

Health and Environmental Risk Assessment National Research Program

Strategic Research Action Plan, 2019 – 2022

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List of Acronyms

AALM	All Ages Lead Model	NCEE	National Center for Environmental Economics
A-E	Air and Energy	NRC	National Research Council
AOP	Adverse Outcome Pathway	NCP	National Contingency Plan
ATSDR	Agency for Toxic Substances and Disease Registry	OAR	Office of Air and Radiation
BMD	Benchmark Dose	OCHP	Office of Children's Health Protection
BMDS	Benchmark Dose Software	OCSP	Office of Chemical Safety and Pollution Prevention
CAA	Clean Air Act	OECA	Office of Enforcement and Compliance Assurance
CERCLA	Comprehensive Environmental Response, Compensation, and Liability Act	OEJ	Office of Environmental Justice
CSS	Chemical Safety for Sustainability	OLEM	Office of Land and Emergency Management
CWA	Clean Water Act	OP	Office of Policy
ECOS	Environmental Council of States	ORD	Office of Research and Development
EPA	U.S. Environmental Protection Agency	OW	Office of Water
ERASC	Ecological Risk Assessment Support Center	PAL	Provisional Advisory Level
ERIS	Environmental Research Institute of the States	PBPK	Physiologically-Based Pharmacokinetic
FIFRA	Federal Insecticide, Fungicide, and Rodenticide Act	PK	Pharmacokinetic
FQPA	Food Quality Protections Act	PFAS	Per-and Polyfluoroalkyl Substances
FY	Fiscal year	PM	Particulate Matter
HAWC	Health Assessment Workspace Collaborative	PPRTV	Provisional Peer-Reviewed Toxicity Values
HERA	Health and Environmental Risk Assessment	QA	Quality Assurance
HERO	Health and Environmental Research Online	RAF	Risk Assessment Forum
HHRA	Human Health Risk Assessment	RCRA	Resource Conservation and Recovery Act
HSRP	Homeland Security Research Program	SARA	Superfund Amendment and Reauthorization Act
HTS	High-Throughput Screening	SDWA	Safe Drinking Water Act
HTTK	High-Throughput Toxicokinetics	SHC	Sustainable and Healthy Communities
IEUBK	Integrated Exposure, Uptake, Biokinetic	SSWR	Safe and Sustainable Water Resources
IRIS	Integrated Risk Information System	StRAP	Strategic Research Action Plan
ISA	Integrated Science Assessment	STSC	Superfund Health Risk Technical Support Center
IVIVE	In vitro-in vivo extrapolation	TSCA	Toxic Substances Control Act
LUST	Leaking Underground Storage Tanks	TSC	Technical Support Center
NAAQS	National Ambient Air Quality Standards	UCMR	Unregulated Contaminant Monitoring Rule
NAM	New Approach Methodologies		

Executive Summary

To protect human health and the environment, the U.S. Environmental Protection Agency (EPA) and its federal, state, and other government partners and external stakeholders must make critical decisions about the risks of exposures to environmental stressors. EPA has designed the Health and Environmental Risk Assessment (HERA) program to develop and apply state-of-the-science research to characterize impacts on human and ecological systems – whether they result from exposure to single, complex, or multiple physical, chemical, or biological stressors – to support and improve EPA’s risk assessment decisions. The HERA program identifies, evaluates, and integrates existing and emerging information from diverse scientific disciplines to rigorously characterize hazard and evaluate exposure-response¹ relationships in support of human health and environmental risk assessments.

Since assessments form key components of the scientific foundation for risk assessment decisions, they can have significant implications for the protection of public health and the environment, as well as for the economy and sustainable development. This HERA Strategic Research Action Plan (StRAP) 2019-2022 highlights how the design of the HERA program aspires to be nimble and flexible to develop science assessment products that better meet the needs of EPA programs and regions, states, tribes, and external stakeholders. The HERA StRAP is designed to be scientifically robust and sufficiently flexible to enable utilization of its outputs and products across decision contexts. It is intended to significantly increase the speed, transparency, and access to HERA research.

The HERA program will provide a portfolio of fit-for-purpose assessment products, analytical approaches, and state-of-the-science applications that support a wide range of environmental decisions. The program is oriented under two broad research topics: (1) Science Assessments and Translation, and (2) Advancing the Science and Practice of Risk Assessment.

- Topic 1, *Science Assessments and Translation*, provides scientific and technical support from development to application of assessment products, throughout the lifecycle of the Agency decision. Emphasis is placed on providing high quality, state-of-the-science, transparent, consistent, and scientifically-defensible assessment products to meet EPA’s diverse statutory and policy needs, and to address requests from EPA programs and regions, states, and tribes for technical support and consultation.
- Topic 2, *Advancing the Science and Practice of Risk Assessment*, focuses on scientific innovations to advance analytic approaches and applications for assessments to improve the accuracy, efficiency, flexibility, and utility of assessment activities served by the HERA program. Emphasis is placed on enhancing hazard characterization, expanding the repertoire of dose-response methods and models, and characterizing the utility of emerging data and new computational tools as applied to risk assessment. Research under this topic enhances and maintains critical assessment infrastructure, including databases, models, and software support.

¹ The HERA StRAP uses the term “exposure-response” generically to describe the relationship between an exposure to a stressor (be it chemical, physical, or biological) and an effect (be it a human health effect or an ecological effect), regardless of the source or route of exposure. In many places, the term “dose-response” is used instead to depict the more common phrasing of the various applications of this concept in human health assessments that grew out of laboratory animal toxicity testing and oral exposure (i.e., dose-response modeling, benchmark dose, internal dose calculations).

This HERA StRAP outlines these research topics and the overall HERA program design. The StRAP serves as a planning guide for the EPA Office of Research and Development's (ORD) research Centers to develop specific products that contribute to the identified outputs that align with EPA program and regional research needs. HERA's scientific results and innovative technologies will support EPA's strategic goals and objectives: to deliver solutions so that Americans have access to clean air, land, and water; to ensure chemical safety (including safe handling and storage of chemicals); and to focus the EPA's robust research and scientific analyses to inform policy making.

HERA will provide priority assessment products, identify critical science issues as they arise, and develop or stimulate advances in approaches and solutions to address emerging challenges, incorporate innovations, and continuously refine applications. Ultimately, this research helps to ensure that decisions by EPA are based on reliable, transparent, and high-quality risk assessment methods, models, and data.

Introduction

Every day, the EPA programs and regions, states, tribes, and external stakeholders must make decisions to ensure that human health and the environment continue to be protected from the known or potential adverse effects of exposure to environmental stressors. These decisions span a large regulatory and non-regulatory landscape, and require different degrees of information to: characterize qualitative and quantitative toxicity information and develop health-protective toxicity values to support air, water, and land management programs; evaluate ecological effects and characterize responses and impacts of exposure to one or more environmental stressors, such as chemicals, land change, disease, and invasive species; characterize potential human health and environmental impact during emergent situations; evaluate chemicals for potential risk from exposure at Superfund sites and in the air, water, soil, and sediment; and interpret and integrate different lines of evidence to support decisions to establish, retain, or revise national pollutant standards. EPA's HERA program is designed to develop and apply state-of-the-science research to characterize the impacts on human and ecological systems whether they result from exposure to single, complex, or multiple physical, chemical, or biological stressors. In doing so, HERA provides key components of the scientific foundation for risk assessments to inform these decisions aimed at protecting human health and the environment.

To assist the Agency in meeting its goals and objectives, HERA, within EPA's Office of Research and Development (ORD), developed this Strategic Research Action Plan for fiscal years 2019–2022 (StRAP FY2019-2022). The StRAP outlines a four-year research strategy to advance the goals and cross-Agency priorities identified in the [FY 2018-2022 U.S. EPA Strategic Plan](#) (U.S. EPA, 2018a). The StRAP builds on prior StRAPs as outlined in the *Human Health Risk Assessment (HHRA) Strategic Research Action Plan, FY2012–2016* and *FY2016-2019* (U.S. EPA, 2012; U.S. EPA, 2015), and continues the practice of conducting innovative scientific research to solve problems encountered by the Agency. In 2019, as part of a reorganization of EPA's ORD, the name of the research program was changed from Human Health Risk Assessment (HHRA) to HERA to better reflect the breadth of the program, which includes environmental assessments such as those presented in the Integrated Science Assessments for secondary National Ambient Air Quality Standards (NAAQS).

The HERA StRAP is one of six research plans, one for each of EPA's national research programs in ORD. The six research programs are:

- Air and Energy (A-E)
- Chemical Safety for Sustainability (CSS)
- Health and Environmental Risk Assessment (HERA)
- Homeland Security Research Program (HSRP)
- Safe and Sustainable Water Resources (SSWR)
- Sustainable and Healthy Communities (SHC)

Research to Support EPA and ORD Strategic Plans

Each of ORD’s six national research programs has developed a StRAP. Collectively, the StRAPs lay the foundation for EPA’s research programs to provide focused research that meets the Agency’s statutory requirements and the goals outlined in the [FY 2018-2022 U.S. EPA Strategic Plan](#) and the [Office of Research and Development Strategic Plan 2018-2022](#) (U.S. EPA, 2018a; U.S. EPA, 2018b). The StRAPs are designed to guide an ambitious research agenda that delivers the science and engineering solutions the Agency needs to meet its goals now and into the future, while also cultivating an efficient, innovative, and responsive research enterprise. The strategic directions and outputs 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 stakeholders.

The FY 2018-2022 EPA Strategic Plan has three overarching goals, with related objectives, describing how the Agency will work toward its mission to protect human health and the environment, and provides the measures ORD will use to evaluate our success. Table 1 presents the Agency goals and objectives, extracted from the EPA Strategic Plan, most pertinent to the HERA research program.

Table 1. Highlights of EPA Strategic Plan Goals and Objectives Relevant to the HERA Research Program

EPA Goal	EPA Strategic Objective
<p>Goal 1 – A Cleaner, Healthier Environment: Deliver a cleaner, safer, and healthier environment for all Americans and future generations by carrying out the Agency’s core mission.</p>	<p>Objective 1.1 – Improve Air Quality: Work with states and tribes to accurately measure air quality and ensure that more Americans are living and working in areas that meet high air quality standards.</p>
	<p>Objective 1.2 – Provide for Clean and Safe Water: Ensure waters are clean through improved water infrastructure and, in partnership with states and tribes, sustainably manage programs to support drinking water, aquatic ecosystems, and recreational, economic, and subsistence activities.</p>
	<p>Objective 1.3 – Revitalize Land and Prevent Contamination: Provide better leadership and management to properly clean up contaminated sites to revitalize and return the land back to communities.</p>

EPA Goal	EPA Strategic Objective
	<p>Objective 1.4 — Ensure Safety of Chemicals in the Marketplace: Effectively implement the Toxic Substances Control Act, and the Federal Insecticide, Fungicide, and Rodenticide Act, to ensure new and existing chemicals and pesticides are reviewed for their potential risks to human health and the environment and actions are taken when necessary.</p>
<p>Goal 2 – More Effective Partnerships: Provide certainty to states, localities, tribal nations, and the regulated community in carrying out shared responsibilities and communicating results to all Americans.</p>	<p>Objective 2.1 — Enhance Shared Accountability: Improve environmental protection through shared governance and enhanced collaboration with state, tribal, local, and federal partners using the full range of compliance assurance tools.</p> <p>Objective 2.2 — Increase Transparency and Public Participation: Listen to and collaborate with impacted stakeholders and provide effective platforms for public participation and meaningful engagement.</p>
<p>Goal 3 – Greater Certainty, Compliance, and Effectiveness: Increase certainty, compliance, and effectiveness by applying the rule of law to achieve more efficient and effective Agency operations, service delivery, and regulatory relief.</p>	<p>Objective 3.3 — Prioritize Robust Science: Refocus the EPA’s robust research and scientific analysis to inform policy making</p>

Statutory and Policy Context

The HERA program supports EPA’s statutory authority and mandates to conduct work under the various environmental statutes listed below, all of which require risk assessment in some form. The risk assessment and risk management actions associated with these statutes are implemented by EPA’s national program offices, including the Office of Land and Emergency Management (OLEM), Office of Water (OW), Office of Air and Radiation (OAR), Office of Chemical Safety and Pollution Prevention (OCSPP), as well as the associated regional offices.

The **Comprehensive Environmental Response, Compensation, and Liability Act (CERCLA)**, the **Superfund Amendments and Reauthorization Act (SARA)**, and the **National Contingency Plan (NCP)** give EPA the authority to respond directly to releases or threatened releases of hazardous substances, pollutants, or contaminants that may endanger public health or the environment. Response actions can be conducted only at sites listed on EPA’s [National Priorities List](#) established under the NCP, which provides the guidelines and procedures needed to respond. These Acts, commonly referred to as Superfund, require research, development, and training to improve EPA’s scientific capability to assess effects and characterize risk to human health and the environment from hazardous substances.

The **Resource Conservation and Recovery Act (RCRA)** gives EPA the waste management authority to control hazardous and non-hazardous waste from “cradle to grave,” including the generation, transportation, treatment, storage, and disposal stages. The law sets forth the framework for a national system of solid waste control including both hazardous ([Subtitle C](#)) and non-hazardous ([Subtitle D](#))

waste requirements, and allows EPA to develop regulations, guidance, and policies to ensure the safe management and cleanup of solid and hazardous waste, and programs that encourage source reduction and beneficial reuse. The 1986 amendments enable EPA to address environmental problems that can result from underground tanks storing petroleum and other hazardous substances.

The **Clean Air Act (CAA)** section 103 mandates that EPA conduct a national research and development program for the prevention and control of air pollution. The 1990 amendments further require EPA to set National Ambient Air Quality Standards (NAAQS) (40 CFR Part 50) for criteria pollutants considered harmful to public health and the environment on a 5-year cycle, and mandate the determination of risks from mobile, area, and major sources of air toxics. Section 112 of the CAA mandates risk assessment, and if needed, application of new control technologies to protect public health from exposures to hazardous air pollutants.

The **Safe Drinking Water Act (SDWA)** requires EPA to use the best available, peer-reviewed science and supporting studies when making decisions. SDWA also requires the EPA to ensure the presentation of information on risk assessment, management, and communication in a manner that is comprehensive, informative, and understandable. The law mandates that the EPA assess the effects of a contaminant on the general population and on groups within the general population, such as infants, children, pregnant women, elderly individuals with a history of serious illness, or other subpopulations that are identified as likely to be at greater risk of adverse health effects due to exposure to contaminants in drinking water than the general population.

The **Clean Water Act (CWA)** establishes the basic structure for regulating discharges of pollutants into the waters of the United States and regulating quality standards for surface waters. The objective of the CWA is to restore and maintain the chemical, physical, and biological integrity of the Nation's waters. Under the CWA, EPA has implemented pollution control programs such as setting wastewater standards for industry and developed national water quality criteria recommendations for pollutants in surface waters.

The **Toxic Substances Control Act (TSCA)** as amended by the Frank R. Lautenberg Chemical Safety for the 21st Century Act of 2016, requires evaluation of potential risks from new and existing chemicals and acts to address any unreasonable risks that chemicals may have on human health and the environment. Specifically, the law provides mandatory requirements for EPA's evaluation of existing chemicals with clear and enforceable deadlines; risk-based chemical assessments with consideration of potentially exposed or susceptible subpopulations (such as infants, children and pregnant women, workers, or the elderly) as well as inclusion of developmental lifestages as part of study design; and increased public transparency for chemical information.

The **Federal Insecticide, Fungicide, and Rodenticide Act (FIFRA)** provides for Federal regulation of pesticide distribution, sale, and use. All pesticides distributed or sold in the United States must be registered (licensed) by EPA. Before EPA may register a pesticide, the applicant must show, among other things, that using the pesticide according to specifications "will not generally cause unreasonable adverse effects on the environment," typically characterized by health and environmental risk assessments.

The **Food Quality Protection Act (FQPA)** of 1996 requires assessment of risk from exposures to pesticides, including aggregate exposures and cumulative risk, and risk to sensitive subpopulations (e.g., infants and children).

Additionally, there are several policies describing children’s environmental health and environmental justice considerations, and the need to address the associated unique vulnerabilities. Children’s health considerations include: [Executive Order 13045: Protection of Children From Environmental Health Risks and Safety Risks](#), which applies to economically significant rules under [E.O. 12866](#) that concern an environmental health or safety risk that EPA has reason to believe may disproportionately affect children; [EPA’s Policy on Evaluating Health Risks to Children](#), which states it is the policy of the EPA to consider the risks to infants and children consistently and explicitly as a part of risk assessments generated during its decision making process, including the setting of standards to protect public health and the environment; and the [2018 Reaffirmation Memo on EPA’s 1995 Policy on Evaluating Health Risks to Children](#). EPA’s Office of Environmental Justice² (OEJ) considers [Executive Order 12898: Federal Actions to Address Environmental Justice in Minority Populations and Low-Income Populations](#), which states that “...Environmental human health analyses, whenever practicable and appropriate, shall identify multiple and cumulative exposures.” One of OEJ’s objectives is to strengthen the scientific foundation for considering environmental justice in decision making, through research on decision-support tools, adverse and cumulative impacts and risks, innovative monitoring, and solution technologies (see [EJ 2020 Action Agenda](#)).

To address EPA’s strategic goals and objectives, HERA will focus research to support priority Agency statutory and policy decisions under the array of environmental Acts and policies and objectives described above. In doing so, HERA will provide the assessment products and technical support needed for risk assessment decisions in line with EPA’s strategic objectives briefly described in Table 1 to: improve air quality; provide for clean and safe water; revitalize land and prevent contamination; ensure safety of chemicals in the marketplace; enhance shared accountability, increase transparency and public participation; and prioritize robust science.

Partner and Stakeholder Engagement

ORD supports EPA’s regulatory and non-regulatory programs by providing the best possible science, technical support, and guidance. ORD worked with its partners to identify high priority research needs and develop the research tools necessary to inform decision making at the local, state, regional, national, and international level. EPA, state, and tribal decision-makers use risk assessments to characterize the nature and magnitude of risks to humans (e.g., residents, workers, vulnerable populations) and ecological receptors (e.g., birds, fish, wildlife) from chemical contaminants and other stressors that may be present in the environment. ORD’s HERA research program contributes to risk assessment decisions by developing and applying research to characterize the impacts on human and ecological systems.

The HERA StRAP was developed with input in 2018 and 2019 from EPA programs and regions, states, tribes, and other stakeholders. The specific assessment topics are directly identified, prioritized, and requested by EPA programs and regions, who also specify the context and timeline for assessment needs. State and tribal priorities are integrated through engagement with the Environmental Council of the States (ECOS) and with tribes through the Tribal Science Council, the National Tribal Toxics Council,

² Environmental justice is the fair treatment and meaningful involvement of all people regardless of race, color, national origin, or income, with respect to the development, implementation, and enforcement of environmental laws, regulations, and policies.

and other tribal organizations. Appendix 1 summarizes the linkages between HERA research outputs and input received from ECOS.

Stakeholder and public engagement are key elements in the various research products planned under the HERA program. Consistent with EPA Strategic Objective 2.2 to *Increase Transparency and Public Participation: Listen to and collaborate with impacted stakeholders and provide effective platforms for public participation and meaningful engagement*, additional input to inform the HERA program was sought through state environmental and public health agencies around specific assessment product activities. Stakeholders and the public are also engaged through dedicated outreach processes (e.g., workshops and public review and comment) routinely embedded in assessment product development, providing transparency, access, and participation.

ORD's strategic measure is to "increase the percentage of research products that meet customer needs", which ORD measures through an annual survey of quality, usability, and timeliness to gauge progress in addressing priorities. This ORD strategic measure was established consistent with the EPA Strategic Goal 3, Objective 3.3 – *Prioritize Robust Science: Refocus the EPA's robust research and scientific analysis to inform policy making* (see Table 1). The primary recipients of HERA products are EPA's regulatory programs – OLEM, OW, OAR, and OCSPP – and regional offices. HERA also works closely with three additional EPA offices: Office of Policy (OP) within the Office of the Administrator, notably OP's National Center for Environmental Economics (NCEE) and Office of Environmental Justice (OEJ); Office of Children's Health Protection (OCHP) within the Office of the Administrator; and the Office of Enforcement and Compliance Assurance (OECA).

HERA will continue its engagement with EPA programs and regions, states, tribes, and other external stakeholders as the research program is implemented, providing ongoing support in the use of research products after they are delivered. In doing so, HERA will evaluate the usefulness and effectiveness of its research in helping to address environmental and public health problems. Additionally, ORD, through HERA and the other five national research programs, will evaluate how the engagements and the design and conduct of the research has informed solutions to the most pressing environmental problems.

Environmental Problems and Program Objectives

Decision making at the EPA covers a large landscape of risk assessment activities. Responding to these needs requires agility to bring together the best available science and technologies to inform decisions in a fit-for-purpose and coherent fashion. The purpose of the HERA program is to develop and apply state-of-the-science research to characterize the impacts on human (including sensitive populations and lifestages) and ecological systems, whether they result from exposure to single, complex, or multiple physical, chemical, or biological stressors, to support and improve EPA's risk assessment decisions. The HERA program identifies, evaluates, and integrates existing and emerging information from diverse scientific disciplines to accurately characterize human or environmental hazards and evaluate qualitative and quantitative relationships. These are key steps in the process to characterize risk (Figure 1). The HERA program works in concert with other ORD research programs and EPA program and regional offices to support and improve decisions, playing a pivotal role with respect to the overall ORD research

portfolio and Agency risk assessment³ and risk management⁴ decisions; see visual example illustrated in Figure 1. Additionally, challenges encountered in the human health and environmental assessment activities of the HERA program identify critical research needs and help to advance the development of new applications, both by research conducted in the HERA program and by stimulating the broader scientific and risk assessment communities.

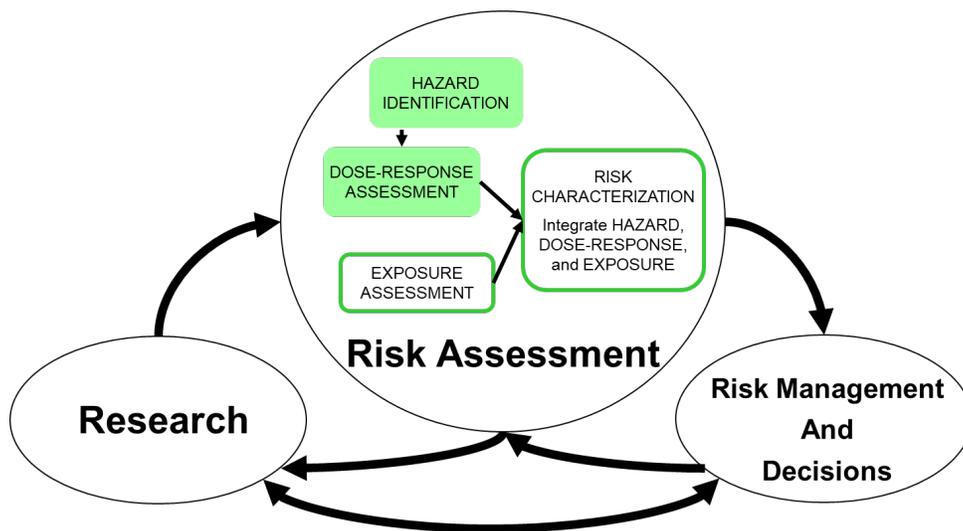


Figure 1. An illustrated example of HERA’s role in human health risk assessment. HERA develops and applies research to advance the hazard identification and dose-response assessment elements (green shaded boxes) of the human health risk assessment paradigm. For health assessments, this generally involves hazard identification based on human health effects and the related dose-response assessment of those health effects as depicted. For ecological assessments, this generally involves evaluation of ecological effects that may occur as a result of exposure to one or more stressors and the evaluation of the environmental responses to the stressor(s). HERA holds a critical position with respect to the overall ORD research portfolio and the Agency risk assessment and decision-making activities. (See <https://www.epa.gov/risk> for more detailed information on risk assessment and risk management).

Problem Statement

EPA and its partners and diverse external stakeholders must make decisions to ensure that human health and the environment continue to be protected from the known or potential adverse effects of a variety of exposures to environmental stressors. The wide range of risk assessment decision contexts

³ Risk assessment provides information on potential health or ecological risks.

⁴ Risk management is the action taken based on consideration of risk assessment and other information (economic, legal, social, technological, political, and public factors).

calls for assessment products, analytical approaches, and expert scientific support that fit the purpose of these various decisions. Research products must be scientifically credible, defensible, and contemporary with evolving technologies and science, whether based on limited data or evidence integrated across thousands of sources.

Program Vision

The HERA program vision is to innovate and advance the science and practice of health and environmental risk assessment by developing a portfolio of fit-for-purpose assessment products and assessment research that meets the needs and priorities of EPA programs and regions, states, tribes, and external stakeholders.

Research Topics and Research Areas

The HERA program is organized around two research topics that are subdivided into research areas (Table 2). Each research area comprises outputs that focus on addressing specific needs (Table 2 and Appendix 3). The products that will be developed to address the outputs are actual deliverables that may take the form of assessments, reports, tools, and journal articles. These products will be determined during research implementation planning in collaboration with Agency program and regional offices to reflect their timing and specific needs.

Table 2. HERA Research Topics, Research Areas, and Outputs

Topic	Research Area	Output
1. Science Assessments and Translation	1. Science Assessment Development	1.1 Portfolio of interim assessment products to support decision making
		1.2 Portfolio of final assessment products to support decision making
	2. Science Assessment Translation	2.1 Technical support to EPA regions and states through the STSC and ERASC
		2.2 Core translational research modules for expert technical support
2. Advancing the Science and Practice of Risk Assessment	3. Emerging and Innovative Assessment Methodologies	3.1 Advance, translate, and build confidence in the application of new approach methods (NAMs) and data in risk assessment
		3.2 Conduct case study applications of rapid assessment methodologies to inform parameters of interest to risk-decision contexts
		3.3 Evaluate and develop improved methods for dose extrapolation and the related uncertainty characterization in human health risk assessment via classical methods and integration of pharmacokinetic models
		3.4 Advance methods for systematic review, including evidence integration
		3.5 Advance methods in dose-response modeling with application to risk assessment

	4. Essential Assessment and Infrastructure Tools	4.1 Innovate, develop, and maintain a suite of essential software and support tools for risk assessment
		4.2 Innovate, develop, and maintain a training program on the advances in risk assessment and systematic review

Topic 1: Science Assessments and Translation

The *Science Assessments and Translation* research topic showcases HERA’s focus on the science and practice of assessment development. HERA has increased emphasis on identifying a range of EPA decision making conditions, including consideration of susceptible populations and lifestages, to support the required priorities of EPA programs and regional offices, and is tailoring the scope of its products to meet demands. The HERA program has also increased emphasis on providing scientific and technical support from development to application of the assessment products, throughout the lifecycle of the decision. In response to these drivers, HERA has recast its assessment workflow. Specifically, the following principles and concepts will inform and guide HERA’s assessment development and application:

- **Solutions-Focused Products:** HERA assessment products will be tailored to a specific decision or application context, including consideration of vulnerable populations and lifestages. HERA will provide expert-driven scientific and technical support from inception to implementation, and through future follow-up activities surrounding assessment products.
- **Increased Transparency:** HERA will continue to increase transparency of assessment products and processes by utilizing various tools, databases, and approaches across the program, such as Health and Environmental Research Online (HERO), Health Assessment Workplace Collaborative (HAWC), and systematic review⁵. Applications of these tools, databases, and approaches will form key pillars of assessment practice and processes across the HERA research program, ensuring increased transparency through documentation and clarity in analyses, evaluations, and conclusions, *a priori* methodology, and increased public access to data and literature.
- **Modular Product Lines:** HERA is implementing a portfolio of assessment products that optimize the application of the best available science and technology. These products will allow HERA to remain flexible and responsive. HERA is also implementing program and project management across its assessment portfolio, allowing assessment teams to quickly identify gaps in necessary expertise, monitor assessment-specific tasks, determine capacity to meet EPA’s needs, and more accurately predict timelines for the completion of assessment products. The integration of project management and business intelligence software will provide real-time data to assess capacity and flexibility to provide scientific and technical support as requested.
- **Modernized Assessment Workflows:** HERA is developing and using automation and machine-learning tools to expedite systematic reviews and incorporate emerging data types. Such an

⁵ Systematic review is a structured and documented process that uses explicit, prespecified scientific methods to identify, select, assess, and summarize findings of similar but separate studies (IOM, 2011). The goal of systematic review is to ensure that the review is complete, unbiased, reproducible, and transparent.

approach leverages data and creates a coherent context for consistent approaches across the portfolio of assessment products.

- **Enhanced Accessibility:** HERA will provide outreach and training within and outside EPA to build familiarity and access to the assessment workflows. Moving forward, modernized assessment workflows will be used to collaborate with other governmental agencies and authoritative bodies to share expertise and expand capacity around key workflow components.

Research Area 1: Science Assessment Development

The Science Assessment Development Research Area is focused on producing high quality, transparent, consistent, and scientifically-defensible assessment products to meet EPA's diverse statutory and policy needs. This research area largely comprises the portfolio of assessment products developed under well-established product lines (e.g., Integrated Science Assessments [ISAs], Integrated Risk Information System [IRIS] assessments, and Provisional Peer-Reviewed Toxicity Value [PPRTV] assessments), yet maintains the agility to produce emerging fit-for-purpose assessment products as prioritized by the Agency.

Combining the assessment products under Research Area 1 enables an overall integrated approach to planning and assessment development. By looking across the assessment space, instead of a siloed perspective (i.e., if research areas were organized by recognized product line [e.g., ISAs, IRIS, PPRTVs]), the program focuses on common steps⁶ of assessment development to more efficiently conduct the research and accommodate innovation and advances in assessment practices. This makes product development within the portfolio more cohesive and fluid. HERA's assessment practices are improved by incorporating resource and scientific capacity considerations upfront, so that fluctuating and escalating needs can be managed, ensuring HERA can deliver timely and responsive products.

All the products in Research Area 1 share a common feature of being developed in close coordination within the Agency. From inception and problem formulation, the assessment products are designed in coordination with EPA program and regional offices, in support of a statutory or policy need. Additionally, all the products in this research area are transparently available to the public and other stakeholders. Substances planned for assessment under the HERA program are listed in Appendix 2. These were identified through regulation⁷ (e.g., the Clean Air Act) or structured nomination processes⁸, and are enumerated on an annual basis.

Program, regional, state, and/or tribal needs. EPA and its partners and diverse stakeholders must make decisions to ensure human health and the environment continue to be protected from the known or potential adverse effects of exposure to environmental stressors—including environmental justice considerations. Such decisions span a large regulatory and non-regulatory landscape and require varying degrees of information: developing health-protective toxicity values to support air, water, and waste

⁶ Conceptually, assessment development comprises the same set of steps regardless of scientific discipline and varying evidence streams: scoping and problem formulation, identification of evidence (literature search and screening), study evaluation and data extraction, analysis, evidence integration, and presentation of conclusions.

⁷ See the following link for the NAAQS process and where the ISAs provide key scientific inputs in the early stages of review: <https://www.epa.gov/criteria-air-pollutants/process-reviewing-national-ambient-air-quality-standards>.

⁸ See the following link for the IRIS Program Outlook resulting from the annual solicitation for input on EPA program and regional office priorities (i.e., nominations) for assessment: <https://www.epa.gov/iris/iris-program-outlook>.

management programs; evaluating ecological effects and characterizing responses and impacts of exposure to one or more environmental stressors such as chemicals, land use change, disease, and invasive species; characterizing potential human health and environmental impacts during emergent situations; screening and prioritization of chemicals for monitoring at Superfund sites and in the air, water, soil, and sediment; characterizing increased susceptibility of early life exposures; evaluating health and environmental effects data to derive benchmark estimates; and interpreting and integrating different lines of evidence to support decisions to establish, retain, or revise national pollutant standards.

Output 1.1: Portfolio of interim assessment products to support decision making. HERA's science assessment development processes are highly coordinated with Agency program and regional offices to ensure assessment products are designed to support statutory or policy needs, are tailored to the specific decision or application context, and reflect the best available science and technology. Identification of substances for assessment development occurs through direct engagement with the EPA program and regional offices. For example, the high priority needs for future IRIS assessments are identified through an annual solicitation for input on program priorities, and PPRTV assessment needs are identified through a structured chemical nomination process with OLEM and the EPA regions. Delivery of timely interim assessment products, such as scoping and problem formulation materials and draft assessments, ensures that HERA is continually engaged with the user community as assessment products are being developed. These interim products are key steps to assessments. They provide the EPA and its partners and external stakeholders with solutions-focused and transparent deliverables that allow for continued engagement to shape the nature of the product and the context for its application, facilitating adaptive implementation and course correction as needed. Products under Output 1.1 may include Integrated Review Plans for NAAQS, IRIS Assessment Plans, Systematic Review Protocols, Evidence Maps, and External Review Drafts.

Output 1.2: Portfolio of final assessment products to support decision making. HERA's final assessment products delivered in Output 1.2 efficiently support a range of decisions, such as informing national standards, establishing clean-up levels at local sites, and setting advisory levels. This collection of fit-for-purpose and timely assessment products provides the integrated scientific evidence needed to characterize effects and potential impacts to human health and the environment. Output 1.2 provides high quality, transparent, state-of-the science, peer-reviewed assessment products (e.g., final Integrated Science Assessments [ISAs to inform the NAAQS], IRIS assessments, PPRTV assessments, etc.). Appendix 2 lists the current portfolio of substances identified for development of fit-for-purpose assessment products to inform decision making. Timelines for delivery of final assessment products are dependent upon statutory need, resourcing, and feedback. For example, delivery of the ISAs is coordinated with OAR in order to inform the setting of both the primary (human health-based) and secondary (welfare-based, e.g., ecology, visibility, materials) NAAQS as required every five years by sections 108(a)(2) and 109(d)(1) of the CAA.

Research Area 2: Science Assessment Translation

HERA's human health and environmental assessors serve as an Agency resource and respond to requests based on HERA assessment product applications, or requests through the ORD Superfund Technical Support Centers (TSCs). The Science Assessment Translation research area includes the range of tailored support activities, modules, and applications developed to address these requests for

technical support and consultation. Additionally, this is an avenue for identifying needs for customized development and administration of training (described in Research Area 4: Essential Assessment and Infrastructure Tools) related to elements of human health and environmental risk assessment. The science assessment translation provided within this research area is extensive, concrete, on-demand, and hands-on. Support primarily addresses Agency program and regional office needs, as well as states, tribes, other federal agencies, international entities, and other external stakeholders. This research area is integral for linking scientific research/assessment products from HERA to Agency decisions, developing critical awareness and linkages between the best available science and Agency decision makers. These linkages facilitate the application of best practices into Agency science assessments and the scientific community and serve as a dynamic conduit from application to research, and vice versa.

Program, regional, state, and/or tribal needs. Communities are faced with an urgent need for coordinated assistance to assess and address existing and emerging environmental challenges. EPA and its partners and stakeholders request, on an as-needed basis, technical support and consultation from ORD. These requests cover a wide variety of topics including those related to human health and environmental risk assessment, plus issues encountered in emergent, crisis-level situations and to address new and emerging Agency priorities. The HERA program provides technical support and consultation on topics related to human health and environmental risk assessment to support the EPA programs and regions, states, and tribes in applying HERA research products to their decision needs, and implementing HERA techniques and tools in their assessment processes. The intended users of the technical support include EPA program offices (OAR, OCSPP, OCHP, OLEM, OW), EPA regions, state environmental and public health agencies and risk assessors, and tribes. Additional groups, including the public, can also benefit from this technical support work in some instances. The HERA program responds to routine and emerging issues with expertise to translate research findings and data, scientific products, and methods to allow for action and, ultimately, timely decisions and effective solutions.

Output 2.1: Technical support to EPA regions and states through the Superfund Health Risk Technical Support Center (STSC) and Ecological Risk Assessment Support Center (ERASC). HERA will continue to provide technical assistance and support in the area of human health and environmental risk assessment for EPA's program offices and regions related to issues of concern at Superfund, RCRA, and Brownfield sites. ORD has five TSCs⁹ to support OLEM and EPA regions, and by extension the states and tribes, by supplying high-quality, quick-response technical support services. HERA manages two of the five ORD TSCs: the Superfund Health Risk Technical Support Center (STSC) and the Ecological Risk Assessment Support Center (ERASC)¹⁰. Although the STSC and ERASC each have their separate areas of expertise, the TSCs all work collaboratively to provide high quality technical support to the Agency. The STSC receives requests for technical assistance on an as-needed basis, which may include interpretation of guidance and assessments, lead (Pb) remediation assessment, complex analyses of surrogate chemicals for data poor chemicals of concern, and evaluation of published health values from EPA and other agencies (e.g., Agency for Toxic Substances and Disease Registry, ATSDR). The STSC publishes quarterly updates and annual reports, in addition to often complex responses to requests, in order to ensure that decision makers have the information necessary to protect the public health of potentially

⁹ For more information on EPA's Technical Support Centers see: <https://www.epa.gov/land-research/technical-support-centers>.

¹⁰ The three other TSCs support engineering, groundwater, and site characterization and monitoring requests. These TSCs are managed by ORD's Center for Environmental Solutions and Emergency Response and are supported by the Sustainable and Healthy Communities (SHC) research program.

exposed populations located near contaminated sites. The ERASC provides state-of-the-science technical information through the development of reports that address broad issues of concern relevant to ecological risk assessments and cleanups at contaminated sites, including Superfund and RCRA.

Output 2.2: Core translational research modules for expert technical support. The HERA program has established connections and a long history of responsive and effective technical engagement with programs, regions, states, tribes, other federal agencies, international entities, and the scientific community. Consequently, the program realizes the importance of having an infrastructure that addresses the criticality and timing of general and specialized technical support. Application of assessment science, beyond the standing assessment product lines, requires the expertise, technical consultation processes, and techniques ready to support risk assessment actions of the EPA program and regional offices who are developing documents for their risk-based decisions. For example, HERA is providing significant technical support for the first 10 Risk Evaluations and the next set of 20 chemicals prioritized under the Lautenberg Chemical Safety for the 21st Century Act, which amended the Toxic Substances Control Act (TSCA). This technical assistance for TSCA can be in the form of evidence maps for the individual chemicals, benchmark dose (BMD) modeling for use in risk evaluations, and transmittal memos providing detailed and expert consultation on scientific issues. Another example is the technical support provided to OAR for addressing scientific issues related to toxicity that arise in the regulation of air toxics under Section 112 of the CAA. Such support can take multiple forms, including development of technical memos or other information that can be made available as part of the public record supporting regulatory actions.

This technical support work is difficult to foresee or plan in the StRAP and requires implementation of responsive strategies and workflows under sometimes high-pressure time demands. HERA is therefore building on the existing technical support infrastructure by developing tools and approaches that will increase readiness to respond efficiently when needs are identified. The program will develop and refine strategies, workflows, and infrastructure, as well as best practices to organize and manage expert technical units of staff to facilitate responsiveness, without the undue delays that can result from the need to develop impromptu approaches. This includes using project management techniques, ensuring the readiness of disciplinary workgroups to provide the technical support, and maintaining constructive connections across ORD experts and coordinators.

Topic 2: Advancing the Science and Practice of Risk Assessment

The HERA program is multidisciplinary and aimed at incorporating scientific innovations to advance analytic approaches and applications for assessments. Research under this topic encompasses efforts to enhance hazard identification, expand the repertoire of dose-response methods and models, and characterize the utility of emerging data and new computational tools as applied to risk assessment. These actions all implement the vision of increasing transparency and reducing uncertainty in assessment science and accelerating the pace of assessment development. These activities are supported by maintenance of critical assessment infrastructure, including databases, models, and software support, to ensure transparency and facilitate understanding and translation to EPA and its partners and external stakeholders.

Topic 2 research addresses gaps observed in the assessment activities undertaken in response to specific needs under Topic 1. Refinements and updates to current approaches will be anchored in assessment

development and are expected to improve the accuracy, efficiency, flexibility, and utility of applications across the large landscape of assessment activities. These research advancements, when illustrated and applied within assessments, will provide new information and demonstrate approaches to the scientific community for consideration by a variety of users. Anticipated users include the EPA's Risk Assessment Forum (RAF), in their role of sharing risk assessment knowledge and approaches across the Agency through the development of Agency-wide risk assessment guidance and methods.

Research Area 3: Emerging and Innovative Assessment Methodologies

Technological and scientific advances in data-driven approaches can address the needs of EPA program offices and regions, states, and tribes by accelerating the pace and transparency of assessments. This research area is aimed at incorporating new and innovative methodologies related to areas including adverse outcome pathways (AOP) and predictive toxicology, rapid evidence evaluation, systematic review, and toxicokinetic and dose-response modeling. These innovative methodologies can be applied across a variety of decision contexts and assessment products covered by HERA. Methods development will address advancement in the use of traditional human and animal data, with a focus on the nature and dynamics of chemical toxicokinetics (e.g., absorption, distribution, metabolism, and excretion) and dose-response methodology, taking into consideration susceptible populations and lifestyles. It will also include the use of *in vitro* data, AOP, and new approach methodologies (NAMs). Advancements in both new and established data streams are needed to improve human health and environmental risk assessment.

The outputs will focus on evaluating and optimizing integration of existing, new, and emerging data streams, techniques, models, tools, or other methodologies for practical implementation in assessing human health and the environment. By clearly articulating the scope, strengths, uncertainties, and assumptions in the application of these methods and approaches, confidence in their utility in the context of risk-based decision making will increase. Ensuring that these methods and approaches are applicable to a range of HERA-relevant product types and decision scenarios is critical for understanding how best to incorporate them into risk assessment.

Program, regional, state, and/or tribal needs. The large universe of legacy substances and chemicals in commerce being measured in the environment, combined with the scarcity of *in vivo* toxicity data for risk assessment purposes, places a significant burden on the Agency and its external stakeholders in assessing the risks of chemicals. Many ongoing and recent advancements have centered around managing the vast amounts of new data and computational tools that have been generated to support chemical risk assessment, as described in the National Research Council's (NRC) 2007 report entitled, "*Toxicity Testing in the 21st Century: A Vision and a Strategy*" (NRC, 2007). The EPA Administrator's 2019 [Directive to Prioritize Efforts to Reduce Animal Testing](#) also committed the Agency to reducing, replacing, and refining animal testing requirements and prioritizing application of alternatives to animal testing into risk assessment. To fulfill this goal, new technological and scientific advances need to be integrated into existing risk assessment frameworks to inform regulatory and non-regulatory decision making. For example, EPA and international regulatory agencies have initiated collaborative case studies focused on considering and applying emerging science in regulatory decisions in order to accelerate the pace of chemical risk assessment (Kavlock et al. 2018). Improved tools and refined methods also continue to be needed to evaluate the many substances of current interest where the available data primarily result from traditional human and animal studies. Both efforts—interpretation of new data streams and improvements in the assessment of traditional data—are necessary and complementary in

supporting Agency decision making. These new and emerging techniques need to be incorporated into the broader context of existing tools, approaches, workflows, and EPA guidance in order to expedite their use in assessments. Additionally, identifying and framing the strengths and limitations of these emerging approaches and data types, in relation to existing approaches, will provide clarity on their utility in different scenarios, along with methods to increase their transparency and understandability.

Output 3.1: Advance, translate, and build confidence in the application of new approach methods (NAMs) and data in risk assessment. EPA programs and regions are often tasked with addressing the potential hazard(s) to human health and the environment from contaminants for which little-to-no data exist (e.g., OLEM's assessment of Superfund and other contaminated sites and OW's Unregulated Contaminant Monitoring Rule [UCMR] efforts). Problem formulation in this context entails basic identification of hazard and associated dose-response analysis to inform various risk assessment actions, from screening and prioritization to quantitation. Considering the lack of repeat-dose toxicity data for a significant number of potentially hazardous chemicals of interest, the utility and availability of new assays and NAMs needs to be leveraged to fill critical data gaps directly responsive to decision-maker needs across EPA programs and regions. Additionally, the Administrator's 2019 *Directive to Prioritize Efforts to Reduce Animal Testing* accelerates EPA's commitment to reduce reliance on animal testing, propelling EPA to innovate, develop, and incorporate new assays and/or NAMs as alternatives to animal testing into risk assessments.

This output encompasses the research required to use and build confidence in the application of information and data from NAMs into risk assessment. This includes results of *in vitro* and *in silico* approaches, -omics or high-throughput screening (HTS) technologies, and concepts in chemical grouping, read-across, and adverse outcome pathways. The anticipated products generated from this output include scientific publications on methods development and proof-of-concept case studies. The products will inform and facilitate the interpretation and characterization of how data from NAMs may ultimately be used to assist in the identification of chemical hazards and quantitative estimates for fit-for-purpose risk assessment applications. This output involves coordinated and collaborative research efforts between scientists within the HERA and CSS national research programs. It will build on data and science generated in CSS to develop assessment solutions within HERA. It will develop approaches to integrate data from new assays and NAMs into human health assessment products and technical support efforts conducted within the HERA program to meet chemical assessment needs. Examples include enhanced data access through interoperability with the CompTox Chemicals Dashboard, and greater harmonization of read-across approaches between the programs.

Output 3.2: Conduct case study applications of rapid assessment methodologies to inform parameters of interest to risk-decision contexts. Output 3.2 includes coordination with CSS on RapidTox. Rapid assessment methodologies need to be developed to integrate evidence from a variety of data streams to inform human health and environmental risk assessments in a manner that is flexible, 'fit-for-purpose,' and responsive to the demands of the Agency and its partners and external stakeholders. The nature of the decision context and acceptable level of uncertainty should be the primary drivers for determining the scope of how different data and tools can be leveraged and applied to support rapid evidence evaluations. The proposed products will provide the foundational research and understanding of these methodologies and approaches, characterizing their advantages, disadvantages, and limitations, to help frame decisions about the types of assessments needed to address EPA's priorities. Practical examples and case studies will be utilized to further develop and refine methodologies for

rapid assessment, and to establish their implementation across a range of HERA products and ongoing activities. This includes the coordination and joint development of the RapidTox Dashboard with CSS, including case study applications for use in HERA hazard-decision contexts.

Output 3.3: Evaluate and develop improved methods for dose extrapolation and the related uncertainty characterization in human health risk assessment via classical methods and integration of pharmacokinetic (PK) models. Pharmacokinetic models are an important component of risk assessments. They can simulate the prediction of an internal dose at a target site from an external chemical exposure, and increase the toxicokinetic understanding and the ability to quantitatively evaluate uncertainties and human variability across various populations and lifestages, including those that are considered susceptible. Physiologically-based pharmacokinetic (PBPK) models are used in supporting quantitative risk assessments, including HERA assessment products and other EPA program office assessments. It is important that these PBPK models be evaluated for potential use; this involves performing often time-consuming quality assurance (QA) evaluations of models selected and integrating model analyses into risk calculations. Estimates of model uncertainty can also differ depending on the model details and available data. In particular, as high-throughput toxicokinetic (HTTK) modeling tools are now becoming mature, risk assessors should be prepared in certain circumstances to apply such models, with appropriate adjustment for uncertainty, in the absence of *in vivo* PK data or more sophisticated model structures. Products from Output 3.3 will strive to decrease the level of effort required to conduct a QA review of essential PBPK models and evaluate uncertainty associated with potential PK model or dosimetry extrapolation approaches (e.g., allometric ($BW^{0.75}$) scaling, use of *in vitro-in vivo* extrapolation (IVIVE) of chemical-specific data, and PBPK models).

Output 3.4: Advance methods for systematic review, including evidence integration. Systematic review approaches are being embraced across the Agency to enhance transparency of human health and environmental risk assessment activities. The use of systematic review methods improves the defensibility of HERA assessment products, making them more useful for informing EPA decisions. While many aspects of systematic review are now being used in HERA health-hazard assessments, some remain in the early stages of development, including how to systematically evaluate mechanistic evidence and approaches for drawing summary evidence integration conclusions across lines of evidence. The application of these systematic approaches to other aspects of HERA-relevant science, including environmental assessments (e.g., ecological) and considerations for dose-response analyses, are only just being envisioned. There are common steps upon which to integrate both human health and environmental assessment practices. Conceptually, the same set of steps makes up the backbone of assessment development regardless of scientific discipline and evidence stream: scoping and problem formulation, identification of evidence (literature search and screening), study evaluation and data extraction, analysis, evidence integration, and presentation of conclusions. It is around these steps that the HERA program will begin integrating systematic review across human health and environmental assessments. Ultimately, HERA and others in the Agency need reliable systematic review approaches that are scientifically sound and can be operationalized in a reasonably consistent manner across assessment products. This output will address and advance some of the existing areas of uncertainty in applying systematic review methods to human health and environmental assessments through products, such as case studies. In addition to developing and optimizing systematic review methods, training is needed for staff in EPA programs and regions, states, and tribes on how to consider and interpret work products developed using systematic review methods (Output 4.2). Similarly, it is critical

to link HERA systematic review methods with existing and emerging efforts to advance new approach methods (Outputs 3.1 and 3.2) and dose-response analysis (Output 3.5), and the development of software tools (Output 4.1). Thus, products within Output 3.4 are closely mapped and interdependent with efforts in these other outputs. Building on prior HERA trainings and collaborations on systematic review, these products will be developed in consultation with EPA programs (e.g., OW, OLEM, and OCSPP), regional risk assessors, and state environmental health agencies.

Output 3.5: Advance methods in dose-response modeling with application to risk assessment. Dose-response modeling is a critical step in a human health assessment, where data from toxicological and epidemiologic studies are modeled for the purpose of establishing points of departure (PODs) used in deriving toxicity values. Although existing methods have improved upon older methodologies (e.g., benchmark dose modeling supplanting the No-Observed-Adverse-Effect-Level methodology), many unresolved issues, uncertainties, and complications remain that require targeted research. This output proposes multiple products that will augment the HERA program's dose-response modeling capabilities, thereby benefitting consumers of HERA human health assessments and/or software products, both within and outside the Agency. This output will address issues related to current modeling practices, such as research into priors for use in Bayesian model averaging, development of a unified suite of models across dichotomous and continuous data, considerations of population incidence of adverse health effects (e.g., for benefit-cost analysis), and application of trend testing for hazard and dose-response purposes. Beyond this, the output will include methods development research on critical expansions to current modeling capabilities, including the consideration of susceptible populations through the development of nested continuous models for continuous developmental toxicity data (e.g., fetal weight), development of multivariate BMD modeling that can be applied to correlated health endpoints (e.g., developmental endpoints, toxicogenomic data), use of high-throughput *in vitro* data to predict *in vivo* dose-responses and derive provisional reference values, exploration of approaches to quantify noncancer risks at environmentally-relevant doses for both animal and human data, and development of methods to quantitatively combine animal and human data for dose-response purposes. These proposed research products will result in dose-response methods that are more precise, robust, and responsive to various needs.

Research Area 4: Essential Assessment and Infrastructure Tools

The portfolio of diverse and multidisciplinary assessment products encompassed in the HERA program are developed through the application of state-of-the-science approaches by knowledgeable experts. This requires the use of software and database tools to provide the necessary infrastructure and to facilitate efficient and transparent assessment development under systematic review methodologies. Models and tools are used to provide the critical link between chemical exposures and estimates of internal dose in order to translate and interpret hazard information. These essential tools facilitate the development of high-quality, transparent, consistent, and scientifically-defensible assessment products. Outputs and related products included in this research area will enable the maintenance and development of new or existing tools and databases used in the assessment process, along with training on these resources and applications. This infrastructure will also be central to HERA's ability to integrate its products with the CSS research program's dashboards and computational tools. Infrastructure tools will allow for broader sharing of assessment materials, products, and practices with others with common interests in assessments. The infrastructure investment ensures that the assessment tools are

relevant, state-of-the-science, well-maintained, and customized for consistent and efficient assessment development and implementation.

Program, regional, state, and/or tribal needs. Software tools and database applications serve as important infrastructure to routinely and consistently provide the high-quality assessments needed by EPA programs, regions, states, and tribes. This research and the subsequent products will maintain existing infrastructure, develop new infrastructure, and provide training in a variety of formats for the use and application of tools, databases, and other state-of-the-science modules in assessment development. This integration and advancement of science and technology can enhance community engagement by translating scientific results into useful information, and give stakeholders improved access to environmental science applicable to decision processes.

Output 4.1: Innovate, develop, and maintain a suite of essential software and support tools for risk assessment. The development of rigorous, transparent, and timely assessments to inform EPA actions requires consistent and reliable infrastructure, including software tools and databases. This output will maintain and continue the development of assessment infrastructure related to each step in assessment development: scoping and problem formulation, identification of evidence (literature search and screening), study evaluation and data extraction, analysis, evidence integration, and presentation of conclusions. Existing tools and databases that have historically supported assessment development will continue to be maintained and enhanced, including the [Health and Environmental Research Online](#) (HERO) database and [Benchmark Dose Modeling Software](#) (BMDS); information toolboxes for exposure science and ecological risk assessment (e.g., [EPA-ExpoBox](#), [EPA-EcoBox](#)) and graphical visualization of estimates of relative exposure and aggregate exposure sources within and across lifestages (e.g., ExpoKids); and models and application support (e.g., Integrated Exposure, Uptake, Biokinetic [IEUBK] model, All Ages Lead model [AALM]). Notably, the AALM, which estimates lead exposures from various media and lead concentrations in blood and other tissues from infancy through adulthood up to 90 years of age, demonstrates the advancement of tools to better estimate exposures to susceptible populations. As new tools and approaches are developed to support assessment needs, this output will provide new infrastructure and ensure interoperability among tools and databases (e.g., HAWC). This infrastructure of interoperable tools and databases will streamline assessment workflows and yield greater efficiency and consistency in developing high-quality, decision-relevant, and defensible assessment products and technical support.

Output 4.2: Innovate, develop, and maintain a training program on the advances in risk assessment and systematic review. Increasing the transparency, efficiency, and scientific rigor of assessment products developed by the HERA research program relies on expertise in current risk assessment methodologies and the support of data access, management, and analysis software and computational tools. Some systematic review methodologies are particularly reliant on software tools that have been developed and operationalized to optimize steps within the systematic review workflow. This output is designed to further develop, implement, and share tailored training products and modules with EPA program and regional staff, partners, and external stakeholders, and to impart literacy and understanding of integrated concepts in risk assessment and tool implementation. This output will develop and maintain a training program on the advancements in human health and environmental assessments via fit-for-purpose modules. These training modules will provide easy access and enhanced partner and external stakeholder engagement for the underlying operational procedures and qualitative and quantitative analyses conducted for human health and environmental assessments produced by the

HERA program. The training program facilitates transparent engagement by increasing and accelerating end-user understanding of HERA tools and concepts.

Program Design

HERA Program Components

In the [FY 2018-2022 U.S. EPA Strategic Plan](#), emphasis is placed on the EPA's Back-to-Basics agenda and applying the rule of law to increase efficiency and effectiveness in Agency activities. In accordance with these priorities, the HERA StRAP was developed to ensure that assessment products are aligned with specific statutory needs of the Agency. HERA will strive to accelerate the pace of assessment product development to assist the Agency in meeting deadlines.

In FY 2018-2019, HERA modernized its approaches by: developing and institutionalizing assessment workflows that are problem formulation-driven; pragmatically implementing systematic review; providing extensive training to HERA scientists and partners; and incorporating technology, software tools, and databases. HERA also transitioned toward developing a portfolio of assessment products, and away from a "one-size-fits-all" approach, to ensure that HERA assessment products will be fit for their intended purpose or decision context, tailored for use, and matched to the current regulatory agenda and any court-ordered deadlines. This approach is consistent with the concept of 'fit-for-purpose' assessments that is increasingly being promoted in the risk assessment field. To maximize HERA's outreach and service, points of contact will be identified for each assessment product needed by an EPA program or regional office. The HERA program and assessment leads will work with partners to understand the context of the decision need, which will then shape the nature of the product and the timeline for its delivery. Frequent check-ins will be incorporated to ensure alignment and allow for course correction, as needed.

HERA will further apply best practices, automation, and computational tools to promote greater throughput and higher productivity overall. This is expected to result in significant increases in speed, transparency, and access to research products. HERA provides in-depth training for staff to energize the culture of change and has incorporated continuous training and train-the-trainer modules into the workflow. In addition, a matrix of cross-HERA workgroups with discipline-specific scientific expertise will be established to ensure that consistent and high-quality products are delivered. Using project and program management tools, HERA will optimize resource allocation and management, which are critical considerations when many of the research activities have overlapping priorities and timelines. Importantly, HERA will maintain a flexible posture and adaptive capacity in order to respond to urgent or unforeseen issues, needs, and priorities in real-time.

The FY 2019-2022 HERA StRAP has a recalibrated focus on developing assessment products and providing the scientific and technical support for applying them to specific decision contexts and throughout all points in the decision making process. In tandem with the assessment products, HERA is investing in advancements in the science and practice of risk assessment that are anchored in assessment development, ensuring that the research remains solutions-focused and driven by the needs of EPA and its partners, external stakeholders, and the public.

Solutions-Driven Research

Consistent with ORD strategies, HERA is renewing and expanding its commitment to produce research that addresses real-world problems and helps EPA and its partners and external stakeholders make timely decisions based on science. This commitment includes exploring ways to improve research processes through the application of a solutions-driven research framework by emphasizing planned partner engagement throughout the research process, starting with problem formulation and informing all elements of research planning, implementation, dissemination, and evaluation. Application of research outputs in cooperation with partners allows the HERA program to test the feasibility, appropriateness, meaningfulness, and effectiveness of the research to solve complex environmental problems. External engagement also provides opportunities to discuss research needs and priorities within the scientific community. A solutions-driven framework highlights the opportunities for close collaboration across ORD research programs, particularly linkages to CSS for high-throughput and NAMs research to respond to identified assessment needs.

ORD is adopting a three-pronged strategy to implement a solutions-driven research framework:

- 1) Apply principles of solutions-driven research broadly across ORD's six national research programs;
- 2) Conduct pilot projects that apply and evaluate methods of solutions-driven research to planning, conducting, applying, and evaluating integrated research that addresses a well-defined and unmet need of partners and stakeholders; and,
- 3) Conduct case studies of previous and current research activities that embody the principles of solutions-driven research, which will help inform a list of best practices.

Risk communication is a central factor in solutions-driven research, allowing people to understand their risks and adopt protective behaviors, as well as informing risk management decisions. ORD will apply advances in the science of risk communication as well as best practices for communicating risk to different audiences across the six national research programs.

Integration Among National Research Programs

EPA's six national research programs work together to identify and address science challenges. Coordination efforts can range from formal integration across the national research programs to collaboration among EPA scientists working on related issues. There are several national research program goals that are relevant to HERA activities. For example, the A-E goal, to assess human and ecosystem exposures and effects associated with air pollutants on the individual, community, regional, and global scale, and the SSWR goal, to support safe drinking water by focusing research on assessing the health impacts of known and emerging chemical and biological stressors, are congruent with HERA program activities. Similarly, several SHC goals correspond with HERA research: providing support to the states and tribes through technical support centers for remediating CERCLA-designated contaminated sites and returning them to productive use; assisting regional, state, tribal, and local leaders in reducing costs and setting science-based cleanup levels in areas designated under CERCLA; characterizing sites and contaminants released from leaking underground storage tanks (LUST) identified under the LUST Trust Fund; and assessing the impact of pollution (e.g., health impact assessments) on vulnerable groups

such as children, tribes, environmental justice communities, and other susceptible populations. More explicit interactions between HERA and CSS or HSRP are described below.

HERA and CSS Integration

Both the Chemical Safety for Sustainability (CSS) and HERA national research programs inform Agency activities related to chemicals and have a history of collaboration and co-evolution. The 2016 Lautenberg Amendment of TSCA brought about several new drivers for further evolution and integration. The new law provides mandatory requirements for EPA to: evaluate existing chemicals with clear and enforceable deadlines; conduct risk-based chemical assessments with consideration of potentially exposed or susceptible subpopulations (such as infants, children and pregnant women, workers, or the elderly), as well as inclusion of developmental lifestages as part of study design; translate new assays, AOPs, and NAMs to enhance their use in risk assessment; and increase public transparency for chemical information. HERA-CSS integration is expected to be a key outcome of ORD's FY19-22 strategic research planning cycle and will advance development of methods for application of new data streams in risk assessment. For example, the joint HERA-CSS development of the RapidTox Dashboard, including the underlying workflows and application considerations, allows decision makers to access and integrate available chemical-specific information in fit-for-purpose applications, such as scoping, screening, prioritization, and/or assessment. Incorporation of systematic review products and advanced assessment methodologies into RapidTox and the [CompTox Chemicals Dashboard](#) enhances the opportunity for more robust integration.

HERA and HSRP Integration

Both the Homeland Security Research Program (HSRP) and HERA share responsibility for providing reliable and timely chemical hazard information to federal, state, tribal, and local decision makers to ensure communities can respond to emergency threats. In coordination with OLEM, HERA and HSRP will collaborate on the development of an emerging fit-for-purpose assessment product, provisional advisory levels (PALs) to support risk-based site-specific decisions during emergency response incidents, that can aid in making critical decisions on site access. This emerging assessment product will be produced under HERA's Research Area 1: Science Assessment Development and HSRP's Research Area 1: Contaminant Fate, Transport, and Exposure.

HERA and Risk Assessment Forum Integration

EPA's Risk Assessment Forum (RAF) and the HERA program share the goals of addressing risk assessment issues and advancing approaches to risk assessment. EPA's RAF facilitates the sharing of risk assessment knowledge and approaches throughout the EPA, while harmonizing Agency risk assessment practices by developing Agency-wide risk assessment guidance and methods. Experts within HERA serve as Forum members, ensuring cross-communication. Through this partnership, key scientific issues in risk assessment across the Agency can be identified as potential research needs to the HERA program, and advancements made within HERA can be shared with risk assessment experts and practitioners across the Agency.

Cross-ORD Integration

In addition to the output-specific connections detailed above, HERA integrates with the five other national research programs (i.e., A-E, CSS, HSRP, SHC, and SSWR) through collaboration on its assessment activities, including incorporation of research results and characterization of new

applications of data and tools. Several cross-ORD strategic areas have also been identified. Examples of the interconnectivity around these strategic areas include:

Nutrients: The cross-ORD nutrient research efforts in the national research programs are focused on reducing excess nutrient loadings that can cause adverse environmental and human health effects. ORD's nutrient research uses an integrated approach that spans media (water, land, and air), types of surface water bodies and groundwater resources, and temporal and spatial scales. This effort develops and applies scientific information and tools to enable states, tribes, and their EPA program office and regional partners to develop cost-effective regulatory and non-regulatory approaches to nutrient reduction. HERA's assessment of atmospherically-deposited oxides of nitrogen on surface water quality draws upon and contributes to this cross-cutting research area.

PFAS: The cross-ORD PFAS research effort addresses the priorities of [EPA's Per- and Polyfluoroalkyl Substances \(PFAS\) Action Plan](#) and provides the science to 1) understand human health (including children) and ecological effects of PFAS; 2) evaluate PFAS occurrence, fate and transport, and exposure; and 3) reduce, remove, and remediate PFAS in the environment (U.S. EPA, 2019a). In this context, HERA will provide toxicity values for a number of relatively data-rich PFAS and contribute to the Agency's efforts to increase knowledge and translation of PFAS toxicity information. In addition, HERA will work with scientists across EPA on PFAS-related activities and collaborate with CSS to develop approaches for high-throughput toxicity evaluations of data-poor PFAS.

Lead: The cross-ORD lead (Pb) research effort is focused on answering the question: "How can EPA mitigation efforts/techniques and coordinated multimedia assessments most effectively reduce exposures and blood lead levels for children in the United States?" ORD's highest priorities with respect to lead include: 1) identifying the most highly exposed communities for targeting intervention actions; 2) generating critical data on the geographic distributions of media-specific lead exposure sources, key exposure factors, bioavailability, and bioaccessibility; 3) updating and evaluating multimedia exposure models for regulatory action; and 4) developing corrosion control strategies, drinking water sampling protocols, and methods to diagnose water distribution system issues. The ORD effort is designed to support the [Federal Action Plan to Reduce Childhood Lead Exposures and Associated Health Impacts](#), under "Goal 4: Support and conduct critical research to inform efforts to reduce lead exposures and related health risks" (U.S. EPA, 2019b). HERA's research contributes to this cross-ORD effort by producing the ISA for the lead (Pb) NAAQS, developing and applying lead models for regulatory decision making, emphasizing children's health concerns, and providing site-specific technical support at contaminated sites.

Wildland Fires: Wildland fires are a persistent and pervasive multimedia issue. Research over the next several years will provide improved understanding of wildland fire impacts on public health and the environment and inform approaches to reduce exposures and risks. An integrated approach will help us better understand the growing importance of wildland fires, identify vulnerable ecosystems and populations (including children's health), and develop effective risk communication and mitigation strategies. HERA's research in health and environmental impacts of air and water pollution will contribute directly to this cross-cutting topic.

Resilience: The cross-ORD resilience effort is focused on integrating ORD's work preparing for and recovering from disasters, including extreme weather events. This research will deliver metrics, methods, and tools that EPA programs, states, tribes, and communities can use to assess their own

vulnerability to, preparedness for, and response and recovery from environmental releases and other conditions due to extreme weather and other disasters. HERA's research will advance the Agency's ability to assess disasters and address resilience and preparedness with respect to immediate emergency response and long-term planning for resilient communities.

Conclusion

Consistent with EPA's FY2018–2022 Strategic Plan, HERA will continue to work closely with EPA program and regional offices, as well as states and tribes, to identify their highest priorities and provide the tailored assessment products and scientific and technical support needed to meet their statutory and regulatory goals. This StRAP maps out the innovations in assessment development and translation science that will be implemented to best position the HERA research program to provide this level of scientific support to the Agency, while maintaining the leading edge of assessment science. HERA is committed to advancing the science and practice of assessments, thereby increasing the confidence, transparency, and pace of assessment products. By fully engaging EPA program and regional offices, HERA will produce fit-for-purpose assessment products that are reliable, decision-relevant, state-of-the-science, transparent, and high-quality. These products will be used to support important and complex Agency decisions to evaluate potential impacts to human health and the environment. HERA's products will advance risk assessment methods and increase confidence in the application of science to support critical Agency decisions.

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Appendices

Appendix 1: State Needs Reflected in ORD Research Planning

The table below lists state needs relevant to the HERA research portfolio, which were identified in the Environmental Council of the States (ECOS) 2016 and 2018 surveys¹¹, and through ORD’s direct outreach to the states¹² in the spring of 2018. These needs are aligned to the research areas planned in the HERA StRAP.

Source	State Need	HERA’s Relevant Research Areas & Example Products
Water		
ECOS 2016 and 2018 Surveys	Water Quality/Surface Water Quality/Groundwater Quality	RA-1 Science Assessment Development. A portfolio of assessment products, including applications of systematic review and evidence mapping to inform priorities.
	Safe Drinking Water and Wastewater Disinfection Byproducts	RA-1; RA-2 Science Assessment Translation. A portfolio of assessment products, including PFAS, arsenic, and chromium. Scientific and technical support.
Cross-Media Emerging Contaminants		
ECOS 2016 and 2018 Surveys	Lack of information on health effects and risk values for chemicals of emerging concern (e.g., PFAS) and existing chemicals	RA-1; RA-3 Emerging and Innovative Assessment Methodologies. A portfolio of assessment products to provide new risk values, including PFAS. Use of systematic review, evidence mapping, and new alternative data/tools to identify and evaluate chemicals of emerging concern, including rapid evaluations. RA-4 Essential Assessment and Infrastructure Tools (models, tools, databases). Modeling and modeling support.

¹¹ The Environmental Research Institute of the States (ERIS) Results of 2018 Biennial Survey on State Environmental Research Needs can be found at: <https://www.ecos.org/wp-content/uploads/2019/04/2018-ERIS-Survey-Summary.pdf>

¹² ORD released a report summarizing how ORD research has supported states in their efforts to protect human health and the environment, entitled: *U.S. EPA Office of Research and Development and Environmental Council of the States: Partners for Meeting State Research Needs, February 2019 Update*. For more information see: https://www.epa.gov/sites/production/files/2018-12/documents/state_stories_december_12_2018.pdf.

Source	State Need	HERA's Relevant Research Areas & Example Products
Air Quality		
ECOS 2016 and 2018 Surveys	Clean Air/Air Quality, including Ozone	RA-1; RA-2. A portfolio of assessment products, including Integrated Science Assessments for NAAQS, and scientific and technical support to translate, interpret, and apply the underlying science.
Waste/Remediation		
ECOS 2016 and 2018 Surveys	Vapor Intrusion	RA-2. Technical and scientific support to translate and apply assessment products.
	Chlorinated solvent groundwater plumes	RA-2. Technical and scientific support to translate and apply assessment products.
Other Support		
Direct State Outreach	Training	RA-2; RA-4. Scientific and technical support; tailored and targeted training programs that include remote learning and on-site multi-day training on topics in assessment workflow, including systematic review, evidence mapping, and support for PBPK modeling. Recent examples include NJ, TX, and CA.

Appendix 2: Environmental Substances Identified for Assessment Under the HERA program

The following table lists the environmental substances formally nominated by EPA program offices for development of fit-for-purpose assessment products to inform decision making. The interim and final assessment products associated with these substances are captured under planned outputs 1.1 and 1.2. The topics for assessment will be enumerated on an annual basis as informed by Agency priorities and HERA resources.

Substance	Nominating National Program Offices, and (Interested Offices ¹³)
<u>Integrated Risk Information System (IRIS) Assessments</u>	
Chloroform	OAR (OLEM, OCHP)
Vanadium Compounds and Vanadium Pentoxide	OAR, OW (OLEM)
Inorganic Arsenic	OW, OLEM (OCHP)
Polychlorinated Biphenyls	OLEM (OCHP)
Methylmercury	OLEM (OCHP)
Hexavalent Chromium	OW, OLEM (OCHP)
Ethyl tertiary butyl ether (ETBE)	OAR, OLEM, OW
Tert-Butyl Alcohol	OAR, OLEM, OW
Perfluorononanoate (PFNA)	OW, OLEM (OCHP)
Perfluorobutyrate (PFBA)	OW, OLEM (OCHP)
Perfluorohexanoic acid (PFHxA)	OW, OLEM (OCHP)
Perfluorohexane Sulfonic Acid (PFHxS)	OW, OLEM (OCHP)
Perfluorodecanoate (PFDA)	OW, OLEM (OCHP)
Inorganic Mercury salts	OLEM (OCHP)
<u>Integrated Science Assessments (ISA)</u>	
Particulate Matter	OAR
Ozone	OAR
NOx/SOx/PM Ecological Criteria	OAR
Lead	OAR
Nitrogen Oxides – Health Criteria	OAR
Sulfur Oxides – Health Criteria	OAR
Carbon Monoxide	OAR
<u>Provisional Peer-Reviewed Toxicity Value (PPRTV) Assessments</u>	
Ammonium picrate	OLEM
Vinyl bromide	OLEM
1-Bromo-2-Chloroethane	OLEM
3,5-Dinitroaniline	OLEM
Inorganic phosphates (monovalent salts)	OLEM
Benzo(e)pyrene	OLEM
Isobutyl alcohol	OLEM
Aluminum phosphate salts	OLEM
Ammonium phosphate salts	OLEM
Amino-2,6-dinitrotoluene, 4-	OLEM
Amino-4,6-dinitrotoluene, 2-	OLEM
Tetramethylphosphoramidate, N,N,N',N'-(TMPA)	OLEM
Phthalic Acid, p-	OLEM
Pentamethylphosphoramidate (PMPA)	OLEM
Pentaerythritol tetranitrate (PETN)	OLEM

¹³ Interested and supporting offices include the EPA offices, not designated as National Program Offices, that expressed interest in the development of fit-for-purpose assessment products to inform decision making for certain substances (e.g., OCHP who is interested in IRIS assessments for chloroform, inorganic arsenic, polychlorinated biphenyls, methylmercury, hexavalent chromium, multiple PFAS [PFNA, PFBA, PFHxA, PFHxS, PFDA], and inorganic mercury salts).

Substance	Nominating National Program Offices, and (Interested Offices ¹³)
Glycidaldehyde	OLEM
Dichloroethylene, cis & trans, 1,2-	OLEM
Crotonaldehyde, trans-	OLEM
Other Toxicity Assessments	
Perfluorobutane Sulfonic Acid (PFBS)	Agency

Appendix 3: Summary of Proposed Outputs for the HERA Research Program in FY2019-2022

The following table lists the proposed, high-level, strategic outputs (including proposed delivery timeframes) for the HERA National Research Program, organized by topic and research area. The outputs may change as new scientific findings emerge. Outputs are planned on a rolling basis, and delivery dates will be identified by individual products, as informed by Agency timing needs and HERA budget appropriations. The HERA research program will continue to engage throughout the research implementation phase as specific products are identified and developed to achieve the research area and output objectives.

Research Area	Program, Regional, State and/or Tribal Need	Output Title
Topic 1: Science Assessments and Translation		
1. Science Assessment Development	Fit-for-purpose assessment products to inform decision making.	1.1 Portfolio of interim assessment products to support decision making (FY20, 21, 22) <i>Fit-for-purpose assessment products (including ISAs, PPRTVs, IRIS, and other targeted assessments) to be enumerated on an annual basis as informed by Agency timelines and HERA resources.</i>
		1.2 Portfolio of final assessment products to support decision making (FY20, 21, 22) <i>Fit-for-purpose assessment products (including ISAs, PPRTVs, IRIS, and other targeted assessments) to be enumerated on an annual basis as informed by Agency timelines and HERA resources.</i>
2. Science Assessment Translation	Solutions and technical support for CERCLA, RCRA, and Brownfield contaminated sites	2.1 Technical support to EPA regions and states through the STSC and ERASC (FY20, 21, 22)
	Technical support to translate, tailor, and apply assessment products (especially for local scale issues)	2.2 Core translational research modules for expert technical support (FY22) <i>For interpretation and application of assessment products.</i>
Topic 2: Advancing the Science and Practice of Risk Assessment		
3. Emerging and Innovative Assessment Methodologies	Approaches to evaluate, use, and apply data and science from new approach methods and alternatives to animal testing to risk assessments	3.1 Advance, translate, and build confidence in the application of new approach methods (NAMs) and data in risk assessment (FY22)

Research Area	Program, Regional, State and/or Tribal Need	Output Title
	that support statutory and regulatory decision making	
	Approaches to accelerate the pace of chemical risk assessment	3.2 Conduct case study applications of rapid assessment methodologies to inform parameters of interest to risk-decision contexts (FY22) <i>Includes coordination with CSS on RapidTox.</i>
	Improved approaches and augmented capacity for quantitative risk assessments and dose extrapolations	3.3 Evaluate and develop improved methods for dose extrapolation and the related uncertainty characterization in human health risk assessment via classical methods and integration of pharmacokinetic (PK) models (FY22)
	Approaches that enhance transparency and defensibility of human health and environmental risk assessment products	3.4 Advance methods for systematic review, including evidence integration (FY22)
	Support and augmented capacity for dose-response modeling in risk assessments	3.5 Advance methods in dose-response modeling with application to risk assessment (FY22)
4. Essential Assessment and Infrastructure Tools	Essential software and support tools for risk assessments	4.1 Innovate, develop, and maintain a suite of essential software and support tools for risk assessment (FY22)
	Tailored and customized training support for risk assessments	4.2 Innovate, develop, and maintain a training program on the advances in risk assessment and systematic review (FY22)