EPA 601/R-12/006 | February 2012 | www.epa.gov/research

United States
Environmental Protection
Agency

Chemical Safety for Sustainability

STRATEGIC RESEARCH ACTION PLAN 2012-2016

SCIENCE

Office of Research and Development
Chemical Safety for Sustainability

Final Draft

EPA 601/R-12/006

Chemical Safety for Sustainability

Strategic Research Action Plan 2012 - 2016

U.S. Environmental Protection Agency
February 2012

Table of Contents

Executive Summary 5
Introduction 9
Program Purpose 10
Research to Support EPA Priorities and Regulatory Requirements 11
Statutory and Policy Contect 11
An Integrated Program Design 16
Producing an Integrated Program 16
Collaborating across Research Programs 16
Developing Partnerships from the Start 17
Research Themes and Priority Science Questions 22
Theme 1. Inherency 22
Theme 2. Systems Models 24
Theme 3. Biomarkers 29
Theme 4. Cumulative Risk 31
Theme 5. Life Cycle Considerations 33
Theme 6. Extrapolation 36
Theme 7. Dashboards 38
Theme 8. Evaluation 40
Conclusion 41
Summary Tables 42
Theme 1. Inherency 43
Theme 2. Systems Models 44
Theme 3. Biomarkers 48
Theme 4. Cumulative Risk 49
Theme 5. Life Cycle Considerations 51
Theme 6. Extrapolation 53
Theme 7. Dashboards 55
Theme 8. Evaluation 57

References 57
Appendix A. Research Program Partners and Stakeholders 59
Appendix B. Definitions 61

Executive Summary

Chemicals provide the key building blocks that are converted into end-use products or used in industrial processes to make products that create jobs and benefit society. Improving the safe production, use and disposal of chemicals is a major priority of research at the U.S. Environmental Protection Agency (EPA) to support decisions and actions the Agency makes to meet its mission to protect human health and the environment. To meet its mission, the Agency needs a research approach that advances science to meet society's current demands for a safer environment but to also meet the social, economic, and environmental health needs of future generations. The Agency must conduct research and analyses that will support the sustainable manufacture and use of chemicals.

> The Strategic Research Action Plan for EPA's Chemical Safety for Sustainability (CSS) research program presents the purpose, design, and themes of the Agency's CSS research efforts to ensure safety in the design, manufacture, and use of existing and future chemicals.

The challenges are formidable: More than 80,000 chemicals are currently listed or registered for use in the U.S., and at least a thousand more are introduced every year. Many of these chemicals have not been thoroughly evaluated for their potential risks to human health, wildlife and the environment, particularly throughout their life cycle (from the collection of raw chemical feedstocks, through their use, and the final disposal of the products that contain them). There is also an increased need to focus on emerging contaminants of concern including endocrine disrupting chemicals (EDC), chemicals that interfere with the activity of hormones in the body, and nanomaterials, materials in a very small size range (~ 1 to 100 nanometers), which can alter the chemical's properties, compared with larger versions of the same chemical, and in turn, influence its exposure and toxicity. Processes and procedures being used today to evaluate and assess the impact of chemicals on human health, wildlife, and the environment were, in general, designed decades ago, are largely based on laboratory tests conducted on animals, and are labor and resource intensive. Further, many of the current tests have not fully incorporated recent advances in chemistry, exposure science, biology, and computer technologies. This combination of factors makes it difficult to meet current demands of evaluating the safety of an ever-increasing number of chemicals.

As a result, a number of important aspects of chemical safety are not adequately understood, including: how to design and produce safer chemicals; how chemicals and their byproducts move through the environment; what the sources of chemical exposure are; what the critical biological processes and toxicity pathways are that chemicals might interact with to cause disease; and what the contribution of exposure to chemicals in the environment is in the overall disease burden of susceptible populations.

CHEMICAL SAFETY FOR SUSTAINABILITY

PROBLEM STATEMENT: Although chemicals are essential to modern life, we lack innovative, systematic, effective, and efficient approaches and tools to inform decisions that reduce the environmental and societal impact of chemicals while increasing economic value.

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.

Thus, transformative approaches are needed to improve the information used in assessments. New approaches developed in the CSS research program will enable EPA to increase the pace at which relevant information can be obtained and integrated into assessment and decision-making. The program will inform and advance sustainable approaches to chemical design, production, and use across product life cycles.

This *Strategic Research Action Plan for EPA's Chemical Safety for Sustainability Research Program* describes the purpose, design, and themes of the Agency's research efforts to help ensure safety in the design, manufacture, and use of existing and future chemicals. It describes how the program was developed with the input of EPA internal partners and external stakeholders from the beginning, how it is aligned with Agency priorities, and how the research portfolio will harness systems-approaches to advance the scientific understanding of the links between chemical exposure, toxicity pathways, and disease or other harmful effect to humans, wildlife, and the environment.

Tools produced through the CSS research program will use systems approaches to advance the understanding of the links between exposures to chemicals and toxicity pathways that lead to the development of disease. At the same time, the research will dramatically increase the efficiency and speed of chemical evaluations. It will allow EPA to evaluate potential effects of chemical exposure on critical life stages, such as the embryo and childhood, and other susceptibility factors, including genetics and co-existing diseases.

Recognizing that humans and wildlife encounter numerous chemicals simultaneously, the CSS research program will develop methods to assess the effects of exposure to multiple chemicals, and methods to assess cumulative chemical risk. Further, the program includes the development of sustainability metrics to measure how changes in parameters that affect hazard and exposure impact the degree to which a chemical is more or less environmentally sustainable throughout its life cycle.

Working in conjunction with partners in EPA regulatory program and regional offices, CSS identified three research goals that guided the development of the overall program:

Research Goal 1

Developing the scientific knowledge, tools, and models needed to conduct integrated, timely, and efficient chemical evaluation strategies.

Research Goal 2
Improving methods for assessment and informing management for chemical safety and sustainability,

Research Goal 3
Providing targeted high-priority research solutions for immediate and focused attention.

The first goal is intended to deliver a suite of tools (i.e.,, data, methods, models) that offers researchers and environmental decision-makers needed resources for improved chemical assessments. The second is focused on the application of the tools for risk assessment and chemical management to ensure the safe and sustainable design, production, and use of chemicals, including the advancement of green chemistry. The third goal is intended to ensure that the high-priority human and environmental health-related specific research needs of the Agency, identified by its program and regional offices, are met while the long-term research solutions are advanced.

The key research outcomes will include:

- **Improved chemical hazard assessments**
  By developing a deeper understanding of the relevant physico-chemical and other inherent properties of chemicals that influence environmental fate, exposure, and biological responses, CSS research will lead to improved chemical assessments.
- **Improved chemical prioritization, screening, testing and quantitative risk assessments**
  By integrating information from multiple biological levels, including pathway-level information, and by using advanced computational techniques (e.g., multi-scale systems models of virtual tissues) to develop predictive models of hazard and exposure, CSS research will provide decision makers with robust risk assessment methods.

  By using consistent, justifiable, and improved use of existing biomonitoring data, dose estimation/exposure reconstruction methods, and diagnostic adverse outcome pathway (AOP) - based biomarkers, EPA risk assessments are improved.
- **Improved understanding of the relationship of chemical exposures and health outcomes to the fetus and children**
  By understanding the molecular pathways and cellular processes underlying adverse pregnancy outcomes and improving methods to assess the impacts of fetal or neonatal chemical exposure at different stages of development and scales of biological organization, CSS research will increase knowledge of health effects after developmental exposure.
- **Development of sustainable risk management approaches**
  By identifying key links in the continuum from the production of a chemical, through its release into the environment, its fate/transport in the environment, the resulting exposures that occur, to the adverse outcomes that result. This will provide the knowledge needed to develop approaches for sustainable risk management approaches that subsequently can be scaled up and delivered to decision makers.

- **Accessible, useful information**
  By sharing research outputs and outcomes in ways that effectively communicate, translate, and transfer the scientific information in a manner most useful to decision-makers.

To address the research areas and desired outcomes, the CSS program was developed around eight main research topics. These topics were selected because they represent the fundamental building blocks upon which an integrated evaluation strategy can be developed to inform environmental and health decisions.

The eight research topics and the questions that they address are:

1. Inherency — How can an understanding of inherent properties of chemicals inform exposure and health outcomes, the design of chemical assays and tools, and sustainable design of chemicals?

2. Systems Models — What are the perturbations (the "toxicity pathway") that occur—from initial contact to final outcome, at all levels of biological organization (i.e.,, molecular, cellular, tissue, organ, whole organism), that occur following exposure to an environmental chemical?

3. Biomarkers — How can useful biomarkers of exposure and effect be optimally developed?

4. Cumulative Risk — What are the ecological and human health risks of real-world environmental chemical exposures (i.e.,, exposures to mixtures of multiple chemicals over time)?

5. Life Cycle — What are the impacts of an environmental chemical over its entire life cycle, from the collection of its raw materials all the way through it manufacture, use, and finally its disposal?

6. Extrapolation — Can improved extrapolation methods be developed for predicting toxicology in the absence of various data (e.g., extrapolating from lab animal to human, *in vitro* to *in vivo*)?

7. Dashboards — What tools can be customized to into useful, accessible interfaces that provide decision-makers with the toxicity data and information they need to support specific regulatory needs?

8. Evaluation — What has been the impact of the CSS research findings and tools on EPA's decision making?

The *Strategic Research Action Plan for EPA's Chemical Safety for Sustainability Research Program* maps out a research program for the next approximately 5 to 10 years. It has been designed with the flexibility needed to leverage scientific breakthroughs, address the emerging priorities and needs of decision makers, shifting resource availability, and other considerations. As such, it is a "living document" that will be updated as needed over that time.

Introduction

Program Purpose

EPA is faced with evaluating thousands of new chemicals each year prior to their commercialization, and is further challenged with determining which environmental chemicals already in commerce may result in adverse effects to pursue risk management actions (Judson et al., 2009). In addition, there are newer forms of chemicals, such as nanomaterials, entering the marketplace at an increased rate. There is also an increased need to focus on emerging health concerns, such as those associated with, for example, endocrine disrupting chemicals, that may require evaluation approaches that differ from traditional methods.

To address these needs, the EPA and NIEHS requested that the National Research Council (NRC) develop an expert report. The resulting report, *Toxicity Testing in the Twenty-first Century: A Vision and Strategy* (NRC, 2007), proposes a shift in chemical testing to one that evaluates perturbations in toxicity pathways, largely using *in vitro* methods. The report, developed at the request of EPA and NIEHS, addressed several concerns about current testing methods, specifically, the desire to (1) reduce the number of animals used in testing, (2) reduce the overall cost and time required to characterize each chemical, (3) increase the level of mechanistic understanding of chemical toxicity, and (4) assess toxicity for real world exposures. The EPA has formally adopted the recommendations of the NRC by developing their *Strategic Plan for Evaluating the Toxicity of Chemicals* (EPA, 2009).

Toxicity Testing in the 21st Century: A Vision and Strategy (NRC, 2007)

"Advances in toxicogenomics, bioinformatics, systems biology, epigenetics, and computational toxicology could transform toxicity testing from a system based on whole-animal testing to one founded primarily on *in vitro* methods that evaluate changes in biologic processes using cells, cell lines, or cellular components, preferably of human origin."

The strategic directions of the CSS research program are tightly aligned with the recommendations of the NRC (NRC, 2007) and EPA's Strategic Plan (EPA, 2009), and also advance research in additional areas important to EPA, such as the exposure and fate of chemicals and nanomaterials, identifying and evaluating adverse outcome pathways, characterizing cumulative risk, and providing bioinformatic tools to enable rapid risk assessment analyses for regulatory decisions.

Looking beyond assessing potential impacts of environmental chemicals, the CSS research program recognizes the need for the design of safer and more sustainable ("green") chemicals. The research is assisting in replacing existing commercial chemicals and materials that pose environmental and health risks by identifying new chemicals that exhibit the desired uses of existing chemicals, but can be manufactured with lower potential adverse impacts.

The long-term vision of the CSS Research Program is that 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 OBJECTIVES

Creating tools that inform sustainable chemical/material design and use

Developing methods for much faster screening and prioritizing

Providing the scientific knowledge and tools to effectively understand real-world risks

Developing assessment approaches that are tailored to specific decision contexts

Considering where impacts may occur throughout a chemical's life cycle.

Integrated, Transdisciplinary Research

To increase the scale of the Agency's decision-support tools, and improve guidance/management for safer chemical design and use, the EPA needs an integrated, transdisciplinary research effort that unites the capabilities of a diversity of experts, including chemists, exposure scientists, biologists, engineers, and economists and other social scientists.

The CSS research program is focused on providing integrated solutions to support of chemical management. The data, methods and tools developed will guide the prioritization and testing process, from screening approaches through more complex testing and assessments. CSS outcomes will be delivered to EPA partners and decision makers in appropriate, accessible forms (NRC, 2009).

By organizing its research to harness a diversity of expertise and support integrated evaluation strategies, the CSS research program will provide state-of-the-science tools and integration techniques to inform risk assessment and risk management activities. Such activities include those used in regulatory decision-making, as well as those utilized in developing, producing and using chemicals.

To maximize relevancy of the research, the CSS research program will focus on the highest priority research needs of EPA's program and regional offices. The program includes training for decision makers and others so that they can fully utilize the tools and research produced.

The research is conducted and/or supported by the EPA Office of Research and Development's three national laboratories, four national centers, and two offices located in 14 facilities around the country and in Washington, D.C, and includes both intramural and extramural (primarily through EPA-awarded STAR research grants and awards) components.

EPA PRIORITIES

Taking action on climate change

Improving air quality

Assuring the Safety of Chemicals

Cleaning up our communities

Protecting America's waters

Expanding the conversation on environmentalism and working for environmental justice

Building strong state and tribal partnerships

Research to Support EPA Priorities and Regulatory Requirements

Statutory and Policy Context

The CSS research program advances EPA's priority, Assuring the Safety of Chemicals (EPA, 2010). The CSS research program uses novel research approaches to address the risks posed by chemicals in industrial and commercial use, as well as risks posed by these chemicals as they degrade or pass through the environment.

Managing chemical risks are covered in legislation and statutes mandated by Congress and implemented by EPA (Table 1). Chemicals are regulated by several program offices under a variety of statutes, and CSS has worked closely with each of these offices in developing this research program. As examples of chemical legislation, both the FQPA (FQPA 1996) and the SDWA Amendments (SDWA Amendments 1996) contain provisions for assessing the potential for chemicals to interact with the endocrine system. Both the CWA and the SDWA require the Office of Water to prioritize possible water contaminants in the Contaminant Candidate List (CCL). The Office of Solid Waste Emergency Response is concerned with the end-of-use disposition of chemicals and is therefore interested in life cycle considerations of chemical use. Internationally, similar pressures to transform the chemical safety assessment paradigm are also present, as exemplified by the REACH program and Cosmetics Directive in Europe and the Canadian Environmental Protection Act in Canada. CSS will enable the Agency to test and regulate numerous chemicals in a more efficient manner, supporting several statutory obligations and policies (Table 1).

Table 1: CSS Research Supports Chemical Risk Management Decisions Mandated by Legislation

Legislation	Acronym	Website
Clean Air Act	CAA	www.epa.gov/lawsregs/laws/caa.html
Toxic Substances Control Act	TSCA	www.epa.gov/lawsregs/laws/tsca.html
Clean Water Act	CWA	www.epa.gov/regulations/laws/cwa.html
Comprehensive Environmental Response, Compensation, and Liability Act	CERCLA	www.epa.gov/superfund/policy/cercla.htm
Federal Insecticide and Rodenticide Act	FIFRA	www.epa.gov/pesticides/regulations/laws.htm
Federal Food, Drug and Cosmetic Act	FFDSCA	www.epa.gov/pesticides/regulations/laws.htm
Food Quality Protection Act	FQPA	www.epa.gov/pesticides/regulations/laws.htm
Safe Drinking Water Act	SDWA	www.epa.gov/lawsregs/laws/sdwa.html
Resources Conservation and Recovery Act	RCRA	www.epa.gov/epawaste/inforesources/online/index.htm

High Priority Chemicals of Concern: Endocrine Disrupting Chemicals

The CSS research program provides support to EPA's Endocrine Disruptor Screening Program (EDSP; www.epa.gov/endo/index.htm). The EDSP screening program is mandated under Amendments to the Food Quality Protections Act (1996) and the Safe Drinking Water Act (1996). By evaluating current endocrine disruption testing protocols, in collaboration with partners in EPA's Office of Chemical Safety and Pollution Prevention, CSS will develop new approaches to advance the current EDSP that includes the use of high-throughput screening and computational models to prioritize chemicals in EDSP. The CSS work to support EDSP will be conducted with partners in the National Institutes of Health and the Food and Drug Administration through the "Tox21 Consortium," a collective effort among governmental scientists to development and use new toxicological methods.

CSS GOALS TO SUPPORT EDSP:

Near-term: Rapidly prioritize thousands of chemicals for the current EDSP Tier 1 Screen (T1S) battery.

Intermediate: Incorporate modern technologies directly into the EDSP T1S to increase the capacity to screen for endocrine disrupting chemicals.

Longer term: Eventually replace the T1S battery with a suite of assays based on non-whole animal methods.

From the EDSP21 Workplan (EPA, 2011b).

High Priority Chemicals of Concern: Nanomaterials

Public health and the environment regulatory agencies were called upon by the White House (Executive Office of the President Memorandum, 2011) to gather information about developments in nanotechnology. The NRC recently released a report on the safety of engineered nanomaterials that provides a strategy for addressing the science needs regarding the potential health and environmental risks of engineered nanomaterials (NRC, 2012). Accordingly, understanding the potential toxicity of nanomaterials is another key focus of the CSS research program.

CSS NANOMATERIAL RESEARCH GOALS:

Identify the nanomaterials, and in what forms, most likely to result in environmental exposure.

Identify the particular properties of a nanomaterial are related to toxicity (nanomaterials of concern).

Identify concentrations of nanomaterials of concern in air, soil, water, and biological systems.

CSS' nanotechnology research is focused on supporting and informing EPA safety decisions made under various environmental statutes the Agency is responsible for upholding. By achieving the goals of the CSS nanomaterial research effort, EPA decision makers will have more information to determine the health risks for various nanomaterials.

CSS research is coordinating with the National Nanotechnology Initiative (see NNI, 2011), and collaborating with the Organization for Economic Cooperation and Development (see OECD, 2001), to generate protocols, data, and

risk assessment approaches to promote the safe development, use and disposal/recycling of nanomaterials.

Research Focus Area: Computational Toxicology (Comp Tox)

Computational toxicology applies mathematical and computer models and molecular biological approaches to predict chemical hazards and risks to human health and the environment (EPA, 2003a; http://www.epa.gov/ncct/). Computational toxicology tools are being developed in CSS research as part of the effort to move toward a 21st century approach to toxicity testing (NRC, 2007) and risk assessment (NRC, 2009) by moving to toxicity pathway based *in vitro* assays. The CSS computational toxicology work will be conducted with partners in the National Institutes of Health and the Food and Drug Administration through the "Tox21 Consortium," a collective effort among governmental scientists to development and use new toxicological methods.

CSS COMP TOX EXAMPLES:

- Dashboards to display integrated toxicity information for partner-specific questions
- Databases of mechanistic, whole animal toxicity, and exposure data (e.g., ACToR, ExpoCast)
- Virtual Liver and Virtual Embryo

Sustainable Molecular Design Approaches

As part of the CSS advancement of science to support regulatory decisions on chemicals, CSS research includes sustainable molecular design of less toxic ("green") chemicals (www.epa.gov/greenchemistry/). Sustainable molecular design draws upon the established principles of chemistry and engineering to build chemicals atom by atom from the ground up with the end goal of removing the inherent risk of the chemical. "Green chemistry technologies" encompass all types of chemical processes including syntheses, catalyses, reaction conditions, separations, analyses, and monitoring. It can, for example, explore existing synthetic pathways to identify opportunities to substitute a greener feedstock, reagent, catalyst, or solvent in place of more toxic ones. In addition, a green chemistry technology can replace the entire synthetic pathway. Green chemistry technologies can have a number of advantages including reduced waste, reduced costs (e.g., eliminating end-of-the-pipe treatment), reduced energy and resource use, and increased product safety which can result in increased competitiveness of the manufacturers. One example of progress in this arena is EPA's Presidential Green Chemistry Challenge Program which has recognized groundbreaking green chemistry solutions to real-world environmental problems. The new technologies recognized over the past 16 years, have significantly reduced the hazards associated with designing, manufacturing and using chemicals, and in turn, have reduced the use or generation of more than 199 million pounds of hazardous chemicals, saving 21 billion gallons of water, and eliminating 57 million pounds of carbon dioxide releases to the air.

CSS research encompasses continued efforts to advance the field of sustainable molecular design. For example, the CSS "Life Cycle" theme research will evaluate life cycle impacts that demonstrate sustainable molecular design approaches for chemicals and identify the costs of these solutions. As another example, the program's Inherency theme research will provide a basis for designing chemicals with lower exposure and toxicity potential. CSS research builds on existing research of cost-efficient resource and energy-efficient methods for synthesizing chemicals and products. CSS researchers are collaborating with academic and industry partners to fundamentally

redefine the design of chemicals used by industry and consumers to reduce the risks of exposure to toxic chemicals.

An Integrated Program Design

The CSS research program uses a transdisciplinary approach to develop and deliver the scientific tools and knowledge necessary to inform chemical safety decisions that advance sustainability. The program integrates skills, expertise, and research from a diversity of fields, including bioinformatics; computational chemistry; green chemistry and engineering; systems biology; molecular, cellular, and biochemical toxicology; exposure science; process modeling; chemical and environmental engineering; and social sciences.

CSS is designed to lower barriers to research collaboration, moving away from what has traditionally been a "stove-piped" approach to environmental science, divided along disciplinary divisions. Instead, the design of the CSS research program ensures a transdisciplinary approach to problem solving and information delivery, including training, cross-organization dialogue, collaboration, and team building. The program will cultivate innovation, leverage efficiencies, and provide the holistic science the Agency needs for chemical safety and sustainability, and other complex, far-reaching environmental challenges.

The CSS research program integrates elements and themes from research efforts previously administered across EPA's Office of Research and Development (ORD) into a seamless, highly-coordinated, transdisciplinary research program. It leverages expertise and resources in ways that realize efficiencies and reinforce common themes and research goals across six formerly separate research programs: Nanotechnology, Computational Toxicology, Safe Pesticides/Safe Products (SP2), Endocrine Disruptors, Human Health Research, and Human Health Risk Assessment.

Collaborating Across Research Programs

In order to meet the needs of the Agency and the nation in addressing complex environmental problems, research integration is critical to both the CSS research program design and the collaborations across all six EPA research programs. EPA's six research programs collaborate to deliver results that meet the science needs of decision-makers while also establishing a broad scientific foundation for a sustainable future. CSS supports the overall effort by providing improved approaches to chemical testing and assessment, and those efforts, in turn, support the research efforts of the other programs. For example, CSS advances in chemical safety and management inform research efforts in air toxics, drinking water, pesticides use in local communities and larger ecosystems, and waste management, remediation, and emergency response.

EPA's Six Integrated Research Programs:

Chemical Safety for Sustainability (CSS)

Human Health Risk Assessment (HHRA)

Air, Climate, and Energy (ACE)

Safe and Sustainable Water Resources (SSWR)

Sustainable and Healthy Communities (SHC)

Homeland Security (HS) Research

There are many examples of collaboration across EPA's six research programs. Examples include:

- The CSS program is providing tools and data to EPA's Sustainable and Healthy Communities (SHC) research program for those contaminants of highest priority and concern to communities, considering susceptibilities and exposures of the most vulnerable populations and life stages.
- CSS and their partners from the Air, Climate and Energy (ACE) research program are developing green chemistry alternatives to existing hazardous air pollutants, such as halogenated solvents considered "hazardous air pollutants" under the Clean Air Act. This work includes developing and evaluating safer cleaning agents and developing chemical screening methods needed for volatile chemicals.
- CSS is collaborating with the Human Health Risk Assessment (HHRA) research program to advance the pathway-based toxicity testing and risk assessment paradigm proposed by the National Academy of Science (NRC, 2009). CSS research complements ongoing EPA single chemical and cumulative risk assessment activities conducted by HHRA, including the Next Generation (NexGen; http://www.epa.gov/risk/nexgen/) risk assessment case studies.
- In collaboration with OW partners and the Safe and Sustainable Water Resources (SSWR) research program, CSS is creating a web-based Office of Water for the 21st Century (OW21) dashboard for evaluating screening, testing, exposure and sustainability information relevant to prioritization of chemicals for the Preliminary Chemical Candidate List (PCCL)/CCL .

Developing Partnerships from the Start

Collaboration with EPA internal partners (program and regional offices) and external stakeholders is vital to the success of CSS so that we can meet their science needs. Accordingly, CSS staff has engaged a broad range of partners and stakeholders since the inception of the research program in January of 2010, ensuring that CSS identified the highest priority research needs.

First, CSS researchers communicated internally with staff from across EPA's Office of Research and Development (ORD) through a series of briefings, workshops, teleconferences, and meetings (called "listening sessions") to identify and define research needs for chemical safety. Pre-briefs and a workshop were then held to prioritize key science questions with EPA research partners.

Following activities to define partner needs, workshops with ORD scientists and management were held to discuss and refine the products of the Chemical Safety and Sustainable research program to ensure that it would produce outputs and outcomes that meet the science needs of the Agency. A second workshop was subsequently held with partners, including the Office of Pollution Prevention and Toxics, the Office of Pesticide Programs (OPP), the Office of Water (OW), and the Office of Solid Waste (OSW), to review the draft CSS research portfolio.

In July, 2010, CSS consulted with EPA's Board of Scientific Counselors (BOSC), to solicit feedback to ensure that the research planning was on the right track. BOSC was established by the Agency to provide advice, information, and recommendations about Office of Research and Development research programs. A draft of the CSS *Research Framework* (U.S. EPA, 2011a) was produced incorporating an inventory of existing chemical safety research and the input from partners and the BOSC. Additional input on the framework was gathered, through public webinars and other means, from external stakeholders, including industry groups, media organizations, other federal agencies and groups such as the American Chemistry Council, the Humane Society of the United States, and the Environmental Defense Fund. CSS also solicited feedback on the *CSS Research Framework* document using *IdeaScale*, an internet-based, social-media inspired platform for generating a community of ideas and capturing open feedback.

In June 2011, a joint Science Advisory Board (SAB) and BOSC meeting was held to review the CSS Framework document, as well as the other five Agency research programs' frameworks. Using feedback from the joint BOSC/SAB meeting, the CSS team developed a *Strategic Research Action Plan* (this document).

Understanding the importance of continual collaboration with EPA partners and external stakeholders, a *CSS Program Office and Regional Outreach Plan* has been developed to guide the future collaboration with EPA partners. In addition, an external stakeholder engagement plan has been developed.

CSS Design Overview

CSS is designed to operate as an integrated research program organized around eight key research topics.

Inherency includes research to understand the relationship between inherent physico-chemical properties (e.g., mass, conductivity, reactivity, heat of combustion) of a chemical

CSS Research Themes:

1. *Inherency*
2. *Systems Models*
3. *Biomarkers*
4. *Cumulative Risk*
5. *Life Cycle Considerations*
6. *Extrapolation*
7. *Dashboards*
8. *Evaluation*

and fate and effects; and human and wildlife health outcomes after chemical exposure. What's more, these properties may change as a chemical moves through the environment or a biological system such as the endocrine system, an organ (e.g., liver) or a whole organism (e.g., the embryo). Key inherency property models can be developed using information from *Systems Models* research which studies the interactions of the chemical with biological and environmental processes and the outcomes. *Biomarkers* are developed that are effective measures of chemical exposure and effects.

The research methods and models developed for a single chemical can be repeated, efficiently identifying the properties of large numbers of other chemicals. This, in turn, allows for science-based generalizations that can be made for predicting the fate and effects outcomes for broader groupings of chemicals.

In *Extrapolation*, scientists can use outcomes of *Inherency* and *Systems* research to build extrapolations that extend the known data for a chemical to additional biological systems (such as different species) and on environmental systems, providing important scientific information in support of specific regulatory and risk assessment decision-making.

Given sufficient information on a number of chemicals, the *Cumulative Risk* of broader classes of chemicals can be predicted. This information then can be used on higher level activities, including the development of *Dashboards*, *Life Cycle Considerations* (including life cycle and sustainability analyses), and *Evaluation* methodologies.

Figure 1 illustrates the overall conceptual model for CSS research, beginning with problem formulation based on identifying the requirements and information needed to support the regulatory actions and mandates of an EPA regional or program office. Once the information needed is identified, the model identifies four levels (in blue in Figure 1)—

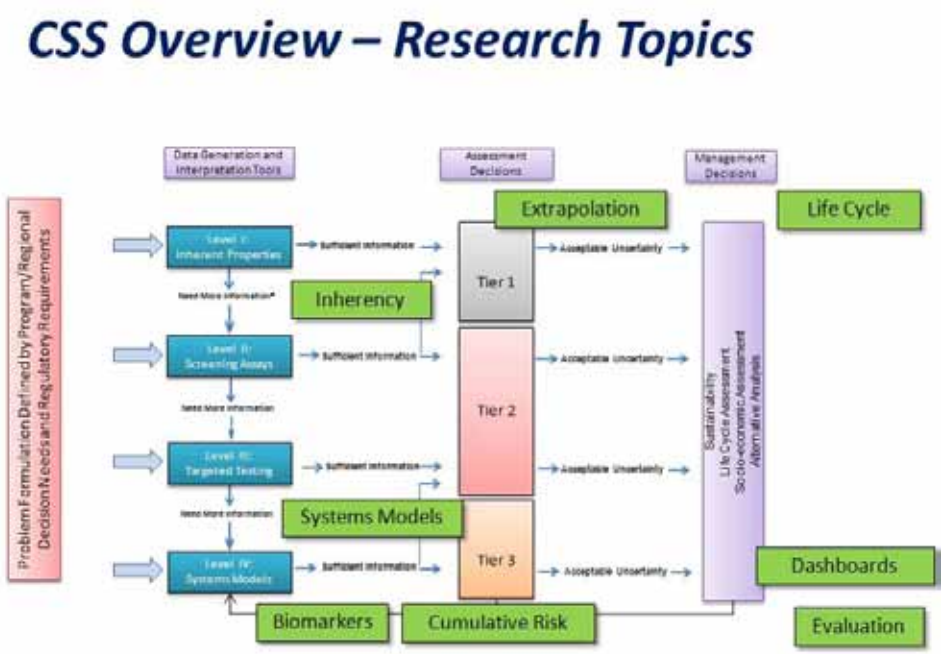

Figure 1. The eight research topics/themes are mapped to a conceptual model to illustrate the integrated nature of the CSS Research Program. From the *Framework for an EPA Chemical Safety for Sustainability Research Program* (U.S. EPA, 2011a). Green boxes, 8 different CSS research themes. Blue rectangles, are the four (I-IV) levels of research approaches to generate data. Gray, pink and orange column of boxes, 3 different assessment tiers.

each of increasing complexity—of research approaches to generate the data needed by the end user (such as an EPA program or regional office) to inform regulatory assessment and management decisions.

Data generated through a particular level's approach may apply directly to a particular assessment or management decision. For example, the information derived from Level I ("Inherent Properties") alone may be adequate for informing a decision (e.g., on the viability of applying a green chemistry approach to chemical management). If not, further resources are devoted to gather more information at that Level or the next. For example, data generated from approaches within Levels I and II ("Screening Assays") may help narrow the range of testing approaches needed for a particular chemical or group of chemicals. Approaches developed under Level IV ("Systems Models") are the scientifically most complex. This may be applied for either very complex assessment and management problems—such as addressing the life stage susceptibility of the cumulative impacts of multiple chemicals and/or exposure pathways,—or for providing information that refines approaches within the other three levels. The assessment decisions also are placed in tiers, recognizing that different types of decision outcomes (as articulated in problem formulation) require assessments with varying types and amounts of information.

The program is designed with a tiered approach that can identify and provide timely, needed information efficiently. The "Management Decisions" portion of the model acknowledges that, in addition to environmental science data, findings, and risk assessments, decision-makers need additional information—such as social/cultural, political, and economic considerations—to fully inform their management strategies.

The CSS research program aims to develop methods and tools to inform the development of enhanced risk prevention or management approaches for both new and existing chemicals. To develop scientific information that leads to improved understanding of how to better create and manage chemicals, CSS research incorporates four key considerations into its research activities: (1) inherent chemical/material properties, (2) life cycle of chemicals, (3) chemical sustainability, and (4) increasing the scope and pace of research to close the large gaps in our current understanding of chemical safety.

1. **Inherency.** *The CSS research program incorporates the consideration of inherent chemical properties into its integrated testing, assessment, and management approaches.*
   Inherency consists of the physical, chemical, and material properties of a chemical—for example, the structure, composition, size, and solubility that arise from a particular chemical formulation. For particles, such properties also include their surface area, surface charge, and aspect ratio. These properties may determine how mobile, persistent, or bioavailable the chemical is in the environment. They also influence the ability of a chemical to interact with biological processes that lead to human disease or adverse outcomes in wildlife species.

   It may be possible in some cases to apply green chemistry approaches during chemical design to alter or otherwise address such inherent properties in ways that reduce environmental impact. Often, however, these also are the properties that give the chemical/material the desirable performance characteristics that make it worthwhile to produce.

2. **Life cycle**. *The CSS research program addresses both new and existing chemical issues and develops tools that can inform the development of sound and feasible assessment and management approaches across the chemical life cycle.*

CSS research considers the life cycle of a chemical (Figure 2) as it relates to chemical safety. Impacts to people or other parts of the environment from chemicals can occur at any point, from the extraction of raw materials for manufacturing a chemical, to processes that create the chemical and incorporate it into products, through the chemical's and product's use to the end of life when it is disposed of or recycled.

CSS research will address the points in the chemical life cycle that may lead to the greatest exposure and impact on human and wildlife health, and how to assess risks from exposure throughout a chemical's life cycle. The research recognizes that each point in a chemical's life cycle also presents an opportunity to utilize sustainable molecular design approaches to avoid or otherwise address concerns about its impact. Such approaches will provide such opportunities for risk prevention early in the life cycle. When those options are not feasible, however, handling measures still may be needed to help manage downstream impacts.

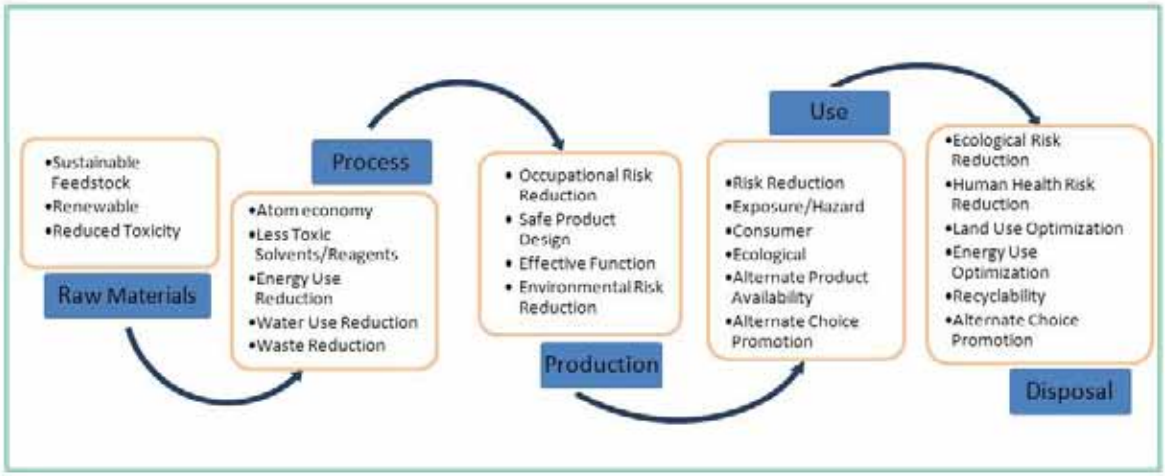

Figure 2. Considering sustainability across a chemical's life cycle.

3. Sustainability. *The CSS research program advances the sustainable use and management across three key areas: (1) what the chemical is, (2) how it is made, and (3) how it is used. Altering any of these three aspects changes the potential of the substance to produce environmental impacts throughout its life cycle and affects sustainability metrics, such as eco-efficiency (the ratio of value delivered to resources consumed).*

Achieving sustainability means creating and maintaining conditions under which humans and nature can exist in productive harmony and that permit fulfilling the social, economic, and other requirements of present and future generations (Council on Environmental Quality, 1969).

Examples of sustainability chemical research include: investigating whether the use of toxic materials is essential to produce a particular chemical when less-toxic materials are available; or, if such alternative materials are not available, whether there are aspects of the current chemical-making process that could be changed to mitigate the impacts of toxic inputs into synthesis and production. The use of a raw material feedstock that requires significant input of water and energy, and identifying an alternative feedstock that has a smaller environmental "footprint" in terms of carbon emissions and resource consumption are also important opportunities that will be investigated through the CSS research program.

4. Closing Assessment Knowledge Gaps. *CSS research is helping revolutionize how chemicals are assessed for potential toxicity to humans and the environment. Research outcomes will increase the pace of chemical screening, testing, and assessment, closing large gaps in the current understanding of chemical safety.*

Traditional chemical toxicity tests, using laboratory tests on whole animals, are expensive and time consuming. As a result, only a small fraction of the more than 80,000 chemicals, currently registered for use in the U.S., have been thoroughly assessed for potential risk. In addition, over a thousand new chemicals are introduced every year.

CSS research is working to revolutionize how chemicals are assessed for potential toxicity to humans and the environment. CSS conducts innovative research that integrates advances in molecular biology, chemistry, high-throughput technology, and computer science to more effectively and efficiently rank chemicals based on hazards and risks. Research outcomes will be rapid exposure data, chemical screening data and other decision-support tools that inform potential risks to humans and the environment, closing the gap in information needs for chemical safety.

Inherency, chemical life cycle, sustainability and improving the pace of research in chemical safety are the fundamental aspects in developing approaches for making existing and new chemicals safer and more environmentally acceptable.

Research Themes and Priority Science Questions

The CSS Research Program consists of eight themes or topics. Brief descriptions of the theme, research objectives, science questions and illustrative products are provided below for each of these.

Theme 1. Inherency

Inherency is defined as the inherent physico-chemical properties that characterize a chemical. These properties influence the potential for humans and wildlife to be exposed to a chemical, and the potential for that chemical to affect the health of humans and/or wildlife, and impact the environment.

Research Objective: Establish a system for compiling and sharing chemical characteristic data and to advance a better understanding the relationships between chemical characteristics and specific toxic responses (including human disease outcomes or population effects in wildlife or ecological systems). Understanding these relationships will, in turn, enhance the ability to predict toxic responses (disease outcomes) for specific chemicals.

Science Questions

What is the relationship between inherent physico-chemical properties and health outcomes, and what data are needed to define these relationships?

What approaches and information can best advance the understanding of physico-chemical or material properties of chemicals, and how can this knowledge be used to predict toxicity, fate, transport, transformation (degradation and metabolism), and toxicologically-relevant exposures?

How can the knowledge of inherent properties be utilized to guide the development of safer product design and use throughout a chemical's life cycle?

Illustrative Outputs, Products, and Outcomes

Example: Understanding the Relationship between Inherent Properties of Nanomaterials and Exposure and Toxicity

EPA researchers are working to improve chemical hazard assessments based upon a deeper understanding of the relevant inherent properties of chemicals that influence environmental fate, exposure, and biological responses. These four products (below) highlight some of the work to understand the inherent properties for nanomaterials, including potential exposures to nanomaterials in consumer products that can be utilized directly in EPA decision-making.

Example Outputs:

(1) Nanoparticles (NPs) in the environment: Methods for the detection and characterization to analyze metal and carbon-based nanoparticles in environmental matrices.

(2) Fate of nanoparticles in the environment: Data on the impacts of inherent particle properties and environmental conditions on their fate in environmental systems.

(3) Leaching of nanoparticles from products: Data on the quantities and speciation of nanoparticles leaching from consumer products containing nanomaterials.

(4) Nanoparticles in the environment: Bioavailablity assessment tools for nanoparticles.

(5) Transport and transformations of nanoparticles in the environment: Experimental and modeling tools for evaluating transport and transformations of nanoparticles in the environment.

(6) Exposure to nanoparticles in the environment: Data and relationships that can be used to link ICPs of NPs to models that predict NP transport, transformation and exposure in the environment.

Research Products contributing to these outputs:

- A report characterizing copper nanoparticles leaching from treated wood. This new research on leaching is needed by OPP and will directly inform decision-making on treated wood products regulated by EPA.
- The development of laboratory and field tests, advanced analytic techniques and quantum chemistry calculations to evaluate the applications, implications and potential risks of surface-altered altered nanoparticles (e.g., titanium dioxide, carbon nanotubes, copper, zinc oxide, and silver) from consumer products in the environment (e.g., landfills, soil, chlorinated and brackish water, biosolids, and wetlands).
- The development and assessment of bioavailability tools for assessing human exposures to silver nanoparticles.
- The development of methods, analyses, and reporting on the detection, evaluation and assessment of release of nanomaterials (e.g., carbon nanotubes) from polymers representative of consumer products.

Outcomes of the research: Improved chemical hazard assessments based upon a deeper understanding of the relevant physico-chemical properties of chemicals that influence environmental fate, exposure, and biological responses. This research is particularly relevant to decision-making for emerging chemicals and materials, such as nanomaterials, whose toxicity is less understood.

Impacts

By establishing information about the relationship between these inherent properties and health outcomes, risk assessment and other regulatory decisions can be better informed. A number of the Inherency research products connect with research performed in other themes of the CSS program (e.g., *Dashboards*, *Cumulative Risk*, and *Life Cycle Considerations*) and together, their outputs advance green chemistry and sustainable design.

Theme 2. Systems Models

Systems models are scaled or multiple-level models that predict or simulate exposure or effects of complex biological or environmental systems.

Research Objective: Generate, utilize, and integrate chemical, biological, and toxicological information at all levels of biological organization (e.g., molecule, cell, tissue, organ, organism), such that the potential toxicity of a chemical can be evaluated with enhanced predictive power.

Science Questions

What are the perturbations at all levels of biological organization, defined as a toxicity pathway, for environmental chemicals? (Related questions: What is the relationship of pathway-level changes to adverse outcomes? and How do we define adversity?)

What are the most appropriate systems models to address the chemical-related environmental problems of greatest impact?

How can information be integrated into virtual organ models?

What new tools and/or models must be developed to ensure precise and efficient hazard and exposure screening across the life cycle of a chemical?

What systems models (e.g., kinetics and dynamics) must be developed and used to address the chemical-related environmental problems with the greatest impact?

The Systems Model theme is the largest of the CSS research themes and will result in a number of major products and outputs. Systems Models research will investigate the "adverse outcome pathway" (AOP), covering the span from chemical exposure all the way through the observation of adverse outcomes, including interactions at all levels of biological organization in humans and wildlife.

Illustrative Outputs, Products, and Outcomes

Example 1: Development and Use of Pathway Perturbation Data

EPA researchers are generating adverse outcome pathway data and studying the relationship between pathway perturbations and particular adverse outcomes. The information will be compiled and methods to utilize the data will be developed to supports Agency screening programs (e.g., EDSP) and risk assessment.

Example Outputs:

(1) Connecting molecular and whole animal effects in a knowledgebase: Compiling information concerning the linkages between endpoints measured, or predicted, at molecular and cellular levels and adverse outcomes at higher levels of biological organization traditionally considered in risk assessments and regulatory decision-making (e.g., organ function in humans; survival, growth/development, and reproduction in wildlife) and depositing this information into a knowledge-base (called "Effectopedia"). The initial focus will be on depositing information about reproductive and developmental toxicity in fish into the Effectopedia.

(2) Predicting species effects after chemical exposure: A web-based tool to support prediction of which species are likely to be susceptible to adverse effects of chemicals that act on specific protein targets.

(3) Developing and applying adverse outcome pathway knowledge, and filling data gaps, to support specific partner needs.

(4) Environmental monitoring approaches: Methods to incorporate biological responses of organisms exposed to environmental stressors into the monitoring of contaminated or remediated sites that are relevant to the Program Offices and Regions. The biological responses used will be based on the biological pathways that are impacted by the exposure(s).

(5) Exposure reconstruction approaches: Recommendations regarding the best method for using biological responses (based on effects on biological pathways) of organisms residing in polluted waters to determine specific chemical exposures of these organisms. Use of these biological responses for determining what the organisms have been exposed to will help Program Offices and Regions in conducting assessments and investigations of polluted waters.

(6) Data sets derived from high-throughput screening of chemicals on Program Office inventories to support the development of signatures, or patterns of activity, for adverse outcome endpoints of relevance to Partners. The outcomes (endpoints) of concern include cancer, developmental neuro-, and developmental immuno-, developmental, reproductive, and systemic toxicity.

(7) Additional screening of regulatory chemical inventories (TSCA21, OW21, EDSP21, and OPP21) will be conducted to provide data sets for prioritization of chemicals on these lists using molecular signatures (i.e.,, patterns of response).

(8) Prioritization of regulatory chemical inventories (TSCA21, OW21, EDSP21, and OPP21) based on *in vitro* molecular signatures (patterns of response) for endpoints of cancer, developmental toxicity, reproductive toxicity.

(9) Completion of EDSP21 workplan for 2000 chemicals: Rapid prioritization of chemicals for further safety evaluation based on potential for both harm and exposure. Non-animal-based (*in vitro*) tests are used to identify the degree to which a substance can damage living organisms (hazard) and to determine pharmacokinetics (how the chemicals accumulate within the body), and computer simulations (based on chemical structure -- inherency -- and mathematical models) are used to derive potential for human contact (exposure. The EDSP21 workplan for prioritization of 2000 chemicals will include both potential hazard identification and chemical-structure-derived exposure potential simulation without pharmacokinetic considerations.

Research Products contributing to these outputs:

- AOP descriptions comparing linkages (e.g., causal) between specific pathway perturbations and reproductive or developmental outcomes in multiple species (e.g., rodents, fish, invertebrates) (reports). These will provide data that support the development of tools and guidance for cross-species extrapolation of effects and hazard.
- Case studies evaluating the utility of transcriptomics, metabolomics, and associated bioinformatic methods for

comparing the nature and severity of biological impairment as a function of space and/or time to assess the efficacy of remediation efforts within the Great Lakes Areas of Concern.

- Completion of high-throughput screening data sets on the first 1000 Endocrine Disruptor Screening Program 21 (EDSP21) chemicals, and *ToxCast*™ Phase II chemical library.
- 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 offices.
- Prioritization and selection of *ToxCast*™ Phase-I and Phase-II chemicals for the TSCA21, OW21, and OPP21 (EPA work plans to utilize 21st century research and methods in these programs) case studies based on endpoints for cancer, developmental toxicity, and reproductive toxicity.

Example 2: Sophisticated Virtual Tissues Models (v-Liver™ and v-Embryo™)

EPA researchers continue to develop the virtual tissue models for the liver and embryo to eventually be used to predict exposures and effects in the developing embryo and in the liver.

Example Outputs:

(1) A computer model to analyze effects of contaminants in food and water on the liver: Linkage of gene expression/pathways with phenotypic outcomes in the intact rodent liver.

(2) Computer models to predict effects on fetal development after maternal chemical exposure: Virtual embryo research integrates important data and scientific knowledge into sophisticated computer models that will simulate and predict adverse events and outcomes in the embryo, fetus and neonate when the mother is exposed to different chemicals.

(3) Delineating pathways of exposure and mechanisms of developmental toxicity using the virtual embryo for risk assessment: The predictions of virtual embryo simulations can be used to understand and test mechanisms of developmental toxicity across different doses, species and life stages. This understanding can provide guidance for life-stage specific targeted research to delineate pathways of exposure and mechanisms in both the fetus and infant.

(4) An integrated strategy for life-stage specific risk assessment: The outcomes of the research will lead to improved understanding of the molecular pathways and cellular processes underlying adverse pregnancy outcomes and better ways to assess the impacts of prenatal and postnatal exposure to chemicals at various stages of development and scales of biological organization.

Research Products contributing to these outputs:

To support the virtual liver model –

- Quantitative dose-response models that are predicted by biological networks governing hepatocyte death and proliferation underlying 20 *ToxCast*™ chemicals with activity on nuclear receptor mediated pathways. This cell agent-based model will estimate the acute and chronic effects of hepatic AOPs and develop a

computational framework to integrate these effects with environmental processes for selected chemicals in EDSP21, TSCA21, OW21, and/or OPP21.

To support the virtual embryo model –

- Integration of angiogenesis information into the virtual embryo using a cell-agent based systems model developed from empirical data and biological knowledge of blood vessel development. The angiogenesis model will be 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, and/or OPP21.

Example 3: Exposure and Effects Information to Support Near-term Regulatory Decision-Making

Example Outputs:

(1) Consumer product use, emissions and other data for informing multi-tier exposure and dose analyses.

(2) Inputs and methods needed to model fate/transport, concentrations, exposures and dose to a variety of environmental chemicals.

(3) Refined Stochastic Human Exposure and Dose Simulation (SHEDS) and new SHEDS-Lite models.

(4) Applications of linked source-to-dose models to address Program Office and Regional priorities for environmental chemicals.

(5) Completion of the TSCA21 workplan for 500 chemicals: Rapid prioritization of chemicals for further safety evaluation based on potential for both harm and exposure. Non-animal-based (*in vitro*) tests are used to identify the degree to which a substance can damage living organisms (hazard) and to determine pharmacokinetics (how the chemicals accumulate within the body), and computer simulations (based on chemical structure -- inherency -- and mathematical models) are used to derive potential for human contact (exposure). The TSCA21 workplan for 500 chemicals will combine high-throughput hazard data, pharmacokinetic data, and exposure simulations to determine chemical prioritization based upon potential risk.

(6) Completion of the EDS21P workplan for 2000 chemicals: Rapid prioritization of chemicals for further safety evaluation based on potential for both harm and exposure (similar to the TSCA21 workplan approach above).

Research Products that contribute to these outputs:

- Simulation tool for modeling PCB and SVOC emissions and transport in buildings, and formaldehyde emissions from aqueous solutions. Revised version of SHEDS-Multimedia (v4) that includes output results for different scenarios, case-studies and sensitivity analyses addressing OPP needs for including dietary and residential scenarios. This product is responsive to a recent recommendation of the FIFRA Science Advisory Panel (SAP, 2010).
- The Exposure Forecaster (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.

Example 4: Systems Models for Ecological Risk Assessment Application

Example Outputs:

(1) Integrated systems approaches linking exposure and outcome.

(2) Integrated systems approaches for predicting individual, population, and ecosystem risk from complex patterns of chemical exposure.

(3) Understanding of inherent properties of modifications that mediate specific nanomaterial (NM) toxicity or other effects.

(4) Identify mechanisms of action for nanomaterials, AOPs, and recommendations for development of alternative and rapid-throughput assays.

(5) Recommendations for the development of models linking inherent properties and adverse outcomes (e.g., QSARs for NMs).

(6) Best current *in vitro* and *in vivo* methods for tier testing of NMs provided to Offices.

(7) AOPs identifying common and sensitive biological receptors predictive of adverse human and ecological outcomes.

(8) Mechanisms of injury, mode of action and AOP for high-throughput and high-content screening methods development.

(9) Credible translatable alternative test methods, guidelines, and endpoints that predict NM *in vivo* toxicity with high confidence.

Research Products that contribute to these outputs:

- Design and recommendations for case studies that demonstrate systems models approaches to evolve from population- to community- to ecosystem-level risk assessment, and provide information on high priority chemicals.
- Data on toxicity of selected nanomaterials, including exposure-response models, uptake, distribution, modes of action, AOPs, and initiating events for non-human species and ecological processes.
- Guidance on the use of ecological nanomaterial toxicity information to identify dose metric(s) of exposure to response, AOPs and absorption, distribution, metabolism, and excretion (ADME) with their inherent chemical properties for development of high throughput and high content testing methods and best practices and test methods for the use of alternative models, tiered testing and *in vivo* tests to assess their toxicity.

Outcomes of the research for all four Systems Models examples (above): Improved chemical prioritization, screening, testing and quantitative risk assessment by integrating information from multiple biological levels, including pathway-level information, and by using advanced computational techniques, such as multi-scale systems models of virtual tissues, to develop predictive models of hazard and exposure.

Impacts

The Systems Model research outcome will have a tremendous impact on EPA toxicity testing, risk assessment and other environmental decision-making as the Agency moves chemical safety assessments into the 21st century. Together, the Systems Model outcomes moves advance the use of the pathway-based toxicity testing and risk assessment paradigm.

Theme 3. Biomarkers

A biological marker, or "biomarker," is a chemical or biological characteristic that is measured or evaluated as an indicator of a biological process and used as a marker of exposure or effect.

Research Objective: Predict health outcomes and exposures based on biomarkers to inform EPA risk assessment and management decisions for human and wildlife health.

Science Questions

How can CSS assess biomarkers that can serve as useful indicators of toxicity for different chemicals and endpoints such as health or wildlife outcomes?

What are the endpoints of concern that require development of biomarkers?

What characteristics are needed for a biomarker to be one that is informative of adverse outcomes to humans?

How can the program assess biomarkers of exposure?

What models need to be developed to better integrate biomonitoring (biomarkers and bioindicators) data into testing systems to help the Agency better understand environmental and health impacts?

Illustrative Outputs/Products/Outcomes

Example: Development of Biomarkers of Effect and Exposure

The *Biomarkers* theme is closely related to the AOP concept of the *Systems Models* research theme as it strives to characterize linkages between external environments, internal (biological) environments and key adverse effects/outcomes. The *Biomarkers'* theme includes research to develop and assess biomarkers of exposure and effect. The research will use linkages between biomarkers and health outcomes to develop biomarker-based predictive tools to aid in defining and understanding the relationship between chemical exposure and health effects.

Example Outputs:

(1) Holistic approaches to foster a better understanding of relationship between exposure metrics and biomarkers, allowing for potential to reconstruct exposures from biomarkers.

(2) Improved methodologies for exposure and dose estimates by integrating biomarker data with supporting information/data (e.g., exposure factors and pharmacokinetic behaviors) into predictive models.

(3) Biomarker-based models for risk assessment.

(4) Biomarker-based model tools to evaluate risk management activities.

(5) Develop and maintain a state of the art panel of biomarkers of effects for use by risk assessors and researchers.

(6) Link biomarkers to key events in an adverse outcome pathway and thereby improve the diagnostic capabilities of the biomarkers in the panel.

Research Products contributing to these outputs:

For biomarkers of exposure -

- Web-based software tool to conduct reverse dosimetry probability calculations for estimating exposure

concentrations that are likely to have produced the observed biomarker concentrations.

- Best practices for integrating existing biomonitoring data into risk assessment demonstrated with a case study. Report will give generalizable guidance for calculating exposure, dose, and target dose; calculating uncertainty; predicting risk; and identifying opportunities for mitigation

For biomarkers of effect -

- Panel of existing bioindicators evaluated for diagnostic capability including (1) robustness of the assay, (2) bioindicator distribution in healthy and affected populations and (3) predictive capability for adverse outcomes.

Outcomes of the research: EPA risk assessments are improved by the (1) consistent, justifiable, and improved use of existing biomonitoring data (e.g., NHANES); (2) availability of dose estimation/exposure reconstruction methods; and (3) availability of diagnostic AOP-based biomarkers with annotations to evaluate published data.

Impacts

The impact of the resulting Biomarkers' research is that the program's partners will possess the tools (e.g., diagnostic biomarkers for AOPs) and methods needed to improve estimates of exposure, dose and outcome, and utilize available biomarker data. In addition, some of the work directly supports the development of biomarkers for emerging contaminants of concern.

Theme 4. Cumulative Risk

Cumulative risk is the combined risks from aggregate exposures to multiple agents of stressors.

Research Objective: Assess the potential human health and environmental outcomes that result from multiple and continuous exposures to chemicals, and provide this information about specific chemical mixtures, including chemical mixtures found in consumer products, to support priority regulatory decisions.

Science Questions

What are the ecological and human health risks of combined real-world exposures to environmental chemicals?

What are the chemical targets at the molecular, cellular, tissue, organ, and whole animal levels?, and can these targets be used to assess cumulative effects?

How can recent scientific advances help describe the impacts of exposures to chemical mixtures?

How can recent scientific advances help describe human variability (e.g., across life stages, population groups)?

What kinds of tools, including computational, systems-based tools, are required to fully describe the overall impact of aggregate exposures on organisms?

What enhancements will be required to describe the impact of factors that affect an organism's response to chemical exposure, such as life stage, gender and aggregate exposures?

What new methods/models are needed to account for exposure from all sources and pathways?

Illustrative Outputs, Products, and Outcomes

Example 1: Effects and Exposure Predictive Tools for Real-World Mixtures

Real world chemical exposures are rarely limited to a single chemical, but involve often complex mixtures of different agents or stressors. This set of products helps identify, predict, assess and prioritize how chemical mixtures interact with humans and wildlife in real-world settings.

Example Outputs:

(1) Predictive tools for identifying and prioritizing real-world mixtures of stressors (environmental, residential, SES, diet, etc.) based on: Sources (including commercial and consumer products); Surrogate exposure and hazard indices; and Toxicity of chemical mixtures.

(2) Methods to predict the effect of chemical mixtures based on outcome pathways.

(3) Methods to select chemical mixtures for testing based on likelihood of toxicity.

Research Products contributing to these products:

- Linked SHEDS and PBPK modeling system to support Food Quality Protection Act (FQPA) cumulative risk assessments.
- Computational method to utilize chemicals' similarities in kinetics and dynamic (response) determinants to optimize clustering and interactions of

clusters of chemicals within complex mixtures.

Example 2: Chemical Mixture Data, Methods, and Models to Support Near-Term Regulatory Decision-Making

Example Outputs:

(1) Evaluation of selected compounds in municipal solid waste landfills.

(2) Final data on the fate and transport of emerging chemicals of interest following land application of biosolids.

(3) Data on the fate and transport of emerging chemicals of interest following land application of biosolids for mixtures identified in CSS cumulative risk research.

(4) Evaluation of selected compounds in municipal solid waste compost.

(5) Data, science and methods to support Agency decisions on perfluorochemicals (PFCs).

(6) Data, methods, and science to inform PCB exposure and mitigate risk to children to support EPA regional decisions.

Research Products contributing to these products:

- Methods and approaches for evaluating the fate and transport of mixtures of emerging contaminants and selected modes of action in wastewater treatment in support of Toxic Substance Chemical Act (TSCA) rule making.
- Preliminary data on the fate and transport of emerging chemicals of interest following land application of biosolids to support of TSCA rule making.
- Data gap analysis on presence, fate and transport of selected compounds in the municipal solid waste stream.
- Evaluation of PFC mixture effects by *in vitro* and *in vivo* models.
- Market trend monitoring for PFCA precursors in consumer articles.
- Data and model results for PCBs in schools to provide information needed to develop improved and cost-effective mitigation and remediation approaches.

Outcomes of the research for both of these Cumulative Risk examples: A set of predictive models from the cellular level to the population level that can be integrated into a source-to-outcome modeling platform that incorporates real world exposure scenarios.

Impact

The impact of the Cumulative Risk research are new data and predictive tools to inform risk management decisions for EPA's priority regulatory, risk assessment and risk management decisions for chemical mixtures.

Theme 5. Life Cycle Considerations

Life cycle is defined as the "cradle-to-grave" (also referred to as "cradle-to-cradle") activities for a product, process, or activity, including the stages of resource acquisition, material manufacture, production, transportation/distribution, use, recycling/reuse, and final disposal.

Research Objective: Utilize data to inform the design of more sustainable, green chemicals by reducing their environmental and human health impacts while recognizing the need for chemicals in a sustainable economy.

Science Questions

How can life-cycle assessments and other innovative tools be integrated with more traditional methods to produce assessments that inform decision making and identify safer and more sustainable approaches?

How can life cycle assessment approaches and methods be applied to decision analysis to reduce uncertainties associated with the analysis of alternatives at multiple decision-making scales or levels?

What are the critical components of a sustainability-driven paradigm for risk management of chemical and product systems that incorporate life cycle factors relevant to environmental, economic, and societal issues?

How can effective and reliable screening-level approaches for life-cycle assessment be developed that can be efficiently and strategically applied to the large number of chemicals?

Illustrative Outputs, Products, and Outcomes

Example:

Transforming EPA's risk management strategy into a holistic approach requires the application of a life cycle perspective to incorporate sustainability into decision-making. The Life Cycle Considerations' research outcomes will inform green chemistry chemical design.

Building on other CSS projects, research in this effort will: develop a data network to meet the emerging assessment needs of EPA program and regional offices to address sustainability; identify research opportunities with respect to the life cycle stages of a chemical; and serve as a platform for research conducted in a holistic, multi-stakeholder manner (e.g., initiating collaborations among EPA, industrial partners and stakeholders) to generate improved sustainability.

Example Outputs:

(1) A database of information about the life cycle of a chemical that will aid in incorporating sustainability in environmental decision making.

(2) A framework to help include sustainability in decision making within the EPA using experiences from case studies with Program Offices and Regions.

(3) Reaction systems, membrane materials, and separation processes will be developed using the principles

of Green Chemistry to address sustainability in chemical processes.

(4) Solutions will be provided and demonstrated for the sustainable design, production and use of chemicals using the principles of Green Engineering to reduce the utilization of energy intensive chemical processes.

(5) Innovative approaches to manufacturing of chemicals will be developed using Sustainable Molecular Design, Life Cycle Material Safety and Chemical Process Indicators.

(6) The development and demonstration of life cycle methods for sustainable design practices for the manufacture, use and evaluation of commercial products.

Research Products contributing to these outputs:

- Preliminary sustainability database design based on a model case of life cycle inventory (LCI) generated for a nano-silver consumer product.
- Extramural research to advance the science and application of life-cycle thinking and assessment for chemicals. This research will be conducted in two academic institutions under EPA's Science to Achieve Results (STAR) Program.
- Demonstration of the successful synthesis and characterization of a cellulose membrane with controllable cross-linking for application in sustainable water treatment.
- Documentation (including through the patent development) describing greener production of nanomaterials to promote sustainable nanotechnologies and mitigate regulatory needs.
- Assess biobutanol as fuel substitute for bioethanol to potentially lessen greenhouse gas emissions: 1) Membrane for the green separation of ethanol from water using combinations of zeolitic and polymeric materials; and 2) 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).
- Demonstration of how the GREENSCOPE (Gauging Reaction Effectiveness for the Environmental Sustainability of Chemistries with a multi-Objective Process Evaluator) sustainability indicator model can evaluate human health and environmental risks, for an example such as manufacturing of biodiesel.
- Demonstration of how the GREENSCOPE sustainability indicator model can implement green chemistry principles through an in-house developed green chemical reaction, which can be applied by OSCPP in educational and evaluation activities and projects.
- International guidance document on product category rules for environmental product claims. This international guidance document will provide direct support to the missions of the Office of Resource Conservation and Recovery (in OSWER) for their Sustainable Products-related efforts and to the Office of Pollution Prevention and Toxics (in OCSPP) for their Environmental Preferable Purchasing Program established for needs expressed within the cross-agency 'Sustainable Products Network'. This work will support a key element of the 'International Product Life-Cycle Partnership' draft proposal for U.S. Commitment for Rio +20 being prepared by the Office of International and Tribal Affairs.

Outcomes of the research: The 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 in order

that sustainable risk management approaches can be scaled up and delivered to decision-makers.

Impact

Chemical decision-making is better informed because of the information about a chemical's toxicity across the entire life cycle. Safer, more sustainable chemicals are available and sustainable molecular design approaches are defined.

Theme 6. Extrapolation

Extrapolation is the technique of estimating a variable outside a known range through calculations based on equations and models built from data based on values and variables from within a known range.

Research Objective: Maximize the use of available data by developing approaches that extrapolate between (1) test organisms and human or ecological receptors, (2) test and real-world exposure durations, (3) laboratory to field conditions, (4) individuals to populations, and (5) *in vitro* **to** *in vivo* **health outcomes.**

Extrapolation methods are needed that improve the reliability and precision of environmental effect estimates. CSS research will address that, characterizing the uncertainty in current risk management decision making that result from extrapolating measured data, and develop new approaches for extrapolation. Research conducted under this topic will maximize the use of available data by developing approaches that extrapolate between test organisms and human or ecological receptors, test and real-world exposure durations, and from laboratory to field conditions.

This research will provide methods that may be used across CSS topic areas for consistency of data interpretation and application.

Science Questions

What enhancements will be required to describe the impact of factors that affect an organism's response to chemical exposure, such as life stage, gender, and aggregate exposures?

How can recent scientific advances help describe human variability, life stages, and population groups?

With the emphasis on developing in vitro assays for toxicity testing, how can we extrapolate from in vitro assay response to in vivo response?

Illustrative Outputs/Products/Outcomes

Example 1: Extrapolation Tools

Example Outputs:

(1) Chemical Class-Based Expert Systems: Automated rule-based decision trees are being developed to predict which chemicals have the potential to disrupt endocrine systems. This is done by testing key chemicals within a chemical class to represent others, determining what is similar about the chemical structures and properties that explain their biological activity, and writing rules that help categorize similar but untested chemicals.

(2) Refined tools that exist for estimating species sensitivity to pesticides and other contaminants: Expansion to add algal toxicity data.

(3) Refined tools that exist for estimating species sensitivity to pesticides and other contaminants: Expansion to add mode of action information.

(4) Refined tools that exist for estimating species sensitivity to pesticides and other contaminants: Guidance to standardize methods.

(5) Population models that incorporate sub-groups of fish or aquatic

invertebrates separated by life stage, age or time.

(6) Methods and models for translating toxicity test endpoints into quantitative estimates of changes in demographic rates, such as fecundity and juvenile survival rates, for use in population-level risk assessment.

Research Products contributing to these outputs:

- Framework for extrapolating *in vitro* to *in vivo* effects from in silico models based on empirical data that predict unbound chemical concentrations *in vitro* from inherent chemical properties.
- Provide definitive interspecies mode of action-based extrapolation models for predicting ecotoxicity to OCSPP.
- Guidance for using population modeling endpoints in risk assessments for any aquatic animal species for which there are traditional toxicity data. Guidance includes an MS Excel model for deriving default population demographic parameters (survival rates for different life stages and fecundity rates) when traditional toxicity data are not available.
- Avian toxicity translator model for extrapolation from individual to population level effects (basic version, MCnest) including a users manual and a technical support manual.

Example 2: Extrapolation Methods to Support Environmental Decision-Making for EDCs

Example Outputs:

Methods and models to apply *in vitro* and in silico derived data to individuals.

Research Products contributing to these outputs:

- Integrated method linking endocrine active substance exposure in the environment with biological effects observed in *in vitro* and *in vivo* assays.
- Guidance document on the use of *in vitro* data for predicting biological effects after exposure to endocrine active substances in non-target species.

Outcomes of the research for both of these examples: An improved understanding of the utility of adverse outcome pathway models that provide increase confidence in the extrapolation of exposure and effects across different levels of biological organization, doses, genders, life stages, species and populations.

Impact

This research will provide methods that may be used by program offices in risk assessment and other decision-making and across CSS research themes to improve consistency of data interpretation and application.

Theme 7. Dashboards

A dashboard is an interactive web site that provides access to the tools and data required to carry out a specific analysis or decision-related task.

Research Objective: Produce dashboards that provide partners with accessible, useful graphical depictions of all available chemical data (e.g., information and studies) related to the user's specific queries to help answer the chemical-related question.

Science Questions

What kind of tools, including computational, systems-based tools, are required to fully describe the overall impact of exposure on organisms?

How can tools be customized to supply the data and information needed by partners to address specific regulatory and environmental questions?

How can inherency, exposure, hazard, and risk management options be integrated to supply a greater degree of certainty in decisions, reduced risk and enhanced sustainability?

Illustrative Outputs, Products, and Outcomes

Example: Prototype Dashboard Development

CSS-produced dashboards will provide decision-makers with web-based tools that produce a summary of information derived from chemical exposure and hazard data, decision-rules, and predictive models. Dashboards will seamlessly integrate information from diverse sources to help partners arrive at more holistic and novel risk assessment and risk management decisions. Dashboard research will produce customized web-based tools based on the queries of partners using the web-based tool.

Example Outputs:

(1) Initial prototype dashboards delivered to Program Offices: Prototype versions of web-based dashboards for evaluating screening, testing, exposure and sustainability information relevant to EDSP21 (potential endocrine disruption), OPP21 (pesticidal actives, inerts and antimicrobials), TSCA21 (prioritizing and assessing new and existing chemicals), OW21 (prioritization of chemicals for the PCCL/CCL and other purposes), HHRA21 (PPRTV and NexGen risk assessments).

(2) Regular updates (6-month cycles) of all EPA program office web-based dashboards, taking into account user feedback and new scientific developments.

Research Products contributing to these outputs:

- Prototype version 1.0 of web-based dashboards followed by updates every six months including: OPP21 (Office of Pesticide Programs for the 21st Century) dashboard for evaluating screening, testing, exposure and sustainability information relevant to pesticidal actives, inerts and antimicrobials.
- 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.

- Prototype version 1.0 of web-based dashboards followed by updates every six months including: TSCA21 (Toxic Substances Control Act for the 21st Century) dashboard for evaluating screening, testing, exposure and sustainability information relevant to prioritizing and assessing new and existing chemicals.
- Prototype version 1.0 of web-based dashboards followed by updates every six months including: OW21 (Office of Water for the 21st Century) dashboard for evaluating screening, testing, exposure and sustainability information relevant to prioritization of chemicals for the Preliminary Chemical Candidate List (PCCL)/CCL and other purposes.
- Prototype version 1.0 of web-based dashboards followed by updates every six months including: HHRA21 (Human Health Risk Assessment in the 21st Century) dashboard for evaluating screening, testing, exposure and sustainability information relevant to PPRTV and NexGen risk assessments.

Outcomes of the research: Communicate, translate, and transfer all available scientific information about chemicals in ways most useful to decision makers.

Impact

The impact of the Dashboards research is an improved ability (including improved efficiency) for CSS partners (EDSP21, TSCA21, OPP, OW, etc.) to make scientifically-based decisions. Providing regulatory decision-makers with user-friendly tools to access all available data about chemicals is critical to the success of EPA's CSS research.

Theme 8. Evaluation

This last CSS research theme evaluates the results and impact of the CSS research program. This effort will develop the tools needed to evaluate the reliability and uncertainty of data, methods, and models developed under the other CSS themes for their collective ability to improve risk assessment and management.

Research Objective: Provide decision analyses, support tools, and feedback mechanisms that inform and enable the optimal delivery and use of CSS data, methods and models, and to evaluate the impact of the CSS research program on EPA decision-making capabilities.

Science Questions

How have CSS research findings and tools impacted and supported EPA's decision making?

What are the measures needed to evaluate the predictive value of the tools (e.g., Dashboards, enhanced ToxCast™) produced from the CSS Research Program?

Do the partners find that the tools and other data from the CSS Research Program will improve environmental decision making, including risk assessment?

How can the critical pieces of information required for different assessment tiers be systematically identified, evaluated, integrated, reviewed, and used in assessments and subsequent management decisions?

Illustrative Outputs, Products, and Outcomes

Example: Assessing CSS Partner Needs, Product Utility, and Program Success

Example Outputs:

(1) Understanding of partner needs and how to measure product utility; information obtained through pro forma surveys and interviews.

(2) Overall program performance and success assessment of CSS research based on understanding of how the partners will benefit from CSS research products.

Research Products contributing to these outputs:

- Initial and follow up Pro forma surveys of program office, regional and external partners.
- A program office and regional partners outreach and engagement plan.

Outcomes of the research: The overall impact of the CSS research is assessed. CSS tools and information are delivered to the partners along with training in order that the partners have an ability to efficiently apply the information. The CSS tools, new assays, and scientific knowledge have increased our confidence in utilizing 21st century pathway-based approaches for priority setting, toxicity testing, and risk assessment.

Impact

The impact of the Evaluation work is that CSS products are developed in response to partner needs, and are then delivered efficiently to partners for use in Agency decisions. Further, the overall impact of the CSS research outputs (information, tools, etc.) on EPA decision-making will be understood.

Conclusion

EPA's Chemical Safety and Sustainable research program presents a comprehensive set of efforts for transforming toxicity testing and performing chemical risk assessment using toxicity pathway-based approaches. The combined products of the program will transform the paradigm of chemical safety assessment to using 21st-century tools and approaches through a number of key activities.

CSS research addresses chemical testing needs, such as the significant backlog of existing and new chemicals that need to be tested for toxicity risks, by rapidly increasing the knowledge base about the key drivers of potential toxicity of chemicals. The heart of the transformation in toxicity testing requires intensive pathway-based research and assay design in order to assess human and wildlife health within part of a larger system (the ecosystem), as EPA moves to a sustainable molecular design approach to chemical safety.

To improve EPA assessments, reliable, pathway-based biomarkers of effect will be developed and needed extrapolation methods will be developed. Risk assessment of multiple chemicals, and exposures to chemicals plus nonchemical stressors, requires new methods and approaches that CSS will provide, and cumulative risk assessment will require methods to use human exposure data. The program anticipates that the Agency will be better positioned to perform its mission of protecting human health and the environment as scientific information becomes digitized and readily available, methods and models to capture the complexities of chemical exposure and hazard in toxicity testing are developed, and approaches focused on development of more sustainable alternatives are provided to decision-makers. Producing user-friendly tools, such as dashboards, will specifically address various partner needs in an efficient manner. Finally, the impact of the CSS research tools, data and new approaches are evaluated through training and feedback.

The *Strategic Research Action Plan for EPA's Chemical Safety for Sustainability Research Program* maps out a research program for the next five to ten years. Partner needs have been the driver of CSS product development. Communication with partners began at the inception of the program development and will continue throughout. In fact, the entire program has moved EPA to adopt a new approach to engage its partners in the research and development process. The plan, however, is a living document and will be updated as science evolves and decision-makers' needs change.

Summary Tables

EPA's Chemical Safety and Sustainable research program presents a comprehensive set of efforts for transforming toxicity testing and performing chemical risk assessment using toxicity pathway-based approaches. The combined products of the program will transform the paradigm of chemical safety assessment to using 21st-century tools and approaches through a number of key activities. The tables (below) are organized by research theme and within theme are organized by research project tasks. Each task number refers to a particular project task that has one or more expected outputs. Outputs were defined by partners and represent synthesized and/or translated research products that are in the format needed by the end user.

Theme 1. Inherency

Science Questions: What is the relationship between inherent physico-chemical properties and health outcomes, and what data are needed to define these relationships?

What approaches and information can best advance the understanding of physico-chemical or material properties of chemicals, and how can this knowledge be used to predict toxicity, fate, transport, transformation (degradation and metabolism), and toxicologically-relevant exposures?

How can the knowledge of inherent properties be utilized to guide the development of safer product design and use throughout a chemical's life cycle?

Outcome: Improved chemical hazard assessments based upon a deeper understanding of the relevant physico-chemical and other inherent properties of chemicals that influence environmental fate, exposure, and biological responses.

Task No.	Outputs	Output Year	Relevance to other CSS Themes
1.1.1	(1) A resource of inherent chemical properties (ICP), molecular descriptors and selected biological activities for chemicals of interest to OCSPP. (2) Provide tools and methods for chemical space analysis and domain of applicability for models to be incorporated into Dashboards.	FY16	2, 3, 4, 5, 7
1.1.2	(1) DSSTox chemical structure files, covering EPA's high-throughput testing programs (*ToxCast*™, Tox21), eco-toxicological databases (ECOTOX), and FDA's food additive database (PAFA), to support predictive modeling and to be incorporated into structure-searching tools and CSS Dashboards (see Theme 7 below).	FY14	2, 5, 7
	(2)Efficient structure-entry process and workflow to update DSSTox central structure inventory, and link new structures to ICP properties and data in CSS Dashboard.	FY16	2,5, 7
1.1.3	(1) Physico-Chemical Properties Calculator, linked to existing EPA models (e.g., EPI Suite, enhanced SPARC) provides molecular properties for building improved environmental fate & transport models.	FY16	2,5, 7

Task No.	Outputs	Output Year	Relevance to other CSS Themes
1.1.3	(2) Integration of Physico-Chemical Properties Calculator with outputs of Tasks 1.1.1 and 1.1.2 to supply ICP for chemicals of Agency interest and to provide key properties for environmental fate & transport models accessed through the CSS Dashboard.	FY16	2,5, 7
	(3)Predict types of chemicals more likely to require metabolic activation to produce animal toxicity, incorporated within an automated workflow and linked to other ICP and toxicity related chemical features for use in CSS Dashboard.	FY16	2,5, 7
1.2.1	(1)Nanoparticles in the environment: Methods for the detection and characterization to analyze metal and carbon-based nanoparticles in environmental matrices.	FY16	1.2.7.7, 2.6.1
	(2) Fate of nanoparticles in the environment: Data on the impacts of inherent particle properties and environmental conditions on their fate in environmental systems.	FY16	1.2.7.7, 2.6.1
	(3) Leaching of nanoparticles from products: Data on the quantities and speciation of nanoparticles leaching from consumer products containing nanomaterials.	FY16)	1.2.7.7, 2.6.1
1.2.2	(1) Nanoparticles in the environment: Bioavailablity Assessment Tools for nanoparticles.	FY16	1.2.2.7, 2.6.1.1, 2.6.1.2
	(2) Transport of nanoparticles in the environment: High throughput protocols for estimating the transport of nanoparticles in environmental systems (e.g., waste water treatment plants).	FY16	1.2.2.7, 2.6.1.1, 2.6.1.2
	(3) Transport and transformations of nanoparticles in the environment: Experimental and modeling tools for evaluating transport and transformations of nanoparticles in the environment.	FY16	1.2.2.7, 2.6.1.1, 2.6.1.2
	(4) Exposure to nanoparticles in the environment: Data and relationships that can be used to link ICPs of nanoparticles to models that predict NP transport, transformation and exposure in the environment.	FY16	1.2.2.7, 2.6.1.1, 2.6.1.2
	(5) Data on emissions produced from the use of diesel fuel containing ceria additive.	FY16	1.2.2.7, 2.6.1.1, 2.6.1.2
1.3.1	(1) Pesticide MOA profiling tool to OPP.	FY15	5, 7
	(2) Database of MOAs and assignment methodology to OCSPP.	FY15	5, 7
	(3) Improved MOA-based QSAR ecotoxicity models to OCSPP.	FY15	5, 7
1.3.2	(1) A molecular-based ligand-biological target resource that can be used to inform toxicity and in silico-*in vitro-in vivo* correlations and extrapolations.	FY15	2,4,5, 7
	(2) A web-accessible (within EPA only [intranet]) in silico/knowledge based ADME (absorption-distribution-metabolism-elimination) resource in support of physiologically-based pharmacokinetic (PBPK) dosimetry models and exposure-dose extrapolation.	FY15	2,4,5, 7

Theme 2. Systems Models

Science Questions: What are the perturbations at all levels of biological organization, defined as a toxicity pathway, for environmental chemicals?
What are the most appropriate systems models to address the chemical-related environmental problems of greatest impact?
How can information be integrated into virtual organ models?

What new tools and/or models must be developed to ensure precise and efficient hazard and exposure screening across the life cycle of a chemical?

What systems models (e.g., kinetics and dynamics) must be developed and used to address the chemical-related environmental problems with the greatest impact?

Outcome: Improve chemical prioritization, screening, testing and quantitative risk assessment by integrating information from multiple biological levels, including pathway-level information, and by using advanced computational techniques, such as multi-scale systems models of virtual tissues, to develop predictive models of hazard and exposure.

Task No.	Outputs	Output Year	Relevance to other CSS Themes
2.1.1	(1) Connecting molecular and whole animal effects in a knowledgebase: Compiling information concerning the linkages between endpoints measured, or predicted, at molecular and cellular levels and adverse outcomes at higher levels of biological organization traditionally considered in risk assessments and regulatory decision-making (e.g., organ function in humans; survival, growth/development, and reproduction in wildlife) and depositing this information into a knowledge-base (called Effectopedia). The initial focus will be on depositing information about reproductive and developmental toxicity in fish into the Effectopedia.	FY16	7, 4
	(2) Predicting species effects after chemical exposure: A web-based tool to support prediction of which species are likely to be susceptible to adverse effects of chemicals that act on specific protein targets.	FY16	6
	(3) Developing and applying adverse outcome pathway knowledge, and filling data gaps, to support specific Partner needs.	FY16	7
2.1.2	(1) Environmental monitoring approaches: Methods to incorporate biological responses of organisms exposed to environmental stressors into the monitoring of contaminated or remediated sites that are relevant to the Program Offices and Regions. The biological responses used will be based on the biological pathways that are impacted by the exposure(s).	FY16	3, 6

Task No.	Outputs	Output Year	Relevance to other CSS Themes
2.1.2	(2) Best practices for surface water samples: Determining the best method to collect, store, and transport surface waters collected in the environment to use in laboratory experiments that look at responses of living cells (not live animals) to exposure to these waters. These experiments will be used to test environmental samples for specific types of biological responses that are known to result in unfavorable effects that are of concern to the Program Offices and Regions.	FY16	
	(3) Exposure Reconstruction Approaches: Recommendations regarding the best method for using biological responses (based on effects on biological pathways) of organisms residing in polluted waters to determine specific chemical exposures of these organisms. Use of these biological responses for determining what the organisms have been exposed to will help Program Offices and Regions in conducting assessments and investigations of polluted waters.	FY16	3
2.2.1	A computer model to analyze effects of contaminants in food and water on the liver: Linkage of gene expression/pathways with phenotypic outcomes in the intact rodent liver.	FY16	
2.2.2	(1) Computer models to predict effects on fetal development after maternal chemical exposure: Virtual embryo research integrates important data and scientific knowledge into sophisticated computer models that will simulate and predict adverse events and outcomes in the embryo, fetus and neonate when the mother is exposed to different chemicals.	FY16	3, 6, 7
	(2) Delineating pathways of exposure and mechanisms of developmental toxicity using the virtual embryo for risk assessment: The predictions of virtual embryo simulations can be used to understand and test mechanisms of developmental toxicity across different doses, species and life stages. This understanding can provide guidance for life-stage specific targeted research to delineate pathways of exposure and mechanisms in both the fetus and infant.	FY16	3, 6, 7
	(3) An integrated strategy for life-stage specific risk assessment: The outcomes of the research will lead to improved understanding of the molecular pathways and cellular processes underlying adverse pregnancy outcomes and better ways to assess the impacts of prenatal and postnatal exposure to chemicals at various stages of development and scales of biological organization.	FY16	7, 8
2.2.3	(1) Develop computer programs to predict the effects of chemicals on hormone activity in the body.	FY16	3, 6, 7
	(2) Develop methods to use information about chemicals from cell and tissue studies to inform the effects of chemicals on hormone activity in the body.	FY16	3, 6, 7
2.3.1	(1) Consumer product use, emissions and other data for informing multi-tier exposure and dose analyses.	FY15	1, 4

Task No.	Outputs	Output Year	Relevance to other CSS Themes
	(2) Physiological data and algorithms supporting the development of PBPK and other dose models.	FY15	1, 4
	(3) Inputs and methods needed to model fate/ transport, concentrations, exposures and dose to a variety of environmental chemicals.	FY15	1, 4
2.3.2	(1) Enhanced environmental models (e.g., IEMS, EFAST, PRZM/ EXAMS, ChemSTEER, WPEM, IAQX) that include the capacity for spatial and/or temporal resolution (inputs/algorithms).	FY16	1, 3, 4, 6
	(2) Refined SHEDS & new SHEDS-Lite models	FY16	1, 3, 4, 6
	(3) PK & PBPK models and toolboxes for environmental chemicals	FY16	1, 3, 4, 6
	(4) Applications of linked source-to-dose models to address Program Office and Regional priorities for environmental chemicals	FY16	1, 3, 4, 6
2.4.1	(1) Integrated systems' approaches linking exposure and outcome	FY16	2, 6
	(2) Integrated systems approaches for predicting individual, population, and ecosystem risk from complex patterns of chemical exposure.	FY16	2, 6
2.5.1	(1) Data sets derived from high-throughput screening of chemicals on Program Office inventories to support the development of signatures, or patterns of activity, for adverse outcome endpoints of relevance to Partners. The outcomes (endpoints) of concern include cancer, developmental neuro-, and developmental immuno-, developmental, reproductive, and systemic toxicity.	FY16	2
	(2) Additional screening of regulatory chemical inventories (TSCA21, OW21, EDSP21, and OPP21) will be conducted to provide data sets for prioritization of chemicals on these lists using molecular signatures (i.e.,, patterns of response)	FY16	2
2.5.2	(1) Prioritization of regulatory chemical inventories (TSCA21, OW21, EDSP21, and OPP21) based on *in vitro* molecular signatures (patterns of response) for endpoints of cancer, developmental toxicity, reproductive toxicity.	FY13	2
	(2) Prioritization of regulatory chemical inventories (TSCA21, OW21, EDSP21, and OPP21) based on *in vitro* molecular signatures (patterns of response) endpoints for systemic toxicity, developmental neurotoxicity and immunotoxicity.	FY16	2

Task No.	Outputs	Output Year	Relevance to other CSS Themes
2.5.3	(1) Completion of TSCA21 workplan for 500 chemicals: Rapid prioritization of chemicals for further safety evaluation based on potential for both harm and exposure. Non-animal-based (*in vitro*) tests are used to identify the degree to which a substance can damage living organisms (hazard) and to determine pharmacokinetics (how the chemicals accumulate within the body), and computer simulations (based on chemical structure -- inherency -- and mathematical models) are used to derive potential for human contact (exposure). The TSCA21 workplan for 500 chemicals will combine high-throughput hazard data, pharmacokinetic data, and exposure simulations to determine chemical prioritization based upon potential risk.	FY16	1, 2, 4, 7
	(2)Completion of EDS21P workplan for 2000 chemicals: Rapid prioritization of chemicals for further safety evaluation based on potential for both harm and exposure. Non-animal-based (*in vitro*) tests are used to identify the degree to which a substance can damage living organisms (hazard) and to determine pharmacokinetics (how the chemicals accumulate within the body), and computer simulations (based on chemical structure -- inherency -- and mathematical models) are used to derive potential for human contact (exposure. The EDSP21 workplan for prioritization of 2000 chemicals will include both potential hazard identification and chemical-structure-derived exposure potential simulation without pharmacokinetic considerations.	FY16	1, 2, 4, 7
2.6.1	(1) Nanomaterials Life Cycle based effects.	FY16	1, 4, 5, 6
	(2) Credible translatable alternative test methods, guidelines, and endpoints that predict NM *in vivo* toxicity with high confidence.	FY16	1, 3, 8
	(3) Mechanisms of injury, mode of action and AOP for HTP and HCS methods development.	FY16	1, 3, 8
	(4) Nano-QSARs and inform green nano chemistry/applications.	FY16	1, 5
	(5) Best current *in vitro* and *in vivo* methods for tier testing of NMs provided to Offices.	FY16	1, 3, 8
	6) AOPs identifying common and sensitive biological receptors predictive of adverse human and ecological outcomes.	FY16	1, 3, 5, 6, 8
2.6.2	(1) Approaches for standardized testing of nanomaterials .	FY12	1
	(2) Quantify acute toxicity of selected nanomaterials.	FY13	1
	(3) Understanding of inherent properties of modifications that mediate specific nanomaterial toxicity or other effects.	FY15	1
	(4) Identify mechanisms of action for nanomaterials, AOPs, and recommendations for development of alternative and rapid throughput assays.	FY15	1
	(5) Recommendations for the development of models linking inherent properties and adverse outcomes (e.g., QSARs for nanomaterials).	FY16	1

Theme 3. Biomarkers

Science Questions: How can CSS assess biomarkers that can serve as useful indicators of toxicity for different chemicals and endpoints such as health or wildlife outcomes?

What are the endpoints of concern that require development of biomarkers?

What characteristics are needed for a biomarker to be one that is informative of adverse outcomes to humans?
How can the program assess biomarkers of exposure?

What models need to be developed to better integrate biomonitoring (biomarkers and bioindicators) data into testing systems to help the Agency better understand environmental and health impacts?

Outcome: EPA risk assessments are improved by the (1) consistent, justifiable, and improved use of existing biomonitoring data (e.g., NHANES); (2) availability of dose estimation/exposure reconstruction methods; and (3) availability of diagnostic AOP-based biomarkers with annotations to evaluate published data.

Task No.	Outputs	Output Year	Relevance to other CSS Themes
3.1.1	(1) Holistic approaches to foster a better understanding of relationship between exposure metrics and biomarkers, allowing for potential to reconstruct exposures from biomarkers.	FY16	2
	(2) Improved methodologies for exposure and dose estimates by integrating biomarker data with supporting information/data (e.g., exposure factors and pharmacokinetic behaviors) into predictive models.	FY16	2
3.1.2	(1) Develop and maintain a state of the art panel of biomarkers of effects for use by risk assessors and researchers.	FY16	2, 7
	(2) Link biomarkers to key events in an adverse outcome pathway and thereby improve the diagnostic capabilities of the biomarkers in the panel.	FY16	2, 7
3.2.1	(1) Biomarker-based models for risk assessment.	FY16	
	(2) Biomarker-based model tools to evaluate risk management activities.	FY16	

Theme 4. Cumulative Risk

Science Questions: What are the ecological and human health risks of combined real-world exposures to environmental chemicals?

What are the chemical targets at the molecular, cellular, tissue, organ, and whole animal levels?, and can these targets be used to assess cumulative effects?

How can recent scientific advances help describe the impacts of exposures to chemical mixtures?

How can recent scientific advances help describe human variability (e.g., across life stages, population groups)?

What kinds of tools, including computational, systems-based tools, are required to fully describe the overall impact of aggregate exposures on organisms?

What enhancements will be required to describe the impact of factors that affect an organism's response to chemical exposure, such as life stage, gender and aggregate exposures?

What new methods/models are needed to account for exposure from all sources and pathways?

Outcome: A set of predictive models from the cellular level to the population level that can be integrated into a source-to-outcome modeling platform that incorporates real world exposure scenarios.

Task No.	Outputs	Output Year	Relevance to other CSS Themes
4.1.1	(1) Predictive tools for identifying and prioritizing real-world mixtures of stressors (environmental, residential, SES, diet, etc.) based on: Sources (including commercial and consumer products); Surrogate exposure and hazard indices; and Toxicity of chemical mixtures.	FY15	2, 3, 4
	(2) Examination and optimization of prototypical AHHS and CCS survey study designs to document real-world mixtures spatially and temporally.	FY15	2, 3, 4
4.1.2	1) Methods to predict the effect of chemical mixtures based on outcome pathways.	FY15	2
	(2) Methods to select chemical mixtures for testing based on likelihood of toxicity.	FY16	2
4.1.3	(1) Evaluation of selected compounds in municipal solid waste landfills.	FY16	
	(2) A reduced list of "indicator chemicals" for routine monitoring of emerging contaminants in wastewater and receiving waters in support of regulatory policy for limits of discharge.	FY16	2
	(3) Final data on the fate and transport of emerging chemicals of interest following land application of biosolids.	FY16	

Task No.	Outputs	Output Year	Relevance to other CSS Themes
	(4) Weight of evidence approach using "indicator chemicals" and selected MOA based bioassays to assess the efficacy of risk management of emerging contaminants in wastewater and receiving waters.	FY16	2
	(5) Evaluation of selected compounds in municipal solid waste compost.	FY16	
	(6) Data on the fate and transport of emerging chemicals of interest following land application of biosolids for mixtures identified in CSS cumulative risk research.	FY16	
4.2.1	Science from the InterAgency Agricultural Health Study (AHS) for use by EPA	FY16	
4.2.2	(1) Data, science and methods to support Agency decisions on perfluorochemicals (PFCs).	FY17	
	(2) Data, methods, and science to inform PCB exposure and mitigate risk to children to support EPA regional decisions.	FY13	
	(3) Data, science, and tools to support OPPT's rulemaking for formaldehyde.	FY17	
	(4) Data, methods, and models for understanding exposure and effects from indoor source emissions for Spray Polyurethane Foam (SPF)-based products.	FY16	
	(5) Data, case studies, and guidance to support EPA next generation assessments for the IRIS, PPRTV and ISA programs.	FY15	
	(6) Social science research on the consumer behavior patterns and trends and how these influence consumer product use and resulting chemical exposure.	FY17	

Theme 5. Life Cycle Considerations

Science Questions: How can life-cycle assessments and other innovative tools be integrated with more traditional methods to produce assessments that inform decision making and identify safer and more sustainable approaches?

How can life cycle assessment approaches and methods be applied to decision analysis to reduce uncertainties associated with the analysis of alternatives at multiple decision-making scales or levels?

What are the critical components of a sustainability-driven paradigm for risk management of chemical and product systems that incorporate life cycle factors relevant to environmental, economic, and societal issues?

How can effective and reliable screening-level approaches for life-cycle assessment be developed that can be efficiently and strategically applied to the large number of chemicals?

Outcome: The 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.

Task No.	Outputs	Output Year	Relevance to other CSS Themes
5.1.1	A database of information about the life cycle of a chemical that will aid in incorporating sustainability in environmental decision making.	FY16	7, 8
5.1.2	A framework to help include sustainability in decision making within the EPA using experiences from case studies with Program Offices and Regions.	FY16	1, 7, 8
5.2.1	Reaction systems, membrane materials, and separation processes will be developed using the principles of green chemistry to address sustainability in chemical processes.	FY16	1, 2, 4, 7
5.2.2	Solutions will be provided and demonstrated for the sustainable design, production and use of chemicals using the principles of green engineering to reduce the utilization of energy intensive chemical processes.	FY14	4, 7
5.2.3	Innovative approaches to manufacturing of chemicals will be developed using sustainable molecular design, life cycle material safety and chemical process indicators.	FY16	1, 2, 4, 7
5.2.4	The development and demonstration of life cycle methods for sustainable design practices for the manufacture, use and evaluation of commercial products.	FY16	7

Theme 6. Extrapolation

Science Questions: What enhancements will be required to describe the impact of factors that affect an organism's response to chemical exposure, such as life stage, gender, and aggregate exposures?

How can recent scientific advances help describe human variability, life stages, and population groups?

With the emphasis on developing *in vitro* assays for toxicity testing, how can we extrapolate from *in vitro* assay response to *in vivo* response?

Outcome: An improved understanding of the utility of adverse outcome pathway models that provide increase confidence in the extrapolation of exposure and effects across different levels of biological organization, doses, genders, life stages, species and populations.

Task No.	Outputs	Output Year	Relevance to other CSS Themes
6.1.1	Chemical class-based expert systems: Automated rule-based decision trees are being developed to predict which chemicals have the potential to disrupt endocrine systems. This is done by testing key chemicals within a chemical class to represent others, determining what is similar about the chemical structures and properties that explain their biological activity, and writing rules that help categorize similar but untested chemicals. The Program Offices use these tools to decide which, of the hundreds of chemicals on Agency chemical lists, should be evaluated first because they are most likely to disrupt one of these endocrine-mediated pathways.	FY16	1, 2, 7
6.1.2	Methods and models to apply *in vitro* and *in silico* derived data to individuals.	FY15	2
6.1.3	Predicting chemical impacts using computational models and small-scale experiments: Validated methods and models for interpretation and extrapolation of data generated by *in vitro* and small-scale *in vivo* systems designed to test interactions of chemicals with biological pathways or targets.	FY16	1, 2, 4, 5
6.2.1	(1) Refined tools that exist for estimating species sensitivity to pesticides and other contaminants: Expansion to add algal toxicity data. (2) Refined tools that exist for estimating species sensitivity to pesticides and other contaminants: Expansion to add mode of action information. (3) Refined tools that exist for estimating species sensitivity to pesticides and other contaminants: Guidance to standardize methods.	FY14	2
6.2.2	Population models that incorporate sub-groups of fish or aquatic invertebrates separated by life stage, age or time.	FY15	2

Task No.	Outputs	Output Year	Relevance to other CSS Themes
6.2.3	Methods and models for translating toxicity test endpoints into quantitative estimates of changes in demographic rates, such as fecundity and juvenile survival rates, for use in population-level risk assessment.	FY16	2

Theme 7. Dashboards

Science Questions: What kind of tools, including computational, systems-based tools, are required to fully describe the overall impact of exposure on organisms?

How can tools be customized to supply the data and information needed by partners to address specific regulatory and environmental questions?

How can inherency, exposure, hazard, and risk management options be integrated to supply a greater degree of certainty in decisions, reduced risk and enhanced sustainability?

Outcome: Communicate, translate, and transfer all available scientific information about chemicals in ways most useful to decision makers.

Task No.	Outputs	Output Year	Relevance to other CSS Themes
7.1.1	Process developed used to gather scientific information that EPA risk assessors need to make environmental decisions. This will help us build useful decision support tools for Partners.	FY14	
7.1.2	We will support existing ORD databases and tools used by decision makers: Maintenance, data input, and upgrade of support tools.	FY16	
7.1.3	Prototype dashboard (decision support tools) for OPP to support ecological risk assessment is delivered. This dashboard will expand and update current OPP decision support tools.	FY15	
7.1.4	(1) Initial prototype dashboards delivered to Program Offices: Prototype versions of web-based dashboards for evaluating screening, testing, exposure and sustainability information relevant to EDSP21 (potential endocrine disruption), OPP21 (pesticidal actives, inerts and antimicrobials), TSCA21 (prioritizing and assessing new and existing chemicals), OW21 (prioritization of chemicals for the PCCL/CCL and other purposes), HHRA21 (PPRTV and NexGen risk assessments). (2) Initial prototype dashboards delivered to Program Offices: Regular updates (6-month cycles) of all EPA program office web-based dashboards, taking into account user feedback and new scientific developments.	FY16	
7.2.1	(1) Dashboards for environmental decision-making: Identification of databases decision-makers use the most. (2) Dashboards for environmental decision-making: Different databases will be combined to provide this information in dashboards using web-services (i.e.,, computer programs web sites use to send information to web-browsers).	FY16	1, 2, 3, 4, 5, 6, 8

Task No.	Outputs	Output Year	Relevance to other CSS Themes
7.2.2	Dashboards for environmental decision-making: Computer programs developed that translate and combine information from different databases using ontologies (i.e.,, dictionaries that computer programs use to organize and link databases).	FY16	1, 2, 3, 4, 5, 6, 8
7.2.3	Dashboards for environmental decision-making: Software developed to build dashboards for web browsers, and to get information from databases using web-services. Free tools will be used that we can easily reuse and maintain.	FY16	1, 2, 3, 4, 5, 6, 8
7.2.4	(1) Dashboards for environmental decision-making: Identify computer models decision-makers use to forecast how chemicals spread in the environment and affect living things. (2) Dashboards for environmental decision-making: Develop software that makes it easy to use these computer models from web-based dashboards.	FY16	1, 2, 3, 4, 5, 6, 8

Theme 8. Evaluation

Science Questions: How have CSS research findings and tools impacted and supported EPA's decision making?

What are the measures needed to evaluate the predictive value of the tools (e.g., Dashboards, enhanced *ToxCast*™) produced from the CSS Research Program?

Do the partners find that the tools and other data from the CSS Research Program will improve environmental decision making, including risk assessment?

How can the critical pieces of information required for different assessment tiers be systematically identified, evaluated, integrated, reviewed, and used in assessments and subsequent management decisions?

Outcome: The overall impact of the CSS Research is assessed. CSS tools and information are delivered to the partners along with training in order that the partners have an ability to efficiently apply the information. The CSS tools, new assays, and scientific knowledge have increased our confidence in utilizing 21st century pathway-based approaches for priority setting, toxicity testing, and risk assessment.

Task No.	Outputs	Output Year	Relevance to other CSS Themes
8.1.1	1) Understanding of partner needs and how to measure product utility; information obtained through pro forma surveys and interviews.	FY12	7
	2) Overall program performance and success assessment of CSS research based on understanding of how the partners will benefit from CSS research products.	FY16	
8.1.2	Overall program performance and success assessment of CSS research based on understanding of how the partners will benefit from CSS research products.	FY16	
8.2.1	(1) CSS product utility improved through regular communication with partners, and employment of partner-informed utility metrics.	FY16	5, 7
	(2) Identification of best practices for future projects and potential future impacts of CSS Program products.	FY16	7
8.2.2	Identification of best practices for future projects and potential future impacts of CSS Program products.	FY16	7
8.2.3	Identification of best practices for future projects and potential future impacts of CSS Program products.	FY16	7

References

Council on Environmental Quality, 1969. National Environmental Policy Act. Available at: http://ceq.hss.doe.gov/nepa/regs/nepa/nepaeqia.htm.

Executive Office of the President, 9 June 2011. Policy principles for the U.S. decision-making concerning regulation and oversight of applications of nanotechnology and nanomaterials. Memorandum for the Heads of Executive Departments and Agencies. Available at: www.whitehouse.gov/

General Accounting Office (GAO), 2009. Biomonitoring: EPA Needs to Coordinate Its Research Strategy and Clarify Its Authority to Obtain Biomonitoring Data (Report 09 353). Available at: http://www.gao.gov/new.items/d09353.pdf.

Judson R., Richard A., Dix D.,Houck K., Martin M., Kavlock R., Dellarco V., Henry T.,Holderman T., Sayre P., Tan S., Carpenter T., and Smith E., 2009. *The Toxicity Data Landscape for Environmental Chemicals*. Environmental Health Perspectives 17(5): 685-695.

National Nanotechnology Initiative (NNI), 2011. NNI Environmental Health and Safety Research Strategy. http://www.nano.gov/node/681 .

National Research Council (NRC), 2006. Human Biomonitoring for Enivronmental Chemicals. Available at: http://www.nap.edu/catalog/11700.html.

National Research Council (NRC), 2007. *Toxicity Testing in the Twenty-first Century: A Vision and a Strategy.* http://dels.nas.edu/dels/rpt_briefs/Toxicity_Testing_final.pdfNRC. 2009. Science and Decisions: Advancing Risk Assessment. Available at: http://dels.nas.edu/Report/Science_Decisions-Advancing-Risk.Assessment/12209

National Research Council (NRC), 2009. *Science and Decisions: Advancing Risk Assessment*. Washington, DC: The National Academies Press.

National Research Council (NRC), 2012. *A Research Strategy for Environmental, Health, and Safety Aspects of Engineered Nanomaterials* . Washington, DC: The National Academies Press. Available at: http://www.nap.edu/catalog.php?record_id=13347

Organisation for Economic Co-operation and Development (OECD), 2001. Environmental Strategy for the First Decade of the 21st Century. Adopted by OECD Environment Ministers. 16 May 2001. Available at: http://www.oecd.org/dataoecd/33/40/1863539.pdf.

U.S. EPA, 2003a. A Framework for a Computational Toxicology Research Program in ORD.

EPA/600/R-03/065. US Environmental Protection Agency, Ofce of Research and Development, Washington, DC. Available at::://www.epa.gov/ncct/download_files/basic_information/comptoxframework06_02_04.pdf

U.S. EPA, 2003b. Framework for Cumulative Risk Assessment. *EPA*/630/P-02/001F. Risk Assessment Forum. U.S. *Environmental Protection Agency*. Washington, DC. Available at: oaspub.epa.gov/eims/eimscomm.getfile?p_download_id=36939

U.S . EPA, 2009. *The U.S. Environmental Protection Agency's Strategic Plan for Evaluating the Toxicity of Chemicals,* EPA/100/K-09/00. Available at: http://www.epa.gov/spc/toxicitytesting/docs/toxtest_strategy_032309.pdf

U.S. EPA, 2011a. *Framework for an EPA Chemical Safety for Sustainability Research Program.* Available at: http://www.epa.gov/ord/priorities/docs/CSSFrameworkMarch2011WorkingDocument.pdf

U.S. EPA, 2011b. Endocrine Disruptor Screening Program for the 21st Century: (EDSP21 Work Plan) The Incorporation of *In Silico* Models and *In vitro* High Throughput Assays in the Endocrine Disruptor Screening Program (EDSP) for Prioritization and Screening Summary Overview A Part of the EDSP Comprehensive Management Plan. Office of Chemical Safety and Pollution Prevention, US Environmental Protection Agency, Washington, DC. Available at: http://www.epa.gov/endo/pubs/edsp21_work_plan_summary%20_overview_final.pdf

Websites:

EPA's Computational Toxicology Research: http://www.epa.gov/ncct/

EDSP: EPA's Endocrine Disruptor Screening Program; http://www.epa.gov/endo/index.htm

EPA's Green Chemistry: www.epa.gov/greenchemistry/

NEPA: National Environmental Policy Act; http://ceq.hss.doe.gov/nepa/regs/nepa/nepaeqia.htm

NNI: National Nanotechnology Initiative; www.nano.gov

REACH: The European Community Regulation for the Registration, Evaluation, Authorisation and Restriction of Chemical substances; http://ec.europa.eu/environment/chemicals/reach/reach_intro.htm

TSCA Chemical Substance Inventory: http://www.epa.gov/oppt/existingchemicals/pubs/tscainventory/basic.html#background

Appendix A. Research Program Partners and Stakeholders

EPA Program and Regional Partners in the CSS Program:

- Innovation Team (ORD)
- National Center for Environmental Assessment (ORD)
- National Center for Environmental Economics (OPEI)
- Office of Air and Radiation (OAR)
- Office of Chemical Safety and Pollution Prevention (OCSPP)
- Office of Children's Health Protection (OCHP)
- Office of Environmental Information (OEI)
- Office of the Science Advisor (OSA)
- Office of Solid Waste Emergency Response (OSWER)
- Office of Water (OW)
- Regions 2, 5, 6, 8, and 9

External Stakeholders:

- Idealscale invites to +1000 Organizations
- Webinars to Stakeholders
  - Participants included:
    - ACC
    - CropLife
    - EDF
    - HSUS
    - NRDC

U.S. Federal and State Government Agencies, and Committees:

- ATSDR/CDC
- California Air Resources Board (ARB)
- CPSC
- Extramural Nano Consortium
- National Toxicology Program, NIEHS
- NCI
- NIEHS/NTP
- NIHCGC
- NIH, NCI, National Nano-Characterization Center
- NIOSH
- NIST
- NNI
- Oak Ridge National Laboratory Center for Nanophase Materials Sciences (CNMS
- State of Illinois
- US Army Corps of Engineers
- USDA
- U.S. FDA
- USFWS
- USGS

International and Foreign Agencies and Organizations:

- CAAT-Europe
- Department of Environment, Food and Rural Affairs (DEFRA), UK
- Environment Canada
- European Chemical Agency (ECA)
- European Commission Joint Research Centre
- Finnish Centre for Alternative Methods (FICAM)
- Institute for Health and Consumer Protection (JRC)
- International Standardization Organization (ISO)
- Korea National Institute of Environmental Research (NIER)
- National Institute for Environmental Sciences (Japan)
- Netherlands Organisation for Applied Scientific Research (TNO)
- OECD

Nongovernmental Organizations and Corporations:

- 4 Rivers
- Agilent Technologies
- American Center for Life Cycle Assessment
- Astellas Pharma Inc.
- BASF

- Biomathematics Consulting
- ChemScreen
- Cytek
- DOW Chemical Co.
- DuPont
- Dupont Haskell Labs
- Emery Oleochemical
- GlaxoSmithKline
- Global Electric Electronics Processing (GEEP) Inc.
- Hoffman-LaRoche Inc
- ILSI/HESI
- Interface, Inc.
- L'OREAL
- Membrane Technology and Research (MTR)
- Merck
- NanoRelease program of ILSI
- Osmose
- Pfizer Inc.
- Polyone Corporation
- Product Carbon Footprint World Forum
- Sanofi Aventis
- Shimadzu
- Stemina Biomarker and Discovery
- Syngenta Crop Protection, Inc.
- ThalesNano
- The Hamner Institutes
- Toxicology Excellence for Risk Assessment (TERA)
- USEtox (www.usetox.org)
- Warner-Babcock
- World Resources Institute
- World Wildlife Fund
- Fraunhofer Institute of Toxicology and Experimental Medicine (ITEM)
- Indiana University
- Johns Hopkins University
- Kunming University of Science and Technology (China)
- Michigan State University
- Mississippi State University
- MIT
- Northern Arizona University
- Oregon Health and Sciences University
- Oregon State University
- Purdue University
- Rice University
- Texas A&M University
- UC Berkeley University of Pannonia (Hungary)
- UCLA
- University of Aarhus (Denmark)
- University of Arizona
- University of Bern (Switzerland)
- University of Cincinnati
- University of Georgia
- University of Houston
- University of Maryland
- University of Michigan
- University of North Carolina-Chapel Hill
- University of St. Thomas
- University of Texas-Austin
- University of Toronto at Scarborough
- Virginia Commonwealth University
- Virginia Tech
- Yale University

Universities (some funded via EPA's NCER STAR program):

- Arizona State University
- Baylor University
- Clemson University
- Colorado School of Mines
- Duke University
- Duke University Center for the Environmental Implications of Nano Technology (CEINT)

Appendix B. Definitions

Aggregate Exposure: Aggregate exposure and risk assessment involve the analysis of exposure to a single chemical by multiple pathways and routes of exposure (from 2001 EPA/OPP Document).

Adverse Outcome Pathway (AOP): The linkage of adverse effects to perturbations in specific toxicity pathways.

Biomarker or biological marker: A chemical or biological characteristic that is measured or evaluated as an indicator of a biological process and used as a marker of exposure or effect.

Chemicals: Intentionally produced or manufactured chemicals, particle, and material, as well as a product into which they are incorporated. It may refer to single chemicals, particles, or materials, or mixtures of chemicals, particles, and/or materials, products, as well as forms of chemicals that are transformed as they move through the environment.

Computational Toxicology: The application of mathematical and computer models and molecular biological approaches to predict chemical hazards and risks to human health and the environment.

Cumulative Risk: The combined risks from aggregate exposures to multiple agents or stressors (EPA, 2003b).

Cumulative Risk Assessment: An analysis, characterization, and possible quantification of the combined risks to health or the environment from multiple agents or stressors (EPA, 2003b).

Dashboard: An interactive web site that provides access to tools and data that are required to carry out a specific analysis or decision-related task.

Endocrine Disrupting Chemical (EDC): An exogenous agent that interferes with the activity (via effects at the level of synthesis, secretion, transport, binding, action, or elimination) of hormones in the body which are responsible for the maintenance or homeostasis, reproduction, development and or behavior.

Extrapolation: Estimate of the value of a variable outside a known range calculated using a model or an equation based on values within a known range.

High-Throughput System (HTS): *in vitro* biochemical or cellular assays that can be run quickly and efficiently (i.e.,, high-throughput) on a large number of compounds to determine their activity on biological targets.

Inherency: The physical, chemical, and biological properties of a chemical, chemical formulation, or product that influence exposure, effects and sustainability.

Inherent Chemical Properties (ICP): Inherent physical and chemical properties.

Life Cycle: The “cradle to grave” (also referred to as “cradle to cradle”) activities for a product, process, or activity including the stages of resource acquisition, material manufacture, production, transportation/ distribution, use, recycling/reuse, and final disposal.

Life Cycle Assessment (LCA): A holistic way to consider multiple environmental and human health issues associated with a product or a process from resource acquisition through manufacture, transportation, distribution, and use, to waste management and disposal. Applied to chemical design and manufacturing, the results of an LCA along with understanding potential social and economic implications of a product or process system provide the basis for moving toward sustainability.

Life Cycle Inventory (LCI): A database of individual life cycle accounting of the energy and material flows into and out of the environment that are associated with producing a material, component, or assembly.

Nanomaterial: A nanoscale material or material that contains nanoscale structures internally or on their surfaces. These can include engineered nano-objects, such as nanoparticles, nanotubes, and nanoplates, and naturally occurring nanoparticles, such as volcanic ash, sea spray, and smoke (from the National Nanotechnology Initiative; www.nano.gov).

Nanoscale: The dimensional range of approximately 1 to 100 nanometers (nm) (1 nm is equivalent to one billionth or 10^{-9} of a meter; from the National Nanotechnology Initiative; www.nano.gov).

Nanotechnology: Nanotechnology is the understanding and control of matter at the nanoscale, at dimensions between approximately 1 and 100 nanometers, where unique phenomena enable novel applications (from the National Nanotechnology Initiative; www.nano.gov).

Outcome: The expected results, impacts, or consequence that a Partner or Stakeholder will be able to accomplish due to ORD research.

Output: Synthesized and/or translated from Products into the format needed by the End User. Outputs should be defined, to the extent possible, by Partners/Stakeholders during Problem Formulation.

Physico-chemical properties: Measurable characteristics of chemical substances relating to physical (e.g., boiling point, mass, conductivity) and chemical properties (e.g., reactivity, heat of combustion, water solubility), also encompassing computable properties based on molecular structures.

Product: A deliverable that results from a specific Research Project or Research Task. This may include (not an exhaustive list) journal articles, reports, databases, test results, methods, models, publications, technical support, workshops, best practices, patents, etc. These may require translation or synthesis for inclusion as an Output.

Rare earth elements (REE): Comprised of scandium, yttrium, and 15 lanthanide elements, of which, cerium, lanthanum, and neodymium are the most abundant. They are found in several minerals; almost all production comes from less than 10 minerals, primarily monazite and bastnasite.

Stochastic Human Exposure and Dose Simulation (SHEDS): A flexible and broadly applicable probabilistic model to estimate exposure and dose.

Sustainability: To create and maintain conditions, under which humans and nature can exist in productive harmony, that permit fulfilling the social, economic, and other requirements of present and future generations (Council on Environmental Quality, 1969).

Sustainable molecular design: Using established principles of chemistry and engineering to build chemicals with the end goal of removing the inherent health and environmental risks of the chemical.

Systems Model: Multiple level or scale models that predict or simulate exposure or effects of complex biological or environmental systems.

***ToxCast*™**: A cost-effective approach, for rapidly prioritizing *in vivo* toxicity testing of large numbers of chemicals developed by the EPA's Office of Research and Development, that integrates data from state-of-the-art high-throughput system bioassays to build computational models to forecast the potential human toxicity of chemicals.

Toxicity Pathways: Cellular and molecular processes and functions that can be perturbed by chemical exposure leading to abnormal biological function.

Workbench: A complex dashboard that allows customization of the set of tools and the workflow for using them.