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United States
Environmental Protection
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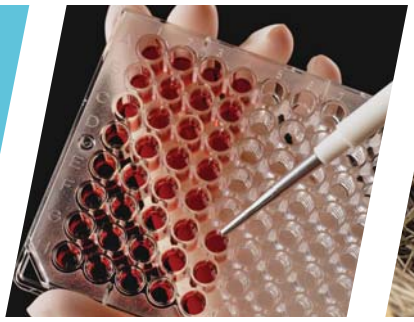
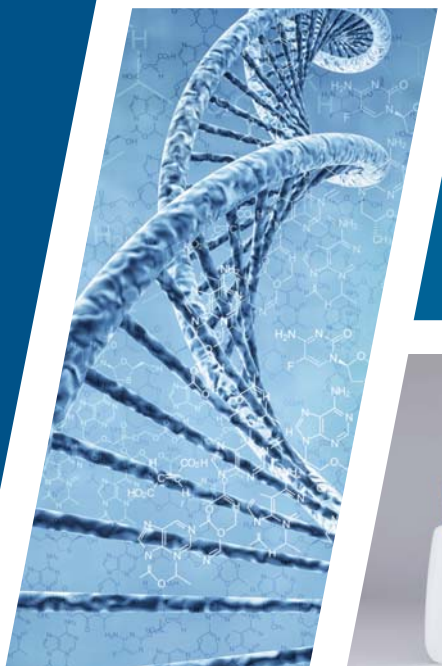


Chemical Safety for Sustainability

STRATEGIC RESEARCH ACTION PLAN 2016-2019



Office of Research and Development
Chemical Safety for Sustainability

EPA 601/K-15/003

Chemical Safety for Sustainability

Strategic Research Action Plan 2016 - 2019

U.S. Environmental Protection Agency
September 2015

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List of Acronyms

ACE	Air, Climate and Energy
ADME	absorption, distribution, metabolism, and excretion
AOPs	Adverse outcome pathways
AOPDD	AOP discovery and development
AOP-KB	AOP Knowledge Base
AOP-Wiki	Adverse Outcome Pathway Wiki
CAA	Clean Air Act
CCL	Contaminant Candidate List
CEH	Children's Environmental Health
CERCLA	Comprehensive Environmental Response, Compensation and Liability Act
CMP3	Chemical Management Plan 3
CPCat	Chemical/Product Categories Database
CPSC	Consumer Product Safety Commission
CSPA	Children's Safe Product Act
CSS	Chemical Safety for Sustainability Research Program
CSS StRAP	Chemical Safety for Sustainability Strategic Research Action Plan
CTS	Chemical Transformation Simulator
CWA	Clean Water Act
DoD	Department of Defense
DTSC	Department of Toxic Substances Control, California
ECHA	European Chemicals Agency
EDSP	Endocrine Disruptor Screening Program
EDSP21	Endocrine Disruptor Screening Program for the 21st Century
ENMs	Engineered nanomaterials
EPA	Environmental Protection Agency
ERA	Ecological Risk Assessment
ESA	Endangered Species Act
FDA	Food and Drug Administration
FFDCA	Federal Food, Drug and Cosmetic Act
FIFRA	Federal Insecticide, Fungicide, and Rodenticide Act
FQPA	Food Quality Protection Act

FWS	(United States) Fish and Wildlife Service
FY	Fiscal Year
HHRA	Human Health Risk Assessment
HSRP	Homeland Security Research Program
HTPK	High-throughput pharmacokinetic
HTS	High-throughput screening
HTT	High-throughput toxicology
LCA	Life-cycle assessment
MCC	Methodologically challenging compounds
MCnest	Markov Chain Nest Productivity Model
NAS	National Academy of Sciences
NCCLCs	Networks for Characterizing Chemical Life Cycle
NEHI	Nanotechnology Environmental Health Implications working group
NIH	National Institute of Health
NIOSH	National Institute for Occupational Safety and Health
NMFS	National Marine Fisheries Service
NNI	National Nanotechnology Initiative
NPD	National Program Director (for one of EPA's research programs)
NSF	National Science Foundation
NSMDS	Networks for Sustainable Molecular Design and Synthesis
OCMs	Organotypic Cell Models
OCSPP	Office of Chemical Safety and Pollution Prevention
OECD	Organization for Economic Cooperation and Development
ORD	Office of Research and Development
OSWER	Office of Solid Waste and Emergency Response
OW	Office of Water
PCRs	Product Category Rules
PIP	Pathfinder Innovation Projects
POD	Points of departure
QSAR	Quantitative Structure Activity Relationship
RCRA	Resources Conservation and Recovery Act
SAR	Structure-Activity Relationships
SDWA	Safe Drinking Water Act

SHC	Sustainable and Healthy Communities
SSWR	Safe and Sustainable Water Resources
STAR	Science to Achieve Results
TIM	Terrestrial Investigation Model
TPO	Thyroperoxidase
TSCA	Toxic Substances Control Act
USDA	United States Department of Agriculture
VISION 20/20	Vision for 2020
VTMs	Virtual tissue models
WebICE	Web-based Interspecies Correlation Estimation

Executive Summary

Chemicals are integral to the American economy and provide key building blocks for the many products that benefit society. Sustainable innovation and use of chemicals call for making decisions and taking actions that improve the health of individuals and communities today without compromising the health and welfare of future generations. Smart new strategies for designing, producing, and using safer chemicals to minimize risks and prevent pollution is a priority for the U.S. Environmental Protection Agency (EPA).

The challenges to meeting this mandate are formidable: Tens of thousands of chemicals are currently in use and hundreds more are introduced into the market every year. Many of these chemicals have not been thoroughly evaluated for potential risks to human health, wildlife and the environment, particularly when considering the consequences of use over a chemical's life cycle (from production to disposal). Current toxicity testing methods for evaluating risks from exposures to individual chemicals are expensive and time consuming. Approaches for characterizing impacts across the chemical/product life cycle are data and resource-intensive.

Characterizing real-world exposures and early indicators of adversity in a way that allows proactive decisions to minimize impacts of existing chemicals as well as to anticipate impacts of emerging materials requires holistic systems understanding. Potential health effects from chemicals are associated with disruption to complex biological processes. For example, evidence is mounting that some chemicals disrupt the endocrine system. Some of these effects relate to chronic exposures to low levels of multiple chemicals. Prenatal and early-life exposures are of particular concern and may lead to health impacts across the lifespan. As a result, there is a need to shift the thinking about how potential for adverse impacts and ultimately risks are evaluated.

Today, EPA and its stakeholders are making decisions on chemical selection, design, and use at the national, regional, and local levels. States, communities, and consumers are demanding robust information on chemicals in products and are driving large retailers and industry to make changes. Tools for evaluating chemical substitutions and product alternatives are evolving to meet the demand for action. However, scientifically vetted approaches remain limited. New approaches are required to increase the pace at which relevant information can be obtained and integrated into decision making, and to ensure that decisions are scientifically supported and sustainable. Key metrics that can be collected as early indicators of changes to the chemical exposure landscape are needed to preempt or rapidly mitigate unanticipated impacts.

To address these challenges, EPA's Chemical Safety for Sustainability (CSS) Research Program is leading development of innovative science to support safe, sustainable selection, design, and use of chemicals and materials required to promote ecological well-being, including human and environmental health, as well as to protect vulnerable species, lifestages, and populations. The ultimate goal is to enable EPA to address impacts of existing chemicals, anticipate impacts of new chemicals and materials, and evaluate complex interactions of chemical and biological systems to support EPA decisions.

Working in conjunction with our partners in EPA regulatory programs and regional offices, we have identified priority needs for information and methods to make better informed, timelier decisions about chemicals. CSS science is strategically scoped within four integrated research topics to support EPA priorities:

1. **Chemical Evaluation:** Advance cutting-edge high-throughput methods in computational toxicology and provide data for risk-based evaluation of existing chemicals and emerging materials.

2. **Life Cycle Analytics:** Address critical gaps and weaknesses in accessible tools and metrics for quantifying risks to human and ecological health across the life cycle of manufactured chemicals, materials, and products. Advance methods to efficiently evaluate alternatives and support more sustainable chemical design and use.

3. **Complex Systems Science:** Adopt a systems-based approach to examine complex chemical-biological interactions and predict potential for adverse outcomes resulting from exposures to chemicals.

4. **Solutions-Based Translation and Knowledge Delivery:** Promote Web-based tools, data, and applications to support chemical safety evaluations and related decisions, respond to short-term high priority science needs for CSS partners, and allow for active and strategic engagement of the stakeholder community.

This *Strategic Research Action Plan for EPA's Chemical Safety for Sustainability Research Program* maps out a research program for the near-term with an eye toward meeting longer term needs to transform chemical evaluation. CSS scientific results and innovative tools will accelerate the pace of data-driven chemical evaluations, enable EPA decisions that are environmentally sound and public health protective, and support sustainable innovation of chemicals and emerging materials.

Introduction

Chemicals are a lynchpin of innovation in the American economy, and moving toward sustainable innovation requires designing, producing, and using chemicals in safer ways. Information and methods are needed to make better informed, timelier decisions about chemicals, many of which have not been thoroughly evaluated for potential risks to human health and the environment. EPA's Chemical Safety for Sustainability (CSS) research program is designed to meet this challenge and supports EPA priority of reducing risks associated with exposure to chemicals in commerce, the environment, products, and food.

To help guide the program to meet its ambitious objectives, EPA's Office of Research and Development (ORD), EPA's science arm, developed this *Chemical Safety for Sustainability Strategic Research Action Plan, 2016-2019* (CSS StRAP), which builds upon the original vision of the research program outlined in the *Chemical Safety for Sustainability Research Action Plan 2012-2016*. The current StRAP evolved through a series of meetings with program and regional partners, among ORD labs and centers involved with CSS, and through interactions with external stakeholders.

The CSS StRAP is one of six research plans, one for each of EPA's national research programs in ORD. The six research programs are:

- Air, Climate, and Energy (ACE)
- Chemical Safety for Sustainability (CSS)
- Homeland Security (HS)
- Human Health Risk Assessment (HHRA)
- Safe and Sustainable Water Resources (SSWR)
- Sustainable and Healthy Communities (SHC)

EPA's strategic research action plans lay the foundation for EPA's research staff and their partners to provide focused research efforts that meet EPA's legislative mandates, as well as the goals outlined in EPA's *Fiscal Year 2014 – 2018 EPA Strategic Plan*. They are designed to guide an ambitious research portfolio that at once delivers the science and engineering solutions EPA needs to meet such priorities, while also cultivating a new paradigm for efficient, innovative, and responsive environmental and human health research.

The StRAP outlines the approach designed to achieve EPA's objectives for advancing chemical safety and sustainability. It highlights how the CSS program integrates efforts with other research programs across ORD to provide a seamless and efficient overall research portfolio aligned around the central and unifying concept of sustainability.

No other research organization in the world matches the diversity and breadth represented by the collective scientific and engineering staff of ORD, their grantees, and other partners. They are called upon to conduct research to meet the most pressing environmental and related human health challenges facing the nation and the world.

Environmental Problems and Program Purpose

Sustainable innovation where chemicals are designed, produced, and used in safer ways to minimize risks and prevent pollution is a priority for EPA. The challenges to meeting this mandate are formidable; approximately 80,000 legacy chemicals are listed in EPA's Toxic Substances Chemical Act (TSCA) inventory; hundreds more are introduced into the market every year. Less than 2000 of these chemicals have health assessments available across federal and state agencies. This translates into only a small fraction that have been thoroughly evaluated for potential risks to human health, wildlife, and the environment, particularly when considering the consequences of use over a chemical's life cycle (from production to disposal). Current toxicity testing methods for evaluating risks from exposures to individual chemicals are expensive and time consuming. Approaches for characterizing impacts across the chemical/product life cycle are data and resource intensive. To address this critical need to evaluate potential for risks associated with thousands of chemicals in commerce, rapid and efficient methods are required to prioritize, screen, and evaluate chemical safety.

Characterizing real-world exposures and early indicators of adversity (or "tipping points") in a way that allows proactive decisions to minimize impacts of existing chemicals as well as to anticipate impacts of emerging materials requires holistic systems understanding. Potential health effects from chemicals are associated with disruption to complex biological processes in human and wildlife populations. For example, evidence is mounting that some chemicals disrupt the endocrine system. The endocrine system regulates biological processes throughout the body and is sensitive to small changes in hormone concentrations. In addition, more complex interactions and outcomes are not addressed well with existing models and assessment tools. Examples include outcomes resulting from chronic low dose exposures to multiple chemicals with similar modes of actions, or exposures to complex mixtures and/or chemicals with multiple modes of action. Prenatal and early-life exposures are of particular concern and additional complexity is associated with the fact that these exposures may lead to health impacts across the lifespan. As a result, there is a need to shift thinking about how potential for adverse impacts and ultimately risk is evaluated.

Today, EPA and its stakeholders are making decisions on chemical selection, design and use at national, regional, and local levels. States, communities, and consumers are demanding robust information on chemicals in products and are driving large retailers and industry to make changes. Tools for evaluating chemical substitutions and product alternatives are evolving to meet the demand for action. However, scientifically vetted approaches remain limited.

Innovations in chemical and material design are rapidly changing the landscape of industrial and consumer products while novel materials, such as engineered nanomaterials, are incorporated to enhance their performance. New approaches are required to increase the pace at which relevant information can be obtained and integrated into decision making, and to ensure that decisions are scientifically supported and sustainable. One goal of these approaches is to avoid regrettable substitutions, which occur when one chemical of concern is replaced by another chemical that later proves to have impacts of similar or greater magnitude. In

addition, key metrics that can be efficiently collected as early indicators of changes to the chemical exposure landscape are needed to preempt or rapidly mitigate unanticipated impacts. Always, the assessments, predictions, evaluations and decisions related to chemical innovation and sustainable use must consider the most vulnerable and sensitive species, lifestages, and communities.

To anticipate and predict impacts of manufacture and use of chemicals and materials that have not yet been developed presents a larger context for the CSS research program. As EPA and stakeholders seek sustainable solutions to complex and dynamic environmental problems, the demand for "validated" forecasts of uncertain future states increases. At the same time, resource constraints limit the capacity to monitor for the continuously changing set and combination of chemicals and materials in commerce. The CSS research program considers the grand challenge of how best to build and deploy modeling capacity in concert with efficient data collection and effective monitoring for robust and agile policy.

Clearly, information and methods are needed to make better-informed, timelier decisions about chemicals. Development of innovative science to support safe, sustainable use of chemicals and materials is required to promote ecological well-being, including human and environmental health, as well as to protect vulnerable species, lifestages, and populations. CSS is designed to meet this challenge and supports EPA priority of reducing risks associated with exposure to chemicals in commerce, the environment, products, and food. The ultimate goal is to enable EPA to address impacts of existing chemicals, anticipate impacts of new chemicals and materials, and evaluate complex interactions of chemical and biological systems to support decisions.

Through its signature research in computational toxicology, CSS draws from and integrates advances in several fields, including information technology, computational chemistry, and molecular biology, to address EPA's data requirements for science-based assessment of chemicals. EPA investments in advanced chemical evaluation and life cycle analytics are providing decision-support tools for high-throughput screening and efficient risk-based decisions.

Problem Statement

Tens of thousands of chemicals are currently in use and hundreds more are introduced into the market every year, many in new and emerging markets such as nanotechnology. Only a small fraction have been thoroughly evaluated for potential risks to human health, wildlife, and the environment. Multiple EPA programs and regional offices must make risk-based decisions for addressing chemicals with inadequate or non-existent hazard and exposure data. Current toxicity testing methods, which are expensive and time consuming, evaluate risks from exposures to individual chemicals. Approaches for characterizing impacts across the chemical/product life cycle are data and resource intensive.

Program Vision

The CSS research program will lead development of innovative science to support safe, sustainable design and use of chemicals and materials required to promote human and environmental health, as well as to protect vulnerable species, lifestages, and populations. CSS research program outputs will enable EPA to address impacts of existing chemicals and materials across the life cycle and to anticipate impacts of new chemicals and emerging materials. The CSS research program will also provide the scientific basis for evaluating complex interactions of chemical and biological systems to support EPA decisions.

Program Design

Building on the 2012-2016 Research Program

Since its inception, CSS research has endeavored to transform chemical evaluation through groundbreaking research, translation, and tools. A number of impactful products have begun to change the landscape of chemical evaluations at EPA. Some examples include:

- EPA's high-throughput toxicity research effort ToxCast uses automated chemical screening technologies to measure changes in biological activity that may suggest potential for hazardous effects. Coupled with related high-throughput exposure estimations from ExpoCast, this multi-year effort is generating and sharing an unprecedented volume of exposure and toxicology data and knowledge transparently through an interactive iCSS Dashboard.
- The Chemical / Product Categories Database (CPCat) compiles information on chemicals found in consumer products. This new publicly available database maps over 40,000 chemicals to a set of terms categorizing use or function for high level exposure evaluation.
- The Web-based Interspecies Correlation Estimation (WebICE) application estimates acute toxicity in aquatic and terrestrial organisms. The Markov Chain Nest Productivity Model (MCnest) quantitatively estimates the impact of pesticide-use scenarios on reproductive success of bird populations. Together these two tools are informing ecological risk assessments, in particular for endangered species.
- The Adverse Outcome Pathway Wiki (AOP-Wiki), created through a joint venture between the European Commission and EPA, is a web-enabled and publicly accessible repository that stimulates and captures new and existing crowd-sourced AOP knowledge from the global scientific community.
- Engaging in international efforts to harmonize green purchasing practices has resulted in application of EPA's life cycle assessment tools to provide clear, comparable information about the environmental impacts of different products evaluated internationally in the development of product category rules.
- To enhance the ability to evaluate environmental health and safety of nanomaterials, fate and transport models have been incorporated to characterize the surface properties of silver nanoparticles and how these properties affect their fate in containment systems. These models have also been used to develop higher throughput methods for characterizing nanoparticle transport through soils and sediments.

These products were derivatives of the original vision of the research program outlined in the CSS 2012-2016 StRAP. Fiscal year 2015 (FY15) planning presented a ripe opportunity to conduct a review of the program and look for ways to integrate the research, strengthen transdisciplinary collaboration, promote and foster innovation, enhance transparency and access to CSS products, and significantly amplify the impact of this important research. The most noteworthy impetus for this integration was the demand to drive the leading edge of science, be prepared to meet the urgent needs of EPA in a timely and responsive fashion, and

achieve this within a budgetary environment that is often unpredictable. CSS rose to this challenge by remodeling the architecture of its research program to be robust, sustainable, anticipatory, agile, transparent, and at all times, responsive.

In evolving the CSS program, we have significantly reformulated key program areas to focus research and design a cohesive and impactful program that meets high priority partner needs. The CSS 2012-2016 StRAP included eight research themes and 21 research projects. To provide further focus and amplify the impact of CSS research, these were integrated into four topics and nine transdisciplinary project areas. The first iteration of the new program was then piloted in FY15, and with input from ORD's lab and center leadership, project scientists, CSS program and regional partners, as well as the joint committee of the Science Advisory Board/ Board of Scientific Counselors (SAB/BoSC). It was refined to improve scientific coordination and the interactions that are foundational to a successful transdisciplinary program. The resulting CSS 2016-2019 StRAP provides the overall framework for CSS research that grew from this planning process.

In the CSS 2016-2019 StRAP, the Chemical Evaluation and Complex Systems Science topics have been designed to support development and integration of the science required to revolutionize capacity for efficient and effective chemical safety risk-based decisions. To this end, expertise in biomarkers, pharmacokinetics, extrapolation, and cumulative risk are embedded throughout to advance the science for evaluating data poor chemicals.

The Life Cycle Analytics topic is designed to provide the science and tools needed to evaluate safety of chemicals and materials (including engineered nanomaterials) in the broader context of how these are designed and used in our society. This is where we consider green chemical design, life cycle impacts, and sustainable use. Here, expertise and emerging science is directed to elucidate relationships between inherent chemical and material properties, function and associated impacts in biological systems. ORD capacity to model human and ecological exposures in combination with key expertise in life cycle impact analysis is being directed to efficiently evaluate alternatives and to fill a gap in available sustainability metrics.

In addition, all CSS research implemented based on this StRAP will: (1) have an increased focus on developmental health, vulnerable lifestages, and susceptible populations; and (2) explore higher-throughput approaches with wider coverage of chemistry and biology.

Finally, with this integration, nearly half of the programmatic resources will be devoted to research translation and knowledge delivery, through tools and applications that enhance and democratize access to CSS scientific knowledge, through partner-driven and partner-focused tailored solutions, and finally through strategic outreach and engagement of the stakeholder community that relies on the products of CSS research and helps ground truth its validity, relevance, and applicability.

EPA Partner and Stakeholder Involvement

The process for developing this StRAP unfolded through a series of meetings with program and regional partners and among labs and centers involved with CSS. The scoping meetings included concurrent participation and engagement from this community and helped map out and balance the diverse partner priorities. Additional focus group meetings with partners allowed more in-depth discussions and further shaping of the plans. This document was

profoundly strengthened by the informed and interactive iteration among these groups over an 18-month period. Along the way, significant interim milestones were posted online in an effort to transparently engage the community of EPA partners and collaborators.

The CSS StRAP is designed to drive the longer term science vision for the program. But within each CSS project, specific case studies are being developed in collaboration with program and regional partners to reflect EPA's near-term priorities. This case study approach ensures that the purpose and the application of CSS science is clearly defined upfront in collaboration with the partners and that the product developed is fit for the intended purpose. In addition, as described in the Research Topics section, the Translation and Knowledge Delivery topic incorporates both partner-driven short term projects and projects through which the applicability of the emerging science will be demonstrated and evaluated (or conceptually "test driven") early on in each CSS project before going too far down a research path. This collaborative approach builds familiarity and confidence in the products of CSS research. Partners are not asked to adopt a final product or tool. Rather, they are engaged and involved in the design and development of the tools, their early adoption for application to case studies, and the exercise of confidence building.

Every project in CSS also has a significant education, outreach, and engagement component first in building and executing case studies, and also more broadly through targeted webinars and panel listening and discussion sessions set up monthly with program and regional partners. This engagement culminates in a face-to-face meeting, held approximately annually across CSS and with partners designed to allow direct interaction among partners and CSS project investigators.

Research planned for the StRAP 2016-2019 also was informed by external stakeholders and partners. The CSS staff and researchers serve on several task groups and are actively engaged on projects with numerous U.S. federal agencies and international organizations as well as with various state and nongovernment organizations. CSS interacts with academia through scientific conferences, informal professional relationships and formal grants and cooperative agreements. These venues afford the opportunity to not only leverage expertise and funding, but also the ability to identify unique niche areas to which CSS can make the greatest scientific contributions. These external engagements are discussed in more detail in the Collaborations and Stakeholder Engagement and Outreach sections later in this document.

Integration across the Research Programs

EPA's six research programs work together to address science challenges that are important for more than one program. Coordination efforts can range from formal integration efforts across the programs at a high level, to collaboration research among EPA scientists working on related issues.

To accomplish formal integration of research on significant cross-cutting issues, EPA developed several "Research Roadmaps" that identify ongoing relevant research and also important science gaps that need to be filled. The Roadmaps serve to coordinate research efforts and to provide input that helps shape the future research in each of the six programs. Roadmaps have been developed for the following areas:

- Nitrogen and Co-Pollutants
- Children's Environmental Health
- Climate Change
- Environmental Justice

The CSS research program is the lead national program for the *Children's Environmental Health (CEH) Roadmap*. Transforming EPA's capacity for considering child-specific vulnerabilities requires that ORD apply advanced systems science and integrate diverse emerging data and knowledge in exposure, toxicology, and epidemiology to improve understanding of the role of exposure to environmental factors during early life on health impacts that may occur at any point over the life course.

The CEH Research Roadmap helps to connect the dots among the research activities being implemented across ORD's research programs. In addition, the vision articulated in this Roadmap serves to focus ORD investment in CEH research on areas where EPA can play a significant leadership role and to ensure this cross-cutting research is integrated and the results are impactful. The CSS program also informs critical research areas identified in the ORD cross-cutting research Roadmaps, as illustrated in Table 1.

The HHRA and CSS programs are working together to evaluate how the new data emerging from computational toxicology can be used to improve efficiency and reduce uncertainty in risk assessment. CSS research is developing approaches to integrate new types of information with existing methods and information to support science-based decisions, and to evaluate the value added of new data. In one example, CSS will generate data needed for HHRA to develop innovative fit-for-purpose assessment products (such as high-throughput toxicity values). Projects in the HHRA program include case studies to characterize the utility of several new approaches applied to different classes of chemicals, various endpoints, and toxicities, and with disparate degrees of supporting evi-

Table 1. Chemical Safety for Sustainability (CSS) research program contributions to critical needs identified by ORD Roadmaps. Multiple checkmarks indicate a larger contribution of CSS activities and interest in the identified science gaps of the Roadmaps than a single checkmark; a blank indicates no substantive role.

ORD Roadmap	CSS Topic Area			
	Chemical Evaluation	Life Cycle Analytics	Complex Systems Science	Translation and Knowledge Delivery
Climate Change		✓✓	✓	
Environmental Justice	✓		✓	✓
Children's Health	✓✓	✓	✓✓✓	✓✓
Nitrogen & Co-Pollutants	✓		✓	

dence for context. Characterizing the utility of these new data and tools for improving risk assessment will build stakeholder confidence and accelerate acceptance for regulatory decision making. Additional coordination efforts among ORD's research programs range from formal integration efforts at a high level, to collaborative research among EPA scientists working on related issues. For example,

- CSS and Safe and Sustainable Water Resources (SSWR) research program are collaborating to develop more efficient ways to assess the toxicity of harmful algal blooms. There are additional collaborations in areas related to contaminants, including pharmaceuticals, found in open or drinking water, as well as new approaches for evaluating their cumulative health impacts.
- CSS and Sustainable and Healthy Communities (SHC) collaborate in areas such as use of chemicals (most recently, silver nanomaterials) in consumer products and relevance to predicting potential children's exposures.
- CSS and Air Climate and Energy (ACE) are planning to collaborate on novel higher throughput assays for cardiopulmonary effects that are being developed in ACE but which may have broader application in CSS.
- Chemical data, including from applications of computational chemistry, can begin to inform evaluation and response strategies in the Homeland Security Research Program (HSRP), as CSS data and dashboards are enriched with more data and information tools, and HSRP is trained as among the stakeholders of CSS.

The projects outlined in the Research Topics section provide additional examples of projects that integrate across national research programs.

Research to Support EPA Strategic Plan

Because chemical manufacture and use has intended and unintended consequences on the quality of the air we breathe, the water we drink, and the communities in which we live, work, and learn, outputs of the CSS research program will broadly support EPA's Strategic Goals in these areas (see box) and inform EPA decisions to sustainably improve human health and the environment. Very specifically, the CSS research program is designed to directly support EPA's Strategic Goal 4: Ensuring the Safety of Chemicals and Preventing Pollution; as well as the Cross-EPA Strategy: Working Toward a Sustainable Future.

Goal 4, objective: Ensure Chemical Safety. Reduce the risk and increase the safety of chemicals that enter our products, environment, and bodies.

Applied Research under Goal 4: EPA chemicals research will provide the scientific foundation required to support safe, sustainable use of chemicals to promote human and environmental health, as well as to protect vulnerable species, lifestages, and populations.

FY 2014 - 2018 EPA Strategic Plan: Goals and Cross-Agency Strategies

EPA Strategic Goals

Goal 1: Addressing Climate Change and Improving Air Quality

Goal 2: Protecting America's Waters

Goal 3: Cleaning Up Communities and Advancing Sustainable Development

Goal 4: Ensuring the Safety of Chemicals and Preventing Pollution

Goal 5: Protecting Human Health and the Environment by Enforcing Laws and Assuring Compliance

Cross-Agency Strategies

- Working Toward a Sustainable Future
- Working to Make a Visible Difference in Communities
- Launching a New Era of State, Tribal, Local, and International Partnerships
- Embracing EPA as a High-Performing Organization

Statutory and Policy Context

Managing chemical risks is covered in legislation and statutes mandated by Congress and implemented by EPA (Table 2). Chemicals are regulated by several EPA 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, amendments to the FQPA and SDWA, both of 1996, contain provisions for assessing the potential for chemicals to interact with the endocrine system. Both the CWA and the SDWA require EPA's Office of Water to prioritize possible water contaminants in the Contaminant Candidate List. EPA's Office of Solid Waste and 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[1] program and Cosmetics Directive in Europe and the Canadian Environmental Protection Act. CSS will enable EPA to test and regulate numerous chemicals in a more efficient manner, supporting several statutory obligations and policies.

One example of a critical EPA mandate that provides important context for design of the CSS 2016-2019 StRAP and selection of relevant case studies is the Endocrine Disruptor Screening Program (EDSP; http://www.epa.gov/endo/). The List of the EDSP Universe of Chemicals contains approximately 10,000 chemicals as defined under FFDCA and SDWA 1996 amendments (http://www.epa.gov/endo/#universe). EPA recently announced and solicited public comment on the use of new technologies (such as high-throughput toxicology data) to substantially speed up screening of chemicals for their potential to disrupt hormones in humans and wildlife, and reduce animal use in screening (http://www.epa.gov/endo/pubs/pivot.htm). This signaled an imminent opportunity to demonstrate the relevance and potential applicability of CSS research to environmental policy in near real time.

In addition to federal legislative mandates, several state initiatives, summarized in Appendix 1, are driving the needed advances in chemical evaluation. To contextualize and obtain additional scientific advice on how the emerging data and science from CSS can be

Table 2. CSS Research Supports Chemical Risk Management Decisions Mandated by Legislation

Legislation	Acronym	Website
Clean Air Act	CAA	www.epa.gov/lawsregs/laws/caa.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 Food, Drug and Cosmetic Act	FFDCA	http://www.fda.gov/regulatoryinformation/legislation/federalfooddrugandcosmeticactfdcact/default.htm
Federal Insecticide, Fungicide, and Rodenticide Act	FIFRA	http://www.epa.gov/agriculture/lfra.html
Food Quality Protection Act	FQPA	http://www.epa.gov/pesticides/regulating/laws/fqpa/backgrnd.htm
Resource Conservation and Recovery Act	RCRA	http://www2.epa.gov/rcra
Safe Drinking Water Act	SDWA	http://water.epa.gov/lawsregs/rulesregs/sdwa/
Toxic Substances Control Act	TSCA	http://www2.epa.gov/laws-regulations/summary-toxic-substances-control-act

[1] http://echa.europa.eu/regulations/reach

translated for use in EPA decision making, EPA commissioned a study by the National Academy of Sciences (NAS). CSS has strategically drawn from the NAS recommendations to address key research gaps that are not being addressed by partners outside EPA. The formative NAS reports are highlighted in Appendix 1.

Research Program Objectives

CSS conducts research to provide the fundamental knowledge infrastructure and complex systems understanding required to predict potential impacts from use of manufactured chemicals and to develop tools for rapid chemical evaluation and sustainable decisions. In addition, CSS research results are translated to provide solutions and technical support to our EPA partners and external stakeholders. CSS research is guided by the following four objectives:

- **Build Knowledge Infrastructure.** Make information publicly accessible. Combine different types of data in new ways to characterize impacts of chemicals to human health and the environment.
- **Develop Tools for Chemical Evaluation.** Develop and apply rapid, efficient, and effective chemical safety evaluation methods.
- **Promote Complex Systems Understanding.** Investigate emergent properties in complex chemical-biological systems by probing how disturbances and changes in one part affect the others and the system as a whole.
- **Translate and Actively Deliver.** Demonstrate application of CSS science and tools to anticipate, minimize, and solve environmental health problems.

Table 3 provides descriptions for each of these objectives as well as their near-and long-term aims in advancing the CSS vision.

In addressing these objectives, specific science challenges were identified which led to the design of the CSS Research Topics described in the next section.

Science Challenge: *Thousands of chemicals have not been evaluated and new chemicals are continually being developed and introduced into commerce. CSS is advancing cutting-edge methods to provide data for higher throughput risk-based evaluation of both existing chemicals and emerging materials. The Chemical Evaluation research topic is designed to address this challenge.*

Science Challenge: *Chemical substitutions and other alternatives designed to solve one environmental health problem may have unintended consequences. CSS is exploring new ways to evaluate risks to human and ecological health across the life cycle of manufactured chemicals, materials, and products. CSS methods will efficiently evaluate alternatives and support more sustainable chemical design and use. The Life Cycle Analytics research topic is designed to address this challenge.*

Science Challenge: *The real world is inherently more complicated than current experimental models of toxicology can depict. CSS research adopts a systems-based approach to examine complex chemical-biological interactions and predict potential for adverse outcomes resulting from exposures to chemicals. The Complex Systems Science research topic is designed to address this challenge.*

Science Challenge: *Decision makers need demonstrated solutions to translate new information into action. CSS promotes Web-based tools, data, and applications to support chemical safety evaluations and related decisions. CSS engages EPA partners and stakeholders to ground truth the transparency, access, relevance, and applicability of our research. The Translation and Knowledge Delivery topic is designed to address this challenge.*

Table 3. Summary of near and longer term aims of CSS research objectives.

CSS Research Objectives			
Objective	**What We Do**	**Near-Term Aim**	**Long-Term Aim**
Build Knowledge Infrastructure	Make information publicly accessible. Combine different types of data in new ways to characterize impacts of chemicals to human health and the environment.	Provide accessible information to support scientific discovery and sustainable decisions.	Generate chemical, biological and toxicological information to advance understanding of relationships between chemical characteristics and potential impacts of use.
Develop Tools for Chemical Evaluation	Develop and apply rapid, efficient, and effective chemical safety evaluation methods.	Improve chemical prioritization, screening, and testing.	Revolutionize chemical assessment for potential risks to humans and the environment.
Promote Complex Systems Understanding	Investigate emergent properties in complex chemical-biological systems by probing how disturbances and changes in one part affect the others and the system as a whole.	Improve understanding of the relationship between chemical exposures and ecological and human health outcomes including to the developing organism.	Predict adverse outcomes resulting from exposures to specific chemicals and mixtures over time and space.
Translate and Actively Deliver	Demonstrate application of CSS science and tools to anticipate, minimize, and solve environmental health problems.	Develop solution-based approaches for evaluating impacts of high priority chemicals in support of innovative and sustainable decisions.	Apply CSS tools to predict impacts of emerging materials, products, and new uses.

Research Topics

Working with program and regional partners to define the scope of the science that will be conducted in the CSS research project areas, CSS used the following specific criteria:

Specific criteria:

- The need is critical, and if CSS does not lead and conduct this research, the science will not be developed by others to address EPA needs. To illustrate, new methods to estimate human and ecological exposures to thousands of chemicals more quickly and efficiently was considered a high priority topic for CSS. On the other hand, additional research to elucidate mechanisms of carcinogenicity (currently led by NIH), was ranked a lower priority – unless used as a specific case study in quantitative development of Adverse Outcome Pathways.

- Research activities contribute broad scientific impact through focus on partner solutions. Development of new methods to assess the behavior of methodologically challenging compounds (MCC) such as perfluorinated compounds met an urgent EPA need, but also provided a foundation for future research on persistence and bioaccumulation of such compounds and in selection of safer alternatives.

- The research approach is innovative and applies emerging science and technology to advance CSS objectives. A recent example is integration of high-throughput bioactivity data from ToxCast with high-throughput exposure estimations from ExpoCast for risk-based prioritization of endocrine disrupting chemicals.

- Research addresses CSS partners' highest research and science priorities. For example, the integrated bioactivity-exposure (risk-based) prioritization described above was tailored for use by the EDSP in application to estrogen receptor mediated pathways (http://www.epa.gov/endo/pubs/pivot.htm).

- Research activities are framed to demonstrate value added of information, tools, and approaches being developed to support EPA decisions.

- All data and tools are developed, evaluated, and translated through application to case examples of interest to partners. Case studies with direct partner engagement or dedicated partner advocate are prioritized.

- Results are transparent and accessible. All data and tools are accessible to EPA partners upon delivery of product and are supported by appropriate QA, documentation and peer reviewed publication(s). Synergies are identified and leveraged among research topics and project areas.

- CSS resources are leveraged through integration across the program and through strategic collaborations with other EPA programs, federal agencies, public and private stakeholders and the global scientific community.

In addition, to facilitate the transformation required to meet CSS vision, address the science challenges, and provide the strategic thrust for Goal 4 in EPA's Strategic Plan, three guiding principles have been applied in shaping this StRAP.

Adopt the AOP framework

Adverse outcome pathways (AOPs) are a conceptual framework intended to enhance the utility of pathway-based data for use in risk-based regulatory decision support. An AOP portrays existing knowledge of linkage

between a direct molecular initiating event and an adverse outcome at a biological level of organization relevant to risk assessment (i.e., actionable). When developed and evaluated in a rigorous manner, AOPs provide a scientifically-defensible foundation for extrapolating from mechanistic data to predicted apical outcomes. Additionally, as individual AOPs are developed, they can be assembled into AOP networks that may aid the prediction of more complex interactions and outcomes resulting from exposure to complex mixtures and/or chemicals with multiple modes of action. By considering AOPs and AOP networks associated with important developmental processes, as well as those associated with disease endpoints of concern, mechanistic toxicology information and epidemiology insights can be brought together for model development and analysis of critical knowledge gaps.

Exploit complex systems modeling to advance mechanistic understanding

A major challenge is to translate AOP frameworks across scales of biological organization (molecules, cells, tissues, populations) and function, while incorporating critical windows of exposure, dose, toxicodynamics, and toxicokinetics. Multiscale modeling and simulation is a powerful approach for capturing and analyzing biological information that is inaccessible or unrealizable from traditional modeling and experimental techniques. For example, virtual tissue models (VTMs) afford the opportunity to develop science without conducting studies in children. By simulating a range of predicted effects, the earliest signs of adversity, or tipping points, can be identified, and new testable hypotheses aimed at improving the accuracy of inferences from *in vitro* data can be developed. These same modeling approaches can be applied to capture the complexity of wildlife interactions with the environment as well as to postulate key environmental determinants of population health.

Promote a life-cycle perspective

A life-cycle perspective is required to evaluate the safety of chemicals and materials in the context of how these are designed and used in society. To evaluate alternatives and options, risk (hazard and potential for human exposure and toxicity) and environmental impact (ecological risks) are characterized for chemicals and materials within the context of the full range of benefits and consequences. Tradeoffs between these risks and factors, such as product functionality, product efficacy, process safety, and resource requirements, are considered. The intent is to promote a knowledge-driven approach that integrates multiple and diverse data streams for decision making based on specific context and priorities. However, regardless of this context, sustainable decisions require consequences of use over a chemical's life cycle (from production to disposal) be evaluated.

These criteria and guiding principles helped to quickly focus the scope of the program on research topics and project areas that promise to have transformative impact within and outside the CSS research program, and that inherently lend themselves to an integrated and collaborative research construct. CSS FY16-19 research is organized by four Research Topics and implemented by transdisciplinary teams of scientists working within and across these topics.

CSS research is often conducted in collaboration with program and regional partners through specific case studies that provide the opportunity to evaluate real-world applicability of its research. In addition, the leading edge of CSS science is driven through transformative research conducted in academia through EPA's Science to Achieve Results (STAR) grants program. Within each topic, collaborations developed with the academic researchers further enable CSS to benefit from and integrate the emerging science, methods, and tools. It also provides an opportunity for academic

researchers to learn about and contribute to research relevant to the science challenges that underpin CSS topics. In addition, several research efforts in CSS germinated through awards in the Pathfinder Innovation Projects (PIP) program, which provides ORD scientists the opportunity to stretch beyond their existing research and experiment with creative ideas that have the potential to transform environmental protection and sustainability. In CSS, these projects are shepherded through their nascent stages, and when ready and applicable, the research or results are applied to or integrated programmatically into CSS. Some of these synergies are provided as examples in describing the CSS topics below.

Three research topics provide core systems science and tools:

1. **Chemical Evaluation**

   Advance cutting-edge methods and provide data for risk-based evaluation of existing chemicals and emerging materials.

2. **Life Cycle Analytics**

   Address critical gaps and weaknesses in accessible tools and metrics for quantifying risks to human and ecological health across the life cycle of manufactured chemicals, materials, and products. Advance methods to efficiently evaluate alternatives and support more sustainable chemical design and use.

3. **Complex Systems Science**

   Adopt a systems-based approach to examine complex chemical - biological interactions and predict potential for adverse outcomes resulting from exposures to chemicals.

A fourth research topic focuses on translation and active delivery of CSS research products, demonstration and application of CSS scientific tools, and knowledge delivery to EPA Partners:

4. **Solutions-based Translation and Knowledge Delivery**

   (1) Promote Web-based tools, data, and applications focused on tailored solutions to support chemical safety evaluations and related decisions; (2) Respond to short-term high priority science needs for CSS partners; and (3) Allow for active and strategic engagement of the stakeholder community.

CSS project areas associated with each of these four topics are described below. The CSS program structure in Figure 1 depicts the dynamic and interdependent relationship between the topics and project areas, and among the research and translational topics.

Integrated research will also be required across these topics and projects to effectively address scientific gaps and provide tools to enable EPA decisions. EPA priorities for specific classes of chemicals, human and ecological health endpoints, and vulnerable species and lifestages will be used to focus case studies, design specific research activities, and further focus this integration. The priority areas for FY16-19 include: **(1) Emerging and methodologically challenging compounds; (2) Endocrine disruption (including thyroid); and (3) Children's environmental health.** Importantly, signature CSS research in **computational toxicology** will exploit new and emerging scientific tools in molecular biology, computational chemistry, and informatics to transform chemical safety evaluation. Table 4 summarizes the scientific challenges addressed by the project areas, the interim outputs they provide that feed into the larger programmatic outputs, as well as the measures of success for these projects.

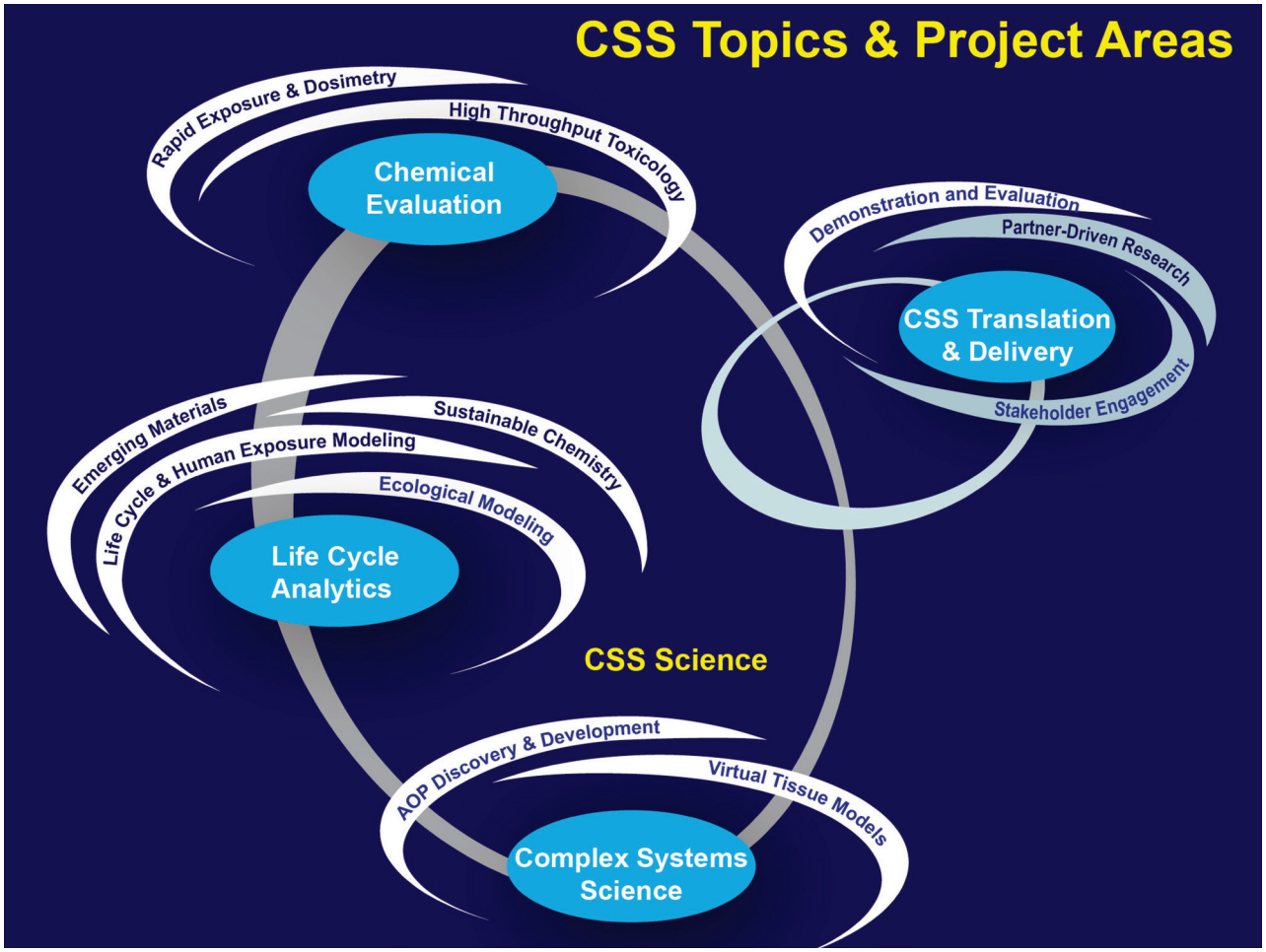

Figure 1. CSS Research Topics and Projects.

Topic 1: Chemical Evaluation

The Chemical Evaluation topic will provide cost-efficient methods and high-throughput data for rapid risk-based evaluation of existing chemicals and emerging materials. One research project area focuses on hazard profiling and a second on exposure forecasting.

Research Project Area: High-Throughput Toxicology

Research in the High-Throughput Toxicology (HTT) project area is driven by limitations of current chemical testing methods and EPA needs to evaluate large sets of chemicals for potential adverse human and ecological health effects. Rapid and efficient methods are required by EPA to prioritize, screen, and evaluate chemical safety for thousands of compounds. The ToxCast research program was initiated to generate data and predictive models on a large number of chemicals of interest to EPA using high-throughput screening methods and computational toxicology approaches to rank and prioritize chemicals. The focus of this project area will be to provide the foundation and contextually relevant tools for extending utility of the HTT strategy to benefit regulatory decisions ranging from chemical prioritization to applications for more in-depth risk decision paradigms.

To provide contextual or fit-for-purpose validation of the HTT testing strategy, guidance and

performance criteria for assay validation will be developed covering appropriate biological domains, technical description and assessments, interpretation of results, and linkages to higher level biological complexity. To broaden the screening approach and fill gaps in coverage of toxicity pathways, there will be collaboration with the Adverse Outcome Pathway project to identify and develop assays for key molecular initiating events for incorporation into the testing program. Data will be generated for key assays and used to generate predictive models covering critical toxicity endpoints. Resources will be devoted to evaluating cutting-edge methods to incorporate and account for xenobiotic metabolism in to the high-throughput testing strategy using a case study approach. Methods will also be evaluated for generating high-throughput screening data on challenging classes of chemicals such as volatiles. The project will build toward a broader and more efficient high-throughput testing strategy, including the use of global assays capable of extensive biological activity recognition. Such assays may serve to prioritize chemicals for more detailed *in vitro* or short term *in vivo* testing, possibly directing the type of testing required.

Examples of research activities in this project area include support to interpret ToxCast data and development of new assays to cover priority endpoints:

- The ToxCast program has used a series of high-throughput assays on a large number of chemicals to rapidly generate toxicity data. Using this data for regulatory purposes requires the ability to interpret technical quality of the data, as well as understand the relationship of these high-throughput assays to biological outcomes. A guideline document will be produced by this project, providing standardized descriptors and methods for interpreting data based upon level of biological complexity. This guideline document will enable evaluation and interpretation of high-throughput ToxCast data in several decision contexts.

- Thyroperoxidase (TPO) catalyzes a critical step in the synthesis of thyroid hormones and inhibition of TPO by environmental chemicals leads to severe and irreversible impacts on brain development. In this project, a novel high-throughput screening assay for TPO inhibition is being developed, validated with 21 well-characterized chemicals, and used to screen the ToxCast Phase I and II chemical libraries (1074 chemicals).

Research in the High-Throughput Toxicology project area will provide rapid and efficient toxicity testing paradigms and data on chemicals and endpoints of interest to the EPA as well as the tools to understand the significance of the results.

Research Project Area: Rapid Exposure and Dosimetry

As data from high-throughput screening methods become available, this new toxicity information must be translated to assess potential risks to human and ecological health from environmental exposures. In concert with the toxicity information, estimates of human and ecological exposures are required as critical input to risk-based prioritization and screening of chemicals. The ExpoCast effort was initiated to ensure that the required exposure science and computational tools are developed and ready to address global needs for rapid characterization of exposure potential arising from the manufacture and use of thousands of chemicals and to support use of emerging toxicity data for risk-based chemical

RESEARCH HIGHLIGHT

ExpoCast includes science and computational tools for rapid characterization of exposure potential arising from the manufacture and use of thousands of chemicals.

evaluation. The focus of the Rapid Exposure and Dosimetry project area will be to develop the data, tools, and evaluation approaches required to generate rapid and scientifically defensible exposure and estimates for the full universe of existing and proposed commercial chemicals.

Tools applied in this project area will include innovative data mining approaches, advanced computational models, and higher throughput analytical methods. The scope of this project will include development, evaluation, and ultimately application of high-throughput computational exposure prediction methods to support regulatory, industry, community, and individual decisions that protect human health and the environment. Research in this project area will also generate and analyze *in vitro* data on key determinants of human pharmacokinetics and develop population-based models for using these data to compare human exposures and hazards. Consideration will be given to identifying chemical classes and aspects of human variability not currently well-characterized by rapid methods including: biological variability (e.g., genetic polymorphisms); behavioral variability (e.g., consumer use) that lead to differences for key demographics; and life stage variability (e.g., children).

Research in the Rapid Exposure and Dosimetry project area will provide high-throughput pharmacokinetic and exposure data and models for risk-based prioritization to address case examples of interest to EPA program office partners. The chemical exposures and potentially hazardous doses predicted by this project will ultimately be applied in the Demonstration and Evaluation project for application of new data streams and rapid assessment approaches to support EPA chemical safety assessments. Results will advance computational exposure science required to transform chemical evaluation.

New Methods in 21st Century Exposure Science

To complement intramural research under the Chemical Evaluation Topic, CSS has funded five universities through the EPA STAR grants program to conduct innovative research to advance methods for characterizing real-world human exposure to chemicals associated with consumer products in indoor environments. One of the cross cutting activities among these grantees was their interest in applications of non-targeted analyses, based on high-resolution mass spectrometry platforms, to screen for xenobiotic chemicals in a variety of environmental and biological media.

RESEARCH HIGHLIGHT

EPA STAR grants are advancing methods for characterizing real-world, indoor exposures to chemicals in consumer products.

Topic 2: Life Cycle Analytics

Research in the Life Cycle Analytics Topic is exploring and advancing new ways to evaluate risks to human and ecological health across the life cycle of manufactured chemicals, materials and products. Under four integrated CSS research projects, methods are being developed and demonstrated to efficiently evaluate alternatives and support more sustainable chemical design and use.

Research Project Area: Sustainable Chemistry

Strategies are required to apply information on inherent chemical properties to predict potential for transformation and activity of compounds in biological and environmental systems. The intersection of recent advances in high-throughput screening (HTS), mechanistic

toxicology, computational chemistry and cheminformatics provide the foundation to identify influential chemical determinants of adverse biological impacts of chemicals and materials. The Sustainable Chemistry project area will take advantage of these advances to improve understanding of chemical features associated with potential for environmental and human health impacts.

RESEARCH HIGHLIGHT

Improved understanding of chemical features in biological and environmental systems informs design and evaluation of safer chemical alternatives.

In this project area, knowledge of inherent chemical properties and features will be explored to distill principles for chemical classes that capture the full range of chemistries represented in commerce. For the set of compounds represented in the ToxCast library, knowledge of chemical features will be applied to inform interpretation of high-throughput toxicity (HTT) data and models. At the same time the HTT data and models will be used to elucidate key features associated with potential for hazard. For select sets of high interest chemicals, mechanistic-based case studies will be conducted to link upstream chemistry with downstream biology incorporating considerations of transformations in real-world biological and environmental systems. This core research will further establish common chemistry principles linking inherent chemical structural features and properties to potential for toxicity, environmental persistence, and transformations in environmental and biological systems.

Examples of research activities in this project area include development and application of computational chemistry / cheminformatics tools to better inform safety and exposure assessments of organic chemicals. Software tools such as the Chemical Transformation Simulator (CTS) are being developed and evaluated through case studies focused on screening carbamate and organophosphorus pesticides as well as high interest flame retardants for toxicity, persistence, bioaccumulation and transformation potential.

The Sustainable Chemistry project area will provide a chemical knowledge resource that consolidates basic chemical data, along with cheminformatics and computational chemistry tools for shared use, and will empower more effective, integrated evaluation of chemicals. Improved understanding of chemical features associated with fate and activity in biological and environmental systems will inform design and evaluation of safer chemical alternatives and support sustainable decisions.

Research Project Area: Emerging Materials

Innovations in chemical and material design are rapidly changing the landscape of industrial and consumer products as novel materials, such as engineered nanomaterials (ENMs), are incorporated to enhance their performance. Scientifically supported approaches are required to efficiently screen for and evaluate potential impacts of ENMs to human health and the environment. The Emerging Materials project area will conduct applied research to develop, collate, mine, and apply information on ENMs to support risk-based decisions on sustainable manufacture and use.

RESEARCH HIGHLIGHT

Through case examples of engineered nanomaterials (including silver nanoparticles and carbon nanotubes), researchers identify key information required to characterize potential for exposure and hazard across the life cycle of the product.

In this project area, a life-cycle perspective is applied and available information synthesized to consider potential for impacts associated with manufacture, use, and disposal of products containing ENM. Through a set of case examples focused on priority and data-rich material classes (including silver nanoparticles and carbon nanotubes), extant information will be mined to identify key information required to characterize material form, potential for exposure, and hazard across the product life cycle for data-poor materials. To address these key gaps, a library of core nanomaterials, including systematically aged materials, will be considered. Interactions between ENMs and biological or other complex media will be explored. And, the complexity of relating nanomaterial features directly to risk will be addressed by considering critical intermediate properties of ENMs that are predictive of potential impacts, and identifying associated functional assays.

Results of the Emerging Materials project area will provide the methods and tools to enable EPA to efficiently evaluate emission, transformation, potential exposure, and impacts of ENMs across the material/product life cycle. The long term impact will be to accelerate the pace at which the safety of existing nanomaterials is assessed and to inform the sustainable design and development of emerging materials and products.

Research Project Area: Life Cycle and Human Exposure Modeling

Evaluation of alternatives for sustainable decisions requires understanding the broad range of impacts to human health and the environment associated with a chemical or product throughout the life cycle. Efficient tools are required to consider, among the broad range of impacts, the potential for exposures to human and ecological species across the chemical life cycle where limited data are available. This project area will take the novel approach of integrating chemical exposure and life cycle knowledge to model and assess human health and ecological impacts of alternatives. Approaches will be developed to efficiently evaluate environmental and human health impacts and metrics identified to quantify tradeoffs between risks and other sustainability factors.

RESEARCH HIGHLIGHT

By integrating chemical exposure and life cycle approaches, researchers will model and assess the human health and ecological impacts of substituting alternative chemicals or processes.

By bringing together two of ORD's leading disciplines in exposure science and life cycle assessments, this project is transforming how scientists in the broader community are attacking these same challenges. Research in this area will be focused on operationalizing sustainability analysis for chemical safety evaluation by leveraging and extending methods in life-cycle assessment (LCA) and exposure modeling to incorporate metrics of human and ecological risk. An approach will be developed that harmonizes the product-centric nature of LCA with the chemical-centric focus of comparative risk analysis by considering chemical function. The two primary objectives of the CSS Life Cycle Assessment and Human Exposure Modeling project are to: (1) develop a framework and database structure that brings together chemical exposure and life cycle modeling; and, (2) develop a tool for evaluating chemical/product impacts in a life cycle assessment framework to support decision making through improved risk and sustainability analysis.

Through application to a select set of case examples of interest to EPA program partners (including building materials/semi-volatile organic compounds), this project area will provide efficient tools and metrics to evaluate chemical impacts across the life cycle and to support alternatives assessment and sustainable chemical use.

Research Project Area: Ecological Modeling

EPA's process for registering and regulating chemical compounds includes a tiered ecological risk assessment (ERA). Within the ERA process, chemicals are first screened using rapid assessment tools that require minimal data and provide conservative estimates of ecological risk. Chemicals determined to present an appreciable risk are subject to higher-level assessments that provide quantitative estimates of ecologically-relevant risk and identify risk mitigation options. For the vast majority of chemicals and species, little or no data exist and refined assessments must rely on modeled estimates of exposure and effects. The Ecological Modeling project area will advance efficient methods to improve risk assessments with limited data availability, as well as more complex approaches that can target data-rich applications.

Research in this project area will integrate existing and novel models into an ecosystem-based framework that combines the fate and transport of chemicals in the environment with improved toxicity interpretation for ecological endpoints based on surrogate species. For assessments which rely on minimal data (e.g., endangered species), this project will develop and evaluate approaches to maximize the use of available information and demonstrate their usefulness in increasing ERA efficiencies, identifying and reducing critical uncertainties, and identifying critical information that would improve decisions. This will be accomplished through proof-of-concept studies that apply advanced molecular, modeling, and landscape analysis methodologies to verify model predictions. For higher tier assessments, including those that characterize spatially varying chemical impacts and impacts to threatened and endangered species, this project will advance the science that will allow EPA to describe chemical impacts in ecologically relevant terms that align with sustainable ecosystem services endpoints.

Research in this project area will focus on developing and evaluating ecological models for endangered aquatic species and wildlife populations exposed to pesticides. A population modeling framework for predicting chemical effects to avian species will integrate three models currently used extensively to assess ERA: (1) TIM (Terrestrials Investigation Model); 2) MCnest (Markov Chain Nest Productivity Model); and (3) HexSim (Spatially explicit individual based model).

The Ecological Modeling project area will provide demonstrated efficient ERA tools that reduce uncertainty for high-priority and methodologically challenging chemicals. The resulting decision framework for using models of various complexities, data requirements, and levels of ecological realism for differing ERA requirements or fit-for-purpose will enhance EPA capacity to protect sensitive ecosystems and species.

RESEARCH HIGHLIGHT

To predict effects of pesticides on endangered aquatic species and wildlife populations, researchers are developing, integrating and evaluating ecological models into an efficient decision framework.

Within the Life Cycle Analytics Topic, CSS has funded complementary extramural research to advance the scientific understanding of potential for chemical impacts across the life cycle and to foster innovation of safer alternatives, including the following:

- **EPA/NSF Networks for Sustainable Molecular Design and Synthesis**
  Investigating the sustainable molecular design of chemical alternatives to determine traits of chemicals that indicate they are functional for their intended purpose and have the least impact on human health and the environment.

- **EPA/NSF Networks for Characterizing Chemical Life Cycle**
  Investigating ways to characterize and predict environmental and health implications of chemicals by following chemicals through their life cycle from design, manufacture, use and disposal.

- **EPA/NSF Centers for the Environmental Implications of Nanotechnology**
  Elucidating the relationship between nanomaterials and potential for environmental exposures, biological effects, and ecological consequences. In addition, these grants have germinated a community-based effort to develop higher throughput approaches to predict toxicological effects associated with those exposures.

- **Systems-Based Research for Evaluating Ecological Impacts of Manufactured Chemicals**
  EPA STAR grants provide integrated, transdisciplinary research to advance scientific understanding of the impacts of manufactured chemicals on ecosystem health. The studies require use of systems-based research to develop innovative metrics and modeling approaches that support evaluation of ecological resilience and inform sustainable risk-based decisions. An important dimension is to translate emerging and advanced methods, data, and computational tools to address complexity of these systems and distill drivers of adverse outcomes to ecological organisms and populations.

Topic 3: Complex Systems Science

Research conducted in the Complex Systems Science topic is focused on building the scientific foundation to predict adverse outcomes resulting from exposures to specific chemicals and mixtures over time and space. The Adverse Outcome and Virtual Tissues project areas are highly complementary. These projects are also very integrated with the projects in the Chemical Evaluation topic.

Research Project Area: Adverse Outcome Pathway (AOP) Discovery and Development

To use new data being generated in the CSS Chemical Evaluation Topic for EPA decisions, there is a need to evaluate the human health and/or ecological relevance of effects observed in *in vitro* or *in vivo* models. Both qualitative and quantitative linkages between measures of biological perturbation provided by new and emerging methods and metrics of adverse outcome relevant to EPA risk-based decisions are required.

The AOP framework provides a systematic and modular structure for organizing and communicating existing knowledge concerning the linkage between molecular initiating events, intermediate key events along a toxicity pathway, and apical adverse outcomes traditionally considered relevant to risk assessment and/or regulatory decision making (i.e., actionable outcomes). When developed and evaluated in a rigorous manner, AOPs provide a scientifically defensible foundation for extrapolating from mechanistic data to predicted apical outcomes. Additionally, as individual AOPs are developed, they can be assembled into AOP networks by evaluating shared nodes or key events in individual pathways. These networks may aid the prediction of more complex interactions and outcomes resulting from exposure to complex mixtures and/or chemicals with multiple

modes of action. AOP networks also afford the opportunity to integrate and evaluate the potential for impacts associated with nonchemical stressors, in addition to chemical stressors. By considering AOPs and AOP networks associated with important developmental processes, as well as those associated with disease endpoints of concern, there is the potential to bring together mechanistic toxicology information and epidemiology insights for model development and analysis of critical knowledge gaps.

RESEARCH HIGHLIGHT

The AOP Discovery and Development team is developing innovative approaches for applying pathway-based bioactivity data, in the context of adverse outcome pathways, to predict biological hazard(s) associated with exposure to complex chemical mixtures.

The AOP Discovery and Development (AOPDD) project area focuses on research that advances predictive applications of the AOP framework and supports the use of alternative data, i.e., other than direct measures of apical toxicity outcomes, as a credible basis for risk-based decision making concerning potential impacts of chemicals on ecological and human health.

For example, to support the application of the high-throughput toxicology and the adverse outcome pathway framework as a basis for decision making, bioactivity measures and hazard predictions must be complemented with understanding of chemical-specific properties that dictate external exposure and tissue-specific dose. The AOPDD project team has conducted case studies focused on acetylcholinesterase inhibitors and thyroid peroxidase inhibitors to demonstrate the use of a novel strategy and workflow for incorporating these considerations.

The AOPDD project team is also developing innovative approaches for applying pathway-based bioactivity data, in the context of adverse outcome pathways, to predict integrated biological hazards which may be associated with exposure to complex mixtures of chemicals present in the environment. Approaches have been demonstrated through case studies either using high-throughput *in vitro* bioassays for the direct testing of surface water extracts, or by mapping chemical concentrations detected in surface waters to sources of chemical-specific bioactivity data.

The research will provide a critical scientific foundation for 21st century approaches to toxicity testing which seek to make increased use of lower cost, higher throughput and/or higher content, *in vitro*, *in silico*, and/or short-term *in vivo* testing for single chemical hazard assessment. It also provides the scientific framework to assess the human/ecological relevance of pathway-based effects across different model systems and address the challenges posed by exposure to multiple stressors in the environment.

Research Project Area: Virtual Tissue Models

Innovation in methods to predict consequences of decisions requires application of ever-advancing and emerging science. A major challenge is to translate AOP frameworks across scales of biological organization (molecules, cells, tissues, populations) and function, while incorporating critical windows of exposure, dose, pharmacodynamics, and pharmacokinetics. Complex models of prototype biological systems are needed that can be probed (experimental) and simulated (computational) analytically to integrate knowledge and identify gaps in knowledge. Multiscale modeling and simulation is a powerful approach for capturing and analyzing biological information that is inaccessible or unrealizable from traditional modeling

and experimental techniques. For example, virtual tissue models (VTMs) afford the opportunity to develop science without conducting studies in children. By simulating a range of predicted effects, the earliest signs of adversity, or tipping points, can be identified, along with new testable hypotheses aimed at improving the accuracy of inferences from *in vitro* data. In the Virtual Tissue Model project area, knowledge-based models of tissues and organ functions that integrate dynamics of cellular function into biological networks governing system behavior are developed and applied to assess informative case examples of developmental toxicity.

RESEARCH HIGHLIGHT

EPA STAR research centers are developing organotypic cell models for high-priority biological systems such as the brain, liver, heart and kidney to accelerate research on the interactions of chemicals with key biological processes.

VTMs are uniquely positioned to capture the connectivity between different scales of biological organization and predict key events in an Adverse Outcome Pathway (AOP). The VTM approach is transformative for ORD as a new way to integrate *in vitro* and *in vivo* data into *in silico* models that can be used to unravel biological complexity and predict performance of a complex biological system with respect to: (a) homeostasis and systems failure (e.g., adaptive versus adverse responses); (b) integrating kinetics-dynamics (e.g., modeling different exposure scenarios); (c) exploring combinations of adverse circumstances that converge onto sensitive pathways and processes (e.g., mixed modes-of-action, cumulative or aggregate exposure, cross-species comparison); and (d) addressing lifestage considerations (e.g., Children's Environmental Health Roadmap). The VTM project area will focus on prenatal developmental toxicity and early postnatal developmental toxicity; however, the concepts and principles for multiscale modeling will be extensible across lifestages and ecological populations.

Research in the VTM project area will provide improved quantitative understanding of the molecular pathways and cellular processes underlying AOPs in building an integrated predictive system. Focused examples considered in the Virtual Tissues Modeling project area will provide improved understanding of the relationship between chemical exposures and ecological and human health outcomes, including impact on the thyroid system and on the developing organism. Ultimately, the vision for 2020 is a platform of experimental and computational models that capture system dynamics for predictive toxicology.

Through the EPA STAR grants program, CSS has also funded complementary extramural research under the complex system science topic to advance scientific understanding and development of methods to enhance capacity for predictive toxicology, including the following:

- **Development and Use of Adverse Outcome Pathways that Predict Adverse Developmental Neurotoxicity**
  Four grants are awarded to develop adverse outcome pathways that map how chemicals interact with biological processes and how these interactions may lead to developmental neurotoxicity. The studies are focused on improving EPA's ability to predict the potential health effects of chemical exposures.

- **Organotypic Culture Models for Predictive Toxicology Center**
  Center grants are awarded to develop Organotypic Cell Models for high-priority biological systems such as the brain, liver, kidney,

testis, breast tissue, heart and neurovascular, and evaluate them as testing platforms for research into the interactions of chemicals with key biological processes. This research will provide new biological insight as to how tissues and organs function during chemical exposures. The data will then be used to develop advanced computational models of how organs and tissues respond to chemicals, and use them ultimately to validate predictive models of human disease or response.

- **Susceptibility and Variability in Human Response to Chemical Exposure**
  The long-term objective of this grant is to uncover the mechanistic linkages between the genome (e.g., variation in DNA sequence among individuals), metabolism (e.g., formation of organ-specific toxic intermediates), and adverse molecular events (e.g., transcriptional changes associated with toxicity) for high interest chemicals.

Topic 4: Solutions-Based Translation and Knowledge Delivery

Research Project Area: Demonstration and Evaluation for Risk-Based Decisions

Work conducted in CSS is generating numerous new approaches and data streams that are intended to benefit environmental decision making by reducing time, cost and/or the uncertainty of decisions. The purpose of this research is to further aid translation of these approaches by evaluating, establishing, and demonstrating their effectiveness to EPA partners and stakeholders. This project will: (1) develop qualitative and quantitative approaches to integrate these new types of information with existing methods and information to support science-based decisions, and (2) evaluate the value added of new data streams, particularly HTP data (experimental and computational), in terms of efficiency, as well as their ability to reduce uncertainty in the risk assessment process. This research will produce an objective framework to systematically evaluate the integration of these new testing and computational methods, and provide measures of confidence and uncertainty to determine "fit-for-purpose" for different EPA actions. The impacts will be that risk assessors will have confidence that the new approaches, data, and tools developed in CSS are scientifically sound and provide value added to environmental decision making. Other research ongoing in CSS will benefit from the lessons learned from this project, as this information will help establish future research priorities within CSS.

RESEARCH HIGHLIGHT

EPA's Office of Chemical Safety and Pollution Prevention is collaborating with ORD, using high-throughput toxicity and exposure data, to develop approaches for screening and prioritizing endocrine disrupting chemicals for more advanced testing.

For example, the EDSP21 program led by EPA's Office Chemical Safety and Polllution Prevention (OCSPP) is collaborating with ORD to use its high-throughput toxicity and exposure data to develop integrated approaches for screening and prioritizing endocrine disrupting chemicals for further testing. These proposed approaches are being evaluated by their Science Advisory Panels (SAP) for adoption into the program. The expectation is that over time, as approaches are developed and "validated" for these applications, their use may be expanded to address the broader universe of chemicals, including chemicals covered by TSCA.

A second example comes out of strategic integration between the CSS and HHRA national research programs. There are over 80,000 legacy or current chemicals listed in the TSCA inventory; less than 2000 of these have health assessments available across federal and state

agencies. Multiple EPA programs and regional offices are tasked with making decisions, in a risk management context, for chemicals with inadequate or non-existent hazard databases. In this example project, CSS would generate data needed for HHRA to develop innovative fit-for-purpose assessment products (such as high-throughput toxicity values or rapid tox).

Research Project Area: Partner-Driven Research

Research conducted in this area will be motivated by CSS partners' high-priority, short-term needs that are not otherwise anticipated or addressed in the StRAP. The project will be defined by the NPD in collaboration with the partner(s) and in consultation with ORD lab/center leadership. Projects within this theme will have deliverables tailored to the needs of the partners, but the research from this project will be otherwise amplifiable and relevant to other efforts in CSS. While the lifespan of a typical project is not expected to exceed 18 months, the effort may give rise to a longer-term research project in CSS through future planning cycles.

For example, the EDSP21 collaboration with OCSPP first began as a partner-driven effort with a narrow focus on the estrogen pathway and a limited number of high-throughput assays. The success of that collaboration, peer reviewed by an SAP and in a variety of peer reviewed journals, led to its development into a full CSS project (described above).

Additionally, in several cases CSS research is developed through engagement of and collaboration with regional partners. This provides an opportunity to provide near-term support to address regional needs and also to evaluate the relevance and applicability of some CSS research in "real-world" contexts. For example, in the Adverse Outcome Pathway Discovery and Development project area, collaborations developed with Region 5 and other federal partners under the Great Lakes Restoration Initiative and the Great Lakes National Program Office have resulted in a biological effects surveillance program. CSS is providing critical support to the development of this program which is necessary to evaluate the impacts of chemicals of emerging concern on Great Lakes fish and wildlife. This project presents a significant opportunity for EPA Office of Water to pursue the applicability of effect-based biomonitoring for evaluating the pollutant burden. Research in this area is being conducted collaboratively with scientists in SSWR conducting similar research in other regional offices.

RESEARCH HIGHLIGHT

Collaborations with EPA Region 5 and other federal partners have resulted in a biological effects surveillance program to evaluate the impacts of chemicals of emerging concern on Great Lakes fish and wildlife.

Research Project Area: Stakeholder Engagement and Outreach

This effort will encompass strategic outreach and engagement of CSS's broad stakeholder community who will serve as a "sounding board" and help ground truth the transparency, access, relevance, and applicability of CSS research. Stakeholders will be engaged through public workshops, tailored webinars and training events, national scientific meetings, strategic collaborations, funded challenges, and other outreach activities. This effort has been shaped by two large stakeholder engagement workshops held in 2014 and led by the NPD team, in collaboration with project scientific leads and partners.

Table 4. CSS Research Topics: Project Areas, Challenges Addressed, Intermediate Outputs, and Measures of Success

Project Areas	Challenges Addressed	Intermediate Outputs	Measures of Success
Topic 1: Chemical Evaluation			
High-Throughput Toxicology	Expand coverage in HTP toxicity screening schemes for high priority biological areas such as endocrine disruption and adverse outcomes such as developmental toxicity. Incorporate xenobiotic metabolism into HTP test methods.	Guidance for evaluating technical performance and biological domain of high-throughput assays. New medium- and high-throughput assays and development of models (signatures) to cover important areas of biological space, high priority adverse outcome pathways and chemical-biological interactions. Approaches for incorporation of xenobiotic metabolism and challenging chemical classes into high-throughput test methods.	HTT assays covering key events in AOPs for estrogenic, androgenic, thyroid, steriodogenesis, and developmental endpoints are fit-for-purpose validated (e.g. for a regulatory application, or by a convening body such as OECD). Increased use of HTT data by program and regional partners as well as other stakeholders for risk-based decisions (e.g. number of downloads of data via Dashboards). High priority chemicals are screened using HTT assays for estrogenic, androgenic, thyroid, steriodogenesis, and developmental endpoints, and the data made publicly available.
Rapid Exposure and Dosimetry	Rapidly characterize potential for real-world exposure to chemicals, including those associated with consumer product use. Develop critical HTP data required to forecast exposure and dose for thousands of chemicals of interest to EPA.	High-throughput pharmacokinetic (HTPK) data and models for risk-based prioritization. High-throughput exposure data and models for risk-based prioritization.	Tools are provided via the iCSS Dashboards to rapidly generate quantitative human exposure and internal dose predictions for large numbers of chemicals. Curated monitoring, chemical, and consumer product usage data are provided to the exposure assessment community. Evaluated exposure predictions for priority chemical lists, including estimates of variability and/or uncertainty, are provided to EPA decision makers.

Project Areas	Challenges Addressed	Intermediate Outputs	Measures of Success
Topic 2: Life Cycle Analytics			
Sustainable Chemistry	Chemical feature sets and models for use with selected AOPs. Strategies to evaluate potential for environmental and human health impacts of new and alternative chemicals to support safer chemical design and chemical screening.	Elucidate chemical properties and structural features associated with potential for environmental and human health impacts. Integrate novel data streams and predictive models for toxicity, environmental persistence and transformations in environmental and biological systems to inform design and evaluation of safer chemical alternatives.	Biologically-informed publicly available SAR/QSAR models developed to identify adverse outcomes that will make use of new HTS data to improve predictive capacity. A Web-based Chemical Transformation Simulator will automate calculation and collection of molecular descriptors for parent chemical and predicted products resulting from transformation in environmental and biological systems for use by decision makers.
Emerging Materials	Develop robust approaches to rapidly and efficiently screen environmental nanomaterial (ENM) for safety in humans and the environment. Identify critical intermediate properties of ENMs that are predictive of potential risks associated with real-world exposures.	Protocols and methods for evaluating engineered nanomaterials in complex biological or environmental systems. Tools to efficiently screen for potential toxicity and exposure based on features of ENMs.	Curated information from ORD ENM research including data on physical chemical characterization parameters and results of release, fate, transport, transformation, and effects studies provided to the assessment community. Set of functional assays based on intermediate properties for efficient evaluation of ENMs are developed and applied to a subset of ENMs.

Project Areas	Challenges Addressed	Intermediate Outputs	Measures of Success
Topic 2: Life Cycle Analytics			
Life Cycle and Human Exposure Modeling	Integrate chemical exposure and life cycle knowledge to model and assesses human health impacts of alternatives. Develop approaches to rapidly evaluate environmental and human health impacts.	Life Cycle Harmonization Tool that will allow greater interoperability of Life Cycle and Exposure databases and tools. Case study evaluation of a chemical/product Life Cycle/Human Exposure Modeling framework. LC-HEM Tool for evaluating chemical/ product impacts in a life cycle assessment framework.	Improved models for considering impacts associated with human exposure are incorporated into LCAs. Modeling and assessment of alternatives is conducted for chemicals/ products with less extensive data. New approaches for more rapid and higher throughput assessments are adopted and used inside/outside EPA.
Ecological Modeling	Rapidly evaluate ecological impacts associated with use of manufactured chemicals with limited data. Capture spatial and temporal dynamics to target critical experimental measurements required to understand chemical impacts on populations of vulnerable ecological species.	Demonstration of ecological risk assessment (ERA) tools that reduce uncertainty for high-priority and methodologically challenging chemicals, comparing ecologically relevant risk assessments to those based on limited data. Decision framework for using models of various complexities, data requirements, and levels of real-world ecological conditions for fit-for-purpose application to differing ERA requirements.	ERA tools are provided to address high-priority and methodologically challenging chemicals being evaluated by EPA program and regional partners. Tools to incorporate risks to terrestrial and aquatic endangered species are applied to inform pesticide risk assessments conducted by EPA and other federal partners.

Project Areas	Challenges Addressed	Intermediate Outputs	Measures of Success
Topic 3: Complex Systems Science			
Adverse Outcome Pathway (AOP) Discovery and Development	Apply AOP framework in concert with new data streams to predict potential impacts of chemicals on ecological and human health to support risk-based decision making.	An Adverse Outcome Pathway knowledgebase that enhances the utility of pathway-based data for risk-based decision making. Case studies demonstrating relevant application of adverse outcome pathway knowledge to risk-based decision making.	Outline and make publicly available putative AOPs that qualitatively link ToxCast assays to potential human and/or ecological hazards. Submit new formal AOP descriptions for review and evaluation by OECD AOP working group. Use AOP networks to predict the effect of a multiple-stressor or mixed MOA exposure in a demonstrative case study.
Virtual Tissue Models (VTMs)	Capture system dynamics in a platform of experimental and computational models for predictive toxicology to support hypothesis development and targeted study to improve understanding of chemical impacts on biological organisms. Assemble pathway data and biological knowledge into dynamic systems models for assessing developmental toxicity.	Integrated predictive system to assemble pathway data, information and knowledge of embryological systems into dynamical VTMs for assessing prenatal developmental toxicity. Integrated predictive system to assemble pathway data, information and knowledge into dynamical VTMs for assessing neuro-developmental toxicity linked to thyroid disruption.	Publicly disseminate novel predictive models for developmental toxicity that can be linked with chemical evaluation (e.g., ToxCast). Provide computational framework to make the knowledge from these models accessible and transparent. Demonstrated case study in which results are translated such that the systems understanding and dynamic model predictions can be used to inform decisions.

Project Areas	Challenges Addressed	Intermediate Outputs	Measures of Success
Topic 4: Solutions-Based Translation and Knowledge Delivery			
Demonstration and Evaluation	Integrate new information with existing methods and infrastructure to develop qualitative and quantitative approaches that support specific EPA science-based decisions. Systematically evaluate new information and approaches to determine when these can be applied "fit-for-purpose" for EPA decisions. Develop measures of confidence and uncertainty to support use of new approaches "fit-for-purpose" by EPA decision makers.	Develop and evaluate a process to produce rapid points of departure (POD) for use in evaluating and managing data-poor chemicals. Develop a framework(s) to evaluate novel groups of assays, methods, and models for hazard ID and/or screening and prioritization.	Guidance on clear frameworks and best practices for incorporation of novel data streams and tools into EPA decision making processes is issued by the NAS. Guidance for how to incorporate and implement more global datasets and models (e.g. ToxCast data, QSAR and ADME models, etc.) into decisions is applied to case studies for EPA program and regional partners and other stakeholders.

Strategic Collaborations

CSS proposes an ambitious and significant paradigm shift in how existing and emerging chemicals and products can be evaluated for safety. The focus is on building predictive capacity and agile responses. The objective is to move from a knowledge-poor management posture to one that is proactive, sustainable, and fostering of innovation. To achieve this paradigm shift, CSS relies heavily on strategic partnerships with dozens of organizations ranging from industry, academia, trade associations, other federal agencies, state government and non-governmental organizations. Strategic partnerships are formalized through numerous types of agreements, including Cooperative Research and Development Agreements, Materials Transfer Agreements and Memoranda of Understanding. Examples of partnerships for advancing potential applications of CSS research are described in Appendix 2.

Anticipated Research Accomplishments and Projected Impacts

The programmatic outputs of CSS FY 2016-2019 StRAP, described in Appendix 3, have been defined in close collaboration with EPA program and regional partners and were designed to meet their needs. To ensure collaborative, integrated, and transdisciplinary research throughout the course of a CSS project and across the CSS program, successful delivery of each output is predicated upon synthesis of results from multiple projects. Note that programmatic outputs will be evaluated and finalized each year based on current information about resources, state-of-the-science, and partner priorities.

Proposed Integrated FY16-19 CSS Program Outputs

FY16: Evaluation framework for high-throughput toxicity (HTT) testing schemes to inform specific EPA chemical evaluation objectives

A framework for evaluating the technical performance of HTT assays, explaining the biological context, and understanding the relationship to adverse outcomes of regulatory concern will be developed to address a range of EPA decisions. The collaborative development of this framework will help EPA lead the global conversation around innovations in evaluation/validation schemes for *in vitro* methods, for analysis of HT/HC data, and for *in vitro* to *in vivo* extrapolations.

FY16: Demonstrated knowledge tools for development of Adverse Outcome Pathways (AOPs) to enable incorporation of pathway level information in EPA decision making

Web-based infrastructure that facilitates organization of toxicological knowledge into adverse outcome pathway (AOP) frameworks will be piloted through application to develop selected AOPs. AOP development includes assembly and evaluation of the weight of evidence supporting mode-of-action based prediction/extrapolation for various EPA assessments. Tools and information will be disseminated to program offices and regional partners. In addition to helping disentangle complex biological pathways, this output is expected to enable more health-protective decisions by identifying earlier markers of adversity along a perturbed biological pathway.

FY 17: Enhanced capacity for using inherent chemical properties to predict potential environmental fate, biological dose, and adverse outcomes to support EPA evaluation of a wide range of compounds

Provide Web-based infrastructure including a dashboard to support elucidation of structure-based chemical feature sets linked to biological activity and chemical properties as well as analytical tools to predict potential for chemical transformation in environmental systems. For selected sets of chemicals and high priority AOPs, identify critical properties and intermediate properties of chemicals and materials that are predictive of potential risks. This output is expected to have broad application to data-poor chemicals and emerging materials, significantly enhancing EPA's ability to anticipate the human health and environmental impacts of manufactured chemicals/materials.

FY17: Evaluated, accessible exposure tools to provide EPA capacity for advanced exposure analysis to support program-specific chemical evaluations and sustainable decisions

Rapid measurement methods and computational approaches to efficiently characterize potential for real-world human and ecological exposure to large sets of data-poor chemicals developed and demonstrated through case

examples based on EPA exposure assessment needs. These tools are expected to enable EPA to make exposure informed and risk-based determinations in a variety of decision scenarios.

FY17: Translation of diverse data streams including high-throughput toxicity (HTT) data to inform EPA chemical evaluation and risk-based assessments

Demonstrate novel approaches for combining data and models produced and developed under other CSS and related projects through application in a variety of decision context to inform specific EPA chemical evaluation objectives. Value of information for chemicals with little traditional toxicity data will be evaluated and uncertainty in risk estimates will be characterized. This output will provide examples that enable EPA to integrate data from any variety of legacy and novel data sources using innovations in computational science and "big data" approaches to make more informed decisions.

FY18: Next generation high-throughput toxicity testing (HTT) chemical evaluation scheme that includes assays to broaden utility and application

Provide increased coverage of toxicity pathways in terms of new assays and models for key AOPs. Expand the types of chemicals that can be screened, and identify methods for incorporating xenobiotic metabolism into *in vitro* assay systems. This output will bring innovations in computational and molecular science to allow EPA to further realize the recommendations of the NRC report, Toxicity Testing in the 21st Century.

FY18: Tools for evaluating impacts of chemicals/materials/products early in development and across their life cycles that can be used to identify critical data needs and support sustainable decisions

Provide Web-based infrastructure to support integration of data related to chemical/material and product characteristics, exposure, and adverse impacts across the chemical/material life cycle. For selected case examples, pilot application of efficient tools and metrics to evaluate chemical impacts across the life cycle to support alternatives assessment and sustainable innovation. These tools will help inform the design of future laboratory and observational studies to enhance their relevance and applicability to EPA decisions. In addition, they will provide opportunities to test and evaluate hypotheses generated in observational studies.

FY19: Tools that shift the framework for evaluating toxicity from direct observation of apical outcomes to characterizing resilience and identifying tipping points that predictably lead to adverse outcomes.

Exploit new data streams to advance systems understanding of early indicators of adversity associated with chemical exposures and begin to build predictive models that enable effective EPA actions to protect human health and the environment including the health of children and other vulnerable lifestages, species, and groups.

Anticipated Accomplishments

Building on the impact of the CSS 2012-2016 research, CSS research will provide the data and methods to infuse 21st century science into EPA decisions. By shifting the thinking and increasing predictive capacity, CSS will lighten the burden of chemical assessment and promote proactive action and sustainable innovation. Anticipated impact of the CSS research program in the next 5-10 years is as follows:

- **Accelerate the pace of data-driven chemical evaluations**
  Develop, collate, and organize information on human and ecological exposure and impacts to provide accessible data to predict and estimate risks from exposures to chemicals efficiently in a manner fit for the specific decision context and regulatory need.

- **Enable decisions that are sustainable and public health protective**
  Provide methods for advanced analysis to assess safety of high-priority chemicals and inform EPA actions to anticipate, manage, and mitigate exposures to contaminants of greatest concern throughout their life cycle.

- **Shift the paradigm of toxicity characterization from apical endpoints to tipping points**
  Advance systems understanding of early indicators of adversity associated with chemical exposures to build predictive models that enable effective EPA actions to protect human health and the environment, including the health of children and other vulnerable lifestages, species, and groups.

- **Apply CSS tools to support sustainable innovation of chemicals and emerging materials**
  Translate and incorporate emerging and high-throughput exposure and toxicology data streams to evaluate impacts of EPA decisions, select safer chemical alternatives or substitutes, and inform the sustainable design and development of emerging materials and products.

Conclusions

Chemicals are integral to the American economy and provide key building blocks for the many products that benefit society. Sustainable development can yield unprecedented benefits to society today without compromising the health and welfare of future generations. Smart new strategies are needed to make decisions that protect public health and promote sustainable chemical design and use.

Chemicals fuel innovation—surface coatings that make buildings more resistant to wear; detergents that allow energy-efficient laundering; preservatives that keep cosmetics and foods fresh. However, depending on their use, chemicals may have harmful impacts on human health and the environment. For instance, evidence is mounting that some chemicals found in everyday products may disrupt the endocrine system and affect the development of children and sensitive ecological species. Novel information and methods are needed to make informed, timely decisions about thousands of chemicals in commerce.

As one of its highest priority goals described in the FY14-18 Strategic Plan, EPA aims to reduce the risks and increase the safety of chemicals that enter our products, environment, and bodies. It proposes to assess and reduce risks posed by chemicals and promote the use of safer chemicals in commerce. CSS research will provide the data and methods to infuse 21st century science into EPA decisions. Importantly, CSS proposes a significant paradigm shift in how existing and emerging chemicals and products can be evaluated for safety. By shifting the thinking and increasing predictive capacity, CSS will lighten the burden of chemical assessment and promote proactive action and sustainable innovation.

Appendix 1: Additional Policy Context and Scientific Advice

In addition to federal legislative mandates, several **state initiatives** are driving the needed advances in chemical evaluation.

The California State Drinking Water and Toxic Enforcement Act of 1986 (also known as Proposition 65) requires the State to publish a list of chemicals known to cause cancer, birth defects, or other reproductive harm. Since its inaugural publication in 1987, this list has grown to include nearly 800 chemicals. Proposition 65 requires businesses to notify Californians about significant amounts of these chemicals in their homes, workplace, drinking water, or environment. The public disclosure is designed to allow informed decisions by the consumer.

More recently, the California Safer Consumer Products Program also strives to reduce toxic chemicals in consumer products. It identifies specific products with potentially harmful chemicals and requires manufacturers to further evaluate whether these chemicals are necessary or safer alternatives exist. The Priority Product Work Plan will identify consumer "Priority Products" that contain "Candidate Chemicals" – those with traits that could harm people or the environment – for public disclosure. It is the first set of product-chemical combinations to be considered by the DTSC under the Safer Consumer Products Regulations.

The State of Washington's Reducing Toxic Threats initiative states that preventing exposures to toxics is the smartest, cheapest, and healthiest way to protect people and the environment. The Children's Safe Product Act (CSPA - Chapter 70.240 RCW) establishes the Children's Safe Product Reporting Rule. It requires manufacturers of children's products to report any sale of products containing a Chemical of High Concern to Children. The CSPA limits the amount of lead, cadmium, and phthalates allowed in children's products and these limits were substantially preempted by federal law. The Washington State Department of Ecology also works with the Consumer Product Safety Commission to ensure compliance with these requirements.

Finally, over the last few years EPA has commissioned the National Academies of Science to provide guidance on the state-of-the-science and approaches for using emerging science to promote effective, health-protective decisions and actions. CSS has strategically drawn from the NAS recommendations to address key research gaps that are not being addressed by partners outside EPA. The formative **National Academy of Sciences Reports** are as follows.

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

Traditional methods used to test chemicals for potential toxicity are expensive and time-consuming. To help address this issue, EPA asked the National Research Council (NRC) of the National Academy of Sciences (NAS) to conduct a comprehensive review of current toxicity testing approaches and propose a long-range vision and strategy for toxicity testing that incorporates emerging methods and technologies. The report's overall objective was to foster a transformative paradigm shift in toxicology based largely on the increased use of *in vitro* systems and computational modeling. The NRC report indicated implementation of the vision would take a substantial commitment of resources, the involvement of multiple organizations in government, academia, industry, and the public, and would take time

(10-20 years) to achieve. EPA's CSS research program has already made significant strides towards realizing the vision in the report.

Science and Decisions: Advancing Risk Assessment (2009)

Science and Decisions provides practical scientific and technical recommendations to address the many challenges facing risk assessments today, including the lack of adequate (exposure and hazard) data leading to uncertainties in assessments, and lengthy delays necessitated by complex assessments. These recommendations are placed within a broader framework for risk-based decision making to allow for more tailored assessments that are fit for purpose. CSS has begun to use this approach to evaluate and demonstrate how the data it generates can be used to augment and accelerate EPA's risk assessment practices.

Exposure Science in the 21st Century: A Vision and a Strategy (2012)

Recognizing that exposure science is a key component for providing the best public health and ecosystem protection, EPA asked the NRC to develop a long-range vision for exposure science in the 21st century, and a strategy for implementing this vision over the next twenty years. This report, along with three other NAS reports, Toxicity Testing in the 21st Century, Science and Decisions: Advancing Risk Assessment, and Sustainability and the US EPA, chart future directions for using innovative technology and scientific advances to better understand how chemicals impact human health and the environment. EPA's CSS research is already aligning with the research recommendations described in the report.

A Research Strategy for Environmental, Health, and Safety Aspects of Engineered Nanomaterials (2012)

In this report, the committee presents a strategic approach for developing the science and research infrastructure needed to address uncertainties regarding the potential EHS risks of ENMs. The committee identified three requirements for the strategy: (1) focus on human and environmental health, (2) provide flexibility to anticipate and adjust to emerging challenges, and (3) provide decision makers with timely, relevant, and accessible information. The committee's conceptual framework is characterized by a life-cycle perspective, a focus on linking key properties of ENMs in complex media to hazard and exposure, and a focus on anticipating significant risks from emerging ENMs.

Design and Evaluation of Safer Chemical Substitutions (2014)

EPA asked NRC to recommend a framework to inform government and industry decisions made about the use of chemical alternatives. A chemical alternatives assessment identifies, compares, and selects safer alternatives to chemicals of concern. The goal was to facilitate an informed consideration of the advantages and disadvantages of chemical alternatives. Alternatives for chemicals such as Bisphenol-A (used in plastic products) and perfluorinated chemicals (used in stain- and grease-resistant products) are currently being used in consumer products. The report, A Framework Guide for the Selection of Chemical Alternatives, considered potential impacts early in chemical design; considers both human health and ecological risks; integrates multiple and diverse data streams; considers tradeoffs between risks and factors such as product functionality; and identifies scientific information and tools required. This framework includes several important unique elements or advancements, such as: an increased emphasis on comparative exposure assessment; and a two-tiered approach to evaluating chemical alternatives that includes health and ecotoxicity, followed by a consideration of broader impacts.

Assessing Risks to Endangered and Threatened Species from Pesticides (2013)

The U.S. Fish and Wildlife Service (FWS) and the National Marine Fisheries Service (NMFS) are responsible for protecting species that are listed as endangered or threatened under the Endangered Species Act (ESA) and for protecting habitats that are critical for their survival. EPA is responsible for registering or reregistering pesticides under the Federal Insecticide, Fungicide, and Rodenticide Act (FIFRA) and must ensure that pesticide use does not cause any unreasonable adverse effects on the environment, which is interpreted to include listed species and their critical habitats. In the report, the NRC reviewed the state-of-the-science and identified research gaps required to support Ecological Risk Assessments for endangered and threatened species.

Review of the Environmental Protection Agency's State-of-the-Science Evaluation of Nonmonotonic Dose-Response Relationships as they Apply to Endocrine Disruptors (2014)

NAS was asked to review EPA's state-of-the-science paper. The purpose of the state-of-the-science paper was to help EPA policy makers determine if NMDRs capture adverse effects that are not detected using current chemical testing strategies and if there are adverse effects that current EPA testing misses. While EPA is interested in all aspects of NMDR, the state-of-the-science paper focused on endocrine disruptors—in particular, estrogen, androgen and thyroid active chemicals. The NAS review included an expert public comment period.

Incorporating 21st Century Science in Risk-Based Evaluations (In progress)

One of the CSS research program's goals is to develop approaches for integrating advances in toxicity testing and exposure science to accelerate the pace and enhance the predictive capacity of risk-based evaluations. In August 2014, EPA requested guidance from the National Academy of Sciences (NAS) on how to foster this integration and take advantage of the broader spectrum of 21st century science emerging from diverse research fields including biotechnology and computational sciences. This resulting NRC study will provide EPA recommendations on integrating new scientific approaches into risk-based evaluations, how best to integrate and use emerging results in evaluating chemical risk, and identify how traditional risk assessment can incorporate new science.

Unraveling Low Dose: Case Studies of Systematic Review of Evidence (In progress)

As a follow-up study to the NAS review of the draft Non-Monotonic Dose Response State-of-the-Science Paper, the National Research Council (NRC) will convene an expert committee to develop a systematic review approach for determining whether EPA's current hazard assessment approach is sufficient to consider evidence of low-dose adverse effects that act via an endocrine-mediated toxicity pathway.

Appendix 2: Examples of CSS Partnerships

National Nanotechnology Initiative (Formed in 2000)

The National Nanotechnology Initiative (NNI) is a U.S. government research and development (R&D) initiative involving the nanotechnology-related activities of 20 departments and independent agencies (including EPA, National Science Foundation, National Institutes of Health, Department of Defense, National Institute of Occupational Safety and Health, Food and Drug Administration, and United States Department of Agriculture). Under its Nanotechnology Environmental Health Implications working group (NEHI), EPA participates in coordinated research to address research to assess the potential human and environmental risks of nanomaterials. The NNI and NEHI advance collaboration and coordination of activities both among U.S.-based agencies and internationally with various regulatory and coordinating bodies primarily in Europe and Asia.

Consumer Products Safety Commission

EPA and the U.S. Consumer Product Safety Commission (CPSC) are collaborating to develop protocols to assess the potential release of nanomaterials from consumer products; develop credible rules for consumer product testing to evaluate exposure; and to determine potential public health impacts of nanomaterials used in consumer products.

Toxicity Testing in the 21st Century (Tox21, established in 2008)

Tox21 pools funding, expertise, chemical research, data and screening tools from multiple federal agencies including EPA, the National Toxicology Program/National Institute of Environmental Health Science, National Center for Advancing Translational Sciences and the Food and Drug Administration. EPA's contribution to Tox21 is primarily through ToxCast, which to date, has screened nearly 2000 chemicals across approximately 700 assay endpoints. Tox21 has screened nearly 8200 chemicals across approximately 50 endpoints. The partnership has worked extremely effectively to enhance the ability to predict the safety of chemicals. Significant improvements have also been made in data access, reliability, and usability for the community of stakeholders inside and outside EPA.

European Chemicals Agency (Established in 2010)

EPA's Office of Chemical Safety and Pollution Prevention (OCSPP) and the Office of Research and Development (ORD) are partnering with the European Chemicals Agency (ECHA) to enhance technical cooperation and to share knowledge, experience and best practices about chemical management practices. ECHA and EPA meet at least quarterly through conference calls and in-person meetings. The partnership is ongoing and has resulted in scientific data exchanges; sharing of regulatory chemical management plans; joint participation in scientific and regulatory workshops; and trainings across both organizations to demonstrate various online chemical databases and tools.

Organization of Economic Cooperation and Development (Established in 2012)

EPA, in collaboration with the international scientific community, the European Joint Research Center, the US Army Corp of Engineers, and the Organization of Economic Cooperation and Development are developing tools to facilitate the use of AOPs to help evaluate chemicals for potential risks. The strategic partnership has resulted in the development of the AOP Knowledge Base (AOP-KB) and the AOP Wiki. The AOP-KB is the foundational Web-based

platform designed to bring together knowledge about how chemicals can prompt adverse outcomes. The AOP Wiki, a module of the AOP-KB, is an interactive virtual encyclopedia for AOP development that is being populated with input from international scientific experts.

California Department of Toxic Substances Control
(Established in 2012)

California's Department of Toxic Substances Control (DTSC) and EPA's Office of Chemical Safety and Pollution Prevention, Region 9, and the Office of Research and Development are collaborating on efforts to advance Green Chemistry practices and activities. The CSS research program's role in the collaboration is to expand the applications of developed CSS tools to inform product and chemical alternative analyses. Specifically, CSS has shared database architecture and chemical information to help California develop publically available chemical information databases.

Health Canada
(Established in 2013)

Health Canada and EPA are collaborating to explore approaches for using new data streams to assess chemicals for potential risks to human health. Health Canada is currently under a regulatory mandate to develop Chemical Management Plan 3 (CMP3). The chemicals in CMP3 include chemicals lacking traditional toxicity data. Health Canada is working with EPA CSS to determine how to use high-throughput screening data and other types of non-traditional chemical data to help fill the data gaps for the chemicals in CMP3.

Appendix 3: Table of Proposed Outputs, Chemical Safety for Sustainability Research Program, FY16-FY19

The following table lists the expected outputs from the Chemical Safety for Sustainability research program, organized by topic. Note that outputs may change as new scientific findings emerge. Outputs are also contingent on budget appropriations.

Project Area	Outputs
Topic 1: Chemical Evaluation	
High-Throughput Toxicology	FY16 - Evaluation framework for high-throughput toxicity testing schemes to inform specific Agency chemical evaluation objectives FY18 - Next generation high-throughput toxicity testing chemical evaluation scheme that includes assays to broaden utility and application
Rapid Exposure and Dosimetry	FY17 - Evaluated, accessible exposure tools to provide Agency capacity for advanced exposure analysis to support program-specific chemical evaluations and sustainable decisions FY18 - Next generation high-throughput toxicity testing chemical evaluation scheme that includes assays to broaden utility and application FY19 - Tools that shift the framework for evaluating toxicity from direct observation of apical outcomes to characterizing resilience and identifying tipping points that predictably lead to adverse outcomes
Topic 2: Life Cycle Analytics	
Sustainable Chemistry	FY17 - Enhanced capacity for using inherent chemical properties to predict potential environmental fate, biological dose, and adverse outcomes to support Agency evaluation of a wide range of compounds FY18 - Tools for evaluating impacts of chemicals/materials/products early in development and across their life cycles that can be used to identify critical data needs and support sustainable decisions
Emerging Materials	FY17 - Enhanced capacity for using inherent chemical properties to predict potential environmental fate, biological dose, and adverse outcomes to support Agency evaluation of a wide range of compounds FY18 - Tools for evaluating impacts of chemicals/materials/products early in development and across their life cycles that can be used to identify critical data needs and support sustainable decisions

Project Area	Outputs
Topic 2: Life Cycle Analytics	
Life Cycle and Human Exposure Modeling	FY17 - Evaluated, accessible exposure tools to provide Agency capacity for advanced exposure analysis to support program-specific chemical evaluations and sustainable decisions FY18 - Tools for evaluating impacts of chemicals/materials/products early in development and across their life cycles that can be used to identify critical data needs and support sustainable decisions
Ecological Modeling	FY17 - Evaluated, accessible exposure tools to provide Agency capacity for advanced exposure analysis to support program-specific chemical evaluations and sustainable decisions FY17 - Enhanced capacity for using inherent chemical properties to predict potential environmental fate, biological dose, and adverse outcomes to support Agency evaluation of a wide range of compounds FY18 - Tools for evaluating impacts of chemicals/materials/products early in development and across their life cycles that can be used to identify critical data needs and support sustainable decisions
Topic 3: Complex Systems Science	
AOP Discovery and Development	FY16 - Demonstrated knowledge tools for development of adverse outcome pathways to enable incorporation of pathway level information in Agency decisions FY17 - Translation of CSS data streams including high-throughput toxicity data to inform Agency chemical evaluation and risk-based assessments FY19 - Tools that shift the framework for evaluating toxicity from direct observation of apical outcomes to characterizing resilience and identifying tipping points that predictably lead to adverse outcomes
Virtual Tissues	FY16 - Demonstrated knowledge tools for development of adverse outcome pathways to enable incorporation of pathway level information in Agency decisions FY17 - Translation of CSS data streams including high-throughput toxicity data to inform Agency chemical evaluation and risk-based assessments FY19 - Tools that shift the framework for evaluating toxicity from direct observation of apical outcomes to characterizing resilience and identifying tipping points that predictably lead to adverse outcomes

Project Area	Outputs
Topic 4: Solutions-Based Translation and Knowledge Delivery	
Demonstration and Evaluation	FY16 - Evaluation framework for high-throughput toxicity testing (HTT) schemes to inform specific Agency chemical evaluation objectives FY17 - Translation of CSS data streams including high-throughput toxicity data to inform Agency chemical evaluation and risk-based assessments
Partner-Driven Research	Products based on short term partner needs for high priority technical support and targeted research.
Strategic Outreach	Products will include public workshops, tailored meetings and webinars, training and strategic collaborations, among others.

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