I. Background: From Framework to Research Action Plan. The Chemical Safety for Sustainability (CSS) research program has been created to address EPA’s recognition that new scientific approaches are needed for the safer manufacture and use of chemicals, and that EPA research has important roles to play in developing these approaches. Because CSS must, first and foremost, provide research products that inform environmental decision making, extensive efforts were made to develop CSS through discussion across EPA and with EPA’s stakeholders.

EPA’s Office of Research and Development (ORD), where CSS is located, began to conceptualize CSS in 2009 and in 2010 engaged EPA’s program and regional offices, as well as non-EPA stakeholders, in the development of CSS. Out of a May 2010 cross-EPA problem formulation meeting, the following 13 chemicals-related problem areas were identified:

- Grouping and prioritizing chemicals
- Chemical-specific effects, dose-response
- Persistence
- Intelligent testing
- Mixtures; source apportionment
- Cumulative risk
- Quantification of dose-response relationships (especially at low doses)
- Biomonitoring data
- Alternatives analysis approaches
- Properties that drive exposure, hazards
- More-efficient and context-relevant assessment methodologies
- Decision-support tools
- Life stage considerations

Out of these problem areas ORD and the other EPA offices worked together to develop the research areas and key science questions around which the CSS Framework was constructed. Input from stakeholders outside EPA then was solicited in early 2011, leading to the current version of the Framework. Developing a plan for implementing the CSS Framework has been the focus for the period April – October 2011. In this document, the CSS Research Action Plan, Version 1 in its current early draft form is summarized at a high level. The plan will undergo further development prior to its release as a public document in October 2011.

II. Relationship between the CSS Framework and the CSS Research Action Plan. Within CSS, the Framework and Research Action Plan serve as complementary companion documents. The basic distinction between the two documents is that the Framework defines the vision and scope of the research program—in broad terms what will be done—and the Research Action Plan describes how the program’s vision will be realized within the scope defined in the Framework.

Both documents were developed through cross-EPA discussions on identifying the major chemicals-related environmental issues facing the nation and what science questions need to be
answered to help address these issues. In the Framework, research areas frame key questions that would need to be answered in order to realize a conceptual model for developing methods, models, tools, and data to implement integrated evaluation strategies for chemicals-related decision making. It is expected that the Framework will provide long-term strategic guidance to CSS, with each research area serving as a touchstone as the research program evolves, to ensure that the activities within the program remain consistent with the problem formulation effort that the Agency underwent to create the CSS Framework.

The CSS Research Action Plan (RAP), as an implementation document, also is being developed through a cross-EPA process. Here, however, the focus is less on strategy and more on action: into what thematic areas (“topics”) would CSS need to be organized in order to engage in cross-disciplinary collaborative efforts (“projects”) that would be implemented through the specific work activities (“tasks”) of ORD intramural investigators and extramural grantees. Whereas the Framework and its research areas are expected to remain stable over time, the RAP’s tasks and projects—and possibly the topics—will change as science progresses and Agency needs for research product evolve. What follows are summary descriptions of the CSS Framework and Research Action Plan.

III. Framework. The CSS Framework describes three research areas that were developed jointly by ORD and its program and regional office partners, with input from external stakeholders. Key science questions were developed by ORD scientists and managers for research areas 1 and 2, and key research implementation questions were developed for Research Area 3.


- What approaches and information can best inform our understanding of physico-chemical or material properties and how they can be used to predict toxicity, fate, transport, transformation (degradation and metabolism), and toxicologically relevant exposure of chemicals?
- How can the knowledge of inherent properties be utilized to guide the development of safer products design and use throughout chemical life cycles?
- What new tools and/or models must be developed to ensure accurate and efficient hazard and exposure screening across the life cycle of a chemical?
- How can effective and reliable screening-level approaches for life-cycle assessment be developed that can be efficiently and strategically applied to large numbers of chemicals?
- What integrated research must be conducted to evaluate the predictive value of information from the CSS research program to overall impact to humans and/or wildlife?
- What hypothesis-directed research is needed to further enhance the value of data acquired in Levels I and II? Specifically, what new testing methods and models are
required that can be used to directly target data needs identified from Levels I and II?

- What are the significant gaps in Levels I and II relative to characterization of hazards and exposures?
- What systems models (e.g., kinetics and dynamics) must be developed and used to address the chemical-related environmental problems of greatest impact?
- What kinds of tools, including computational, systems-based tools, are required to fully describe the overall impact of exposures on organisms?
- What enhancements will be required to describe the impact of factors that affect an organism’s response to chemical exposure, such as life stage, gender, and aggregate exposures?
- What models need to be developed to better integrate biomonitoring (biomarkers and bioindicators) data into testing systems to help us better understand environmental and health impacts?

**Research Area 2: Improving Methods for Assessment and Informing Management for Chemical Safety and Sustainability.**

- How can the critical pieces of information required for different assessment tiers be systematically identified, evaluated, integrated, reviewed, and used in assessments and subsequent management decisions?
- How can relative potencies and/or dose response be estimated for more rapid risk assessment? Can upstream events that predict well-characterized public health risks based on traditional data be identified? How can recent scientific advances help describe adaptation, adding to disease background, and implications for low-response rates?
- How can tools such as life-cycle assessment complement more traditional environmental assessment methods for integrated assessments that inform decision making and identify safer and more sustainable approaches?
- How can recent scientific advances help describe human variability, life stages, and population groups? How can recent scientific advances help describe the impacts of exposures to mixtures? How can we determine whether new assessment methods actually decrease uncertainty and help lead to better decisions?
- How can inherency, exposure, hazard, and risk management options be integrated to supply a greater degree of certainty in decisions, reducing risk and enhancing sustainability?
- How can chemical life cycle approaches and formal life cycle assessment methods be used in risk management practices to not only reduce risk, but also enhance sustainability?
• What are the critical components of a sustainability-driven paradigm for risk management of chemical and product systems that incorporate life cycle factors relevant to environmental, economic, and societal issues?

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

Research Area 3: Targeting High-Priority Research Needs for Immediate and Focused Attention.

• On an annual (or some other regular) basis, what are the highest priority chemical management needs that can best be addressed by EPA in a timely manner through the Integrated Evaluation Strategy?

• What are the opportunities for integrating outputs of Research Areas 1 and 2 into the near-term, high-priority needs of chemical management programs?

Outcomes. The Framework also identifies key outcomes that will be advanced through the CSS research program. They are:

• Information is digitized and available

• Key linkages are identified in the continuum between the production of a chemical, its release, fate/transport of a chemical in the environment, the resulting exposures, and its adverse outcomes.

• Biomarkers of exposure are developed that enable the reconstruction of conditions that led to the observed results or relate to the health outcome.

• Critical pathways that are perturbed by environmental chemicals and lead to toxicity and adverse effects in humans and other species are identified.

• Complexities of exposure and dose in high throughput assays are captured.

• Predictive models of hazard and exposure to prioritize further screening and testing are developed.

• Quantitative risk assessment is improved and uncertainties are reduced by using advanced computational techniques such as multi-scale systems models of virtual tissues.

• The knowledge gained in improving human health risk assessment is applied to ecological risk assessment.

• The development of sustainable risk management approaches is scaled up for use in decision making.

• Scientific information is communicated, translated, and transferred in ways most useful to decision makers.
IV. Research Action Plan. Development of the CSS RAP was initiated through an April 2011 meeting with scientists and managers from ORD and program and regional office partners. In preparation for the meeting, groups of ORD and partner representatives met for 4-5 weeks to brainstorm on science ideas aligned with key elements of the Framework research areas (inherency, screening, targeted testing, systems models, risk assessment, risk management, and targeted research) as well as by the “product” areas of endocrine-disrupting chemicals, nanomaterials, other chemicals (i.e., not EDCs or nanomaterials), and chemical issues of particular relevance to the Office of Water’s Candidate Contaminant List. A solicitation for Step One ideas was sent to all of ORD and 224 were submitted and presented in one of ten breakout groups at the April meeting. Out of this meeting, the CSS Implementation Team identified major topics from the breakout sessions that captured the essence of the Step Ones and that organize the RAP in a manner that advances the Framework’s Research Areas. Projects were identified under each of the eight topics; although they are numbered, there is no meaning attached to the order in which they are listed. Every topic serves to advance one or more of the Framework’s three research areas and key outcomes. Table 1 illustrates the relationship between the RAP topics and the Framework elements. These relationships, including relationships to Framework outcomes, are also displayed in figures under each research topic descriptions that follow. While more relationships could be identified, those identified here represent what EPA believes are the key relationships between the Framework elements and the RAP topics.

Table 1. Which Framework Elements Are Addressed Under Which RAP Topics

<table>
<thead>
<tr>
<th>RAP Topic</th>
<th>Inherency</th>
<th>Systems Models</th>
<th>Life Cycle Considerations</th>
<th>Extrapolation</th>
<th>Biomarkers</th>
<th>Cumulative Risk</th>
<th>Dashboards</th>
<th>Evaluation</th>
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CSS Research Topic: Inherency

The CSS inherency research topic will develop integrated approaches to inform the design of new chemicals and materials, as well as to support efficient prioritization and evaluation of tens of thousands of existing chemicals. Inherent chemical properties (ICP) are broadly defined as features or properties of chemicals that can be computed or modeled directly from molecular structure (e.g., QSAR models), or as measurable attributes of substances, formulations, and materials. Inherent properties also determine function and performance of substances in products and are thus important in green chemistry design. Inherent properties of a substance can determine transport, fate, persistence, and exposure, and can determine environmental transformations and biological interactions that can lead to adversity. Identifying and characterizing key ICP metrics that determine a chemical's functional properties, fate and adverse effects are central to CSS.

The EPA regulates a vast universe of chemicals and materials. The scope of this universe as well as the large number of ICPs, which are useful for design or risk characterization, drive the need for expanded research in inherency. Computational toxicology, HTS technologies, analytical chemistry, materials design, and metrology will all contribute to inherency projects. Increasing availability of large, standardized public databases and tools pertaining to chemicals, materials and their effects (e.g., ToxRefDB, ECOTOX, ACToR, OECD Toolbox), are promoting greater use of ICP information. These trends drive collaboration across industries and government agencies, further fueling development of integrated approaches. The CSS research program will leverage EPA's data and modeling resources and expertise in chemical inherency to provide leadership in the consolidation and development of decision support tools and approaches for informing green chemistry design, and chemical hazard and risk assessment.

Figure 1. Relationship of Inherency Topic to CSS Framework
Research Program

Inherency research must encompass not only tools and approaches for the direct measurement and computation of a wide range of chemical properties, but must develop the capability to determine regions of chemical space within which models can be applied. ICPs used to model chemical attributes or activities must be validated against existing data or newly generated data. Guidance in constructing chemical groupings (e.g. categories) for modeling can come from chemical inherency.

Project 1. Determine and Characterize Inherent Chemical Properties (ICP)

The goal of this activity is to enumerate key properties of chemicals or materials that capture salient features of the chemical class or substance, and that are important for characterizing and modeling function, hazard, fate and exposure. This involves developing and evaluating methods for calculating or predicting properties, where possible; determining and compiling measured values where necessary; and building data systems (database, dashboards) to store properties and to enable rapid calculation of properties for new chemicals for further use or application in models. All such activities rely on accurate representation of the substance under study (potentially including stereochemistry), which in turn must be captured and stored in accessible and computable databases. In addition, computational approaches for generating molecular features from structure can be useful for data mining and model development. Such features can be rapidly computed and stored as molecular fingerprints for use in organizing and navigating a large chemical space into smaller, more chemically-meaningful categories. Specific inherent properties include: 2D and 3D chemical structure representations; fate, transport and exposure model parameters; reaction parameters and products; properties related to toxicity pathways; reference spectra for different analytical chemistry techniques; and physical aspects of engineered nanomaterials. Inherent properties will be used to characterize the chemical spaces of interest to EPA for different applications. The Agency’s current tools for ICP will be inventoried and evaluated for their efficacy in these regions of chemical space. Where regions of chemical space are already well covered by measured data, existing (or new) models will be used to generate predictions for related chemicals. Where important regions of chemical space are data poor, new measurement or modeling activities may be needed to build baseline data sets for further modeling and prediction. We will develop standardized databases spanning the combined chemical inventories and consolidating measured and calculated properties of chemicals and materials. These form the basis for extrapolations to new chemicals and the construction of more complex models. Open source or freely available tools will be used to place chemicals into various types of categories or read-across families. Linkages between these databases and databases of biological interactions from many other sources will serve as a foundation for building pathway-based QSARs, etc.

Project 2. Nanomaterial-specific Inherency Issues

Nanomaterials research will be conducted within several CSS topics. However, nanomaterials pose special challenges for inherency because many of the ICP useful for modeling of traditional chemicals are less relevant, whereas a complex interplay of physical dimensions and chemical
properties are of greater importance for these materials. Key life cycle and health determinant properties of nanomaterials vary significantly along the size/dimensionality continuum of the particles, which in turn is determined by complex interactions with external and biological environments. This Project focuses on these nano-specific ICP, recognizing that many of the tools in #1 can be incorporated into the overall assessment of nanomaterials once these broader characterizations are available. A critical need is to collaborate with national and international consortiums to develop a standardized nanomaterial ontology that is able to capture ICP needed for material function and risk assessment. A related goal is to develop a systematic naming convention for nanomaterials that is specific enough to capture key unique chemical and physical determinants, but sufficiently generic to be applied to similar synthetic processes and products. Inherency characterization of nanomaterials would include property metrics such as average or mean chemical composition, size and shape distribution, purity, surface coatings, etc. From these metrics, descriptor sets tied to the basic ontology could be used for predicting a broader suite of properties. These would inform experimental design and synthesis, to assess toxicity, and to be used for developing QSAR or property-based prediction models. Calculated and measured properties would be captured in the database systems developed under #1. Focused experimental efforts will be needed to characterize the ICP of nanomaterials spanning the range of materials EPA is likely to encounter, as well as to test representative selections of materials along these continuums in biological assays. This would include HTS assays on nanomaterials as well as other physical, spectral, compositional, and activity property measurements. Collaborations with NIST or other external groups will establish a reference nanomaterial repository that can be accessed by EPA researchers over time.

**Project 3. Build modeling capabilities to link ICP to metrics and outcomes relevant to risk characterization and risk management**

Whereas individual properties of a substance may be useful in isolation (e.g., volatility can determine inhalation exposure), placing a chemical and its ICP in a larger context of available data and within a group of related chemicals is more likely to be informative for use in chemical design, hazard screening, risk assessment, or LCA. Under this Project, models will be built that use ICP to predict end-use metrics. These activities could include development of chemical classification and analog-identification methodologies, determination of structure-alerts for defined toxicities, chemical signature/fingerprints linked to toxicity pathways, exposure, chemical category, etc. These could be rule-based systems for predicting whether a chemical crosses some hazard or exposure threshold based on chemical fragments, and could be useful to evaluate new chemicals or to inform green chemical design. To facilitate these efforts, feature/property fingerprints of EPA chemical libraries will be developed as part of sub-activities #1 and #2. All ICP tools, including outside publicly accessible resources, will be made available from within web-based systems that can be accessed in-house or externally. This capability would be integrated with the Dashboard research topic. Such a tool may incorporate elements of, and is similar in concept to the OECD QSAR toolbox. However, a web-based tool would allow databases and models to be updated in near real-time, and the interface and outputs to be customized for Agency (and end-user) needs, including an automated workflow for the addition of new chemicals and associated ICP. Using this repository of ICP information, tools will be developed to automatically analyze a chemical inventory for substances that may pose potential
for exposure or hazard, prioritizing them for re-evaluation based on new information. The ICP databases will provide information required to address outputs under other CSS research topics.


One major CSS goal is to test, validate and promote the wide adoption of tools and models to reduce uncertainty in risk assessment and risk management decisions and to drive decisions towards sustainability. Critical to this are data, methods, and models that efficiently characterize and predict ICP throughout the lifecycle of a material or product. Development and demonstration of these tools will empower users and designers of new chemicals or products to assess potential environmental impacts in the design phase of greener products and chemicals. Tools to predict function and risk will need to be integrated to address green design tradeoffs. For design of new chemicals, the structure alert or QSAR models developed in Project #3 will be directly applicable especially in the green chemistry research performed in the **LCC research topic**. For many of the applications under this Project, the data systems of #1 will require tools to allow comparison of a chemical with its alternatives. ICP models must be integrated within current LCA models / techniques. External customers of these tools will include the chemical industry, product formulators, regulators, and product evaluators who translate lifecycle impacts into purchasing decisions. Internal customers include those groups responsible for making risk assessment and risk management decisions and those groups responsible for developing risk management tools, such as described in the **LCC research topic**. These customers also need models for production attributes that are outside of the ICP. These include water and energy usage in synthesis and manufacturing, use of rare or non-renewable inputs, solvent use, and other manufacturing wastes. Demonstration projects will apply these tools to real environmental problems, showing that they can be used successfully in the design, synthesis, deployment and disposal of chemicals and products in ways that reduce or eliminate toxic substances. These projects will be in partnership with outside groups (industry, universities) to both leverage external knowledge and assets and to provide the user-base for project outputs. Demonstration projects might include “what if” computer modeling as well as synthesis of alternatives to existing problem chemicals.
CSS Research Topic: Systems Models

The overall goal of this research topic is to advance development of the scientific understanding and tools to address the identification, characterization and analysis of critical response pathways and networks in humans, other mammalian and non-mammalian species, and ecosystems. The effort will integrate existing knowledge and models related to production, use, exposure, and biological response to establish systems-level linkages. The effort is intended to develop systems for multiple uses from rapid prioritization of chemicals for testing to complex risk assessments. Additionally, it will leverage high-throughput screening (HTS) data and assays probing lower levels of biological organization that may be faster and cheaper than whole systems measurement or modeling. This research effort recognizes the inherent complexity and resiliency of dynamic systems, which complicates predictions of responses to perturbation. A systems-level perspective provides an approach to account for the effect of specific perturbation(s) across levels of organization within the system (i.e., molecular to ecosystems).

We aim to identify and model those pathways and networks of biological pathways through which adaptive response to stressors can be overcome and/or maladaptive response induced, leading to disruption of homeostasis and adverse outcomes.

Elucidating processes and pathways is vital for reconstructing the dynamic networks of interacting elements of complex systems. Potentially hundreds of key exposure and biological pathways may be involved in homeostasis and may lead to diverse adverse outcomes during
particularly susceptible life stage and developmental processes. The *systems pathways topic* focuses on the inference and quantitative description of such key pathways connecting processes across different levels of organization within any relevant system, and between systems. Identification and understanding of systems pathways will be accomplished through: assay or other technologies to measure fundamental system components and behaviors, knowledge-based tools for mining their inter-relationships, and computational models to simulate systems-level function(s) and complex interactions. This approach will result in new data, tools, and models that fully integrate toxicology and exposure science to study, characterize, and predict the complex interactions between humans, biota, and environmental chemicals, and non-chemical stressors that lead to adverse outcomes.

Due to the complexity of human and ecological systems, addressing systems pathways will require approaches that address linkages across the entirety of the source-to-outcome continuum for chemicals, products, and their interactions with other stressors. A major challenge will be to understand and ultimately reduce the uncertainties associated with decision-making. For example, systems pathway models, both qualitative and quantitative, are needed to reduce uncertainty derived from incomplete understanding of the relationships between molecular and cellular effects *in vitro* and the sorts of adverse outcomes to be avoided in humans and the environment. Also critical to this issue is characterization of the uncertainty related to the use of specific tools, the dynamic mechanisms of injury and recovery, and the emergent properties inherent to complex, adaptive biological systems. The systems pathway topic emphasizes metrics of biological inherency (i.e., the innate aspects of biological systems that must be characterized to develop qualitative and quantitative models of AOPs) as a central tenet of research activities, toward the goal of elucidating systems-level properties (fragility or resilience to different perturbations) and using these key factors as metrics to expand functional understanding of the more traditional source-to-outcome continuum. Finally, it is crucial to link this understanding of biological processes to real-world exposures which include the levels, frequency, and durations of exposure, as well as exposures at different life stages or of susceptible populations.

Several considerations underlie the Systems Pathways topic. The first is to determine the best practices for system characterization. Standardized approaches assure both proper scientific and statistical analysis as well as interoperability between many parallel research efforts. This includes the conceptual definition of systems-level function (input-output processing) and research that elucidates key parts of a system (components) and their connectivity (networks). The goal here is not to hamper cutting edge research; rather it is to ensure that the best methods are used when available and known, and to ensure interoperability. A second important consideration for systems modeling is both building and using tools to analyze network state dynamics. Representation and analysis of complex systems in this manner is essential to interpret results from high-throughput and high-content studies and to unravel quantitative metrics of systems-level function(s). A third important consideration pertains to biological inherency. For example: how does systems-level function naturally evolve in time or resolve from a perturbation; what features account for resiliency (robustness) and/or adaptation; and what degree of variability renders a system vulnerable to adverse effects associated with stressor exposure? This is central to life stage research, which refers to a distinguishable time frame in an individual's life characterized by unique and relatively stable behavioral and/or physiological characteristics that are associated with development, adolescence and growth,
pregnancy and lactation, and advanced age. A fourth consideration is elucidating the structural (multi-level or multi-scale) relationships within and among systems that influence source-to-outcome events: that is, how does the function at one level of organization within a system affect other levels of organization with which it interacts, and what outputs of one system are inputs to another system? This is central to modeling the source-to-outcome continuum because of the diverse nature of research at each level/scale and the need for integrative models.

The key to the success of this program is feedback from both testing of the systems models as well as use for risk assessment and management. Testing will generate new hypotheses and regulatory use will help prioritize data gaps. An example would be the creation of a crude explanatory systems model (termed coarse-graining) where new hypotheses are generated and tested. If regulatory use requires further model refinement, then empirical results from these experiments are used to refine the model (e.g., terms are added/removed, parameters are adjusted, and mathematical relationships are re-defined). The cycle continues with the generation of new hypotheses, and experiments to test those hypotheses, with the results leading to refinement of the model as needed to met regulatory requirements.

Figure 3. Relationship of Systems Models Topic to CSS Framework

Research Program

Leveraging cross-ORD integration is essential to systems pathways research due to the need for interdisciplinary expertise and frequent interaction among chemists, exposure scientists, biologists, toxicologists, bioinformaticians, modelers, and risk assessors. This topic also interfaces and complements existing work plans for OCSSP/OW ‘21st Century Tools for Chemical Programs’ by structuring research in a way that makes it feasible to continue addressing near-term high priority needs of chemical management programs, while simultaneously building the knowledge and tools required for long-term objectives of the CSS program.
Four projects are proposed that will build and/or use tools for modeling exposure, effects, and outcomes that identify factors responsible for system resilience, which will lead to more sustainable mitigation (Figure 4). The notion of multi-scale behavior and related modeling issues will be critical for addressing how any new tools/models from this research are better than what is currently used. Other cross-cutting benefits would be guidance and best practices for using systems tools/models for risk mitigation (e.g., predict and/or test how changes in mitigation will decrease exposure and thus lower hazard) and translation of systems model tools for use in driving better chemical development.

*Project 1. Systems-level approach to Adverse Outcome Pathway (AOP) Discovery*

This project will employ integrated systems biology approaches to discover, define, and model adverse outcome pathways (AOPs) relevant to human and ecological risk management. AOPs can be viewed as conceptual frameworks that portray causal and predictive linkages between molecular-cellular disruption (initiation of a toxicity or disease pathway) and adverse outcomes of regulatory significance (individuals or populations). This project will formalize and expand the description, inference, and dissemination of AOPs, through a systems-level approach that identifies critical targets of biological perturbation, regardless of source, relates these perturbations to adverse outcomes that result from to real-world chemical exposures. While initial research will focus on individual chemicals, or classes of chemicals with common adverse outcomes, the AOPs developed will be applicable to mixture of chemicals. In addition, this Project considers variability related to life stage and susceptibility. For example: research focusing on how exposure to pollutants may be impacted by life stage, determining unique biological responses across susceptible life stage, and mapping the developmental windows of vulnerability. The result will be new knowledge and knowledge-bases of AOPs, key events and molecular pathways that can be used in many of the other topics. For example, AOPs identify key molecular events for which biomarkers may need to be developed (Biomakers topic). In addition, key information in a computable and searchable format, leading to, for example, digital libraries that can facilitate the synthesis and application of knowledge about AOPs (Dashboard topic) or inform hypothesis-based experimentation based on predictions from systems models.

*Project 2. Systems modeling of specific tissues and multi-organ pathways*

Toxicity often is the result of interference with the emergent properties of multicellular systems and is, therefore, at times difficult to understand from a traditional reductionist approach. Particularly, the propagation of initiating events to a higher level of biological organization generally entails tissue-level changes that represent key events. For example: the complexity of ADME may be captured by mathematical models, but existing PBPK models do not adequately describe blood flow within an organ such as the liver, leading to the need to understand the quantitative relationship between microdosimetry, cellular injury, and disease progression. Also, research focusing investigation on the intrinsic properties of a tissue that account for so-called 'windows of susceptibility' and pathways by which specific cellular perturbation(s) lead to pathogenesis, depending on an individual's life stage is another example. This project will focus research on specific tissues and multi-organ circuits to build and use tools that help us think about and organize information from one scale into higher levels of...
biological organization, while taking advantage of HTS data and in vitro assays probing lower levels of biological organization that may be faster and cheaper for study than whole systems measurement. The result will be new methods and mechanistic models using systems biology to consider any relevant interactions between molecules in a cell, different cells in a complex tissue, or between multiple tissues and organ systems of humans and other species. Considerations include, for example, chip-based platforms combining cell types and nanotechnology to reconstruct specific tissue and organ functions that could speed evaluation of chemicals, empirical linkage models that couple the output from one system into the input of another system, and virtual tissue models (e.g., liver, embryogenesis, cardio-pulmonary function, etc.) that integrate both intrinsic and extrinsic properties that together characterize systems-level susceptibility and vulnerability of specific biological processes.

Project 3. Systems approaches to assess human and ecological risks

Efforts to improve human health risk assessment have benefited from the technologies and knowledge gained by genome-scale research and drug discovery approaches; however, further research is needed to understand critical systems and pathways to sustain both human and non-human species, their populations and communities. This project will focus on methods, models, and tools to better assess impacts of chemicals by analyzing key pathways at molecular, organismal, population, and community levels. For assessing ecological risk, research will be extended to address whole ecosystem levels. A mechanistically-based approach to hazard identification, combined with appropriate information on exposure metrics, will be developed to directly support decision-making about chemical management options for human health and ecological risk assessments and identify areas for new research and technology development.

Project 4. Screening and Prioritization Methods

The pharmaceutical and biotechnology industries have leveraged high throughput screening methods to identify potentially efficacious new molecular drug entities, identify potential toxicity, and to screen plant seeds for metabolic mutants. The key to successful development of these methods is that they are based on an understanding of the underlying biology of the system. Building upon these lessons and technologies, and leveraging the task products from this and other CSS Research topics, this Project will focus on systems-based development of chemical screening and prioritization methods.
CSS Research Topic: Life Cycle Considerations

This topic explores the application of a life cycle perspective to holistically manage the impacts of chemicals, products, and compounds across their life cycle, including production, distribution, use, disposal and/or recycle, while maintaining the benefits provided by the use of these materials. Research in this area will help identify the essential elements of, and opportunities for applying, sustainability-driven risk management for preventing, mitigating, and remediating impacts at scales that address tens, hundreds, or even thousands of materials or chemicals and gauging the effectiveness of selected sustainability metrics which fully capture relevant environmental, economic, and societal issues, the commonly accepted pillars of sustainability. For more detail on the concepts for sustainability, as they are presented here, the reader is referred to Section II of the CSS Framework (June 1, 2011) document. The focus of this topic is not to conduct actual assessments, except as pilots or proof-of-concept activities, but rather to develop methodologies that can be applied by government, industry, and other stakeholders.
For sustainability assessments, evaluation of the environmental impacts is often made using standardized Life Cycle Assessment (LCA) methodology [ISO 2006] and covering a wide range of impact categories, including global warming, stratospheric ozone depletion, human toxicity, ecotoxicity, smog formation, acidification, eutrophication, land use, and resource depletion [U. S. EPA 2006]. To develop comprehensive management practices that not only reduce impacts but also enhance environmental sustainability, there is a need to integrate LCA with other established environmental tools (life cycle risk assessment (LCRA), material flow analysis (MFA), etc.) as well as new tools to fill knowledge gaps and provide information on human performance and productivity, while considering the pillars of sustainability [Jeswani 2010; Som 2010]. Assessments of this scope will require knowledge of manufacturing and disposal processes, usage levels, disposal rates, environmental fate and transport properties, bioavailability, bioaccumulation, and toxicity. The results can then be used to guide decision makers and researchers as they seek to implement sustainable solutions through the use of green chemistry and green engineering concepts [Anastas and Warner 1998; Anastas and Zimmerman 2003] in setting best practices and attainable standards for the processes by which products are designed, made, used, and disposed.

![Diagram of Framework Outcomes]

**Figure 5. Relationship of LCC Topic to CSS Framework**

**Research Program**

Connected with research to be conducted under CSS program will be work conducted through a life-cycle based center being established through ORD’s STAR (Science to Achieve Results) program. This academic center is to be the Center for Material Life-Cycle Safety which will: 1) integrate physical and social science research, 2) develop tools and metrics for evaluating the entirety of the material’s life-cycle impacts, and 3) apply sustainability principles, industrial ecology, green chemistry and green engineering. The approaches developed in the Center should apply to as broad a range as possible of existing materials with adaptability for incorporation of emerging materials. This Center should draw together various scientific disciplines to develop its approaches, including but not limited to the following: materials science; chemistry; biology;
toxicology; exposure measurement, modeling, and assessment; ecology; risk assessment; engineering; and social and behavioral science. This topic is complementary to each of the other topics and has key tasks that can be integrated with potential work in other topics based on risk management for sustainability as shown in Figure 1.

**Risk Management for Sustainability**

![Diagram of Risk Management for Sustainability](image)

**Figure 6. Incorporation of Risk Management for Sustainability into other CSS Topics**

**Project 1. Risk Management for Sustainability**

This project involves research that will transform ORD’s research from being narrowly focused to a holistic approach by addressing a broad range of environmental impacts through the advancement and incorporation of fundamental knowledge for key biological, chemical, and physical processes associated with chemicals and products as they interact with air, water, ecosystems, and individuals. Ultimately, stakeholders must make decisions using sound science to manage the life cycle of chemicals, compounds, and products from their design to their use, disposal, and reuse or recycle. An effective risk management strategy requires efficient data compilation, proper application of assessment tools to identify relevant impacts, development of strategies to mitigate these impacts, and a consistent method to integrate this knowledge to formulate a comprehensive solution. This project and Project 2 specifically focus on holistic methods to facilitate information (data) compilation and application of assessment tools. Mitigation and solution implementation have been broken out in detail in Project 3 in this topic and Project 4 (Decision Analysis) in the Evaluation topic to account for the intricate nature of research they require. Ultimately, the tasks of all four projects must be integrated for successful risk management for sustainability.

Data planning and management are critical for integration and transfer of results across disciplines and stages of research. Large, high quality collections of data pertaining to chemicals, biological effects, biological processes and exposure scenarios are recognized as essential.
foundations of risk management. Development and expansion of these data resources across the Agency is needed to provide the data foundation for a number of approaches including computational toxicology, inherency, hazard screening, prioritization, and life-cycle-based assessments. ORD methods will help the Agency obtain these data. Additional effort will integrate these databases with currently available data systems across the federal government to capture data describing all three pillars of sustainability. The integrated data sets will be used to develop a sustainability assessment protocol built around the integration of life-cycle based tools (LCA, LCRA, MFA, etc.) that is fully capable of capturing both the broad environmental impacts (climate change, eutrophication, resource depletion, etc.) of chemicals and products and site-specific risks to human and ecosystem health. This protocol will not only address the benefits of these materials, but will also seek to address the need for quick-screening assessments to help the Agency handle the large volume of emerging chemicals, products, and processes.

Project 2. Environmental Detection, Fate and Transformation to Characterize Exposure and Determine Environmental Health and Ecological Impacts

Numerous contaminants of emerging concern, including endocrine disrupting compounds, pharmaceuticals, personal care products, nanomaterials, etc. have been detected in the environment as a result of their production (natural and synthetic), use, and disposal. The primary data gaps impeding the holistic assessment of these materials are related to their concentration, transport, fate and potential transformation/degradation within the environment. Information on the biological effects of these contaminants and their by-products, both as single entities and mixtures, throughout the life stages of the exposed organisms is needed in the determination of human and ecological health risks. New, improved, efficient and cost effective analytical and biological (e.g., biomarker, biomonitoring, bioassay) tools are needed in order to be able to collect this information on the numerous contaminants already present in the environment, as well as compounds/products under development. This research is envisioned to include both laboratory experimentation and environmental sampling and monitoring in order to enhance existing and develop new methods, models, and tools that are applicable to life stages and scale. These methods and tools refers to development of analytical and biological procedures for existing contaminants and contaminants of emerging concern in environmental matrices, and ecological organisms.

Project 3. Sustainable Approaches to Chemicals (Products) and Processes

Sustainable approaches attempt to design materials and services to comply with the principles of economic, social, and environmental sustainability. These efforts rely on sustainability assessment tasks (Task 1.1) to first identify the impacts associated with existing chemicals, products, and processes. To aid the assessment process, this Project will develop comprehensive linked models and impact assessment methodologies which will incorporate the diverse knowledge contained within the integrated data bases created in Task 1.1 to accurately capture the economic, social, and environmental risks to both humans and ecosystems. This will involve systematically evaluating the various modeling tools for use in the life cycle perspective and cataloging their outputs in terms of life cycle stages and primary interest (humans or ecosystems) to devise an approach for integration. Once these risks have been identified, they
must be communicated to researchers within ORD to use the principles of green chemistry and green engineering to develop mitigation strategies ranging from novel green manufacturing techniques to sustainable remediation practices. These approaches will be especially useful when dealing with consumer products because they offer the promise of engaging not just the chemical safety component of CSS, but also promoting important sustainability concepts such as product cost, energy analysis and social impact to society. By providing easy-to-access to information consumers and producers can use, and with technical transfer actions, they can select environmentally benign products and reduce their (or their organization’s) environmental impact. This project by being focused on sustainable approaches will closely link to activities associated with such EPA programs as the Design for the Environment (DfE), and research focused on the health and environmental impacts associated with the design, manufacture, use and disposal and/or recycling of electronic components.

**CSS Research Topic: Extrapolation**

For the Agency to make informed risk assessment and risk management decisions, it relies upon biological and computational models and sampling at the environmental, ecosystem, and community levels. In all of these cases, some form of extrapolation must occur, which entails the use of data-informed or default uncertainty factors. Extrapolation allows both inference about sensitivities that cannot be measured directly as well as comparison between different types of measurements in order to assess consistency and performance of various measurements.

The objectives of this research topic are to: 1) develop databases and knowledge bases that facilitate and optimize the sharing of these data, ultimately interfacing with the Decision Support Dashboard topic; 2) in support of the Systems Pathway topic, develop new or improved methods and tools to reduce the uncertainty associated with high priority systems research; 3) develop new science and tools to improve extrapolation between priority wildlife species and to address specific environmental risk issues required by the Endangered Species Act (ESA).

Extrapolation methods apply to many situations, for instance, between animal species (Sample and Arenal, 1999), between various dosing regimens (Rodriguez et al., 2009), from small clinical population to sensitive sub-population (Jamei et al. 2009), from sentinel species to food web (Forbes et al., 2008), from high-throughput in vitro assay to in vivo conditions (Rotroff et al., 2010). Systems-oriented thinking is leading to the development of tools for encoding diverse prior knowledge into a single mathematical model that can predict the impacts of chemical perturbations either from inherent (e.g. structural) chemical properties or limited high-throughput in vitro data. The advent of virtual systems allows basic biological knowledge to be combined with knowledge of toxicity pathways to reduce the uncertainties in extrapolating for across chemicals with limited data (Shah and Wambaugh, 2010). Similarly, exploiting network and probabilistic data integration methods, commonly applied to clandestine networks and defense/intelligence problems, can improve extrapolation from chemical exposures and biomarkers to disease endpoints. Ecological fate and transport models similarly use knowledge of the behavior of well-known chemicals to improve extrapolation of exposure and effects of less well-studied chemicals (Rosenbaum et al., 2008).

This research topic will spur research that investigates methods of extrapolation, identifies data gaps preventing effective extrapolation and increase uncertainty, and improves uncertainty.
factors used in risk assessment. This topic will focus both on data generated by the other CSS topics, as well as existing and external data. By generating new data of greater quality in order to elucidate factors that will allow extrapolation of this and already existing data sources to relevant, real-world situations this Research topic will enable better risk assessments and improved decision-making regarding risk management choices.

Figure 7. Relationship of Extrapolation Topic to CSS Framework

Research Program

Although extrapolation is not explicitly mentioned by name in the CSS Framework, it is an essential piece of many of the CSS Outcomes. Thus, whether we are applying data from high throughput screening, computational virtual tissue models, or systems pathways approaches, there will always be some level of uncertainty due to extrapolation from the system where the data were gathered up to the human or ecological sensitive subpopulation level. However, extrapolation is not limited to moving up or down the biological complexity ladder. Extrapolation also must address issues of utilizing information from data-rich chemicals to inform assessment and management decisions regarding data-poor chemicals. The Extrapolation Research topic was deliberately made its own topic, rather than subsuming it within the other topic on purpose. The Extrapolation topic addresses certain cross-cutting issues among all of the projects within the topic. By keeping these together within the same topic, we ensure that the groups working on these projects will be able to share their results more quickly and efficaciously. This will also result in better knowledge sharing and transfer from the human health side to the ecological side, and vice versa.

Project 1. Development of new tools for extrapolation: Accessible knowledge bases for decision support
To best serve the program and regional offices, the context for data must be communicated clearly between the data curators/generators (ORD) and the users (the program and regional offices). New tools, both computer software and laboratory assays/methods, must be developed to facilitate quantitative extrapolation. Software tools, including formal workflows and specifications for the sharing of information, will enhance interoperability between multiple data sources and allow accessibility so that decision making is transparent and alternatives are easily investigated. New \textit{in vitro} and \textit{in vivo} technologies may already exist (e.g. high-throughput in vitro screens, zebrafish models), or be possible (e.g. environmental media degradation assays), that would allow new data to be obtained to decrease uncertainty of extrapolations, particularly with respect to environmental fate and transport models. These data need to be captured in useful knowledgebases.

Cutting-edge software advances will be used in this topic will align with the Decision Dashboards topic. The difference between these two topics is that software tools for extrapolation will be developed herein, and employed in Dashboards. These new software paradigms include the use of new data interoperability standards created by the World Wide Web Consortium. These new standards, including the Web Ontology Language (OWL), the Resource Description Framework (RDF), and eXtensible Markup Language (XML) form the backbone of the emerging Semantic Web. The Semantic Web is a new concept where computers will be able to understand the context surrounding data, and perform simple first-order logic operations. For instance, using the Semantic Web, a computer will understand that the concept of a chemical has certain inherent properties, that hepatocyte has specific pathways given a specific state (e.g., specific disease, normal), and that there are knowable species similarities and differences in these pathways.

\textit{Project 2. Development of new tools for extrapolation: In silico, in vitro and in vivo}\n
Both health effect and fate/transport models have data needs that are generally unmet by the throughput of traditional testing. For this reason medium- and high-throughput, \textit{in vitro} and \textit{in vivo} (e.g. zebrafish) experiments are attractive for augmenting computational models (e.g. QSAR). However, translating the artificial context in which high throughput experiments are performed to predicted (simulated) “real world” contexts is a crucial step for making use of high-throughput data. For example, to back-calculate potentially detrimental environmental exposures, the bioavailability and dermal absorption of chemicals and nanoparticles must be assessed to determine whether 100\%, 50\% or 0\% of a compound actually gets into the body. The challenges posed by extrapolation of \textit{in silico} and \textit{in vitro} to \textit{in vivo} as complex as those involved in translating across species.

A central tenant of the CSS \textit{Framework} is to use a tiered approach to evaluating risks of exposure and effects, i.e., cost effective resource utilization matched to the specific needs of particular decisions (CSS Framework Figure 3). Effective use of medium- and high-throughput assays in human health and ecological risk assessment will require cost efficient tools and methods that address extrapolation issues. The overall goal of this research will be to decrease the uncertainties in extrapolating across these boundaries. The outcomes and products from these Tasks are essential for advancing both risk assessment and risk management.
Project 3. Intraspecies Variability – Extrapolating across sensitive subpopulations

Genetic variability in populations can be much greater than that exhibited by inbred model organisms, pools of ex vivo human cells, or in vitro clonal cell lines. There is a great need to identify cellular pathways, that when perturbed, lead to adverse outcomes. Many of these pathways may be subject to large inter-individual and inter-species variation. For instance, high-throughput assays already exist that allow rapid identification of chemical affinity for specific metabolizing enzymes known to be highly variable in the general human population (e.g., CYP3A4). Changes with life-stage and presence of psychosocial stressors also present similar variability challenges. Use of biomarkers for both stressor exposure and bioindicators for activity of adverse cellular pathways for human populations and environmental species will begin to identify these problems as they occur, but new methodologies are needed to anticipate them. Tools are needed that model susceptibility factors that underlie or may exacerbate known adverse outcomes. New in vitro and in vivo screens for genetic susceptibility factors to chemical perturbation should be identified and used when available and developed when they are not. Together these tools will allow extrapolation from idealized in vivo scenarios and inexpensive high-throughput data to real-world population variability.

Project 4. Extrapolating to higher levels of biological organization

EPA needs methods to extrapolate risk observed and/or predicted at the individual level to that of the population-level for key wildlife species, especially those protected under the Endangered Species Act. This requires development of integrated environmental and biological modeling approaches that incorporate the spatial structure of chemical stressors, habitat quality, and wildlife populations across large spatial scales and regions. At a still higher level of biological organization, EPA needs models to understand how chemical stressors cascade through ecosystems, creating indirect exposures and effects to additional wildlife species and ecosystems. Careful examination should be made of the determinants of species differences in toxicokinetics (e.g., hematocrit, expression of metabolizing enzymes and transporters, expression of signaling molecules, and affinities of compounds for proteins including sex hormones) in order to bridge human and ecological risk assessment. Additionally, mechanistic models, structural models (QSAR), and high-throughput experiments should be developed to allow comparison of the environmental fate of novel chemicals and nanomaterials to relatively rich chemicals. Ultimately this work will facilitate rapid identification of at-risk ecological species and potential for ecological accumulation in order to allow decision makers to make comparisons of sustainability metrics between alternative chemicals.

CSS Research Topic: Biomarkers

The overall goal of research in this research topic is to develop the scientific knowledge and tools that will allow us to use biomonitoring data to improve both single chemical and cumulative risk assessments. A second goal is to improve our understanding of the fundamental processes and linkages along the exposure-dose-effects continuum that lead to risk.
Agency chemical risk assessment and risk management decisions have historically been informed by exposure and hazard science and information produced by the Office of Research and Development and other science organizations. Currently, the linkage and translation of exposure and hazard data into human or ecological risk is conducted independently, and in many instances using sparse data that result in large data gaps and scientific uncertainties. The term biomarker has been used to describe indicators of exposure, effect, and/or susceptibility. Herein, biomarkers of exposure are defined as indicators that infer exposure or environmental concentrations from internal doses of exogenous chemicals, whether in the form of the parent compound, environmental degradates(s), or the metabolized chemical(s). Biomarkers of exposure can also be used to predict dose at the target organ or response pathway. Bioindicators of effect are defined as the measurement of biochemical or physiological changes within an organism that are indicative of injury or disease. Bioindicators of effect are often used to probe and understand systems pathways, as well as predict adverse outcomes. Together, biomarkers and bioindicators are natural tools to bridge scientific gaps and reduce uncertainties in our understanding of risk due to their potential to be simultaneously measured and/or predicted in the same system.

Technological and scientific advances in analytical and clinical chemistry, bioinformatics, and systems modeling have resulted in the enhanced collection, reporting, analysis, and interpretation of human and ecological biomarkers/bioindicators by numerous scientific and medical organizations. Scientists can apply sophisticated models and informatic tools to link exposure and effects biomarker data and make inferences (reverse and forward) regarding exposure and potential health outcomes. Interpretation of these biomarker data may be further enhanced by understanding other factors that influence the individual’s or population’s susceptibility. These include lifestage, genetic polymorphisms, etc. - factors that can be measured as biomarkers of susceptibility, along with other factors impacting exposure, dose, and biological response.

With further development, biomarkers will provide valuable tools for understanding cumulative risks. Bioindicators related to adverse outcome pathways (AOPs) should provide predict tools to evaluate the cumulative impacts of multiple stressors. In addition, the concept of the “exposome”, representing the totality of exposures received by a person during their lifetime (Wild, 2005, Rappaport, 2011), provides an integrating framework for evaluating extant biomarker data and developing critical suites of biomarkers to inform cumulative assessments.

This research topic will integrate and build on the innovative systems concepts described by Ankley et al. (2010), Kramer et al. (2011), Sobus et al. (submitted), Pleil et al. (2010), Chiu et al. (2010), and Edwards et al. (2008). New and advanced approaches will be developed and demonstrated for linking information at multiple levels of biological organization to understand relationships among molecular indicators of bioactivity and health and exposure metrics at the individual and population level relevant for risk assessment, prevention, and management.
Research Program

The biomarker topic fulfills a critical role in addressing complex and advanced risk assessments that focus resources on fewer chemicals requiring reduced uncertainty. Activities proposed under this research topic are responsive to the several of the Grand Challenges in the CSS as shown in the graphic on the first page of this topic. Of direct relevance is research to develop new biomarkers and to enhance the interpretation and use of biomarkers for understanding and exposure, toxicity, and risk. Of equal importance will be the development and use of bioindicators (including proteomic, genomic, and metabolomic markers) to understand key events in molecular and cellular biology that are impacted by chemical exposure. Finally, biomonitoring information can be used to understand the molecular, cellular, and systems biology-level processes in ecologically important species. The biomarker topic complements research outlined in all the other CSS topics. Specifically, biomarkers research will be coordinated and integrated with the CSS systems pathways, cumulative risk, evaluation, and extrapolation topic to build and apply the integrated knowledge and tools required for long-term objectives of the CSS program. The science and tools developed here may be applied to both the communities (SCHRP) and air (ACE) program projects within ORD.

Over the next 10-15 years, research in ORD’s biomarker topic, organized around the three major projects outlined below, will focus on designing, evaluating, and implementing the next generation of “systems” approaches and tools for integrating, interpreting, and applying biomarkers in future risk assessment and risk management activities. Figure 5.1 graphically shows how the three biomarker projects are integrated with each other and across other CSS research topics. The figure also shows how the research effort shifts among the projects over time. Projects will start producing the research outputs in the short-term (0-2 years), medium-term (3-5 years), or long-term (>5 years) time frame.
Research within this area will be coordinated and implemented collaboratively with Agency Program and Regional Offices and with collaborating Federal and non-Federal Agencies/organizations, including ORDs STAR Grantees. Through its Biomonitoring workgroup led by ORD, the Agency has an ongoing, successful collaboration with the Centers for Disease and Control (CDC). The purpose of the work group is to identify chemicals of interest to EPA program offices and regions for biomarkers development and incorporation into the NHANES biomonitoring survey. It is intended that this collaboration with CDC will continue to provide value tools and data that can be used within this topic. It is anticipated that major collaborations will be developed with NIEHS through their Exposure Biology Initiative and with the National Center for Children’s Health and Development through the National Children’s Study.

Project 1. Inventory, Link and Evaluate Biomarker State of the Science

This project is designed to establish the foundation upon which the long-term biomarker program will be built. This requires, first and foremost, an understanding of the appropriate uses of biomarkers for exposure and risk assessments (see Sobus et al.). Given a framework with which to apply biomarker data, it is necessary to evaluate current-use biomarkers, models, and approaches (e.g., sample collection, lab analysis, quantitative methods) to identify critical knowledge gaps. Thus, a biomarker knowledge-base will be a valuable resource for evaluating the state-of-the-science. As with all other tools and data within CSS, this knowledge-base will feed directly into the Dashboard data repository, and will facilitate compilation of the most up-to-date information on biomarkers. It also offers a unique opportunity to establish common terminology (ontology) for biomarker research across human health and ecological research, and exposure and health-effects research, a critical component for the transdisciplinary research needed in this area. In the near term (0-2 years), extant biomarker data in the knowledge-base will be used, to the maximum extent given known limitations, to support Agency risk assessment/risk management activities. Concurrently, the knowledge-base will help formulate research hypotheses to shape the biomarker program; these hypotheses will be the drivers for targeted research studies, new biomarker development, and systems-integration across the source-to-outcome continuum.

Project 2. Develop and Evaluate Approaches, Tools and Models to Link and Interpret Biomarkers (forward and reverse)

A biomarker knowledge-base (see project 1) reflecting the state-of-the-science will be used to identify and prioritize gaps in the tools and models needed to link biomarkers across the source-to-outcome continuum. Current risk assessment/risk management activities leverage existing biomarker data to the maximum extent possible. This utilization of limited, or even unsuitable, resources inevitably leads to uncertainties in Agency decisions. Reducing these uncertainties requires the use of new biomarkers/bioindicators that can be measured accurately, efficiently and sustainably, as well as robust quantitative tools to link (1) biomarkers backward to exposure sources, (2) biomarkers to bioindicators, and (3) bioindicators forward to health outcome. Human and ecosystem vulnerabilities and susceptibilities are implicit across these linkages, and will be addressed within each research activity. While individual labs and centers have specific
expertise and may focus heavily one of the above linkages (e.g., NERL-biomarker backward to exposure source; NHEERL-bioindicators forward to health outcome), it is expected that research will be entirely collaborative where appropriate to facilitate high-impact transdisciplinary research outputs.

**Project 3. Case Studies for Evaluating Biomarkers**

With integrated research in mind, case studies of high priority/data rich compounds will be performed with the goal of linking source-to-outcome using combined resources. These case studies will be critical for evaluating biomarkers/bioindicators in “real world” systems, testing research hypotheses as identified in project 1, and evaluating 21st century approaches to toxicity testing.

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**Figure 9. Integration of CSS Biomarker Topic Research with Other CSS Topics and the Anticipated Shift in Research Emphasis Over Time**

CSS Research Action Plan, DRAFT v.1 dated 14 June 2011, p. 26
**CSS Research Topic: Cumulative Risk**

Humans and other species (collectively defined as receptors) are continuously exposed to varying environmental concentrations of different chemical and non-chemical stressors (e.g., habitat quality, disease state, noise) through their daily activities (U.S. EPA, 2009). Chemical stressors from multiple sources (natural, manufactured, or anthropogenic [e.g., source/product emissions, pharmaceuticals]) move continuously through the environment based on their physical/chemical properties and fate and transport processes. Receptors come into contact with chemical stressors based on their geographic location, diet, and their air and water exposure. Once exposed to one or more chemical stressors, a series of biological changes and potential adverse health outcomes may result based on: the frequency, duration, and timing of the exposure(s); the hazard potential of the mixture(s); and the susceptibility (e.g., lifestage) of the individual or population.

Non-chemical stressors may exacerbate or predispose individuals or populations to these chemical exposures and resulting effects. For instance, noise can induce endocrine and autonomic nervous system disturbances, which may in turn interact with other factors associated with cardiovascular disease (Berglund & Lidvall, 1995) and increase susceptibility to other stressors that induce cardiovascular effects. Noise can also affect an animal’s ability to attract mates (NPS, 2010). In humans, socioeconomic status influences both exposure and susceptibility because it determines diet, choice and availability of housing, and access to health care, all of which in turn affect overall health and susceptibility to other stressors. Proximity to human development may similarly affect other organisms’ diets/substrates and habitat quality.

Assessing critical lifestage and lifetime receptor risk requires an understanding of:

- the frequently encountered mixtures of stressors
- availability and quality of housing or habitat
- dietary quantity and quality
- socioeconomic status or competition for ecological resources
- the hazard potential of the chemical mixtures
- the interactions and cumulative impacts resulting from multi-scale spatial/temporal receptor-stressor relationship(s)
- the performance of risk management strategies on exposure and effects, and
- information to promote the design of chemical products with lower environmental impact and increased economic benefits.

Agency chemical risk assessments have often focused on single or classes of manufactured chemicals and have evaluated human and ecological risk independently based on available science and data. Agency risk management decisions must consider all chemicals introduced into the environment, such as household products, foods, agricultural products, and pharmaceuticals. The lack of high quality chemical data (especially for TSCA chemicals),
receptor evaluation endpoints (e.g., susceptible individuals/populations, viability of endangered wildlife species [U.S. EPA, 2005; Barnthouse et al., 2008; Spurgeon et al., 2010; U.S. EPA, 2009]), and chemical and biological performance data for risk management strategies result in large gaps and uncertainties in these assessments. In addition, decision-makers use different approaches for media-specific assessments with outputs and decisions that aren’t readily transferable to other mixtures, geographic regions, or species. The Food Quality Protection Act (FQPA, 1996) tasked the Agency to move from aggregate assessments for single pesticides to consider cumulative risk for pesticides based on mode of action. Internal and external Agency advisory boards and the National Academy of Sciences (NAS) asked the Agency to consider cumulative risk more broadly (NAS, 2008, 2009). These groups further recommend the application of harmonized approaches for assessing and managing risks to humans and other species. These approaches should be based on a comprehensive understanding of the real-world mixtures of stressors, the hazard potential of these mixtures, and the performance of risk management strategies. They must also be representative of potential adverse outcomes that result from exposures during critical lifestages and over the lifetime. These challenges require the development and evaluation of the next generation of science, data, tools, models, and approaches for sustainable cumulative risk assessment and risk management activities (U.S. EPA, in press).

**Figure 10. Relationship of Cumulative Risk Topic to CSS Framework**

**Research Program**

Over the next 10-15 years, ORD will plan and implement innovative, transdisciplinary research organized along three projects outlined below to provide solutions to the Agency’s highest priority human health and ecological cumulative risk needs, including needs identified by the scientific community (Sheldon et al., 2009; Mason et al., 2007; Teuscheler et al., 2002, Suter 2010). Figure 2 graphically shows how the three cumulative risk topic projects are integrated across other CSS research topics. As identified below, each project will start producing research outputs in either the short-term (0-2 years), medium-term (3-5 years), or long-term (>5 years) time frame.
ORD scientists, along with scientists and managers from the Program/Regional Offices and other collaborating Federal, State and non-governmental agencies and organizations (e.g., USGS, NOAA, CDC, STAR grantees), will design and evaluate user-friendly data, tools, models, and approaches to support cumulative risk assessments and corresponding risk management actions for addressing human and ecosystem health. Research designed and implemented through the cumulative risk topic will be coordinated with and informed by the on-going and planned activities of the Risk Assessment Forum. Concurrently, ORD will build on our existing mixtures research activities to inform the design of the new research while simultaneously supporting immediate and near-term needs for the Human Health Risk Assessment (HHRA) Research Program, OCHPP, and others (e.g., generation of data necessary to support pending Agency decisions). The integrated ORD cumulative risk research will develop and evaluate: alternative approaches for surrogate species; predictive models that rapidly identify and screen chemical mixtures and chemical/non-chemical stressor combinations; high throughput approaches and tools for identifying priority real-world environmental mixtures; spatial and temporal exposure scenarios for targeted receptors; techniques for hazard identification and assessing adverse impacts on biological systems; and risk management strategies which support sustainability. The integrated exposure and effects research will develop and refine approaches for humans and wildlife species, and will include considerations of risk based on critical lifestages and other susceptibility factors. The prioritization approach will be based on the development of integrated rankings that holistically consider exposure and human/other species’ health and identifies those groups (either by lifestage, population, or species) that have the greatest likelihood of being affected.

The cumulative risk research will be informed by the priorities established in other CSS topics (primarily from systems pathways, but also from biomarkers, evaluation, and extrapolation). It will build the integrated scientific knowledge and tools required for the long-term CSS program objectives. It will also focus on research to directly inform high priority Program Office and Regional cumulative risk assessment/management actions. The research described here also complements and will provide research inputs to the ORD Human Health Risk Assessment Program, as well as ORD’s air (ACE), water (SSWR), and communities (SCHRP) programs.

Project 1. Develop and evaluate current tools, models, and data available to support cumulative risk assessment and risk management activities

Cumulative risk assessments are currently conducted by multiple organizations using many different methods with many different endpoints. The overall goal of this project is to develop a basic understanding of the current approaches that are being used, assemble the available data, identify innovative approaches and tools for developing stressor groups, and to developing an understanding and approaches for linking exposure and toxicity data for integrated assessments. The task outputs from this project will feed directly into the Dashboard data repository thus making the information immediately available to EPA and other researchers for discovery and for conducting cumulative risk assessments. Research will be coordinated with the five other new ORD research programs, Agency Program and Regional Offices, and Federal and non-Federal Agencies/Organizations especially for developing data inputs. We will work with organizations such USGS, CDC, HUD, NOAA, NASA, and others to gain real-world environmental data (to be maintained within Dashboards). We will also be working with
organizations such as the Fish and Wildlife Services, National Park Service, HHS, Star grantees, Census Bureau to gain real-world data on receptors (to be maintained within Dashboards).

**Project 2. Develop and evaluate integrated tools for informing next generation risk assessment and risk management activities**

The task outputs of this project will be the knowledge, data, and tools for performing quantitative assessments of the cumulative impact of groups of stressors on the targeted receptor(s) to inform environmental decision-making. The scientific knowledge will be used by ORD (collaborating with ORD’s HHRA program) to inform the development of harmonized human and ecological health guidelines for cumulative risk assessment and risk management activities. Work under this project will include approaches that use adverse outcome pathway (AOP) systems models to explore outcomes from multiple stressors. Approaches for integrating pathway information developed through high throughput screening assays into assessment activities will also be addressed. This later activity will be conducted in collaboration with and will provide inputs to the Dashboards and Human Health Risk Assessment Program.

**Project 3. Application, translation and transfer of approaches, tools, and models for selected risk assessment and risk management activities**

This project will provide the science knowledge, methods, and techniques (including those under development) that can be used for immediate and near-term Agency risk assessment and risk management needs. Included in this project is the on-going translation and transfer of task outputs from projects 1 and 2 to directly support specific Agency cumulative risk assessment and risk management activities. Current mixtures research that is a high priority to our Agency partners (HHRA, OCSPP, and others) will be completed under this project. Task outputs from all three projects will feed directly into the Human Health Risk Assessment Program.
CSS Research Topic: Dashboards and Decision Support Framework

The objective of this effort is to provide actionable information about chemicals and stressors in order to meet specific EPA program office needs for 21st Century tools for chemical programs (EDSP21, TSCA21, OW21, OPP21, HHRA/NexGen). The proposed system is based on a decision-support framework and will address specific decision-making requirements identified by partners and stakeholders, leverage existing tools and databases, and build new tools and databases where necessary. The main deliverables of this activity are: (a) a modular knowledge management framework that organizes disparate information on chemicals across CSS programs, including: inherency, hazard, fate, exposure, and sustainability; (b) web-based interactive visualization tools ("Dashboards") that are graphical interfaces to existing computational tools and data repositories; and (c) a library of ‘widgets’ that can be combined into new dashboards to provide high-level summary information to support decision-making across program offices.

Due to the highly integrative nature of this research activity, it relies heavily on all CSS programs. The proposed knowledge management framework provides a unifying conceptual model that links inherent chemical properties (ICP) to their expected real-world impacts, ranging from sources to health and ecological outcomes [Evans et al, 2011]. It leverages the Framework...
for Integrated Research and Systems Thinking (FIRST), which is based on a holistic view of the resource flows and interactions among industry, environment and society. Supporting the framework will be an analytic workbench that draws upon established EPA methods, including Risk Assessment, Life Cycle Assessment (LCA) and Comprehensive Environmental Assessment (CEA). The workbench will also draw upon emerging methods from EPA’s computational toxicology research program (CTRP) and will incorporate understanding of chemical fate and effects, from initial source to prediction of potential adverse outcomes. The required knowledge will be derived from databases, knowledge bases, expert systems and decision-support tools developed across ORD’s exposure, effects, risk assessment and risk management labs and centers.

Coupling databases with web-based interactive visualization tools (Fox et al, 2011) will be essential to CSS integration across technologies and focus areas. Given the multidimensional data deluge from 21st Century biological sciences, a wealth of data has been, and will continue to be, generated that can guide further research and aid in making expert judgments. This research topic will organize, integrate and translate information from multiple sources, providing visually-driven exploratory tools that support EPA decision-making by maximally leverage knowledge as it is gained across all CSS research topics. Users (both expert and novice) will have ready access to comprehensive information along the continuum from chemical structure, and the behavior thus imparted, to the resulting chemical exposures and risks of environmental and/or health impacts. The tools will include selected indicators of environmental sustainability, reflecting either degradation or depletion of natural resources [Fiksel, 2010]

Customized, web-based dashboard interfaces will be developed that draw upon the available databases, knowledgebases, programmatic workflows, and computational models and tools. This will require the establishment of compatibility and interoperability between national and international databases and modeling tools. These dashboard interfaces will be designed to support chemical-specific life cycle assessments and decision making within EPA, as well as product development, manufacturing, and use decisions in the private sector.

Delivering the above decision support tools will involve two main interconnected research activities. First, the end-users will be engaged in discussions to clarify and prioritize their requirements. Second, a rapid, iterative prototyping approach will be used to develop dashboards and to obtain feedback from end-users. We propose to use a web-based modular architecture that will enable us to efficiently and incrementally deploy existing in-house or public domain tools in the short-term. This will also allow us to identify key gaps in analysis capabilities and to focus ORD resources effectively. In addition, the work will include development of advanced tools that support public and private sector decisions on sustainable product development, manufacturing, and use.
Research Program

The proposed research will provide program office partners with an unprecedented integration of critical decision-relevant information in a highly visual format while allowing the user to evaluate the underlying decision support tools and raw data used to generate each report. Using a comprehensive knowledge-based framework will enable simultaneous consideration of health-related information and broader sustainability concerns, taking into account the full chemical life cycle. This will facilitate complex trade-off analyses regarding the risks and benefits of alternative chemical compounds, and will support innovative efforts to design and develop environmentally benign chemicals and chemical management practices. This research topic will address the Framework outcomes of digitizing and making available existing information; and technology transfer, translational science, and science communication. Due to the highly integrative nature of the proposed work, it depends on the output of most of the other CSS research topics.

Project 1. Program-Specific Dashboards

The decision-support tools will be customized to meet specific needs of EPA program offices. These needs have been documented in the work-plans developed for “21st Century Tools for Chemical Programs” namely, EDSP21, TSCA21, OW21, and OPP21, and the developing Interagency Advancing the Next Generation of Risk Assessment Program documents. In summary, a framework is needed for prioritization, targeted testing, pathway analysis (across the source-to-outcome continuum), systems-based analysis, and evaluating options for sustainability.
Project 2. Knowledge Management and Decision Support Tools

Data warehouses provide structured access to large amounts of data, however, there is an unmet need for robust tools that can: (a) capture institutional wisdom about key linkages across disparate data domains to characterize the human health and environmental impacts of chemicals, and (b) organize this information in a decision-making context. A knowledge management framework based on open-source semantic web tools will cost-effectively link disparate EPA data sources providing transparent and coherent access to relevant information. In addition, it will enable the development of re-usable decision support tools that leverage domain expertise and computational inference to meet the evolving needs of EPA program offices. As described above, end-users will be provided with custom “Dashboards” tailored to their information requirements. The dashboard and related decision support tools will employ the knowledge-based framework for prioritization, targeted testing, pathway analysis, systems-based analysis, and sustainability considerations. Each dashboard will include “drill-down” options to allow users to access and evaluate raw data and underlying assumptions driving higher level dashboard output.

Illustration of Potential Research Outputs

The general design of an interactive dashboard interface is illustrated in Figures 13 and 14. Figure 15 illustrates the workflow schematic underlying such a dashboard.
Figure 13. The user is presented with a set of choices to customize the dashboard. These choices determine the data, widgets, etc. available for the user’s custom dashboard display.
Figure 14. A mock dashboard is displayed, created using the choices in (a). Adjustments are still available, via sliders or buttons corresponding to the choices in (a). Users can save the analysis so that the current state of the dashboard may be reloaded later.
**CSS Research Topic: Evaluation**

Evaluation research focuses on assessing methods, assays, and practices to help others understand the reliability and utility of an assay, method, or application to be used in risk assessment, risk management and decision making. This research will develop approaches for estimating and characterizing the value in technologies and methods used in CSS to help inform their use in risk assessment, risk management, and decision making.

In order to better utilize the methods, assays, and practices used within CSS, this research program will focus on the following research activities: 1) development of value of information methods and models to focus future CSS research activities that will characterize the degree of confidence provided by different types of data, new technologies and applications to risk.
assessment and decision making; 2) research to evaluate the comparability of 21st-century approaches (e.g., non-animal, high throughput) with traditional inputs into assessments in ways that enhance support for, and increase confidence in, environmental decision making; 3) research that evaluates and characterizes the reliability and utility of new data, assays, and models to characterize risk, including case studies to elucidate sources of uncertainty, levels of uncertainty, and ways to increase relevance and decrease uncertainty for given target contexts (e.g., for a given ecosystem impact or risk management alternative), especially as it pertains to risk assessment and risk management decisions; 4) case studies and research to determine if and how new data or new assessment methods may increase the utility and decrease uncertainty in risk characterizations, leading to better decisions.

Evaluation research is essential for using new or alternative approaches to risk assessment and management activities. The outputs from the other CSS research topics must be evaluated to determine that the methods being produced and the data being generated are reliable, predictive, and have utility if applied to characterize risk of various contexts or to compare risk management alternatives. Thus, the outputs must be evaluated to determine if and how they will best be utilized in risk assessment, risk management, and decision making. Outputs from this research topic will also feed back into the other CSS research topics. For instance, value of information research within this research topic may characterize confidence in the output of other research topic approaches, delineate their reliability and utility to provide guidance for their application, or evaluate uncertainty from the output of other research topics, thus driving future research and improving accuracy.

![Figure 16. Relationship of Evaluation Topic to CSS Framework](image)

**Research Program**

This research topic will result in methods that help to focus future CSS research in areas that further reduce uncertainty in extrapolations; decision models and decision analysis methods that
better characterize reliability and utility of data and assays for given applications in risk assessment or risk management; determinations if increased accuracy is leading to better decisions; evaluation and characterization of the sources and levels of uncertainty, and ways to improve the relevance, utility and reliability of data and methods in risk assessment and risk management decisions. Integrated transdisciplinary research is essential for the success of activities under this research topic. It will require the expertise and interaction of chemists, biologists, toxicologists, computational biologists and modelers, bioinformaticians, risk assessors, and risk managers. It is envisioned that as legacy and CSS outputs are generated, they will require evaluation by risk managers and risk assessors to determine how they can utilize the information, and they may require additional expertise to help understand the reliability of these new data for different applications, including uncertainties associated with the new methods or data, or to understand how these new methods and data impact confidences in a type of decision (e.g., screening versus regulatory standard) or understanding of a process (e.g., life cycle of particular production).

**Project 1. Value of Information Methods and Models**

This project will generate value of information methods and models that characterize the utility and reliability of new data and methods to reduce uncertainty and improve their reliability and flexibility in decision making. The goal of this type of research is to improve the relevance and utility of assays and models developed by CSS research for decision making by characterizing the reliability, utility and uncertainty of their use in various assessment and risk management decision applications. This research will also impact future CSS research, by investigating the current value of information used in risk assessment, risk management, and decision making, and to identify ways of improving the foundational quality of the data on which inferences are based and reducing overall uncertainty in extrapolation or application of these new methods and models by focusing on specific areas for future research. This type of research will ensure the overall economic sustainability of the CSS program and its outputs, by identifying future research topics that may have the greatest impact on risk assessment, risk management, and decision making. This research will also identify future research needs in risk assessment, risk management, and decision making.

**Project 2. Utility and Reliability of Data and Models Used in Risk Assessment, Risk Management, and Decision Analysis**

The challenge to evaluation research in general is the ability to characterize the reliability and utility of data and models to understand resultant uncertainty and sensitivity in decision models and decision analysis methods. One of the goals of CSS is to integrate information from inherency, exposure, hazard, and risk management options to lead to an overall increase in the accuracy of characterizations, thus reducing risk and creating a higher degree of certainty in decision making.
Project 3. Research to Evaluate If and How New Assessment Methods Improve Accuracy and Lead to Better Decisions

A challenge in evaluation research is deciding when a new assessment method or model is ready for use in the risk assessment or regulatory environment. Robust measures of reliability and utility are needed for incoming methods and models but also for existing methods and models so that appropriate comparisons can be made and data generated from CSS and be readily incorporated.

Relationships Between Research Topics

CSS has been designed to operate as an integrated research program. Figure 17 illustrates the relationship between topics. As described in the Framework, the chemical life cycle should be considered in the formulation of most, if not all, CSS projects and tasks, and therefore is relevant to all other research topics. Systems pathways questions serve as points of departure for further elaboration of focused activity under the inherency, biomarkers, extrapolation, cumulative risk, and evaluation research topics. Methods, models, tools, and other information feed into the development of dashboards and other products with direct decision-support applications. Interactions also will occur among the topics in the middle of the circle, such as between extrapolation and evaluation. In all cases, relationships will form, dissolve, reform as progress advances in addressing science questions and new questions, projects, and tasks are developed.

Figure 17. Relationships Between CSS Research Topics
V. Conclusion. This version1 draft of the CSS Research Action Plan, while a major step forward in designing a realigned ORD program to address 21st-century needs for environmental science information and tools related to chemicals, will undergo further elaboration between June and October 2011. Tasks will be described within projects, and links from those tasks to specific program and regional office needs will be described. However, this version of the draft CSS RAP does reflect EPA-wide agreement on major areas of research that ORD should undertake to advance chemicals-related research, and the key topics under which the work to implement this research should be organized. This is an opportune time for the EPA Science Advisory Board and ORD Board of Scientific Counselors to provide input on the CSS research program as described in the Framework and draft Research Action Plan.