



Chemical Safety for Sustainability

Strategic Research Action Plan, 2016-2019 (Preliminary Draft)

U.S. EPA
Office of Research and Development
Washington, DC 20460

PRELIMINARY DRAFT NOTICE: This Strategic Research Action Plan, 2016–2019 is a preliminary draft. It has not been formally released by the U.S. Environmental Protection Agency (EPA) and should not at this stage be construed to represent Agency policy, nor the final research program.

Table of Contents

I.	<u>EXECUTIVE SUMMARY</u>	2
II.	<u>INTRODUCTION</u>	2
III.	<u>PROGRAM PURPOSE</u>	3
	III.A. PROBLEM STATEMENT	3
	III.B. PROGRAM VISION	3
IV.	<u>RESEARCH SUPPORTS EPA PRIORITIES AND MANDATES</u>	4
	IV.A. STATUTORY AND POLICY CONTEXT	4
	IV.B. EPA PRIORITIES	4
V.	<u>RESEARCH OBJECTIVES</u>	6
VI.	<u>ANTICIPATED RESEARCH ACCOMPLISHMENTS</u>	7
VII.	<u>PROGRAM DESIGN</u>	7
	VII.A. PROGRAM EVOLUTION	8
	VII.B. PRODUCING AN INTEGRATED PROGRAM	9
	VII.C. PARTNER AND STAKEHOLDER INVOLVEMENT	11
VIII.	<u>RESEARCH TOPICS</u>	12
IX.	<u>CONCLUSION</u>	21
	<u>APPENDIX A. CSS FY 16-19 RESEARCH OUTPUTS</u>	22

I. Executive Summary

[To be completed in Final Strategic Research Action Plan]

II. 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 science-based, more-timely decisions about chemicals, many of which have not been thoroughly evaluated for potential risks to human health and the environment. The EPA's Chemical Safety for Sustainability Research Program (CSS) is designed to meet this challenge and supports the agency priority of reducing risks associated with exposure to chemicals in commerce, the environment, and products and food.

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 and populations. CSS research program outputs will enable the Agency to address impacts of existing chemicals and materials across the lifecycle as well as to anticipate impacts of new chemicals and emerging materials. The CSS research program also provides the scientific basis for evaluating complex interactions of chemical and biological systems to support Agency decisions.

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

- Integrate CSS research
- Prioritize research to focus on key areas where CSS will lead science
- Demonstrate how research will be translated and actively delivered for use in Agency decision making
- Evaluate impact of CSS outputs on partner needs
- Explore and incorporate collaboration and leveraging opportunities across the National Programs and with external stakeholders.

The CSS StRAP is one of six research plans, one for each of EPA's national research programs in ORD. EPA's strategic research action plans lay the foundation for EPA's research staff and their partners to provide focused research efforts that meet the Agency's legislative mandates, as well as the goals outlined in the *Agency'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 the Agency needs to meet such priorities, while also cultivating a new paradigm for efficient, innovative, and responsive government and government-sponsored environmental and human health research.

This *Strategic Research Action Plan* outlines the approach designed to achieve EPA's objectives for advancing chemical safety and sustainability. It highlights how the Chemical Safety for Sustainability research program integrates efforts with other research programs across EPA's Office of Research and Development 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 EPA's Office of Research and Development, 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.

III. Program Purpose

III.A. Problem Statement

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, more-timely decisions about chemicals, many of which have not been thoroughly evaluated for potential risks to human health and the environment. The EPA's Chemical Safety for Sustainability Research Program (CSS) is designed to meet this challenge.

III.B. Program Vision

CSS will lead development of innovative science to support safe, sustainable use of chemicals and materials required to promote ecological wellbeing, including human and environmental health, as well as to protect vulnerable species and populations.

The CSS overarching priorities are to:

- Enable the Agency to address the impact of existing chemicals and materials/products across the lifecycle.
- Enable the Agency to anticipate the impacts of new chemicals and materials/products across the lifecycle.
- Enable consideration and evaluation of complex interactions of chemical and biological systems to support Agency decisions.

IV. Research Supports EPA Priorities and Mandates

IV.A. Statutory and Policy Context

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

Table 1. EPA Regulatory Drivers for CSS Research		
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/federalfooddrugandcosmeticactfdca/default.htm
Federal Insecticide 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
Resources Conservation and Recovery Act	RCRA	http://www.epa.gov/epawaste/laws-regs/index.htm
Safe Drinking Water Act	SDWA	www.epa.gov/lawsregs/laws/sdwa.html
Toxic Substances Control Act	TSCA	www.epa.gov/lawsregs/laws/tsca.html

Table 1. CSS research supports chemical risk management decisions mandated by legislation.

IV.B. EPA Priorities

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 of the EPA's Fiscal Year 2014-2018 Strategic Plan and inform

Agency 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. The strategic research plan described in this StRAP is intended to fulfill the needs described in the Applied Research needs associated with this goal, and to anticipate and position the Agency to meet its longer term goals.

EPA Strategic Goal 4, objective:

Ensure Chemical Safety. Reduce the risk and increase the safety of chemicals that enter our products, our environment, and our 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 and populations. Innovative research will provide the tools to:

- Assess safety of high-priority chemicals and advance our understanding of the cumulative risks that may result from multiple chemical and non-chemical stressors.
- Enhance chemical screening and testing approaches for priority setting and context-relevant chemical assessment and management.
- Inform Agency actions and help local decision makers manage and mitigate exposures to contaminants of greatest concern.
- Promote innovations in green chemistry and green engineering to help encourage use of safer chemicals in commerce.
- Evaluate human health and ecological risks associated with new chemical substitutes designed to promote safer alternatives.
- Provide the systems understanding needed to adequately protect the health of children and other vulnerable groups.

In addition, this CSS research meets Agency’s Cross-Agency Strategies as follows:

- **Working Toward a Sustainable Future:** by incorporating sustainable chemicals and materials innovation, founded on knowledge and tools that help evaluate their safety throughout their lifecycle to human health and the environment, and in particular vulnerable and susceptible populations.
- **Working to Make a Visible Difference in Communities:** by democratizing access to CSS data and tools, by actively engaging stakeholder communities, and working to develop tailored solutions to meet the needs of communities.
- **Launching a New Era of State, Tribal, Local, and International Partnerships:** by engaging international partners to advance the science of chemical safety evaluations and to globally lead and coordinate adoption of new testing and evaluation strategies; by engaging state, tribal, and local partners in translating the products of CSS research and actively delivering them for tailored application to local decision contexts.
- **Embracing EPA as a High-Performing Organization:** by closely coordinating with EPA program and regional partners to develop research solutions that are timely and relevant to their needs; by advancing computational and predictive toxicology to accelerate the pace of decision

making; by promoting data generation and public access through iCSS dashboards; and by enhancing transparency in the bench-to-policy evolution of CSS products.

V. Research Objectives

CSS research is conducted to provide the fundamental knowledge infrastructure and complex systems understanding required to predict potential impacts from use of manufactured chemicals, as well as 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 Agency partners and external stakeholders.

Table 2. CSS Research Objectives			
CSS Research	What We Do	Near Term Objective	Long Term Objective
Build Knowledge Infrastructure	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

Table 2. Summary of near and longer term components of CSS research objectives.

VI. Anticipated Research Accomplishments

The Outputs of CSS FY 16-19 StRAP (described in more detail in the Appendix and in Figure 3) have been defined in close collaboration with EPA Program and Regional partners and were designed to meet their needs. Building on the impact of the CSS 2012-2016 research, these outputs are expected to accomplish the following:

- (1) **Accelerate the pace of data-driven chemical safety evaluations:** Information on human and ecological exposure and impacts is incorporated into ORD integrated applications to provide accessible data and tools to support Agency program- and decision-specific needs for chemical safety evaluation.
- (2) **Enable the Agency to use 21st Century Science to make sustainable and public-health protective decisions:** Evaluated, efficient chemical evaluation methods are developed to provide and enhance agency capacity for advanced analysis to support program-specific environmental health evaluations and sustainable decisions.
- (3) **Shift the paradigm of toxicity characterization from apical endpoints to “tipping points”:** Complex systems information across all levels of organization associated with adverse outcomes is incorporated into predictive modeling to inform Agency risk-based assessments.
- (4) **Apply CSS tools to support sustainable innovation and evaluation of chemicals and emerging materials:** Tools are developed and applied to incorporate emerging and high-throughput (HTP) exposure and toxicology data streams to evaluate impacts of agency decisions on safe and sustainable innovation and use of manufactured chemicals and materials across the product lifecycle.

VII. Program Design

The CSS research program integrates advances in information technology, computational chemistry, and molecular biology to improve Agency prioritization of data requirements and science-based assessment of chemicals through signature research in Computational Toxicology. USEPA investments in advanced chemical evaluation and lifecycle analytics are providing decision support tools for high-throughput screening (HTS) and efficient risk-based decisions.

The CSS Strategic Research Action Plan 2016-2019 (StRAP) provides the overall framework for CSS research. Fiscal year 2016 (FY16) planning presents a ripe opportunity to conduct a review of the program and look for ways to integrate the research, enhance transdisciplinary collaboration, promote and foster innovation, enhance transparency and access to CSS products, and significantly amplify the impact of this important research. This document builds on the original vision of the research program outlined in the CSS Strategic Research Action Plan 2012-2016.

VII.A. Program Evolution

The CSS program has endeavored to integrate and focus on a handful of research topics for optimal impact. The most noteworthy driver for this integration was the demand to drive the leading edge of science, be prepared to meet the urgent needs of the Agency 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.

The resulting program builds on the original vision of the research program outlined in the CSS Framework and the CSS 2012-2016 StRAP (Figure 1). The CSS 2012-2016 StRAP included 8 research themes and 21 research projects. This CSS 2016-2019 StRAP proposes 4 research topics and 9 integrated, transdisciplinary project areas.

In evolving the CSS program, we have significantly reformulated key areas of the program to focus research and design a cohesive, high impact program to meet high priority partner needs.

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, metabolism, extrapolation, and cumulative risk are deployed 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, lifecycle 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 lifecycle impact analysis is being directed to efficiently evaluate alternatives and to fill a gap in available sustainability metrics.

In integrating the research program, it became eminently evident that a research program such as CSS would fail to deliver impact if it merely rested on the laurels of its research. 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

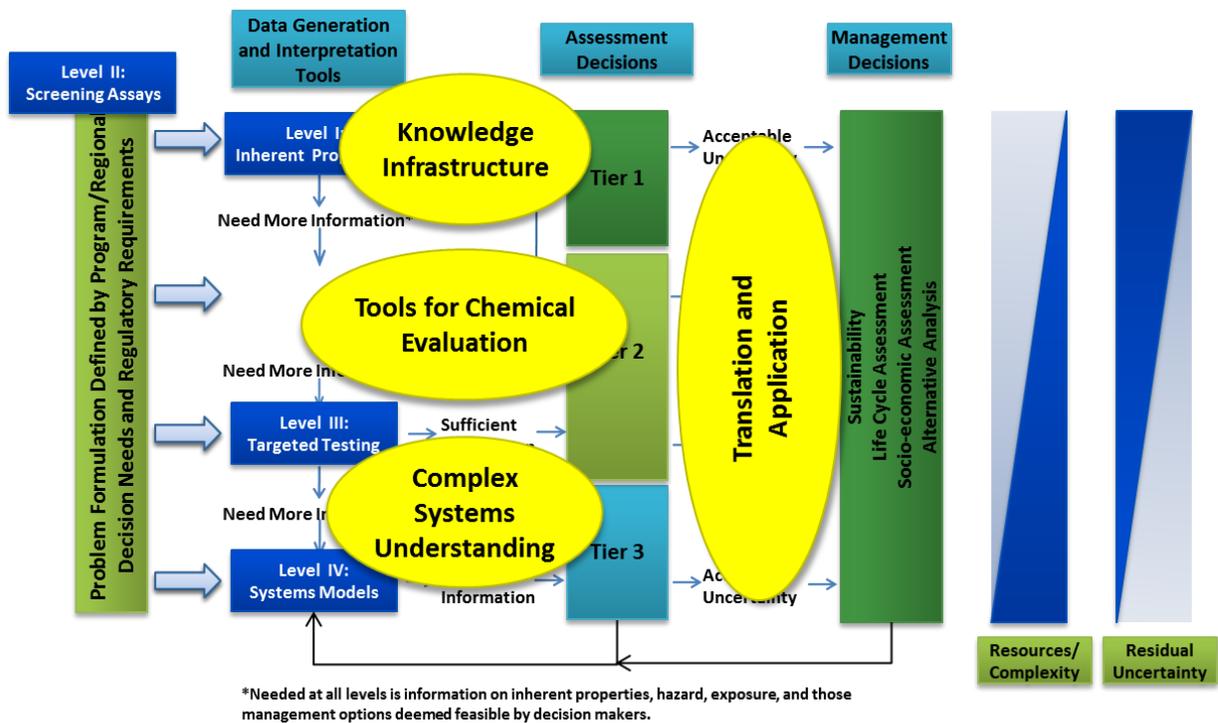


Figure 1. Mapping of CSS FY 16-19 Objectives to Framework Research Tiers described in the CSS 2012-2016 StRAP, demonstrating the continuous evolution, integration, and innovation of the Program within the construct of its foundational framework.

VII.B. Producing an Integrated Program

Cross-Program Integration: CSS will be integrating with the other National Research Programs (NRPs) through critical research areas identified in the ORD cross-cutting research roadmaps. The CSS had the lead on developing ORD’s Children’s Environmental Health Research Roadmap (see CEH roadmap). This roadmap inventories and coordinates research in CSS with complementary CEH research in the ACE, SHC, SSWR, and HHRA programs. Through StRAP planning over the course of the next year additional opportunities to integrate with the other NRPs to address gaps identified in the other three roadmaps (Climate, Nitrogen, and Environmental Justice) will be explored.

Current CSS research plans call for integration and collaboration with the HHRA research program. Integration includes specific activities that have been scoped strategically and described within the CSS Demonstration and Evaluation project area (see section VII) and collaboration will focus on HHRA projects characterizing use of new data in NCEA assessments.

Additional opportunities for integration are being identified based on feedback from program partners and ORD scientists. These opportunities for integration will be explored in the coming months as the National Research Programs (NRPs) complete development

of the StRAPs. Potential opportunities for integration and leveraging across the NRPs include:

- ACE, SSWR, SHC: Lifecycle analysis
- ACE: HTT for air pollutants [(Result of two successful Pathfinder Innovation Projects (PIPs))]
- SSWR: Effect-based monitoring
- SHC: Accessible exposure information
- HSR: Rapid screening tools

Cross agency integration: CSS proposes a significant paradigm shift in how existing and emerging chemicals and products can be evaluated for safety. The focus is on predictive capacity and agile responses. The objective is to move from a knowledge poor management posture to one that is proactive, sustainable, and fostering innovation. To achieve this paradigm shift, CSS relies heavily on strategic partnerships in the US and internationally. Examples of partnerships for advancement and potential applications of research results include the following.

- Tox21: trans-federal partnership for advancing toxicity testing in the 21st Century
 - Additional collaborations with the European Commission, Canada, as well as with the private sector and public health advocacy groups.
 - Organization for Economic Cooperation and Development (OECD): Related international collaborations for advancing development and application of molecular screening tools, the Adverse Outcome Pathway Framework
- National Nanotechnology Initiative (NNI): trans-federal partnership for advancing sustainable development and evaluation of nanomaterials
 - Targeted collaborations with industry

STAR Grants Program: STAR grants topics solicited and funded through the CSS program are designed to advance fundamental science required to evaluate and promote safe, sustainable chemical development and use. In addition, STAR grants topics are funded through CSS to apply emerging and cutting edge technologies in biology and chemistry to advance methodologies for computational exposure and toxicology. In addition to providing chemical safety stakeholders with advanced tools, these investments enlarge the network of academic disciplines, institutions, and young scientists with an awareness of, and expertise in, computation exposure and toxicology required to promote human and ecological health. Where feasible, RfA's are developed to take advantage of significant science investments made by other Agencies such as NSF and NIH and by international funding organizations.

Many grantees receiving STAR support actively embrace collaborations with CSS scientists. These cooperative activities provide a venue for disseminating CSS data and tools to the larger scientific community while enriching CSS research through exposure to emerging science in a vast array of disciplines.

CSS STAR Grant Topics that have been solicited and or awarded over the course of the last few years include:

- Centers for the Environmental Implications of Nanotechnology (In conjunction with NSF)
- Development and Use of Adverse Outcome Pathways that Predict Adverse Developmental Neurotoxicity
- EPA/NSF Networks For Characterizing Chemical Life Cycle (NCCLCS)
- EPA/NSF Networks for Sustainable Molecular Design and Synthesis (NSMDS)
- Organotypic Culture Models for Predictive Toxicology Center
- 21st Century Methods for Exposure Science
- Systems-Based Research For Evaluating Ecological Impacts Of Manufactured Chemicals

VII.C. Partner and Stakeholder Involvement

The process for developing this StRAP unfolded through a series of meetings with program and regional partners, among labs and centers involved with CSS, and through interactions with external stakeholders. This document was profoundly strengthened by the informed and interactive iteration among these groups.. To transparently engage the community of EPA partners and collaborators the CSS staff shared significant milestones and interim milestones of this process through accessible shared platforms.

In defining the scope of the science for project areas, the following criteria were considered:

- If CSS does not lead and conduct this research, the science will not be developed by others
- Research approach is innovative and applies emerging science and technology
- Research project areas are framed
 - to advance sustainable chemical development, manufacture and use
 - promote human and ecological health and protect vulnerable organisms
 - to demonstrate valued added of information, tools, approaches being developed to support Agency decisions
- Research addresses CSS partners' highest research and science priorities
 - Priority chemicals/material: endocrine disrupting chemicals (EDCs), flame retardants, fragrances, carbon nanotubes (CNTs), other OPPT workplan chemicals
 - Priority endpoints: endocrine disruption developmental toxicity
 - Priority receptors: vulnerable and sensitive ecological species and children
 - All data and tools developed, evaluated, and translated through application to case examples of interest to partners
- Results are transparent and accessible

- All data accessible to EPA partners upon delivery of product
- All tools accessible to EPA partners upon delivery of product
- Data and tools supported by appropriate QA, documentation and peer reviewed publication
- Research is timely, relevant, responsive, and impactful - CSS research contributes broad scientific impact through focus on partner solutions
- Synergies within and among project areas - CSS resources are leveraged through integration across the program

These criteria helped 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.

VIII. Research Topics

In the CSS, research is organized by topics and implemented by transdisciplinary teams of scientists working within and across these topics. To provide further focus and amplify the impact of CSS research in the coming years, the eight themes described in the CSS 2012-2016 StRAP have been reduced to four Research Topics (Figure 2).

Three research topics provide core systems science and tools:

Chemical Evaluation: Advance cutting-edge methods for chemical prioritization, screening & testing. Provide the data for risk-based evaluation of existing chemicals and emerging materials.

Complex System Science: Adopt a systems-based approach to examine the complex interactions among exposures and biological effects. Predict adverse outcomes resulting from exposures to chemicals.

Lifecycle 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.

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:

Solutions-based Translation and Knowledge Delivery: promotes web based tools, data, and applications focused on tailored solutions to support chemical safety evaluations and related decisions, responds to short-term high priority science needs for CSS partners, allows for active and strategic engagement of the stakeholder community.

Chemical Safety for Sustainability

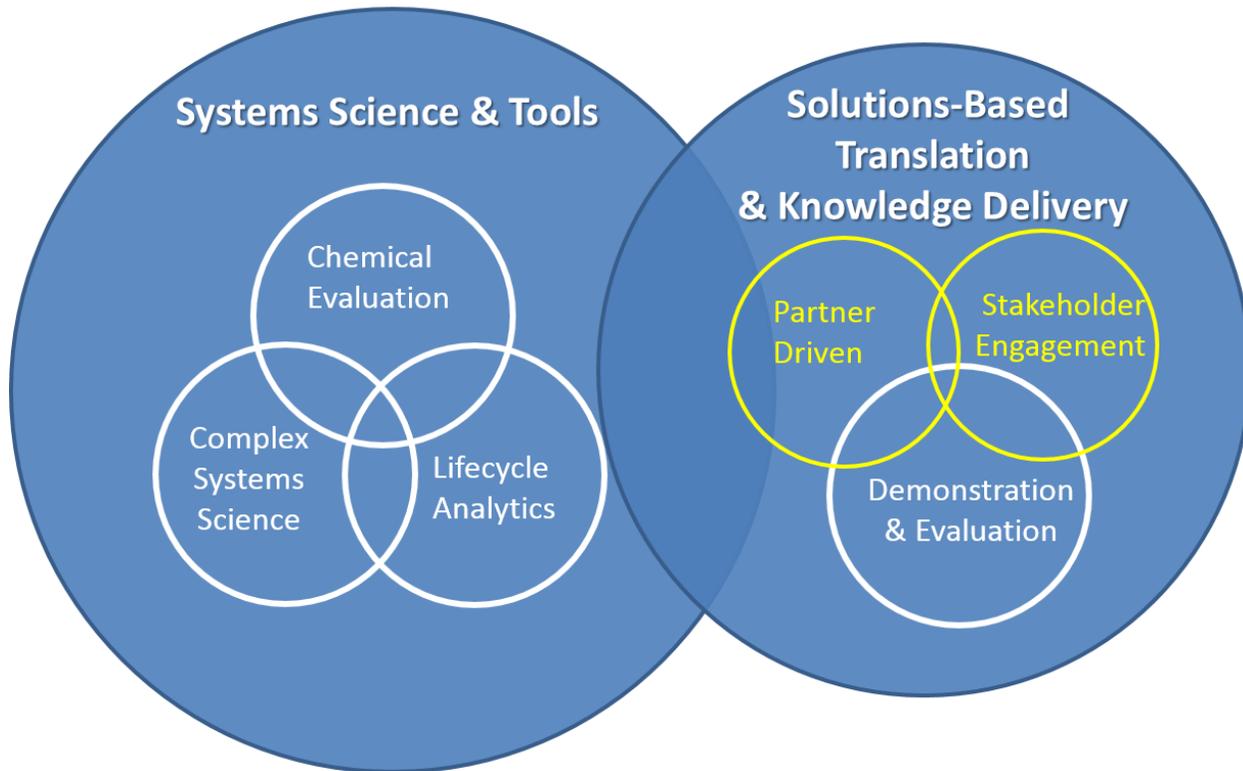


Figure 2. CSS program includes three research topics (left) and one translation topic, anchored in a ‘demonstration and evaluation’ component that translates research results to fit for purpose applications to address the Agency’s priorities.

New CSS integrated research project areas within each research topic are described at a strategic level below. Integrated research will also be required across these topics and project areas to effectively address scientific gaps and provide tools to enable Agency decisions. Agency priorities for specific classes of chemicals, human and ecological health endpoints, and vulnerable groups will be used to design CSS cross-cutting research and to further focus this integration. The CSS cross-cutting research areas for FY16-19 include: **(1) Emerging and methodologically challenging compounds; (2) Endocrine disruption (including thyroid); and (3) Children’s environmental health.** Importantly, cross-cutting CSS research in **computational toxicology** will exploit new and emerging scientific tools in molecular biology, computational chemistry, and informatics (i.e. computational toxicology) to **transform chemical safety evaluation.**

Topic 1: Chemical Evaluation

1. High Throughput Toxicology

Agency Research Drivers

- Current chemical testing is expensive and time consuming
- Only a small fraction of chemicals have been fully evaluated for potential adverse human health effects
- Rapid and efficient methods are required to prioritize, screen, and evaluate chemical safety

Science Challenge

- Expand coverage of high priority biological areas such as endocrine disruption and adverse outcomes such as developmental toxicity
- Develop approaches for incorporation of xenobiotic metabolism and challenging chemical classes into high-throughput test methods

Innovative Research Approach

- Adapt emerging and improving technologies in high-throughput screening assays for rapid testing of chemical toxicity
- Develop and incorporate assays for key molecular initiating events
- Evaluate cutting-edge methods to account for and incorporate xenobiotic metabolism
- Evaluate methods for generating high-throughput screening data on classes of chemicals that are not amenable to current methods
- Build toward a broader and more efficient high-throughput testing strategy, including the use of global assays capable of extensive biological activity recognition

Anticipated Impact

- Rapid and efficient toxicity testing paradigms.
- Accessible data on chemicals and endpoints of interest to the Agency.
- Translation tools to support interpretation of results from high-throughput toxicity schemes to inform decisions on chemical safety

2. Rapid Exposure and Dosimetry

Agency Research Drivers

- Only a small fraction of chemicals have been fully evaluated for potential impacts to ecological and human health
- Rapid risk-based evaluation of chemical safety requires prediction of potential hazard, exposure, and dosimetry
- Efficient methods and tools are required to develop exposure data and high-throughput estimates of exposure and dosimetry for thousands of chemicals

Science Challenge

- Develop, apply, and evaluate advanced measurement methods and computational approaches to efficiently characterize the potential for real-world human exposure to chemicals, including those associated with consumer product use

Innovative Research Approach

- Develop and apply innovative data collation and mining approaches
- Develop and apply advanced analytical chemistry methods to screen environmental and biological samples for large sets of chemicals and metabolites
- Combine innovative statistical and mechanistic modeling approaches to forecast potential exposures for thousands of chemicals and evaluate results

Anticipated Impact

- Advance computational exposure science required to revolutionize chemical safety evaluation
- Evaluated exposure predictions for use in risk-based evaluation of thousands of existing and new chemicals
- Provide the exposure component for the EDSP21, TSCA21, and Chemical Contaminants List case studies to support the screening of hundreds to thousands of chemicals

Topic 2: Complex Systems Science

1. Adverse Outcome Pathway (AOP) Discovery and Development

Agency Research Drivers

- There is a need to evaluate the human health and/or ecological relevance of effects observed in in vitro or in vivo models
- Quantitative linkages are required between measures of biological perturbation provided by new and emerging methods and metrics of adverse outcome relevant for Agency risk-based decisions
- AOP is a conceptual framework designed to aid evaluation of the relationships between measures of a stressor-induced perturbation and adverse outcomes at a level of biological organization considered relevant to support action

Science Challenge

- Advance predictive applications of the AOP framework and support 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

Innovative Research Approach

- Employ novel bioinformatic and computational approaches to mine scientific literature and data in support of AOP development
- Assemble individual AOPs into networks that may aid prediction of more complex interactions and outcomes resulting from exposure to complex mixtures, multiple stressors, and/or chemicals with multiple modes of action

Anticipated Impact

- AOP knowledge base that enhances the utility of pathway-based data for decision making.

2. Virtual Tissues

Agency Research Drivers

- Innovation in methods to predict consequences of decisions requires translation of ever-advancing and emerging science
- 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.

Science Challenge

- Develop systems to assemble pathway data, information, and knowledge of biology into dynamic VTMs for assessing developmental toxicity
- Provide a platform of experimental and computational models that capture system dynamics for predictive toxicology

Innovative Research Approach

- Apply enabling and emerging technologies in executable biology, morphogenesis, synthetic biology, and mechanical forces at the cellular level to measure and model complex systems dynamics for high priority biological pathways

Anticipated Impact

- Improved understanding of the relationship between chemical exposures and ecological and human health outcomes, including impact on the developing organism
- Capacity to predict adverse outcomes resulting from exposures to specific chemicals and mixtures over time and space

Topic 3: Life-Cycle Analytics

1. Sustainable Chemistry

Agency Research Drivers

- Strategies are required to evaluate the potential for environmental and human health impacts of new and alternative chemicals and materials prior to being introduced into commerce

Science Challenge

- Exploit recent advances in high-throughput (HTP) screening, mechanistic toxicology, and computational chemistry to identify influential chemical determinants of adverse biological impacts

Innovative Research Approach

- Collate and mine knowledge of inherent chemical properties and features to distill principles
- Apply knowledge of chemical features to inform interpretation of HTP toxicity data and models; apply HTP toxicity data and models to elucidate key features associated with potential for hazard

- Conduct mechanistic research to link upstream chemistry with downstream biology incorporating considerations of transformations in real-world biological and environmental systems

Anticipated Impact

- Chemical knowledge resource that consolidates basic chemical data resources along with cheminformatic tools for shared use
- Improved understanding of chemical features associated with potential for environmental and human health impacts

2. Emerging Materials

Agency Research Drivers

- Innovations in chemical and material design are rapidly changing the landscape of industrial and consumer products as novel materials, particularly engineered nanomaterials (ENMs), are incorporated to enhance their performance
- Scientifically-supported approaches are required to incorporate emerging materials, including ENMs, into current systems such as FIFRA and TSCA for evaluating applications of manufactured chemicals

Science Challenge

- Provide science and tools to enable the Agency to efficiently evaluate impacts of ENMs and anticipate impacts of new materials

Innovative Research Approach

- Focus on understanding ENM features to predict impacts of ENMs under real-world conditions
- Develop and characterize a library of core nanomaterials including systematically aged materials
- Develop an understanding of interactions between ENMs and biological or other complex media
- Address the complexity of relating nanomaterial features directly to risk by considering critical intermediate properties of ENMs that are predictive of potential impacts

Anticipated Impact

- Identified material features that drive the potential for toxicity or exposure to support read across and categorization
- Methods to efficiently characterize ENMs in the full range of media and across the material lifecycle
- Tools to predict emission, transformation, potential for exposure, and impacts of ENMs across the material/product lifecycle

3. Lifecycle and Human Exposure Modeling

Agency Research Drivers

- 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

Science Challenge

- Develop a framework and database structure that integrate chemical exposure and life-cycle impact assessment modeling
- Develop a tool for efficiently evaluating environmental and human health impacts of use across the chemical/product life cycle to support sustainability analysis and risk-based decisions

Innovative Research Approach

- Operationalize 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
- *Develop an approach to harmonize the product-centric nature of LCA with the chemical-centric focus of comparative risk analysis by taking chemical function into account*

Anticipated Impact

- Efficient tools and metrics to evaluate chemical impacts across the life cycle and to support alternatives assessment and sustainable chemical use

4. Ecological Modeling

Agency Research Drivers

- For the majority of chemicals, little or no data exist to evaluate exposure and effects of chemical use on ecological systems
- High-throughput screening methods provide opportunities to incorporate biological-effects information for untested and untestable species
- Evaluation of risks to threatened and endangered species from exposures to chemicals such as pesticides, requires consideration of population effects and spatial distribution of potential impacts

Science Challenge

- Advance efficient methods to improve risk assessments with limited data availability, as well as more complex approaches that can target data-rich applications

Innovative Research Approach

- Integrate environmental fate and transport modeling tools with ecological impact assessment tools
- Apply advanced computational approaches to make the most of limited data and assess the value of obtaining additional information
- Develop rapid approaches using minimal data and identify critical parameters required to address the full range of temporal and spatial scales required for EPA decision making

Anticipated Impact

- Demonstrated efficient ERA tools that reduce uncertainty for high priority and methodologically challenging chemicals.
- Decision framework for using models of various complexities, data requirements, and levels of ecological realism for differing ERA requirements or fit-for-purpose.

Topic 4: Solutions-Based Translation and Knowledge Delivery

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. Through the Solutions-based Translation and Knowledge delivery topic, CSS commits to actively translating the results of its research, from data to information to knowledge. This is integral to developing solutions to meet the needs of the Agency and its partner and stakeholder communities, with the goal to advance the mission of sustainability, and of improved human and environmental health and wellbeing.

This topic includes one project area, ‘Demonstration and Evaluation for Risk-Based Decisions.’ The purpose of this project area is to further aid translation of these new approaches by evaluating, establishing, and demonstrating their effectiveness to EPA partners and stakeholders. Two additional related activities, Partner Driven and Stakeholder Engagement, help to continuously fill the pipeline of research from planning/scoping to knowledge delivery. These two activities are described later in this section and are depicted in Figure 2.

1. Demonstration and Evaluation for Risk-Based Decisions

Agency Research Drivers

- New analytical approaches and data streams are being generated with the intention of reducing time, cost, and/or uncertainty of risk-based chemical management decisions
- There is a need to evaluate the added value of new data streams and build confidence in computational methods

Science Challenge

- Develop qualitative and quantitative approaches to integrate new information with existing methods and infrastructure to support science-based decisions
- Produce a broadly-supported framework to systematically evaluate the integration of new testing and computational methods, and provide measures of confidence and uncertainty to determine whether they are “fit-for-purpose” for EPA actions

Innovative Research Approach

Identify and implement case studies incorporating:

- High-throughput screening (HTS) data from ToxCast, Tox21, and other sources
- High or medium throughput exposure predictions, metabolite measurements/predictions, and dosimetry models
- Read-across methods
- Modeling of uncertainty and variability

Anticipated Impact

- CSS science will be translated and applied to inform specific Agency decisions
- Risk assessors will have confidence that new approaches, data, and tools developed in CSS are scientifically sound and provide added value to environmental decision-making

For example, the EDSP21 program led by EPA's Office of Chemical Safety and Pollution Prevention 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 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 would identify an area of integration between the CSS and HHRA National Research Programs. There are over 80,000 legacy or current chemicals in commerce; less than 2,000 of these have health assessments available across federal and state agencies. Multiple Agency programs and regions 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).

Partner-Driven Research (PDR)

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 areas will be defined by the NPD in collaboration with the partner(s) and in consultation with lab/center leadership. Tasks within this project area will have deliverables tailored to the needs of the partners, but the research from this project area will be otherwise amplifiable and relevant to other efforts in CSS. While the lifespan of a typical PDR project area is not expected to exceed 18 months, the effort may give rise to a longer-term research project area in CSS through future planning cycles.

For example, the EDSP21 collaboration with OCSPP first began as a PDR 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, led to its development into a full CSS project areas described above.

Stakeholder Engagement

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 which has been shaped by two large stakeholder engagement workshops held in 2014 as well as smaller tailored

engagements will be led by the NPD team, in collaboration with project scientific leads and partners.

IX. Conclusion

[To be completed in final Strategic Research Action Plan]

Appendix A. CSS FY 16-19 Research Outputs

Table of Proposed Outputs, Chemical Safety for Sustainability FY16-19

FY16 (1)

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

A framework for evaluating the technical performance of HTT assays, explicating the biological context, and understanding the relationship to adverse outcomes of regulatory concern will be developed to address a range of Agency 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 (2)

Demonstrated knowledge tools for development of Adverse Outcome Pathways (AOPs), including relevant biomarkers and bioindicators, to enable incorporation of pathway level information in Agency 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 Agency assessments. Tools and information will be disseminated to program office and regional partners. In addition to contributing to deconvoluting complex biological pathways, this output is expected to enable more health protective decisions by identifying earlier markers of adversity down a biological pathway.

FY 17 (1)

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

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 the Agency's ability to anticipate the human health and environmental impacts of manufactured chemicals/materials.

FY17 (2)

Evaluated, accessible exposure tools to provide agency 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 Agency exposure assessment needs. These tools are expected to enable the Agency to make exposure informed and risk-based determinations in a variety of decision scenarios.

FY17 (3)

Translation of diverse data streams including high-throughput toxicity (HTT) data to inform Agency 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 Agency 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 the Agency 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 (1)

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 the Agency to further realize the recommendations of the NRC report **Toxicity Testing in the 21st Century**.*

FY18 (2)

Tools for evaluating impacts of chemicals/materials/products early in development and across their lifecycles 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 lifecycle. For selected case examples, pilot application of efficient tools and metrics to evaluate chemical impacts across the lifecycle 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 Agency decisions. In addition, they will provide opportunities to test and evaluate hypotheses generated in observational studies.

FY19 (1)

Tools for evaluating adverse impacts that shift the toxicity framework from evaluation of apical outcome to characterization of resilience and identification of ‘tipping point’

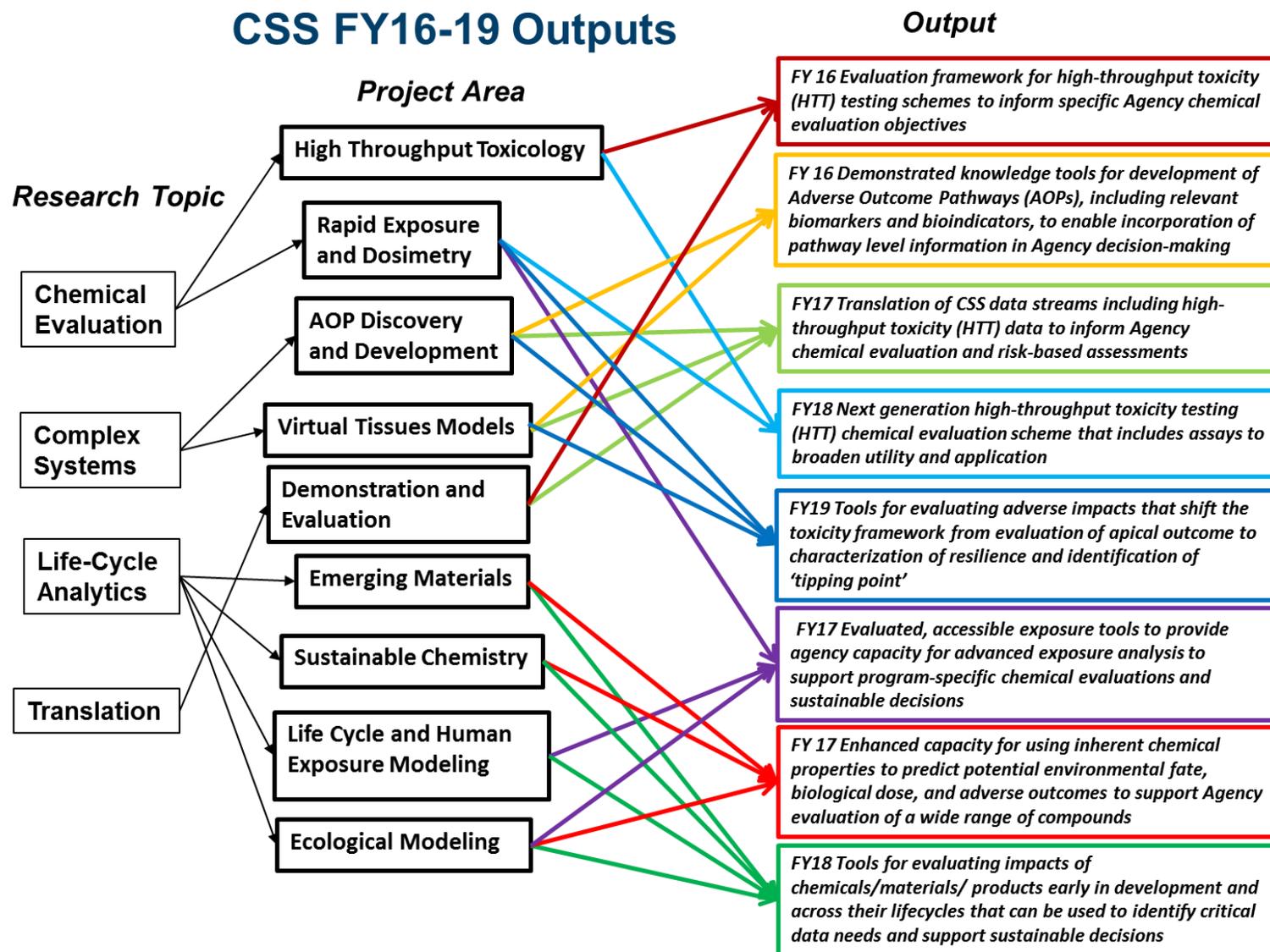


Figure 3. Mapping of CSS Research Topics, Project Areas and associated Outputs for FY16-19. In most cases, products from more than one project area will feed into each Output. Additional Outputs may be developed.