EPA 601/K-15/002 | November 2015 | www.epa.gov/research

United States
Environmental Protection
Agency

Human Health Risk Assessment

STRATEGIC RESEARCH ACTION PLAN 2016–2019

Office of Research and Development
Human Health Risk Assessment

EPA 601/K-15/002

Human Health Risk Assessment

Strategic Research Action Plan 2016–2019

U.S. Environmental Protection Agency
November 2015

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List of Acronyms

ACE	Air, Climate, and Energy Research Program
AOP	Adverse Outcome Pathway
BBDR	Biologically-Based Dose Response
BMDS	Benchmark Dose Software
CAAC	Chemical Assessment Advisory Committee
CASAC	Clean Air Scientific Advisory Committee
CRA	Cumulative Risk Assessment
CSS	Chemical Safety for Sustainability Research Program
EDSP	Endocrine Disruptor Screening Program
HSRP	Homeland Security Research Program
HTS	High-Throughput Screening
IRIS	Integrated Risk Information System
ISA	Integrated Science Assessment
MCDA	Multi-Criteria Decision Analysis
MCL	Maximum Contaminant Level
MIE	Molecular Initiating Event
MOA	Mode of Action
MSD	Multipollutant Science Documents
NAAQS	National Ambient Air Quality Standard
NRC	National Research Council
OAR	Office of Air and Radiation
OSWER	Office of Solid Waste and Emergency Response
OW	Office of Water
PAL	Provisional Advisory Level
PBPK	Physiologically-Based Pharmacokinetic
PM	Particulate Matter
PPRTV	Provisional Peer-Reviewed Toxicity Values
RATE	Risk Assessment Training and Experience
RfC	Reference Concentration (inhalation)
RfD	Reference Dose (oral)
SAB	Science Advisory Board
SHC	Sustainable and Healthy Communities Research Program
SSWR	Safe and Sustainable Water Resources Research Program

Executive Summary

To protect human health and the environment, state, local and federal governments, and others must make daily decisions about the risks of exposures to environmental contaminants. EPA has designed the Human Health Risk Assessment program to develop and apply state-of-the-science risk assessment methods to estimate human health and environmental risks from exposures to individual chemicals, chemical mixtures, and mixtures of chemicals and non-chemical stressors to support and improve environmental decisions. This program identifies, evaluates, integrates, and translates existing and emerging scientific information from diverse scientific disciplines to accurately assess hazard and characterize risks.

This plan highlights how the HHRA program was developed with input from EPA program and regional offices and from external sources, including nonprofit and research organizations, private industry, and scientists from a range of disciplines across the academic community. The program emphasizes stakeholder engagement to both inform the development of its assessment products, as well as to gain feedback on the utility of products to users.

The HHRA program is designed to provide a comprehensive set of risk assessment products and analytical approaches that will support a wide range of environmental management decisions. The research objectives of the program are:

Objective 1: Characterizes risks
Efficiently support a range of decision making with an agile, fit-for-purpose portfolio of robust and responsive assessment products that characterize risks and potential impacts to human health and the environment.

Objective 2: Advance and refine assessment approaches
Refine risk assessments by identifying critical issues and advancing analytical approaches and applications to incorporate new science, methods and technologies.

Objective 3: Enhance and engage
Enhance data access and management systems to support transparency and efficiency; provide outreach and engage stakeholders to ensure support, training, and tailoring of assessment priorities and products.

To achieve these overarching objectives and address their respective scientific challenges, research projects are organized into four topic areas: (1) Integrated Risk Information System (IRIS); (2) Integrated Science Assessments; (3) Community and Site-specific Risk; and (4) Advancing Analyses and Applications. In concert the topics provide priority assessment products, identify critical 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 risk-based decisions by federal, State, local, and tribal agencies and the public to protect public health and the environment are based on reliable, transparent and high-quality risk assessment methods, models, and data.

Introduction

Every day, the U.S. Environmental Protection Agency (EPA) and its diverse stakeholders must make decisions to protect human health and the environment from the known or potential adverse effects of exposure to environmental pollutants. Such decisions span a large regulatory landscape and require different degrees of environmental pollutant risk information: developing health-protective reference values to support air, water and waste management programs; evaluating data on chemicals provided in pre-manufacturing notices; characterizing potential public and environmental health impact during emergent situations; screening and prioritization of chemicals for monitoring at Superfund sites and in the air and water; evaluating health and ecological 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. EPA's Human Health Risk Assessment (HHRA) program is designed to provide robust and responsive risk assessment support to risk management decisions aimed at protecting human health and the environment. The HHRA program is the world leader in providing both an essential portfolio of risk assessment products and in undertaking targeted and innovative methods development to advance risk analysis.

This *Human Health Risk Assessment (HHRA) StRAP* presents the strategic plan for this national program to develop support to Agency decision making and regulatory actions. The HHRA plan is one of six research plans, one for each of EPA's national research programs in ORD. The six research programs are:

- Air, Climate, and Energy (ACE)
- Chemical Safety for Sustainability (CSS)
- Homeland Security Research Program (HSRP)
- Human Health Risk Assessment (HHRA)
- Safe and Sustainable Water Resources (SSWR)
- Sustainable and Healthy Communities (SHC)

The HHRA plan articulates how this program is integrated into the overall research portfolio of the Agency's Office of Research and Development (ORD), so as to most efficiently and best apply that research to identify hazards, characterize potential human health and environmental risks, and to inform, engage, and develop capacities of its assessment clients. The 2016–2019 *StRAP* for the HHRA national program was developed using considerable input and support from partnerships with EPA program and regional offices requiring risk assessment products, as well as outside stakeholders, nonprofit human health and research organizations, private industry, and colleagues across the scientific community involved in human health and ecological risk assessment.

EPA's strategic research action plans lay the foundation for EPA's research staff and their partners to provide focused research efforts that meet the Agency's legislative mandates, as well as the goals outlined in the Agency's *Fiscal Year 2014–2018 EPA Strategic Plan*. They are designed to guide an ambitious research portfolio that at once delivers the science and engineering solutions the Agency needs to meet such priorities, while cultivating a new paradigm for efficient, innovative, and responsive government and government-sponsored environmental and human health research and scientific assessment.

No other research organization in the world matches the diversity and breadth represented by the collective scientific and engineering staff of EPA's Office of Research and Development, their grantees, and other partners. They are called upon to conduct research to meet the most pressing environmental and related human health challenges facing the nation and the world.

Environmental Problems and Program Purpose

Decision making in the Agency and by its stakeholders to protect public health and the environment covers a large landscape of risk assessment activities and requires agility to bring the best available science and technologies to inform those decisions in a fit-for-purpose fashion. The purpose of the HHRA program is to develop and apply state-of-the-science risk assessment methods to estimate human health and environmental risks from exposures to individual chemicals, chemical mixtures, and mixtures of chemicals and non-chemical stressors to support and improve environmental decisions. The HHRA program identifies, evaluates, integrates and translates existing and emerging scientific information from diverse scientific disciplines to accurately assess hazard and characterize risks.

The HHRA portfolio of assessment applications ranges from rapidly estimating hazards for screening and prioritization for further testing and assessment, through development of provisional assessments for site-specific cleanup decisions, to extensively vetted assessments in support of decisions on national standards. Identifying critical issues and research needs, as well as providing advances in analyses and application of new data and tools, are critical components necessary to keep assessment products credible and contemporary with the state of the science. The HHRA program is uniquely positioned to advance new approaches in support of the risk management decisions and regulatory needs of various stakeholders, including Agency program and regional offices as well as state/tribal environmental protection programs and interested communities.

The significant impact of the HHRA program is demonstrated in the use of its assessment products to support risk management efforts and through recognition of its research contributions. The recent Integrated Risk Information System (IRIS) evaluation of the health risks of inhaled Libby amphibole asbestos is an example of the importance of HHRA program efforts. Libby, Montana was designated a Superfund site in 2002, and in 2009, EPA determined that conditions in the town constituted a public health emergency with cleanup required at thousands of properties. The IRIS assessment of Libby amphibole asbestos involved novel approaches to estimate cancer risks and it included the first evaluation of non-cancer effects for asbestos material. The completion of this IRIS assessment in 2015 has provided scientific support to the EPA Office of Solid Waste and Emergency Response (OSWER) and Region 8 for the cleanup and related risk management activities at the Libby Superfund site.

Other HHRA program products, such as the Integrated Science Assessments (ISAs), provide the scientific basis for setting the National Ambient Air Quality Standards (NAAQS), which are the most impactful environmental standards established by EPA. The ISA for Particulate Matter (PM) evaluated thousands of studies and was the basis in 2012 for the EPA decision to revise the PM NAAQS. The importance of

this scientific assessment is demonstrated by the estimated net public health and economic benefits of attaining the revised NAAQS, which are estimated from $3.7 billion to $9 billion in 2020[1].

Rapid assessment responses by the HHRA program for several recent emergent contamination situations also supported swift and significant risk management decisions that drew national attention. In January 2014, scientists in the HHRA program provided input on the drinking water health advisory issued to address the spill of crude 4-methylcyclohexanemethanol into the Elk River in Charleston, WV. HHRA scientists also derived an inhalation screening level, and both assessments supported emergency response actions and guided remediation. HHRA scientists also assisted EPA Region 2 at the Reich Farms Superfund site in Toms River, NJ. HHRA scientists developed a Provisional Peer-Reviewed Toxicity Value (PPRTV) assessment for Styrene-Acrylonitrile Trimer and subsequently participated in a community meeting on the final risk-based cleanup decision (to protect both children and adults) based on the provisional reference dose. The scientific foundation for cleanup decisions at more than 1000 National Priority Sites across the country, and for dozens of drinking water standards and health advisory levels, has been based on IRIS and PPRTV assessments.

Assessment activities such as these often raise critical scientific issues and stimulate the advancement of new methods and applications. HHRA scientists are actively contributing to the scientific community, as evidenced by the 2015 Best Paper in Toxicological Sciences Award that they, together with CSS colleagues, received for a joint publication on risk assessment from the Society of Toxicology (SOT) Board of Publications (Thomas et al., 2013).

As illustrated in Figure 1, the HHRA program plays a pivotal role in the overall ORD research portfolio by translating research of other programs and characterizing its application and utility in assessment activities. Additionally, challenges encountered in the assessment activities of the HHRA program identify critical research needs and help to advance the development of new applications both by innovative analyses and methods development by the HHRA program, as well as by stimulating the broader scientific community to conduct research that supports risk assessment. Often assessments advance new areas of scientific endeavor because challenges of interpretation and insights on potential risks arise as research results or new tools are applied and characterized in context with data on human exposure conditions, evaluation of other endpoints, and consideration of lifestages and other susceptibilities.

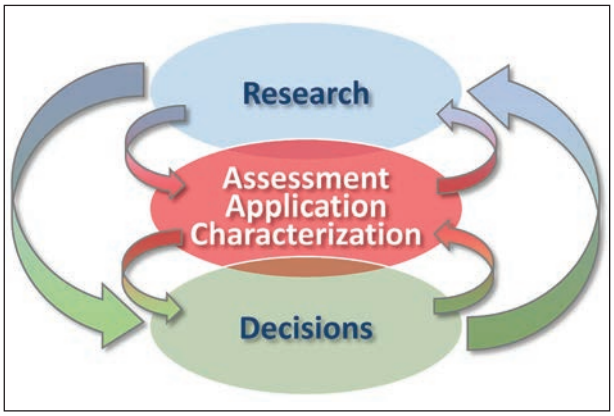


Figure 1. Position of HHRA Program (center red oval) with Respect to Overall ORD Research Portfolio and Agency Risk Management Activities. **Information, data, and tools developed in ORD partner research programs are incorporated into HHRA assessment products and approaches to support risk-based decisions (information flow illustrated by left side arrows), and insights on their utility or new challenges identified in those applications inform new assessment approaches and research areas (research needs illustrated by right side arrows).**

[1] US EPA (2012) Regulatory Impact Analysis for the Final Revisions to the National Ambient Air Quality Standards for Particulate Matter. http://go.usa.gov/ccGtC

Problem Statement

Every day, EPA and diverse stakeholders must make decisions to protect human health and the environment from the known or potential adverse effects of a variety of exposures to environmental pollutants. The wide range of risk management decisions calls for risk assessment products and analytical approaches that tailor assessments to fit the purpose of these various decisions. Assessment products must be scientifically credible and contemporary with evolving technologies, whether based on very limited data or when integrating evidence across thousands of sources.

Program Vision

Risk-based decisions by EPA, state/local/tribal agencies, and the public to protect public health and the environment are based on reliable, transparent and high-quality risk assessment methods, models, and data. The HHRA program supports this vision by identifying, evaluating, integrating, and applying relevant data from a variety of scientific disciplines to characterize the risk from exposures of individual chemicals, chemical mixtures, and mixtures of chemicals and non-chemical stressors. The assessments generated by the HHRA program inform a variety of risk management decisions, and serve to identify critical scientific issues and advance analytical approaches for their resolution.

Program Design

The HHRA program is comprised of four highly interdependent and leveraged topics that have been enhanced based on partner and stakeholder involvement. In concert the topics provide priority assessment products, identify critical issues as they arise, and develop or stimulate advances in approaches and solutions to address emerging challenges, incorporate innovations, and continuously refine applications. The four topic areas, discussed in more detail below, are as follows and the overall program structure is represented in Figure 2:

- **Integrated Risk Information System (IRIS)** to develop hazard and dose-response assessments for priority chemicals;
- **Integrated Science Assessments (ISAs)** to characterize the health and environmental effects of criteria air pollutants and support decisions to retain or revise the National Ambient Air Quality Standards (NAAQS);
- **Community and Site-specific Risk** to provide rapid response assessments and cumulative risk methods to address Superfund site assessment, emergency response, sustainability, and community concerns; and
- **Advancing Analyses and Applications** to address science challenges affecting hazard, exposure or dose-response analyses and to incorporate scientific, technical and communication innovations that improve characterization of human and environmental impacts and application of that science to address critical environmental protection needs.

Building on 2012–2016 Program

This StRAP builds upon and continues to advance the HHRA program as outlined in the *Human Health Risk Assessment Strategic Research Action Plan, FY2012–2016*. The 2016–2019 StRAP responds to ongoing review and oversight by the Chemical Assessment Advisory Committee (CAAC) and the Clean Air Act Science Advisory Committee (CASAC) of the Agency Science Advisory Board (SAB), and has been developed with consideration of recommendations in a January 2015 report of a joint review provided by the SAB and the Executive Coun-

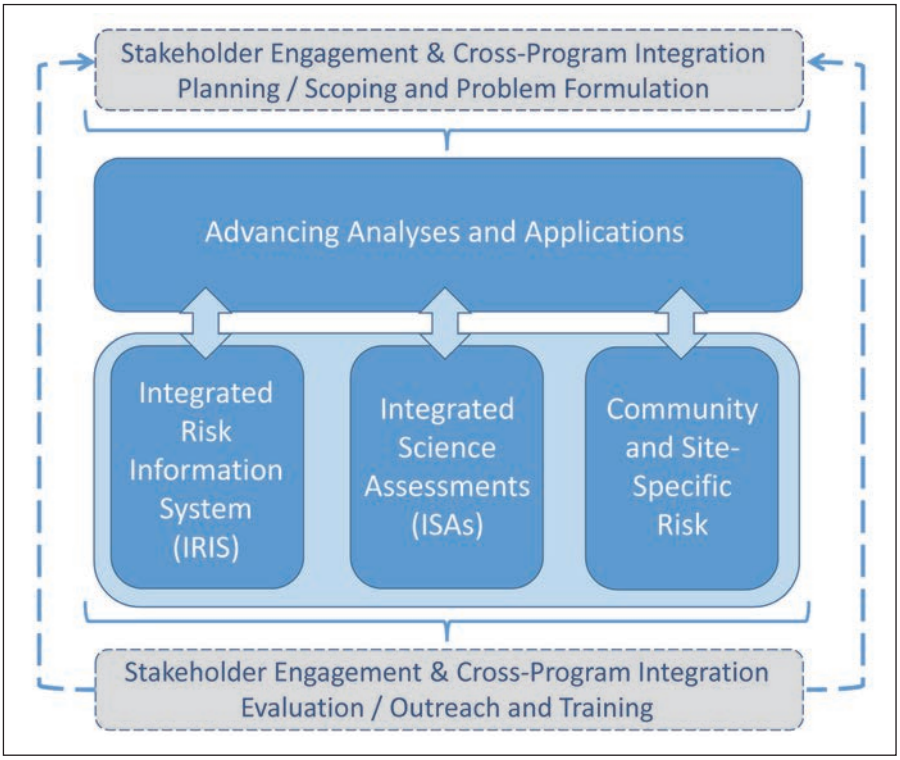


Figure 2. Structure of the Human Health Risk Assessment (HHRA) program. The program design starts with problem formulation and scoping with stakeholders and other research programs (denoted in grey module at top). Development of new methods of analysis and application of these advancements into the portfolio of assessment products (IRIS, ISAs, PPRTVs, emergency estimates, etc., indicated in the light blue block) results in identification of critical issues that inform and stimulate research and new methods development. Evaluation of the utility of these activities feeds back to problem formulation and scoping. Additionally, training and outreach activities enhance stakeholder engagement and builds capacity in risk assessment communities for understanding and application of new technologies and approaches.

cil of the Board of Scientific Counselors (BOSC) held in July 2014 (U.S. EPA, 2015). The HHRA program constantly evolves as its products are assessed for their utility in meeting Agency needs as new scientific opportunities arise and as new challenges and needs are identified in the risk assessment and management arenas. For example, the HHRA program is developing new assessment approaches and products based on computational tools developed via coordination with the CSS research program. Likewise, emerging technologies such as sensors will require guidance on analytical considerations, interpretation, and application in risk assessment approaches.

EPA Partner and Stakeholder Involvement

The HHRA program was restructured in 2014 to emphasize stakeholder engagement and cross-program integration in order to both inform the problem formulation of its assessment products and methods development work, as well as to provide feedback on the utility of the results of these efforts to end users as depicted in Figure 2. This initial "up front" involvement of stakeholders in the design of assessment activities was recommended by the NRC report *Science and Decisions* (NRC, 2009). By implementing the recommendations,

EPA greatly enhanced stakeholder engagement throughout the IRIS program and was subsequently recognized by the NRC (NRC, 2014). Such input on problem formulation and on the scope of activities, including prioritization and pacing, occurs in the HHRA program via development and integration of its projects and tasks with the other ORD research programs, and in collaboration with HHRA program partners and stakeholders. In addition, the program is conducting scientific workshops to convene experts and stakeholders to discuss critical science issues and opportunities in human health risk assessment. Further, the IRIS program organizes public science meetings to support problem formulation and to discuss the available scientific evidence and issues early in the assessment development process. Recently, EPA arranged with the NRC to identify and arrange for subject matter experts to contribute to these meetings, to assure a well-informed discussion that sets the stage for well-targeted and efficient assessment development.

Activities conducted under the HHRA program are responsive to the priorities and the needs of EPA's program and regional offices (see Appendix C for a list of HHRA partners and stakeholders). The HHRA program conducts regular meetings with its program partners. One of HHRA's regular planning partner meetings for two sequential years was devoted to development of the *HHRA 2016–2019 StRAP* with particular focus on two of its topic areas, Community and Site-specific Risk and Advancing Analyses and Applications. Initial proposals to address critical science challenges were discussed at a large planning meeting with program partners in May 2014, and then a revised portfolio of projects and a draft StRAP were reviewed at another one in March 2015. This document represents further refinement based on additional comments. The large-scale planning meetings are complemented by regular partner meetings and communications that occur throughout the year.

Also included in HHRA outreach is its risk assessment training and experience (RATE) program comprised of over 30 specific modules covering hazard identification, exposure assessment, dose-response assessment, benchmark dose modeling, PBPK modeling, mixtures guidance and cumulative risk assessment. These training modules have been provided internally to EPA program and regional offices, to various states, and internationally. Further, the HHRA program has worked with the Environmental Council of the State's (ECOS) Interstate Technology and Regulatory Council to develop a risk assessment training program that targets state risk assessors, increasing capabilities and consistency in risk assessments conducted by federal, state and tribal organizations.

The HHRA program components receive tens of thousands of webpage views annually by users, and substantial outreach occurs using email listservs. Many thousands subscribe to the HHRA Bulletin and over 500 to the ExpoBox Bulletin. Thousands more also subscribe to receive important updates for the IRIS program and Benchmark Dose Software (BMDS).

Integration across the Research Programs

HHRA integrates with the other National Research Programs through collaboration on its assessment activities, including incorporation of research results and by characterization of new applications of data and tools. As illustrated in Figure 3, examples of HHRA program integration with the other research programs include the following:

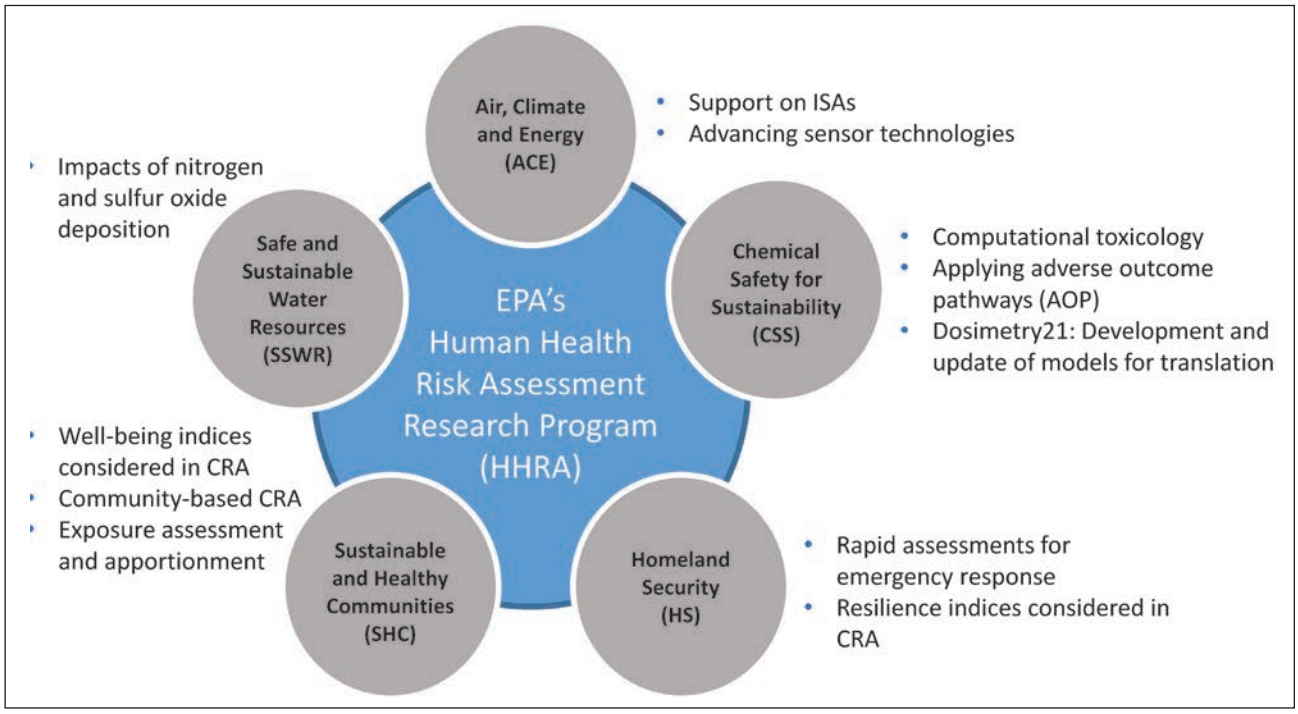


Figure 3. Integration of Human Health Risk Assessment (HHRA) research program with other ORD research programs. The HHRA program utilizes research and applies tools in its assessment products as well as develops assessment approaches and methods to inform needs in the other programs.

- **Air, Climate, and Energy (ACE)**
  Incorporation of NAAQS research (including climate as a welfare effect) and understanding multipollutant mode of action into ISAs; IRIS assessments of air toxics;

- **Chemical Safety for Sustainability (CSS**)
  Computational toxicology, applying adverse outcome pathways, and dosimetry;

- **Homeland Security Research Program (HSRP)**
  Incorporation of resiliency into cumulative risk assessment methods and coordination on rapid response assessment;

- **Safe and Sustainable Water Resources (SSWR)**
  Assessment of deposited oxides of nitrogen and sulfur on surface water quality; and

- **Sustainable and Healthy Communities (SHC)**
  Development of Cumulative Risk Assessment (CRA) methods and decision analytic software to provide "place-based" community assessment, link health and ecology impacts to well-being, and support multi-criteria decision assessment (MCDA).

The HHRA program has a specific integration area with the CSS program to characterize the application and utility of the tools and data streams being developed by CSS scientists. This collaboration is intended to enhance understanding of the foundational data and computational techniques involved in the development of new tools so that they can be appropriately applied in various risk assessment products. Characterizing the utility of these higher throughput data and computational tools in

the context of various assessment activities will facilitate understanding and build confidence in their application to various qualitative and quantitative fit-for-purpose risk assessment needs, thereby accelerating acceptance of new approaches by the EPA program offices and regions as well as external stakeholders. Applying high-throughput screening (HTS) data may enhance efficiency of rapid assessment for emergency response. Incorporating mechanistic insights and understanding of adverse outcome pathways (AOPs) and virtual tissue descriptions in the CSS program can inform dose-response analysis for key events along the spectrum of pathogenesis represented in a hypothesized mode of action (MOA) for a given chemical assessment. Updating dosimetry models will facilitate response analysis and translation of diverse data types at various levels of observation.

The HHRA program also informs critical research areas identified in the ORD cross-cutting Research Roadmaps, as depicted in Table 1. HHRA program products are incorporated across all of the roadmaps: the ISA projects are evaluating the role of criteria pollutants on climate forcing; evaluation of lifestage susceptibility and approaches to assessment are integral to children's health; and cumulative risk assessment (CRA) methods form the conceptual basis for understanding key biological, social, spatial, and environmental factors and how they contribute to disproportionate risk of concern to environmental justice.

HHRA assessment activities are also integrated and coordinated with other interagency working groups and collaborative relationships through the National Center for Environmental Assessment (NCEA), in which the HHRA program represents the large majority of resources. NCEA currently has two Memoranda of Understanding (MOU), one with the Agency for Toxic Substances and Disease Registry (ATSDR), and a second with the National Institute for

Table 1. HHRA Research Program Contributions to Critical Needs Identified by ORD Roadmaps

The number of checkmarks indicate the relative size of the contribution of HHRA activities and interest in the identified science gaps of the roadmaps; a blank indicates no substantive role. As indicated, HHRA is not the lead research program for any of the ORD roadmaps, but its topic areas provide significant contributions to each of them.

ORD Roadmap	HHRA Topic Area			
	IRIS Assessments	ISA Assessments	Community and Site-specific Risk	Advancing Analyses and Applications
Climate Change		✓✓	✓	
Environmental Justice	✓	✓	✓	✓
Children's Health	✓	✓✓	✓	✓
Nitrogen & Co-Pollutants	✓	✓✓		

Occupational Safety and Health (NIOSH). An additional MOU with the Food and Drug Administration (FDA) is nearing completion. Close relationships and integration also occur with international organizations dealing with environmental health risks including the World Health Organization (WHO), the International Agency for Research on Cancer (IARC) and the United Nations Environment Programme. NCEA has targeted efforts through a cooperative agreement with WHO to specifically collaborate on evaluation of priority chemicals in the ISA and IRIS programs. Further, NCEA has the lead role for EPA in the WHO Chemical Risk Assessment Network, a cross-organizational coordinating group including the International Programme on Chemical Safety[2].

Access to data for use in risk assessments is facilitated by scientific staff networks with other federal agencies conducting primary environmental health research, particularly at the National Institutes of Health - National Institute of Environmental Health Sciences (NIEHS) and National Toxicology Program (NTP) and at the Centers for Disease Control and Prevention's National Center for Environmental Health. The HHRA program also continues to improve its use of information science tools to improve the efficiency and transparency of its assessment activities and the accessibility of its scientific resources, including both the Integrated Risk Information System (IRIS)[3] and the Health and Environmental Research Online (HERO) database[4].

Research to Support EPA Strategic Plan

In support of EPA's mission to protect human health and the environment, the Agency's Strategic Plan identifies five strategic goals and four cross-agency strategies (Figure 4).

As described in the later section, the accomplishments and projected impacts of the HHRA program address all of the Strategic Goals in the *FY 2014–2018 EPA Strategic Plan*. These include Goal 1, "Addressing Climate Change and Improving Air Quality"; Goal 2, "Protecting America's Waters"; Goal 3, "Cleaning Up Communities and Advancing Sustainable Development"; and Goal 4, "Ensuring the Safety of Chemicals and Preventing Pollution." The HHRA program also supports the cross-agency strategies within this plan, specifically "Working Toward a Sustainable Future" and "Making a Visible Difference in Communities."

EPA Strategic Plan (FY2014–2018)
Goals and Cross-Agency Strategies

EPA Strategic Goals

Goal 1: Addressing Climate Change and Improving Air Quality

Goal 2: Protecting America's Waters

Goal 3: Cleaning Up Communities and Advancing Sustainable Development

Goal 4: Ensuring the Safety of Chemicals and Preventing Pollution

Goal 5: Protecting Human Health and the Environment by Enforcing Laws and Assuring Compliance

Cross-Agency Strategies

- **Working Toward a Sustainable Future**
- **Making a Visible Difference in Communities**
- **Launching a New Era of State, Tribal, Local, and International Partnerships**
- **Embracing EPA as a High-Performing Organization**

Figure 4. FY 2014–2018 EPA Strategic Plan: Goals and Cross-Agency Strategies.

[2] World Health Organization. Chemical Risk Assessment Network. http://www.who.int/ipcs/network/en/
[3] U.S. EPA. Integrated Risk Information System. http://www.epa.gov/iris/
[4] U.S. EPA. Health and Environmental Research Online. http://hero.epa.gov/

Statutory and Policy Context

As a regulatory agency, Congress authorizes EPA to write regulations that explain the critical details necessary to implement environmental laws. In addition, a number of Presidential Executive Orders (EOs) play a central role in EPA activities[5].

A selection of the laws for which the HHRA program helps to support the EPA's statutory authority and mandates to conduct work is shown below. The HHRA program also is responsive to and supports several EOs and EPA policies. See Appendix 2 for details.

- 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. The Integrated Science Assessments (ISAs) that are developed under the HHRA program serve as the basis for decisions on NAAQS by the Agency's Administrator.

- The **Safe Drinking Water Act (SDWA)** authorizes research and assessments focusing on microbes (e.g., Cryptosporidium), disinfection byproducts, and other regulated and unregulated chemical and radiological contaminants such as arsenic, sulfate, and radon. The law also mandates that risks are quantified for general and sensitive populations (e.g., infants, children, pregnant women) as part of benefit-cost analysis when Maximum Contaminant Levels (MCL) are established. Other research provisions address risks associated with waterborne disease, complex mixtures and unregulated contaminants (e.g., development of the Contaminant Candidate List).

- The **Comprehensive Environmental Response, Compensation, and Liability Act (CERCLA)** of 1980, commonly known as Superfund, requires 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 **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 **Resource Conservation and Recovery Act (RCRA)** gives EPA the authority to control hazardous waste from "cradle to grave," including the generation, transportation, treatment, storage, and disposal of hazardous waste. Evaluating control technologies requires health and environmental assessments. The law also sets forth a framework for the management of non-hazardous solid wastes. The 1986 amendments enabled EPA to address environmental problems that could result from underground tanks storing petroleum and other hazardous substances.

- The **Food Quality Protection Act (FQPA)** of 1996 requires assessment of risk from exposures to pesticides, including aggregate exposures and cumulative risk

[5] U.S. EPA. Laws and Executive Orders. http://go.usa.gov/ccGuQ

and risk to sensitive subpopulations (e.g., infants and children).

- The **Toxic Substances Control Act (TSCA)** of 1976 provides EPA with authority to require reporting, record-keeping and testing requirements, and restrictions relating to chemical substances and/or mixtures.

Research Program Objectives

The three main HHRA program objectives support the vision of protecting public health and the environment by providing state-of-the-science risk assessments; refining risk assessment approaches and advancing innovative applications; and providing stakeholder engagement and support by promoting transparency, efficient access to tools and products, and training to enhance understanding and build capabilities. The three objectives of the HHRA program listed below are mutually informative and integrated in order to most efficiently identify, evaluate, characterize and communicate science-based solutions to address current and emerging challenges in human health and environmental risk assessment.

Objective 1: Characterize risks

Efficiently support a range of decision making with an agile, fit-for-purpose portfolio of robust and responsive assessment products that characterize risks and potential impacts to human health and the environment.

Objective 2: Advance and refine assessment approaches

Refine risk assessments by identifying critical issues and advancing analytical approaches and applications to incorporate new science, methods and technologies; and

Objective 3: Enhance and engage

Enhance data access and management systems to support transparency and efficiency; provide outreach and engage stakeholders to ensure support, training, and tailoring of assessment priorities and products.

The following narratives for each program objective provide a brief overview of the objectives and the critical assessment issues and key drivers. Each objective addresses broad scientific challenges that are intended to enable EPA scientists to apply their expertise and innovation in shaping specific solutions.

Objective 1: Characterize risks

Efficiently support a range of decision making with an agile, fit-for-purpose portfolio of robust and responsive assessment products that characterizes risks and potential impacts to human health and the environment.

The first objective is to continue to provide state-of-the science, peer-reviewed assessments and associated technical support activities for the Integrated Risk Information System (IRIS) used by various program offices, development of Integrated Science Assessments (ISAs) and Multipollutant Science Documents (MSDs) to support review of the National Ambient Air Quality Standards (NAAQS), and Provisional Peer-Reviewed Toxicity Value (PPRTV) assessments for decision making at hazardous waste sites. The priorities for these products are described below (see Research Topics section). Oversight is provided by established standing scientific committees such as the Agency's Chemical Assessment Advisory Committee (CAAC) of the Science Advisory Board (SAB) for IRIS assessments and the Clean Air Scientific Advisory Committee (CASAC) of the SAB for the ISAs.

The following challenges must be addressed in order to meet Objective 1 and sustain the HHRA program's assessment portfolio representing the state-of-the science:

Science Challenge 1: *Systematically identify, evaluate, integrate, and translate relevant scientific evidence to assess human health effects of chemicals for priority Agency decisions;*

Science Challenge 2: *Systematically identify, evaluate, integrate, and translate relevant scientific evidence to assess human health and environmental impacts of criteria air pollutants; and*

Science Challenge 3: *Provide tools and advance analyses to help EPA programs and communities rapidly identify and address risks of emerging exposures and prioritize testing.*

Objective 2: Advance and refine assessment approaches

Refine risk assessments by identifying critical issues and advancing analytical approaches and applications to incorporate new science, methods and technologies.

The HHRA program is uniquely positioned to characterize the appropriate use of new tools and approaches to risk assessment. The HHRA product portfolio spans the range from screening or prioritization, across rapid assessments for emergency response or relatively data-poor derivations in the PPRTV program, to the evaluation of highly sophisticated and data-rich studies and evidence integration for the Integrated Science Assessments (ISAs) supporting the National Ambient Air Quality Standards (NAAQS) as depicted in Figure 5. The varying regulatory requirements relate to the type and extent of foundational scientific evidence, the prognostic capacity of a given tool, and the degree of verification or confidence in the application of new data or in a newly measured key event to serve as a surrogate versus established endpoints and outcome measures in assessments. The application of emerging data and new biotechnology tools will be characterized in that context, and their relative contributions and utility may differ depending on the specific assessment arena – i.e., fitting the application of the new data to the purpose or problem formulation of the assessment activity. Objective 2 of the HHRA program is thus aimed at continuously refining risk assessment approaches and advancing new analyses that incorporate emerging technologies to ensure that HHRA assessment products keep contemporary with the state-of-the-science.

Critical issues identified through the assessment development efforts that are the focus of Objective 1 support identification and prioritization of the research foci of Objective 2 in the HHRA program. HHRA also avails itself of advances and strives to address issues that arise as challenges in the larger scientific community in applying emerging biotechnology. The list of challenges for Objective 2 of the HHRA program includes the following:

Science Challenge 1: *Evaluate and implement approaches for systematic review, evaluation and integration of evidence, including factors affecting bias, to enhance efficiency and accuracy of assessment development including automated data mining;*

Science Challenge 2: *Broaden exposure assessment technology with exposure factors for translation of exposure, bioavailability, and dose estimates (both human and ecological) to flexibly address different exposure scenarios;*

Science Challenge 3: *Improve prioritization and rapid response by evaluating and incorporating new data streams and developing rapid assessment approaches;*

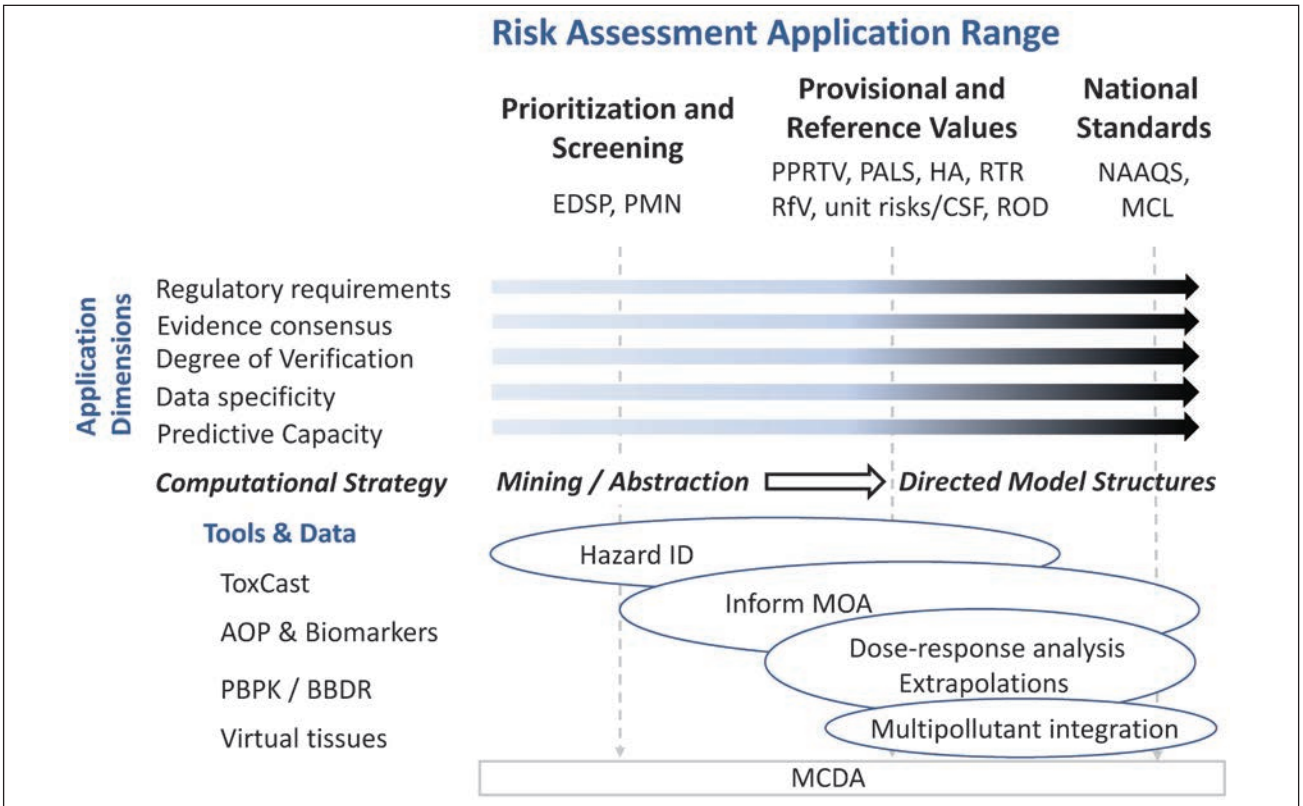
Science Challenge 4: *Develop approaches to incorporate current understanding of key events, AOPs, and biomarkers to increase accuracy of predictions of disease pathogenesis; inform MOA; and better characterize critical endpoints of relevance to HHRA (respiratory, cardiovascular, neurotoxicity, developmental, reproductive toxicity, liver);*

Science Challenge 5: *Update dosimetry modeling approaches to predict a profile of internal dose metrics, including portal-of-entry effects, across all exposure routes to support use of MOA, AOPs and aggregate or cumulative risk applications;*

Science Challenge 6: *Advance decision analytic and probabilistic approaches to more fully characterize dose-response functions and uncertainty, and thereby better inform benefit-cost analyses;*

Science Challenge 7: *Refine dose-response analysis by characterizing determinants of the entire spectrum of the response surface including concentration, duration, and timing to support exposure-scenario specific assessment and consideration of life-stage; and*

Science Challenge 8: *Expand CRA methods to advance "place-based" community risk characterizations, apportion multimedia exposures and risk to various receptors, incorporate multiple stressors, consider epigenetics and susceptibility, and support multi-criteria decision analysis and sustainability.*



Assessment Acronyms: EDSP = Endocrine disruptor screening program; PMN = premanufacturing notice; PPRTV = Provisional peer-reviewed toxicity value; RfV = Reference value (e.g., reference dose); CSF = Cancer slope factor; PALS = Provisional advisory levels; RTR = Residual technology review; HA = Health advisory; ROD = Record of decision; NAAQS = National Ambient Air Quality Standard; MCL = Maxiumum contaminant level

Figure 5. Range of application dimensions required across risk assessment landscape varies based on "fit for purpose." Figure 5 illustrates the range in critical dimensions for regulatory requirements, scientific evidence, predictive capacity, and degree of verification required of applications across the assessment landscape. This ranges from screening and prioritization to support of national standards (see insert for assessment acronyms). The type of computational strategy employed, such as data mining/abstraction or read-across approaches versus directed model structures (e.g., physiologically-based pharmacokinetic, PBPK; or biologically-based dose-response, BBDR; models), also shifts along this axis. The domain and role of specific tools and data (illustrated for products of the CSS program) may be different depending on the assessment context. As an example, adverse outcome pathways (AOPs) or biomarkers might both identify a hazard or inform mode of action (MOA) considerations for dose-response analyses. Ultimately, all components can be incorporated into multi-criteria decision analysis (MCDA) for transparent integration and evaluation of risk and uncertainty.

Objective 3: Enhance and engage

Enhance data access and management systems to support transparency and efficiency; provide outreach and engage stakeholders to ensure support, training, and tailoring of assessment priorities and products.

The third objective of the HHRA program is aimed at continual improvements in technologies supporting efficient assessment development and at outreach to improve understanding of risk assessment issues and methods in order to foster development of institutional capabilities and consistency in risk assessments developed by various stakeholders. Further development and improvement of the Health and Environmental Research Online (HERO) system[6] supports enhanced assessment development and transparency through access to scientific literature underlying assessment products. Software and technical support such as benchmark dose software (BMDS) enables stakeholders to apply advances that the HHRA program develops in dose-response and evidence integration approaches. Outreach efforts can take the form of public workshops, seminars, training sessions as well as varied communication approaches (e.g., Web posting, emails, and blogs). Challenges in this objective area include the following:

Science Challenge 1: *Enhance data access and management systems to support transparency and efficiency; and*

Science Challenge 2: *Develop and apply effective methods for stakeholder engagement and risk assessment training to varied audiences.*

An overview summary of the aims in the HHRA research program, both near- and longer-term, to achieve these objectives and address critical science challenges is provided in Table 2.

Table 2. Summary of Near and Long-term HHRA Program Aims to Achieve Objectives and Address Science Challenges

Objective	What We Do	Near-term Program Aim	Long-term Program Aim
Characterizes risks — *Efficiently support a range of decision making with an agile, fit-for-purpose portfolio of robust and responsive assessment products that characterize risks and potential impacts to human health and the environment*	Tailor risk assessment products to meet the range of assessment needs in an agile, fit-for-purpose fashion while maintaining established credibility and scientific quality and increasing productivity	Accelerate completion of the current successful array of risk assessment products for priority pollutants and program partners while updating operating procedures for evidence integration and derivation efficiency; implement updating process for older IRIS assessments	Expand assessment products to ensure an efficient and agile portfolio that addresses critical areas of assessment needs, including characterization of acute, short-term and episodic exposures; integration of endpoints across species to support community concerns regarding cumulative risk and sustainability; and to develop information to support benefit-cost analyses for a larger array of endpoints

[6] http://www.epa.gov/HERO

Table 2. (continued) Summary of Near and Long-term HHRA Program Aims to Achieve Objectives and Address Science Challenges

Objective	What We Do	Near-term Program Aim	Long-term Program Aim
Advance and refine assessment approaches — *Refine risk assessments by identifying critical issues and advancing analytical approaches and applications to incorporate new science, methods and technologies*	Characterize and advance assessment approaches with contemporary and emerging biotechnology data and computational methods	Facilitate the characterization and application of new data streams and emerging computational tools by developing and advancing case study applications of new science across the exposure-dose-response continuum for various disease endpoints; improve assessment methods including systematic review and approaches to exposure and dose-response	Transition risk assessment approaches to incorporate systems biology understanding of disease, implement mature computational toxicological modeling approaches, express risk and uncertainty probabilistically, and integrate emerging sensor technologies
Enhance and engage — *Enhance data access and management systems to support transparency and efficiency; provide outreach and engage stakeholders to ensure support, training, and tailoring of assessment priorities and products*	Provide system infrastructure and manage access to assessment products and data/ knowledge bases to ensure transparency and efficiency while developing stakeholder engagement and building capacity to support appropriate implementation of new approaches	Maintain and expand current risk assessment tools and databases to incorporate new approaches as they are developed; develop and provide risk assessment training to EPA programs and national and international partners	Evolve and upgrade infrastructure to create connectivity and provide interoperable, modular computational capacity to implement new approaches, access data sources, engage stakeholders, and support training and communication

Research Topics

Three of the four topic areas in the HHRA research program are devoted to developing specialized assessment products. The fourth topic is an overarching topic area which informs all assessments by advancing risk analyses and applications. The program is highly integrated and leveraged. As shown in Figure 6, nine project areas are targeted so that those projects involved with assessment activities identify issues and methods development needs, while the project areas to advance analyses and applications bring the state-of-the-science to maturity by providing characterizations and building confidence, thereby ensuring agile analyses and applications.

The HHRA National Program Director (NPD), in consultation with ORD senior managers, prioritizes efforts by balancing direct program support with advancement of new risk methods. The bulk of HHRA resources support Projects 1 through 5, which provide assessment products directly to EPA programs and regions, thus addressing the program partners' highest priorities. To maintain the credibility of these assessments and increase the efficiency of their production, both near- and longer-term

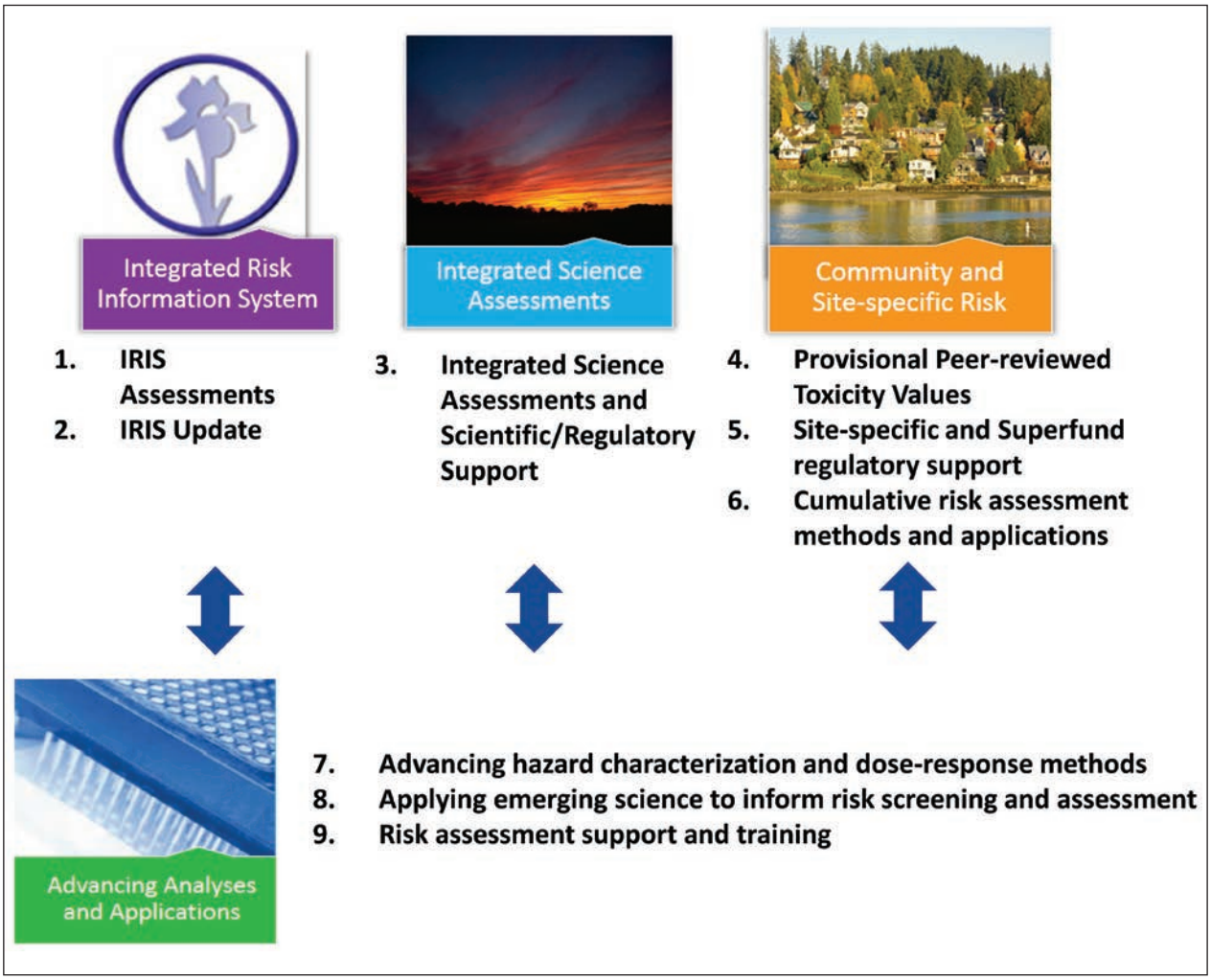


Figure 6. The four topic areas and nine projects of the Human Health Risk Assessment (HHRA) research program.

commitments to Projects 6 through 9 are required to advance risk assessment methods, incorporate emerging scientific developments and maintain critical infrastructure such as databases. Limited resources currently available to the HHRA program require the targeting of tasks within Projects 6 through 8, which is accomplished by considering the value and impact of new analyses and methods on HHRA assessment products, as well as the status of complementary research efforts by the other national programs, notably CSS, which provides input to some tasks in Project 8, and SHC, which collaborates on community-based approaches. Project 9 advances program efficiency and transparency (e.g., via the HERO system), provides software for use of new approaches in the public domain, and supports the Agency and external risk assessment training efforts. HHRA in-house staffing, availability of extramural resources, Agency and Congressional direction, and independent advisory recommendations (e.g., EPA's SAB and BOSC) also are considered in decisions on resource allocation to HHRA activities. The following section summarizes key activities and illustrates anticipated products arising from the resources committed to the HHRA program.

Topic 1: Integrated Risk Information System (IRIS)

Integrated Risk Information System (IRIS) assessments developed by HHRA scientists are peer-reviewed, qualitative, and quantitative health hazard and dose-response assessments on environmental pollutants of relevance to EPA's mission to protect human health and the environment[7]. IRIS assessments are widely used by EPA's programs and regions, as well as outside of the Agency by states, international organizations and the public, to support a wide range of decisions. EPA and the risk assessment/risk management community consider IRIS the premier source of health hazard and dose-response information for environmental pollutants.

Project 1: IRIS Assessments

This HHRA project is devoted to maintaining the credibility and responsiveness of the IRIS program. A strong, scientifically rigorous IRIS program is of critical importance, and the HHRA research program continues to make changes that: (1) improve the scientific integrity of IRIS assessments; (2) improve the productivity of the IRIS program; and (3) increase transparency so that issues are identified and debated early in the IRIS process. In 2009, the IRIS program announced a revised 7-step assessment development process shown in Figure 7. Since that time, the National Research Council made recommendations related to improving the development of IRIS assessments and advancing risk assessment in general, including the importance of up-front planning and scoping in the risk assessment process (NRC, 2011). EPA is implementing additional changes to the IRIS program based on the NRC recommendations (Appendix D) and an evaluation of these changes has been well received (NRC, 2014). These changes will help EPA produce more high quality IRIS assessments each year in a timely and transparent manner to meet the needs of the Agency and the public.

PROJECT 1 HIGHLIGHTS
IRIS Assessments

- **IRIS assessments produced with state-of-the science to address Agency priorities**
- **Enhanced production efficiency and stakeholder engagement**
- **Public science meetings**
- **Problem formulation opportunities**
- **IRIS Handbook of Operating Procedures to support transparent and tractable methods**

[7] http://www.epa.gov/iris

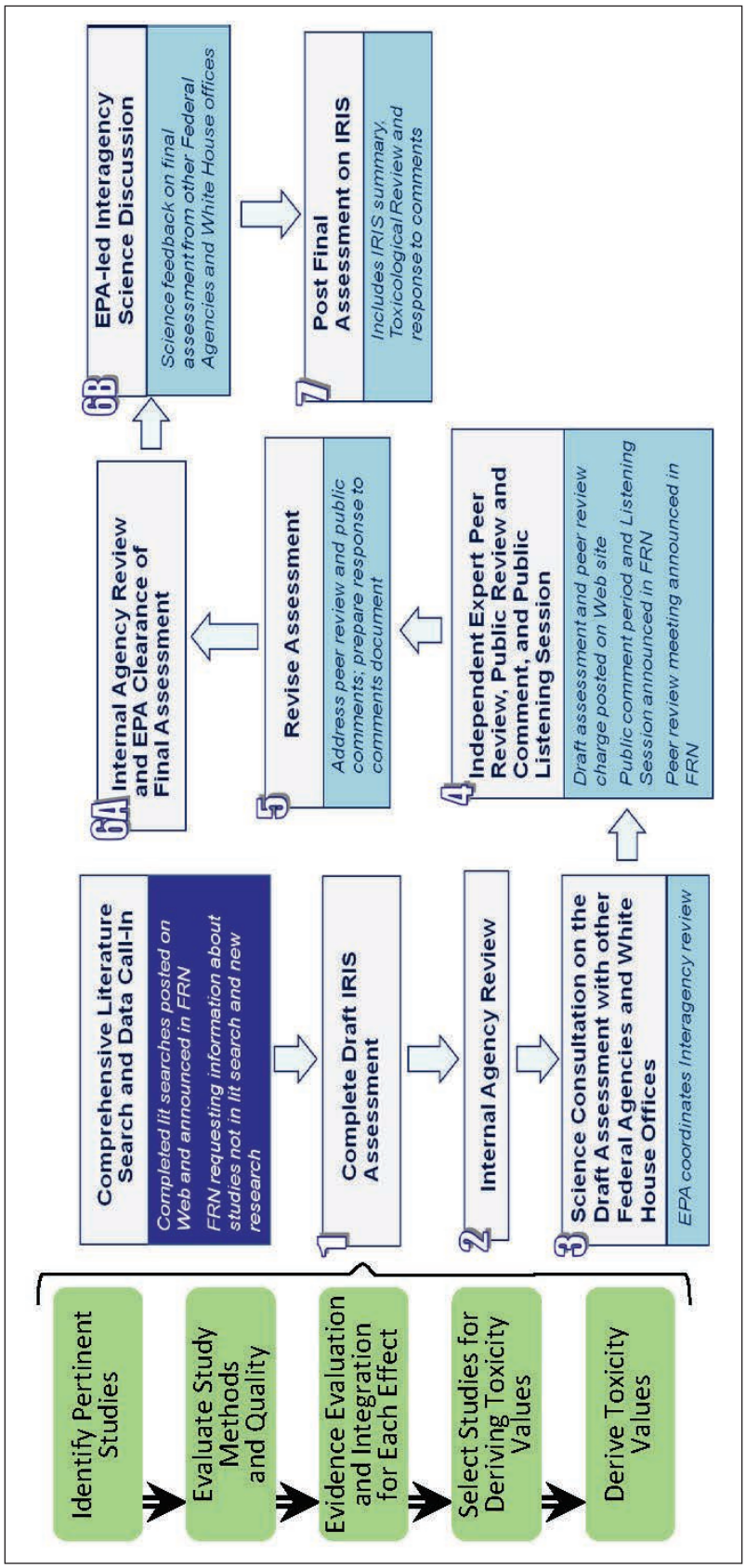


Figure 7. Seven steps in assessment development process of IRIS program and work flow of disciplinary work groups (denoted as green boxes).

The formation of disciplinary work groups is another enhancement to the IRIS program that ensures scientific expertise is strategically targeted to characterize potential adverse health effects and endpoints. HHRA scientific experts in these work groups identify issues and advance approaches to address challenges specific to their areas. For example, techniques are under development for meta-analysis of epidemiological studies and the use of AOPs to help elucidate windows of susceptibility for developmental effects. The IRIS program is also developing a Handbook of Operating Procedures to provide transparency and enhance understanding of IRIS assessments by Agency partners and external stakeholders.

Project 2: IRIS Update

This project will update the existing IRIS database and implement plans to maintain its currency. During the past two decades, the IRIS program has focused on a relatively small number of scientifically complex, resource-intensive assessments. This has left the rest of the IRIS database untouched, to the point that today, more than 80% of the hundreds of IRIS assessments are more than 20 years old. Even recent assessments can become out-of-date as new studies become available and scientists understand more about the many ways chemicals can affect human health. This situation is not unique to IRIS, rather, it is common to human health assessment programs worldwide.

PROJECT 2 HIGHLIGHTS
IRIS Update

- **Process to prioritize and update IRIS assessments**
- **Streamlined approach to update older assessments**

EPA remains committed to continue to strengthen the IRIS program and increase transparency and productivity. The IRIS program has developed a multi-year agenda, which provides information about the status of active assessments and highlights assessments scheduled to begin in the future[8]. The program is working to improve the IRIS database including an effort to evaluate chemical assessment needs both within and outside of EPA and the resources required to meet those needs. Further, the program is developing a process to update and maintain finalized IRIS assessments that do not warrant a full reassessment through the IRIS process.

Topic 2: Integrated Science Assessments (ISAs)

The HHRA program regularly develops ISAs (formerly Air Quality Criteria Documents) as a major component of its research portfolio[9]. The ISAs are developed on a 5-year cycle in response to regulatory requirements and provide the scientific basis for the EPA Administrator's decisions on setting NAAQS for the criteria pollutants (particulate matter, ozone, lead, carbon monoxide, and sulfur and nitrogen oxides) that are ubiquitous in ambient air due to numerous and diverse mobile and stationary sources. Attainment of the NAAQS for these pollutants has been estimated by the Office of Management and Budget (OMB) and EPA to provide significant public health and environmental benefits to the American public that far exceed the cost of control programs. The direct benefits of EPA's air programs include the reduced incidence of a number of adverse human health impacts, including premature death and disease, improvements in visibility and avoided damage to trees, agricultural crops and other vegetation.

[8] http://www.epa.gov/IRIS
[9] U.S. EPA Integrated Science Assessments. http://www.epa.gov/isa

In planning and developing ISAs, the HHRA program works in very close collaboration with the primary client office, the Office of Air and Radiation's (OAR) Office of Air Quality Planning and Standards (OAQPS), as well as CASAC and other stakeholders as shown in Figure 8. ORD's ACE research program conducts intramural laboratory-based research and extramural research through the Science to Achieve Results (STAR) grants program in support of ISA development. The ISAs incorporate and synthesize research findings from the ACE research program and others into the assessment documents. Early in the development process, HHRA convenes a workshop with the client office and the scientific community to identify the most policy-relevant science issues. A draft integrated review plan for each ISA is then developed that includes the ISA which is the responsibility of HHRA, and the complementary Risk and Exposure Assessment, if warranted, and a Policy Assessment, both of which are the responsibility of OAQPS. All external review drafts of these complementary assessment products undergo public comment and rigorous peer review by the CASAC. In addition, draft ISAs are reviewed internally and through workshops covering specific scientific areas of the assessment.

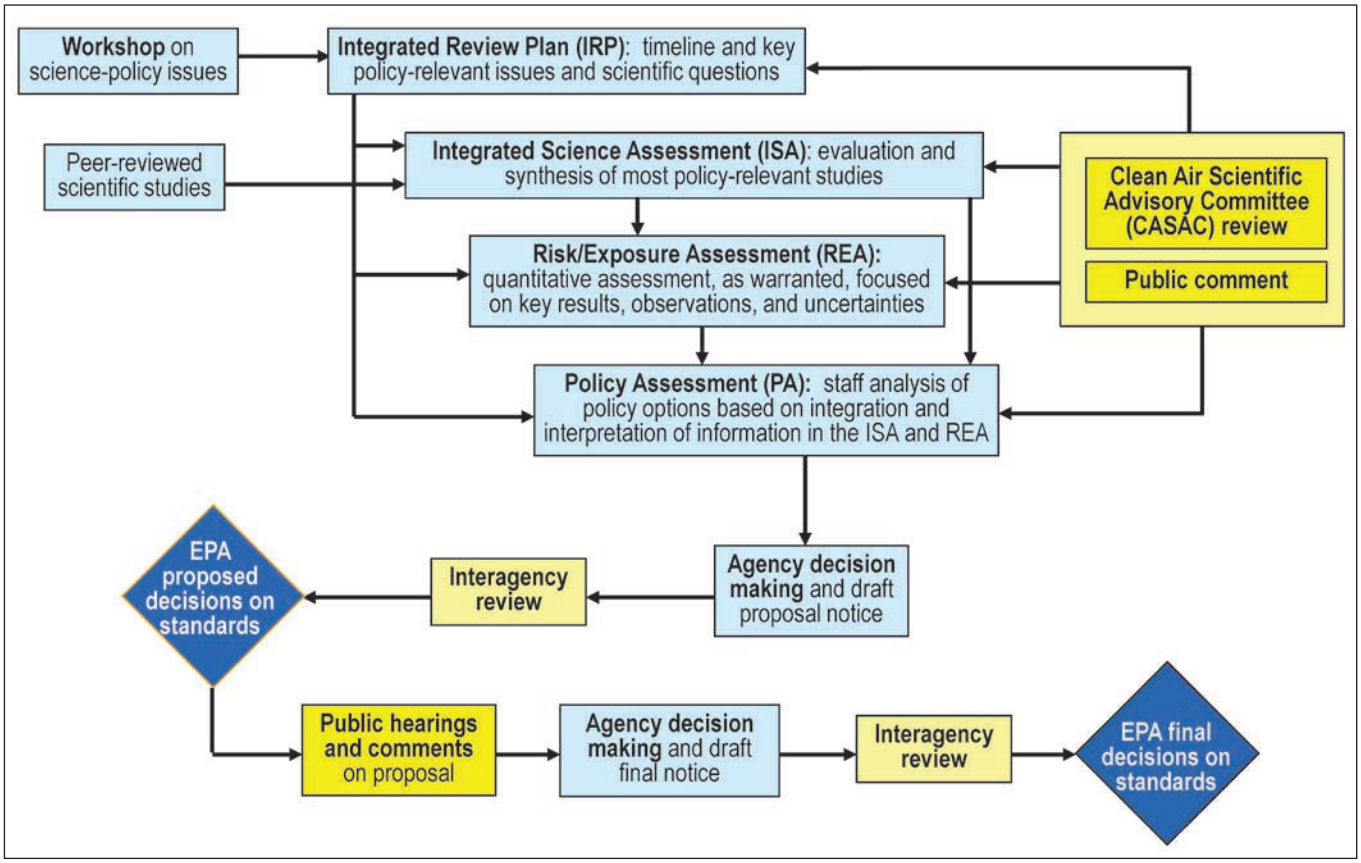


Figure 8. Development process and role of Integrated Science Assessments in support of decisions to retain or revise the National Ambient Air Quality Standards for the criteria air pollutants.

Project 3: Integrated Science Assessments and Science/Regulatory Support

Tasks in this project support these efforts of planning, developing the ISAs, providing regulatory support regarding their implementation, and advance specific scientific approaches and solutions to issues that arise. In this next FY2016–2019 period, the HHRA program expects to be supporting ISA and regulatory support to OAR regarding the final promulgation on the SO_2 primary (health) and NO_2 primary (health) NAAQS in FY18 and the secondary (welfare) NAAQS in 2019 for SO_2 and NO_2, while also initiating development of the ISA for PM. Support to OAR regarding implementation of ISA to policy assessment and rulemaking for decisions regarding review, retention, or revision of the NAAQS will also be provided for these same pollutants. A more detailed schedule of ISA activities can be found in Appendix A.

The evaluation of data and development of these ISAs often identify issues that the HHRA program endeavors to resolve. For example, recognizing that individuals are not exposed to a single pollutant in isolation but rather to a complex mixture of air pollution, HHRA and ACE scientists have planned to work in consultation with EPA offices to develop MSDs to support the reviews of the primary (health-based) and secondary (welfare-based) NAAQS. These MSDs are intended to aid in evaluation of the combined health effects of the exposures to mixtures of air pollutants, as well as providing a more effective evaluation of health effects of exposures to single pollutants in a multipollutant context than what is currently provided using single pollutant ISAs. Such understanding supports strategic roadmaps regarding climate, addresses environmental justice (EJ) issues, informs understanding of MOA for respiratory effects, and advances cumulative risk-characterization methods. At present, budget constraints have delayed development of MSDs but, as resources permit, the development of these assessments will proceed.

Science advancements also derive from the ISA assessment activities such as an approach to the determination of causality for the toxicity of lead (Pb) used coherence of the MOA across human and ecological species (Lassiter et al., 2015). Additional advancements on applying insights from data evaluations in support of the other ISAs are anticipated.

PROJECT 3 HIGHLIGHTS
ISA Assessments and Scientific/ Regulatory Support

- **ISA assessments for SO_2, NO_2, PM and NO_x/SO_x ecological effects**
- **Regulatory support to OAR regarding rule development and risk/exposure/ policy assessment**
- **Advances in application of new science to characterize critical effects and interactions of criteria pollutants**

Topic 3: Community and Site-Specific Risk

Significant progress in environmental protection has occurred in the United States over the past decades, but many challenges remain, and some communities are disproportionately impacted. While many environmental problems are global, national and regional in nature, their impacts are experienced most acutely at the community level. For example, every day, communities face challenges with management of municipal and hazardous waste. The HHRA program directly supports risk management decisions related to waste sites through development of Provisional Peer Reviewed Toxicity Value (PPRTV) assessments.

Project 4: PPRTV Assessments

PPRTV assessments provide toxicity values derived for use in EPA's Superfund program when a value is not available in the IRIS database. The PPRTV assessments are used by the Superfund program and regional decision makers when making site-specific cleanup decisions, such as when to pursue monitoring for a contaminant of concern. The implications of these decisions include improvements in human health in the vicinity of Superfund sites, reduction or reversal of damages to natural resources, reduction of harm in emergency situations, improved economic conditions and quality of life in communities affected by hazardous waste sites, improved environmental practices by industry, and advances in science and technology.

PROJECT 4 HIGHLIGHTS
PPRTV Assessments

- **≥ 12 assessments annually to support OSWER regulatory decisions**
- **Implementation of improvements in systematic review and application of other analysis advances as they become available**
- **Application of new data streams and computational methods as utility is characterized by case studies**

Priorities for PPRTV development are based on the needs of the Office of Solid Waste and Emergency Response (OSWER) and evaluated annually. PPRTV assessments are derived following a review of the relevant scientific literature using the same methods, sources of data, and guidance on dose-response analysis used by the IRIS program. All PPRTVs receive internal review by a panel of EPA scientists and external peer review by independent scientific experts and are publicly available[10]. Applying new data streams, read-across approaches, and computational tools to enhance the supporting data/knowledge bases and efficiency of derivation for PPRTV values is an active area of research in the HHRA program.

Project 5: Site-specific and Superfund Technical Support

Communities are also faced with an urgent need for coordinated assistance to assess and address issues of chemical and other environmental contamination, and additionally are now presented with new sensing or monitoring information that is difficult to interpret. EPA's HHRA program is frequently called upon to quickly assist in these situations, often in the face of large scientific uncertainties due to data gaps. Project 5 is structured with tasks to address these needs.

EPA provides rapid risk assessment and technical consultation regarding both health and ecological impacts through five technical support centers, two of which are supported by the HHRA program: the Superfund Technical Support Center and the Ecological Risk Assessment Support Center[11]. The HHRA program provides such support directly to the Homeland Security research program as the lead for the Agency on emergency contamination situations. The HHRA program develops approaches to respond to these emerging, often crisis-level, chemical/substance issues with sound science that allows for quick action and, ultimately, quick decisions and effective solutions. The HHRA program anticipates

[10] U.S. EPA. Provisional Peer-Reviewed Toxicity Values for Superfund. http://hhpprtv.ornl.gov

[11] The other three technical support centers, the Ground Water Technical Support Center, the Engineering Technical Support Center, and the Site Characterization and Monitoring Technical Support Center, are supported by ORD's Sustainable and Health Communities (SHC) research program.

developing new assessment approaches by means of an expanded product line to enhance rapid response and screening capabilities and to augment toxicity value derivation procedures for health assessments.

PROJECT 5 HIGHLIGHTS
Site-specific and Superfund Technical Support

- Quarterly reports on support provided via the technical support centers
- Rapid assessment support to emergent situations
- Special assessment assignments as novel Agency priorities arise
- New assessment products to rapidly predict risk

Project 6: Cumulative Risk Assessment (CRA) Methods and Applications

To address the desire by communities to understand and conduct local or "place-based" assessments, another major project area of research under this topic is expanding CRA methods, developed to integrate and evaluate impacts of chemical and non-chemical stressors on the environment and health, as shown in Figure 9. Current CRA activities includes strategic coordination and science support to the EPA's Risk Assessment Forum Technical Panel on CRA[12] and providing training on CRA methods.

Understanding the various key biological, social, spatial, and environmental factors and how they contribute to disproportionate risk will facilitate support on environmental justice and faster application to communities. Specific analyses and case studies are anticipated to continue and will advance approaches useful to both qualitative and quantitative consideration of cumulative risks (Gallagher et al., 2015). Analyses will look at specific interactions, including PM and decreased heart rate variability, access to green space with asthma and allergy occurrences, and psychosocial stress with chemicals that alter the hypothalamic pituitary adrenal (HPA) axis. Other case studies may include scenario-specific studies in collaboration with regional partners. A new task is devoted to consideration of approaches to incorporate susceptibility and the role of epigenetics. Evaluation of exposure modeling and guidance on how to apportion exposure and risk of mixtures to phthalates and to both human and ecological receptors in various media is another task anticipated to help advance application of cumulative risk assessment. A forthcoming vision paper will provide recommendations to advance CRA to include ecological assessment using MCDA to support transparency in valuation. Another case-study will explore implementation of a model that explores factors influencing sustainability.

PROJECT 6 HIGHLIGHTS
Cumulative Risk Assessment (CRA) Methods

- Advance cumulative risk methods to characterize interactions of chemical and non-chemical stressors
- Scenario-specific case studies to explore CRA implementation
- Development of approaches for the integration of ecological and human endpoints using multi-criteria decision analysis (MCDA)
- Consideration of susceptibility and epigenetics
- Evaluation of exposure and risk apportionment across media

[12]U.S. EPA. Risk Assessment Forum. http://www.epa.gov/osa/risk-assessment-current-projects

Future work with the HSRP and SHC programs is expected to consider how to integrate resiliency and well-being indices under development in those programs into the CRA framework. Research and work supporting CRA is central to advancing the EPA Risk Assessment Forum's CRA Guidelines, and will position the HHRA program to better address place-based assessments activities and thereby support sustainability, climate, and goals articulated in the EJ roadmap.

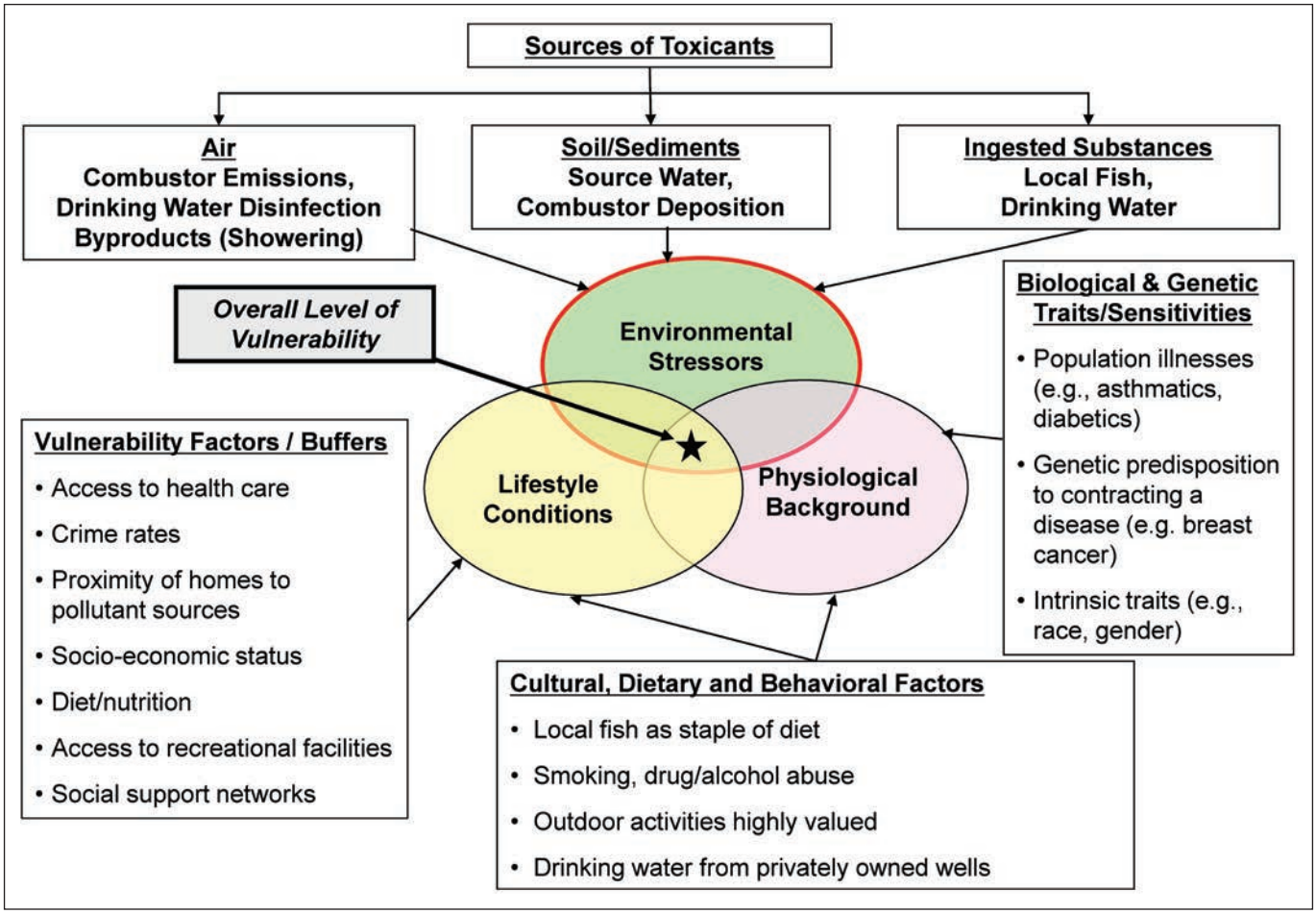


Figure 9. CRA framework illustrating various potential roles of chemical and non-chemical stressors and buffers. Current areas of emphasis in HHRA are interaction of ecological and human stressors, and active collaboration with the HSRP and SHC programs to consider resiliency and well-being indices.

Topic 4: Advancing Analyses and Applications

The HHRA program is multidisciplinary and aimed at incorporating scientific innovations to advance analytic approaches and applications. Projects under this topic are targeted at 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. Another project enhances and maintains databases and software support to ensure transparency, and facilitates understanding and translation to Agency partners and external stakeholders. These projects are critical to keeping assessment activities contemporary with emerging concepts in exposure sciences, advances in biotechnology, and the evolution of computational approaches and systems biology for understanding disease processes and ecosystem impacts. Refinements to current approaches are expected to improve the accuracy, efficiency, flexibility, and utility of applications across the large landscape of assessment activities served by the HHRA program and position it to be more agile and to better support characterization of wellness and sustainability.

Project 7: Advancing Hazard Characterization and Dose-Response Methods

Tasks in this project advance new approaches and refine procedures to address specific challenges that arise across HHRA assessment activities. Systematic review methods were recommended by the National Research Council (NRC, 2011) and aid transparency of assessment activities and inform evidence integration for determination of hazard. Steps include identifying relevant studies and evaluating their quality, identifying relevant endpoints for human health risk evaluation, evaluating mechanistic information, synthesizing study results within an evidence stream for a health effect (e.g., human, animal, mechanistic), and integrating qualitative and quantitative information across evidence streams. A task on advancing systematic review will continue to evaluate case studies, incorporate feedback from workshops conducted with stakeholders, and compare available approaches in order to develop tailored tools to HHRA assessment products. This work will result in consistent and transparent approaches for systematic review across HHRA assessment products.

PROJECT 7 HIGHLIGHTS
Advancing Hazard Characterization and Dose-Response Methods

- **Advancing systematic review methods**
- **Case studies to apply adverse outcome pathways (AOPs) and mode of action (MOA) to inform hazard characterization and dose-response**
- **Expansion of dose-response models**
- **Approaches to benefit-cost and uncertainty analyses**
- **Characterizing determinants of risk to support assessment of acute, short-term and episodic exposures**
- **Workshops on critical challenges**

Assessment activities have also identified more powerful statistical methods for dose-response and trend analysis that may improve quantification. More robust methods such as Bayesian approaches and model averaging for uncertainty analyses may also improve quantitative approaches and ensure better coverage of response. These methods will be evaluated with case studies and code developed to support subsequent implementation.

The HHRA program anticipates that in order to advance and achieve the vision proposed by the National Research Council for exposure

science and toxicology testing, these concepts must be applied in risk assessment approaches. As understanding of systems biology advances, mechanistic insights should help to incorporate other measures such as biomarkers and effects at different levels of biological organization into risk assessment for a fuller characterization of the spectrum of a disease outcome and the key events of pathogenesis. For example, how do new data mining tools for *in vitro* measures at the genomic level inform dose-response? As our understanding of the key events for different endpoints or diseases evolves, building bridges to systems biology requires construction of methods that can incorporate data on biomarkers from various disease dimensions (e.g., early or late-stage) in various tissues (e.g., blood or liver) of different species, and the ability to incorporate high-throughput data and AOPs with different degrees of verification.

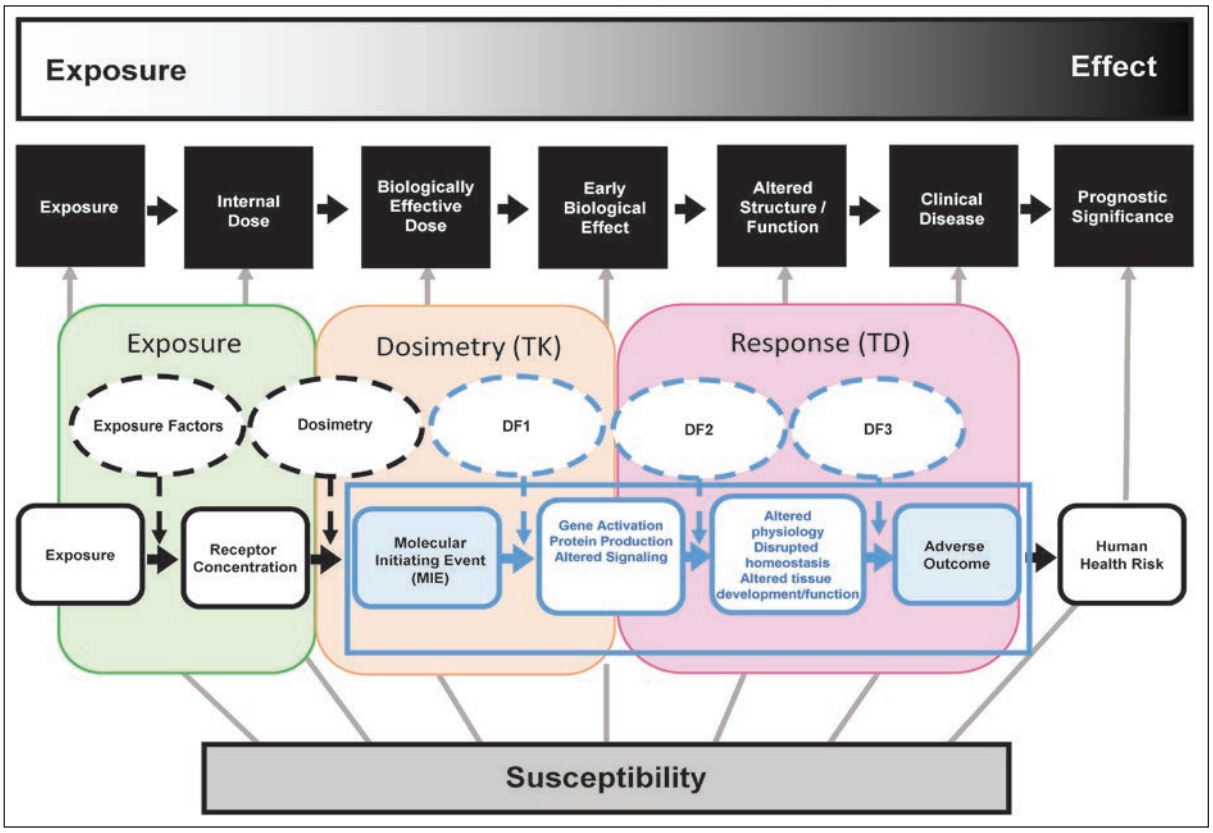


Figure 10. Conceptual construct showing the relationships of computational models and schematics developed for biomarkers, AOPs and MOA applied to risk assessment. The scheme of key events along the exposure-dose-response continuum is based on that of Schulte (1989) as proposed for biomarkers and modified by Jarabek et al. (2009) for mode of action (MOA). The blue box and blue-bordered key events outline elements of an adverse outcome pathway (AOP) described by Villeneuve et al. (2014). Key events of pathogenesis are depicted as solid border nodes, key event relationships are depicted as solid directed arrows between key events, and determining factors (DF) that control or may modify those relationships (e.g., ventilation rate; absorption, distribution, metabolism or elimination; repair, etc.) are depicted as dashed ovals and arrows. The areas covered by components of a biologically based dose-response (BBDR) model structure to support quantitative dose-response analysis are shown as the following: exposure models (green); dosimetry or physiologically based pharmacokinetic (PBPK) models of toxicokinetics (TK) to describe tissue delivery (orange); and tissue response or toxicodynamics (TD) models (pink). Markers or considerations of susceptibility inform all components of the continuum. For example, lifestage or disease state factors may influence parameter values for exposure, dose, and response.

The prognostic significance of various key events relative to more traditional endpoints and disease outcomes needs to be established to employ AOPs and MOA in risk assessment. Figure 10 provides a conceptual construct of the relationships among biomarkers, AOPs, and MOA, the types of computational models that can inform and improve the accuracy of descriptions for those relationships, and where considerations of susceptibility (e.g., due to lifestage or disease) may modify those relationships. Several applications of this knowledge are applied in tasks under Project 7.

A fuller characterization of disease pathogenesis also necessitates consideration of the nature of toxicity and how this relates to the various exposure scenarios that may require assessment. Real-world exposures include single acute duration increases in exposure and fluctuations in exposure levels (including repeated episodic increases). To best address these variables, accumulation of effects or the chemical must be characterized, and consideration given to susceptible life stages or windows of vulnerability. Determinants such as the concentration, duration, and timing of exposures for different classes of chemicals based on physicochemical characteristics (e.g., aldehydes versus volatile organic chemicals) and specific endpoints of interest across HHRA risk assessment products will be evaluated by targeted case studies aimed at developing new assessment products to characterize risks from various exposures.

Benefit-cost analysis is widely employed in evaluating environmental policies, enjoys widespread acceptance, and is required by Executive Order and certain statutes. Case studies will be used to explore extension of methods to qualitatively and quantitatively address benefit-cost and uncertainty analyses through review of literature, evaluation of available methods, and use and possible development of software. These will be targeted at critical disease outcome and effect measures of interest to partner program offices.

Other specific issues arise in various assessment activities or as emerging science and understanding evolve. For example, the IRIS assessment for inhaled methanol required development of methods to address endogenous background levels. The HHRA program devotes special workshops to discuss and evaluate specific issues as they arise in assessments with the broader scientific community and stakeholders. These workshops not only inform the specific assessments, but also enhance understanding and appreciation of current scientific challenges and thereby stimulate new research and methods to accelerate their application in assessments. As examples, past and near-term planned workshops to be convened by the HHRA program are devoted to the following issues:

- MOA for development of mouse lung tumors (2014)
- Workshop on systematic review methods (2014)
- Epigenetics workshop (September 2015)
- Advancing systematic review (December 2015)
- Temporal issues for environmental pollutants: Health effects and methodologies for estimating risk (January 2016)
- Characterizing and communicating uncertainty in human health risk assessment (2016)

Project 8: Applying Emerging Science to Inform Risk Screening and Assessment

This project is devoted to characterizing the utility of new data streams and computational tools, such as those developed by the CSS program and increasingly available from other sources such as the National Institutes of Health (NIH), university consortiums, and the clinical arena. The HHRA program plans to approach this characterization of HTS and other data mining outputs as applied to informing and improving HHRA risk assessment products in a step-wise fashion. Emerging data streams will be evaluated in the exposure-dose-response context of risk assessment in order to understand what key biological, spatial, or temporal features the new measures or computational tool may represent (Figure 10). This understanding is the basis for building confidence in and building capacity for employing emerging technologies across the assessment landscape spanning from research prioritization to risk screening, and ultimately quantitative dose-response analysis (Figure 5).

The HHRA program will approach the implementation of these new data and tools both from the perspective represented by understanding the significance of molecular initiating events (MIE) for chemicals with different physicochemical properties and associated with potential AOPs for predicting specific endpoints; as well as from the perspective of developing approaches for integrating these data and endpoints to describe different diseases. These are viewed as complementary approaches that evaluate evidence along the same continuum of potential disease pathogenesis.

The utility to characterize risk of various data from alternative, HTS platforms or approaches such as structural read-across/ quantitative structure-activity relationship (QSAR), *in vitro* biological activity assays (e.g., ToxCast), and toxicogenomics will be evaluated for different classes of chemicals and various endpoints commonly encountered in risk assessment. These case study characterizations should support the development of new assessment products and refined approaches to derivation of PPRTV and IRIS assessments.

Development of a disease - based data integration approach will begin with case studies of specific disease outcomes of interest to HHRA assessment priorities, such as that underway for inorganic arsenic. The approach will build on lessons learned in the report *Next Generation Risk Assessment: Incorporation of Recent Advances in Molecular, Computational, and Systems Biology* (U.S. EPA, 2014). This report was a collaborative effort by the CSS and HHRA programs and points to future directions for stronger collaboration and innovative applications of new data streams and computational approaches in risk assessment. Collaboration with the CSS program for developing screening and read-across applications is ensured by having HHRA scientists participate on the Demonstration and Evaluation project within CSS; these same scientists are involved in tasks that then apply the tools developed directly into informing PPRTV assessments or for developing new assessment products.

Another task is devoted to revising dosimetry adjustments to address multiscale integration of data in order to advance the application of AOP/MOA or biomarker data. Current models and guidance on choice of dosimetry models will be updated to describe potential dose metrics for key events at different levels of organization for portal-of-entry effects in the respiratory tract and other critical target tissues. These updates are necessary to inform both evidence integration approaches and to facilitate quantitative dose-response analyses in keeping with the NRC vision represented by Exposure21 and Tox21 recommendations (NRC 2007; 2011). This task and others on exposure will also evaluate how best to integrate with exposure modeling platforms.

Exposure assessment is also a key component integral to characterizing hazard and risk and an area of rapidly emerging scientific advances. There is broad recognition that the risk estimates used to protect human health and ecosystems would be improved with better exposure data (NRC, 2012). With the recent development of large environmental and chemical databases and personal and environmental sensors, there is great opportunity to improve methods to more accurately characterize exposure (e.g., intensity, frequency, duration, and route). However, to utilize the diverse array of newly available data for exposure assessments, methods are required to translate and adapt data into well-established exposure protocols. A task in Project 8 on the evaluation and application of new exposure data and methods is targeted to do so.

EPA's EXPOsure toolBOX (EPA-Expo-Box)[13] is a toolbox created by HHRA scientists to assist individuals from within government, industry, academia, and the general public with assessing exposure. It is a compendium of exposure assessment tools that links to guidance documents, databases, models, reference materials, and other related resources. Exposure assessment resources are organized into six Tool Sets, each containing a series of modules that can be accessed from the link below. In addition, links to resources on other over-arching topics can be accessed from the Quick Finder menu at the top of the homepage. EPA -Expo-Box also contains an Exposure Factors module which has been designed to improve the accessibility and usability of data from *EPA's Exposure Factors Handbook: 2011 Edition* (U.S. EPA, 2011). Work in this task will update EPA-Expo-Box and exposure factors data as new and improved tools and data become available. HHRA scientists will also develop new tools for accessing and updating data on ingestion factors and collaborate with the SHC research program to consider potential approaches for collecting soil and dust ingestion data.

Other new products under this task include development of the Exposure Factors Interactive Resource for Scenarios Tool (ExpoFIRST) and EPA-Eco-Box. ExpoFIRST is a standalone tool that draws from data in the EPA's Exposure Factors Handbook for quick, easy, and flexible development of human exposure scenarios. EPA-Eco-Box is being developed as a Web-based toolbox providing links to guidance documents, databases, and other relevant information for ecological risk assessors.

Another product in this task represents a joint venture with the National Institute for Occupational Safety and Health (NIOSH) Center for Direct Reading and Sensor Technologies. The analytical considerations underlying specific sensors and their interpretation will be a continued collaboration with other research programs employing such technologies including ACE, HSRP, and SSWR. Considerations for analytical characterization and guidance on interpretation of sensor data in risk assessment will be developed.

PROJECT 8 HIGHLIGHTS
Applying Emerging Science to Inform Risk Screening and Assessment

- **Characterizing utility of new data streams and computational tools applied to risk assessment products**
- **Case study exploration of disease-based data integration approaches**
- **Updated dosimetry models and guidance to support the application of adverse outcome pathway (AOP) key events and mode of action (MOA) in dose-response analyses**
- **Expanded exposure assessment tools and guidance**
- **Analytical considerations and interpretation guidance for selected emerging sensor data**

[13] http://www2.epa.gov/expobox

Project 9: Risk Assessment Support and Training

By providing high-quality targeted tools, data, and training, EPA enables consistency in assessment approaches by various stakeholders, enhancing the quality of assessment products and confidence in risk-based decision making. Stakeholder engagement regarding the output of the HHRA program is enhanced by training on risk assessment methods and outreach regarding risk assessment activities and applications. Feedback on the utility of various assessments, including their scope and content, cycles back to the problem formulation input for the program in the future.

Tasks under this project involve updating and maintenance of critical software infrastructure with enhanced features including data access, interoperability with other ORD models and databases, and transparency of assessments, such as the HERO database[14] of studies used in assessments and BMDS for dose-response modeling[15]. New software modules to support advances in evidence integration and extend dose-response methods will be developed. Training modules on new tools are also included to inform the risk assessment community of methods and advances in risk analysis, and to support consistency in risk assessment development.

One example of training that HHRA scientists have developed is the RATE program, a comprehensive set of risk assessment training modules in the four primary areas of hazard identification, dose-response assessments, exposure assessment, and risk characterization for both human health and ecological risk assessment. Additional areas of focus for guidance and training are risk management, risk communication, and new approaches in human health risk assessment methodology. Risk assessment training sessions using the RATE materials have been used in multiple national and international training efforts and support many of the ORD research programs by broadening the knowledge base of involved staff. The HHRA program will continue to support this training as an important resource for its program partners and external stakeholders.

PROJECT 9 HIGHLIGHTS
Risk Assessment Support and Training

- **Updating and maintenance of the Health and Environmental Research Online (HERO) database and benchmark dose software (BMDS) to support assessment activities and stakeholder engagement**
- **Enhanced features for interoperability and data access**
- **New modules to support advances in evidence integration and dose-response analyses**
- **Training to support understanding and consistency of risk assessment development**

[14] http://hero.epa.gov
[15] http://www2.epa.gov/bmds

Anticipated Research Accomplishments and Projected Impacts

The HHRA program has developed nine integrated project areas to provide a program structure that emphasizes efficient assessment development while advancing needed risk assessment-related analyses and applications. During the development of chemical assessments, cross-cutting issues may arise, and their resolution leads to advances in the state-of-the-science, as well as advancing knowledge and consistent use of methods and models by the risk assessment community. Anticipated accomplishments under these project areas are briefly listed below and selected proposed outputs are presented in table format in Appendix A. These HHRA program activities also inform the four ORD roadmaps (Climate Change, Children's Environmental Health, Environmental Justice, and Nitrogen/Co-pollutants).

Topic 1: Integrated Risk Information System (IRIS)

The IRIS program will continue to produce robust and responsive assessments to characterize risks addressing Agency priorities. The program is implementing enhancements to the efficiency of its process and stakeholder engagement, providing more opportunity for participation in problem formulation and tailoring the scope of its assessments. A multi-year plan resulting from significant program partner input will ensure that the highest priorities for the Agency will be addressed and timely, and a process to update IRIS assessments will ensure that assessments remain based on the most relevant and current information for key chemicals. Incorporating advances in assessment methods will include application of systematic review methods for hazard characterization and evidence integration, and new methods for dose-response analysis and insights from mechanistic understanding will be applied when mature. Public science meetings and ongoing website upgrades will enhance communication of the program's progress and status, while a handbook of operating procedures will provide both education, transparency, and consistency regarding assessment development. The HHRA program is committed to maintaining IRIS as the premier source of health hazard and dose-response information for priority environmental pollutants.

Topic 2: Integrated Science Assessments (ISAs)

The HHRA program will continue to work in close collaboration with the primary client office, OAR, OAQPS, as well as CASAC and other stakeholders, to develop ISAs as a major component of its research portfolio to identify, interpret, and characterize data on the health and environmental effects of exposure to criteria air pollutants. The HHRA program also provides sustained scientific and technical support during the development of exposure, risk, and policy assessments by OAQPS, and during national rule development. Advances in scientific understanding of the MOA and key events of the disease pathways for these pollutants will help integrate the evidence for determining these risks as well as inform approaches for other HHRA assessment products such as the IRIS assessments. During the FY2016-2019 period, other innovations in analysis approaches are anticipated as the HHRA program grapples with characterizing the health and welfare effects of SO_2 and NO_2. New insights on determinants of PM toxicity will inform ISA development and use as the scientific basis for decisions to retain or revise the NAAQS.

Topic 3: Community and Site-specific Risk

The HHRA program will continue to support the risk management decisions required by the Office of Solid Waste and Emergency Response (OSWER), and to address community needs. Annual production of PPRTV assessments targeted to the priorities of OSWER will continue to provide the scientific support for decisions on the management of municipal and hazardous waste sites. Application of new data streams and approaches will occur as their utility is characterized and may extend to additional assessment products for rapid response to urgent contamination situations. Significant technical support will continue to aid regions in implementation and understanding of these assessments. Efforts on extending and targeting cumulative risk assessment methods to integrate multiple stressors will help communities understand and characterize their "place-based" concerns. Specific case studies and approaches will be explored to develop exposure and risk apportionment to different exposure media (air, water, land) and to provide for the integration of ecological and human effect measures. We also anticipate that work on the role of susceptibility and epigenetic markers will be developed into a framework for incorporating these considerations into CRA approaches, thereby ensuring relevancy and that the latest innovations in biomonitoring are addressed.

Topic 4: Advancing Analyses and Applications

Projects in this area cut across the entire HHRA program portfolio to ensure that its assessment products will keep contemporary with emerging concepts in hazard and dose-response assessment, exposure sciences, advances in biotechnology, and the evolution of computational approaches and systems biology for understanding disease processes and ecosystem impacts. Refinements to current approaches are expected to improve the accuracy, efficiency, flexibility, and utility of applications across the large landscape of assessment activities served by the HHRA program and position it to be both more agile and better support characterization of wellness and sustainability. Sustaining support of databases and software will ensure transparency of assessments and facilitate communication and consistency of assessment development. Training will increase both understanding of methods and stakeholder capability for applying assessment advances. Some specific areas to be advanced are: refinements to systematic review, extensions of dose-response analyses for model averaging and data integration, and approaches to benefit-cost analyses and uncertainty characterization. Updates to dosimetry models will facilitate the use of MOA and AOP insights and inform new approaches to the characterization of acute, short-term, and episodic exposures. Application of emerging sensor data will include both analytical considerations and interpretation, while updates to exposure assessment tools will continue to be developed to translate and describe factors that influence exposure characterization.

Conclusions

Human health risk assessment is the process of analyzing information to estimate the potential for an environmental pollutant to harm exposed persons and ecosystems, and the assessment documents that are the product of this process are fundamental to environmental management decision making. Scientific evidence from diverse disciplines must be systematically identified, consistently evaluated for scientific merit and relevance, and integrated to support development of human health and environmental risk assessments. By fully engaging the scientific and policy communities in the HHRA program, EPA is producing reliable, transparent, and high-quality assessments while identifying the scientific research needed to advance future assessments and ensure effective translation and communication of the Agency's assessment methods, models, and data. The outcome of this HHRA Strategic Research Action Plan will be highly influential scientific assessments used to support important and complex Agency decisions to protect human health and the environment, coupled with advances in risk assessment methods that increase confidence in the application of science to support such decisions.

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Appendix 1

Proposed Outputs, Human Health Risk Assessment Research Program FY16–19

The following table lists the expected outputs from the Human Health Risk Assessment research program, organized by topic. Note that outputs may change as new scientific findings emerge. Outputs are also contingent on budget appropriations.

Topic 1	Integrated Risk Information System (IRIS)
Project 1	**IRIS Assessments**
IRIS document components	Annually released to the public for priority chemicals following the multi-year agenda posted on the IRIS website: • Scoping and problem formulation packages • Literature searches and study tables • Interagency review drafts • External peer review drafts • Final assessments
IRIS scientific and technical consultations	HHRA scientists provide scientific support to assessments by identifying issues and advancing solutions; Technical support to program offices regarding implementation of IRIS assessments in regulatory applications (e.g., OAQPS residual technology review, OW contaminant candidate list, OSWER records of decision)
Stakeholder engagement and outreach for IRIS program	Bi-monthly scientific meetings on assessment activities; Regular meetings with program partners regarding priorities
IRIS Handbook of Operational Procedures	Ongoing guidance on assessment approaches and process
Project 2	**IRIS Updates**
Decision Strategy	FY16 Develop approach for identifying assessments that should be updated with high priority FY16 Develop efficient processes for developing and reviewing updated assessments in a short time
Reviews and updates	FY16-19 Implement IRIS update decision strategy and regularly review IRIS values.

Topic 2	Integrated Science Assesssments (ISA)
Project 3	**Integrated Science Assessments**
ISA science issue workshops	Convene scientific experts to review and identify scientific or policy issues prior to initiation of ISA development
ISA document drafts	Release external peer review drafts for Clean Air Scientific Advisory Committee and public reviews • FY16 1st draft NO_2 & SO_2 secondary (welfare) ISA • FY16 2nd draft NO_2 & SO_2 secondary (welfare) ISA • FY16 1st draft of ISA for PM • FY17 2nd draft of ISA for PM Release final ISA documents in support of National Ambient Air Quality Standards (NAAQS) • FY16 Final rulemaking on lead • FY16 SO_2 primary (health) • FY17 NO_2 & SO_2 secondary (welfare) • FY18 Final rulemaking on SO_2 primary (health) and NO_2 primary (health) • FY19 Final rulemaking on NO_2 & SO_2 secondary (welfare)
ISA-related scientific and regulatory support	Support to Office of Air and Radiation regarding implementation of ISA to policy assessment and rule making for decisions regarding review, retention or revision of the NAAQS • FY16 Integrated review plan for PM ISA • FY16-18 NO_2 primary (health) ISA • FY16-18 SO_2 primary (health) ISA
ISA-related scientific advancements	Multipollutant science document health issues; Multipollutant science document on the effects of the criteria pollutants on climate forcing; Publications and scientific analyses to support the ISAs

Topic 3	Community and Site-specific Risk
Project 4	**Provision peer-reviewed toxicity values (PPRTV) assessments**
PPRTV assessments	≥12 developed annually in support of OSWER site management decisions
Project 5	**Site-specific and Superfund Regulatory Support**
Superfund Technical Support Center and Ecological Risk Assessment Support Center	FY16-19 Provide on-going support to EPA regional offices for Superfund risk assessment activities and scientific support for ecological risk assessment
Report on technical support	FY16-19 Provide quarterly reports on technical support
Emergent issues and other Agency priorities	FY16-19 Annually provide rapid assessment response (e.g., West Virginia MCHM spill) or other scientific support on Agency priorities as requested by programs, regions, EPA Science Advisory or Administrator
Project 6	**Cumulative Risk Assessment Methods and Applications**
Approaches to cross-species data integration to support cumulative risk assessment (CRA)	FY17 Publication of case study(s) to advance incorporation of ecological risk assessment into CRA framework FY18 Develop multi-criteria decision analysis approaches to integrate ecological and human health indices and aid transparency of valuations
Incorporating multiple stressors	FY16 Publication of journal manuscript describing use of directed acyclic graphs for drawing causal inference in CRA FY17-19 Case studies and methods development to characterize risks posed by multiple chemical and non-chemical stressors to human health.
Incorporating susceptibility information into CRA	FY16 Report from science workshop on epigenetics and CRA FY19 Publication of a framework for interpreting epigenetic information in risk assessment
Apportioning multimedia exposure and risk across human and ecological receptors	FY17 Modeling of dermal and inhalation exposures to diethyl- and di(1-n-butyl) phthalate to inform evaluation of mixtures FY18 Apportioning multimedia exposure and risk across human and ecological receptors FY16-19 Support Risk Assessment Forum activities on cumulative phthalate exposures

Topic 4	Advancing Analyses and Applications
Project 7	**Advancing Hazard Characterization and Dose-Response Methods**
Advancing methods for systematic review and evidence integration	FY16 Scientific workshop report on advancing systematic review FY17 New methods to improve evidence identification, evaluation and evidence integration FY17 Refine study quality evaluation approaches
Advancing quantitative methods	FY18 Develop multivariate dose-response analysis methods FY19 Report on best practices for non-parametric, semi-parametric, and parametric dose-response modeling methods FY19 Report on methods to advance meta-analyses and Bayesian approaches
Advancing methods for benefits and uncertainty analyses	FY18-19 Case studies to evaluate approaches to probabilistic derivation of reference values to support benefits analysis
Characterizing determinants of risk: Concentration, duration and timing of exposure	FY17 Publish workshop report on Temporal Issues for Environmental Pollutants: Health Effects and Methodologies for Estimating Risk FY19 Report on evaluation and quantification of early-life exposures for non-cancer and cancer outcomes FY19 Concentration-duration-response surface evaluation and interpretation to support derivation of assessments of acute, short-term, episodic and lifetime exposures
Scientific workshops on major risk assessment methodology issues	FY16-19 Convene scientific workshops held with subject matter experts to address current challenges and advance approaches to risk assessment
Project 8	**Applying Emerging Science to Inform Risk Screening and Assessment**
Disease-based integration of new data types	FY19 Case study(s) of disease-specific assessment of multiple environmental risk factors to illustrate integrated use of multiple, new advanced biological data types
Characterization and quantitative application of high-throughput screening (HTS) and other data-mining derivations	FY18 Case studies to characterize the utility of HTS and other data for various classes of chemicals and various endpoints commonly encountered in risk assessment FY18 Adverse outcome pathway (AOP) footprinting: hazard grouping and quantitative analysis for mixtures assessment of toxicologically uncharacterized stressors

Dosimetry21: Advancing multiscale dosimetry models to incorporate AOP/Mode of Action (MOA) and biomarker data	FY16-17 Convene Federal community of practice to develop an issue paper for NRC review and report regarding need for multiscale measurement and models to address application of AOP/MOA or biomarker data and realize vision of Tox21 and Exposure21 reports FY19 Development of a suite of model structures including portal-of-entry for each route and implementation via development of methods and case studies to implement anticipated NRC recommendations
Evaluation and application of new exposure data and methods	FY17 Advancements and updating of Exposure Factors Handbook (Draft food intake) FY17 Release of ExpoFIRST - quick, easy, and flexible development of human exposure scenarios (ß and final) FY18 Release of EPA-Eco-Box - quick, easy, and flexible development of ecologic risk assessment scenarios (draft and final) FY16-18 Collaboration with NIOSH Center for Direct Reading and Sensor Technologies and the cross-agency Air Sensors Health Group to develop criteria for analytical characterization, integration of sensor data with dosimetry modeling, interpretation of sensor data on application to risk assessment, and recommendations regarding best practices for management and curation of sensor data.
Project 9	**Risk Assessment Support and Training**
Development and maintenance of essential software and support tools	FY16-19 Update and maintain software supporting critical infrastructure activities including data access (IRIS website) and assessments (Health and Environmental Research Online); benchmark dose software, PBPK/dosimetry software, etc. FY16-19 Development of new software modules to implement advances in evidence integration and dose-response methods and applications of new data streams and mechanistic data mining
Development and application of risk assessment training	FY16-19 Provide ongoing outreach to states, regions, program offices and international entities interested in training on risk assessment approaches and techniques

Appendix 2.

Executive Orders and EPA Policies HHRA Supports

Executive Order 13045: Protection of Children from Environmental Health Risks and Safety Risks, which states that each federal agency "(a) shall make it a high priority to identify and assess environmental health risks and safety risks that may disproportionately affect children; and (b) shall ensure that its policies, programs, activities, and standards address disproportionate risks to children that result from environmental health risks or safety risks."

EPA's 1995 Policy on Evaluating Risk to Children, which states that "It is the policy of the U.S. Environmental Protection Agency (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."

Executive Order 12898: Federal Actions To Address Environmental Justice in Minority Populations and Low-Income Populations, which states that "(a) Environmental human health research, whenever practicable and appropriate, shall include diverse segments of the population in epidemiological and clinical studies, including segments at high risk from environmental hazards, such as minority populations, low-income populations and workers who may be exposed to, substantial environmental hazards" and "(b) Environmental human health analyses, whenever practicable and appropriate, shall identify multiple and cumulative exposures."

EPA's 2011 Environmental Justice Action Plan ("Plan EJ 2014"), which established measurable commitments that address the Agency's national environmental justice priorities. These priorities created an Agency-wide focus on matters that environmental justice advocates and others have identified as critical environmental justice issues. In 2015, EPA is developing the EJ 2020 Action Agenda, the Agency's next overarching strategic plan for environmental justice.

Executive Orders 12866, 13563 and OMB Circular A-4, which guide the analysis of the costs and benefits of Federal regulatory decisions, including the assessment of the public health and environmental benefits associated with regulatory options. HHRA health assessments play a crucial role in the assessment of the benefits of actions taken by EPA; potential improvements in how noncancer dose-response is quantified, as discussed elsewhere in this document, have been identified as important to advancing EPA benefits analysis for regulatory support.

Appendix 3.

Research Program Partners and Stakeholders

Note: HHRA works with many partner and stakeholder organizations, and new partnerships are continually forming; therefore, this list is not comprehensive.

EPA Board of Scientific Counselors (BOSC)

EPA Clean Air Scientific Advisory Committee (CASAC)

EPA Science Advisory Board (SAB)
- *Chemical Assessment Advisory Committee (CAAC)*

EPA Regions 1 – 10

Office of Air and Radiation (OAR)
- *Office of Air Quality Planning and Standards (OAQPS)*
- *Office of Transportation and Air Quality (OTAQ)*

Office of Chemical Safety and Pollution Prevention (OCSPP)
- *Office of Pesticide Programs (OPP)*
- *Office of Pollution Prevention and Toxics (OPPT)*
- *Office of Science Coordination and Policy (OSCP)*

Office of Children's Health Protection (OCHP)

Office of Environmental Justice (OEJ)

Office of Policy (OP)
- *National Center for Environmental Economics (NCEE)*

Office of the Science Advisor (OSA)

Office of Solid Waste and Emergency Response (OSWER)
- *Office of Emergency Management (OEM)*
- *Office of Underground Storage Tanks (OUST)*
- *Office of Superfund Remediation and Technology Innovation (OSRTI)*
- *Office of Resource Conservation and Recovery (ORCR)*
- *Office of Program Management (OPM)*

Office of Water (OW)
- *Office of Ground Water and Drinking Water (OGWDW)*
- *Office of Science and Technology (OST)*

Other Governmental Stakeholders

Agency for Toxic Substances and Disease Registry (ATSDR)

California's Environmental Protection Agency (Cal/EPA)
- *Office of Environmental Health Hazard Assessment (OEHHA)*

Centers for Disease Control and Prevention (CDCP)

Department of Defense (DoD)
- *Air Force Research Laboratory (AFRL)*
- *Army Corps of Engineers (ACE)*
- *Army Public Health Command*
- *Defense Advanced Research Projects Agency (DARPA)*
- *Naval Medical Research Unit (NAMRU)*

Department of Labor
- *Occupational Safety and Health Administration (OSHA)*

Food and Drug Administration (FDA)
- *National Center for Toxicological Research (NCTR)*

National Academy of Sciences (NAS)

Government Accountability Office (GAO)

National Institutes of Health (NIH)
- *National Cancer Institute (NCI)*
- *National Institute of Environmental Health Sciences (NIEHS)*
  - Chemical Genomics Center (CGC)
  - National Toxicology Program (NTP)

Texas Commission on Environmental Quality (TCEQ)

Nongovernmental Organizations

Alliance for Risk Assessment (ARA)

American Public Health Association (APHA)

American Chemistry Council (ACC)
- *Long-Range Research Initiative (LRRI)*

Environmental Working Group (EWG)

Environmental Defense Fund (EDF)

Environmental Council of the States (ECOS)

Interstate Technology and Regulatory Council (ITRC)

Integrated Life Sciences Institute (ILSI)
- *Health and Environmental Science Institute (HESI)*

National Resource Defense Council (NRDC)

Appendix 4. Enhancements to IRIS Program

The IRIS program develops human health assessments that provide health effects information on environmental chemicals to which the public may be exposed, providing a critical part of the scientific foundation for EPA's decisions to protect public health. In their report *Review of the Environmental Protection Agency's Draft IRIS Assessment of Formaldehyde*, the National Research Council (NRC) made several recommendations to EPA for improving IRIS assessments and the IRIS program (NRC, 2011). The NRC's recommendations were focused on the first step of the IRIS process, the development of draft assessments. Consistent with the advice of the NRC, the IRIS program is implementing these recommendations using a phased approach and is making the most extensive changes to assessments that are in the earlier stages of the IRIS process.

EPA agreed with the NRC's 2011 recommendations for the development of IRIS assessments and is fully implementing them consistent with the report's "Roadmap for Revision," which viewed the full implementation of their recommendations by the IRIS program as a multi-year process. In response to the NRC's 2011 recommendations, the IRIS program has made changes to streamline the assessment development process, improve transparency, and create efficiencies in the program. The NRC has acknowledged EPA's successes in this area. Their May 2014 report *Review of the Integrated Risk Information System (IRIS) Process*, finds that EPA has made substantial improvements to the IRIS program in a short amount of time (NRC, 2014). They also provide several recommendations which they say should be seen as building on the progress that EPA has already made.

This appendix provides a brief summary of the status of enhancements to the IRIS program. Strengthening and streamlining the IRIS program is an ongoing priority for the HHRA program. As the IRIS program continues to evolve, the HHRA program is committed to evaluating how well its approaches promote constructive public discussion with its stakeholders, as well as reviewing how these approaches can more effectively facilitate subsequent assessment development. Enhanced stakeholder engagement will help to ensure transparency and the use of the best available science in IRIS assessments. More information on the IRIS program's recent enhancements can be found at http://go.usa.gov/cc7MB and http://go.usa.gov/cc7FT.

Enhancements to the Development Process

The IRIS program is implementing the following, which will help meet the goal of producing high-quality assessments that are tailored to program needs in a timely and transparent manner:

- Internal planning and scoping meeting to identify EPA needs, followed by a public meeting to identify the available scientific information for the chemical under assessment.
- Publicly release the literature search and search strategy, evidence tables, exposure-response figures and information on key scientific issues for the chemical. Convene a public meeting to discuss these materials.
- Publicly release a draft assessment and peer review charge for comment at a public meeting (these may be revised as needed after the public meeting).

Improving the Science of IRIS Assessments

The following changes were either implemented or are in progress to improve the quality and clarity of IRIS assessments:

- Implemented a new document structure that is clear, concise and systematic.
- Incorporated a preamble that describes the application of existing EPA guidance and the methods and criteria used in developing the assessments.
- Strengthened its practices for peer review and protection against conflict of interest.
- Dedicated a specific Chemical Assessment Advisory Committee (CAAC) of the Science Advisory Board (SAB) to review IRIS assessments. More information on the SAB CAAC can be found at: http://go.usa.gov/cc7GW.
- Created Discipline-Specific Workgroups and Interdisciplinary Science Teams to evaluate endpoint-specific and disciplinary issues relevant to an assessment. These groups coordinate across assessments to ensure consistency, solve cross-cutting issues, and advance scientific understandings that contribute to decision making in IRIS assessments.
- Adopted systematic review methods and information management tools to improve study selection and analyses including improvements to the following:
  - Evidence Identification: Literature Collection and Collation Phase
    A separate section provides a detailed description of the literature search and associated search and screening strategy to identify and select pertinent studies.
  - Evidence Evaluation for Hazard Identification - The IRIS program is in the process of improving and standardizing the approach to evaluating evidence and standardizing the documentation of this evaluation.
  - Developed standardized presentation of evidence tables and exposure-response arrays to succinctly summarize study design and findings.
  - Improved process for selecting studies for dose-response evaluation.
  - Currently evaluating considerations for combining data for dose-response modeling and analysis.

Enhancements to Improve Productivity and Transparency in the IRIS Program

- Improved workforce planning to help increase assessment output and improve scientific evaluation.
- Conducting a survey of EPA program and regional offices to identify and evaluate client demands and the resources required to meet user needs.
- Focused staff attention on a smaller number of assessments to ultimately increase the efficiency and output of the program.
- Established a set of "stopping rules" for new data and scientific issues to help ensure that IRIS assessments are not delayed by new research findings or ongoing debate of scientific issues after certain process points have passed. Additional information about the stopping rules is available at http://go.usa.gov/cc76W.
- Improved stakeholder engagement in the IRIS process throughout assessment development through the conduct of IRIS Public Science meetings. These meetings benefit from the participation of independent experts identified by the NRC who provide input on the scientific and technical aspects of IRIS chemical assessments.
- Holding peer consultation science workshops which may focus on the state of the science for a particular chemical or provide a forum for discussion with experts about certain cross-cutting scientific issues that may impact the development of a scientifically complex assessment.

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