Chemical Safety for Sustainability (CSS)

Synopsis of the 2023 – 2026 Strategic Research Action Plan

Vision: The Chemical Safety for Sustainability (CSS) national research program is focused on addressing the pressing environmental and health challenge of a lack of sufficient information on chemicals needed to make informed risk-based decisions. The impetus for the program is to meet the needs of the Agency's program and regional offices, states, tribes, and external stakeholders while performing transformative research, leading to improved science-based approaches that build broader understanding of biology, chemical toxicity, and exposure.

Approach: While research under CSS has realized significant accomplishments over the last several years, the long-term vision remains ambitious. The approach to achieving this vision continues to focus on three key components. However, the emphasis within the areas may be re-aligned to account for addressing current priorities relevant to climate change and environmental justice. First, CSS will develop the science needed to reduce, refine, and replace vertebrate animal testing to the extent that the replacement approaches are, at least, as informative as *in vivo* tests. The second component for CSS is accelerating the pace of chemical assessment to enable our partners and stakeholders to make informed and timely decisions concerning the potential impacts of environmental chemicals on human health and the environment. The third component of CSS's long-term vision is to provide leadership to transform chemical testing, screening, prioritization, and risk assessment practices.

Realization of the CSS vision will require development of the computing infrastructure, digital resources, computational models, new approach methodologies (NAMs), and interpretive frameworks needed to capture the complexity of toxicology on the organismal level, including the effects of chemical mixtures. CSS will need to develop ecological modeling frameworks and approaches to extrapolate known or predicted effects on organisms to population and community level effects. To achieve this vision, CSS will work with Agency, federal, and international partners, as well as stakeholder experts from academia and professional societies.

Organization: CSS is organized around three broad research topics that include similar areas of disciplinary expertise and capability relevant to the partner needs: Chemical Evaluation, Complex Systems Science and Solutions-Driven Translation and Knowledge Delivery. While the organization of ongoing research remains consistent with the previous broad research topics, the emphasis within the areas will be re-aligned to account for completed activities and newer priorities including addressing climate change and environmental justice, potential early life stage susceptibility, mixtures, cumulative exposures, applicability of NAMs, and synthetic biology. Climate change and environmental justice research will be integral to the program as oppose to standalone areas. The research areas under each topic reflect the multiple scientific domains involved in achieving the goals of the CSS program. The foundational measurement techniques, data sets, models, and tools developed within each scientific domain allow CSS to be nimble and responsive in applying expertise to priority and emerging topics. By design, CSS research is integrated across research areas. Further, research will be coordinated with other National Programs and all Centers to be additive to those efforts.

Topic 1: Chemical Evaluation. Research under this topic will provide rapid methods and high-throughput data for risk-based evaluations of new and existing chemicals and emerging materials. This topic will emphasize development and application of new approach methodologies to rapidly generate exposure and hazard information for chemicals (including safer alternatives) and emerging materials and technologies. Current Research Areas along with new or increased areas of emphasis are as follows:

- ***Research Area 1: High-Throughput Toxicology (HTT)***
  Focuses on hazard profiling of chemicals using rapid toxicity testing approaches.
- ***Research Area 2: Rapid Exposure Modeling and Dosimetry (REMD)***
  Focuses on modeling and forecasting as well as data collection and methods to inform chemical exposures across various scenarios relevant to human and ecological exposure assessments.

- ***Research Area 3: Emerging Materials and Technologies (EMT)***
  Addresses hazard and exposure data needs of engineered products that are often not amenable to the types of approaches used to characterize conventional chemicals (current focus on engineered nanomaterials).

New or Increased Emphasis within these areas may include the following:

- Better, faster, cheaper NAMs for human and ecological species.
- Toxicity testing of mixtures (coordinate with HERA).
- Investigate exposure factors relevant to and modeling of exposures for tribes and communities impacted by environmental justice concerns.
- Exposure to real-world scenarios, e.g., exposure to multiple chemicals concurrently.
- Generate Interim Transcriptomic Assessment Products (ITAPs) for use in screening assessments.
- Explore use of newer analysis methods (e.g., non-targeted analysis) for identifying chemical contamination in environmental media after large catastrophic environmental events (e.g., wildland fires). (Collaborate/coordinate with other Programs)
- New focus on synthetic biology.

Topic 2: Complex Systems Science. Research conducted in this topic will build the scientific foundation to predict adverse outcomes resulting from chemical exposures in various biological contexts. This topic will develop interpretive frameworks and models to put complex information into biological, chemical, and toxicological context. Current Research Areas are as follows:

- ***Research Area 4: Adverse Outcome Pathways (AOP)***
  Focuses on delineating perturbations of specific biological pathways and applying that knowledge to predict apical outcomes based on mechanistic effects.
- ***Research Area 5: Virtual Tissue Modeling (VTM)***
  Bridging the gap between molecular/cellular endpoints and apical outcomes by developing tissue-on-a-chip and *in silico* models, with an emphasis on human developmental endpoints.
- ***Research Area 6: Ecotoxicological Assessment and Modeling (ETAM)***
  Develops integrated approaches to model ecological outcomes across broad taxonomic and ecological scales.

Topic 3: Solutions-Driven Translation and Knowledge Delivery. Research in this topic will deliver data and information resources relevant to chemical safety evaluations in a scientifically robust, transparent manner. This work will aid the translation of these approaches by evaluating, establishing, and demonstrating their effectiveness to EPA partners and stakeholders. The intended impact is for risk assessors and decision makers to have confidence that the new approaches, data, and tools developed in CSS are scientifically sound and improve environmental decision making. Current Research Areas with new or increased areas of emphasis are as follows:

- ***Research Area 7: Chemical Safety Analytics (CSA)***
  Provides curated chemical information and develops predictive approaches for chemical safety evaluations.
- ***Research Area 8: Informatics, Synthesis, and Integration (ISI)***
  Emphasizes the integration of chemical information across scientific domains, and the translation of scientific findings to facilitate better access to that information to support decision making.

New or Increased Emphasis within these areas may include the following:

- Integration of data, models, and tools to support decision making.
- Operationalize next generation read across technologies for addressing prioritization of chemicals (including e.g., CECs, antimicrobials).
- Operationalize NAMS to increase utility for decision-making.
- Operationalize ITAP for screening assessments.