



# Human Health Risk Assessment

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## Strategic Research Action Plan, 2016-2019 (Preliminary Draft)

U.S. EPA  
Office of Research and Development  
Washington, DC 20460

**PRELIMINARY DRAFT NOTICE:** This Strategic Research Action Plan, 2016-2019, is a preliminary draft. It has not been formally released by the U.S. Environmental Protection Agency (EPA) and should not at this stage be construed to represent Agency policy, nor the final research program.

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## I. Executive Summary

*[To be completed in Final Strategic Action Plan for the Human Health Risk Assessment Program.]*

## II. Introduction

This *Human Health Risk Assessment Strategic Research Action Plan, 2016-2019* presents the strategic plan for the Environmental Protection Agency's (EPA) Human Health Risk Assessment research program, and how that program is integrated into the overall research portfolio of the Agency's Office of Research and Development (ORD).

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.

This *Strategic Research Action Plan* was developed using considerable input and support from partnerships from within EPA program offices and regions, as well as from outside stakeholders, nonprofit human health and research organizations, private industry, and colleagues across the scientific community.

The plan builds upon and continues to advance the research outlined in the action plan released in June 2012: *Human Health Risk Assessment Strategic Research Action Plan, 2012-2016*. That plan is one of six, one for each of ORD's national research programs.

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.

**NOTE:** The focus of discussion at the July 2014 SAB/BOSC meeting will be on Objective 2: Refine risk assessments by identifying critical issues and advancing analytical approaches and applications to incorporate new science, methods, and technologies (see pp 6-9), Topic A: Research to Advance Analyses and Applications (see pp 13-14), and Topic D: Community and Site-Specific Risk (see pp 17-19).

### III. Program Purpose

Every day, the U.S. Environmental Protection Agency (EPA) must make decisions about environmental pollutants that impact human health and the environment. There are currently more than 80,000 chemicals in commerce, and more are introduced each year. Only a small fraction of these chemicals have been adequately assessed for potential risk, often because of limits in existing data, tools, and resources.

The EPA's Human Health Risk Assessment (HHRA) research program supports risk management decisions to protect human health and the environment.

The purpose of HHRA research program is to develop and apply state-of-the-science risk assessment methods to estimate health and environmental risks from exposures to chemicals, mixtures, and non-chemical stressors. The HHRA program identifies, evaluates, integrates and translates existing and emerging scientific information from different scientific disciplines to accurately assess hazard and characterize risks. Its portfolio of assessment applications ranges from rapidly estimating hazard for screening and prioritization of further testing and assessment, through development of provisional peer-reviewed toxicity values, to extensively vetted assessments in support of national standards. Thus, the HHRA research program is uniquely positioned to support 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.

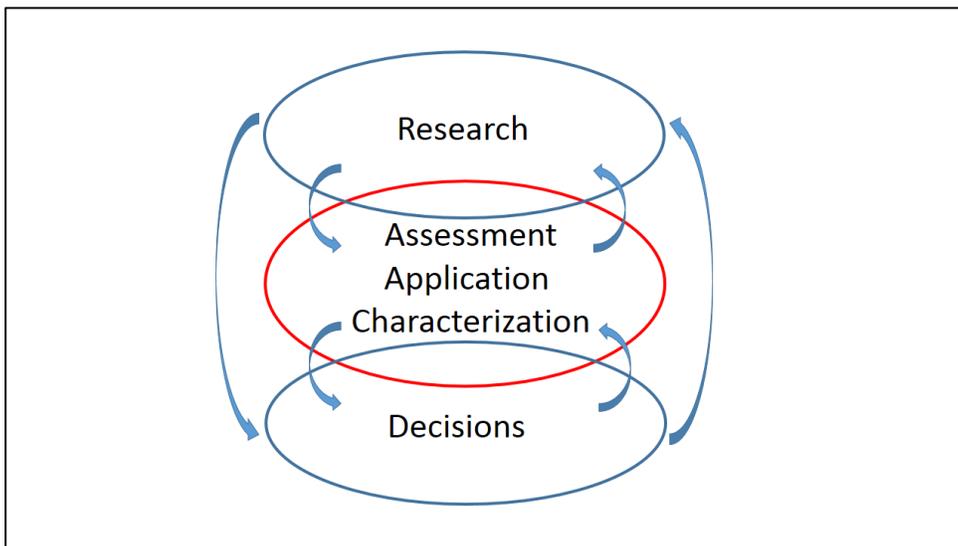
As part of the larger Office of Research and Development strategy, the HHRA research program works in concert with other ORD research programs and program partners to identify, analyze, translate, and characterize research as applied in its various assessment activities to support and improve environmental decisions. This pivotal role of the HHRA program with respect to the overall ORD research portfolio and Agency risk management decisions or regulatory activities is illustrated in Figure 1. Additionally, challenges encountered in the assessment activities of the HHRA research program identify critical research needs and help to advance the development of new applications both by research conducted in the HHRA research program and by stimulating the broader scientific and risk management communities.

#### III.A. Problem Statement

Predicting impacts and protecting human health and the environment depend on bringing the best available science to describe potential hazards and to characterize risks for a variety of exposure scenarios. The wide range of decisions made by EPA and other stakeholders requires a comprehensive suite of application products and analytical approaches that tailor assessments to fit the purpose of these various management decisions.

### III.B. Program Vision

Risk-based decisions by the 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 research 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, mixtures and non-chemical stressors. The assessments generated by the HHRA research program inform a variety of risk management decisions, and serve to identify critical scientific issues and advance analytical approaches for their resolution.



**Figure 1.** Position of HHRA Research Program (center red oval) with Respect to Overall ORD Research Portfolio and Agency Risk Management Activities

## IV. Research Supports EPA Priorities and Mandates

### IV.A. Statutory and Policy Context

The HHRA research program supports EPA’s statutory authority and mandates to conduct work under:

- 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 CAA 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

research 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, arsenic, sulfate and radon. The SDWA 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 are established. Other research provisions address risks associated with waterborne disease, complex mixtures and unregulated contaminants (e.g., development of Contaminant Candidate List).
- The **Food Quality Protection Act (FQPA)** of 1996 requires assessment of risk from exposures to pesticides, including aggregate exposures and cumulative risk and risk to sensitive subpopulations (e.g., infants and children).
- 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 **Resource Conservation and Recovery Act (RCRA)** directs EPA to conduct research and address risks to human health and the environment from the management of hazardous and other solid wastes.

The HHRA research program also is responsive to and supports several Executive Orders and EPA policies. See Appendix B for details.

#### IV.B. EPA Priorities

The HHRA program addresses all of the Strategic Goals in the *Fiscal Year 2014-2018 EPA Strategic Plan*, i.e., 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". HHRA research also supports the cross-agency strategies within this plan, specifically "Working Toward a Sustainable Future" and "Making a Visible Difference in Communities."

Activities conducted under the HHRA research 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 stakeholder). The HHRA research program conducts regular meetings with its program partners. An annual meeting held in May 2014 was focused on the early development of this Strategic Research Action Plan for research on challenges in two of its topic areas, Community and Site-specific Risk and Research to Advance Analyses and Applications.

## V. Research Objectives

The three main research objectives of the HHRA program 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 education.

### Objective 1

**Characterize risks and potential impacts to human health and the environment with a suite of state-of-the-science assessment products tailored to address a range of decisions regarding exposure to pollutants.**

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 (MSD) to support review of the National Ambient Air Quality Standards (NAAQS), and Provisional Peer-Reviewed Toxicity Values (PPRTV) for decision making at hazardous waste sites. The priorities for these products are described in the program design and 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) for the ISAs.

#### *Challenges:*

*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.*

*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 - Research Objective 2 is a focus of the July SAB/BOSC meeting

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

Objective 2 is 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

within Objective 1 may also provide problem formulations consistent with the research foci of Objective 2. Other issues arise as challenges in applying emerging biotechnology or disciplinary advances in the larger scientific community, or in applying research and data developed in other EPA ORD programs such as that from the Chemical Safety for Sustainability (CSS) research program.

The HHRA research program supports a range of regulatory activities by its partners in a fit-for-purpose fashion as illustrated in Figure 2. 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 an endpoint to serve as a surrogate versus established outcome measures in assessments. The use of new data or tools must typically be characterized in this context, with the application fitting the purpose or problem formulation of the assessment activity.

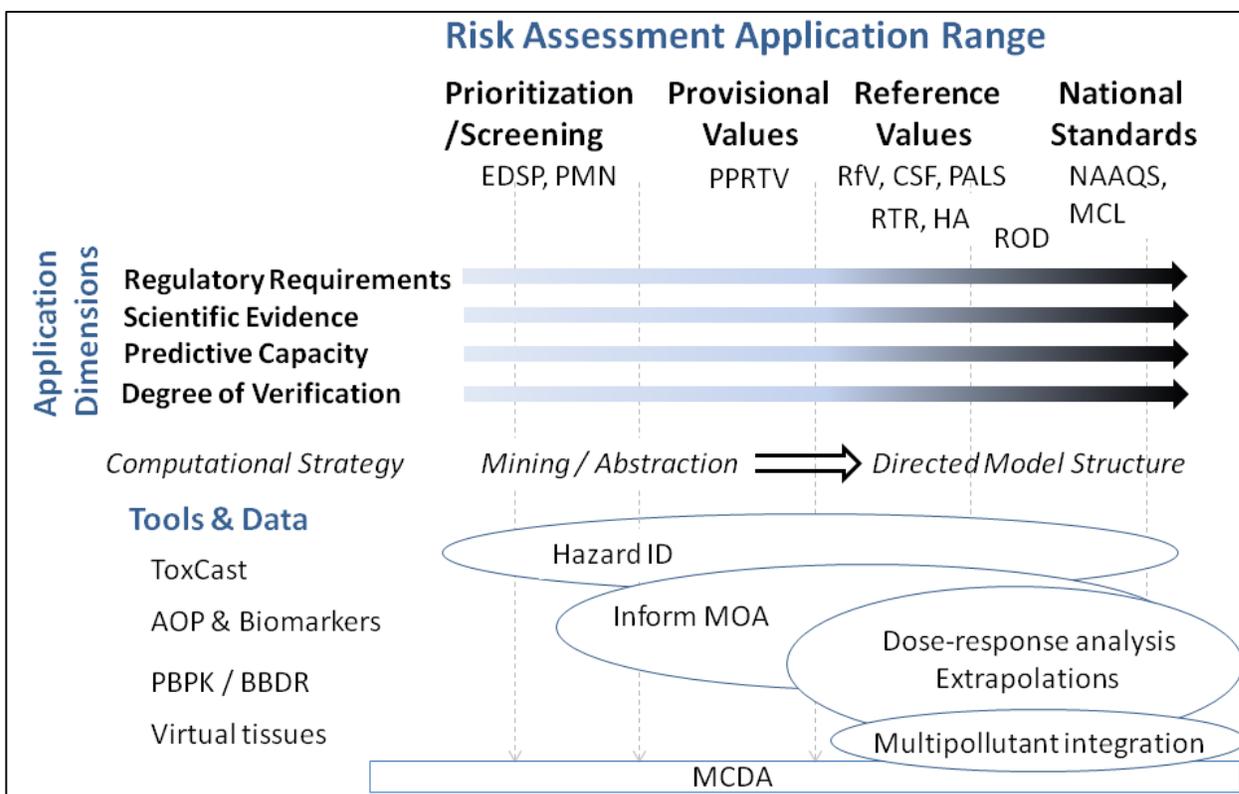
*Challenges:*

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

*Science challenge 2: Broaden exposure assessment technology to translate exposure and dose estimates to flexibly address different exposure scenarios.*

*Science challenge 3: Update dosimetry modeling approaches to predict a profile of internal dose metrics across all routes to support use of Mode of Action (MOA), Adverse Outcome Pathways (AOP) and aggregate or cumulative risk applications.*

*Science challenge 4: Expand cumulative risk assessment methods to advance “place-based” community risk characterizations and support sustainability*



**Figure 2. Range of application dimensions required across risk assessment landscape varies based on “fit for purpose”. Role of tools and data may be different depending on assessment context. (Acronyms provided in Appendix F).**

A focal area within this research objective is developing a strong bridge to the Chemical Safety for Sustainability (CSS) research program for efficient evaluation and application of new data streams and tools that this research program develops. The report “*Next Generation Risk Assessment: Incorporation of Recent Advances in Molecular, Computational, and Systems Biology*” (U.S. EPA 2014) was a collaborative effort by the two research programs and points to future directions for innovative applications of new data streams and computational approaches in risk assessment. As our understanding of the key events for different endpoints or diseases evolves, building bridges to systems biology requires construction of analytical 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 adverse outcome pathways (AOP) with different degrees of verification.

*Science challenge 5: Improve prioritization and rapid response by evaluating and incorporating new data streams and developing rapid assessment approaches.*

*Science challenge 6: Develop approaches to incorporate current understanding of key events, AOP, 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 7: Refine dose-response analysis by advancing approaches for risk and uncertainty characterization across spectrum of duration and dose.*

*Science challenge 8: Advance decision analytic and probabilistic approaches to more fully characterize dose-response functions and thereby better inform benefit-cost analyses.*

### Objective 3

#### **Develop and employ state of the art risk assessment technologies and engage stakeholders to ensure support, training, and tailoring of assessment priorities and products.**

This objective is aimed at continual improvements in technologies supporting efficient assessment development and at outreach to improve understanding of risk assessment issues and methods and to foster development of risk assessment capabilities by various stakeholders. Development and continual improvement of the Health and Environmental Research Online (HERO) system ([www.epa.gov/HERO](http://www.epa.gov/HERO)) supports enhanced assessment development and transparency through access to scientific literature underlying assessment products. Outreach efforts can take the form of public workshops, seminars and training sessions and varied communication approaches (e.g., web posting, emails, blogs).

#### *Challenges:*

*Science challenge 1: Enhance data access and management systems to support transparency and efficiency.*

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

### Cross Cutting Objectives

The HHRA research program is a full partner with collaborations with all of ORD's cross-cutting research roadmaps: Children's Environmental Health, Nitrogen and Co-Pollutants, Climate Change, and Environmental Justice (EJ). HHRA additional interactions across the National Research Programs include:

- Chemical Safety for Sustainability (CSS) – Evaluation and application of new data in risk screening and assessment
- Safe and Sustainable Water Resources (SSWR) – Assessment of deposited oxides of nitrogen and sulfur on surface water quality
- Homeland Security Research Program (HSRP) – Incorporation of resiliency into cumulative risk assessment methods and coordination on rapid response assessment

- Sustainable and Healthy Communities (SHC) - Development of Cumulative Risk Assessment (CRA) methods and decision analytic software to support “place-based” community assessment and link health and ecology to well-being
- Air, Climate and Energy (ACE) – incorporation of NAAQS research (including climate as a welfare effect) into Integrated Science Assessment; IRIS assessments of air toxics

## VI. Anticipated Research Accomplishments

### Research Objective 1:

- *Complete state-of-the-science IRIS assessments for priority pollutants, at an increasing pace, by developing and applying systemic review and evidence integration approaches.*
- *Complete ISA and associated scientific analyses and consultations to support regulatory decisions on NAAQS for particulate matter, ozone, carbon monoxide, lead, and sulfur and nitrogen oxides.*
- *Complete  $\geq 12$  PPRTV assessments annually to support effective risk management decisions at hazardous waste sites.*

### Research Objective 2:

- *Develop EPA-Expo-Box extensions to support program and community risk assessments using state-of-the-science methods that describe, evaluate and translate different exposure scenarios and experimental designs and thereby tailor characterizations of hazards and impacts on human health and the environment.*
- *Update approaches for dosimetry by analysis and application of recent and mature model structures.*
- *Expand cumulative risk assessment (CRA) methods to support place-based risk assessments including evaluation of chemical and non-chemical stressors on ecosystems, community health, and well-being.*
- *Identify, integrate, and characterize the application of new technologies and other emerging data streams into risk assessments to support prioritization and rapid screening of risks for hundreds to thousands of chemicals; these efforts are closely linked with the CSS demonstration and evaluation activities.*
- *Refine exposure and response analyses to reflect current understanding of AOP and biomarkers for better integration of key events and description of MOA for different diseases.*
- *Advance approaches to utilize probabilistic and other science advancements to more fully describe exposure-dose-response surfaces for noncancer endpoints to support risk characterization and benefits assessment.*

### Research Objective 3:

- *Hold public science workshops to engage the scientific community in discussions of challenging issues that affect numerous risk assessments*
- *Provide technical support and consultation to partners and stakeholders regarding exposure assessments, evaluation of ecological impacts, and health assessments*

- *Support transparency and efficiency of assessment activities through improvements to HERO for access to the scientific literature and assessment data management*
- *Conduct risk assessment training for Agency partners, State/local/tribal and international organizations, and through professional meetings attended by communities, nongovernmental and private sector scientists to advance understanding, transparency, and consistency in risk assessment methodology*
- *Develop and conduct advanced approaches to support stakeholder participation in risk assessment issues*

## VII. Program Design

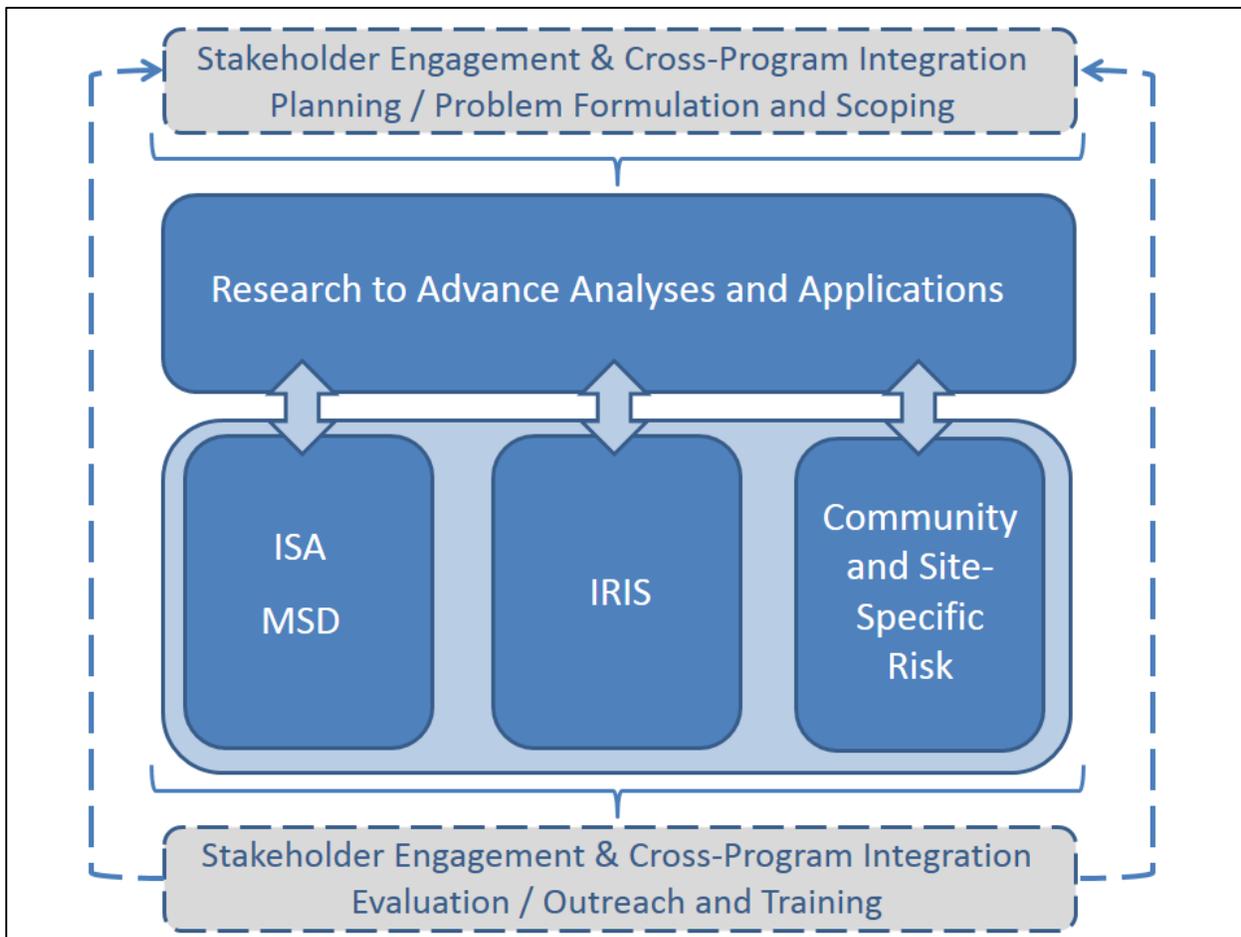
### VII.A. Evolution from Current Research Program

The HHRA research program is comprised of four highly interdependent and leveraged topics that have been enhanced and in concert 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:

- **Research to Advance Analyses and Applications** across the below 3 topics to address challenges identified in exposure or dose-response analysis and to incorporate innovations that improve characterization of human and environmental impacts.
- **Integrated Risk Information System (IRIS)** to develop hazard and dose-response assessments for priority chemicals.
- **Integrated Science Assessments (ISA) / Multipollutant Science Documents (MSD)** to characterize the health and environmental effects of criteria air pollutants.
- **Community and Site-specific Risk** to provide rapid response assessments and cumulative risk methods to address Superfund site assessment, sustainability characterization, and community concerns.

### VII.B. Partner Involvement in Research Planning

In recent years, the HHRA research program has evolved to more formally include problem formulation and scoping into its research and assessment activities as depicted in Figure 3. This initial, “up front” involvement of stakeholders in the design of assessment activities was recommended by the NAS report “Science and Decisions” (NAS, 2009). Such input on problem formulation and on the scope of its assessment and research activities, including prioritization and pacing, occurs in the HHRA program via development and integration of its projects and tasks with the other the ORD research programs, and in collaboration with HHRA program partners and stakeholders. As an example, EPA internal and public input recently resulted in a change to the scope of the assessment for inorganic arsenic (NRC, 2013).



**Figure 3.** Structure of the Human Health Risk Assessment (HHRA) research program. Design of research projects or assessment activities starts with problem formulation and scoping with other research programs and stakeholders. Research to advance analyses and applications informs all assessment areas and these in turn identify critical issues for research. Evaluation of the utility of these activities feeds back to problem formulation and scoping. Training and outreach activities additionally enhance stakeholder engagement.

#### VII.C. Collaboration with Stakeholders

HHRA assessment activities are coordinated through interagency working groups and collaborative relationships. The HHRA research program 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 Occupational Safety and Health (NIOSH). Close relationships also are maintained with international organizations dealing with environmental health risks, including cooperative agreements with the World Health Organization (WHO) through its International Programme on Chemical Safety (IPCS) and through the Chemical Risk Assessment Network, the International Agency for Research on Cancer (IARC) and the United Nations Environment Programme. 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.

These understanding and agreements increase communication and cooperation in the development of toxicological assessments, reduce duplication of efforts on chemical assessments, and foster harmonization and development of new risk assessment methods. In addition to these efforts, the HHRA research program is working with the Environmental Council of the State's (ECOS) Interstate Technology and Regulatory Council to develop a risk assessment training program that could be used across the 50 states.

## VIII. Research Topics

### VIII.A. Research to Advance Analyses and Applications (focus of July 2014 SAB/BOSC meeting)

Research in the HHRA research program is multidisciplinary and aimed at incorporating scientific innovations to advance analytic approaches and applications. This is 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 research program and position it to better support characterization of wellness and sustainability. Research in the HHRA program is cross-cutting and informs the entire portfolio of specific topic areas shown as the merged background block (light blue) of assessment activities and products in Figure 3.

Examples of some cross-cutting issues that must be addressed in order to advance approaches and applications in risk assessment include the following: refining exposure assessment and dosimetry methods to flexibly address different durations, doses, and endpoints; determining factors that dictate susceptibility for different life stages; characterizing uncertainty and variability in risk estimation procedures; incorporating new computational methods and data streams to inform prioritization and assessments; harmonizing traditionally separate approaches to noncancer and cancer endpoints based on systems biology, adverse outcome pathways, and understanding of disease networks, and including consideration of background exposure and background disease processes in the population; bridging epidemiological and clinical data with exposure and disease biomarkers to integrate key events, determine prognostic significance of endpoints, and inform MOA descriptions; extending cumulative risk assessment methods to integrate ecological endpoints, ecosystem services, and indices of resiliency and wellness; and approaches to support benefit-cost analysis for various health endpoints.

Specific issues also arise in various assessment activities. For example, the IRIS assessment for inhaled methanol required development of methods to address endogenous background levels. The HHRA research 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 serve to enhance understanding and appreciation of current scientific challenges and thereby stimulate new research and methods. Recent workshops convened by the HHRA research program were devoted to the following issues:

- Factors influencing the uptake and carcinogenicity of ingested hexavalent chromium (2013)
- Mode of action for development of mouse lung tumors (2014)

Advancing exposure assessment methods and guidance is another cross-cutting area of active research and endeavor in the HHRA program. EPA's EXPOSure toolBOX (EPA-Expo-Box) 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 6 Tool Sets, each containing a series of modules that you can access from the table 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). EPA-Expo-Box is available at: <http://epa.gov/risk/expobox/>

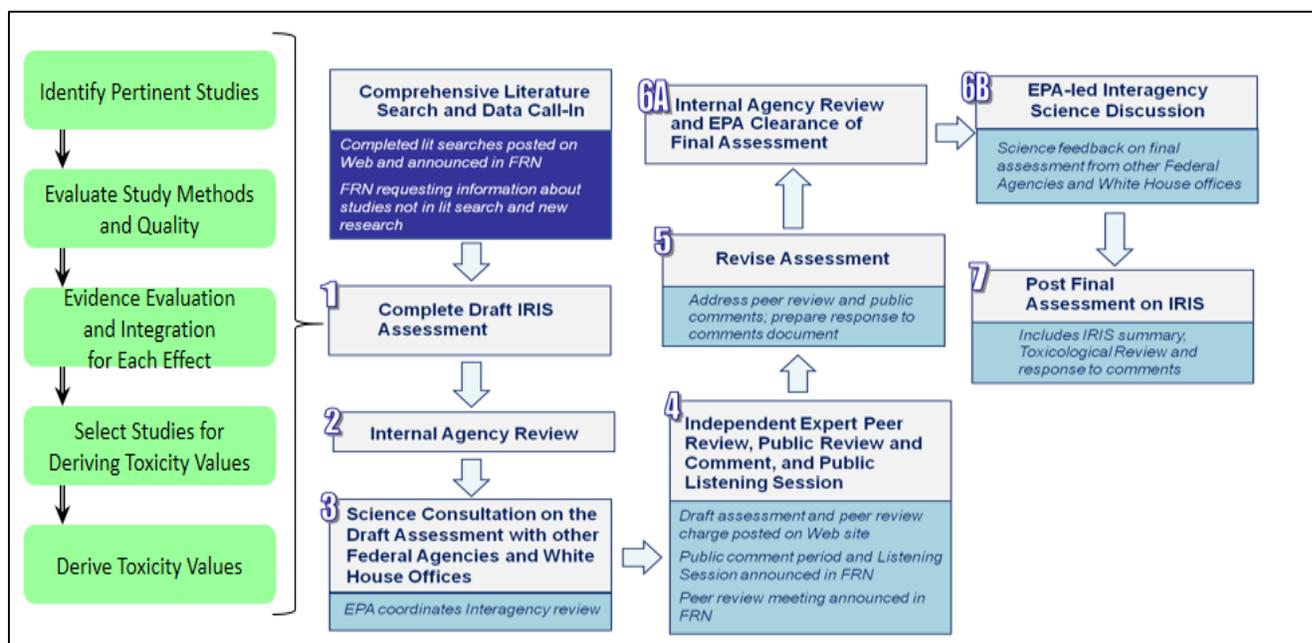
The HHRA research program has three topics devoted to developing specialized assessment products: the Integrated Risk Information System, Integrated Science Assessments, and Community and Site-Specific Risk products.

#### VIII.B. Integrated Risk Information System

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 policies to protect human health and the environment. 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 decision-making. EPA and the risk assessment/ risk management community consider IRIS the premier source of health hazard and dose-response information for environmental pollutants.

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 assessments; 2) improve the productivity of the Program; and 3) increase transparency so issues are identified and debated early in the IRIS process. In 2009, the IRIS program announced a new 7-step assessment development process shown in Figure 4. Since that time, the National Research Council (NRC) 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, 2014). EPA is implementing additional changes to the IRIS Program based on the NRC recommendations (Appendix D). 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.



**Figure 4.** Seven steps in assessment development process of IRIS program and work flow of disciplinary work groups (denoted as green boxes).

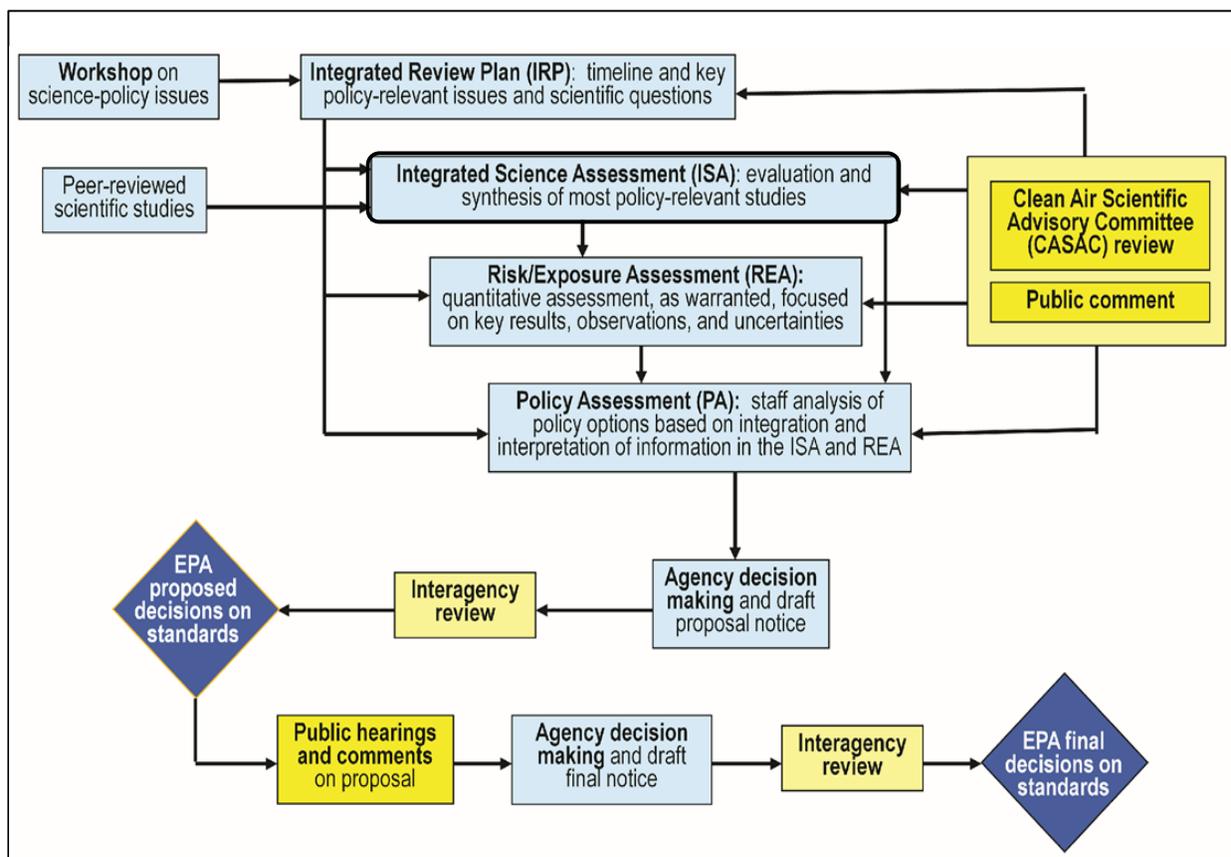
Another enhancement to the IRIS program that ensures scientific expertise is strategically targeted to characterize potential adverse health effects and endpoints is the formation of disciplinary work groups. HHRA scientific experts in these work groups also identify issues and advance approaches to address challenges specific to their areas. For example, development of techniques are underway for meta-analysis of epidemiological studies and the use of AOP to help elucidate windows of susceptibility for developmental effects.

### VIII.C. Integrated Science Assessments (ISA) / Multipollutant Science Documents (MSD)

The HHRA research program regularly develops ISAs (formerly Air Quality Criteria Documents) as a major component of its research portfolio. 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 mobile and other 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.

In planning and developing ISAs, the HHRA research 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 the Clean Air Scientific Advisory Committee (CASAC) and other stakeholders as shown in Figure 5. ORD’s Air Climate and Energy (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 (IRP) for each ISA is then developed that includes the ISA which is the responsibility of HHRA, and the complementary Risk and Exposure Assessment (REA, if warranted) and a Policy Assessment (PA) 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 5.** 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.

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 are now working in consultation with EPA offices to develop multipollutant science documents (MSD) to support the reviews of the primary (health-based) and secondary (welfare-based) NAAQS. These MSD aid in evaluation of the combined health effects of the exposures to mixtures of air pollutants, as well as 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 EJ issues, and advances cumulative risk characterization methods.

#### VIII.D. Community and Site-Specific Risk (focus of July 2014 SAB/BOSC meeting)

Communities today are faced with trying to understand new sensing or monitoring information and often are faced with an urgent need for coordinated assistance to assess and address issues of chemical and other environmental contamination. EPA's HHRA research program is frequently called upon to quickly assist in these situations, often in the face of large scientific uncertainties due to data gaps. Support provided via the Superfund technical support center provides rapid risk assessment and technical consultation regarding both health and ecological impacts.

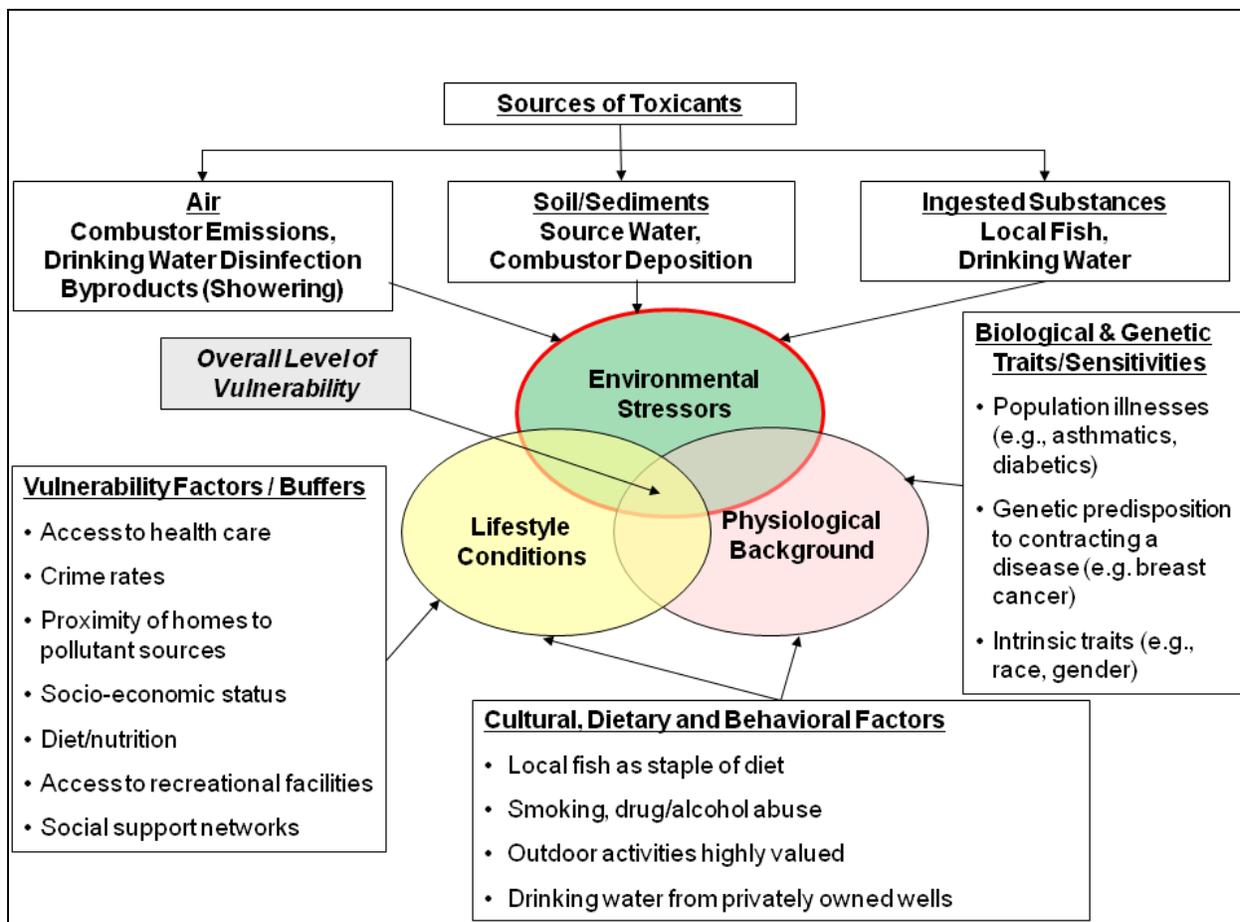
The HHRA program is devoted to developing approaches to respond to these emerging, often crisis-level, chemical/substance issues with sound science that allow for quick action and, ultimately, quick decisions and effective solutions. Scientists in the HHRA program are also working on methods to provide the science to support decision-making at cleanup sites, developing tools to help understand community risk, or providing rapid responses to ensure that decision-makers have the tools they need to address emerging community concerns about environmental chemicals. Specific work under this topic includes quick turn-around exposure and risk assessments, technical support on health or ecological risks to support different Superfund sites or regional concerns, the development of Provisional Peer Reviewed Toxicity Values (PPRTVs), and the development of methods and tools for conducting cumulative impact and risk assessments. Taken together, this work helps ensure that EPA's programs and regions have the tools and information they need to make decisions and address community concerns.

PPRTVs are toxicity values derived for use in EPA's Superfund program when a value is not available in the IRIS database. PPRTVs are used by the Superfund program and regional decision-makers when making site-specific clean-up 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. Priorities for PPRTV development are based on needs of the Office of Solid Waste and Emergency Response (OSWER) and evaluated annually. PPRTVs are derived following a review of the relevant scientific literature using the same methods, sources of data and

guidance used by the IRIS program to derive values. All PPRTVs receive internal review by a panel of EPA scientists and external peer review by independent scientific experts and are publicly available (<http://hhpprtv.ornl.gov>). [Note: The PPRTV program is not part of the focus of the July 2014 SAB/BOSC meeting]

A major area of research under this topic is expanding the cumulative risk assessment (CRA) methods developed to integrate and evaluate impacts of chemical and non-chemical stressors on the environment and health as shown in Figure 7. Current support to CRA includes strategic coordination and science support to the EPA's Risk Assessment Forum Technical Panel on CRA (<http://www.epa.gov/raf/>), specific analyses and case studies, providing training on CRA methods, and specific attention to advancing evaluation of ecological assessment endpoints. A forthcoming vision paper will provide recommendations to advance CRA to include ecological assessment, and future work with the HSRP and SHC programs is expected to integrate resiliency and wellness 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 EJ goals.

Stakeholder engagement regarding the output of the HHRA program is enhanced by training on risk assessment methods and outreach regarding research 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. One example of training that HHRA scientists have developed a program entitled Risk Assessment Training and Experience (RATE), a comprehensive risk assessment training course which includes 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 program by broadening the knowledge base of involved staff.



**Figure 6.** CRA framework illustrating various potential roles of chemical and non-chemical stressors and buffers. Current area of emphasis in HHRA is incorporating ecological endpoints and future work will incorporate HS resiliency and SHC wellness indices.

A Table linking Research Objectives to the Research Topics, Science Challenges, and Project Proposals is provided in Appendix E.

## IX. Conclusion

*[To be completed in Final Strategic Action Plan for the Human Health Risk Assessment Program.]*

## Appendix A. Examples of Proposed Outputs,

### Human Health Risk Assessment Research Program FY16-19

#### **Topic 1: Research to Advance Analyses and Applications**

- Evidence integration tools and guidance
- New exposure modules and capabilities in EPA Expo-Box
- Updated dosimetry models and methods
- Characterization of dose and duration dependencies to adjust assessments for different exposure scenarios and inform benefit analyses
- Approaches to integrate biomarkers, AOP and HTS/HC data to predict potential for liver, cardiovascular, and respiratory diseases
- New endpoints to characterize developmental toxicity
- Virtual tissue applications that inform MOA and AOP for liver and developmental risk analysis
- Decision criteria to guide application and characterize utility of new data and tools in assessments
- Probabilistic approaches to response analysis

#### **Topic 2: Integrated Risk Information System (IRIS)**

- Components of chemical assessments prioritized by program partners including the following for each: systematic literature reviews, evidence tables and graphical representation of dose-response arrays; external peer review drafts; interagency review drafts
- SAB CAAC review of chemical assessments
- Stakeholder engagement by convening
  - Bimonthly public science meetings on selected chemicals
  - Scientific workshops on chemical-specific challenges
  - Completed IRIS assessments on chemicals prioritized by program partners

#### **Topic 3: Integrated Science Assessments (ISA) / Multipollutant Science Documents (MSD)**

- Integrated Review Plans for update of ISAs for particulate matter (PM) primary NAAQS and carbon monoxide (CO) primary NAAQS.
- Public workshops on science/policy issues for update of ISA to support development of primary NAAQS for PM and CO.
- CASAC review of IRP for ISAs of primary PM NAAQS and primary CO NAAQS.
- Produce CASAC/public reviews drafts of ISAs to support primary SO<sub>2</sub> NAAQS, primary PM NAAQS, and primary CO NAAQS; and of an ISA for secondary NO<sub>2</sub> & SO<sub>2</sub> NAAQS.

- Complete final ISAs to support the primary NO<sub>2</sub> NAAQS, primary SO<sub>2</sub> NAAQS, primary PM NAAQS, and primary CO NAAQS; and an ISA for the secondary NO<sub>2</sub> & SO<sub>2</sub> NAAQS.

#### **Topic 4: Community and Site-specific Risk**

- Complete ≥ 12 PPRTVs as prioritized by OSWER
- Provide assessments for emergent situations
- Provide technical support on assessments or expert consultation to OSWER and regions regarding health effects or ecological impacts
- Identifying high-throughput points of departure by incorporating CSS data/outputs
- Hazard grouping and quantitative analysis for cumulative risk assessment
- Create decision criteria and context for characterization of new applications

## Appendix B. 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.

**Executive Orders 12866, 13563 and OMB Circular A-4**, which guide the analysis of the costs and benefits of Federal regulatory decisions, which includes 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 C. Research Program Partners and Stakeholders

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 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**

Army Corps of Engineers (ACE)  
Agency for Toxic Substances and Disease Registry (ATSDR)  
California’s Environmental Protection Agency (Cal/EPA)  
    Office of Environmental Health Hazard Assessment  
Centers for Disease Control and Prevention (CDCP)  
Department of Defense (DoD)  
Defense Advanced Research Projects Agency (DARPA)

Food and Drug Administration (FDA)  
    National Center for Toxicological Research (NCTR)  
National Academy of Sciences (NAS)  
Government Accountability Office (GAO)  
National Institutes of Environmental Health Sciences (NIEHS)  
National Toxicology Program (NTP)  
Texas Commission on Environmental Quality (TCEQ)  
National Institutes of Health (NIH)  
    Chemical Genomics Center (CGC)  
National Institute of Occupational Health and Safety (NIOSH)

**Nongovernmental Organizations**

Alliance for Risk Assessment (ARA)  
American Public Health Association (APHA)  
American Chemistry Council (ACC)  
    Long range research initiative (LRR!)  
Environmental Working Group (EWG)  
National Resource Defense Council (NRDC)  
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)

## Appendix D. 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 on-going priority for the HHRA research program. As the IRIS Program continues to evolve, the HHRA research program is committed to evaluating how well our approaches promote constructive public discussion with our stakeholders, as well as reviewing how our 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://www.epa.gov/IRIS/process.htm> and <http://www.epa.gov/IRIS/pdfs/irisprocessfactsheet2013.pdf>.*

**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 clearer, more concise and systematic.
- Incorporated a preamble that describes the application of existing EPA guidance and the methods and criteria used in developing the assessments.
- Dedicated a specific Chemical Assessment Advisory Committee (CAAC) of the Scientific Advisory Board (SAB) to review IRIS assessments. *More information on the SAB CAAC can be found at: <http://yosemite.epa.gov/sab/sabpeople.nsf/WebCommitteesSubcommittees/Chemical%20Assessment%20Advisory%20Committee>*
- Created Discipline-Specific Workgroups and Interdisciplinary Science Teams to evaluate endpoint specific and disciplinary issues relevant to assessment. These groups coordinate across assessments to ensure consistency, solve cross-cutting issues, and advance scientific understanding that contributes to decision-making in IRIS assessments.
- Strengthened its practices for peer review and protections against conflict of interest
- 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 Integration 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. This step in the systematic review process involves a uniform evaluation of a variety of methodological features
  - 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
- Conducting a need assessment (in progress) to identify and evaluate client demands and the resources required to meet user needs.
- Focused staff attention on a smaller number of assessments and ultimately increased 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://www.epa.gov/iris/pdfs/IRIS\\_stoppingrules.pdf](http://www.epa.gov/iris/pdfs/IRIS_stoppingrules.pdf).

## Appendix E. Summary of HHRA StRAP Research

For this draft Strategic Research Action Plan for the HHRA program a number of current and potential projects have been identified as shown in the following table. All of the projects listed under Research Objective 1 are currently underway, whereas many of the projects listed under Objective 2 and some listed under Objective 3 are proposed and awaiting project selection decisions based on EPA program partner needs, input from the SAB/BOSC, and resource availability.

<b>Research Objective 1:</b>	<b>Research Topic</b>	<b>Science Challenge</b>	<b>Projects</b>
<p>Characterize risks and potential impacts to human health and the environment with a suite of state-of-the-science assessment products tailored to address a range of decisions regarding exposure to pollutants.</p>	<p>Integrated Risk Information System (IRIS)</p>	<p>Systematically identify, evaluate, integrate and translate relevant scientific evidence to assess human health effects of chemicals for priority Agency decisions</p>	<p>Conduct scoping and problem formulation for chemical assessments prioritized by program partners</p> <p>Produce preliminary systematic literature review, evidence tables, and graphical representation of dose-response arrays for chemicals prioritized by program partners</p> <p>Convene bimonthly public science meetings to discuss draft assessment materials (scoping and problem information material; preliminary literature review and evidence tables; draft assessments)</p> <p>Complete IRIS assessments as prioritized by program partners</p>
	<p>Integrated Science Assessments (ISA) and Multipollutant Science Documents (MSD)</p>	<p>Systematically identify, evaluate, integrate and translate relevant scientific evidence to assess human health and environmental impacts of criteria air pollutants</p>	<p>Develop draft integrated review plans (IRP) for update of ISA for primary NAAQS of particulate matter (PM) and carbon monoxide (CO)</p> <p>Hold public workshops on science / policy issues for update of ISAs to support development of primary NAAQS for PM and CO</p> <p>Produce CASAC / public review drafts of ISA to support primary NAAQS for oxides of sulfur, PM, and CO</p> <p>Produce CASAC / public review drafts of ISA to support secondary (welfare) NAAQS for oxides of nitrogen and sulfur (NOx/SOx)</p> <p>Complete final ISAs to support the primary NAAQS for NO<sub>2</sub>, PM, SO<sub>2</sub> and CO</p> <p>Complete final ISAs to support the secondary (welfare) NAAQS for NOx/SOx</p> <p>Provide science support to Office of Air and Radiation and Office of General Council on all NAAQS</p>
	<p>Community and Site-specific Risk</p>	<p>Provide tools and advance analyses to help EPA programs and communities rapidly identify and address risks of emerging exposures and prioritize testing</p>	<p>Complete ≥ 12 PPRTV/yr assessments as prioritized by OSWER</p> <p>Provide assessments for emergent situations. Provide technical support on assessments or expert consultation to OSWER and regions regarding health effects or ecological impacts</p>

<b>Research Objective 2:</b>	<b>Research Topic</b>	<b>Science Challenge</b>	<b>Potential Projects</b>
<p>Refine risk assessments by identifying critical issues and advancing analytical approaches and applications to incorporate new science, methods and technologies.</p>	<p>Research to Advance Analyses and Applications</p>	<p>Evaluate and verify approaches for systematic review and evidence integration, including factors affecting bias, to enhance efficiency and accuracy of assessment development including automated data mining</p>	<p>Develop data science and integration tools; including protocols for evaluation and integration of human, laboratory animal, and mechanistic data</p> <p>Compare approaches to quantify risk of bias and evaluate impact on assessment methods</p> <p>Catalog number and types of hazards using text mining and analytics</p> <p>Advance data science and meta-analytic techniques to improve data visualization and integration</p>
		<p>Broaden exposure assessment technology to translate exposure and dose estimates to flexibly address different exposure scenarios</p>	<p>Improve accessibility to exposure factors data by upgrading web-based software</p> <p>Identify data gaps and prioritize dosimetry research needs</p> <p>Develop repository of exposure information to aid planning and scoping of IRIS assessments</p> <p>Develop approaches to create context and translate dose from <i>in vitro</i>, biomonitoring, clinical, and other study designs via reverse toxicokinetic (RTK) and PBPK modeling to human exposure scenarios</p> <p>Upgrade EPA Expo-Box software capability to operationally link with dosimetry models and rapid risk platform (e.g., ACToR)</p> <p>Enhance understanding of connection between ecological and human health by updating wildlife exposure factors handbook</p>
		<p>Update dosimetry approaches to predict a profile of internal metrics across all routes to support use of MOA, AOP and aggregate or cumulative risk applications</p>	<p>Construct comprehensive suite of model structures to estimate profile of metrics for each exposure route</p> <p>Update guidance on application of dosimetry modeling in derivation of health estimates</p>

<b>Research Objective 2:</b>	<b>Research Topic</b>	<b>Science Challenge</b>	<b>Potential Projects</b>
<p>Refine risk assessments by identifying critical issues and advancing analytical approaches and applications to incorporate new science, methods and technologies.</p> <p>(continued)</p>	<p>Research to Advance Analyses and Applications</p> <p>(continued)</p>	<p>Expand cumulative risk assessment methods to advance “place-based” community risk characterizations and support sustainability</p>	<p>Incorporate GEAE and ecosystem services into CRA methods to characterize environmental stress</p> <p>Advance use of AOP into CRA methods to characterize and integrate ecological and health endpoints</p> <p>Collaborate with HS research program to evaluate and apply resiliency into CRA methods</p> <p>Collaborate with SHC research program to evaluate and apply well-being indices into CRA methods</p>
		<p>Improve prioritization and rapid response by evaluating and incorporating new data streams and developing rapid assessment approaches</p>	<p>Collectively incorporate CSS data / outputs from QSAR, read-across SAR, ToxCast, and IVIVE RTK to develop high-throughput points of departure (POD) and evaluate application to derivation of screening reference values (sRfV)</p> <p>Collaborate with CSS to generate and evaluate data-derived extrapolation factors for use with sRfV</p> <p>Develop hazard grouping and quantitative analysis of mixtures for rapid risk assessment using AOP footprinting</p>
		<p>Develop approaches to incorporate current understanding of key events, AOP, and biomarkers to increase accuracy of predictions of disease pathogenesis, inform MOA and better characterize critical endpoints of relevance to HHRA (respiratory, cardiovascular, neurotox, developmental, reproductive toxicity, liver)</p>	<p>Develop and evaluate use of clinical biomarkers to bridge key events and enhance understanding and application of AOP and MOA for critical endpoints in risk assessment</p> <p>Develop data mining and decision analytic approaches to facilitate integration of chemical and disease data from diverse sources and data types (HT/HC, AOP, biomarkers, clinical, epidemiological) to inform MOA and characterize critical endpoints</p> <p>Explore hierarchical Bayesian and systems network biology approaches to advance meta-analytic capabilities</p> <p>Survey and advance network analytic approaches to identify and develop POD for critical endpoints</p> <p>Collaborate with CSS to apply virtual liver and embryo models to improve prioritization and support MOA and AOP applications in assessments</p>

<b>Research Objective 2.</b>	<b>Research Topic</b>	<b>Science Challenge</b>	<b>Potential Projects</b>
Refine risk assessments by identifying critical issues and advancing analytical approaches and applications to incorporate new science, methods and technologies.  (continued)	Research to Advance Analyses and Applications  (continued)	Develop approaches to incorporate current understanding of key events, AOP, and biomarkers to increase accuracy of predictions of disease pathogenesis, inform MOA and better characterize critical endpoints of relevance to HHRA (respiratory, cardiovascular, neurotox, developmental, reproductive toxicity, liver)	Collaborate with CSS and SHC programs to develop evidence-based benchmark response guidance to use hormonal changes and AOP / MOA information to improve characterization of reproductive and developmental effects  Develop application criteria to characterize utility of different data and approaches depending on problem formulation and decision context
		Refine dose-response analysis by advancing approaches for risk and uncertainty characterization across spectrum of duration and dose	Develop toxicity values based on probabilistic approaches, including integration schemes to characterize prognostic value of key events and biomarkers  Develop probabilistic approaches for integration of different data types (mechanistic, in vitro, epidemiological)  Enhance visualization capability to display response as a function of dose and duration for different endpoints
		Advance decision analytic and probabilistic approaches to more fully characterize dose-response functions and thereby better inform benefit-cost analyses	Collaborate with program offices and the National Center for Environmental Economics to incorporate temporal and exposure (dose) dependencies into benefit-cost analyses

<b>Research Objective 3.</b>	<b>Research Topic</b>	<b>Science Challenge</b>	<b>Potential Projects</b>
<p>Develop and employ state of the art risk assessment technologies and engage stakeholders to ensure support, training, and tailoring of assessment priorities and products.</p>	<p>Research to Advance Analyses and Applications</p>	<p>Enhance data access and management systems to support transparency and efficiency</p>	<p>Develop enhanced interface between Health Effects Research Online (HERO) and DRAGON modules with Aggregated Computational Toxicology Resource (ACToR) to share chemical databases and ontologies</p>
		<p>Develop and apply effective methods for stakeholder engagement and risk assessment training to varied audiences</p>	<p>Convene scientific workshops to advance solutions to challenging issues identified in assessment activities</p> <p>Explore methods to encourage broader public participation</p> <p>Collaborate with the ACE program on interpretation of real-time data from new air sensor technologies</p> <p>Conduct Risk Assessment and Training Experience (RATE) program courses as requested or required</p> <p>Develop new modules for RATE program to advance understanding of new approaches</p>

## Appendix F. Acronyms

ACE	Air, Climate and Energy Research Program
AOP	Adverse outcome pathway
CAAC	Chemical Assessment Advisory Committee
CASAC	Clean Air Scientific Advisory Committee
CO	Carbon monoxide
CRA	Cumulative risk assessment
CSF	Cancer slope factor
CSS	Chemical Safety for Sustainability Research Program
EDSP	Endocrine disruptor screening program
HA	Health advisory
HSRP	Homeland Security Research Program
HTS	High-throughput screening
IRIS	Integrated risk information system
IRP	Integrated review plan
ISA	Integrated science assessment
MCDA	Multi-criteria decision analysis
MCL	Maximum contaminant level
MOA	Mode of action
MSD	Multipollutant science documents
NAAQS	National ambient air quality standard
NO <sub>2</sub>	Nitrogen dioxide
NRC	National Research Council
PAL	Provisional advisory level
PMN	Pre-manufacture notice
PM	Particulate matter
POD	Point of departure
PPRTV	Provisional peer-reviewed toxicity values
RATE	Risk assessment training and experience
RfC	Reference concentration (inhalation)
RfD	Reference dose (oral)
ROD	Record of decision
SAB	Science Advisory Board
SHC	Sustainable and Healthy Communities Research Program
SSWR	Safe and Sustainable Water Resources Research Program
SO <sub>2</sub>	Sulfur dioxide
RTR	Risk and technology review

## Appendix G. References

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