Framework for an EPA

Chemical Safety for Sustainability

Research Program

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Contents

Executive Summary

Chemicals provide many key building blocks that are converted into end-use products or used in industrial processes to make products that benefit society. Ensuring the safety of chemicals and their associated products is a key EPA mission. For this mission, we need an approach for evaluating the safety of chemicals and products that allows for consideration of society's current demands, and does not compromise the ability of future generations to meet their needs.

Current processes and procedures for evaluating and assessing the impact of chemicals on human health, wildlife, and the environment were, in general, designed decades ago. Many of these approaches have not fully incorporated recent advances in exposure science, biology, and computer technologies. As a result, we do not understand fully how chemicals come in contact with organisms, how they interact with biological processes, and how those interactions progress to adverse outcomes in individuals and populations. Current approaches are resource- and time-intensive, making it difficult to meet the demands of evaluating the safety of an ever-increasing number of chemicals in commerce. Thus, transformative approaches are needed to improve the information used in assessments. New approaches will enable us to both increase the pace at which relevant information can be obtained and integrated into assessment and decision making, and inform sustainable approaches to chemical design, production, and use across chemical, material, and product life cycles.

EPA is creating the Chemical Safety for Sustainability (CSS) research program to address these needs. Enhancing scientific approaches for understanding current and emerging chemicals is essential for effective environmental decision making in the 21st Century. Through the CSS research program, EPA will develop decision-support tools that can be applied to evaluating chemicals currently in commerce, as well as to informing the development of future chemicals with less environmental impact.

Tools produced through the CSS research program will use systems approaches to understand the links between exposure and toxicity pathways involved in disease. These approaches will allow EPA to evaluate the impact of chemicals on life stages and other susceptibility factors such as genetics and co-existing diseases. Additionally, the CSS research program will develop sustainability metrics to measure how changes in parameters that affect hazard and exposure impact the degree to which a chemical is more or less environmentally sustainable throughout its life cycle. Approaches designed to evaluate chemical safety will enhance our understanding of the properties of molecular structure, function, and formulation relevant to exposure and biological

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

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

effects across chemical life cycles. The ultimate goal is to ensure safety in the design, manufacture, and use of new and existing chemicals.

To increase the scale of our decision support tools and to improve guidance/management for safer chemical design and use, we need an integrated, transdisciplinary research effort that unites the capabilities of chemists, exposure scientists, biologists, engineers, and economists and other social scientists. The CSS research program described in this document is focused on providing integrated solutions in support of chemical management. The data, methods, and tools developed in the CSS research program will guide the prioritization and testing process from screening approaches through more complex testing and assessment that are appropriate to the decision needs. By organizing its research to support integrated evaluation strategies, the CSS research program will provide state-of-the-science tools and integration techniques to inform risk assessment and risk management activities. Such assessment and management activities include those used in regulatory decision making as well as those utilized in developing, producing, and using chemicals. The CSS research program will focus on the highest priority, chemical-specific research needs of EPA's program and regional offices as well as those of other decision makers.

I. Introduction

Background and Science Needs. New scientific approaches are needed for the safer manufacture and use of chemicals. Currently, there are more than 100,000 chemicals registered in the European Registration, Evaluation, Authorization, and Restriction of Chemicals (REACH) Program; 84,000 chemicals on the Toxic Substances Control Act (TSCA) inventory; and each year about 1,000 new industrial chemicals and pesticides are introduced into commerce. Only a small fraction of these chemicals has been assessed for potential risk, often because of limitations in existing data, tools, and resources. The contribution of environmental pollutants to disease is unknown, but it may be significant. For example, the World Health Organization (WHO) estimates that nearly a quarter of the global disease and death burden can be attributed to environmental factors (WHO, 2006). How much of this is associated specifically with chemicals, materials, and products also is unknown.

> In the CSS research program, ***chemicals*** refer to intentionally produced or manufactured chemicals, particles, and materials, as well as products into which they are incorporated. It may refer to single chemicals, particles, or materials, or mixtures of chemicals, particles, and/or materials, products, as well as forms of chemicals that are transformed as they move through the environment.

Current testing and assessment approaches are labor and resource intensive and lack data sufficient to meet decision-making needs. Also, current approaches do not meet the environmental challenges posed by the large and growing number of chemicals. Therefore, new integrated chemical prioritization, testing, assessment, and management methods are needed. Such approaches must consider a chemical's life cycle from its design to its use, disposal, and reuse or recycling. The long-term scientific solution to meeting this challenge is environmentally sustainable chemical production and use. Developing testing, assessment, and risk reduction approaches to ensure chemical sustainability will require the generation of environmental and health data. To do so, we need approaches that identify what specific data are essential to make better decisions to prevent, where possible, and to assess and manage, where necessary, risks to humans and the environment from chemicals.

In September 2009, the EPA Administrator announced Essential Principles for Reforming Chemicals Management Legislation to inform efforts in Congress to strengthen the Toxic Substances Control Act (TSCA). She also outlined a comprehensive approach to enhancing chemical management under existing laws. The Principles state that:

- Chemicals Should be Reviewed Against Safety Standards That are Based on Sound Science and Reflect Risk-based Criteria Protective of Human Health and the Environment;
- Manufacturers Should Provide EPA with the Necessary Information to Conclude That New and Existing Chemicals are Safe and Do Not Endanger Public Health or the Environment;
- Risk Management Decisions Should Take into Account Sensitive Subpopulations, Cost, Availability of Substitutes, and Other Relevant Considerations;
- Manufacturers and EPA Should Assess and Act on Priority Chemicals, Both Existing and New, in a Timely Manner;
- Green Chemistry Should Be Encouraged and Provisions Assuring Transparency and Public Access to Information Should Be Strengthened; and
- EPA Should Be Given a Sustained Source of Funding for Implementation.

EPA's Priorities

Taking action on climate change

Improving air quality

Assuring the safety of chemicals

Cleaning up our communities

Protecting America's waters

Expanding the conversation on environmentalism and working for environmental justice

Building strong state and tribal partnerships

EPA is supporting the approach outlined in the Principles by creating the CSS research program. The CSS research program will develop enhanced chemical screening, prioritizing, and targeted testing methods, tools, and data, as well as new approaches for using scientific information in chemical assessment and management that are more adaptable to multiple decision-making needs. The research and development products from the CSS research program will benefit the regulation and use of existing pesticides and industrial chemicals and enhance green chemistry and engineering opportunities for the design, production, and use of both new and existing chemicals.

CSS's research products also will support community-level decisions by providing tools and data used by EPA's Sustainable and Healthy Communities research program for those contaminants of highest priority and concern to the community, considering susceptibilities and exposures of the most vulnerable populations. Better approaches to chemical testing and assessment also will inform air toxics- and drinking water-related national, regional, and local decision making, as well as decisions on waste management, remediation, and emergency response. Decision makers need targeted, credible, and usable information to inform their decisions, and the CSS research program is focused on developing tools, methods, and data to support those decisions.

CSS Objectives

Creating tools that inform sustainable chemical/material design and use

Developing methods for much faster screening and prioritizing

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

Developing assessment approaches that are tailored to specific decision contexts

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

EPA Research Context. Existing science and technology information and the current approaches for generating that information can advance EPA's mission only so far. Addressing the environmental challenges of the 21st Century—such as climate change adaptation, energy efficiency, and avoiding risk shifting—will require the integration of research across environmental science disciplines. Therefore, EPA will need to do its work differently to meet current and future environmental challenges. To help lead America toward an environmentally sustainable future, EPA faces two major challenges:

1. Making faster and better informed decisions , guided by science, on the problems already facing us; and
2. Getting out in front of tomorrow's problems by identifying and applying approaches that better inform and guide environmentally sustainable behavior.

To that end, EPA is realigning its 12 current research areas into four integrated program areas:

- Air, Climate, and Energy
- Safe and Sustainable Water
- Sustainable and Healthy Communities (Built and Natural Environments)
- Chemical Safety for Sustainability

The EPA research program will be rounded out by the existing programs of Human Health Risk Assessment and Homeland Security, which integrate findings from these transdisciplinary programs into assessments that inform decisions.

Figure 1 represents four realigned EPA research programs that are interrelated and fit within larger EPA and stakeholder contexts. To provide scientific information and tools that advance environmental sustainability, the four research program areas must contribute to and reinforce one another, and jointly work with decision makers both inside and outside EPA. The Agency recognizes that a CSS research program cannot by itself fully address all issues related to chemicals, and must work with other EPA research programs to further understanding of the human and ecological impacts associated with chemical production, use, disposal, and the ecological resource burdens (e.g., water footprint) associated with chemical industry supply chains because of their reliance on ecosystem goods and services. As part of the larger context within which the CSS research program will operate and to complement existing EPA assessment activities, sustainability assessment and decision making for chemicals must account for the benefits to society associated with chemicals and products as well as the risks. Appendix D illustrates the relationship between the current EPA research programs, the new realigned research programs, and the structure of the EPA Strategic Plan.

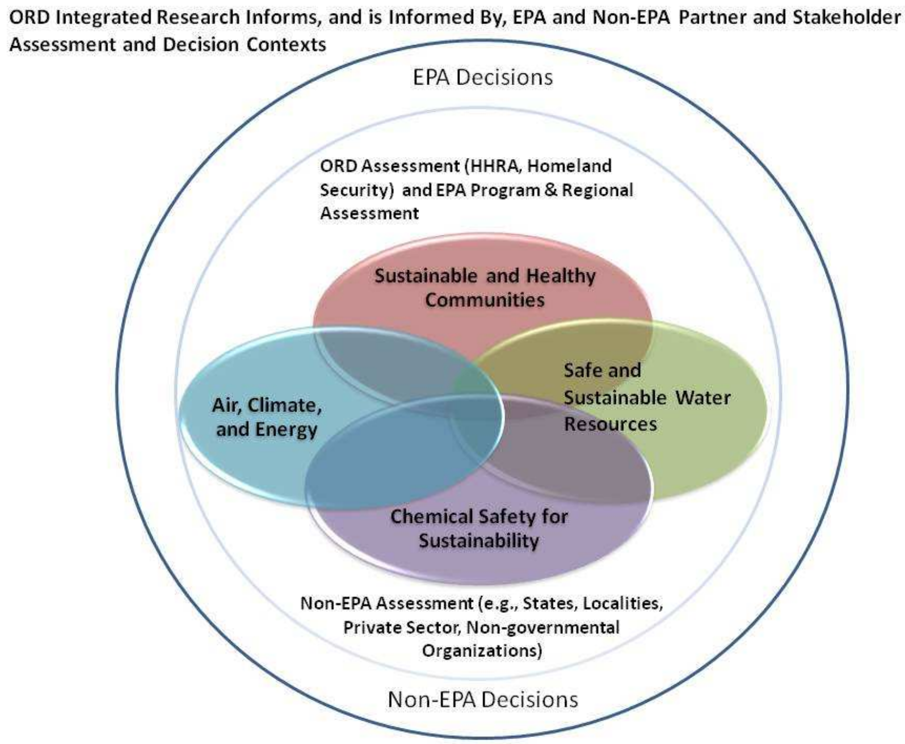

Figure 1. Integrated EPA Research Programs Within EPA and Non-EPA Partner and Stakeholder Contexts

Although the CSS research program will advance several EPA priorities, it addresses one in particular, *Assuring the Safety of Chemicals* (USEPA 2010), and is EPA's vanguard effort in the realignment of EPA research to address Agency priorities. EPA is applying a new approach, integrated transdisciplinary research, to ensure that the realigned research program provides innovative science and engages end users of its research products from research planning through the delivery and application of the research findings and products.[1]

[1] **Integrated Transdisciplinary Research (ITR)** is the bringing of people together from different disciplines, perspectives, and experiences to define problems, conduct research, and deliver products and outcomes.

II. Achieving CSS Research Program Outcomes That Advance Sustainability

The CSS research program seeks to develop methods and tools to inform the development of enhanced risk prevention or management approaches for both new and existing chemicals. To develop scientific information that leads to improved understanding of how to better create and manage chemicals, CSS research must incorporate three key considerations into its research activities: the chemical **life cycle, inherent chemical/material properties,** and **sustainability.**

Life Cycle. Figure 2 illustrates the CSS research program's perspective on the chemical life cycle. Impacts to people or other parts of the environment from chemicals can occur at any point from the extraction of raw materials for chemical manufacture to processes that create the chemical and incorporate it into products through the chemical's and product's use and at its end of life, when it is disposed of or recycled.

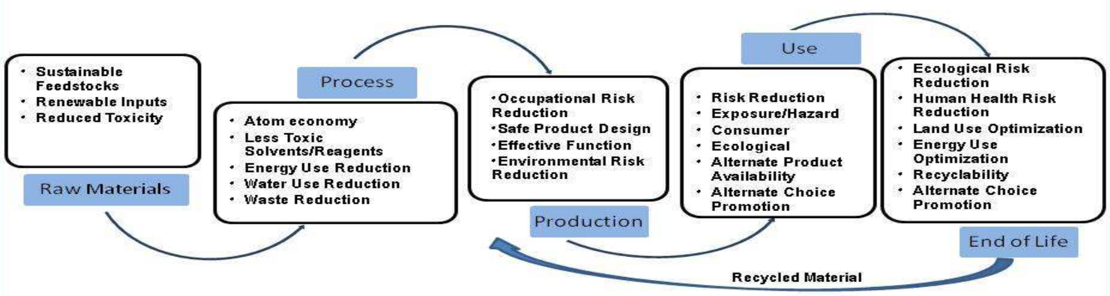

Figure 2. Considering Sustainability Across A Chemical's Life Cycle

Therefore, consideration must be given to what points in the life cycle present what types of vulnerabilities to people or wildlife, and what these vulnerabilities—when coupled with potential impacts—tell us about how to estimate risks posed by the chemical. At the same time, each point in a chemical's life cycle presents an opportunity to avoid or otherwise address concerns about environmental (i.e., human and ecological) impact. Green chemistry and other safer-by-design approaches may provide opportunities for risk prevention early in the life cycle; however, when those options are not feasible, control or handling measures may help manage downstream impacts. *The CSS research program seeks to develop methods and tools that can inform the development of sound and*

Chemical Life Cycle Approach. The application of the cradle-to-grave life cycle perspective to chemical design, manufacture and use, with the aim to manage potential risk of exposure and impacts.

Life-Cycle Assessment (LCA). A holistic way to consider multi-media environmental issues associated with a product or a process from resource acquisition through manufacture, transportation, distribution, and use, to waste management and disposal. Applied to chemical design and manufacturing, LCA allows the comparison of ecological performance of synthesis processes, and guides process developers in identifying opportunities for improvement.

feasible assessment and management approaches across chemical life cycles.

The CSS research program considers the decision context for chemicals from the perspective of prevention decisions for new chemicals and management decisions for existing chemicals. Although approaches such as green chemistry may be feasible for decision making on either existing or new chemicals, they may have greater advantages during chemical design or development. In some cases, green chemistry approaches may not be viable, and the only way to mitigate impacts from some existing and new chemicals will be through management controls. *The CSS research program will address both new and existing chemical issues.*

Inherency and Sustainability. *Inherency* consists of the physico-chemical and material properties of the chemical—for instance, the structure, composition, size, and solubility that comprise a chemical formulation; or if it is a particle, its surface area, surface charge, aspect ratio, etc. These properties may determine, for instance, how mobile, persistent, or bioavailable the chemical is in the environment. They also may influence the ability of a chemical to interact with biological processes that lead to human disease or adverse effects in wildlife species. It may be possible in some cases to apply green chemistry approaches during chemical design to alter or otherwise address such inherent properties in ways that reduce environmental impact. Often, however, these also are the properties that give the chemical/material the desirable performance characteristics that make it worthwhile to produce. *The CSS research program seeks to incorporate consideration of inherent chemical properties into its integrated testing, assessment, and management approaches.*

Sustainability refers broadly to the socioeconomic and environmental impacts of chemical use, including implications for human health and well being, environmental resource protection, and economic prosperity. The CSS research program will focus upon *environmental sustainability*, which consists of two main aspects: (a) the consumption of environmental resources, including materials, energy, water, and other ecosystem services; and (b) the generation of waste and emissions that may affect human health or degrade the environment. A full understanding of sustainability requires accounting for these environmental impacts over the full life cycle of a chemical, including resource extraction, transport, production, incorporation into products, product distribution and use, and eventual disposal or recycling of the product and its constituents. Moreover, it is important to understand the potential social and economic implications of the chemical life cycle, including issues such as environmental justice and competitive advantage.

Investigating environmental sustainability involves three principal dimensions: what the chemical is, how it is made, and how it is used. Altering any of these three dimensions changes the potential of the substance to produce environmental impacts throughout its life cycle and affects sustainability metrics, such as eco-efficiency (i.e., the ratio of value delivered to resources consumed). For instance, one might question whether the use of toxic starting materials is really necessary in making a particular chemical if less-toxic starting materials are available. Or, if such alternative starting materials are not available, then one might investigate whether there are aspects of the current synthesis process that could be changed to mitigate the impacts of such toxic inputs into chemical synthesis and production. Likewise, one might question the use of a raw material feedstock that requires a significant input of water and energy, and identify an alternative feedstock that has a smaller environmental “footprint” in terms of carbon emissions and resource consumption.

Approaching inherency and sustainability from a life-cycle perspective is important for several reasons. First, particular physico-chemical or material properties of a chemical may change as it moves through the environment, not only transforming what the chemical looks like but also its potential impact on biological systems. Therefore, decisions to alter properties need to consider not only how those altered properties will affect the chemical’s environmental impact in its as-produced state, but also as it is used and as it enters the environment. Second, understanding the environmental sustainability of a chemical will require knowing how the chemical’s potential for environmental impact changes over time and space. For instance, a chemical may require more energy to produce than alternatives, but if less of it is used in products than alternative chemicals, it may present less potential for environmental exposure. Life-cycle assessment (LCA) methods provide a rigorous approach toward investigating these issues, and can report a variety of impacts at the mid-point for an entire product system, including, but not limited to, potential contribution to eutrophication, acidification, global warming, ozone depletion, human health toxicity, ecological toxicity, smog formation, and natural resource use. Thus, LCA methods can be used to identify how a particular decision may shift environmental burdens across complex systems.

Inherency, sustainability, and the chemical life cycle go hand-in-hand in developing approaches for making existing and new chemicals safer and more environmentally acceptable. For this reason, they are fundamental aspects of the CSS research program.

Key Concepts: Integrated and Transdisciplinary. The CSS research program will require EPA to pursue a transdisciplinary approach to develop the scientific tools and knowledge necessary to inform decisions that advance sustainability. As a transdisciplinary research program, the CSS research program will integrate skills, expertise, and research from diverse fields, such as bioinformatics; computational chemistry; green chemistry and engineering; systems biology; molecular, cellular, and biochemical toxicology; exposure science; process modeling; chemical and environmental engineering; social sciences, including but not limited to economics; decision science; and life-cycle assessment. The integrative nature of the CSS research program distinguishes it from multidisciplinary approaches that bring disciplines together, but do not alter the respective approaches or other contributions that the individual disciplines bring to the problem. *To move away from what currently in EPA is mainly a disciplinarily stove-piped approach to environmental science, implementing the CSS research action plan will require certain specific steps—including training, cross-organization dialogue, and team building exercises—to ensure that a transdisciplinary approach is integral to EPA’s research planning, implementation, and product-delivery practices.*

An Integrated Evaluation Strategy. EPA supports the growing recognition within the environmental science and regulatory communities that more advanced science is needed to inform the sustainable development and use of chemicals. EPA believes this can best be achieved by scientific information developed through integrated evaluation strategies.[2] Figure 3 illustrates EPA's view on how an integrated evaluation strategy can best meet the decision-support needs of EPA's offices and other environmental decision makers.

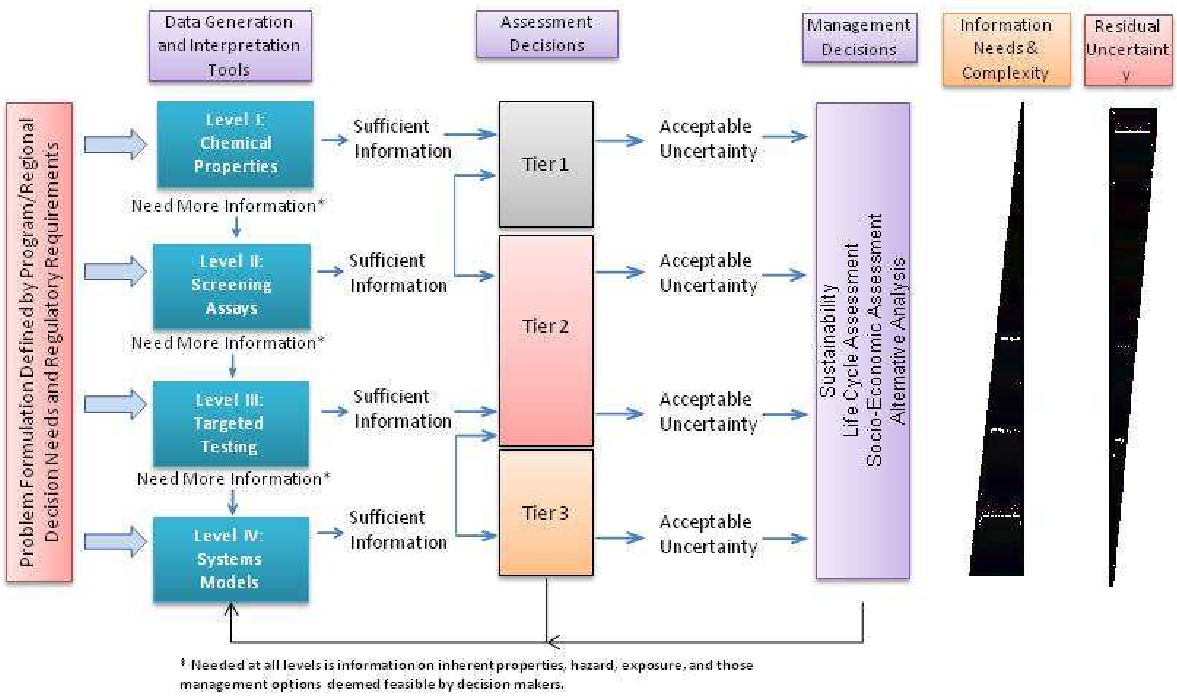

Figure 3. The CSS Research Program's Perspective on an Integrated Evaluation Strategy for Environmental Data Development and Decision Making

In Figure 3, the relationship between testing, assessment, and management research for chemicals is driven by problem formulation as defined by decision-making needs. The amount of resource utilization is adjusted for each level to provide efficient and timely data to address the needs of particular decisions. For instance, early in the chemical- or product-development process, simple screening approaches may be

[2] Van Leeuwen CJ, Patlewicz GY, Worth AP. Intelligent Testing Strategies. In: Van Leeuwen CJ and Vermeire TG (Eds.). Risk Assessment of Chemicals: An Introduction. Springer, 2007, 467-509. Available: http://www.springerlink.com/content/kk84568kg5047733/fulltext.pdf; Doull J, Borzelleca JF, Becker R, Daston G, et al. Framework for use of toxicity screening tools in context-based decision-making. *Food Chem Tox*, 2007;45(5):759-796. Available: http://www.sciencedirect.com/science/article/B6T6P-4M81C10-3/2/199da32170440f75151223a30ffe0fd2; http://www.oecd.org/document/42/0,3343,en_2649_34365_36283562_1_1_1_1,00.html

adequate to identify chemicals or products whose development should not be pursued. Some chemicals or products may need to be evaluated beyond screening and may require more-thorough assessment to determine where in their life cycle the greatest potential for hazard and/or exposure exists. For regulatory purposes, as the potential impact of the decision increases, data needs may increase. This will increase the resource costs of the assessment, but should reduce uncertainty in estimates of environmental impact.

The strategy that the CSS research program envisions for EPA and others' use includes four types of approaches (illustrated by the blue boxes in Figure 3) of increasing complexity. The bars to the far right of the figure show how resource needs increase with needs for reduced scientific uncertainty in estimates of risk and impact. As shown, the evaluation approaches range from an initial risk assessment that requires few resources, to evaluate large numbers of chemicals while tolerating high levels of uncertainty, to a more complex, advanced risk assessment (or ranking) that requires substantial resources, to evaluate only a few chemicals with lower levels of uncertainty. Although shown as discrete levels, the sequence actually represents a continuous process that proceeds until sufficient information to support a particular decision has been obtained.

Each level and tier within the strategy integrates information on inherent properties, exposure, hazard, and risk management, although the focus may shift between approaches. Property evaluation uses an understanding of chemical properties to predict exposure, hazard, and degradation in the environment, as well as for informing the design of chemicals with less environmental impact. Screening provides tools to improve the decision makers' ability to screen and prioritize chemicals with such decision contexts as (but not limited to) addressing high production volume chemicals, characterizing and addressing air toxics, compiling drinking water contaminant candidate lists, and remediating Superfund sites. Most of the EPA's risk assessments currently are conducted using historically accepted targeted testing approaches, and this is very resource intensive. An integrated evaluation strategy streamlines the process by providing approaches that require data collection only for those specific effects, groups of chemicals, and exposures that are needed for a particular type of decision. Finally, integrated modeling approaches can be applied to inform enhanced risk assessments for those chemicals suspected of nearing or exceeding the threshold of acceptable health risk and for which risk management options are limited or controversial. Assessments needing integrated modeling approaches may require substantial data as well as new science and new tools to describe the risk fully and to reduce the uncertainty associated with the risk assessment or risk management strategies, and/or the life cycle assessment or life cycle management strategies.

III. CSS Research Areas

By organizing the CSS research program in a manner consistent with the integrated evaluation strategy, the major research products will include state-of-the-science knowledge and tools to integrate fully with the Agency's approaches to risk assessment and risk management. New to the CSS research program is the development and application of green chemistry and engineering, design principles, and life cycle approaches to inform management decisions that can lead to sustainable practices. Consistent with the integrated evaluation strategy illustrated in Figure 3, each research area will deliver its own outputs to support decision outcomes as well as support and inform outputs delivered by the other CSS research areas.

The CSS research program will achieve scientifically based outcomes through three research areas. Research Area 1 (RA 1), *Developing the Scientific Knowledge, Tools, and Models for Integrated Evaluation Strategies* will be informed by intelligent testing, using an integrated system of higher throughput decision support tools to help focus and prioritize assessment of both existing and new chemicals.

In Research Area 2 (RA 2), *Improving Assessment Approaches and Informing Management for Chemical Safety and Sustainability,* the amount and quality of scientific evidence supporting a given assessment or management approach will vary with the nature of the problem and the intended decision to be addressed. RA 2 will develop approaches that are more responsive to the varied specific decision contexts.

In Research Area 3 (RA 3), *Targeting High Priority Research Needs for Immediate and Focused Attention,* integrated evaluation and context-relevant assessment approaches will be applied to specific, critical research needs that are required to fulfill regulatory mandates. In particular, RA 3 will focus on addressing the Agency's highest priority, near-term needs.

The following narrative for each research area describes the major Agency issues, the science needed for making specific decisions, and the research topic area for investigation. These problems were identified in a series of problem formulation workshops with key science advisors and senior staff from across EPA. Science questions to be addressed are presented for each RA Level. These questions will be used by EPA research staff to develop research projects. For these problems to be adequately addressed, research will need to be ground-breaking and innovative. For this reason, the questions are stated as broad concepts to allow staff to apply its expertise and innovation in shaping specific research projects.

Research Area 1: Developing the Scientific Knowledge, Tools, and Models for Integrated Evaluation Strategies. Rapid and efficient risk assessment requires integrated testing methods that apply broad, predictive approaches, including those that use high-throughput tools, to incorporate information on toxicity and exposure pathways using systems approaches and consideration of the entire chemical life cycle. The overall goal of RA 1 is to develop the scientific knowledge, tools, and models that are needed to optimize data needs for different types of assessment and management decisions. Research in this area will inform assessments and decision making on impacts to humans and wildlife at the individual and population levels. (Risks to communities of people and to ecological systems are addressed in other EPA research programs.) The sections below describe the research for each level in this research area, as well as identify key science questions that must be addressed. Although the emphasis of this research area is on developing and refining tools and models, the testing and evaluation of these tools will be an integral component of the research. Research at each level should loop back to provide data for lower levels. As an example, results from *in vitro* testing may inform quantitative structure-activity relationships (QSAR) or other Level I methods. In addition, research at all levels should address important vulnerabilities associated with risk, such as life-stage vulnerabilities.

Level I. Chemical Properties. Research in this level will develop and use information on chemical properties to help predict toxicity in biological systems, fate/transport in the environment, exposure to humans and ecosystems, ADME in living systems, and product use or substitution. Such approaches will address the properties of the parent chemical as well as degradates and metabolites. During several decades, QSAR tools have been developed to provide exposure and effects inputs in ranking and prioritization screens for *in vivo* screening and testing programs. The application of other advanced computational tools and molecular technologies should improve our ability to predict the impacts of a chemical's structure on environmental and biological functions. Research in this area will expand the understanding of chemical properties to inform the design of safer chemicals and products.

RA 1, Level I Science Questions

Question 1. 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?

Question 2. How can the knowledge of inherent properties be utilized to guide the development of safer products design and use throughout chemical life cycles?

Level II. Prioritization and Screening. The goal of research in Level II is to develop a broad spectrum of highly efficient methods to generate the necessary data to prioritize chemicals for further testing. This research will develop and evaluate integrated exposure and hazard screening approaches for prioritizing chemicals and informing efficient testing for exposure scenarios and human and ecological health endpoints of concern. It will combine high-throughput screening bioassays with computational chemistry to build statistical and computational models for forecasting potential toxicity in humans and wildlife, as well as develop models for estimating exposure over chemical life cycles. As technology develops, the enhanced tools will be used to predict the types of adverse effects expected based on Level I information, and will strategically select standardized bioassays to test the validity of the predictions. Research in Level II also will address the extent to which the activation of predictive pathways likely would be manifest in humans and/or wildlife under various exposure scenarios.

Research at this level also will include development of efficient and systematic methods to evaluate the processes associated with the manufacture, use, reuse, and disposal of chemicals and their related products, and to understand how such processes affect the *inherent environmental impact* associated with a particular chemical. Describing such processes entails understanding what resources are used to make the chemical or its related products, what emissions result from the manufacturing process, how the chemical or product is used, and its eventual degradation or disposal. Consideration of chemical processes is needed to understand the impacts that result from resource utilization, waste generation, and the impacts of use throughout a chemical's life cycle.

RA 1, Level II Science Questions

Question 1. 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?

a) What endpoints of concern require development of new screening methods?
b) What new methods/models are needed to account for exposure from all sources and pathways?
c) How can life-stages/susceptibility be incorporated into the prioritization and screening processes?
d) How do you account for the full range of environmental degradates and metabolites?
e) What characteristics of an assay are required for it to be informative of adverse outcomes to humans?

Question 2. 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?

Level III. Hypothesis-Driven Targeted Research. An integrated evaluation strategy for chemical assessment and management will incorporate the results of Levels I and II to determine which chemicals need targeted exposure and toxicity data to fill the critical data gaps required to assess, prevent, and manage environmental health impacts. Level III research will support integrated evaluation of high-priority chemicals or classes of chemicals. Taken together, the research in Levels I, II, and III will help decision makers move away from the current practice of subjecting each chemical of concern to a comprehensive battery of toxicity tests or gathering extensive exposure data. In keeping with these principles, the goal of Level III research, as informed by Level I and Level II research, is to develop efficient methods to determine which specific hazard data, groups of chemicals, and exposure information are essential for chemical safety.

Level III research will address the difficult question of how to interpret the available screening and inherency data obtained from Levels I and II to inform and focus further testing. For example, can medium and low-throughput models be developed that are more efficient than current guidelines for *in vivo* testing and targeted exposure research? Furthermore, Level III research also will address identification of toxicity pathways for key target tissues, organs, and life stages. At this time, the examination of the relationships between the molecular and cellular targets of chemicals and the traditional endpoints of toxicity is at an early stage of development; however, knowledge of toxicity pathways offers the possibility of targeting specific *in vivo* tests to characterize more fully potential hazards and exposures. In turn, the results obtained from Level III research will verify the reliability of predictions based on activation of toxicity pathways.

RA 1, Level III Science Questions

Question 1. What integrated research must be conducted to evaluate the predictive value of information from of the CSS research program to overall impact to humans and/or wildlife?

Question 2. 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?

Question 3. What are the significant gaps in Levels I and II relative to characterization of hazards and exposures?

Level IV. Systems-Level Understanding of Complex Environmental Risk. The overall goal for Level IV is to develop the scientific understanding and tools required to address reliably the most demanding problems in risk assessment. These problems can be for existing chemicals or for new chemicals that have been evaluated through Levels I, II, or III. Level IV evaluations apply, for the most part, to those chemicals with high hazard and/or exposure potential. Level IV testing evaluations will be used to reduce the uncertainty associated with high-priority risk assessments and help define what specific additional data are needed to do so.

The nature of Level IV problems will require systems approaches that fully integrate exposure science, and toxicology, including life-stage susceptibility, to study, characterize, and predict the complex interactions of environmental chemicals with humans and wildlife that lead to adverse health outcomes. Research at Level IV will characterize the uncertainty and variability introduced by the dynamic mechanisms of injury and recovery, and the susceptibility of the developing biological systems that puts them at most risk.

RA 1, Level IV Science Questions

Question 1. What systems models (e.g., kinetics and dynamics) must be developed and used to address the chemical-related environmental problems of greatest impact?

Question 2. What kinds of tools, including computational, systems-based tools, are required to fully describe the overall impact of exposures on organisms?

Question 3. 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?

Question 4. 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.** The goal of this research area is to integrate efforts to improve the next generation of risk assessment and risk management approaches under development across EPA and elsewhere. It aims to provide approaches that enable faster and more efficient assessment and management decisions, with reduced uncertainty and increased information to guide actions in the direction of environmental sustainability. New chemical risk assessment and management methods will support a broad array of decisions, ranging from screening and prioritization to major regulatory decisions for humans and wildlife. Informed by efforts within Research Area 1, the new chemical risk assessment and management methods in Research Area 2 will incorporate data on chemical inherency, exposure, and hazard. These new assessment and management methods also will incorporate information from life cycle assessment and other methodologies that can provide more realistic and environmentally relevant assessments than simply focusing on a chemical without considering the environmental context within which the chemical is used. These new methods must incorporate the means to assess vulnerabilities from inherent and extrinsic factors that lead to differential susceptibilities; therefore, they can inform community and environmental justice mandates being planned in EPA's Sustainable and Healthy Communities program for assessing and mitigating environmental impacts.

RA 2.1 Next Generation Risk Assessment Approaches. EPA's approaches to risk assessment are changing in response to advances in molecular systems biology and the understanding of gene-environment interactions, as well as in response to several important reports from the National Research Council (NRC), and the large volumes of high-throughput, high-content, and other test data becoming accessible from EPA, through approaches following the Tox21 recommendations, and Europe's REACH program. To manage this change, EPA is developing the next generation of risk assessment methods that are more responsive to the varied specific decision contexts. These varied decision contexts for risk assessments can be roughly divided into the following three tiers:

- Tier 1 focuses on assessing the inherent properties of chemicals for green chemistry decisions, and rapid screening and ranking of thousands of chemicals. It also can be informed by high-throughput analyses of chemical properties, exposure, and hazard from RA 1 Levels I and II.
- Tier 2 focuses on more-targeted assessments. Although Tier 2 is still reliant on higher-throughput assays and exposure data, those data are augmented with targeted data using a tiered approach to testing. Tier 2 will require the

development (and acceptance by decision makers) of new, higher-throughput approaches from RA 1 Levels I-III.

- Tier 3 focuses on very detailed assessments for a limited number of chemicals, utilizing all feasibly incorporated, policy-relevant emerging and traditional data and methodologies from RA 1 with Levels I-IV all contributing. These complex assessments are reserved for situations of greatest concern and with the greatest potential for improvements in sustainable approaches to making and using chemicals.

Efficient use of resources argues for risk assessments using only the amount and quality of scientific evidence that are needed given the nature of the problem being addressed. For example, in Tier 1, a screening and prioritization assessment would have fewer data and analysis requirements than higher Tier 2 or Tier 3 assessments and be compatible with data derived from RA 1 Levels I and II. By taking advantage of an integrated, tiered evaluation strategy, these assessments will be feasible on a greater number, and perhaps the majority, of chemicals to which people and wildlife are exposed. This feasibility is the result of several key advantages over current approaches: (1) thousands of chemicals can be assessed simultaneously using high-throughput and high-content approaches; (2) fewer resources should be needed for data generation than with testing all chemicals using every possible animal test; and (3) human disease processes, cell systems, and pathway targets can be studied directly.

Research to support Tier 2 assessments eventually could replace approaches employed in Provisional Peer Reviewed Toxicity Value (PPRTV) assessments currently used to support Superfund clean-up decisions and other risk characterizations of industrial chemicals and nanomaterials that are not as data intensive as EPA's larger-scale, more-complex assessments. The goal of using Tier 2 assessments to replace the PPRTV approach would be to utilize information on toxicity pathways to reduce what are sometimes large uncertainties inherent in assessment of data-poor chemicals. The use of *in silico* virtual models that describe adverse outcome pathways that are perturbed by chemicals/stressors will facilitate extrapolation of risk estimates and predictions from data-rich examples to more data-poor examples.

For chemicals that pose the highest exposure and/or hazard potential, Tier 3 will provide support for major regulatory-level assessments in conjunction with extensive data and modeling, similar to major Integrated Risk Information System (IRIS) and criteria air pollutant assessments conducted for such chemicals as benzene and ozone, respectively. The incorporation of molecular endpoints of disease and systems biology will help inform our understanding of environmental causes of disease and help to reduce uncertainty about the cumulative influences of the additive effects of chemical exposure to background disease in the population. The efforts in the Tier 3 arena with data-rich examples also will inform approaches for data-poor chemicals and environmental mixtures. This research effort probably would include development of decision analysis tools for each of the tiers that likely would be informed by value of information techniques.

For the chemicals posing the greatest risks, the systems biology models of RA 1 Level IV will provide innovative and unique opportunities to derive improved risk-related information for human and ecological species. In combination with the risk management tools described in Research Area 2, these next-generation risk assessments will better support decisions that promote safer products and greater sustainability. The major challenge for this new approach is to develop integrated assessments that begin with screening thousands of chemicals and finish focused on the most critical chemicals and issues relevant to human health and wildlife. This approach has the potential to support management decisions for thousands of chemicals in commerce.

RA 2.1 Risk Assessment Science Questions

Question 1. 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?

Question 2. 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?

Question 3. 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?

Question 4. 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?

Question 5. How can we determine whether new assessment methods actually decrease uncertainty and help lead to better decisions?

RA 2.2 Sustainable Risk Management Approaches. The goal of this research area is to develop and evaluate risk management approaches with the throughput to address the large number of new and existing chemicals and incorporate the types of data generated through the application of approaches developed in RA 1 and the assessment methods from RA 2. The CSS research program proposes to help enable the incorporation of sustainability metrics into risk management decisions, using life-cycle assessment and other system-based methodologies. Importantly, the approaches in RA 2.2, although intended to be useful in regulatory contexts, are expected to have even greater application to decision making by those who design, produce, and use chemicals.

The application of green chemistry principles will be a critical part of the process. For new chemicals, the goals are to ensure safer chemicals and safer products beginning with chemical or product design, development, and manufacture, and extending to their use and end-of-life considerations. For existing chemicals, the goals are to develop methods for identifying exposure and mitigation strategies that effectively reduce these exposures. Transparency in decision making, coupled with public outreach and education, will be an important part of this research program as it will impact the use and selection of products.

Several key requirements or principles will guide development of the CSS research program on sustainable risk management. First, any risk management decision-support tool or method must incorporate consideration of inherent chemical properties. The second requirement for sustainable risk management is taking a life cycle approach. In some cases, this means considering the life cycle when developing management strategies. In other cases, formal LCA methodologies will be useful for establishing a baseline of environmental sustainability for existing chemicals, identifying "hot spots" of greatest risk, and identifying improvement options with the greatest potential value. LCA provides an internationally standardized environmental assessment tool (ISO 14040 and 14044) for comparing alternatives to both new and existing chemicals, products, processes, supply chains, and services related to a chemical. The numerous challenges in addressing the effects of varying spatial and temporal scales in modeling environmental impacts across the life cycle and how to incorporate these variations in decision support tools must be addressed.

The third requirement for developing sustainable risk management is the expansion of life-cycle considerations to incorporate economic and societal factors into characterizations of environmental impact, recognizing that formal LCA methods focus on the environmental aspect of sustainability.[3] Life Cycle Costing (LCC)[4] is a candidate for economic analysis, and Social Life Cycle Assessment (SLCA)[5] tools could be developed on the basis of social indicators. For the purposes of this framework, LCC and SLCA can be characterized as socio-economic assessments. Developing life cycle tools addressing environmental, economic, and social factors will be part of the CSS research program, to enable the Agency and other decision makers to assess fully the sustainability potential of chemical and product systems.

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[3] Sustainability includes consideration of all three pillars—environment, economy, and society—across the life cycle stages. Accordingly, Life Cycle Sustainability Analysis (LCSA) is an integration of life-cycle assessment (LCA), life cycle costing (LCC), and social LCA. It is important to ensure that the product system boundaries largely are consistent across all three pillars, the same functional unit is applied, and impacts for all three pillars are assessed from cradle-to-grave.

[4] Life Cycle Costing is a method for calculating costs throughout the life cycle of a product. This type of economic assessment as it relates to sustainability differs from traditional cost accounting in that it takes into account the costs across the product system throughout the entire life cycle—not just manufacturing costs.

[5] Social Life Cycle Assessment methodologies for assessing the impacts to society of a product are not as mature as methods for assessing environmental and economic impacts. Several initiatives and organizations, as well as the international community, have given thought to the underlying core values, principles, and standards that should guide social assessments, and researchers are actively developing methods for applying these principles and standards to products.

RA 2.2 Sustainable Risk Management Science Questions

Question 1. 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?

Question 2. 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?

Question 3. 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?

Question 4. 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. Even as the CSS research program is providing the foundation for a transformation in the current business practices for chemical management, it is necessary to be mindful that there are time-critical research needs for fulfilling regulatory mandates that require EPA involvement and investments. RA 3 will, therefore, be focused on how to incorporate into the integrated evaluation strategy those methods, models, and data that address the highest priority needs as determined by regular discussions between the senior managers of the CSS research program and those of the EPA partner offices and other stakeholders.

RA 3 Research Planning Implementation Questions

Question 1: 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?

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

IV. Outcomes the CSS Research Program Is Designed to Help Achieve and Examples of Types of Products that Can Address Them

There are a number of key outcomes that can advance EPA's transformation of the processes by which new and existing chemicals and products are evaluated for potential impacts on human health and the environment.[6] This section identifies those outcomes and under each outcome provides one example of a possible future CSS research product to help achieve those outcomes.

[6] US EPA, *The U.S. Environmental Protection Agency's Strategic Plan for Evaluating the Toxicity of Chemicals,* EPA/100/K-09/001, March 2009.

Outcome: **Information is digitized and available.** Much of the existing, or legacy, information on the effects of chemicals is dispersed throughout a large number of agencies and is not in forms needed for modern types of computer-assisted analyses. Efforts are needed to ensure compatibility and interoperability of various national and international databases. To enable computational models based on human (as opposed to solely laboratory animal) data, particular emphasis must be placed on data from systematic studies of chemical effects in humans The flood of data emerging from the REACH program in Europe is only likely to exacerbate this problem.

> *CSS Product Example:* **User-friendly portal to comprehensive existing and developing chemical data sets.**

Outcome: **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.**

> *CSS Product Example:* **Life cycle approaches to chemical design, manufacture, use and disposal that identify opportunities to avoid or address human or ecological effects of chemicals.**

Outcome**: Biomarkers of exposure are developed that enable the reconstruction of conditions that led to the observed results or relate to the health outcome**. Research is needed to design studies for developing and evaluating tools to interpret the results of exposure biomarker studies and linking these results to indicators of first biological response.

> *CSS Product Example:* **A suite of tools and approaches for interpreting and applying biomonitoring data in risk assessment.**

Outcome: **Critical pathways that are perturbed by environmental chemicals and lead to toxicity and adverse effects in humans and other species are identified.** Until recently, the tools generally have been lacking to identify the key events in molecular and cellular biology that are impacted by chemical exposure. The definition of these pathways and the development of assays for them is a critical part of advancing the state of chemical toxicology.

> *CSS Product Example:* **Assays that predict adverse outcomes, including *in-vivo* toxicology endpoints, factors of susceptibility and life stage, developmental processes, and human diseases.**

Outcome: C**omplexities of exposure and dose in high throughput assays are captured.** Perhaps the largest limitation of a high-throughput, cell/pathway/protein-based approach is its inability to account for the processes of absorption, distribution, metabolism, and elimination (ADME), and in the special case of pregnancy and lactation, for processes of maternal transfer of the toxicant or its metabolites across the placenta to the fetus, and via lactation to the infant. Most current *in vitro* test systems lack the dynamic features of each of these steps. A related Outcome is to combine exposure in a systems approach that provides information of the magnitude, frequency, and duration of the dose that reflect real-world conditions. Besides aspects of ADME, robust quality control procedures are needed to confirm the identity of chemicals in the test systems, a major issue as the assays are scaled to application to libraries of thousands of chemicals. Furthermore, the physical-chemical properties of some chemicals (volatility, reactivity, solubility) will present challenges in delivering them to *in vitro* test systems.

> *CSS Product Example:* **Systems models that represent ADME and can be tested through application of *in-vitro* methods.**

***Outcome:* Predictive models of hazard and exposure to prioritize further screening and testing are developed.**

> *CSS Product Example:* **The next generation of tools for predicting and linking exposures to causal adverse health outcomes.**

***Outcome:* Quantitative risk assessment is improved and uncertainties are reduced by using advanced computational techniques such as multi-scale systems models of virtual tissues.** Application of systems biology approaches that use multi-scale computational models of virtual tissues are needed to integrate information at various levels of biological organizations (molecular, cellular, and tissue level) and to afford an understanding of the emergent properties.

> *CSS Product Example:* **A set of predictive models from the cellular level to the population level that can be integrated into a source-to-outcome modeling platform, for use in reducing uncertainty and variability in risk assessment.**

***Outcome:* The knowledge gained in improving human health risk assessment is applied to ecological toxicology.** To date, little attention has been paid to understanding the molecular, cellular, and systems biology-level processes in ecologically important species, and these issues will need to be addressed to utilize fully the complete transformation of toxicity testing.

> *CSS Product Example:* **A set of integrated approaches for assessing risks from the individual to population level of humans and wildlife.**

***Outcome:* The development of sustainable risk management approaches is scaled up for use in decision making.** For chemicals yet to be designed, challenges include having the appropriate variety of tools to be able to ensure that the thousands of new chemicals and their associated products designed each year are safer than those they will be replacing. For existing chemicals, identifying and developing strategies that effectively reduce exposures and toxicity will be a challenge. To date, assessment of the effective reduction in risk has been done largely on a chemical-by-chemical basis. It is not sustainable, however, to identify and develop approaches that prevent, mitigate, or remediate one chemical at a time.

CSS Product Example: **Identify 5-10 innovative sustainable solutions for priority chemicals of interest to the Agency that require scale-up or further testing and evaluation to move them into the marketplace.**

Outcome: **Scientific information is communicated, translated, and transferred in ways most useful to decision makers.**

CSS Product Example: **Science transfer partnerships to enhance the application of CSS products to specific decisions or other needs.**

V. Applying CSS Research Products for More Efficient Results: Two Examples

As research is conducted to address the science questions under Section IV, the resulting products will bring us closer to achieving the overall goals and vision of the CSS research program. Two examples are described briefly below to demonstrate how the application of the program's research products will help move environmental decision making toward advancing environmental sustainability. They demonstrate how better integrated testing strategies as developed and applied through the CSS research program will lead to greater efficiencies and better informed decisions by the Agency so that it can focus its attention, resources, and/or requirements on those most critical areas (e.g., chemicals, pathways, species).

Nanotechnology LCA. EPA's Office of Research and Development (ORD) and Office of Chemical Safety and Pollution Prevention (OCSPP) are developing a life-cycle assessment of nanomaterial-containing lithium-ion batteries. The LCA has three objectives: (1) encourage the movement toward energy independence and greenhouse gas reduction by advancing the green development of next-generation batteries; (2) inform decisions on advanced lithium-ion battery technologies, including product improvements, while the industry is young; and (3) promote and demonstrate the importance of life-cycle thinking in developing new applications for emerging materials such as nanoparticles. Information on carbon nanotube effects and exposure most certainly will be needed for this LCA to be accomplished. Such information includes how inherent properties of various types of carbon nanotubes influence their hazard and exposure potentials. Just as important, however, are knowledge and information from the various sectors that are making the nanomaterials, using nanomaterials to make batteries, and developing applications for the batteries' use. Therefore, EPA is partnering with companies and trade associations, such as Altairnano, Johnson Controls, and the Rechargeable Battery Association; research organizations such as the Rochester Institute of Technology and Argonne National Laboratory; and non-profit technology groups such as the National Alliance for Advanced Technology Batteries, and NextEnergy

Corporation, to develop LCA methods for nanomaterials. These new relationships and inputs into the development of EPA research products are essential for developing LCA tools that are useful to and useable by those who make chemicals, materials, and products, and are reflective of how the broader EPA research program will engage with others in its conduct of integrated, transdisciplinary research to advance environmental sustainability.

Prioritization, Screening, and Testing Chemicals: Endocrine Disruptors. ORD and OCSPP have for many years invested resources for the development and validation of the Tier 1 battery of 11 *in vitro* and short-term *in vivo* assays for the Agency's Endocrine Disruptors Screening Program (EDSP) to screen chemicals for their potential to interact with the endocrine system. EPA has issued the first set of Test Orders covering 67 chemicals. Industry has 2 years from the receipt of the Test Order to undergo screening and to submit data to the Agency. The first list of chemicals was selected based only on their presence in humans and the environment through multiple pathways of exposure and focused on pesticides and high-production volume chemicals in pesticide formulations. The Agency will review the results from the submitted EDSP Tier 1 data and determine which chemicals, if any, should proceed to more definitive EDSP Tier 2 testing in one or more multigeneration or life-cycle assays (e.g., rodent, amphibian, avian, fish, invertebrate). Using this current process to continue to identify chemicals for screening, having them screened, and making decisions about more definitive testing, is not sustainable to evaluate the tens of thousands of chemicals that fall within the purview of EPA. Research products from the CSS research program, however, are anticipated to contribute significantly in improving the efficiency of the Agency's mandated EDSP:

- *Prioritization* – EPA has the ability to apply high-throughput tools to screen thousands of chemicals for a wide variety of molecular and cellular interactions. Results from this screening are anticipated to contribute critical biological information that then can be used with other data to prioritize chemicals that are predicted to interact with the endocrine system, and thereby, enabling the Agency to make better informed decisions as to which chemicals should be screened and the order in which they should be screened.
- *Screening and Testing* – It is anticipated that with additional research, some of the CSS research program's high-throughput screening may displace the need for the *in vitro* assays in the current EDSP Tier 1. In addition, with even further enhancements and research to find appropriate high-throughput methods to characterize absorption, distribution, metabolism, and excretion of chemicals, the CSS research products ultimately may lead to even more informed decisions as to what other types of assays, if any, may be needed in a first Tier of screening, and what targeted testing may be needed at a higher Tier.
- *Developing and Testing Hypotheses: Contributions to Interpretation* – The results from screening thousands of chemicals using high-throughput screening likely will lead to the identification of numerous hypotheses that will need to be

further assessed (e.g., how does a particular molecular signature relate to a toxic end point in whole animals). Intramural EPA scientists can implement research to address these hypotheses and provide information that will be valuable in helping in the interpretation of the industry data. EPA research also will enable the comparisons of data from high-throughput screening, the EDSP Tier 1 battery submissions, and standard whole animal testing. Data from this line of research will feed back into the integrated evaluation strategies and continue to confirm or refine the paradigm.

VI. Next Steps for Developing the CSS Research Program

An EPA portfolio analysis will be conducted to evaluate how well the projects, skills, and capabilities of the Agency's current research program align with the needs identified in this framework document. Following the portfolio analysis, EPA will develop a Research Action Plan (RAP) in collaboration and consultation with Agency scientists, EPA program and regional offices, and other stakeholders. The RAP will describe how EPA will conduct the CSS research program, including the rationale, approach, and product delivery timelines for the research. EPA also will work with partners and stakeholders to identify metrics to assess the CSS research program's effectiveness in providing timely and relevant scientific information, consistent with an EPA integrated evaluation strategy that informs decisions on chemical safety. Appendix E provides a timeline for development of the CSS Research Action Plan.

VII. References

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Appendix A. Agency Offices and Regions Participating in the Development and Implementation of the CSS Research Program

Office of Chemical Safety and Pollution Prevention (primary partner)

Region 6 (ORD Lead Region for Fiscal Years 2008-2010)

Office of Water

Office of Solid Waste and Emergency Response

Office of Air and Radiation

Office of Children's Health Protection

Office of the Science Advisor

Region 2

Office of Policy, Economics, and Innovation

Office of Environmental Information

Office of the Chief Financial Officer

Office of Enforcement and Compliance Assurance (including Office of Environmental Justice)

Office of International and Tribal Affairs

Appendix B. CSS Research Program Development

The CSS research program is being constructed using resources and expertise from all or parts of six existing research programs (Nanotechnology, Computational Toxicology, Safe Pesticides/Safe Products, Endocrine Disruptors, Human Health Research, and Human Health Risk Assessment). Preliminary discussions were held among the leaders of the aforementioned programs to begin scoping out a draft problem statement and draft vision for the new research program. These discussions used a number of previous reports (e.g., USEPA 2005, NRC 2007, USEPA 2009, USEPA 2010) as a foundation from which to initiate the creation of a truly integrated research program.

The CSS research program's problem identification stage began with a meeting of EPA Program and Regional Offices with ORD on May 13, 2010. Representatives for this meeting were identified following an invitation issued through the Agency's Science Policy Council. The broad problem areas identified in the May 13, 2010, meeting were taken to a meeting of EPA scientists from all the laboratories, centers, and offices held on May 27, 2010, at which time key science questions were identified. This information was used by the EPA CSS Steering Committee to develop the first draft of the current framework. Restructuring of the problem areas resulted in the three main issues discussed in the current document (Intelligent Testing, Improved Risk Assessment and Management Activities, and Targeted Testing Efforts). The revised research areas and science questions were taken back to the EPA Program Offices and Regions for review and comment at a meeting on July 8, 2010. Using input from the July meeting, the EPA Steering Committee revised the framework into the current document. Concurrent with its development of research areas and science questions, EPA conducted a portfolio snapshot of existing research based on resources targeted for transition to the CSS research program in the fiscal year (FY) 2012 budget year. This snapshot will be used for portfolio evaluation and development throughout FY 2011. The final meeting with the EPA Program Offices and Regions prior to finalizing this Framework document was held on October 25, 2010. As a result of this meeting, refinements were made to this document, including revision of a number of the key science questions and an improved description of the relationships between research areas.

Appendix C. CSS Steering Committee Members

Robert Kavlock, Director, National Center for Computational Toxicology, and interim National Program Director for CSS

Kay Austin, Associate Director, Economics, Exposure, and Technology Division, Office of Chemical Safety and Pollution Prevention

Stan Barone, Assistant Center Director, National Center for Environmental Assessment (Human Health Risk Assessment)

Mary Belefski, Senior Scientist, Office of Chemical Safety and Pollution Prevention (retired)

Ila Cote, Senior Scientist, National Center for Environmental Assessment

Kevin Crofton, Senior Scientist, National Health and Environmental Effects Research Laboratory

Sally Darney, acting National Program Director for Human Health Research

David Dix, acting Deputy Director, National Center for Computational Toxicology

Elaine Francis, National Program Director for Pesticides and Toxics (Endocrine Disruptors and Safe Pesticides/Safe Products) Research

Brian Kleinman, Budget Analyst, Office of Resource Management and Administration

Dorothy Miller, American Association for the Advancement of Science Fellow, Office of Resource Management and Administration

Jeff Morris, National Program Director for Nanotechnology Research

Pasky Pascual, acting Assistant Center Director, National Center for Environmental Research

Julian Preston, Associate Director for Health, National Health and Environmental Effects Research Laboratory

Linda Sheldon, Associate Director for Health, National Exposure Research Laboratory

Joe Williams, Assistant Laboratory Director, National Risk Management Research Laboratory

Appendix D. Relationship Between Current and New EPA Planning Structure and the EPA Strategic Plan Structure

EPA United States Environmental Protection Agency

Resource Crosswalk to new ORD Program/Project Structure
Under the Agency's New Strategic Plan

Former Program/Project (P/P) Structure	Goal	Objective	New P/P	
Global Change Research	Goal 1: Taking Action on Climate Change and Ensuring Air Quality	Objective 1.1: Address Climate Change	Air, Climate, & Energy	Global Change Research
Air Research				Air Research
Sustainability Research (partial)				
Human Health and Ecosystems Research (partial)		Objective 1.2: Improve Air Quality		Other Research
Drinking Water	Goal 2: Protecting America's Waters	Objective 2.1: Protect Human Health	Safe and Sustainable Water Resources	Drinking Water Research
Water Quality		Objective 2.2: Protect and Restore Watersheds and Aquatic Ecosystems		Water Quality Research
Human Health and Ecosystems Research (partial)	Goal 3: Cleaning Up Our Communities	Objective 3.1: Promote Sustainable and Livable Communities	Sustainable Communities (Built & Natural Environments)	Human Health Research
Fellowships				Ecosystems Research
Pesticides & Toxics Research (partial)				
Sustainability (partial)				Other Research
Land (Excluding Nanotechnology)				
Homeland Security	Goal 4: Assuring the Safety of Chemicals	Objective 4.1: Assure Chemical Safety	Homeland Security	
Human Health Risk Assessment (partial)			Human Health Risk Assessment	
EDCs Research			Chemical Safety and Sustainability	EDCs Research
Computational Toxicology Research				
Human Health & Ecosystems Research (partial)				Computational Toxicology Research
Human Health Risk Assessment (Next Gen)				
Pesticides & Toxics Research (partial)				Other Research
Land				
Air (Nanotechnology)				
Sustainability				

Office of Research and Development

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Appendix E. Timeline for Development of the CSS Research Action Plan (RAP) by the CSS Research Action Teams (RAT)