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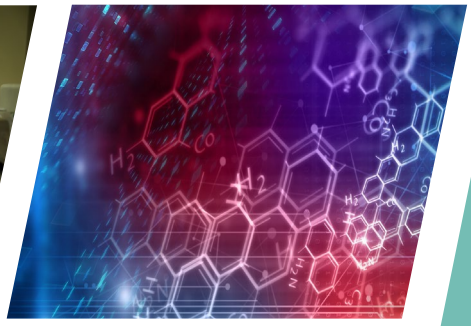
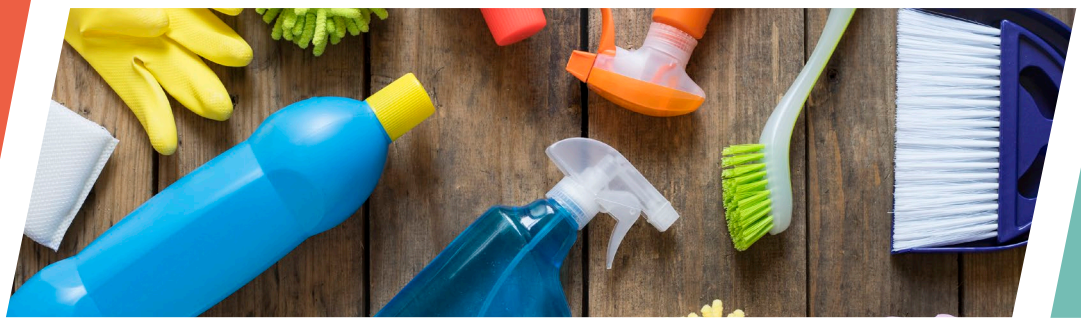
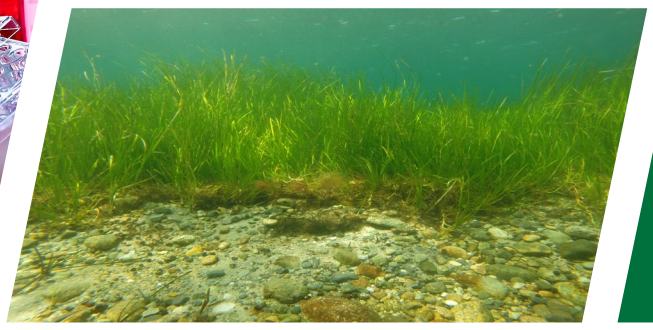



Chemical Safety for Sustainability

STRATEGIC RESEARCH ACTION PLAN FISCAL YEARS 2023-2026





Office of Research and Development
Chemical Safety for Sustainability Research Program

Chemical Safety for Sustainability (CSS)

STRATEGIC RESEARCH ACTION PLAN

Fiscal Years 2023–2026

(Draft as of March 28, 2022)

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List of Acronyms

ACE	Air, Climate, and Energy
ADME	Absorption, distribution, metabolism, and excretion
CAA	Clean Air Act
CERCLA	Comprehensive Environmental Response, Compensation, and Liability Act
CIECs	Contaminants of Immediate and Emerging Concern
CSS	Chemical Safety for Sustainability
CWA	Clean Water Act
EDSP	Endocrine Disruption Screening Program
EPA	U.S. Environmental Protection Agency
ERA	Ecological risk assessment
ESA	Endangered Species Act
FFDCA	Federal Food, Drug, and Cosmetic Act
FIFRA	Federal Insecticide, Fungicide, and Rodenticide Act
FQPA	Food Quality Protection Act
HERA	Health and Environmental Risk Assessment
HSRP	Homeland Security Research Program
HTTK	High-Throughput Toxicokinetic
MCCs	Methodologically Challenging Chemicals
NAMs	New Approach Methods
NTA	Non-targeted analysis
NRP	National Research Program
OAR	Office of Air and Radiation
OLEM	Office of Land and Emergency Management
ORD	Office of Research and Development
OW	Office of Water
P3	People, Prosperity and the Planet
PFAS	Per- and Polyfluoroalkyl Substances
PRST	Program offices, Regions, States, Tribes
QSAR	Quantitative structure-activity relationship

RA	Research Area
RACT	Research Area Coordination Team
RCRA	Resource Conservation and Recovery Act
SBIR	Small Business Innovation Research
SDR	Solutions-Driven Research
SDWA	Safe Drinking Water Act
SHC	Sustainable and Healthy Communities
SSWR	Safe and Sustainable Water Resources
STAR	Science to Achieve Results
StRAP	Strategic Research Action Plan
TSCA	Toxic Substances Control Act
UVCB	Unknown or variable composition

Definitions

Office of Research and Development (ORD): Scientific research arm of EPA that conducts leading-edge research to inform Agency decisions and support partner needs, including state, Tribal, and community partners.

National Research Program (NRP): ORD's overall research effort is organized around six integrated and transdisciplinary national programs and closely aligned with the Agency's strategic goals and cross-Agency strategies. ORD is a matrixed organization with research direction coming from its six NRPs, each being guided by a Strategic Research Action Plan that identifies the most pressing environmental and public health research needs with input from many internal and external partners and stakeholders.

Strategic Research Action Plan (StRAP): A description of the overarching direction of ORD's research in a specified timeframe and under a specific research program. Each of ORD's NRPs is guided by a StRAP to structure and coordinate research activities. A StRAP includes a description of identified environmental and public health challenges, research priorities, and ORD's approach to meeting the challenges.

Topic: Overarching research focus under a NRP that encompasses Research Areas, Outputs, and Products.

Research Area: Science area or body of research and expertise assembled to address partner needs in the protection of human health and the environment. It encompasses problem statements, which are delineated through Outputs. Research Areas are nested under Topics and are composed of Outputs, which are composed of Products.

Output: A statement of the results to be achieved in pursuing a Research Area problem statement. It is not a tangible deliverable but encompasses Products that are deliverables. They are designed and developed to address specific partner needs that draw on the scientific knowledge and expertise represented in research areas. An Output can be expressed in many ways, such as an intended intermediate outcome, a purpose, aim, goal, or target. Outputs are composed of Products and nested within Research Areas, which are nested within Topics.

Product: A tangible scientific or technical deliverable. It addresses the research needs of ORD and ORD's partners. Products are nested within Outputs, which are nested within Research Areas, which are nested within Topics.

Partner: An EPA program office, EPA region, representative of a state, or a representative of a Tribe—often referred to as PRST.

Program, Regional, State, and Tribal (PRST) needs: A description of research needs related to human health and the environment as identified by EPA program offices, EPA regional offices, states, and/or Tribes.

Executive Summary

The Environmental Protection Agency's (EPA) Chemical Safety for Sustainability (CSS) National Research Program (NRP) 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 shared health and environmental protection goals of the Agency's program and regional offices, states, and Tribes while performing transformative research, leading to improved science-based approaches that build broader understanding of biology, chemical toxicity, and exposure.

The current CSS Strategic Research Action Plan (i.e., StRAP 4) reflects the priority needs of Agency partners guided by overarching strategic goals. Further, StRAP 4 is informed by the Administration's priorities and established through extensive, systematic consultations and engagements. The CSS StRAP 4 research is engrained in the statutory authorities that authorize research to fulfill the Agency's mission. While the organization of ongoing research remains consistent with the broad research topics under previous StRAPs, the emphases within the areas are re-aligned to account for completed activities and newer cross-cutting priorities such as addressing climate change and environmental justice, potential for early lifestage susceptibility, cumulative impacts (mixtures, real-world exposures), and contaminants of immediate and emerging concern (CIECs).

A key issue with current chemical safety assessment is that traditional approaches have been unable to keep pace with innovations in chemical design, synthesis, and use. CSS has a history of conducting innovative science and is a hub of global scientific expertise and leadership in many areas, such as computational toxicology and exposure, high-throughput toxicology, and complex systems science. CSS will continue to do the following:

- Develop the science needed to reduce, refine, and replace vertebrate animal testing consistent with Agency policies.
- Accelerate the pace of chemical assessment to enable our partners to make informed and timely decisions concerning the potential impacts of environmental chemicals on human health and the environment.
- Provide leadership to transform chemical testing, screening, prioritization, and risk assessment practices.

While continuing our core research activities, we envision that the program will further incorporate cross-cutting research priorities. To be effective over the course of the StRAP, the program will not only develop robust scientific data and innovative tools, but also interpretative frameworks. To achieve this, CSS commits to work collaboratively with our partners (and the broader scientific community, including U.S. and international governmental agencies and non-governmental entities) to translate the science such that the information and tools can be transparent and useful for decision making.

Introduction

The Environmental Protection Agency (EPA), along with federal partners, states, and Tribes, plays a central role in evaluating the potential impacts of chemicals on human health and the environment. EPA strives to provide efficient, transparent, and scientifically robust approaches to evaluating chemical safety while continually improving these approaches in response to scientific and technological advancements. To achieve this, EPA applies advanced toxicological and exposure methods, data, tools, models, and information access to make better-informed and more timely decisions about the safety of chemicals, many of which have not been thoroughly evaluated for potential risks to human health and the environment. EPA's Chemical Safety for Sustainability (CSS) National Research Program (NRP) is designed to support the goal of reducing risks associated with exposure to chemicals in commerce and the environment.

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—re-aligned as appropriate to address current priorities. First, CSS will develop the science needed to reduce, refine, and replace vertebrate animal testing consistent with Agency policies and the goals articulated in the NAMs workplan. The second component is accelerating the pace of chemical assessment to enable our partners 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 not only the robust scientific development of new data and innovative tools, but interpretive frameworks that make the information and tools transparent and useful for decision making. To achieve this vision, CSS will work with Agency partners as well as the broader scientific community, including U.S. and international government agencies and non-governmental entities.

To assist the Agency in meeting its goals and objectives, the CSS Research Program developed this Strategic Research Action Plan (StRAP) for fiscal years 2023–2026 (FY23-26). The CSS StRAP is one of six of the following research plans for each of the NRPs in EPA's Office of Research and Development (ORD):

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

The StRAPs outline four-year research strategies to deliver the research necessary to support EPA's overall mission to protect human health and the environment. The StRAPs are designed to guide an ambitious research portfolio that delivers the science and engineering solutions the Agency needs to meet its goals now and into the future. They also inform our partners and the public of the program's strategic direction over the next four years. The CSS StRAP FY23-26 builds upon the previous StRAP FY19-22, and where appropriate, continues research efforts to address longer-term strategic research objectives that can bridge between the four-year research planning cycles.

The strategic directions and Research Areas (RAs) identified in each StRAP serve as planning guides for ORD's research Centers to design specific research products to address the needs of EPA program and regional offices, states, Tribes, and external partners. Partner engagement is an essential part of the StRAP development process to identify research needs to be addressed.

Solutions-Driven Research

ORD is committed to producing research results that address real-world problems, inform implementation of environmental regulations, and help EPA partners make timely decisions based on sound science. This commitment includes exploring ways to improve research processes through the application of a solutions-driven research (SDR) framework. SDR is a specific research approach that emphasizes partner engagement and integration of tasks to develop research that is directly along the path to a solution or decision. Solutions-driven research emphasizes the following:

- Planned partner engagement throughout the research process, starting with problem formulation and informing all elements of research planning, implementation, dissemination, and evaluation.
- A focus on solutions-oriented research Outputs identified in collaboration with partners.
- Coordination, communication, and collaboration both among ORD researchers and between researchers and partners to develop integrated research that multiplies value to partners.
- Cooperation with partners to apply research results to develop solutions that are feasible, appropriate, meaningful, and effective.

ORD is applying principles of solutions-driven research broadly across its six NRPs. ORD will also monitor how we engage with our partners and how we design and conduct our research to ensure that it informs solutions for our partners' most pressing environmental problems. By doing this, we are engaging in translational science, which will continually improve and increase the value of our research for our partners. Our emphasis on translating science is exemplified by the Outputs listed in this StRAP—they provide solutions to problems identified by our partners.

Program Vision

The CSS NRP addresses the pressing environmental and health challenge posed by insufficient information on chemicals necessary for informed, risk-based decision making. Its impetus is to meet the needs of the Agency's program and regional offices, states, and Tribes while performing transformative research, leading to improved science-based approaches that build broader understanding of biology, chemical toxicity, and exposure. Realization of the CSS vision will require a commitment to work collaboratively with our partners to translate the science so that the resulting information and tools can be transparent and useful for decision making.

Managing risks from exposure to chemicals to protect human health and the environment, including the support of scientific research, is authorized and/or mandated in several statutes. The CSS research portfolio is largely focused on requirements authorized under the Toxic Substances Control Act (TSCA); the Federal Insecticide, Fungicide, and Rodenticide Act (FIFRA); the Food Quality Protection Act (FQPA); the Federal Food, Drug, and Cosmetic Act (FFDCA); the Clean Water Act (CWA); the Safe Drinking Water Act (SDWA); the Resource Conservation and Recovery Act (RCRA); the Comprehensive Environmental

Response, Compensation, and Liability Act (CERCLA); the Endangered Species Act (ESA); and the Clean Air Act (CAA). Chemical assessment, regulation, and management associated with these statutes are implemented by EPA's program offices, including the Office of Chemical Safety and Pollution Prevention (OCSPP), the Office of Land and Emergency Management (OLEM), the Office of Water (OW), and the Office of Air (OAR). CSS works closely with each of these offices to ensure that research is designed to support current and future needs. Furthermore, due to the fundamental nature of CSS's work, CSS data, tools, and models are often used to inform decisions made under other authorities, both federal and state.

Strategic Direction

Relationship to EPA and ORD Strategic Plans

The FY 2023-2026 EPA Strategic Plan is designed to implement the Administrator's priorities for the next four years. This Strategic Plan identifies four cross-cutting strategies and seven strategic goals with related objectives, describing how the Agency will work toward its mission to protect human health and the environment.

EPA's Strategic Plan outlines the need for chemical safety research to support EPA's responsibilities under TSCA, FIFRA, and ESA. CSS research has a focus on supporting Goal 7 of the Agency's Strategic Plan, to **Ensure Safety of Chemicals for People and the Environment** under Objective 7.1: *Ensure Chemical and Pesticide Safety* and Objective 7.2: *Promote Pollution Prevention*. CSS research will also support Goal 1, to **Tackle the Climate Crisis** and Goal 2, to **Take Decisive Action to Advance Environmental Justice and Civil Rights**. CSS research will also support three Cross-Agency Strategies: **Ensure Scientific Integrity and Science-Based Decision Making (**Strategy 1); **Consider the Health of Children at All Life Stages and Other Vulnerable Populations** (Strategy 2); and **Strengthen Tribal, State, and Local Partnerships and Enhance Engagement** (Strategy 4).

ORD will develop its own Strategic Plan to respond to and build upon the FY 2023-2026 EPA Strategic Plan.. ORD's Strategic Plan will align with the StRAPs for ORD's six research programs, which outline specific research activities that address objectives of the Agency's Strategic Plan.

Changes from FY19-FY22 StRAP

CSS is organized around three broad research topics that include similar areas of disciplinary expertise and capability relevant to partner needs: Chemical Evaluation, Complex Systems Science, and Knowledge Delivery and Solutions-Driven Translation to Support Chemical Safety Decision Making. While the organization of ongoing research remains consistent with the previous broad research topics, the emphases within the areas are re-aligned to account for completed activities and newer cross-cutting priorities such as addressing climate change, environmental justice, potential for early lifestage susceptibility, cumulative impacts (mixtures, real-world exposures), and contaminants of immediate (e.g., Per- and Polyfluoroalkyl Substances (PFAS), Pb) and emerging concern. Climate change and environmental justice research will be integral to the program as opposed to standalone areas.

Partner Engagement

Development of ORD's StRAPs has been informed by ongoing and extensive engagement with EPA program and regional offices and external (non-EPA) partners. ORD's partner engagement during strategic research planning ensures a collaborative, transparent, and highly coordinated research portfolio that delivers the data and information that Agency program and regional offices need, and provides resources that help states, Tribes, local communities, and other partners. ORD relies on partner engagement as an essential component throughout the research cycle and especially during problem formulation to identify partner research needs and develop the research Outputs outlined in the StRAPs.

The CSS Research Program engages partners at different levels and stages throughout the research cycle to identify and discuss their research needs. Building from engagement during StRAP FY19-22 planning and implementation, engagement methods for the CSS StRAP FY23-26 included the following:

- Recurring dialogues and meetings with EPA program and regional offices.
- Listening sessions with external partners, including state, Tribal, and local partners.
- Workshops with ORD staff and EPA program and regional offices.
- Participation in EPA state and Tribal organization meetings (e.g., Environmental Council of the States, Tribal Science Council).

The CSS Research Program will continue to engage with our EPA partners and state, Tribal, and local organizations as we implement the research program outlined in the StRAP, support our research products after they are delivered, and evaluate the usefulness and effectiveness of our research in helping solve environmental and public health problems.

Research Topics and Research Areas

Please refer to Appendices 1-4 for additional detail on partner needs, cross-cutting priorities, and Outputs (including the numbering scheme).

Topic 1: Chemical Evaluation

Research under Topic 1 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 NAMs to rapidly generate exposure and hazard information for chemicals (including safer alternatives) and emerging materials and technologies.

Research Area 1: High-Throughput Toxicology (HTT)

For most chemicals, the availability of data and information to assess the potential toxicity to humans and other species is limited or incomplete. Existing chemical inventories and the introduction of new chemicals have driven the need for rapid assessment approaches. The HTT Research Area (RA) is focused on addressing the limitations of current chemical testing methods and fulfilling EPA's need to evaluate large numbers of chemicals for potential adverse human and ecological effects. The HTT RA will design, develop, and apply NAMs for hazard testing of chemicals (including CIECs) and chemical mixtures. The resulting data will inform a tiered approach to toxicology testing, which may include traditional methods for a reduced number of chemicals prioritized by HTT methods. These high-throughput

approaches will rapidly generate chemical hazard data on specific endpoints of interest to partners (e.g., developmental neurotoxicology, toxicological effects from inhalation exposure, and other priority endpoints) and should help prioritize, screen, and evaluate chemical safety for thousands of compounds while reducing reliance on traditional toxicity tests. Work under this RA is intended to be complementary to research conducted under the HERA program and may involve collaborative research efforts between scientists within the HERA and CSS programs. For example, data generated by CSS may inform HERA assessment solutions.

Work under the HTT RA addresses many priority needs of CSS partners. The Agency's NAMs workplan outlines goals for reducing the use of animal testing while continuing to protect human health and the environment. HTT Outputs (CSS.1.1, CSS.1.2, CSS.1.3, CSS.1.4, CSS.1.5) will work towards the goal of providing a structured framework and building confidence in applying NAMs across a broad variety of chemicals and decision contexts. Advancing a tiered, high-throughput toxicity testing strategy will be a focus (CSS.1.1), including providing structured and computationally accessible data (CSS.1.2). Novel technologies and approaches will be developed to address methodologically challenging chemicals (CSS.1.3) as well as challenges with existing high- and medium-throughput methods (CSS.1.4). Work will also inform data gaps in chemical safety evaluations for priority toxicological endpoints, such as endocrine disrupting mechanisms, manifestations of toxicity in the respiratory system, developmental neurotoxicity, and immunotoxicity (CSS.1.5). Within the HTT RA, there will be a continued focus on advancing a tiered testing evaluation for PFAS (CSS.1.6). Cross-cutting priorities are integrated into this RA. For example, research that includes toxicity testing of mixtures will provide information on cumulative impacts (CSS.1.1, CSS.1.2, CSS.1.6). Also, work on priority toxicological end points such as developmental neurotoxicity (CSS.1.5) will address vulnerable and sensitive subpopulations and the potential for early lifestage susceptibility.

Research Area 2: Rapid Exposure and Dosimetry (RED)

The RED RA will develop methods, data, tools, models, and approaches to rapidly generate scientifically defensible exposure and dosimetry estimates for new and existing chemicals and chemical mixtures found in commerce and in the environment. This research will involve the development or expansion of critical exposure-relevant data and associated computational models for priority exposure pathways; the results from these models will be integrated into predictive consensus frameworks and evaluated with relevant monitoring data, including data generated with emerging high-throughput measurement approaches. In concert with the toxicity information generated in the HTT RA, new high-throughput toxicokinetic (HTTK) data and models will be developed to enable the direct comparison of HTT data with consensus exposure predictions. Estimates of human and ecological exposures developed in RED represent critical inputs for high-throughput, risk-based prioritization and screening of chemicals and chemical mixtures. The exposure and toxicokinetic data and predictions developed in this RA will consider and provide valuable information to identify or characterize vulnerable and sensitive subpopulations and early lifestage susceptibility; address populations experiencing disproportionate adverse impacts, for example, from climate change disasters; inform identification of emerging contaminants of concern; characterize cumulative risks for chemical mixtures in the environment; and accelerate the rate of chemical evaluations. Work under this RA is intended to be complementary to research conducted under the HERA program and may involve collaborative research efforts between scientists within the HERA and CSS programs. For example, data generated by CSS may inform HERA assessment solutions.

The RED RA addresses a broad range of priority partner needs, including many of the cross-cutting Agency priorities. Outputs will address the collection and curation of necessary exposure-relevant data (CSS.2.1) and work on HTTK tools (CSS.2.2), both of which enable high-throughput exposure modeling predictions for chemicals (CSS.2.3). Work to support lifecycle assessments and sustainable chemistry will also be included (Output CSS.2.4), in addition to next-generation chemical exposure monitoring—specifically, development, evaluation, and evidence to increase confidence in the use of non-targeted analysis (NTA) methods for exposure assessment (Outputs CSS.2.5 and CSS.2.6). The RA will include a focus on enabling rapid exposure evaluations for PFAS (Output CSS.2.7). Cross-cutting priorities related to environmental justice (CSS.2.1, CSS.2.2, CSS.2.3, CSS.2.5, CSS.2.6), cumulative impacts (CSS.2.2, CSS.2.3, CSS.2.5, CSS.2.6), vulnerable and sensitive subpopulations and the potential for early lifestage susceptibility (CSS.2.1 and CSS.2.3), and climate change (CSS.2.5, CSS.2.6, CSS.2.7) will be addressed, as appropriate, throughout this RA. In particular, advances in exposure models allowing for estimation of chemical exposure developed under RED will incorporate multiple cross-cutting priorities. For example, mining of data on co-exposures can be used to address demographic differences relevant to populations experiencing disproportionate adverse impacts. Further, NTA methods can be effectively used to address real-world mixtures including those associated with catastrophic events brought on by climate change generally, as well as to disproportionately impacted communities.

Research Area 3: Emerging Materials and Technologies (EMT)

Innovations in chemical and material design are rapidly changing the landscape of industrial and consumer products. Emerging materials and technologies often have unique physicochemical properties, warranting specialized approaches for evaluating hazard and exposure, and necessitating an evaluation of the environmental impacts of their use. In addition, investigation of novel products of synthetic biology, genome editing, and metabolic engineering is needed to support risk assessment of emerging biotechnology products. The EMT RA will develop, collate, mine, and apply information on emerging materials and technologies to support risk-based decisions, including potential impacts of disproportionately affected populations.

Safety assessments of emerging materials require information on human and ecological exposure from consumer products and environmental releases. The EMT RA will address the additional data needed to characterize potential release of and exposure to these chemicals and materials, and subsequent environmental impacts of emerging materials on humans and ecological species (Outputs CSS.3.1, CSS.3.2). Novel products of synthetic biology, genome editing, and metabolic engineering will also be addressed (CSS.3.2). Research in this area will address relevant cross-cutting priorities related to cumulative impacts (CSS.3.1, CSS.3.2) and environmental justice (CSS.3.1, CSS.3.2) potentially associated with incidental exposures.

Topic 2: Complex Systems Science

Research conducted under Topic 2 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 mechanistic information into biological, chemical, and toxicological context, moving from foundational to actionable decision making.

Research Area 4: Adverse Outcome Pathways (AOP)

Employing data from NAMs into decision making, such as those being generated by the HTT and RED RAs, requires understanding the role of perturbation of one or more biological pathways on measured toxicological endpoints. The AOP framework provides a systematic and modular structure for organizing and communicating existing knowledge concerning the linkage between molecular initiating events (e.g., chemical protein-interaction), intermediate key events along a toxicity pathway, and apical adverse outcomes considered relevant to risk assessment or regulatory decision making. AOPs provide a scientifically defensible foundation for extrapolating from mechanistic data to predicted outcomes. AOP networks can be assembled by evaluating shared nodes or key events in individual AOPs, providing insight into the complex interactions among biological pathways. Quantitative understanding of key event relationships can be modeled to predict thresholds of toxicological response for adverse outcomes of regulatory concern, while also being used to address intrinsic and extrinsic factors that influence susceptibility. Whether through individual AOPs or AOP networks, the interactions of multiple chemicals present in both simple and complex mixtures will be assessed to facilitate analyses of more realistic environmental exposure scenarios relevant to cumulative risk and impact assessments. This RA will continue to develop AOPs for high-priority pathways that may also be used for assessing the effects of real-world exposures to mixtures and the effects of climate change. The application of well-developed and curated AOPs to address partner needs is addressed through case studies under the Integration, Translation, and Knowledge Delivery (ITK) RA.

Investigation of AOPs in this RA is a critical component in the continued development and application of NAMs, to achieve the goals of characterizing the risks for thousands of data-poor chemicals and reducing the use of animal testing. Work across this RA will build confidence in the use of NAMs by developing actionable, fit-for-purpose AOPs (Output CSS.4.1) that provide mechanistic relevance to the hazards being assessed, conducting strategic *in vitro* and *in vivo* studies for high-priority AOPs (Output CSS.4.2), and investigating the biological points of departure and susceptibility factors needed for quantitative application of AOPs (Output CSS.4.3). The utility of AOPs in informing risks and associated management actions will also be demonstrated (Output CSS.4.4). The RA will include a focus on AOPs relevant to PFAS (Output CSS.4.5). AOPs potentially provide an opportunity to address multiple cross-cutting issues. Customized workflows that build from the AOP framework in a systematic and modular manner can be used effectively to address climate change (CSS.4.1, CSS.4.2, CSS.4.3, CSS.4.4), cumulative impacts (CSS.4.1, CSS.4.2, CSS.4.3, CSS.4.4, CSS.4.5), environmental justice (CSS.4.1, CSS.4.2, CSS.4.3), and children's health (CSS.4.1, CSS.4.2, CSS.4.3, CSS.4.5). The overall integration of fit-for-purpose AOPs will provide options to account for high-priority AOPs relevant to populations experiencing disproportionate adverse impacts as well as vulnerable and sensitive subpopulations, including early lifestage susceptibility.

Research Area 5: Virtual and Complex Tissue Modeling (VCTM)

To bridge the gap from molecular changes to endpoints used in conventional hazard identification or risk assessment, models of biological systems are needed that can be experimentally probed and computationally simulated. Virtual tissue models connect *in vitro* molecular and pathway perturbations with *in vivo* tissue- and organ-level observations. The VCTM RA will focus on developing organotypic culture models, engineered microphysiological systems, and *in silico* agent-based and computational models to test hypotheses regarding organ-specific toxicity of priority chemicals for major routes of exposure (e.g., inhalation, oral), including pathways and endpoints relevant to human toxicity across

early lifestages or for disease states to inform risk-based assessments of new and existing chemicals. To support tiered toxicity-testing approaches, the VCTM RA will focus on computational and experimental models at the cellular, organ, or tissue level in an effort to help predict potential *in vivo* health effects.

Development, characterization, and application of organotypic and complex tissue models to bridge between *in vitro* and organismal assays will be addressed (Output CSS.5.1), as well as the development and application of *in silico* agent-based and computational models to evaluate the effects of chemicals on biological pathways (Output CSS.5.2). VCTM can provide a means to account for variability that may be associated with differing degrees of vulnerability and sensitivity. To advance the understanding of the impact of these differences, research to identify or characterize vulnerable and sensitive subpopulations and early lifestage susceptibility, address populations experiencing disproportionate adverse impacts (for example, from climate change disasters) as well as cumulative impacts, are now integrated into VCTM (CSS.5.1 and CSS.5.2).

Research Area 6: Ecotoxicological Assessment and Modeling (ETAM)

A tiered risk assessment approach is typically used to evaluate and regulate the potential impacts of pesticides and other chemicals on ecological resources. Chemicals are first screened using rapid assessment tools that require minimal data, followed by more detailed and complex assessments for selected chemicals and scenarios. For chemicals and ecological species with limited data, assessments must rely on modeled estimates of exposure and effects. The ETAM RA will advance efficient and integrated modeling approaches to improve risk assessments of chemicals with limited data, as well as more complex, refined approaches that can address data-rich applications. The integrated models span the sequence of events typical of ecological toxicity, including environmental release, fate and transport, exposure, internal dosimetry, metabolism, and toxicological responses relevant to organismal- and population-level effects in species of interest to Agency decisions. Further, the effects of climate change will be a key consideration in developing the Outputs in this RA.

The ETAM RA addresses a wide range of partner priorities related to ecotoxicology. The EPA is under legislative mandates to evaluate the potential health and ecological effects of new and existing pesticides. Work to inform pesticide risk assessments is included in this RA (Output CSS.6.1). Further, assessing the safety of pesticides specifically to pollinators is an Agency priority (Output CSS.6.2). More generally, to inform ecological risk assessments and decisions, data are needed on the adverse effects of chemical stressors to ecologically relevant aquatic and terrestrial species (Output CSS.6.3), and approaches are needed for using surrogate species in these assessments Output (CSS.6.4). A focus on improving ecological methods and models related to PFAS will be included in this RA (Output CSS.6.5). Research under ETAM offers a valuable opportunity to address cross-cutting issues like climate change (CSS.6.1, CSS.6.2, CSS.6.3, CSS.6.4) and cumulative impacts (CSS.6.5) in an integrated way. For example, research in this area will develop and demonstrate ecological models to characterize environmental contaminants for risk assessment at national, regional, and local scales. This range of scales can be used to understand environmental conditions affecting populations experiencing disproportionate adverse impacts, for example, from climate change.

Topic 3: Knowledge Delivery and Solutions-Driven Translation to Support Chemical Safety Decision Making

Regulatory decisions in chemical safety are complex and involve the interpretation of multiple data streams across a wide variety of disciplines. Research under this Topic will focus on continuing to improve the underlying chemical and biological knowledge, efficient management and integration of knowledge and information, and developing mature software tools 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. 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.

Research Area 7: Chemical Characterization and Informatics (CCI)

Chemistry and the use of structural information to predict properties and activities of chemicals are a fundamental part of chemical safety decision making. The CCI RA will focus on providing the high-quality chemical structures and advancing the computational models and analog approaches used to predict those properties. The chemical structures and associated identifiers will be extensively curated and quality checked to ensure the information is accurate. Research will include quantitative structure-activity relationship (QSAR) models for physicochemical properties and chemical transformation as well as systematic approaches to read across and cross-species extrapolation. This research will improve the understanding of chemical fate and activity in organisms (human and ecological receptors) and the environment through the use of cheminformatics and bioinformatics, which will provide important input relevant to understanding priorities in climate change, populations experiencing disproportionate adverse impacts, and real-world exposure to chemical mixtures. Work under this RA is intended to be complementary to research conducted under the HERA program and may involve collaborative research efforts between scientists within the HERA and CSS programs. For example, data generated by CSS may inform HERA assessment solutions.

The CCI RA will address many foundational partner needs. The generation and curation of data relevant to chemical substances, structures, and properties (Output CSS.7.1) are required for a broad array of Agency decisions and are needed to develop and refine structure activity relationship models in support of risk assessment (Output CSS.7.3). In addition, the Agency utilizes chemical categories and analog approaches to fill data gaps in TSCA (Output CSS.7.4) and performs cross-species extrapolation in ecological risk assessments (ERAs) generally and specifically for the Endangered Species Act (ESA) (Output CSS.7.2). The CCI RA will also include a focus on investigation of PFAS (Output CSS.7.5). The cross-cutting priority of cumulative impacts (CSS.7.1, CSS.7.5) will be addressed in this RA through the analysis of chemical mixtures occurring in real-world scenarios.

Research Area 8: Integration, Translation and Knowledge Delivery (ITK)

High-throughput NAMs, coupled with continually expanding amounts of traditional hazard and exposure data, enable more informed chemical safety decisions, assuming data are accessible and can be integrated. The ITK RA will integrate and translate chemical information to better inform partners' specific needs. The RA serves to bring together work from across the CSS portfolio, and to translate CSS research for use in chemical safety decision making, ranging from prioritization to risk determinations. Efforts in this RA will build confidence in the use of CSS data by building and supporting systems to

ensure that key data, tools, and models are appropriately managed, tracked, and satisfy quality standards. As the keystone for data dissemination and translation in the CSS research program, this RA will also support efforts to ensure cross-disciplinary tools and knowledge are available and accessible in forms convenient for partners, both through tool availability and through directed translation and communication efforts. Work under this RA is intended to be complementary to research conducted under the HERA program and may involve collaborative research efforts between scientists within the HERA and CSS programs. For example, data generated by CSS may inform HERA assessment solutions.

By integrating and translating chemical information from across the CSS portfolio, the ITK RA will inform and address priority needs of Agency partners for a range of chemical safety decisions. The availability and accessibility of well-documented data to support decision making is needed to support the efficient implementation of mandates under chemical safety legislation (e.g., TSCA, FIFRA). In the ITK RA, data availability and accessibility will be addressed through both integration of data systems (Output CSS.8.1) and subsequent knowledge delivery (Output CSS.8.2). In addition, the need to synthesize information across multiple scientific domains for the implementation of legislative mandates will be addressed through cross-disciplinary integration, decision support workflows, and applied case studies (Output CSS.8.3). ITK will include a specific focus on strengthening the science to support new chemicals evaluation (Output CSS.8.4) and improved translation of research through training, outreach, and engagement (Output CSS.8.5). With an increased emphasis on improved integration and translation of information from across all RAs, ITK will support all Agency cross-cutting priorities.

Implementing the Strategic Research Action Plan

In collaboration with EPA program, regional, state, and Tribal partners, ORD scientists and engineers design specific research products responsive to the Outputs outlined in the StRAPs. During the implementation of the previous FY19-22 StRAPs, ORD piloted a successful process in which Research Area Coordination Teams (RACTs), made up of ORD scientists and engineers, EPA program and regional staff, and state members, collaborated to determine the individual research products responding to each Output. ORD is continuing this process for the FY23-26 StRAPs.

Each Output in the StRAPs is reviewed by a RACT, which develops goals and objectives for the Output and establishes criteria for the work needed to accomplish it. ORD researchers propose research products, which the RACT reviews and refines to ensure products will meet the goals and objectives of the Output and reflect the timing and specific needs of EPA program and regional, state, and Tribal partners. RACT members serve as liaisons to their programs or organizations, which ensures that ORD's partners are able to provide input into the proposed research products. Products developed to address the Outputs may take the form of assessments, reports, tools, methods, journal articles, or other deliverables.

Throughout implementation of the StRAPs, ORD's researchers develop and deliver products. Research to deliver StRAP products is implemented by staff scientists and engineers at research laboratories and facilities in twelve locations across the country, which collectively comprise ORD's four Centers and four Offices. EPA staff are joined in this endeavor by a network of collaborators and partners within and external to EPA. In addition to the extensive intramural research program outlined in the StRAPs, ORD's research portfolio includes extramural research programs that complement or add special focus areas to the overarching program.

Cross-Cutting Research Priorities

For priorities that cut across their programs, ORD's six NRPs will work together to integrate efforts, provide a research portfolio aligned around the Agency's goals, and assist all of EPA's program and regional offices, as well as states and Tribes. Where appropriate, the NRPs will combine efforts to conduct research that advances the science and informs public and ecosystem health decisions and community efforts on the following cross-cutting priorities (Appendix 4):

- Environmental Justice
- Climate Change
- Cumulative Impacts
- Community Resiliency
- Children's Environmental Health
- Contaminants of Immediate and Emerging Concern

EPA program and regional offices and external (non-EPA) partners and stakeholders will also be engaged for these integrated efforts. Long-term, innovative, and multi-disciplinary research is needed to make progress on these complex issues to support a sustainable pathway towards equitable distribution of social, economic, health, and environmental benefits.

Appendix 1: Summary of Proposed Outputs Mapped to Program, Regional, State, and Tribal (PRST) Needs and Cross-Cutting Priorities

The following table lists the proposed CSS Research Program Outputs organized by topic and mapped to PRST needs and Cross-Cutting Priorities. It should be noted that the Outputs might change as new scientific findings emerge and are also contingent on budget appropriations. See Appendix 2 for more detailed descriptions of the PRST needs, Appendix 3 for detailed descriptions of the Outputs, and Appendix 4 for detailed descriptions of Cross-Cutting Priorities.

Research Area	Output	PRST Need(s) and Cross-Cutting Priorities
Topic 1: Chemical Evaluation		
CSS.1 High-Throughput Toxicology (HTT)	CSS.1.1 Advance a tiered, high-throughput toxicity testing strategy	• Tiered toxicity testing strategies • Building confidence in new approach methods (NAMs) • Cumulative impacts and mixtures
	CSS.1.2 Provide structured and computationally accessible data to support tiered toxicity testing	
	CSS.1.3 Develop and apply novel technologies for improving chemical hazard identification for methodologically challenging chemicals	• Tiered toxicity testing strategies • Challenging chemicals and methods
	CSS.1.4 Develop and apply novel technologies for improving chemical hazard identification to address limitations of existing methods	
	CSS.1.5 Inform data gaps in chemical safety evaluations for high-priority toxicological endpoints	• Tiered toxicity testing strategies • Priority toxicological endpoints • Vulnerable and sensitive subpopulations • Children's environmental health • Building confidence in NAMs
	CSS.1.6 Advance a tiered testing evaluation for Per- and Polyfluoroalkyl Substances (PFAS)	• Contaminants of immediate and emerging concern (CIECs) • Cumulative impacts and mixtures

Research Area	Output	PRST Need(s) and Cross-Cutting Priorities
Topic 1: Chemical Evaluation		
CSS.2 Rapid Exposure and Dosimetry (RED)	CSS.2.1 Collect and curate exposure-relevant data	• Exposure factor data • Vulnerable and sensitive subpopulations • Children's environmental health • Environmental justice
	CSS.2.2 High-throughput toxicokinetic (HTTK) tools to support *in vitro* to *in vivo* extrapolation	• Toxicokinetics • Environmental justice • Cumulative impacts and mixtures
	CSS.2.3 Refine exposure models that enable high-throughput exposure predictions for chemicals	• Chemical exposure models • Building confidence in NAMs • Cumulative impacts and mixtures • Vulnerable and sensitive subpopulations • Children's environmental health • Environmental justice
	CSS.2.4 Inform life cycle risk assessments for new and existing chemicals	• Chemical exposure models • Cumulative impacts and mixtures
	CSS.2.5 Develop and evaluate next-generation monitoring methods for exposure assessment	• Next-generation chemical exposure monitoring • Cumulative impacts and mixtures • Environmental justice • Climate change
	CSS.2.6 Build confidence in the use of NTA for exposure assessment through applications	
	CSS.2.7 Develop methods, data, approaches, and frameworks to enable rapid exposure evaluations for Per- and Polyfluoroalkyl Substances (PFAS)	• CIECs • Cumulative impacts and mixtures
CSS.3 Emerging Materials and Technologies (EMT)	CSS.3.1 Evaluate environmental impacts of emerging materials on human and ecological species	• Emerging materials and technology • Cumulative impacts and mixtures • Environmental justice
	CSS.3.2 Support for risk assessments of novel products of synthetic biology, genome editing and metabolic engineering	

Research Area	Output	PRST Need(s) and Cross-Cutting Priorities
Topic 2: Complex Systems Science		
CSS.4 Adverse Outcome Pathways (AOP)	CSS.4.1 Develop actionable, fit for purpose high-priority AOPs to grow the AOP Knowledgebase	• Building confidence in NAMs • Climate change • Cumulative impacts and mixtures • Environmental justice • Vulnerable and sensitive subpopulations • Children's environmental health
	CSS.4.2 Develop and conduct strategic *in vitro* and *in vivo* studies that support development of high-priority AOPs	
	CSS.4.3 Conduct studies to elucidate and define biological points of departure and susceptibility factors that need to be considered for quantitative application of AOPs	
	CSS.4.4 Demonstrate the utility of AOPs along with data derived from various sources to inform risks and associated management actions	• Building confidence in NAMs • CIECs • Cumulative impacts and mixtures • Climate change
	CSS.4.5 Develop AOPs relevant to human health and ecological impacts of Per- and Polyfluoroalkyl Substances (PFAS) and evaluate applicability across species, chemical groupings, and mixtures	• Building confidence in NAMs • CIECs • Cumulative impacts and mixtures • Vulnerable and sensitive subpopulations • Children's environmental health
CSS.5 Virtual and Complex Tissue Modeling (VCTM)	CSS.5.1 Develop, characterize, and apply organotypic and complex tissue models that bridge between *in vitro* and organismal assays for decision-relevant endpoints	• Vulnerable and sensitive subpopulations • Children's environmental health • Tiered toxicity testing strategies • Building confidence in NAMs • Cumulative impacts and mixtures • Environmental justice
	CSS.5.2 Develop and apply *in silico* agent-based and computational models to evaluate the effects of chemicals on biological pathways	
CSS.6 Ecotoxicological Assessment and Modeling (ETAM)	CSS.6.1 Develop and demonstrate ecological models to characterize risk of environmental contaminants for risk assessment at national, regional, and local scales	• Pesticide risk assessment • CIECs • Threatened and endangered species models • Climate change
	CSS.6.2 Develop methods and data to assess the impacts of pesticides on pollinators	• Pollinators • Climate change

Research Area	Output	PRST Need(s) and Cross-Cutting Priorities
Topic 2: Complex Systems Science		
CSS.6 Ecotoxicological Assessment and Modeling (ETAM)	CSS.6.3 Identify, assemble, and curate toxicity data for ecologically relevant species for risk assessment (ECOTOX)	• Chemical impacts on aquatic and terrestrial species • Climate change
	CSS.6.4 Advance approaches for using surrogate species in ecological risk assessment	• Cross-species extrapolation of toxicity • Climate change
	CSS.6.5 Improve ecological methods and models for predicting exposure, accumulation, and effects of Per- and Polyfluoroalkyl Substances (PFAS)	• CIECs • Challenging chemicals and methods • Cumulative impacts and mixtures
Topic 3: Knowledge Delivery and Solutions-Driven Translation to Support Chemical Safety Decision Making		
CSS.7 Chemical Characterization and Informatics (CCI)	CSS.7.1 Generate and curate data relevant to chemical substances, structures, samples, and properties	• Chemical curation and informatics • Cumulative impacts and mixtures
	CSS.7.2 Develop data, tools, and models to support cross-species extrapolation for human health and ecological assessments	• Cross-species extrapolation of toxicity
	CSS.7.3 Develop new and improve existing structure activity relationship models to support risk assessment	• Chemical curation and informatics
	CSS.7.4 Advancing chemical categorization approaches for aiding the interpretation and prediction of bioassay and toxicity outcomes	
	CSS.7.5 Advancing use of structural, mechanistic, and toxicokinetic data to support categorization and classification of Per- and Polyfluoroalkyl Substances (PFAS)	• CIECs • Cumulative impacts and mixtures
CSS.8 Integration, Translation and Knowledge Delivery (ITK)	CSS.8.1 Integrating data systems to enable knowledge delivery	• Data availability and accessibility
	CSS.8.2 Knowledge delivery and interoperability in support of chemical safety decisions	• Data availability and accessibility • Building confidence in NAMs

Research Area	Output	PRST Need(s) and Cross-Cutting Priorities
Topic 3: Knowledge Delivery and Solutions-Driven Translation to Support Chemical Safety Decision Making		
CSS.8 Integration, Translation and Knowledge Delivery (ITK)	CSS.8.3 Cross-disciplinary integration and applied case studies to support chemical safety decision making	• Decision support and translation • Building confidence in NAMs • Environmental justice • Climate change
	CSS.8.4 Innovative science to support new chemicals evaluation	• Tiered toxicity testing strategies • Building confidence in NAMs • Data availability and accessibility • Decision support and translation
	CSS.8.5 Translation of research for chemical safety decision making through demonstration, training, outreach, and partner engagement	• Decision support and translation • Building confidence in NAMs • Environmental justice • Climate change

Appendix 2: Descriptions of Program, Regional, State, and Tribal (PRST) Needs

The following describe, in more detail, the PRST needs summarized in the body of the Chemical Safety for Sustainability Research Program StRAP for each Research Area and as listed in Appendix 1.

- **Building confidence in new approach methods (NAMs):** Achieving the goals of characterizing the risks for thousands of data-poor chemicals and reducing the use of animal testing—while continuing to protect human health and the environment—requires the development and implementation of new methods and approaches that demonstrate equivalent or better scientific quality and relevance than existing approaches (TSCA Section 4(h)). As outlined in the EPA NAMs workplan, achieving these goals involves the continued development and application of NAMs. NAMs can be used for evaluating the toxicity of chemicals as well as characterizing exposure and toxicokinetics. To build confidence in these new methods, integrated and synthesized knowledge is needed to establish the scientific rationale that support their use in evaluating the potential human health or ecological risks that are of management or regulatory concern—for example, within the Endocrine Disruption Screening Program (EDSP). This work should inform incorporation of NAMs into human and ecological risk assessment.
- **Tiered toxicity testing strategies:** Tiered testing strategies are used to evaluate chemical safety in an efficient, risk-based context. These strategies typically use higher throughput (HT) approaches to prioritize chemicals for subsequent testing and to screen chemicals for potential hazards. The tiered strategies include a range of test methods including HT assays, novel technologies, and relevant traditional methods, where appropriate. While progress has been made on development of high-throughput testing methods, there is a continuing need to demonstrate, evaluate, and apply them. In addition, continued refinement and development of downstream data management and processing are needed to provide actionable data to support tiered decision making for both human health and ecological risks.
- **Priority toxicological endpoints:** In Agency risk assessments, there exist a number of priority endpoints that characterize the potential hazard of a chemical. The understanding of chemical perturbation of estrogen, androgen, and thyroid signaling, steroid biosynthesis (e.g., as part of the EDSP), manifestations of lung toxicity, developmental neurotoxicity (DNT), and immunotoxicity endpoints are all of interest. There is a need for evaluating alternative approaches for all priority endpoints, including valid *in vitro* methods and modeling approaches.
- **Vulnerable and sensitive subpopulations:** Chemical assessments under TSCA must include consideration of risks to vulnerable and sensitive subpopulations and lifestages. Since TSCA promotes less reliance on traditional animal testing, NAMs (that reflect the best available knowledge of human developmental biology and exposure) are needed to address these sub-populations and lifestages, including potential adverse developmental outcomes.
- **Toxicokinetics:** Acceptance and use of *in vitro* data for hazard characterization is limited, in part, by uncertainties associated with extrapolation of dosimetry and metabolism. Most *in vitro* systems lack the biotransformation capabilities of intact *in vivo* systems, raising the possibility of over-estimating the hazard of compounds that may be rapidly metabolized *in vivo* or under-estimating the hazard of compounds that may be transformed to more active metabolites. Additionally, there is a need to understand the possible lifestage differences in metabolism, which may impact assessment of risk.

- **Challenging chemicals and methods:** There is a need to develop novel technologies to address methodologically challenging chemicals (MCCs) as well as to address challenges with existing methods (e.g., the need to develop new toxicological assays when existing assays do not meet a need) to inform chemical risk assessments. MCCs are chemicals whose physicochemical, behavioral, and toxicological properties are not well understood, and which typically fall outside of the domain of applicability of existing assays, models, and analytical methods. Challenges with existing *in vitro* methods arise, for example, when characterizing the inhalation toxicity of volatile, semi-volatile, and aerosolized chemicals.
- **Exposure factor data:** Models to estimate exposure to chemicals in consumer or occupational use products require a variety of inputs, including information on chemical ingredients and product composition, product use patterns (e.g., duration and frequency of product use), and human behavioral data, including how behaviors may vary by lifestage or between consumers and occupational users. For life cycle risk assessments, there is a need for automated standardized emission and waste inventories. For many chemicals and product types, there remain critical gaps in this information.
- **Chemical exposure models:** Chemical exposure evaluations require approaches to estimate exposure for a variety of high-priority pathways, including scenario-specific models particular to consumer products and materials in the indoor environment, as well as occupational, ambient, and ecological pathways. Chemical exposure models are also needed to inform life cycle risk assessments for new and existing chemicals. Consideration must also be given in chemical exposure evaluations to lifestage differences which may impact assessments. When appropriate, ORD models should be harmonized with program office models.
- **Next-generation chemical exposure monitoring:** Chemical assessments under TSCA, emergency response scenarios, and other chemical assessments consider exposure and conditions-of-use information which may be reflected in monitoring data. Traditional monitoring, while considered the gold-standard of exposure data, is resource- and time-intensive. Therefore, methods and tools (e.g., NTA methods) are necessary to bring next-generation high-throughput monitoring data into agency decision making.
- **Emerging materials and technology:** Safety assessments of emerging materials (e.g., novel products of synthetic biology, nanopesticides, nano/micro plastics, engineered nanomaterials, and incidental nanomaterials) require information on human and ecological exposure from consumer products and environmental releases. Additional data are needed to characterize potential release of and exposure to these chemicals and materials.
- **Pesticide risk assessment:** FIFRA mandates that EPA evaluate the potential health and ecological risks of new and existing pesticides. Though a substantial amount of data is required in submissions to evaluate pesticides, additional testing may be needed to further evaluate toxicological pathways of concern. In others, further analysis and interpretation of the data are required to inform decision-relevant endpoints.
- **Pollinators:** Assessing the safety of pesticides to pollinators is an Agency priority, as detailed in the Pollinator Protection Strategic Plan. Additional methods and data to support evaluation of effects in honeybees and other non-Apis bees are needed; in particular, methods to identify effects to other species of bees when honeybees are not a suitable surrogate. Honeybee colony simulation models continue to be a critical tool informing pesticide safety assessments. Further, examination of the relative sensitivity of the honeybee to non-Apis bees and other insect pollinators (e.g., butterflies) is needed.

- **Chemical impacts on aquatic and terrestrial species:** The ECOTOX Knowledgebase, containing data on adverse effects of single chemical stressors to ecologically relevant aquatic and terrestrial species, is a critical tool used in ecological risk assessments and decisions. There exists a need for the Knowledgebase content to reflect the current state of knowledge, and for enhanced analysis capabilities and improved data acquisition and retrieval methods.
- **Cross-species extrapolation of toxicity:** Chemical safety assessments are often conducted with limited or no toxicological data for the animal or plant species of interest. Further, it is frequently impractical to generate new data for those species. Therefore, the sensitivity of each species must be estimated based on scientifically based methods of cross-species extrapolation. The problem is compounded for ecological assessments by the large number of species in the wild and is particularly problematic for species listed under the Endangered Species Act.
- **Threatened and endangered species models:** The Endangered Species Act outlines requirements to consider potential impacts from the cumulative exposure to multiple environmental chemicals, including pesticides. There is a need to further develop methods used to complete national level endangered species risk assessments for hundreds of pesticides and thousands of threatened and endangered species.
- **Chemical curation and informatics:** Curated chemical structures and scientifically defensible physicochemical properties, metabolism and transformation products are required for Agency chemical safety decisions. However, such data may not be available for chemicals of interest. There is a need to advance methods for describing and storing chemical structures, increasing the availability of physicochemical properties (through measurement or modeling), and applying read-across and chemical categorization techniques to support decision making.
- **Data availability and accessibility:** Chemical safety decisions and management can be hindered by the lack of ready access to the ever-expanding array of data, tools, and models. Data used to support decision making must be well documented and meet relevant quality criteria standards. Though many chemical safety resources are available, obtaining access to and integrating multiple data sources can be time-consuming and complex. Readily available and accessible resources can support the efficient implementation of mandates under chemical safety legislation (e.g., TSCA, FIFRA).
- **Decision support and translation:** In the implementation of legislative mandates, there often exists a need to synthesize information across multiple scientific domains (e.g., bringing together chemical exposure and toxicity data to investigate the potential impacts on human health and the environment). Decision support tools and prioritization workflows may be needed to support chemical safety decisions. Further, case study applications showing the use of data, models, and tools in decision making are needed to build confidence needed for regulatory acceptance. Outreach and engagement that include demonstration and training are recognized needs for appropriate application of the data and tools in decision making.

Appendix 3: Output Descriptions

The following describe, in more detail, the Chemical Safety for Sustainability Research Program Outputs listed in Appendix 1. Outputs are planned under each Topic and respective Research Area (RA).

Topic 1: Chemical Evaluation

RA CSS.1: High-Throughput Toxicology (HTT)

Output CSS.1.1: Advance a tiered, high-throughput toxicity testing strategy

There is a continuing need to demonstrate and apply emerging technologies to provide actionable information to support tiered decision making and address key information needs of assessments. This Output is intended to produce hazard information using a tiered testing approach in support of defensible, non-traditional, fit-for-purpose risk assessment applications. Tiered testing strategies typically use higher throughput (HT) approaches and high-content methods (e.g., transcriptomics, phenotypic profiling, and other methods) to screen chemicals for potential hazards followed by targeted assays to confirm activation or inhibition of a particular cellular pathway or molecular target. Data from HT assays along with other traditional and novel methods will be used to build confidence in the use of NAMs for decision making. Both human and ecological receptors may be covered under this Output. Examples of activities that could be covered include methods/assay development (as needed); generating data from developed assays (e.g., high-throughput transcriptomics (HTTr)), high-throughput phenotypic profiling (HTPP; cell painting), ecotoxicogenomics; case studies that link HT/high-content approaches; confirmation by targeted assays; *in vivo* studies to inform rapid chemical assessments; non-HT studies (e.g., 90 day studies) to build confidence in NAMs results; likely tissue or organ effects using organotypic culture models (e.g., as provided under the VCTM RA); and data generation for real-world mixtures identified in RED that may have relevance to disproportionately impacted populations, or are a result of catastrophic climate change events. This Output involves coordination and collaborative research efforts between scientists within the HERA and CSS research programs.

Output CSS.1.2: Provide structured and computationally accessible data to support tiered toxicity testing

To support the advancement of NAMs, there is a need for well-documented, curated hazard information from varied available sources including *in vitro,* human, and animal studies. Work may include expansion of existing databases (e.g., ToxValDB, ToxRefDB, InvitroDB) through extraction and curation of data from the published literature, or pipelining of data generated from high-throughput (HT) assays (e.g., HTTr, HTPP). Efforts under this Output will include the development of computational or modeling tools, including new approaches to data interpretation in the context of risk assessment (e.g., data mining and machine learning techniques to automate data collection, curation, and pipelining) may all be employed, to make data interpretable in the context of risk assessment applications.

Output CSS.1.3: Develop and apply novel technologies for improving chemical hazard identification for methodologically challenging chemicals

MCCs are chemicals whose physicochemical, behavioral, and toxicological properties are not well understood, and which typically fall outside of the range of current assays, models, or analytical methods. There is a need to develop and apply approaches for measuring or modeling the toxicity and

exposure of these MCCs, including mixtures, to inform assessments and decision making. It is the intent to develop and apply novel technologies to address this need.

Output CSS.1.4: Develop and apply novel technologies for improving chemical hazard identification to address limitations of existing methods

To support the advancement of NAMs with the goal of reducing the use of animals for testing, there is a need for development of new medium- to high-throughput methodologies and approaches to improve chemical hazard identification when existing methods are not sufficient to provide the necessary information. Work included under this Output may include improvements to medium- to high-throughput assays (e.g., xenobiotic metabolism, repeated dose), development of novel technologies to assess chemical hazard of mixtures from formulations/complex mixtures, and repeated dosing to inform cumulative impacts research and address challenges related to assessment of inhalation toxicology.

Output CSS.1.5: Inform data gaps in chemical safety evaluations for high-priority toxicological endpoints

In agency risk assessments, information and analysis are needed on priority endpoints for chemical assessments. This Output is intended to address the continued need to develop datasets, models, assays, and frameworks for understanding chemical perturbation of estrogen, androgen, and thyroid signaling, and steroid biosynthesis (e.g., as part of EDSP). In addition, research to reduce uncertainty for developmental neurotoxicity and other toxicological endpoints (e.g., immunotoxicity) deemed high priority by program partners will be addressed in the Output. Research under this Output may include both fit-for-purpose analyses of existing HT assay data as well as generation of new data, analyses, and/or methods.

Output CSS.1.6: Advance a tiered testing evaluation of bioactivity for Per- and Polyfluoroalkyl Substances (PFAS)

Per- and polyfluoroalkyl substances (PFAS) chemicals are frequently being detected in a variety of environmental media. As a class, PFAS chemicals are structurally diverse and typically lack adequate exposure and hazard information needed to support decisions. This Output is intended to generate additional data to continue refining PFAS categories, identify potential effects of individual PFAS, develop points of departure and toxicity values for data-poor PFAS, and address effects of environmentally relevant PFAS mixtures. The Output will be guided by the objectives of the EPA's PFAS Strategic Roadmap, to meet the goals of program offices (e.g., the National PFAS Testing Strategy). The research could inform chemical grouping and mixtures strategies. A library of PFAS chemicals that could be used to leverage research will continue to be maintained.

RA CSS.2: Rapid Exposure and Dosimetry (RED)

Output CSS.2.1: Collect and curate exposure-relevant data

A wide variety of exposure relevant data are necessary to support chemical safety decision making for priority chemicals and mixtures. Relevant data streams include those that describe chemical source, release, and fate and transport, as well as those that characterize human and ecological receptor populations. These data streams are often highly heterogeneous, and must be curated and harmonized to be fit-for-purpose for use as input for chemical exposure models both within and outside of ORD. This Output will cover both the curation of reported exposure-relevant data and new laboratory experiments

to collect measured data, harmonization of meta-data, and subsequent expansion of established databases (e.g., CPDat, ChemExpoDB, MMDB, FuSE). Data types of interest may include chemical use data (including information about chemical functional role); chemical source data (e.g., reported or measured concentrations in consumer products or articles); human behavior patterns (including consumer product habits and practices); human (general population, consumer, occupational), ecological, and environmental chemical monitoring data; chemical production, release, or emission data; and built-environment characteristics. The scope of this Output includes the curation of existing data and generation of new, relevant experimental data. Where available, data specific to populations and settings of interest will be targeted, including data related to occupational settings, data specific to early lifestage exposures, and data informing investigation of exposures in populations experiencing disproportionate adverse impacts to inform environmental justice concerns. Methods used in this Output may include implementation of emerging tools in data mining, text mining, and machine learning to ensure that exposure factor information is optimally representative of current conditions and trends (e.g., in chemical use or manufacture, product formulation, or human/consumer behavior). The data delivered under this Output will be used to support partner decisions related to prioritization of large chemical inventories, individual chemical assessments, or as input for chemical exposure models.

Output CSS.2.2: High-throughput toxicokinetic (HTTK) tools to support *in vitro* to *in vivo* extrapolation

Toxicokinetics (TK) provide critical information for interpreting both toxicological data (*in vitro* and *in vivo*) and exposure information (for example, biomonitoring). However traditional TK methods require intensive, chemical-specific *in vivo* data generation and TK data is unavailable for most chemicals. HTTK tools fill the TK data gaps by using generic, physiologically based TK (PBTK) or empirically based compartmental models that can be parametrized with TK data rapidly measured *in vitro* or predicted *in silico*. This Output covers further developments of high-throughput toxicokinetic (HTTK) models and tools; measurement and prediction of TK parameters; and evaluation of the performance of HTTK approaches. Development of TK models includes models that reflect exposure routes of interest; lifestages of interest; non-human species of interest; challenging chemistries; and absorption, distribution, metabolism, and excretion (ADME) processes of interest. Measurement and prediction of TK parameters include new and existing *in vitro* TK measurement techniques; new *in vitro* culture models for absorption, metabolism, and excretion; *in silico* approaches to rapidly predict TK parameter values; disposition of chemicals within *in vitro* test systems, and approaches to estimate population TK variability, particularly for potentially sensitive or highly exposed sub-populations and lifestages. The addition of new measurement techniques, *in vitro* methods, or *in silico* models will focus on TK parameters that contribute to the highest uncertainty in existing HTTK models for environmental chemicals (e.g., restrictive vs. nonrestrictive clearance; active transport, slowly cleared compounds). Evaluation of HTTK performance includes ongoing collection, curation, and experimental generation of *in vivo* measured TK data, as well as statistical and computational methods for quantitative comparison of these TK data with HTTK predictions. This Output involves coordination and collaborative research efforts between scientists within the HERA and CSS research programs.

Output CSS.2.3: Refine exposure models that enable high-throughput exposure predictions for chemicals

Risk-based analysis of chemicals requires estimates of both toxicity and exposure. Exposure estimates (for example, measured biomonitoring concentrations or exposure predictions for humans or ecological

species) are unavailable for most of the tens or hundreds of thousands of chemicals thought to be present in commerce and the environment. Exposures are complex, involving multiple sources, pathways, and routes, and largely determined by behaviors and location (i.e., time-activity patterns). New and improved exposure models are needed that can address this complexity while still being able to address thousands of chemicals. In general, research covered in this Output will align with and complement existing models in use by program partners. This Output includes refinement and development of high-throughput exposure models that address key chemical sources (e.g., consumer products and articles, biosolids), exposure pathways (e.g., consumer, occupational, and ambient pathways), and human and ecological receptor populations. Methods will also be developed for quantification of both uncertainty and variability in exposure predictions, and to continue refinement of consensus statistical modeling frameworks that integrate the predictions of various exposure models with other exposure-relevant data. Of particular interest is the development of new models for exposure-relevant human behaviors that incorporate demographic or geographic specificity and harmonization of existing ORD and program partner models. The various models developed under this Output may allow for the prediction of exposures across lifestages (including early lifestages), the consideration of other susceptible or highly exposed populations (e.g., workers), the prediction of chemical co-exposures to inform cumulative impacts research, and investigation of exposures in populations experiencing disproportionate adverse impacts to inform environmental justice concerns.

Output CSS.2.4: Inform life cycle risk assessments for new and existing chemicals

Conceptual models are used to understand and quantify chemical releases from various well-defined industrial activities associated with the conditions of use for the substance. These industrial activities can occur throughout the chemical life cycle and involve any aspect of synthesis, product manufacturing, facility transfer, and end-of-use management (recycling, recovery, reuse, or disposal). The various activities may be regulated by separate EPA statutes (e.g., TSCA, municipal solid waste management under RCRA). Often there are data gaps associated with the various activities throughout the chemical life cycle and generic activity models are used to address those gaps, including for the estimation of workplace and ambient releases. These data and generic activity models may be necessary for evaluating exposure to both new and existing chemicals. Work under this Output is intended to develop new and improved models and tools for estimating common scenario needs, provide data and methods for estimating new chemical applications, develop end-of-use models for chemical disposal and life cycle releases, and provide support for occupational exposure modeling. Work will complement existing generic scenarios and models in use by program partners. Generic scenario and end-of-use research will support life cycle chemical risk evaluations and should be able to support alternatives assessments.

Output CSS.2.5: Develop and evaluate next-generation monitoring methods for exposure assessment

Next-generation monitoring methods are necessary to inform the diversity and magnitude of chemical exposures in a wide variety of scenarios. In particular, new monitoring methods are needed to rapidly characterize chemicals of immediate and emerging concern (CIECs), real-world mixtures, substances of unknown or variable composition (UVCBs), and methodologically challenging analytes. NTA methods, which utilize high-resolution mass spectrometry, allow the identification of previously unknown or understudied chemicals, and the characterization of complex chemical mixtures, in consumer products and virtually all environmental and biological media. NTA methods further allow rapid quantitation and risk-based prioritization of newly identified analytes. Work under this Output will focus on the

development of analytical and computational tools that will enable defensible and transparent implementation of NTA methods to support rapid chemical evaluations. This includes the development of proof-of-concept software and web applications to support ORD researchers and partners. This also includes the development of standardized performance metrics, benchmarks, and guidance for the global NTA research community. Guidance on NTA method performance evaluation will be developed in close coordination with the international Benchmarking and Publications for Non-Targeted Analysis (BP4NTA) workgroup. Performance metrics and benchmarks will be established considering data from EPA's Non-Targeted Analysis Collaborative Trial (ENTACT).

Output CSS.2.6: Build confidence in the use of NTA for exposure assessment through applications

Building confidence in the use of NAMs for exposure assessment is necessary before such methods can be adopted for use in chemical safety decision making. Applications of NAMs, including in regulatory-relevant contexts, can build confidence in their ability to provide sound data to inform exposure assessment. The application of NTA methods will be covered in this Output, including but not limited to: measurement of chemicals in various media using NTA, including biosolids or identification of CIECs; the use of NTA methods to inform climate change research, specifically, identification of chemicals in environmental media after catastrophic events such as wildfires or flooding; and advancing the understanding of the exposome to inform cumulative impacts research.

Output CSS.2.7: Develop methods, data, approaches, and frameworks to enable rapid exposure evaluations for Per- and Polyfluoroalkyl Substances (PFAS)

Concern over exposure to and potential health effects of per- and polyfluoroalkyl substances (PFAS) has increased significantly as more is learned about their widespread environmental presence, persistence and bioaccumulative potential. The limited measurement, monitoring, toxicokinetic and toxicologic data currently available is inadequate to inform risk evaluations across this diverse group of chemicals. This Output is intended to address key data gaps that include but are not limited to measurement and characterization of PFAS emissions; biotransformation, degradation, and/or fate in a broad range of environmental media and source substances; collection and/or generation of PFAS biomonitoring data; and continued consideration of *in vitro* toxicokinetics, including metabolism, transport/uptake, protein binding and disposition to refine current *in vitro-in vivo* extrapolation approaches to predict internal dosimetry. Continued analytical evaluation of PFAS quality and stability in biological matrices and screening stocks used across CSS research areas is planned. The resulting data will be employed in a wide range of modeling efforts that will advance and refine modeling of direct and indirect PFAS exposure, provide a PFAS-specific exposure modeling workflow, and inform other efforts describing PFAS biotransformation/fate, exposure reconstruction, and dosimetry. The data will also be made available for subsequent *in silico* model development. The research will leverage the development of these methods, data, and approaches to refine and expand current PFAS toxicokinetic and exposure NAMs and models. The Output will be guided by the objectives of EPA's PFAS Strategic Roadmap, to meet the goals of program offices (e.g., the National PFAS Testing Strategy).

RA CSS.3: Emerging Materials and Technologies (EMT)

Output CSS.3.1: Evaluate environmental impacts of emerging materials on humans and ecological species

Safety assessments of emerging materials require evaluation of the environmental impacts of emerging materials on humans and ecological species. Emerging materials of relevance and interest to Agency partners may include nanopesticides, nano/micro plastics, engineered nanomaterials, and incidental nanomaterials, depending on partner interest. Specifically, support to program offices for implementation of an evaluation framework for nanomaterials under FIFRA is an ongoing need. Research relevant to the impact of emerging materials on disproportionately impacted communities to inform environmental justice concerns, and on work to inform cumulative impacts research, is of particular interest.

Output CSS.3.2: Support for risk assessments of novel products of synthetic biology, genome editing and metabolic engineering

Over the last decade, there has been explosive growth in development of novel products of biotechnology through genome editing, synthetic biology, and metabolic engineering. Consequently, the scale, scope, and complexity of biotechnology products that EPA is mandated to make prompt regulatory decisions on has increased greatly. When these products have unique properties and uncertain risks, they pose additional regulatory challenges. This is true for many novel biotechnology products such as engineered microbes (regulated under TSCA, as amended by the Frank R. Lautenberg Chemical Safety for the 21st Century Act) and biopesticides (regulated under FIFRA). Safety questions remain regarding potential impacts to human health and the environment from these products. The goal of this research is to improve the certainty and timeliness of biotechnology risk assessments made by OPPT and OPP. More broadly, this will increase opportunities to realize the potential benefits of novel biotechnology while avoiding unintended consequences. Research from this Output will address needs prioritized by OPPT and OPP for new data and models to inform risk assessments of engineered microbes and biopesticides that are intended for open release into the environment. Focus areas will include but are not limited to long-term stability and reliability of synthetic biology microbial biocontainment strategies and potential for horizontal transfer of genetic material out of and into related microorganisms; ecological impacts of synthetic biology genetic constructs in microbial genomes for bacteria or fungi used as biofertilizers, bioremediation agents, and biosensors; and impacts of various formulants on biopesticidal substances.

Topic 2: Complex Systems Science

RA CSS.4: Adverse Outcome Pathways (AOP)

Output CSS.4.1: Develop actionable, fit for purpose high-priority AOPs to grow the AOP Knowledgebase

To increase efficiency and reduce costs and animal use associated with chemical safety assessment, EPA's program offices and regions are interested in incorporating data from NAMs, including *in vitro* assays or *in silico* models, into their decision making. However, biological effects (molecular initiating events) measured or predicted using NAMs are typically not the apical adverse outcomes that have been traditionally used in regulatory decisions. Thus, linking pathway-based biological effects (e.g., binding to

a receptor, activation of transcription factors, inhibition of an enzyme activity, metabolomic changes, alteration of gene expression/epigenetics) to probable apical hazards will help facilitate the use of NAMs. The AOP framework provides a systematic approach to organizing and synthesizing existing knowledge that supports extrapolation from pathway-based biological effects to apical hazards. To be effective, a broad knowledgebase of AOPs linking measurable biological effects to adverse outcomes of significance to risk assessment is needed. Work under this Output would develop fit-for-purpose AOPs deemed high-priority by partners, AOPs relevant to Agency-wide priorities (e.g., contaminants of immediate and emerging concern), and AOPs that capture the relatively non-specific interactions of environmental chemicals with biological systems. The Output includes work needed to undergo comprehensive technical review with the goal of endorsement from the OECD. This work may include experimentation to fill data critical gaps along with literature reviews, and technical review submissions.

Output CSS.4.2: Conduct strategic *in vitro* and *in vivo* studies that support development of high-priority AOPs

This Output is intended to provide partners with products that foster development of a common, integrating framework with which to link chemical hazard and exposure information from NAMs and better understand linkages between molecular initiating events and apical endpoints, particularly non-transient/relatively fixed human and ecological impacts at the whole organism level. AOPs provide a scientifically defensible foundation for extrapolating from NAMs data to predicted apical outcomes, potentially increasing confidence in the use of NAMs data in risk assessment and regulatory decision making. Successful AOP development for pathways deemed high priority by partners requires sufficient fundamental knowledge about biological pathways that is in part derived from experimental studies. This includes identification of relevant biological effects measurable by NAMs and generation of strategic confirmatory *in vivo* experimental testing refinements or human-based organotypic models and microphysiological systems to demonstrate effects at the tissue, organ, and organism-levels and are linked with apical endpoints of regulatory concern. Complementary efforts using both NAMs and traditionally derived data would help provide the scientific knowledge to support their use in evaluating the potential human health or ecological consequences that are of management or regulatory concern.

Output CSS.4.3: Conduct studies to elucidate and define biological points of departure and susceptibility factors that need to be considered for quantitative application of AOPs

The organizational scaffold of an AOP defines requisite key events (KEs) bridging early molecular effects with adverse outcomes of regulatory interest. By assigning quantitative relationships for these KEs, one can establish points of departure that may be measured in short-term assays for chemical screening, create computational models for predictive assessments, and provide critical characterization of the link between internal dose associated with the KEs and external exposure that will facilitate the required dose-response analyses. Quantitative relationships are dependent on extrinsic and intrinsic modifying factors that may shift dose-response relationships for defined AOPs following exposure to an environmental toxicant. These factors may include prior exposures (e.g., early lifestage exposure to environmental chemicals, which alters developmental programming), pre-existing conditions, age, and genetic/epigenetic-based susceptibilities. By capturing this type of information in AOPs, key susceptibilities can be defined and quantified (e.g., environmental justice concerns), informing cumulative impacts research and risk determination.

Output CSS.4.4: Demonstrate the utility of AOPs along with data derived from various sources to inform risks and associated management actions

Environmental authorities increasingly detect CIECs in environmental media. However, the toxicological data required to inform decision making can be lacking, particularly for complex mixtures of contaminants. This makes it difficult for managers to assess which CIECs pose risks, the types of effects to expect, and how to prioritize, monitor, and manage relevant risks. AOPs and AOP networks are intended to address these needs, in particular related to real-world mixtures, and can be used to identify and address data gaps that currently lead to uncertainty in chemical safety evaluations. This Output is intended to demonstrate how pathway-based data from existing sources (e.g., Adverse Outcome Pathway Database (AOP-DB), ECOTOX knowledgebase, ToxCast database) or from effects-based monitoring and surveillance approaches can be used, along with AOPs, to inform risks and associated management actions.

Output CSS.4.5: Develop AOPs relevant to human health and ecological impacts of Per- and Polyfluoroalkyl Substances (PFAS) and evaluate applicability across species, chemical groupings, and mixtures

Given the large number of PFAS of concern, knowledge gaps cannot be adequately addressed solely through collection of data from whole animal tests. Consequently, there is a need to develop predictive approaches to support assessment of PFAS. These predictive approaches feature databases (e.g., ECOTOX, electronic medical records) and tools like computational models, pathway-based *in vitro* assays, and short-term *in vivo* tests with molecular/biochemical endpoints. While these tools can produce biological response data more efficiently than conventional whole-animal tests, linking mechanistic information to the apical endpoints facilitates application of the data to risk assessment. Application of the AOP framework to challenges associated with assessing human health and ecological effects of PFAS addresses several practical needs, including (a) developing predictive assessment approaches; (b) organization/integration of complex biological datasets to identify critical knowledge and evidence gaps; (c) enhancement of the use of observational and mechanistic data for effects prediction to support decision making; (d) focus testing on endpoints, species, lifestages, and taxa of most concern for given chemicals; and (d) support assessment of effects of PFAS mixtures. The Output will be guided by the objectives of the EPA's PFAS Strategic Roadmap, to meet the goals of program offices (e.g., the National PFAS Testing Strategy).

RA CSS.5: Virtual and Complex Tissue Modeling (VCTM)

Output CSS.5.1: Develop, characterize, and apply organotypic and complex tissue models that bridge between *in vitro* and organismal assays for decision-relevant endpoints

Tiered testing strategies are used to evaluate chemical safety in an efficient, risk-based context. These strategies typically use higher throughput approaches to screen chemicals for potential hazards and prioritize chemicals for subsequent testing. There is a need to develop, demonstrate, and apply organotypic and complex tissue models that can reduce uncertainty and ensure use of the best available science in high-throughput testing strategies, with a focus across all lifestages relevant to priority target tissues. Specifically, the integration and evaluation of phenotypic responses from human-based organotypic and complex tissue model systems will help bridge the gap between the molecular pathway endpoints measured in high-throughput *in vitro* assays with the tissue and organ apical effects observed with *in vivo* toxicity studies. In addition to organotypic and complex tissue modeling, work may use

microphysiological systems for hazard characterization or further AOP development. Results from this Output may be used to better understand the effects of chemicals on early lifestages, the impacts of exposure to cumulative stressors, and concerns of disproportionately impacted communities.

Output CSS.5.2: Develop and apply *in silico* agent-based and computational models to evaluate the effects of chemicals on biological pathways

Chemical assessments typically rely on apical endpoints at the tissue, organ, or organism-level to derive quantitative points of departure or classify and label hazards. In addition, under chemical safety legislation (e.g., TSCA, FIFRA, FFDCA), EPA considers risks to vulnerable subpopulations and early lifestages, with a goal of reduced reliance on traditional animal testing. Thus, NAMs are needed to address adverse outcomes that reflect the best available knowledge of human biology at different scales corresponding to the various key events in AOPs that may serve as the basis of response analyses. To meet this research need, computational (*in silico*) models are an essential part of the NAMs portfolio. This Output is intended to build and test computer models of development and homeostasis for critical routes and target tissues (e.g., inhalation, pregnancy, development, kidney). These sophisticated computer models will recapitulate normal tissue biology as well as simulate the response of a virtual biological system to chemical perturbation and other stressors. Outputs of the simulation provide a unique and essential prospective mechanistic prediction of tissue, organ, or lifestage-specific toxicological effects *in vivo* that could supplement or supplant animal studies. Multiscale models under this Output will enable mechanistic inference into tissue, organ, lifestage, or disease specific toxicological and toxicokinetic responses along the adaptive to adverse continuum.

RA CSS.6: Ecotoxicological Assessment and Modeling (ETAM)

Output CSS.6.1: Develop and demonstrate ecological models to characterize risk of environmental contaminants for risk assessment at national, regional, and local scales

Ecological Risk Assessment (ERA) must consider the context (environment, species, additional stressors) within which exposure and effects occur. However, toxicity test results are usually generated in controlled laboratory-conducted experiments that must be translated to an ecological context to understand how they inform risk. For every federal action, including chemical registration and developing water quality standards, the ESA requires the assessment of the action for thousands of species. Other regulatory statutes such as FIFRA and TSCA require the protection of diverse ecological communities from chemical exposure. In both scenarios, risk is based on toxicity tests that are typically conducted in controlled laboratory settings for model species and require several extrapolations prior to application in ERA including 1) inter-species, 2) lab-to-field, and 3) individual to population. Approaches to these extrapolations must be compatible with exposure models and flexible to be incorporated with spatial data layers (e.g., crop coverage) for integrative ERAs. Toxicity translators are mathematical models that use ecological theory to make such extrapolations from available toxicity data to inform ERA under realistic exposure scenarios. Development, application, and demonstration of the models developed under this Output can be used to refine evaluations where screening estimates indicate a potential risk. Approaches will be flexible to allow for consideration of species-specific factors that may influence risk, as well as probabilistic approaches that can quantify the likelihood of effects. Products under this Output will continue or develop bodies of research on pesticides, federally listed species, climate change, and adverse outcome pathway development.

Output CSS.6.2: Develop methods and data to assess the impacts of pesticides on pollinators

Pollinator assessments are a key aspect of Agency ERAs, and honeybees continue to be used as a surrogate for other species of bees. Methods are needed to identify exposure to other species of bees in areas where honeybees are not a suitable surrogate. Furthermore, an examination is needed to determine the relative sensitivity/toxicity of honeybees to non-Apis bees, as well as other insect pollinators (e.g., butterflies). Work under this Output may include the development of a tiered approach to toxicity testing of honeybees and other pollinators as well as investigation to understand potential linkages between declines in pollinators and the impacts to plants covered by the Endangered Species Act.

Output CSS.6.3: Identify, assemble, and curate toxicity data for ecologically relevant species for risk assessment (ECOTOX)

The ECOTOXicology Knowledgebase (ECOTOX) is the world's largest compilation of ecotoxicity data, available publicly through a web-based database of curated single-chemical toxicity data for ecologically relevant species, including aquatic life, terrestrial plants, and wildlife. Curated data may include that which informs the impacts of changing temperatures due to climate change. There is a continual need to identify, assemble, and describe available evidence on the adverse effects of chemical stressors for use in risk assessments and regulatory decisions comprehensively and systematically. Relevant work includes continued literature searches and review, data extraction from relevant studies, regular updates to the Knowledgebase after inclusion of curated data, and a framework to support study evaluation. This Output provides data for chemical effects on aquatic and terrestrial organisms to program partners (e.g., Office of Water, Office of Pesticide Programs, Office of Pollution Prevention and Toxics, Office of Land and Emergency Management, Regional Offices) for risk evaluation and criteria/benchmark development. The ECOTOX data curation pipeline uses systematic methods that meet the need for reproducibility and data transparency.

Output CSS.6.4: Advance approaches for using surrogate species in ecological risk assessment

ERAs of chemicals largely rely on the use of toxicity test data collected from standardized model organisms and traditional whole organism biological responses. These data are used to represent potential chemical effects in the risk characterization of a vast diversity of plant, invertebrate and vertebrate species. Surrogacy of toxicological responses, metabolism and bioaccumulation in species and biological responses of measured results in common test species are commonly applied to infer results in species not tested. Limited empirical toxicity data is available across species and generating such data is impractical both in terms of cost and animal use. While development of predictive toxicology tools for chemical assessment has been ongoing for some time, application and integration of current scientific advances such as (but not limited to) advanced multi-omic and bioinformatic approaches, within the context of AOPs, to understand taxa-specific responses to chemical exposures may provide a mechanistic basis for improved interspecies extrapolations and refine toxicity predictions. Additionally, recent Agency policy mandates require a significant reduction in whole organism vertebrate testing—leading to a need for not only the use of predictive toxicology tools to augment effects characterizations, but to potentially replace traditional testing methods. Work under this Output is expected to address the goal of development of new methods, extrapolation tools and models, or the refinement and evolution of existing methodologies to improve the predictivity and reliance on surrogate species in ERAs.

Output CSS.6.5: Improve ecological methods and models for predicting exposure, accumulation, and effects of Per- and Polyfluoroalkyl Substances (PFAS)

Ecological methods and models for exposure, accumulation, and effects are an integral part of EPA's tiered approach to ERA for chemicals of concern, particularly per- and polyfluoroalkyl substances (PFAS). Initially, chemicals are evaluated using rapid assessment tools that require minimal data and provide conservative estimates of risk. Research is required to support the development of models for bioaccumulation across aquatic food webs and species consumed by humans and wildlife. In addition, work with NAMs that enables the rapid collection and analysis of mechanistic data, such as novel biological and genomic endpoints, is required to support the development and testing of AOPs and other frameworks that will help inform the chemical categories used to group assess the diverse universe of PFAS and should be consistent with the potential population-level effects of PFAS. New models and approaches appropriate for PFAS are needed to complement or replace those currently used to predict exposure and effects that require extrapolations extending orders of magnitude beyond existing data and yield predictions with an unacceptably high level of uncertainty. The research will be guided by the objectives of EPA's PFAS Strategic Roadmap, to meet the goals of program offices (e.g., the National PFAS Testing Strategy). The purpose of this Output is to continue to identify and curate existing exposure and effects information from the scientific literature, generate field and laboratory data to fill in gaps, and develop new models and approaches for predicting the ecological accumulation and effects of PFAS.

Topic 3: Knowledge Delivery and Solutions-Driven Translation to Support Chemical Safety Decision Making

RA CSS.7: Chemical Characterization and Informatics (CCI)

Output CSS.7.1: Generate and curate data relevant to chemical substances, structures, samples, and properties

Chemistry serves as the primary integrator of data for supporting research across the CSS program. A well-curated database of chemical substance information—including chemical structures and associated properties, as well as linkages to the chemical sample library, available as part of the ToxCast screening program—is necessary. The generation (through experimental measurement, or by extraction from previously published sources) and curation of data on chemical identifiers, structures, physicochemical properties, and transformation data (products, rates, and associated measurement conditions) into established databases (e.g., DSSTox, ChemProp) will be included under this Output. Generation of data may also include modeling to predict potential metabolites and environmental transformation products (e.g., those generated by the Chemical Transformation Simulator (CTS) and other predictive tools). Curation may include registration of new chemicals in ORD databases; establishing linkages of chemical identifiers (including structures) to associated data; and registration, mapping, and updates of priority chemical lists (e.g., the TSCA inventory). Related cheminformatics research such as incorporating new standards for chemical identifiers (e.g., updates to InChI versions), or developing appropriate information management solutions for chemicals that currently cannot be effectively represented using existing structure-based approaches (e.g., mixtures) or UVCBs (i.e., substances of unknown or variable composition, complex reaction products and biological materials) will also be carried out.

Output CSS.7.2: Develop data, tools, and models to support cross-species extrapolation for human health and ecological assessments

Human and environmental risk assessments for chemicals use a limited number of model organisms to generate toxicity data, which are subsequently extrapolated to species of concern. For ecological assessments this can involve extrapolation of effects from a few surrogate species to many thousands. While it would be ideal to conduct an adequate level of *in vivo* toxicity tests to explicitly address questions regarding species differences in chemical sensitivity, it is not feasible (particularly for threatened/endangered species). Further, testing resources are limited, there is an international interest to reduce animal use, and there exists an ever-increasing demand to evaluate more chemicals in a timely and sometimes expedited manner. Bioinformatics is a valuable tool that can be used to understand conservation of biological pathways through sequence, structural, and functional comparisons across species. Advancing computational and bioinformatics approaches that rapidly maximize the use of existing data through tools such as the Sequence Alignment to Predict Across Species Susceptibility (SeqAPASS) tool, are necessary for cross-species chemical safety evaluations. Additionally, it is important to characterize data quality, define the domain of applicability, and identify strengths and limitations for these tools, including through the use of laboratory studies when necessary.

Output CSS.7.3: Develop new and improve existing structure activity relationship models to support risk assessment

Quantitative structure-activity relationship (QSAR) models provide an automated method for the estimation of all types of chemical safety relevant endpoints for data-poor chemicals. To provide robust QSAR models to inform chemical evaluation, it is important to adopt a set of modeling best practices (e.g., the OECD QSAR framework), as well as clearly define domain of applicability approaches. In addition, there is a need to investigate cheminformatics approaches to model management and versioning to enable real-time model predictions and data provenance. The Output may include development of automated workflows to transform raw experimental data to modeling data sets and then to QSAR models. The endpoints should be consistent with Agency priorities, and may include the prediction of toxicities, *in vitro* bioactivities (HTT), toxicokinetics (RED), and environmental fate and physicochemical properties to support exposure modeling (RED, ETAM). Where feasible, the predictive performance of models should be compared with current models being used by the program offices to ensure fit for purpose application. Finally, this Output may include research into the interplay between dataset attributes (e.g., size, noisiness, curation level, source disparities) and model quality (predictive performance) to better estimate the uncertainty of the predictions and to provide guidance in improving QSAR modeling strategies in the future.

Output CSS.7.4: Advancing chemical categorization approaches for aiding the interpretation and prediction of bioassay and toxicity outcomes

Data on the toxicity and properties of environmental chemicals or their transformation products is often limited or unavailable. In addition, QSAR models are available for a limited number of endpoints of concern, and predictions for some chemicals may fall outside of the model's prediction applicability domain. Thus, for many chemicals and endpoints, there are insufficient or unsuitable data available to support a global QSAR model approach. Approaches that focus within more localized areas of chemistry, or within structure-bounded chemical categories, have the potential to expand the reach of SAR

approaches and yield useful predictive insights. Multiple approaches, including but not limited to read-across (e.g., GenRA), thresholds of toxicological concern (TTC), chemotype enrichment (e.g., ToxPrints), and custom fingerprint representations, may be utilized in this Output to assess chemical, metabolic, and biological similarity, and quantify uncertainties in predictions. These approaches operate within localized regions of chemical space that become synonymous with the operational definition of "chemical categories". Flexible means of creating structure-based categories suited to Agency programs and applications, and the structure-based articulation of historical categories used within the Agency, will allow for structure/substructure/similarity-based search and analysis tools to be more readily and systematically applied to Agency programs. This Output involves coordination and collaborative research efforts between scientists within the HERA and CSS research programs.

Output CSS.7.5: Advancing use of structural, mechanistic, and toxicokinetic data to support categorization and classification of Per- and Polyfluoroalkyl Substances (PFAS)

Per- and polyfluoroalkyl substances (PFAS) are frequently being detected in a variety of environmental media. PFAS chemicals are structurally diverse and typically lack adequate information needed to inform conventional risk evaluations on individual substances. To address this challenge, the Agency is pursuing a categorization approach that is informed by structure, mechanistic, and toxicokinetic information. The research will be guided by the objectives of EPA's PFAS Strategic Roadmap, to meet the goals of program offices (e.g., the National PFAS Testing Strategy). This Output is intended to be developed in coordination with and be responsive to the needs of multiple Program Office (e.g., OCSPP, OLEM, OW) and other partners, and may include continued development and refinement of PFAS categories for multiple decision contexts, development of QSAR models for physicochemical properties of PFAS, modeling of biodegradation of PFAS and mapping to parent substances, and related data generation, integration, modeling, and analysis.

RA CSS.8: Integration, Translation and Knowledge Delivery (ITK)

Output CSS.8.1: Integrating data systems to enable knowledge delivery

Measurement and modeling efforts across the CSS portfolio continue to generate a wealth of data. For data to be used in support of regulatory decision making, it needs to be stored and managed in a manner that is appropriately versioned and meets relevant quality standards. In addition, experimental and computational data across the CSS portfolio should be available for integration with other data streams and knowledge delivery tools. Findability, Accessibility, Interoperability, and Reuse (FAIR) principles of scientific data management should be adopted as appropriate and relevant. The research in this Output will continue to develop new and refine existing transactional data management systems and software for all of the overarching topical focus areas in CSS (e.g., toxicology, exposure, dosimetry, chemistry, ecotoxicology, hazard, etc.). The data management systems and software that will enable tracking data provenance and origin, versioning of data, facilitating data curation, and data quality review, will be developed, maintained, and supported under this Output (e.g., DataHub, ChemReg, ChemTrak, Factotum, ToxDCT, DAT, HTTr pipeline software package, HTPP software, ToxCast pipeline software (tcpl)). The Output will also integrate data management systems (e.g., through development of internal application programming interfaces (APIs) for system integration, support for programmatic registration of chemicals in ORD databases and associated lists from other systems such as exposure and hazard databases, or automated retrieval of experimental and predicted physicochemical and fate and transport properties). The data management systems developed under this Output will be inherently

coupled to products encompassing data generation, analysis, and curation across the CSS portfolio and will be a precursor for the knowledge delivery tools.

Output CSS.8.2: Knowledge delivery and interoperability in support of chemical safety decisions

The accessibility of data generated within the CSS portfolio for Agency and external partners ensures that the work of the CSS program is readily available to support chemical safety decisions. In addition, the broader scientific community utilizes CSS data for a variety of research activities. Key work of this Output should focus on enhancing the accessibility of CSS data, models, and tools for partners and the scientific community, while adopting FAIR principles as appropriate and relevant. The development (including modification of existing tools to accommodate new data streams or functionalities and integration of existing tools), maintenance, and support of key user interfaces (UIs) for data delivery (e.g., CompTox Chemicals Dashboard, ECOTOX, SeqAPASS, CTS, Web-ICE, AOP Knowledgebase) under this Output will address this need. In addition to UIs, development of internal or external application programming interfaces (APIs) for the purposes of interoperability and knowledge delivery to partners and the scientific community is also important. Cohesive strategies for knowledge sharing within the Agency, and with other governmental agencies or external partners, should be coupled with these knowledge delivery and visualization tools. The development of UIs and APIs (specifically, those designed to deliver information to partners and the scientific community) under this Output should be driven by stated partner needs and is intended to support the breadth of the CSS portfolio, relevant support for decision making (e.g., TSCA chemical evaluations), and other agency risk assessments.

Output CSS.8.3: Cross-disciplinary integration and applied case studies to support chemical safety decision making

The greatest impact of the work of the CSS program can be realized when data and models that span scientific domains are brought together for a specific application, decision context, or to investigate a hypothesis (e.g., an analysis which brings together exposure and toxicity data or models). In addition, demonstrating the utility to partners of CSS work products through applied case studies can maximize the value of investments in CSS research. This Output will include integrated work efforts in the form of decision support tools or workflows (e.g., RapidTox, Minnesota Toxic Free Kids chemical prioritization workflow, or the Public Information Curation and Synthesis (PICS) approach for TSCA and biosolids); demonstration of the application and utility of models, tools, and other mature CSS research products from all Research Areas through applied case studies incorporating the unique decision contexts of relevant partners; case studies under the Accelerating the Pace of Chemical Risk Assessment (APCRA) collaboration; and operationalizing models to demonstrate their utility for specific hazard and/or risk predictions to inform ongoing or future partner needs. The usefulness of such tools, workflows, and case studies is maximized when they are developed with a solutions-driven approach, collaborating with partners throughout the development process.

Output CSS.8.4: Innovative science to support new chemicals evaluation

The review of new chemical substances prior to their introduction into U.S. commerce is required under the TSCA legislation (Section 5). There is a need to refine and update the approaches, methods and tools used to evaluate the chemistry, environmental release/fate, hazard (human health and ecological), and exposure (environmental and human [occupational, general population, and consumers]) of new chemicals and efficiently integrate this information to evaluate the human and environmental risks in a

timely and transparent manner. This Output will contribute to modernizing the information used in decisions related to new chemical submissions. Specific research efforts may include representations and linkages of UVCB substances; updating and refining chemical category and analog approaches; developing and maintaining a library of new chemicals for testing; structure-based predictions of chemical properties, hazard, environmental fate/transport, or amenability for NAMs; *in vitro* toxicity testing and modeling of these data; application of modeling approaches to *in vitro* to *in vivo* extrapolation of dose; further development and/or demonstration of rapid exposure estimation tools for occupational, general population, and consumer scenarios; automated literature mining of available information; and integration of all of this information in a risk-informed workflow. Research will include consideration of priority areas such as susceptible populations, environmental justice, and others, as appropriate. This Output will be informed by research carried out under other research areas in the CSS portfolio such as HTT, RED, AOP, ETAM, and CCI, as well as the HERA program.

Output CSS.8.5: Translation of research for chemical safety decision making through demonstration, training, outreach, and partner engagement

Focused outreach (to Partners and the broader scientific community) to increase awareness and utility of CSS data, models, and tools will support the goal of seeing the greatest impact of the investment in CSS work. Demonstrating and facilitating the use of mature CSS research products from all Research Areas through communications, training, and other forms of education will encompass the work of this Output. This Output involves coordination and collaborative outreach efforts between scientists within the HERA and CSS research programs.

Appendix 4: Cross-Cutting Research Priorities

Working together on Agency priorities that cut across the six National Research Programs (NRPs), ORD will integrate efforts, provide a research portfolio aligned around the Agency's goals, and assist all of EPA's program and regional offices as well as states and Tribes. Where appropriate, the NRPs will combine efforts on the following cross-cutting priorities to conduct research that advances the science and informs public and ecosystem health decisions and community efforts. Although research efforts have been highlighted for each of these cross-cutting priorities, this does not mean that the research efforts only support that priority; the efforts may cut across priorities.

NRPs: Air, Climate, and Energy (ACE); Chemical Safety for Sustainability (CSS); Health and Environmental Risk Assessment (HERA); Homeland Security (HS); Sustainable and Healthy Communities (SHC); and Safe and Sustainable Water Resources (SSWR). The Strategic Research Action Plans for the NRPs are available on ORD's website at epa.gov/research/strategic-research-action-plans-2023-2026.

Environmental Justice

ORD's NRPs will integrate research efforts to identify, characterize, and solve environmental problems where they are most acute, in and with communities that are most at risk and least resilient. Research will strengthen the scientific foundation for actions at the Agency, state, tribal, local, and community levels to address environmental and health inequalities in vulnerable populations and communities with environmental justice and equity concerns. Coordinating research efforts will lead to a better understanding of how health disparities can arise from unequal environmental conditions, including impacts from climate change and exposures to pollution, and inequitable social and economic conditions. By working across NRPs, and through partner engagement, information, tools, and other resources will be developed that help support decision-making and empower overburdened and under-served communities to take action for revitalization.

Integrated Efforts Across National Research Programs	
ACE	Understand inequities in air pollution exposures and impacts, and impacts of climate change, accounting for social, cultural, and economic determinants that can lead to disproportionate exposures and impacts. Develop science to support effective interventions to reduce air pollution exposures and impacts, and adaptation and resilience measures to address climate impacts, including excessive heat (urban heat islands), flooding, and wildfires.
CSS	Investigate factors relevant to exposures for populations experiencing disproportionate adverse impacts from chemical exposures.
HERA	Expand the identification and consideration of information on susceptibility and differential risk in assessments, advance the evaluation of chemical mixtures and improve cumulative risk assessment practices to better characterize and assess health disparities.
HS	Assess and address community needs and vulnerabilities to ensure equitable incident management during disaster response and recovery by analyzing the community-specific cumulative impacts and the social implications of environmental cleanup; and by identifying potential interventions.
SHC	Identify risks and impacts to vulnerable communities and groups and improve the ability of communities to address cumulative impacts from contamination, climate (e.g., natural disasters and extreme events), and other stressors on health and the environment.
SSWR	Help provide clean and adequate drinking water and tools for stormwater management and urban heat island mitigation.

Climate Change

Understanding and addressing climate change impacts to human health and the environment is a critical component of ORD's research. To be effective, climate change research must be scientifically broad and systems-based. Where appropriate, the NRPs will integrate efforts to avoid duplicative efforts, fill critical gaps, and provide results that reflect the multiplicity of impacts and needs associated with climate change. Each NRP recognizes the critical need for continued communication with ORD partners to ensure that we are taking advantage of opportunities for collaboration, integration, and understanding.

Integrated Efforts Across National Research Programs	
ACE	Better understand and characterize air pollution and climate change and their individual and interrelated impacts on ecosystems and public health and identify and evaluate approaches to reduce the impacts of climate change through mitigation of climate forcing emissions, adaptation strategies, and building resilience in communities and ecosystems. Model energy, emissions, and environmental impacts of transformations in the nation's energy, transportation, and building sectors, and identify approaches to increase equitable benefits of those transformations.
CSS	Explore the use of newer analysis methods for identifying chemical contamination in environmental media after large catastrophic environmental events, such as wildland fires.
HERA	Continue development of assessments of air pollutants to inform climate policy efforts and leverage expertise, approaches, tools, and technologies in support of further climate change impact assessments.
HS	Enhance capabilities and develop new information and tools to maximize relevance and support for response and recovery from natural disasters related to climate change.
SHC	Integrated systems-approach research applicable to challenges that communities, including those with contaminated sites, face in preparing for and recovering from the impacts of natural disasters and climate change, ensuring that approaches are beneficial and equitable for the communities at risk.
SSWR	Improve resiliency of water resources and infrastructure to mitigate impacts related to climate change, including coastal acidification and hypoxia, harmful algal blooms, wildland fires, drought and water availability, stormwater flooding and combined sewer overflows, and urban heat islands.

Cumulative Impacts

Addressing the cumulative impacts of exposure to multiple chemical and non-chemical stressors is necessary for EPA to fulfill its mission to protect human health and the environment with the best available science. Cumulative Impacts refers to the total burden—positive, neutral, or negative—from chemical and non-chemical stressors and their interactions that affect the health, well-being, and quality of life of an individual, community, or population at a given point in time or over a period of time. It is the combination of these effects and any resulting environmental degradation or health effects that are the focus of ORD's cumulative impacts research. The NRPs will integrate efforts to improve understanding of cumulative impacts and develop and apply the necessary models, methods, and tools to conduct real-world assessments of cumulative impacts that result in both adverse and beneficial health and environmental effects. With this information, internal and external partners can

make informed, scientifically credible decisions to protect and promote individual, community, and environmental health.

Integrated Efforts Across National Research Programs	
ACE	Develop measurement methods and approaches to characterize ambient air quality and deposition, and human and ecosystem exposures to chemical (including criteria pollutants and air toxics) and non-chemical (including built environment, social, and climate-related) stressors, and health impacts from exposure to the combination of chemical and non-chemical stressors
CSS	Development and application of new approach methodologies to rapidly generate exposure and hazard information for chemicals, chemical mixtures, and emerging materials and technologies (including safer alternatives).
HERA	Research to advance the evaluation of chemical mixtures and improve cumulative risk assessment practices to better characterize and assess health disparities in communities with environmental justice and equity concerns.
HS	Through a focus on resilience equity, ensure that information and tools include the multitude of stressors impacting a community when used to support incident response. Research will recognize that resilience to an incident is directly impacted by the cumulative impacts of the incident and other stressors affecting a community.
SHC	Address the risks and impacts to improve the ability of communities to address cumulative impacts from contamination, climate, and other chemical and nonchemical stressors on health and the environment.
SSWR	Support human health ambient water quality criteria for chemical mixtures through research using bioassays and risk management, and assessment for exposure to groups of regulated and unregulated disinfection byproducts (DBPs) and opportunistic pathogens.

Community Resiliency

It is critical that communities have the knowledge and resources needed to prepare for and recover from adverse situations, such as natural disasters, contamination incidents, and failing infrastructure. Through combined research efforts, the NRPs will provide information and resources that support and empower communities to make science-based decisions to withstand, respond to, and recover from adverse situations.

Integrated Efforts Across National Research Programs	
ACE	Improve evaluations of climate change adaptation and mitigation measures and community resiliency to extreme events in a changing climate, such as wildfire, floods, heat waves, and drought—especially for vulnerable and disadvantaged communities experiencing environmental injustice.
CSS	Efforts relevant to chemical safety evaluations will be leveraged with other NRP activities.
HERA	Continue to expand the portfolio of assessment products to improve understanding of potential human health and environmental impacts of contamination incidents.
HS	Generate resources and tools for environmental cleanup, risk communication, outreach, building relationships, and community engagement to improve equitable community resilience for environmental contamination incidents and other disasters.
SHC	Increase resilience by reducing potential risks, promoting health, and revitalizing communities.
SSWR	Support coastal resilience by advancing monitoring, mapping, and remote sensing and by the economic valuation of coastal resources. Improve the performance, integrity, and resilience of water treatment and distribution systems through research on water infrastructure and water quality models.

Children's Environmental Health

From EPA's 2021 Policy on Children's Health, "children's environmental health refers to the effect of environmental exposure during early life: from conception, infancy, early childhood and through adolescence until 21 years of age." Environmental exposures that impact health can occur before conception, and during pregnancy, infancy, childhood, and adolescence; and include long-term effects on health, development, and risk of disease across lifestages. Much of ORD's research is relevant to communities, including susceptible and vulnerable populations. Where appropriate, the NRPs will combine efforts to conduct research that will inform public health decisions, advance our scientific understanding of early-life susceptibility to environmental stressors, and inform community efforts that create sustainable and healthy environments protective of all lifestages.

Integrated Efforts Across National Research Programs	
ACE	Explore air pollution and climate health impacts within different lifestages and populations, including overburdened groups. Assess vulnerabilities to air pollution for those with chronic illnesses and sequelae from respiratory viruses. Research social determinants of health, and air pollution impacts resulting from different exposure time-activity patterns.
CSS	Research will build the scientific foundation to predict adverse outcomes resulting from chemical exposures in various biological contexts, including early life-stage susceptibility.
HERA	Continue to evaluate health effects, over the course of a lifetime, from environmental exposure to stressors during early life (i.e., from conception to early adulthood) to inform decision-making and advance research on methods to properly characterize risks to children.
HS	Improve and develop decision-support tools and cleanup capabilities to make children less vulnerable during response to, and recovery from, contamination incidents.
SHC	Address the risks and impacts to vulnerable communities and lifestages, including underserved/overburdened communities, and improve the ability of communities to address cumulative impacts from contamination, such as site clean-ups of per- and polyfluoroalkyl substances (PFAS) and lead; climate, such as natural disasters and extreme events; and other stressors on health and the environment.
SSWR	Evaluate health effects and toxicity related to algal toxins and expanded research that will explore exposure risks for lead, DBPs, and—through quantitative microbial risk assessment models—for high priority opportunistic pathogens in drinking water (e.g., *Mycobacterium*, *Pseudomonas*, *Naegleria fowleri*).

Contaminants of Immediate and Emerging Concern

Contaminants of immediate and emerging concern (CIECs) include chemical substances that may cause ecological or human health impacts and are either new or existing contaminants of increased priority. The NRPs will work with EPA partners in the program and regional offices, along with input from Agency leadership, to identify the highest priority contaminants (broadly defined to include chemical, biological, and other

categories as appropriate), including those of immediate concern, such as PFAS and lead, that warrant further research attention.

Integrated Efforts Across National Research Programs	
ACE	Develop and evaluate measurement methods and approaches to characterize sources of air pollutants and climate forcing pollutants, such as measurement of emissions of criteria pollutant precursors and air toxics, including emerging concerns, such PFAS and EtO.
CSS	Continue to develop new approach methods for CIECs with a focus on applying these, as appropriate, for prioritization, screening, and risk assessment for decision making.
HERA	Continue and expand the portfolio of assessment products, as well as advance risk assessment models and tools, to better characterize potential human health and environmental impacts of new and existing contaminants.
HS	Predict the movement of chemical, biological, and radiological contaminants in the environment resulting from environmental contamination events and develop tools and methods for effective characterization, decontamination, and waste management.
SHC	Advance site clean-ups of PFAS and lead to protect vulnerable groups, especially children.
SSWR	Research on PFAS, including innovative drinking water and wastewater treatments, support for future drinking water regulations, the development of aquatic life criteria, management in water resources, and evaluation of land-applied biosolids; contaminants of emerging concern (CECs), lead, opportunistic pathogens, and DBPs in drinking water; cyanobacterial metabolites other than microcystin (e.g., anatoxin, saxitoxin, and nodularin); microplastics in sediments and surface water; and CECs (non-PFAS) in wastewater treatment systems and biosolids.