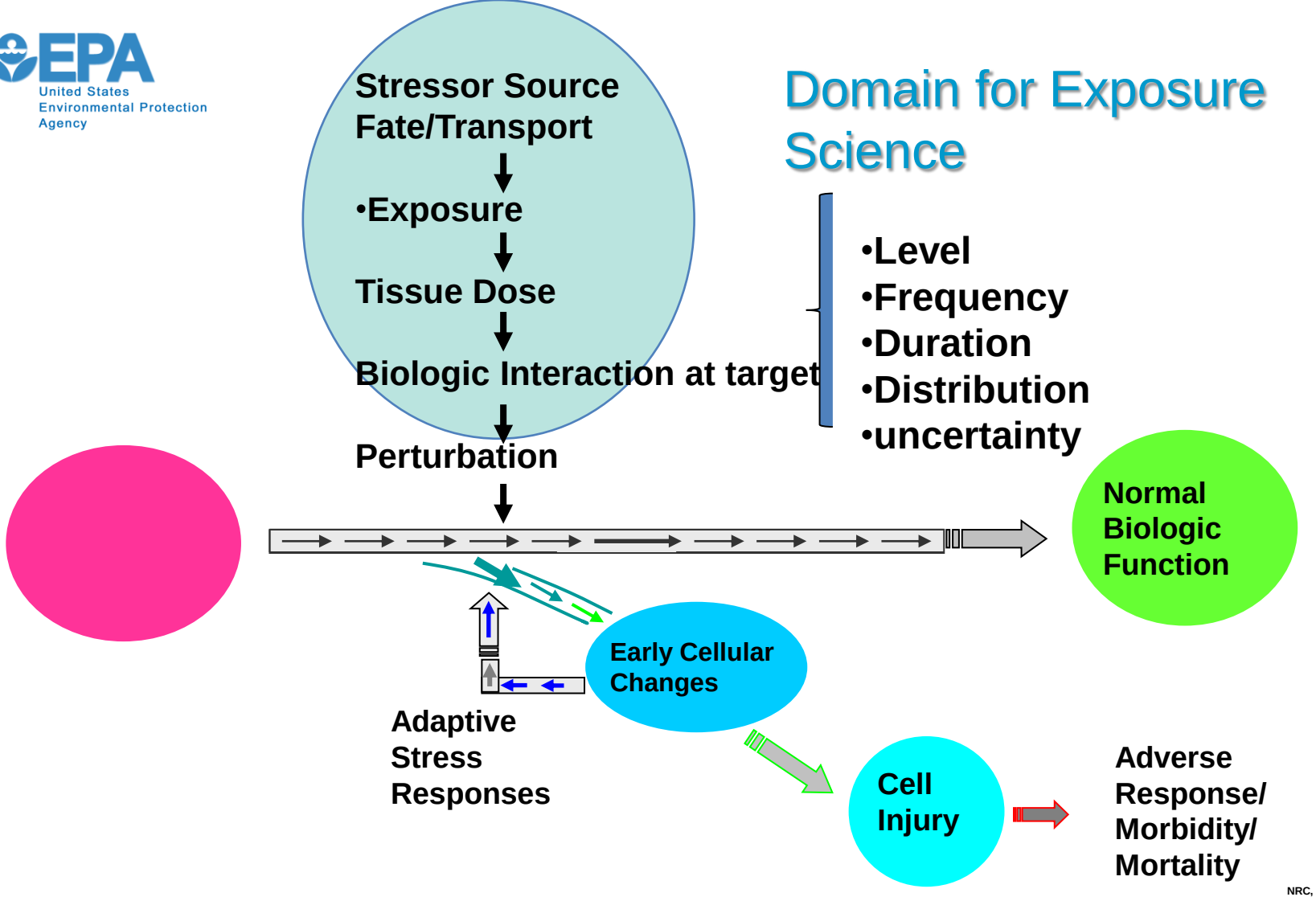
Strategic Goals

- Toxicity Pathway ID and Screening
- Pathway Based Risk Assessment
- Institutional Transition



Relative (%) Emphasis of the Three Main Components of this Strategic Plan over its Expected 20-year Duration.

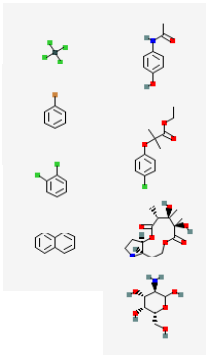
Domain for Exposure Science



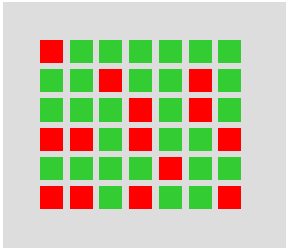
Integration: Exposure and dose at target will determine perturbation and adverse outcome

Toxicity Testing in the Twenty-first Century: A Vision and a Strategy, NAS, June 2007.

EPA CompTox Research

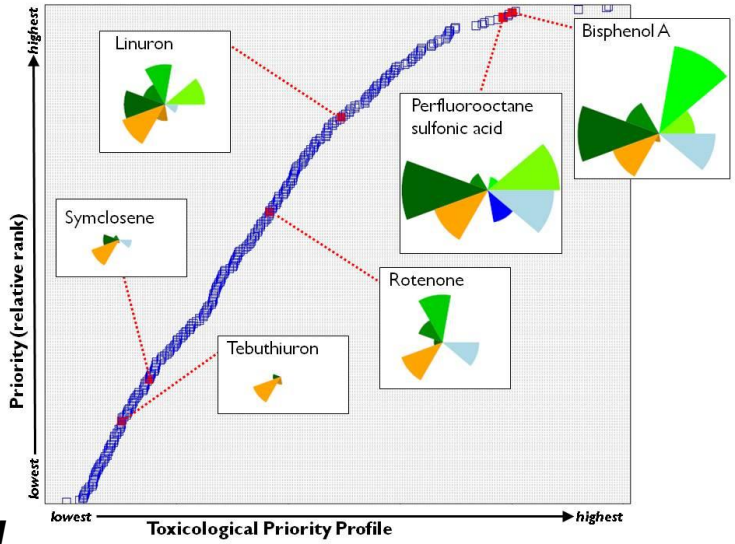


Thousands of chemicals



High throughput biology and chemistry

Bioinformatics/ machine Learning



Predictive toxicology and exposure science

Benefits

-Less expensive
-More chemicals
-Fewer animals
-Solution Oriented

-Innovative
-Multi-disciplinary
-Collaborative
-Transparent

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CompTox: Current and Future Applications

- Prioritization of chemicals based on high throughput biological and chemical profiling
- Targeted testing based on outcomes from predictive computational models
- Using the Adversary Outcome Pathway (AOP) concept to focus traditional in vivo testing and support higher throughput risk assessment

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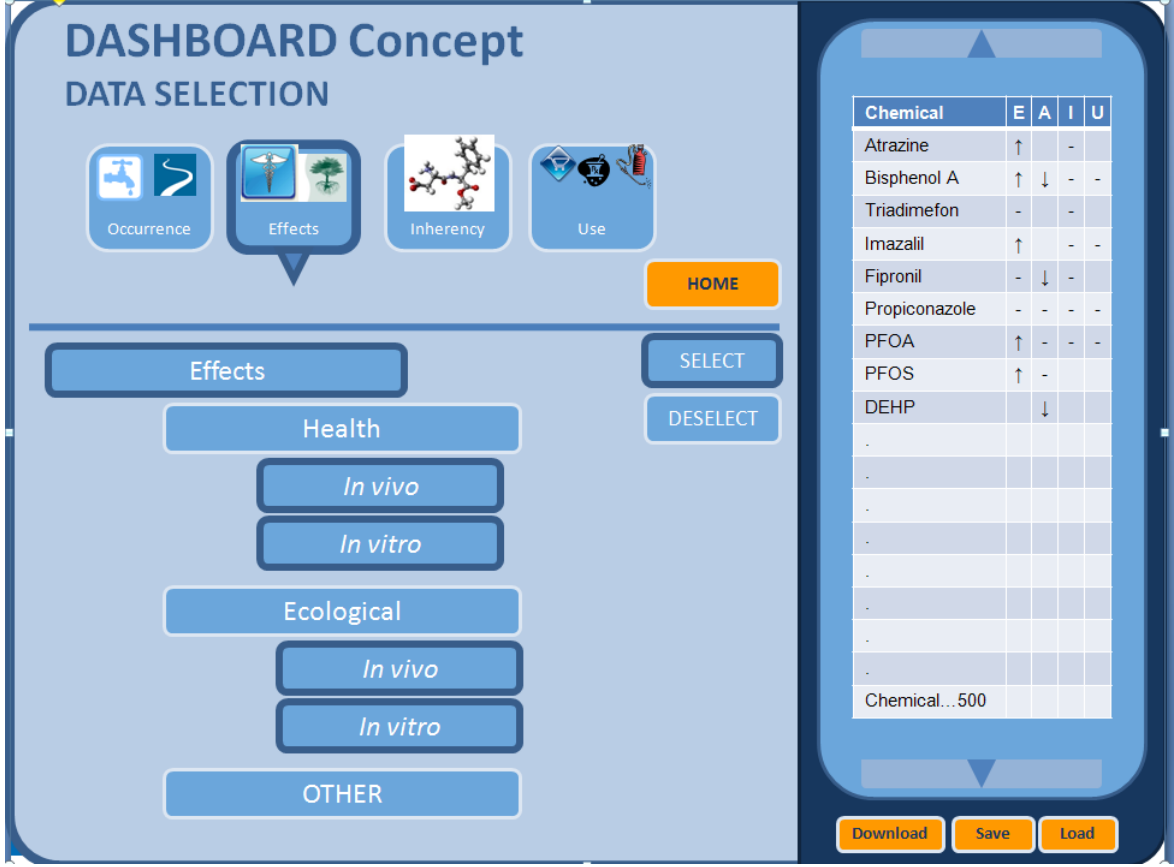
- **Encompasses:**
  - **-Computational tools**
  - **-Databases**
  - **-Web sites**

- **Goal is to make ORD research results readily available to decision-makers**
  - **-EPA Programs and Regions**
  - **-External stakeholders (eventually)**

- **Dashboard projects are not stand-alone**
  - **-Integrate outputs from across CSS and ORD research projects**



CSS Dashboards for FY12 / 13

- EDPS21 – Provide tools to prioritize chemicals for EDSP Tier 1 testing
- OW21 – Support prioritization around the CCL process
- TSCA21 –Support prioritization built around OPPT's *TSCA Workplan Chemicals: Methods Document*
- OPP21 – support modeling needs of the pesticides program
- OPP / EFED Uber tool – Supporting ecological risk assessment
- Infrastructure Development
  - Databases and tools to support development of other custom dashboards both inside and external to EPA

CompTox Priorities

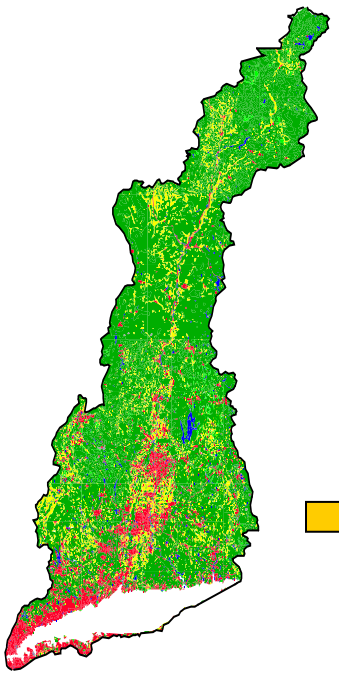
- Continued proactive communication and outreach
- Chemical Properties (Inherency)
  - Develop methods for characterizing the physical and chemical properties that influence bioavailability and bioactivity
  - Quality searchable structure database of ToxCast and Tox21 chemicals
- Systems Models
  - Toxicity Forecaster (ToxCast) for Predictive Models
    Complete high-throughput screening data sets on EDSP21 chemicals, and ToxCast Phase II chemical library
  - Exposure Forecaster (ExpoCast) for Predictive Models
    High-throughput exposure predictions for prioritization of ToxCast and Tox21including exposure metrics and fate and transport modeling of large chemical libraries
  - Virtual Tissue models
  - Dynamic molecular networks predicting kinetics and effects on selected EDSP21/TSCA21/OW21 chemicals in embryo, liver and endocrine systems
- Dashboard Tools
  - Office of Water: prioritize chemicals for future drinking water contaminant lists (CCL)
  - Office of Chemical Safety and Pollution Prevention: Help prioritize order chemicals are queued for testing in the EDSP Tier 1 screening battery (2,000 chemicals now) and high-throughput exposure predictions for prioritization of initial ToxCast, TSCA21 and EDSP21 chemicals including exposure metrics and fate and transport modeling of large chemical libraries.

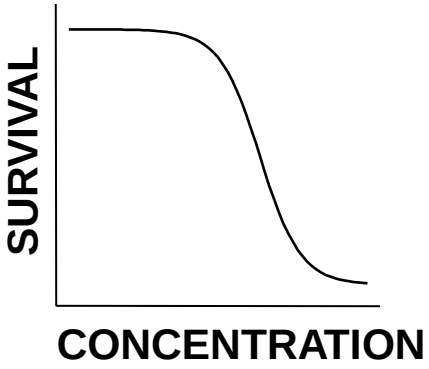
Exposure Research in CSS

- Inherency 1.0 (including nano)
  - ICP data generation
  - Domain of Applicability models
- Systems Models 2.0
  - Exposure screening and prioritization
  - Exposure metrics/exposure factors
  - Data to parameterize exposure/PBPK models
  - Linked exposure/dose models for higher tiered assessments
- Biomarkers 3.0
  - Linking exposure and effects
- Cumulative Risk 4.0
  - Next generation tools
  - Targeted cumulative risk research
- Dashboards 7.0
  - Databases and Dashboard applications (etc., Ubertool)

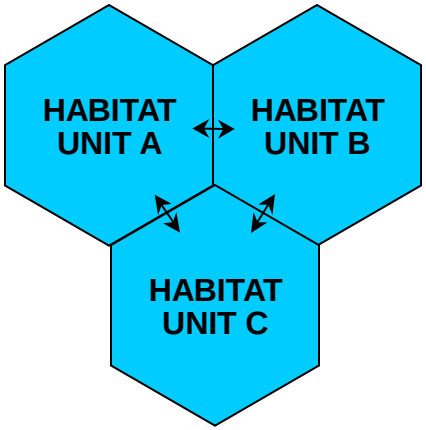
CSS 2.4.1: Predicting ecological outcomes from exposure to chemicals and other stressors

Problem statement: While regulations have traditionally been based upon adverse biological effects of chemicals to individuals, environmental sustainability requires healthy populations, communities and ecosystems.





$$n_{t+1} = An_t$$



Spatial and temporal characterization of stressors

Exposure-response habitat-response relations

Population models

Spatially explicit models

CSS 2.4.1: Predicting ecological outcomes from exposure to chemicals and other stressors

Research Approach:

- This research will develop integrated systems approaches that will provide the frameworks and mechanisms to account for relevant environmental, chemical, biological and ecological information, resulting in more efficient, comprehensive, and realistic ecological risk assessments.

- This research will culminate in the testing of integrated systems and their components to develop guidance to link chemical exposures and ecological effects.

- Methods and diagnostic metrics will be developed for well-studied chemicals and those of emerging concern that more accurately predict realistic spatial and temporal distributions of chemicals in various environments.

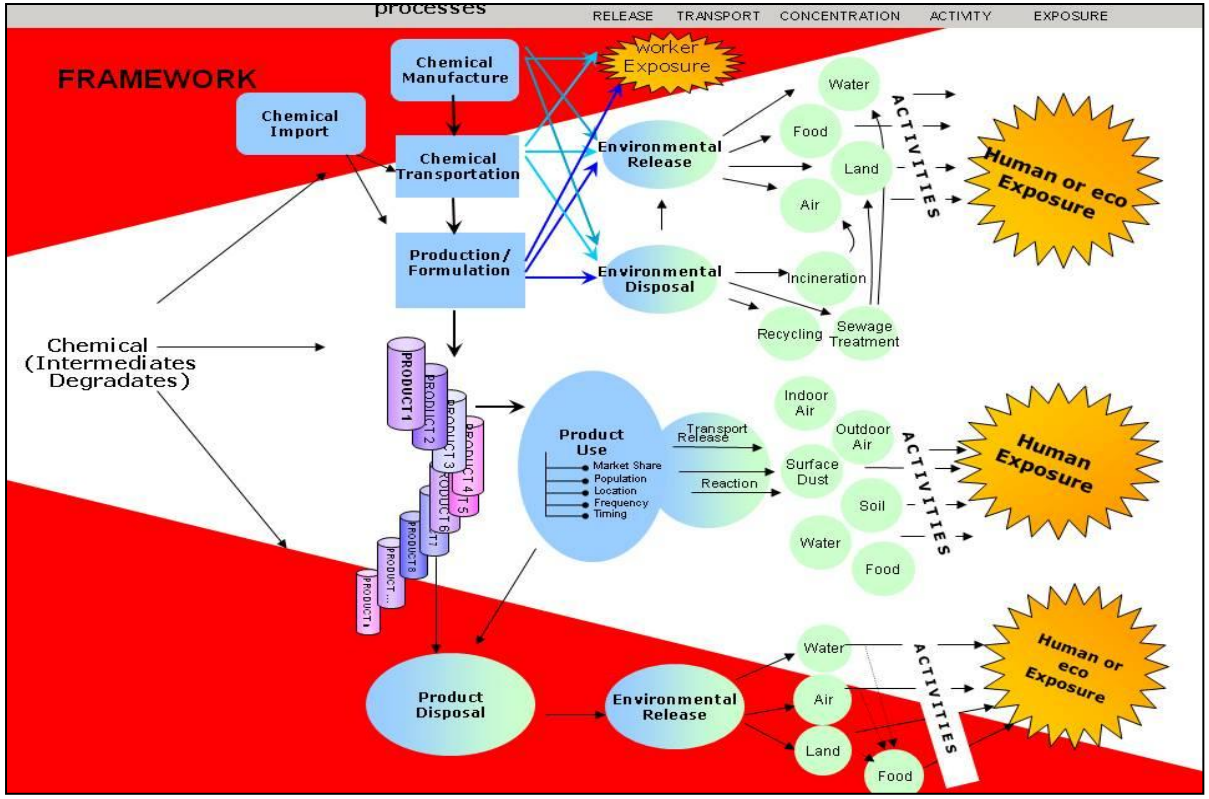
Task Outputs:

- Recommended systems approaches for use in regulatory context to assess ecological risks at the population, community and ecosystem levels from chemicals and other stressors

ExpoCast™: Exposure Science for Prioritization and Toxicity Testing

- Recognizes critical need for exposure information to inform
  - Chemical design and evaluation
  - Health risk management
- Goal
  - Advance characterization of exposure required to translate findings in computational toxicology to support exposure and risk assessment
  - Together with ToxCast™ help EPA determine priority chemicals
- Approach
  - Mine and apply scientific advances and tools in a broad range of fields
  - Develop novel approaches for evaluating chemicals based on potential for biologically-relevant human exposure

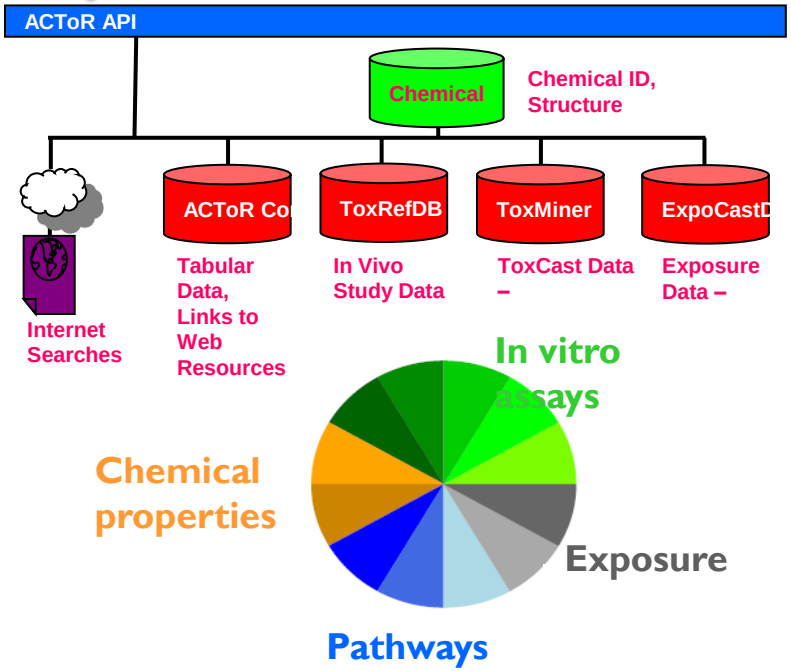
Exposure Across the Chemical Lifecycle



Identifies scenarios, populations, and population life-stages with highest exposures

Prioritization: Recent ExpoCast Activities

- **Data Access**
  - Incorporating and Linking Exposure Information into ACToR
  - ExpoCastDB
- **Mining**
  - Integrated Chemical Prioritization Scheme
  - *Partnering to Develop Exposure Indices for Rapid Prioritization of Chemicals in Consumer Products*
  - *Intake Production Ratio*
- **Modeling**
  - Prioritization Model Challenge
  - High Throughput Exposure Estimates
  - *Rapid modeling of SVOC exposure in indoor environment*



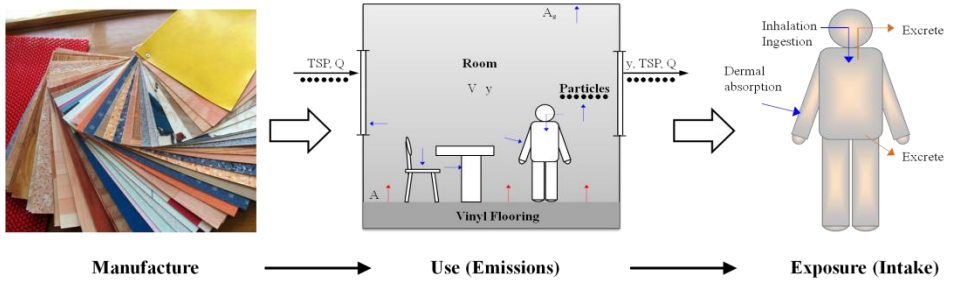
Prioritization: Consumer Use Chemicals

- Intake-Production Ratio (Bill Nazaroff, Berkeley, et al, submitted)
  - Population-level dimensionless ratios quantifying exposure intensity
  - Different chemicals uses lead to different degrees of opportunity for exposure (measures exposure intimacy for manufactured chemicals)

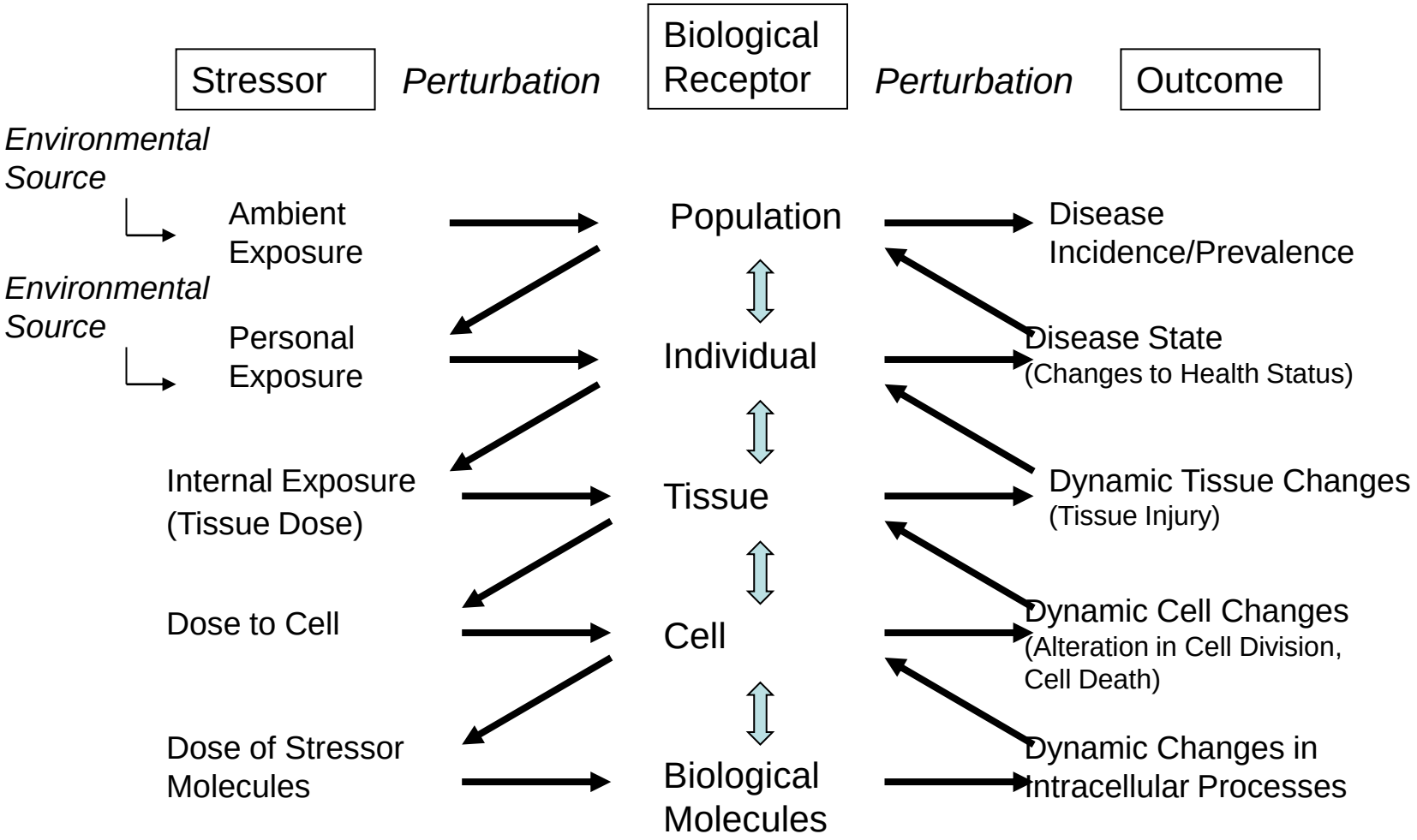
IPR for selected chemicals in the United States.

Chemical	IPR (OM ppm)
bisphenol A (BPA)	$1x10^{-1}$
butyl benzyl phthalate (BBzP)	$1x10^{2}$
di(2-ethylhexyl) phthalate (DEHP)	$1x10^{2}$
di(isobutyl) phthalate (DiBP)	$1x10^{3}$
di(n-butyl) phthalate (DnBP)	$1x10^{2}$
Triclosan	$1x10^{4}$

- Exposure to SVOCs in Consumer Products (John Little, VT, et al, submitted)
  - Propose suite of mechanistic models
  - Key determinants based on product use category
  - Rapid exposure assessment and alternative evaluation.



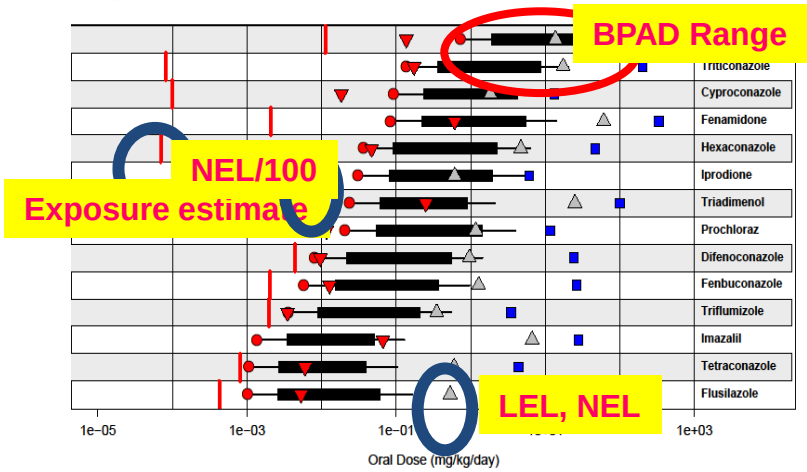
TT21C: Exposure at All Levels of Biological Organization



Cohen Hubal, JESEE, 2008

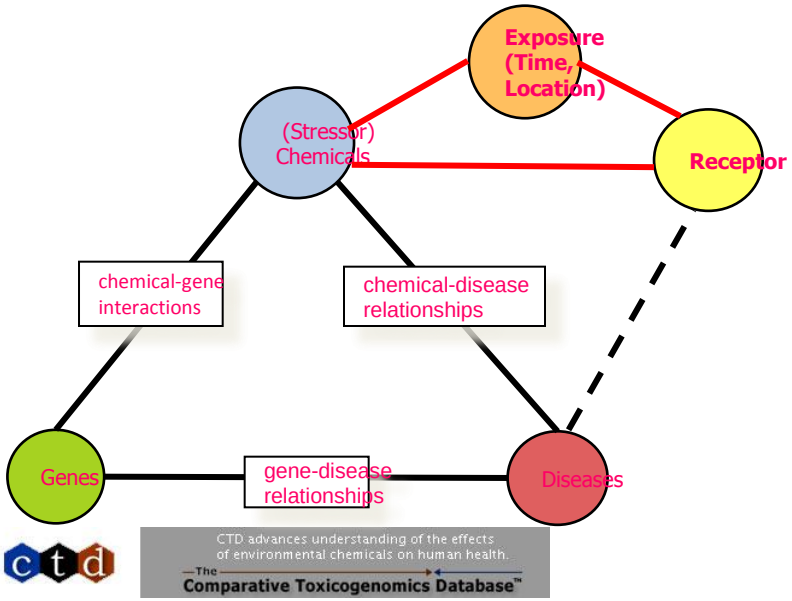
Toxicity Testing in the 21st Century (TT21): Recent ExpoCast Activities

- **Inform Design of Toxicity Testing**
  - Selecting Doses for ToxCast *In Vitro* Testing – Nanomaterials
  - Application of Biogeographical Methods to Chemical Co-Occurrence Data to Identify Priorities for Mixture Research

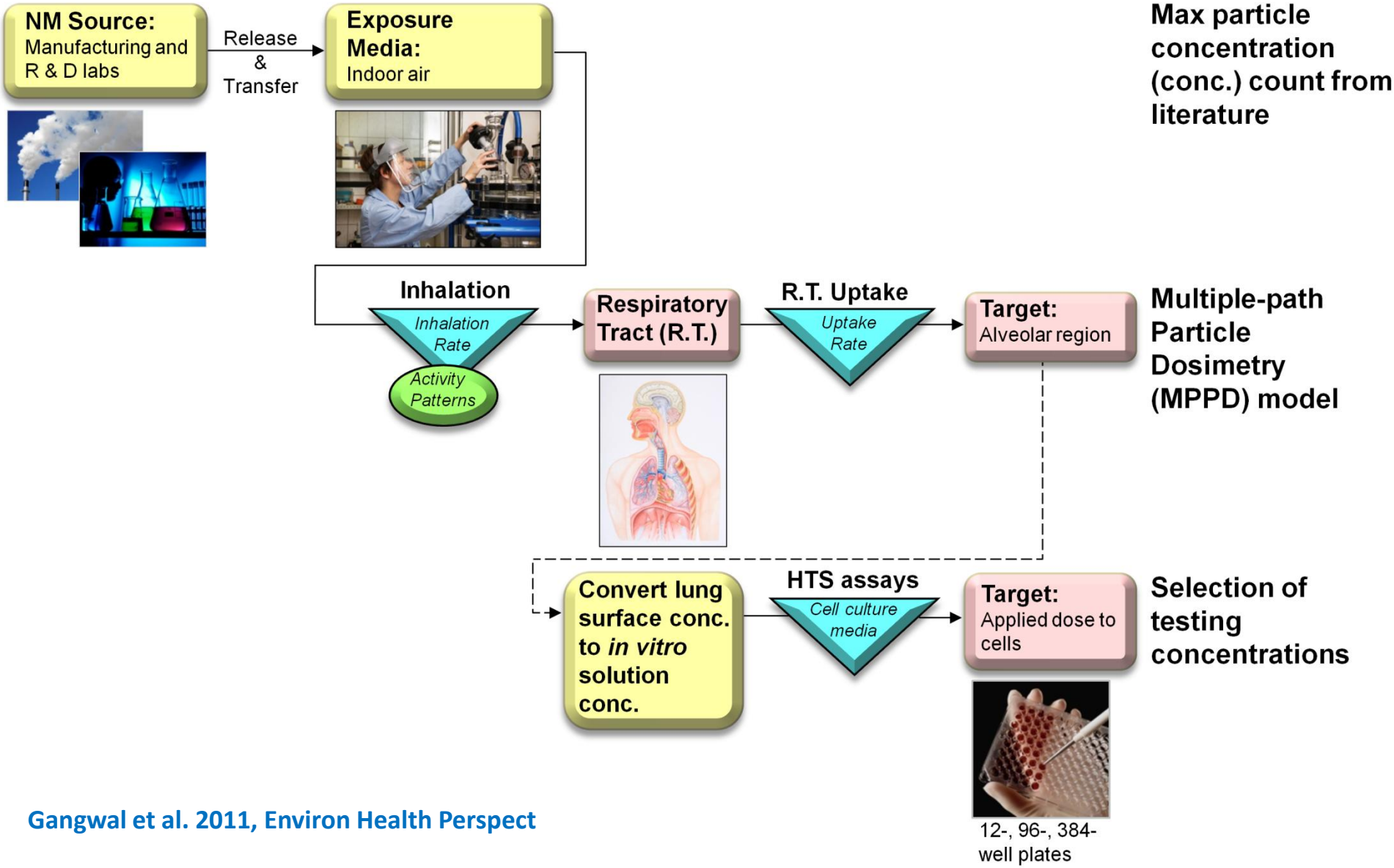


- **Translate in vitro Results for Risk Assessment**
  - *Combining ToxCast, Dosimetry and Exposure*
  - *ExpoDat2012: Exposure determinants for high throughput risk assessment (HTRA)*

- **Relate Real-World Exposures with Tox Pathway Perturbations**
  - *ExO: An Exposure Ontology*



TT21C: Selecting Doses for ToxCast Nano Pilot

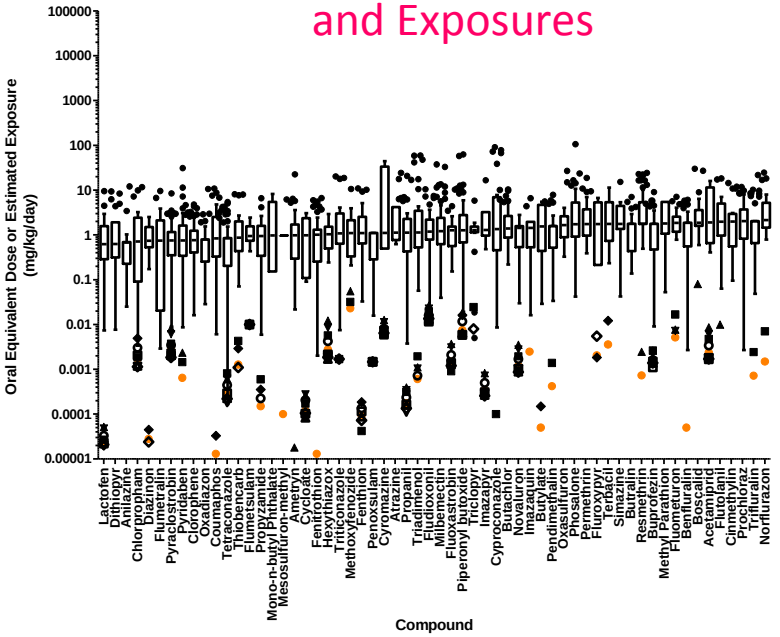


Gangwal et al. 2011, Environ Health Perspect

ExpoDat2012- Exposure Determinants for High Throughput Risk Assessment

- Focus on operationalizing high throughput exposure assessment
- Case study will focus on developing exposure limits for comparison to oral equivalent doses derived from ToxCast
- Chemicals selected to cover broad range of properties and uses

Comparing Oral Equivalent Doses and Exposures



Wetmore et al, 2011, Tox Sci

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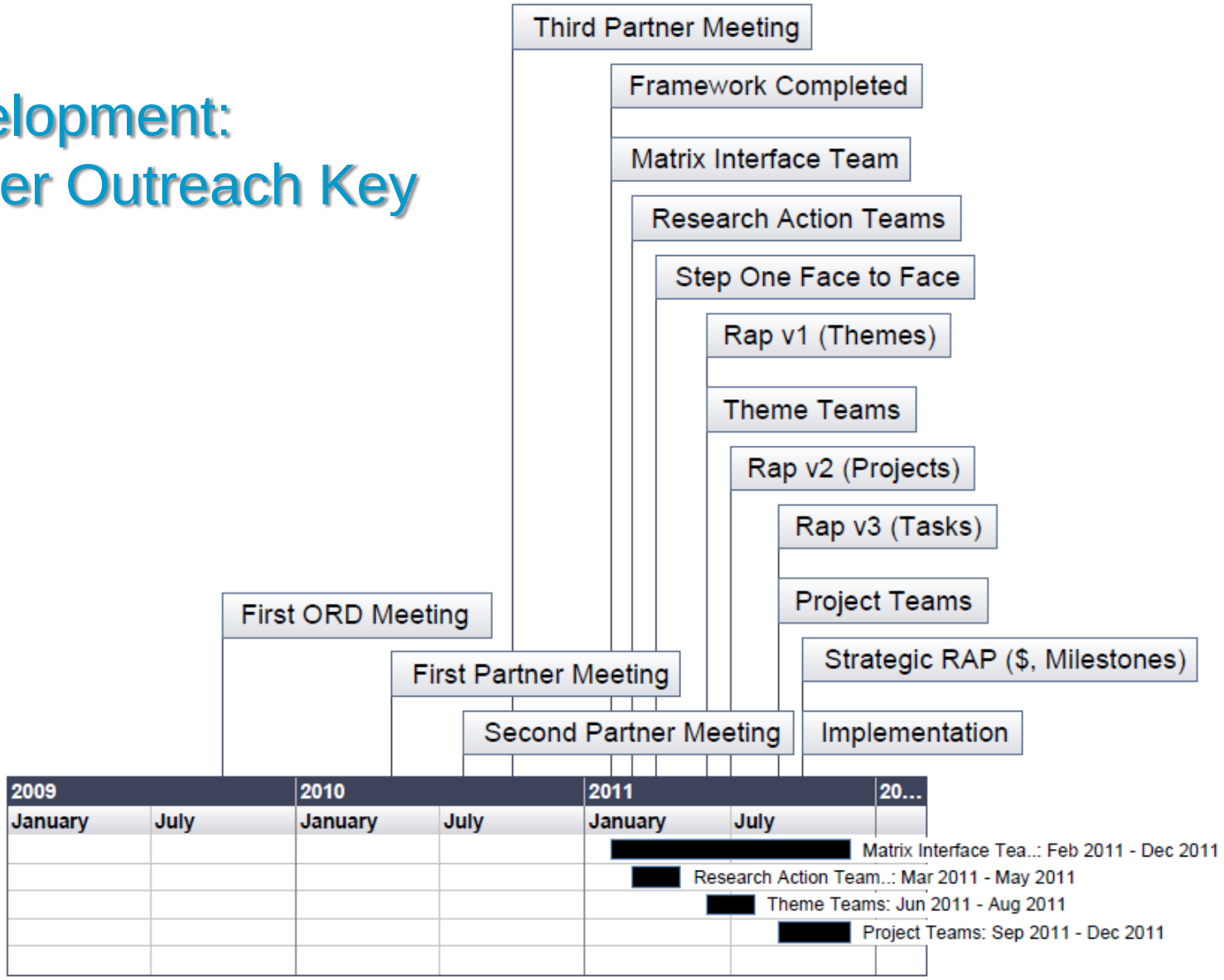
ExpoCast Research Contributes toward Key Outcomes of CSS

- Information digitized and made available
- Key linkages identified in the continuum between the production of a chemical, release, fate and transport, exposure, and adverse outcome
- Complexities of exposure and dose captured in high throughput assays
- Predictive models of exposure to prioritize further screening and testing developed
- Quantitative risk assessment improved and uncertainties reduced by advanced computational techniques

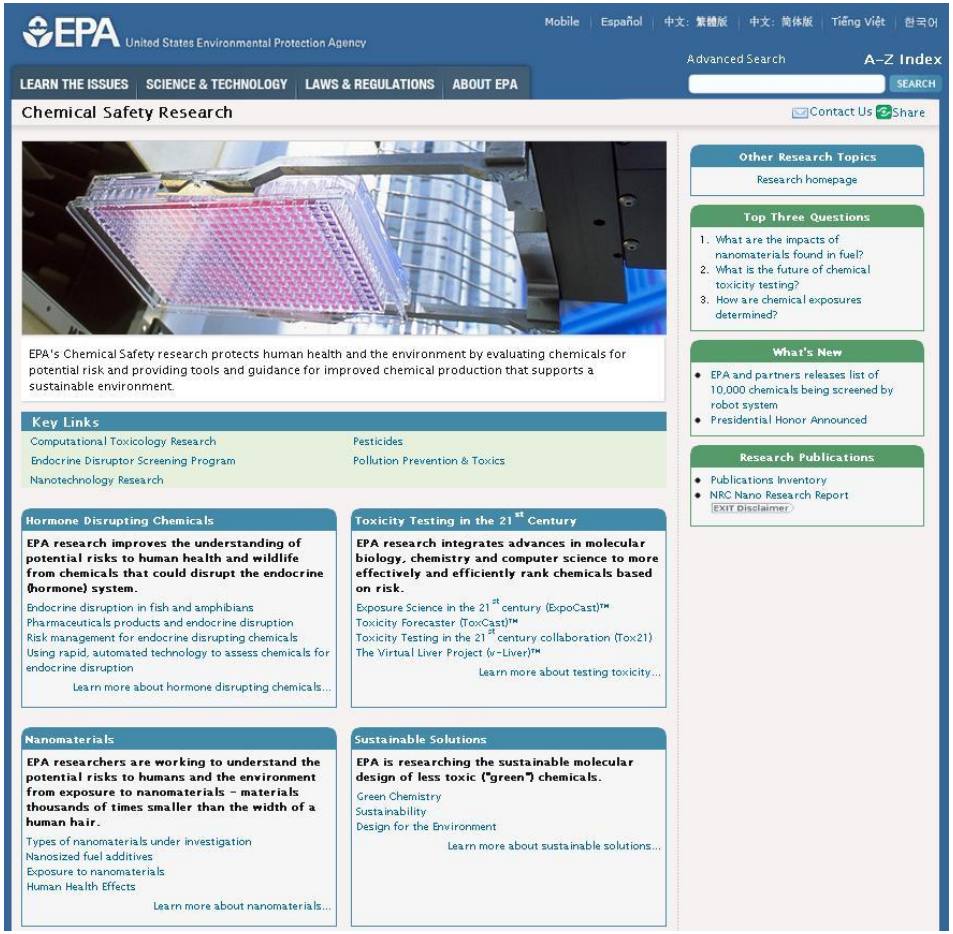
United States Environmental Protection Agency

CSS Development: Stakeholder Outreach Key



CSS Communications & Outreach

- Showcase the great research conducted
- Package research so that it resonates with audiences
- Increase awareness, interest in & usage of CSS research tools
- Establish/enhance partners involved with research
- Increase positive media coverage about CSS research
- Increase support for research



New chemical safety web page

CSS Target Audiences

- Internal EPA (Program Offices & Regions)
- US Congress/OMB
- Media
- International Partners
- Academic Institutions
- Industry
- Non EPA Federal Agencies
- Stakeholder Groups/NGOs

Packaging that Resonates: High Profile Research & Consistent Messages

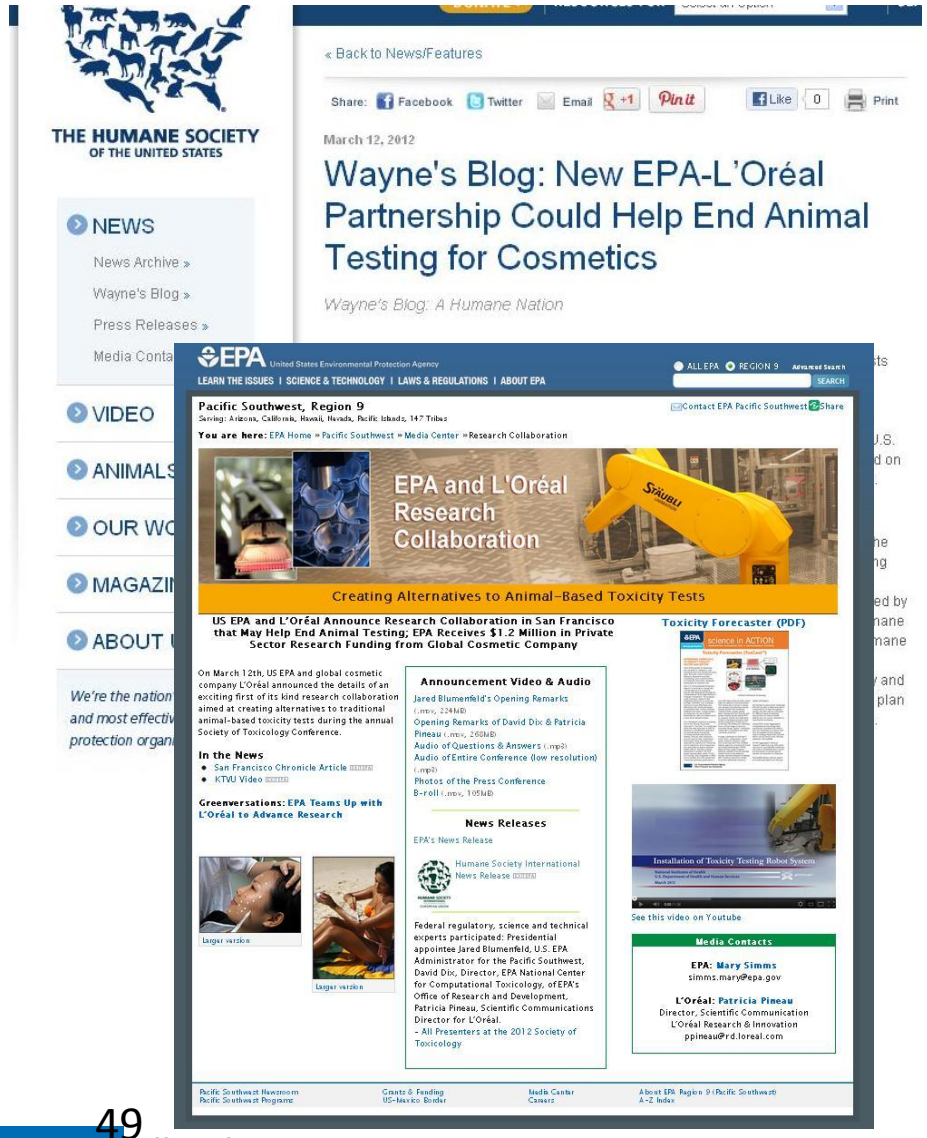
Ideas:

- Nanomaterials
- Endocrine Disruption Research
- Computational Toxicology
- Exposure research
- Chemical Safety Databases & Tools
- Sustainability
- High profile: PCBs, spray foam, etc

Consistent Key Messages:

- EPA research
- CSS
- Packaged research

Communications Output: US EPA and LOREAL announce research collaboration

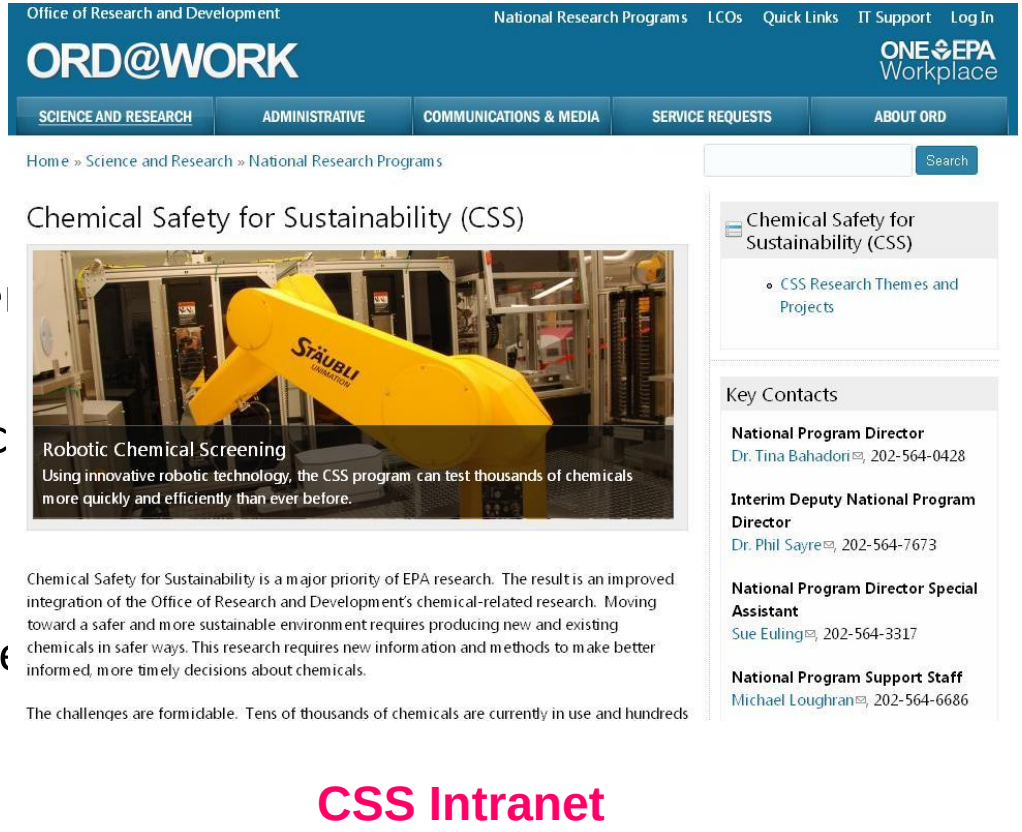


Efforts included:

- News release, interviews and media coverage
- Partners Amplified
- Event at SOT
- Blogs
- Tweets
- Worked with EPA Region 9 to promote
- Region 9, ORD and LOREAL spoke
- Invited SOT attendees & media

EPA Program Office and Region Strategies

- Surveys
- Program Offices & Regional representatives on project teams
- Cross training PO to understand research
- Regular Program Office manageme meetings
- Share iterations of research produc during workshops
- CSS webinars, Intranet and Wiki
- Online Research Management Syste
- Customized dashboards outreach



CSS Intranet

General Charge Questions

- First-Year Progress
  - How are the ORD research programs progressing in the first year of implementation? Are the research activities planned for FY 13 and future years appropriate for answering the science questions in the Strategic Research Action Plan?
- Sustainability
  - How are ORD programs contributing to sustainability through their research plans and activities? What advice does the SAB and BOSC have for each research program about advancing sustainability in future research?

General Charge Questions (cont.)

- BALANCING IMMEDIATE PROGRAM NEEDS AND EMERGING ISSUES
  - As we consider science for the future, while budgets continue to shrink, how should ORD balance its commitments in the Strategic Research Action Plan with the need to advance science on emerging issues?

Chemical Safety for Sustainability Charge Questions

- Is the CSS program well positioned to support EPA needs in the three key areas of endocrine disrupting chemicals, nanotechnology, and computational toxicology research?

- How well has the exposure component of the CSS research program progressed since its inception?