



Human Health Risk Assessment (HHRA)

Research and Assessment Framework

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Executive Summary

The Human Health Risk Assessment (HHRA) program provides state-of-the-science, independently peer reviewed human health assessments for existing chemicals and chemical mixtures that find their way into our air, water, and land. The HHRA program plays a unique role in serving the needs of Environmental Protection Agency (EPA) programs by incorporating, integrating, and coordinating the use of scientific information as a foundation for regulatory decision making.

Problem: Agency decisions must be based on defensible scientific evaluations of data relevant to assessing human health impacts. Currently, the demand for such assessments is not being fully met, particularly in terms of the number of existing and new chemicals in need of assessment, the types of risk characterization outputs needed to inform decision making, and the tools and data needed to support assessments.

Vision: The Agency will generate timely, credible human health risk assessments to support all priority Agency risk management decisions, thereby enabling the Agency to better predict and prevent risk.

The four primary research themes of the HHRA program are:

- (1) Integrated Risk Information System (IRIS) health hazard and dose-response assessments;
- (2) Integrated Science Assessments (ISA) of Criteria Air Pollutants;
- (3) Community Risk and Technical Support for exposure and health assessments; and
- (4) Methods, models, and approaches to modernize risk assessment for the 21st century.

Theme 1 – IRIS impacts: Given the broad usage of IRIS assessments by EPA program and regional offices, as well as the general public, Theme 1 products/outcomes could potentially have social, environmental, economic, or human-health effects. Intended impacts of IRIS products/outcomes include: a reduction of disease and optimal distribution of resources. Unintended impacts continue to be that chemicals with no hazard and dose-response assessments are considered to be safe until evaluated. These omissions in the IRIS and other health hazard assessments could lead to a systematic bias and unintended impacts, whereby the wrong risk management options could be selected.

Theme 2 – ISA impacts: Attainment of the National Ambient Air Quality Standards (NAAQS) 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. The direct benefits of the Clean Air Act (CAA) include reduced incidence of a number of adverse human health effects, improvements in visibility, and avoided damage to agricultural crops and other vegetation. These results have been accomplished in the face of a growing population, number of vehicles, and economy.

Theme 3 – Community Risk and Technical Support impacts: The development of PPRTVs enables OSWER to make clean up decisions at contaminated superfund sites. This has economic implications for the responsible party and surrounding communities. Examples of other intended social impacts include: rapid response to community concerns and emerging issues, response to environmental justice concerns through the incorporation of non-chemical stressors into community risk assessment. These outputs will positively contribute to protecting public’s health, including reducing the risk of sensitive populations.

Theme 4 – Methods, Models, and Approaches to Modernize Risk Assessment impacts: The outputs of this theme will increase efficiency and effectiveness of the Agency risk assessment programs by bringing innovative approaches forward and applying them to mine databases and link information to users’ needs in a more effective fashion so assessments can be done quickly and more transparently. Moving forward with additional dose-response approaches, particularly in the noncancer arena, will allow greater utility in comparing different risk relationships between and among chemical-induced adverse health outcomes. Quantitative analysis of uncertainty, derivation of central estimates and confidence limits on estimates of risk is another need driven in part by those who wish to use risk assessment results in the context of formal decision analysis or in cost-benefit analysis.

Table of Contents

- Executive Summary..... i
- List of Stakeholders..... i
- List of Acronyms..... iv
- I. Introduction..... 1
 - 1. Regulatory/Statutory and Policy Context for the Research 1
 - 2. Addressing the Priorities Identified in EPA’s Strategic Plan 2
 - 3. Program Design..... 2
 - 4. Integration with Other Research Programs in ORD/EPA..... 3
 - 5. Integration with other Federal Agencies 4
 - 6. Partner and Stakeholder Involvement in the Problem Formulation Process... 4
 - a) Relevance and the Planning Process 5
 - b) Human Health Risk Assessment Colloquium 6
 - c) Environmental Justice (EJ) Action Plan..... 6
 - d) Regional Science Liaisons recommendations on Children’s Risks issues..... 7
- II. Research Themes..... 7
 - 1. Integrated Risk Information System (IRIS) health hazard and dose-response assessments (Theme 1) 7
 - 2. Integrated Science Assessments (ISA) of Criteria Air Pollutants (Theme 2)... 9
 - 3. Community Risk and Technical Support (CRTS) for exposure and health assessments (Theme 3) 10
 - 4. Methods, models, and approaches to modernize risk assessment for the 21st century (Theme 4) 11
- III. Human Health Risk Assessment Program Outcomes and Impacts 12
- IV. References 17
- Appendix A – IRIS Process..... 18
- Appendix B – IRIS Assessments on FY 2011 Agenda..... 19
- Appendix C – ISA Process..... 20
- Appendix D – ISA Gant Chart..... 21

List of Stakeholders

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EPA's Board of Scientific Counselors (BOSC)
Clean Air Science Advisory Committee (CASAC)
Science Advisory Board (SAB)
National Academy of Sciences (NAS)
NAS Best committee
Government Accountability Office (GAO)
National Institutes of Environmental Health Sciences & National Toxicology
Program (NIEHS & NTP)
Centers for Disease Control and Prevention (CDCP)
Agency for Toxic Substances and Disease Registry (ATSDR)
National Institutes of Health (NIH) Chemical Genomics Center
California's Environmental Protection Agency (Cal/EPA), Office of Environmental
Health Hazard Assessment
FDA National Center for Toxicological Research
Department of Defense

Nongovernmental Organizations

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)
American Public Health Association (APHA)
American Chemistry Council (ACC)
Integrated Life Sciences Institute (ILSI) – Risk 21

List of Acronyms

APHA	American Public Health Association
ACC	American Chemistry Council
ACE	Air, Climate and Energy
ATSDR	Agency for Toxic Substances and Disease Registry
BOSC	Board of Scientific Counselors
CAA	Clean Air Act
Cal/EPA	California's Environmental Protection Agency
CASAC	Clean Air Science Advisory Committee
CDCP	Centers for Disease Control and Prevention
CERCLA	Comprehensive Environmental Response, Compensation, and Liability Act
CRTS	Community Risk and Technical Support
CSS	Chemical Safety and Sustainability
ECOS	Environmental Council of the States
EDF	Environmental Defense Fund
EJ	Environmental Justice
EPA	Environmental Protection Agency
EWG	Environmental Working Group
FR	Federal Register
FSSRC	Federal Standing Science Review Committee
GAO	Government Accountability Office
HHRA	Human Health Risk Assessment
HSR	Homeland Security Research
ILSI	Integrated Life Sciences Institute
IRIS	Integrated Risk Information System
ISA	Integrated Science Assessments
ITRC	Interstate Technology and Regulatory Council
MOU	Memoranda of Understanding
NAAQS	National Ambient Air Quality Standards
NAS	National Academy of Sciences
NCEE	National Center for Environmental Economics
NIEHS	National Institutes of Environmental Health Sciences
NIH	National Institutes of Health
NRC	National Research Council
NRDC	National Resource Defense Council
NTP	National Toxicology Program
OAP	Office of Atmospheric Programs
OAQPS	Office of Air Quality Planning and Standards
OAR	Office of Air and Radiation
OCFO	Office of Chief Financial Officer
OCHP	Office of Children's Health Protection
OCSPP	Office of Chemical Safety and Pollution Prevention
OEHHA	Office of Environmental Health Hazard Assessment

OEJ	Office of Environmental Justice
OEM	Office of Emergency Management
OGC	Office of the General Counsel
OGWDW	Office of Ground Water and Drinking Water
OIAR	Office of Indoor Air and Radiation
OP	Office of Policy
OPM	Office of Program Management
OPP	Office of Pesticide Programs
OPPT	Office Pollution Prevention and Toxics
ORCR	Office of Resource Conservation and Recovery
ORD	Office of Research and Development
OSCP	Office of Science Coordination and Policy
OSRTI	Office of Superfund Remediation and Technology Innovation
OSA	Office of the Science Advisor
OST	Office of Science and Technology
OSWER	Office of Solid Waste and Emergency Response
OTAQ	Office of Transportation and Air Quality
OUST	Office of Underground Storage Tanks
OW	Office of Water
OWM	Office of Wastewater Management
PALs	Provisional Advisory Limits
PPRTVs	Provisional Peer Reviewed Toxicity Values
RAF	Risk Assessment Forum
RAP	Research Action Plan
RCT	Research Coordination Team
REACH	Registration, Evaluation, Authorization and Restriction of Chemicals
SAB	Science Advisory Board
SHC	Sustainable and Healthy Communities
SSWR	Safe and Sustainable Water Resources
TSCA	Toxic Substances Control Act

I. Introduction

At present, there are nearly 150,000 chemicals registered in the European Registration, Evaluation, Authorization and Restriction of Chemicals (REACH) Program and over 84,000 chemicals on the Toxic Substances Control Act (TSCA) inventory. An additional 1,000 new chemicals are introduced into commerce each year. Only a small fraction of these chemicals have been adequately assessed for potential risk. This is often because of limitations in existing data, tools, and resources.

Problem: Agency decisions must be based on defensible scientific evaluations of data relevant to assessing human health impacts. Currently, the demand for such assessments is not being fully met, particularly in terms of the number of existing and new chemicals in need of assessment, the types of risk characterization outputs needed to inform decision making, and the tools and data needed to support assessments.

In order to address this challenge, in FY 2012, EPA is realigning and integrating the work of its research programs. Under the new structure, the HHRA program will continue to provide the risk-based approaches for assessments and methods necessary to guide EPA's actions to protect public health and the environment. The human health assessments that are developed by this program are used extensively by EPA Program and Regional Offices, as well as other parties, to make decisions, develop regulatory standards for environmental contaminants, and manage cleanups. The HHRA program will continue to evolve in order to meet today's complex environmental challenges as demonstrated by the recent innovations in the integrated science assessments for criteria air pollutants and through coming improvements to the draft development process for IRIS assessments.

Vision: The Agency will generate timely, credible human health risk assessments to support all priority Agency risk management decisions, thereby enabling the Agency to better predict and prevent risk.

1. Regulatory/Statutory and Policy Context for the Research

EPA Programs and Regions are the principal customers for risk assessment information under many of EPA's implementing statutes. For example,

- 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. This program includes assessment of risks, development of methods and tools for analysis of data, and development of Integrated Science Assessments (ISAs) to serve as the basis for review of the National Ambient Air Quality Standards (NAAQS) on a 5-year cycle. The 1990 CAA Amendments further mandate determination of risks from mobile, area, and major sources of air toxics.
- The **Safe Drinking Water Act** (1974 amended in 1996) authorizes research and assessments focusing on microbes (e.g., *Cryptosporidium*), disinfection byproducts, arsenic, sulfate, and radon, including effects on sensitive

subpopulations. Other research provisions address risks associated with waterborne disease, complex mixtures, and unregulated contaminants.

- The **Food Quality Protection Act** (1996) mandates research and assessment of risk from exposures to pesticides, including aggregate exposures and cumulative risk and risk to sensitive subpopulations.
- The **Comprehensive Environmental Response, Compensation, and Liability Act** (CERCLA; Superfund, 1980) requires research, development, and training to improve EPA's scientific capability to assess and evaluate effects on, and risk to, human health from hazardous substances.

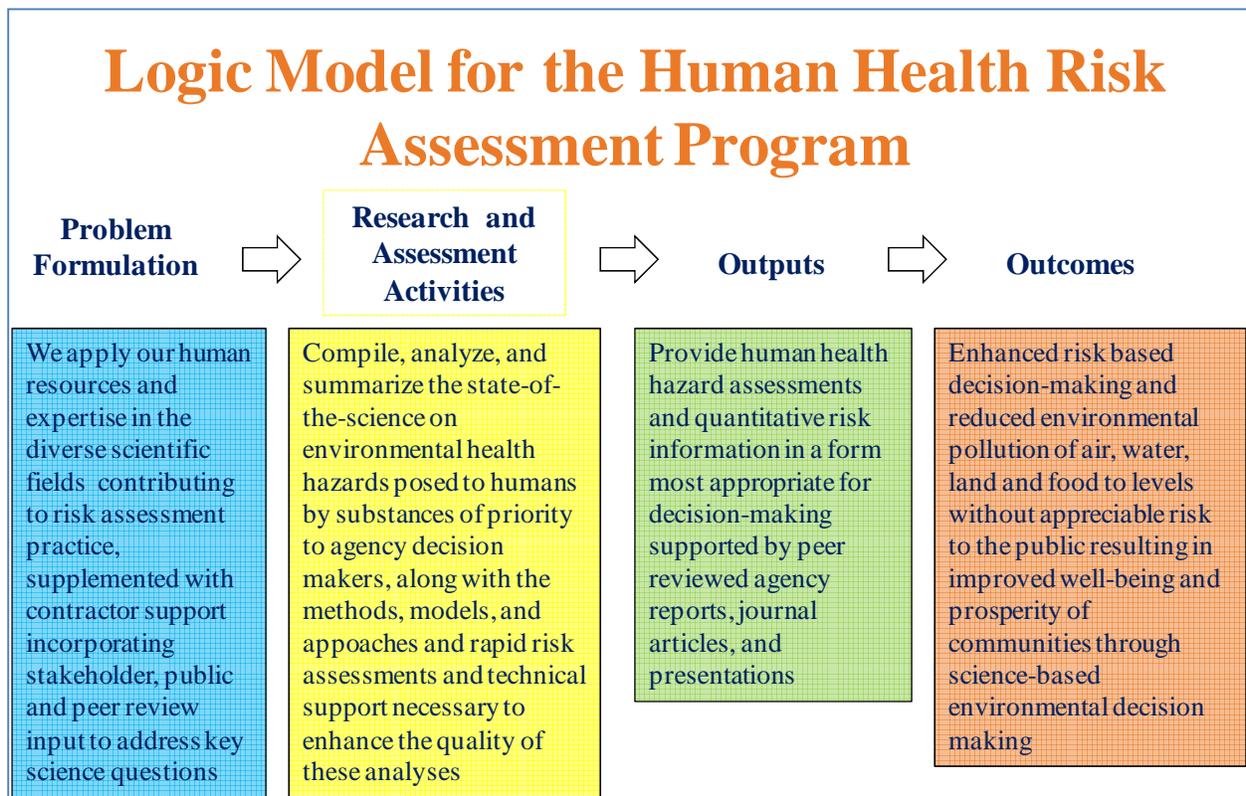
2. Addressing the Priorities Identified in EPA's Strategic Plan

The HHRA program falls squarely under assuring the safety of chemicals. The Program also has a direct relationship to other EPA strategic goals by integrating the science for media-specific chemical hazards and providing assessment methods to achieve the goals of ensuring air quality, protecting America's water, and cleaning up our communities.

3. Program Design

The HHRA program is an existing multidisciplinary program which is designed as the interface between the Office of Research and Development (ORD) research and Agency decision makers. The program's four themes and outputs are aligned with partner identified needs. These four themes produce a complement of high value health assessments with method development and application of emerging science to modernize risk assessment. The HHRA program also includes a sizable component of technical support to meet partner and stakeholder needs. The program did not require a drastic revision of its major themes from the previous multi-year plan in 2007; however, the emphasis has changed in the methods area in response to recent National Academy of Sciences (NAS) recommendations and a separate theme on community risk and technical support has been created.

Figure 1 – Logic Model for the Human Health Risk Assessment Program



4. Integration with Other Research Programs in ORD/EPA

The HHRA program occupies a critical position as the integrator of many aspects of ORD’s research portfolio by bridging research in other ORD national programs. While the other programs are generating new findings and data, HHRA provides the linkages through state of the art science assessments to decision-makers in EPA Program Offices and Regions who must make regulatory, enforcement, and remedial action decisions. ORD research products are synthesized and integrated into timely and relevant assessments under HHRA and these assessments inform other National Research Programs. Examples of these synthesis products include:

- Exposure Factors Handbook and Child-Specific Exposure Factors Handbook – Sustainable and Healthy Communities (SHC); Safe and Sustainable Water Resources (SSWR)
- Integrated Risk Information System (IRIS) health assessments – SSWR; SHC; Air, Climate and Energy (ACE); Chemical Safety and Sustainability (CSS)
- Provisional Peer Reviewed Toxicity Values (PPRTVs) – SHC; CSS, Homeland Security Research (HSR)
- Integrated Science Assessments (ISA) for criteria air pollutants – ACE, SHC
- Cumulative Risk Assessment – SHC, SSWR and CSS
- PPRTVs can be used in Provisional Advisory Limits (PALs) in homeland security research

5. Integration with other Federal Agencies

Beyond EPA, HHRA program's products are widely recognized as the principal environmental health risk assessment benchmarks in the United States and the world, exemplified by IRIS outputs, ISAs, and guidance documents. Although non-regulatory and non-binding in nature, these health risk assessment products, and the scientific analyses therein, are referenced in many federal, state, local, and stakeholder environmental decisions. The HHRA program builds close relationships with partner federal, state, and international organizations, both in accessing sources of toxicological and epidemiological data and through collaborative risk assessment development activities.

Access to data is facilitated through scientific staff networks with other federal agencies conducting primary environmental health research, particularly the National Institutes of Health-National Institute of Environmental Health Sciences (NIH-NIEHS) National Toxicology Program and the Centers for Disease Control and Prevention (CDC)-National Center for Environmental Health. Assessment activities are coordinated through interagency working groups and collaborative relationships. The HHRA Program has two *Memoranda of Understanding* (MOU); one with the California Environmental Protection Agency's (Cal/EPA) Office of Environmental Health Hazard Assessment (OEHHA) and the other with the Agency for Toxic Substances and Disease Registry (ATSDR). These MOUs increase communication and cooperation in the development of IRIS 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 program is working with the Environmental Council of the States' (ECOS) Interstate Technology and Regulatory Council (ITRC) to develop a risk assessment training program that could be used across the 50 states.

Close relationships are also maintained with international organizations dealing with environmental health risks, including the World Health Organization through its International Programme on Chemical Safety, the International Agency for Research on Cancer, and the United Nations Environment Programme.

6. Partner and Stakeholder Involvement in the Problem Formulation Process

EPA regularly evaluates the science assessment development processes to ensure it is transparent and participatory in nature. The HHRA program evaluates and implements the recommendations from Agency Programs, EPA's Board of Scientific Counselors (BOSC), the Clean Air Scientific Advisory Committee (CASAC), the Science Advisory Board (SAB), the National Academy of Sciences (NAS), and the Government Accountability Office (GAO). The HHRA program is committed to implementing recommendations that enhance scientific credibility of agency decisions, improves transparency and the overall program efficiency and effectiveness. In addition, specifically as it relates to IRIS, the HHRA program has engaged the Federal family members of the interagency reviewers in both science consultations and discussions on specific assessments and overarching science discussions as it relates to human health risk assessment.

a) Relevance and the Planning Process

The planning process for the HHRA Research Action Plan (RAP) closely links to the needs of EPA's program and regional offices. Agency partner involvement spans from the broad scale of preparation of the draft HHRA RAP to the more focused and iterative scale specific to each of the themes, particularly the selection and prioritization of IRIS assessments and PPRTVs and the timing of ISAs. The result is the HHRA efforts are well targeted and timed to meet the needs of the Agency programs.

A research coordination team (RCT) will be formed for HHRA to provide consultation throughout the program development and to continually get feedback on products. RCT members will be designated by their respective offices to represent their organizational needs and resources. The RCT planning process will be supplemented by briefings to senior program managers on proposed RAP activities and outputs. The results of the planning process include alignment and prioritization of planned ORD activities over the 3-5-year cycle of the RAP. The draft RAPs prepared through this process will undergo internal EPA review by program, regional, and laboratory representatives. RCT planning will be an ongoing activity, recognizing that the RAP is living document subject to revision as programmatic needs and scientific developments alter priorities.

On a more focused scale, ongoing planning processes exist for a number of specific activities under the HHRA RAP. Formal planning of the IRIS assessment agenda occurs through a request to EPA Programs and Regions for nominations of priority substances for assessment. Additionally, a Federal Register Notice is published requesting nominations for the IRIS agenda, and other federal Agencies, as well as any other stakeholders or members of the public, may submit nominations. This is supplemented by an IRIS update process that has been instituted to determine if newly published literature might impact existing, older IRIS assessments, and hence warrant consideration for revision.

A formal planning process is used with the Office of Air and Radiation, to coordinate the scope and timing of the ISAs produced by ORD with the Risk and Exposure Assessment and Policy Assessments produced by OAR. This plan and the various products from ORD and OAR are reviewed by CASAC with opportunity for public comment. Revisions to the ISAs are planned every 5 years subject to the requirements of the CAA, taking into consideration resource constraints, Office of Air Quality Planning and Standards (OAQPS) priorities, and court deadlines.

PPRTVs are prepared on an ongoing basis at the request of the Office of Solid Waste and Emergency Response (OSWER) for those substances found at clean-up sites and for which no IRIS value is available. An OSWER directive for site specific assessments lists IRIS as the first tier in a hierarchy of toxicity values to be used for Superfund risk assessment, as IRIS is the preferred source for human health toxicity values. PPRTV assessments are listed by OSWER as tier 2 toxicity values. The Department of Defense and the Environmental Council of the States (ECOS) have agreed to this same hierarchy for their health assessments programs

<https://fortress.wa.gov/ecy/clarc/FocusSheets/httpwwwepagovoswerriskassessmentpdf/hhmemo.pdf>).

Due to the extent of this planning and programmatic input on priority needs, the outputs of the HHRA program are very closely linked to their programmatic use in hazardous site assessments and regulatory considerations. IRIS quantitative cancer and non-cancer risk values are accorded priority consideration in OSWER and regional site clean-up evaluations and are a critical consideration in many regulatory determinations by EPA's other programs. ISAs constitute the scientific basis for review of the NAAQS for criteria air pollutants. The HHRA program's models, methods, and guidance outputs generally serve as the standard for Agency health hazard assessment practice and are influential on a national and international scale.

Additionally, HHRA scientists' participation in various Agency activities provides important input to development of the program. For example, in the past year HHRA scientists have participated in an Agency Human Health Risk Assessment Colloquium, a symposium on the Science of Disproportionate Impacts, and a workshop on Children's Environmental Health Protection.

b) Human Health Risk Assessment Colloquium

In October 2010, EPA's Risk Assessment Forum (RAF) sponsored a human health risk assessment colloquium that brought together 120 risk assessors from EPA's Regions and Program Offices to consider recent recommendations from three recent National Research Council (NRC) reports (*Science and Decisions*, *Phthalates and Cumulative Risk*, *Toxicity Testing in the 21st Century*) that might be considered by the Agency. EPA risk assessors and managers discussed what advances were needed in risk assessment, focusing on: the NAS's recommendations; Agency priorities, particularly environmental justice and children's health, taking stock of existing guidance documents; and best practices in conducting human health risk assessment. This three day face to face meeting led to the formulation an Action Plan for future directions in human health risk assessment at EPA, considering NRC recommendations, and incorporating Agency priorities. The action plan included prioritization of a number of efforts in the context of RAF Agency action plan with specific activities for HHRA to undertake in uncertainty and variability, unified approach to dose-response and defaults, and cumulative risk assessment.

c) Environmental Justice (EJ) Action Plan

Under Plan EJ 2014, EPA has committed to building a strong scientific foundation for supporting environmental justice (EJ) and conducting disproportionate impact analysis, particularly methods to appropriately characterize and assess cumulative impacts. These efforts will help to ensure that EPA brings the best science to decision-making around environmental justice issues.

The science and research activities described in the Agency EJ2014 plan build upon discussions and recommendations from EPA's Science of Disproportionate Impacts Analysis Symposium (March 17-19, 2010) and an EJ regulatory analysis technical

workshop (June 9-10, 2010). These discussions were framed within the context of identifying research and scientific needs that are necessary to ensure that environmental justice concerns and social disparities in environmental health are incorporated in EPA's decisions for the purpose of advancing EPA policy on environmental justice. Symposium participants suggested several actions for EPA to take in order to reduce data gaps in the area of environmental justice, overcome limitations in the theories and methods for conducting research on environmental health disparities and particularly research supported by the federal government, and limitations in practice of risk assessment at the EPA.

Recommendations from this stakeholder workshop yielded number recommendations relevant to the HHRA program. Key among these is recommendations for the HHRA program are the need to: develop analytic and assessment tools and data collection approaches that can be used by community health advocates and EJ groups; adopt multi-media cross-program approaches to addressing cumulative environmental exposures in stakeholder communities, and as well as restructuring risk assessment to better account for multiple stressors; increase community capacity to assess their environment; develop a more holistic understanding of environment and health; and integrate environmental justice in all its decisions.

d) Regional Science Liaisons recommendations on Children's Risks issues

EPA's Office of Science Policy sponsored a workshop that brought together scientists, risk assessors, and staff from EPA's regions, Office of Research and Development (ORD), and EPA's program offices to explore existing guidance, guidelines, and policy papers to fully consider the special vulnerabilities of children when assessing health risk of environmental exposures. This workshop highlighted best practices and ongoing efforts within the HHRA program in both preconference webinars and the face to face workshop titled Children's Environmental Health Protection: Translating Science into Risk Assessment Practice Regional Science Workshop, February 1-3, 2011. Findings from this workshop will help inform HHRA's work.

II. Research Themes

The four primary research themes of the HHRA program are: (1) Integrated Risk Information System (IRIS) health hazard and dose-response assessments; (2) Integrated Science Assessments (ISA) of Criteria Air Pollutants; (3) Community Risk and Technical Support for exposure and health assessments; and (4) Methods, models, and approaches to modernize risk assessment for the 21st century.

1. Integrated Risk Information System (IRIS) health hazard and dose-response assessments (Theme 1)

Science Question What are the important human health effects of chemicals for priority Agency decisions?

EPA's HHRA program prepares peer reviewed, qualitative and quantitative health hazard assessments on environmental pollutants of major relevance to EPA's regulatory mandates. EPA program and regional offices frequently use these assessments in their decision-making. The Agency disseminates the assessments to the public on the IRIS Internet database.

EPA and the risk assessment/risk management community consider IRIS the premier source of hazard and dose-response information for environmental pollutants. EPA released a revised IRIS process in May 2009 (Appendix A) to streamline and accelerate completion of these critical science assessments (<http://www.epa.gov/iris/process.htm>). As of January 2011, more than 550 health hazard assessments were available through IRIS (<http://www.epa.gov/iris>).

The IRIS program has implemented a number of actions to increase the transparency and encourage public participation. For example, EPA is currently developing a stakeholder-driven process for updating existing IRIS files that are more than 10 years old (IRIS update project see below). In addition, the IRIS chemical assessment Tracking System (IRIS Track) was created in 2005 to allow the public to monitor the status of chemical assessments that are in the development process. IRIS Track is currently undergoing revision to increase utility and transparency. Additionally, literature reviews of assessments under development are publicly available and announced in the Federal Register (FR). As part of the IRIS process, public listening sessions, which are announced in the FR and on the IRIS Web site, are being conducted to allow interested parties to orally comment on external review draft assessments. All draft human health assessments developed in EPA's IRIS Program are subjected to rigorous, open, independent external peer review and are provided to the public for review and comment. Comments received from the public on the external review draft assessment are provided to the external peer review panels to promote public involvement in the scientific process. Responses to external review comments and public comments are included in the final assessments and become part of the public record.

In 2009, a FR notice was released explaining the IRIS update project. The availability of new data is used to reach a preliminary determination regarding the need for an update of an IRIS assessment. Toxicity values on the database that are more than 10 years old have been identified, screened, and prioritized based on Agency needs; the first group of 15 high priority assessments has been selected for update. A Federal Standing Science Review Committee (FSSRC), consisting of reviewers from EPA and other Federal agencies has been assembled. For external review, an independent contractor will lead and conduct external peer reviews. Among the first 15 assessments, six are in the final stages of development and are expected to begin review by the FSSRC in June 2011. A second batch of nine assessments will be ready for the FSSRC by December 2011, and a Federal Register notice announcing new set of 20-30 chemicals will be published by June 2011. These updates will be peer reviewed and publicly available on the IRIS Web site. Lessons learned from the pilot project are being integrated into SOPs.

Other significant activities under this theme will include improving IRIS database utility to users. Improving the search function in IRIS and key words associations will increase its utility to both chemical managers and users of the data bases. The intention is to review and update current search terms and functions to improve functional searches using Boolean strategies. This effort will benefit chemical managers and others who are looking for existing literature and assessment on related chemicals, adverse outcomes, or modes of action.

2. Integrated Science Assessments (ISA) of Criteria Air Pollutants (Theme 2)

Science Question: What are the human health and environmental hazards of criteria air pollutants?

Congress requires that EPA regularly summarize the state-of-the-science for the six criteria air pollutants—ozone, particulate matter, sulfur and nitrogen oxides, carbon monoxide, and lead—to assist EPA’s Office of Air and Radiation in developing the National Ambient Air Quality Standards (NAAQS). These ISAs (formerly Air Quality Criteria Documents) are major science assessments that focus mainly on human health effects but also include assessments of environmental impacts for secondary standards. EPA released a revised NAAQS review process (Appendix B) in May 2009 to accelerate the delivery of these critical science assessments and the development of the supporting documents for NAAQS (<http://www.epa.gov/ttn/naaqs/review.html>).

Sections 103, 108, and 109 of the CAA govern the establishment, review, and revision of the NAAQS and direct the Agency to issue air quality criteria for identified pollutants that reasonably may be anticipated to endanger public health or welfare. HHRA produces ISAs that evaluate the latest relevant available scientific information addressing the nature and extent of health and welfare effects associated with exposure to ambient concentrations of the particular pollutant. The ISAs are reviewed and revised as part of the HHRA program on a regular 5-year cycle in response to statutory requirements. ORD conducts laboratory research pursuant to the CAA under the other national programs, especially the Air, Climate, and Energy (ACE) program. The ISAs incorporate and synthesize research findings from ORD and others into these assessment documents.

In developing ISAs, HHRA scientists and external authors evaluate, integrate and synthesize evidence from the areas of atmospheric chemistry, ecology, dosimetry, toxicology, epidemiology, exposure, and sources, ambient concentrations and measurement methods. HHRA has a close collaboration in the planning and execution of ISA preparation with the recipient Office of Air Quality Planning and Standards (OAQPS) (see diagram of process in Appendix B). In the new ISA process the draft integrated plan for each ISA is reviewed by Clean Air Scientific Advisory Committee (CASAC). Draft ISAs are reviewed internally and through workshops covering specific areas of the assessment. External review drafts undergo public comment and detailed scrutiny by the CASAC. The final ISA provides the scientific support for risk and exposure assessments conducted by OAQPS and for policy decisions on potential revisions of the NAAQS.

The establishment and periodic review of NAAQS for the six criteria air pollutants has focused on single pollutant approaches, evaluating the independent effects of exposure to these air pollutants. However, it has long been recognized that individuals are not exposed to a single pollutant in isolation, rather to a complex mixture of air pollution that varies in time and space. While there has been a movement to shift from single to multipollutant approaches in evaluating air pollution-induced health effects, characterizing the health impacts of exposure to air pollutant mixtures presents a significant challenge to the scientific and regulatory communities. As an important initial step in overcoming these challenges, HHRA and ACE scientists are working in consultation with EPA offices (OAQPS, Office of the General Counsel (OGC)) to develop a multipollutant science assessment (MSA) to support the reviews of the primary (health-based) NAAQS. This assessment will allow for an evaluation of the combined health effects of 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 ISA. It is anticipated that the multipollutant science assessment will serve as a companion document to the individual pollutant Integrated Science Assessments (ISAs).

The assessment products from the Integrated Science Assessment and Multipollutant Assessment projects are used directly to inform decision making by the Agency. To support the development of these products, EPA also develops capabilities within and external to EPA to ensure full understanding and utilization of science. These capabilities are developed by advancing the methods used in assessment development and through targeted risk assessment training activities.

3. Community Risk and Technical Support (CRTS) for exposure and health assessments (Theme 3)

Science Question: What tools and analyses can ORD provide to help EPA programs and communities assess exposure and rapidly scope the risks of emerging issues?

Coordinated assistance to assess and address issues of chemical and other environmental contamination in communities is an urgent need. These issues might come in the form of crisis-level needs for quick turn-around technical support, or they might be longer-term, but unplanned for, needs for risk assessment expertise. The Community Risk and Technical Support (CRTS) theme will provide essential technical assistance through the HHRA program to EPA's programs and regions. The CRTS theme will directly impact the regions, improving their ability to quickly find technical assistance on human health risk issues within ORD. Importantly, the CRTS theme requires rapid response to ensure that decision-makers in the regions have the tools they need to address a community's concerns and emerging issues. The CRTS theme will provide rapid risk assessments, combining problem formulation and state of the art exposure information and tools with hazard information.

The CRTS theme will include several key components of the HHRA program that are critical for offering rapid risk assessment and technical support. Formalizing and more clearly articulating HHRA's ability to provide rapid risk assessment and technical support will improve the regions' and program offices' ability to access critical applied expertise when dealing with environmental health problems. HHRA scientists offer unique capabilities in problem formulation, hazard, dose-response and exposure assessment, and the development and use of risk assessment tools to Agency decision-makers. Development of provisional peer reviewed toxicity values (PPRTVs) is a critical need for the Superfund Program and those in the regions making clean-up decision. This well-established part of the HHRA program will be highlighted as a feature of the CRTS theme. Developing tools and guidance for exposure assessment will provide HHRA's customers with critical information to help understand the extent and route of exposure. Support for conducting cumulative impact assessments is a well understood need; however, solutions have not been as quick to follow. HHRA's work in this area will offer innovative approaches and tools that can be used by EPA's Programs and Regions. Finally, the development and refinement of support and application tools will offer needed training in risk assessment and make the Agency's products more transparent.

The CRST theme will offer applied technical support for risk-based decision-making and ultimately contribute to protecting the public's health and cleaning up contaminated communities, key to EPA's mission and one of its strategic goals.

4. Methods, models, and approaches to modernize risk assessment for the 21st century (Theme 4)

Science Question: How can ORD better meet the needs of decision makers by modernizing risk assessment to incorporate recent scientific innovations, including molecular biology and computational sciences?

Risk assessment must be modernized for the 21st century. There is both the need for different risk characterizations and the opportunity that new kinds of data can help us meet those needs. In October 2010, Agency risk managers were asked to identify key unmet risk assessment needs in their decision-making at the Risk Assessment Forum Human Health Risk Assessment Colloquium. Three priority needs were consistently identified across risk managers:

- (1) making informed decisions about the large number of compounds lacking health assessments;
- (2) considering cost-benefit and risk-risk tradeoff for chemicals and effects lacking quantitative estimates of the incremental risk/benefit with changing exposure; and
- (3) considering the combined effects of multiple chemical and non-chemical stressors without cumulative assessments of sufficiently wide scope.

Adding to this, the revolutions in molecular biology and computational sciences lead to a wider array of data sources on a larger number of compounds available for use in risk assessment, as well as informatics-based tools to systematically mine, analyze, and integrate those data. These data and tools have the potential to fulfill some unmet risk assessment needs.

Recent recommendations from the National Research Council (NRC), the SAB, and the BOSC recognize both the need and the opportunity to modernize risk assessment, while also pointing to a number of promising approaches for integrating them. For instance, *Toxicity Testing in the 21st Century* (NRC, 2007) lays out a vision and strategy for utilizing recent scientific advances to efficiently prioritize and assess a large number of chemicals, a need reiterated in *Science and Decisions* (NRC, 2009). NRC (2009) also recognized the need for improved approaches to dose-response quantification for across both cancer and non-cancer effects in order to better support Agency decisions. In addition, *Phthalates and Cumulative Risk* (NRC, 2008) advocated expansion of the scope of cumulative risk assessments. At the same time, recognizing the complexity of the Agency and assessment decisions, NRC (2009), along with the SAB (2010) and the BOSC (2009), recommended expanding the use of decision-support sciences in order to determine the risk assessment approach best suited to inform each risk management situation.

Therefore, the projects in this theme are oriented around the priority Agency risk management needs, taking advantage of the advances in molecular biology and computational sciences, and using approaches informed by recommendations from a number of expert advisory bodies. The scientific products developed through this program undergo external peer review and are disseminated through the published literature and EPA websites. These new methods, models, and approaches feed into the health assessments that are critical for Agency decision-making. Incorporating these advances in risk assessment methods into HHRA assessments enhances the overall quality and objectivity of the assessments and the HHRA program.

III. Human Health Risk Assessment Program Outcomes and Impacts

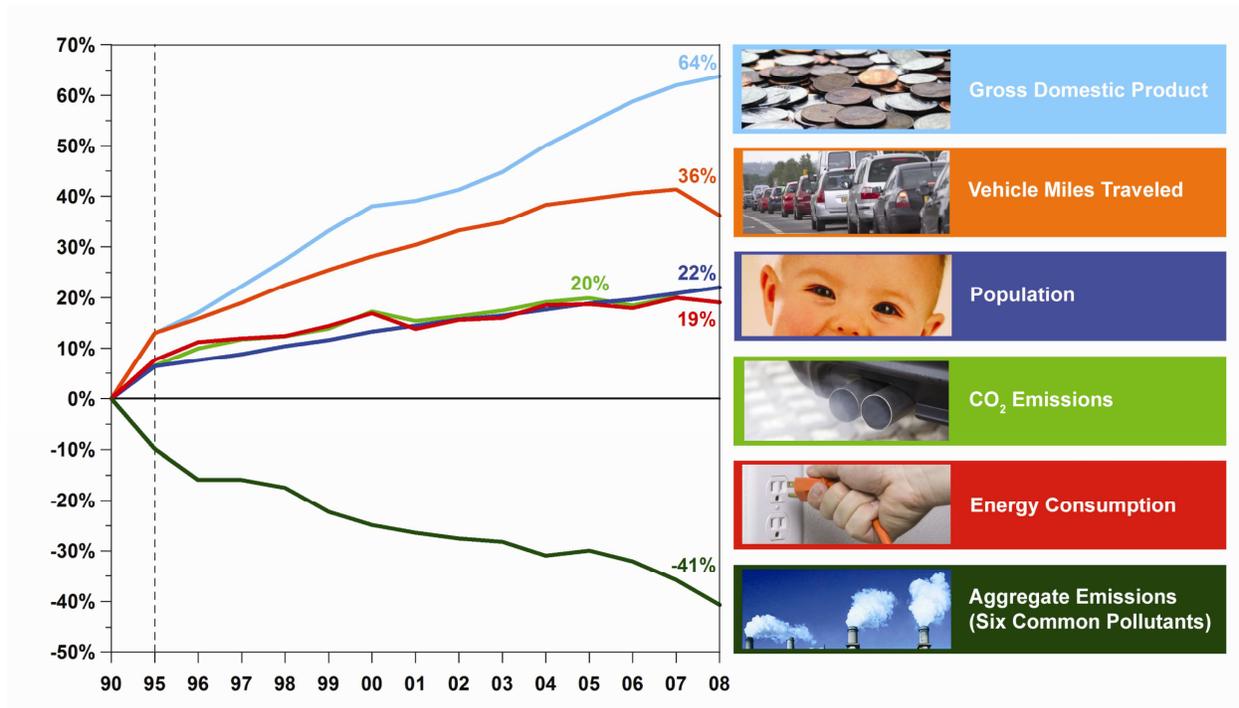
HHRA research products/outcomes may have both intended and unintended social, economic, environmental, or human health effects.

Theme 1 – IRIS impacts: Given the broad usage of IRIS assessments by EPA program and regional offices, as well as the general public, Theme 1 products/outcomes could potentially have social, environmental, economic, or human health effects. Intended impacts of IRIS products/outcomes include: a reduction of disease and optimal distribution of resources. Unintended impacts continue to be that chemicals with no hazard and dose-response assessments are considered to be safe until evaluated. These omissions in the IRIS and other health hazard assessments would lead to a systematic bias and unintended impacts, whereby the wrong risk management options could be selected.

Theme 2 – ISA impacts: Attainment of the National Ambient Air Quality Standards (NAAQS) 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. Air

pollution has dramatically decreased over the 30 years of the program's existence. The direct benefits of the Clean Air Act (CAA) from 1970 to 1990 include reduced incidence of a number of adverse human health effects, improvements in visibility, and avoided damage to agricultural crops and other vegetation. These results have been accomplished in the face of a growing population, number of vehicles, and economy (See Figure 2).

Figure 2 – Comparison of Growth Areas and Emissions



According to the OMB, the EPA's Clean Air Program is the largest nonmilitary Federal program in terms of cost and economic benefits to society. Theme 2 contributes directly and significantly to this national effort to reduce the adverse health and ecological effects caused by air pollution, directly resulting in healthy communities that have clean air and sustainable ecosystems.

In spite of these successes, public health and the environment continue to be impacted by air pollution. More than 100 million people live in areas that exceed current air pollution standards and many ecosystems are imperiled by atmospheric pollutants. Children, people with preexisting diseases and high-exposure groups are particularly at risk. Economically disadvantaged populations can experience higher exposures and can be at increased risk because they often reside in less desirable polluted areas (e.g., near freeways). Additionally, as science progresses more sensitive methods and a more robust understanding of human and ecologic health continue to reveal previously unknown impacts even while pollution levels are decreasing.

Theme 3 – Community Risk and Technical Support impacts: The potential for both intended and unintended social impacts related to Theme 3 products/outputs is wide-

ranging. Examples of intended social impacts include rapid response to community concerns and emerging issues resulting in clean up or other risk management decisions and response to environmental justice concerns through the incorporation of non-chemical stressors into the assessment of community risks. As with any program focused on the communities where people live and work, there is always the potential for unintended social impacts. . For example, knowing the risk of chemical contamination in a community could potentially contribute to increased levels of social stress or the knowledge that a person is living on or near a contaminated site may create difficulties for that person in selling his/her property.

Additionally, there are potential economic impacts associated with the CRTS theme. For example, the development of PPRTVs enables OSWER to make clean up decisions at contaminated superfund sites. This has economic implications for the responsible party. As with all HHRA products/outputs, Theme 3 outputs are intended to positively contribute to protecting the public's health, including reducing the risks that environmental contaminants pose to sensitive populations. The environmental impacts of Theme 3 products will ultimately result in the cleaning up of contaminated communities.

Theme 4 - Methods, Models, and Approaches to Modernize Risk Assessment impacts: The outputs of this theme will increase efficiency and effectiveness of the Agency risk assessment programs by bringing innovative approaches forward and applying them to mine databases and link information to users' needs in a more effective fashion so assessments can be done quickly and more transparently.

Quantitative analysis of uncertainty, derivation of central estimates and confidence limits on estimates of risk is another need driven in part by those who wish to use risk assessment results in the context of formal decision analysis or in cost-benefit analysis. Moving forward with additional dose-response approaches particularly in the non-cancer arena will allow greater utility in comparing different risk relationships between and among chemical-induced adverse health outcomes. The current approaches that employ single point estimates do not allow for consideration of benefits analysis of many non-cancer outcomes and the burden of disease. The unintended impact in cost benefits analysis and decision making is that these effects on burden of disease are not fully evaluated.

Table 1 – EPA Strategic Goal 4: Assuring the Safety of Chemicals

Theme 1: Integrated Risk Information System (IRIS) health hazard and dose-response assessments			
Science Questions	Outputs	Outcome	Linkages
1. What are the important human health effects of chemicals for priority Agency decisions?	Individual IRIS assessments, IRIS updates assessments	IRIS database has greater utility and transparency to users	Serves multiple programs and regions priority needs as well as external stakeholders. Integrates research from ACE program on hazardous air pollutants and advances from the CCS program on into assessments.
Theme 2: Integrated Science Assessments (ISA) of Criteria Air Pollutants			
Science Questions	Outputs	Outcome	Linkages
2. What are the human health and environmental hazards of criteria air pollutants?	Individual ISAs for NO _x , SO _x , PM, ozone, CO, Pb; Multipollutant assessment	Provides the science basis for the Administrator’s decisions on each NAAQS.	Significant technical and decision support is provided to OAR/OAQPS and Administrators office. Integrates research from ACE program into ISAs and multipollutant assessment.
Theme 3: Community Risk and Technical Support for exposure and health assessments			
Science Questions	Outputs	Outcome	Linkages
3. What tools and analyses can ORD provide to help EPA programs and communities assess exposure and rapidly scope the risks of emerging issues?	Rapid risk assessments, technical support, individual PPRTV s, Exposure factors handbook updates/exposure tool box, Cumulative impact assessments	Regional, state and other site specific assessors have risk-based information they need for screening level decisions, records of decisions and permitting.	Serves priority needs at multiple scales including national, regional and community needs. Integrates research from CCS, SHC, SSWR, and ACE programs into assessments. HHRA risk assessments are required for risk-based decisions which provide metrics for Risk/Risk evaluation of trade offs and cost benefits analysis. Risk-based metrics will be critical to the development of sustainable solutions in SHC program.

Theme 4: Methods, models, and approaches to modernize risk assessment for the 21st century

Science Questions	Outputs	Outcome	Linkages
<p>4. How can ORD better meet the needs of decision makers by modernizing risk assessment to incorporate recent scientific innovations, including molecular biology and computational sciences?</p>	<p>Informatics-based tools to accelerate risk assessment development; Approaches for hazard and dose-response assessment with limited or no in vivo data; Methods for quantifying incremental risk with dose, and their uncertainty and variability, across all endpoints; Methods for predicting contributions and interactions among multiple chemical and non-chemical stressors to adverse health outcomes.</p>	<p>Risk assessments are conducted more rapidly and with greater transparency and reproducibility; health effects assessments on a much wider range of chemicals are available to decision makers; decision makers can conduct cost-benefit and risk-risk tradeoff analyses on a wider range of chemicals and effects; cumulative assessments addressing a broader scope of stressors are available to support decisions.</p>	<p>Serves multiple programs and regions priority needs as well as external stakeholders. Products will also be utilized in outputs of other themes of HHRA and by Program Offices and others.</p>

IV. References

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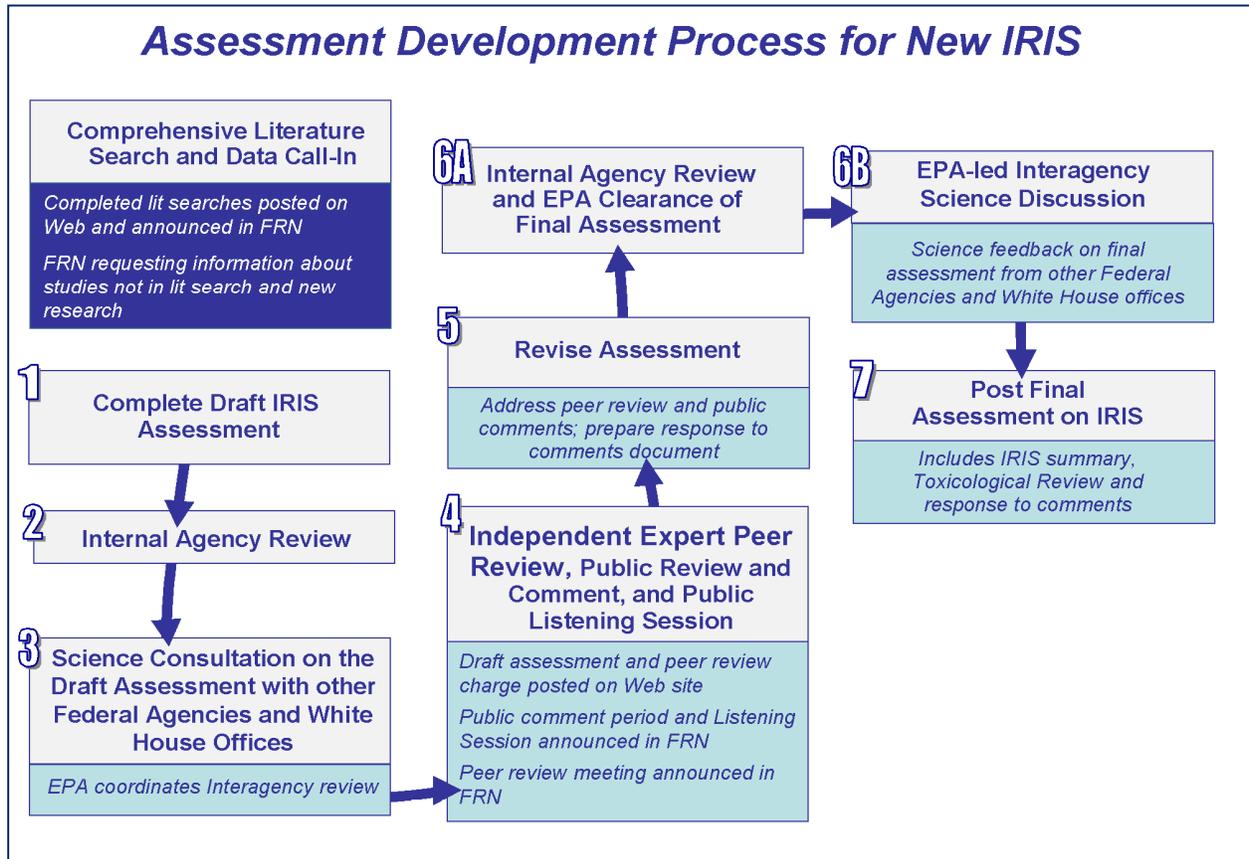
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Appendix A – IRIS Process



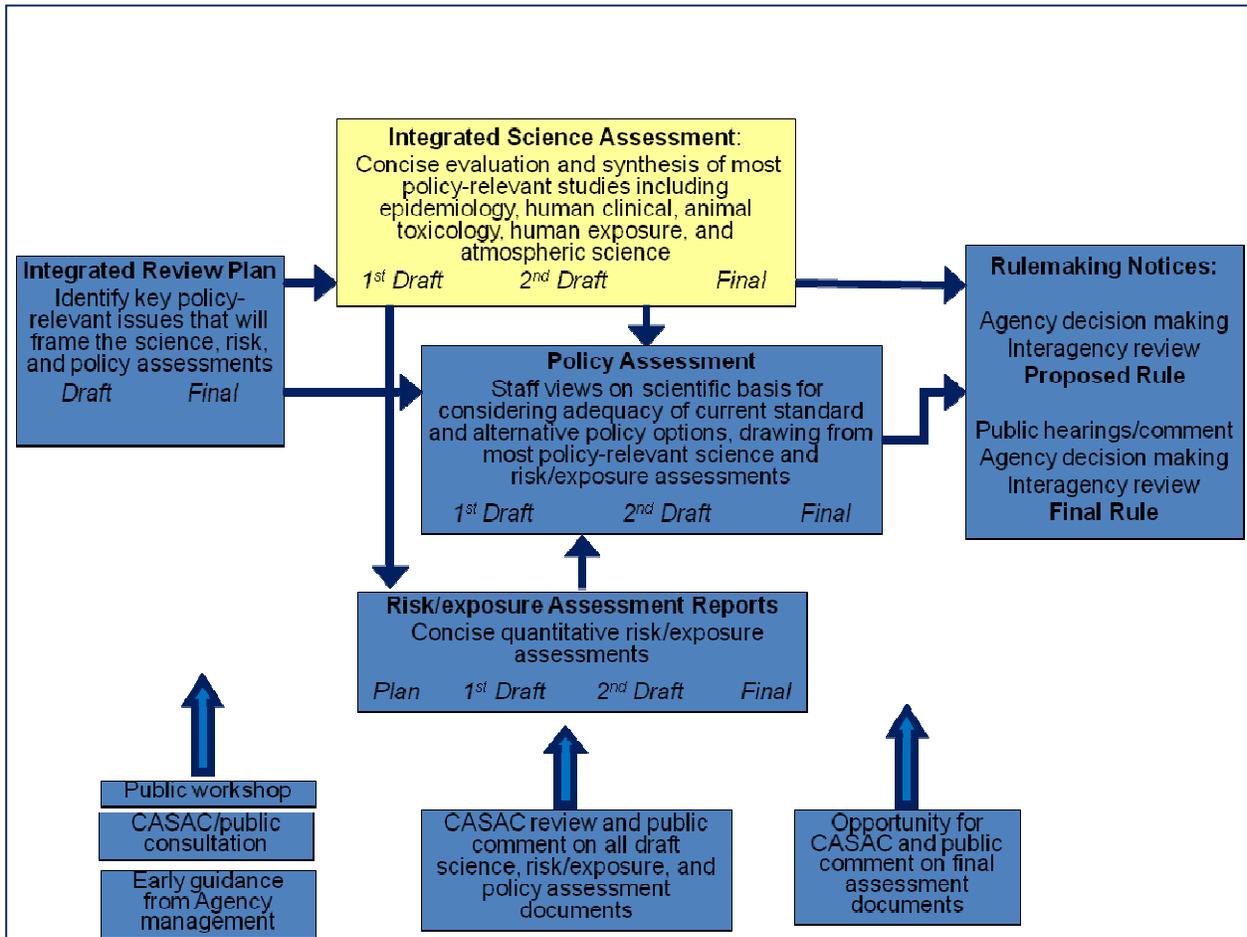
Appendix B – IRIS Assessments on FY 2011 Agenda

Table 2: IRIS assessments that are the current focus of the Program for completion in FY 2011

Tier 3	Tier 2	Tier 1
Asbestos (Libby)	Acrylonitrile	Beryllium (cancer)
Chromium VI (oral)	Arsenic (cancer)	Copper
Dichloromethane	Arsenic (noncancer)	1,2-Dichlorobenzene
Dioxin	Benzo[a]pyrene	1,3-Dichlorobenzene
Formaldehyde	Chloroform	ETBE
Methanol	Diisobutyl phthalate (DIBP)	Hexachloroethane
MTBE	butyl benzyl phthalate (BBP)	Mirex
PAH mixtures	di(2-ethylhexyl) phthalate (DEHP)	Platinum
PCBs (noncancer)	Dibutyl phthalate (DBP)	Uranium
Phthalate cumulative assessment	Dipentyl phthalate (DPP)	Urea
Tetrachloroethylene	Diisononyl phthalate (DINP)	Biphenyl
Trichloroethylene	1,4-Dichlorobenzene	Butanol, n-
Chromium VI (inhalation)*	Ethylene oxide (cancer)	Butanol, t-
	Tetrahydrofuran (THF)	chloroethane
Manganese	Trichloroacetic acid	diethylphthalate
	Acetaldehyde	Hexabromocyclododecane
	Ammonia	Trimethylbenzene, 1,2,4-
	Cadmium	Trimethylbenzene, 1,3,5-
	Cobalt	Vanadium pentoxide
	DEHA	Alkylates
	Dioxane, 1,4- (inhalation)*	Antimony
	Hexachlorobutadiene	Carbonyl sulfide
	Naphthalene	DIPE – on hold
	Nickel	TAAE – on hold
	RDX	
	Vinyl acetate	
	Ethylene dichloride	
	Styrene	
	Tungsten	
	TAME – on hold	
	Ethylbenzene	

*New entries due to route-specific assessments being undertaken on different timelines. Note that for chromium VI, the immediate need was for an assessment of the oral pathway of exposure. An assessment of the inhalation pathway will follow. For 1, 4-dioxane, an assessment for the inhalation pathway was not possible due to a lack of suitable studies. During external peer review of the draft assessment, new studies on the inhalation pathway were published that will be considered on a different timeline. Assessments listed as on hold are based upon Ramazzini cancer bioassay Issues.

Appendix C – ISA Process



Appendix D – ISA Gant Chart

