Human Health Risk Assessment
Multi-Year Plan
2007- 2012

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Preface

The Office of Research and Development (ORD) multi-year plans (MYPs) present ORD's proposed research and development activities in a variety of areas over the next 5-8 years, assuming constant funding. The MYPs serve to outline the direction of ORD's activities and to communicate this program within ORD and with others. Developing MYPs permits ORD to consider the strategic directions of the Agency and how research and development activities can evolve to best contribute to the Agency's mission of protecting human health and the environment. MYPs are considered to be "living documents" meaning that ORD intends to update the MYPs on a regular basis to reflect the current state of the science, resource availability, and Agency priorities. ORD will update or modify future performance information contained within this planning document as needed.

The Human Health Risk Assessment Multi-Year Plan (HHRA MYP) was originally completed in December 2005 based on the "ORD Multi-Year Planning Guidance Update" (2002). Planning input was sought from ORD-National Center for Environmental Assessment (NCEA) and Risk Assessment Forum staff, and from EPA Programs, Regions, and other ORD laboratories and centers through the Human Health Research Coordination Team (RCT). Internal Agency review was conducted through the RCT process and managed independently by the ORD Office of Science Policy. Peer review comments were also sought from the ORD Science Council through a process managed by designated Science Council members. Additional meetings were held to solicit input from managers and directors in EPA Program Offices; including the Office of Water, Office of Air and Radiation, Office of Prevention Pesticides and Toxic Substances, and Office of Solid Waste and Emergency Response.

The present document represents an update to the 2005 document reflecting program developments and emerging directions. This updated draft HHRA MYP was reviewed by designated ORD Science Council members and submitted for external peer review by the Board of Scientific Councilors (BOSC) in August 2007. Appreciation is extended to all the EPA staff and to the BOSC members who contributed to the preparation and review of this draft HHRA MYP.

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Executive Summary for Human Health Risk Assessment Program

Interim National Program Director: Rebecca Clark

The HHRA program plays a unique role in serving the needs of EPA programs by incorporating, integrating and coordinating the use of scientific information as a foundation for regulatory decision making. Currently, there are nearly 150,000 chemicals registered in the European REACH Program and over 84,000 chemicals on the Toxic Substances Control Act (TSCA) inventory, and each year about 1,000 new chemicals are introduced into commerce. Only a small fraction of these chemicals have been assessed adequately for potential risk, often because of limitations in existing data, tools, and resources. HHRA 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.

To address this challenge, in FY 2012, EPA is realigning and integrating the work of its base research programs. Within that new structure, the Human Health Risk Assessment (HHRA) program will continue to provide the risk assessments necessary to guide EPA's actions to protect public health and the environment. The program develops human health assessments that are used extensively by EPA Program and Regional Offices and other parties to make decisions, develop regulatory standards for environmental contaminants, and manage cleanups. The HHRA program will continue to evolve to meet today's complex environmental challenges, developing multi-pollutant science assessments for health and climate effects (as called for by the Clean Air Scientific Advisory Committee (CASAC) and other scientific reviews such as the 2004 NAS report on Air Quality Management).

Three complementary and integrated areas comprise the HHRA program:

IRIS and other health hazard assessments: 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 use these assessments to support their decision-making. The Agency disseminates the assessments to the public on the IRIS Internet database.[a] EPA and the risk assessment/risk management community consider IRIS the premier source of hazard and dose-response information for environmental pollutants. As of January 2010, more than 550 health hazard assessments were available through IRIS. EPA released a revised IRIS process in May 2009 to streamline and accelerate completion of these critical science assessments (http://www.epa.gov/iris/process.htm).

Methods, Models and Approaches to Improve Risk Assessment Science: High quality risk assessments require state of the art methods. HHRA assessments incorporate contemporary scientific advances to develop methods and models to enhance their quality and objectivity. In addition, they support decision-making by EPA's Program and Regional Offices. These scientific products receive external peer review, and then EPA disseminates them through the published literature and EPA websites.

[a] Available at: http://www.epa.gov/iris.

Integrated Science Assessments: Congress requires that EPA regularly summarize the state-of-the-science for criteria air pollutants—ozone, particulate matter, sulfur and nitrous 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 risk assessments that undergo rigorous external peer review by the CASAC. EPA released a revised NAAQS review process in May 2009 to speed up the delivery of these critical science assessments and the development of the supporting documents for NAAQS (http://www.epa.gov/ttn/naaqs/review.html).

In FY 2008, an evaluation by EPA's Board of Scientific Counselors (BOSC)—a federal advisory committee comprised of independent expert scientists and engineers—concluded that the HHRA program "has been highly responsive to the needs of the program offices and regions," producing products that are critical to EPA's regulatory mission and form the foundation for regulatory decisions and policies. This prospective and retrospective review evaluated the program's relevance, quality, performance, and scientific leadership. The evaluation found that the program is making substantial and satisfactory progress; has clearly defined milestones; and provides additional essential support to EPA programs to respond to unscheduled emergency needs. In July 2010, the BOSC reviewed the mid-cycle report on the progress of the HHRA program in implementing its previous recommendations. The BOSC affirmed its previous evaluation of the relevance of the program and noted significant progress on its previous recommendations. EPA is using the BOSC's evaluation and recommendations to help revise its strategic plan, implement, and strengthen the program over the next five years. It is anticipated that a revision of the HHRA multiyear plan will follow the development of other National Program research action plans and integrate products of these other plans into risk assessments and decision support tools useful to decision makers inside the Agency and outside the Agency.

FY 2012 Activities and Performance Plan:

In FY 2012, EPA will continue to develop IRIS and other health hazard assessments. EPA will continue to streamline the new IRIS process to ensure the program effectively meets the needs of EPA, the Federal Government and the American public. The program will make significant progress on health hazard assessments of high priority chemicals (e.g. formaldehyde, trichloroethylene, dichloromethane, arsenic, chromium VI, methanol, benzo[a-]pyrene, and Libby asbestos), complete work for interagency science consultation, external review, or posting on the IRIS web page.[b] In addition, EPA will develop assessments of health effects for chemicals found in environmental mixtures and including PAHs, dioxins, phthalates and PCBs. These cumulative approaches will increase the number of chemicals that are addressed by the IRIS Program and are based upon the expressed needs of the Agency. The HHRA program will continue to lead innovation in risk assessment science based on expanding scientific knowledge.

EPA will develop Provisional Peer Reviewed Toxicity Values (PPRTVs) and other health hazard assessments to support program and regional decision-making. EPA will respond with science assessment support on chemical contaminant issues requiring quick action and, ultimately, quick decisions and solutions (e.g., PCBs in schools, Mountaintop Mining, Katrina, World Trade Center disaster and BP oil spill). Responding to real-world issues and crises is a key part of EPA's

[b] Available at: http://www.epa.gov/IRIS/

mission to protect human health and the environment and one the BOSC suggested was relevant to HHRA.

The Agency will continue to lead the development of risk assessment approaches, methods, and models to enhance the quality and objectivity of assessments through the incorporation of contemporary scientific advances. EPA will continue to develop approaches for applying mode of action in risk assessment and improve quantification of health risks, such as Physiologically Based Pharmacokinetic and Biologically Based Dose Response modeling, as well as characterizing environmental exposure and risk to susceptible populations.

EPA will continue to implement of Health and Environmental Research Online (HERO) to support a more continuous process to identify, compile, characterize, and prioritize new scientific studies for human health and ecological assessment development. HERO lends transparency to the process of assessment development by allowing access to the data used for scientific decisions.

In addition, EPA will continue to develop ISAs of criteria air pollutants, as a mandated prerequisite to EPA's review of the NAAQS and effectively meet court ordered deadlines to provide these assessments. The ISAs provide important scientific analyses in support of many of EPA's important rulemakings. In FY 2012, the program will release final ISAs for ozone and lead, which will be used by EPA's Office of Air and Radiation to support development of the NAAQS, and create state-of-the-science methods for continuous evaluation of assessments of new scientific information on criteria air pollutants. The HHRA program will also begin exploring multi-pollutant assessment approaches as called for by the 2008 CASAC consultation on EPA's draft plan for review of the Primary NAAQA for Carbon Monoxide and the 2004 NAS report on Air Quality Management.

Integration of ORD other ITR programs products into HHRA

As part of EPA's effort to integrate research programs to deliver more innovative, sustainable solutions to our environmental problems, numerous programs will dovetail and coordinate. The next generation risk assessment research in the Chemical Safety and Sustainability research program will advance risk assessment approaches by incorporating knowledge derived from recent advances in molecular biology, systems biology and gene-environment interactions in human disease. The HHRA program will use information gained from this program to strengthen the development of risk assessments, resulting in improved approaches for assessing environmental impacts and new approaches for preventing negative impacts resulting from chemical exposure. The Air, Climate and Energy (ACE) program will provide critical research on both criteria air pollutants and air toxics to meet the assessment and regulatory needs for single and multi-pollutant decisions. The Safe and Sustainable Water Resources program will provide research on pollutants in water and their health impacts which can be incorporated into state of the art health assessments. The Sustainable and Healthy Communities program's effort on community health research will help inform the development of new approaches and the refinement of existing approaches for community risk assessments, helping the Agency understand the cumulative impacts of chemical and non-chemical stressors that impact human health.

Human Health Risk Assessment (HHRA) Multi-Year Plan, Final

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Introduction

Human health risk assessment is a process by which information is analyzed to determine if an environmental hazard might cause harm to exposed persons. It is the essential intermediary means by which primary data and published literature are compiled, analyzed and summarized for application to decision-making in real-world situations. Risk assessment in the federal government is based on the tenets outlined by the National Academy of Sciences (NAS 1983, 1994), namely hazard identification, dose-response assessment, exposure assessment, and risk characterization, as a foundation for subsequent risk management decisions. This science-based framework for decision-making is central to U.S. EPA's implementation of its statutory responsibilities and to its mission to protect human health and the environment. The Human Health Risk Assessment (HHRA) Multi-Year Plan (MYP) serves as a primary EPA mechanism to implement this process, linking laboratory and field science with the use of this information by EPA Programs, Regions and the broader community. To achieve this goal, the HHRA program directs efforts toward:

< Providing qualitative and quantitative health hazard assessments of priority environmental contaminants for incorporation in applied risk assessments. [These assessments are exemplified by the Integrated Risk Information System (IRIS) Toxicological Reviews and Summaries, reference doses (RfDs), reference concentrations (RfCs), oral cancer slope factors (CSF) and cancer inhalation unit risks and Provisional Peer Reviewed Toxicity Values (PPRTVs)];

< Preparing Integrated Science Assessments [ISAs; formerly Air Quality Criteria Documents (AQCD)] for criteria air pollutants as a mandated component of EPA's review of National Ambient Air Quality Standards (NAAQS);

< Conducting environmental risk assessments of national importance, such as potential health impacts in the aftermath of Hurricane Katrina and Rita, the attack on the World Trade Center, and the reassessment of the health risks posed by dioxin;

< Developing models, methods and guidance to incorporate the latest scientific advances into EPA risk assessment practice, thereby maintaining the scientific quality and objectivity of EPA assessments consistent with the state-of-the-science;

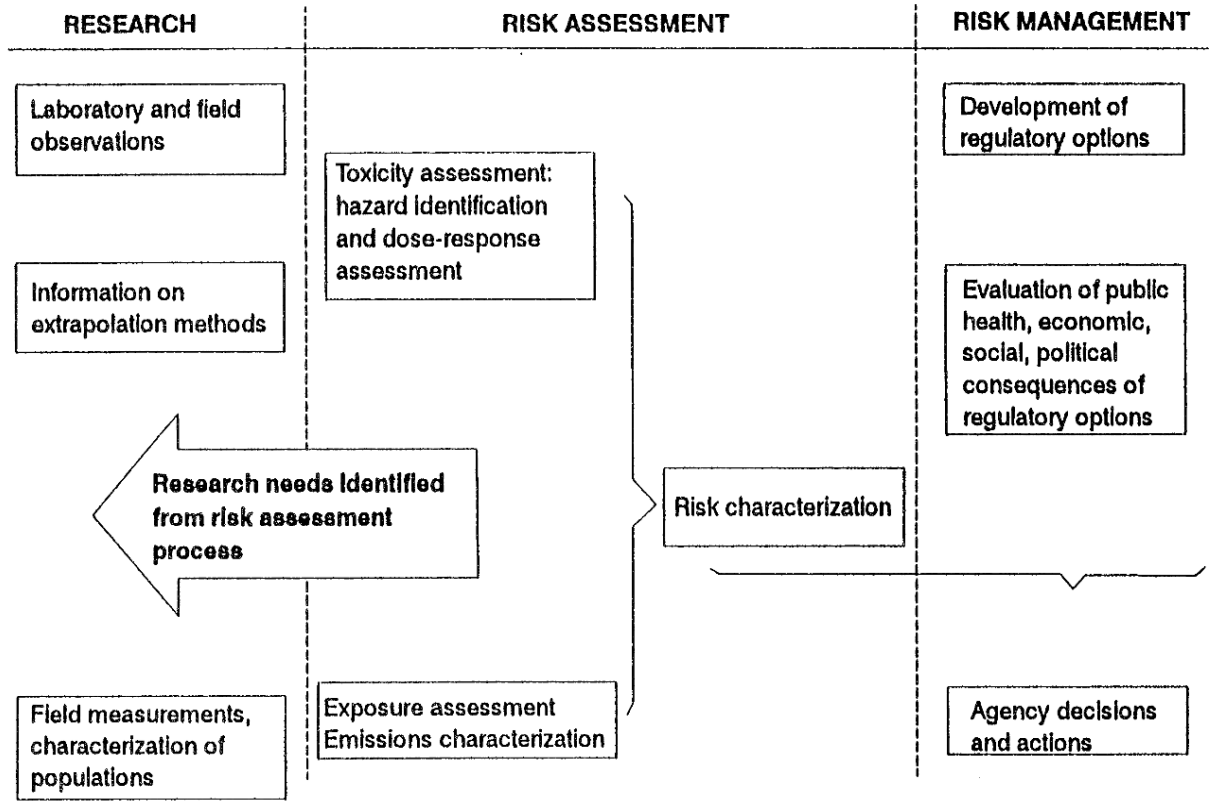
< Identifying, evaluating and conveying to the scientific community key uncertainties and research needed to improve health risk assessments through laboratory, field and methods research.

The principal purposes of ORD's MYPs are planning and communication – communication among ORD laboratories and centers, and communication between ORD and the

EPA Programs, Regions, and broader science community. The risk assessment MYP differs from other ORD MYPs in that it does not describe plans for conducting or funding primary research. Rather, the HHRA program draws on data and research for developing primary methods generated under other ORD MYPs. Activities under the HHRA program also receive substantial information from the published literature and other federal, private, and international organizations. This information is then analyzed and prepared for use by EPA Programs and Regions to respond to their regulatory and decision-making needs in a timely manner.

Figure 1 shows the flow of information from research, through risk assessment, to risk management (NRC 1983; revised 1994). Primary data generation refers to laboratory and field observations and measurements, along with information on extrapolation methods. Risk assessors use this information to evaluate the hazardous properties of environmental agents and the extent of human exposure to these agents. As noted by the NAS (NRC, 1994), although conducting a risk assessment involves research of a kind, it is primarily a process of gathering and evaluating extant data and imposing science-policy choices. The product of this evaluation is a characterization statement regarding the probability that exposed populations might be harmed and to what degree, expressed quantitatively and/or qualitatively. Because risk assessment provides an organized profile of the current state of knowledge on a substance and systematically elucidates scientific uncertainties, it can provide valuable guidance to research scientists regarding the types of data that can most effectively improve understanding. Risk management is maintained as a distinct process where additional considerations regarding public health, economic, social and political consequences are factored into agency decisions and actions.

Figure 1: NAS/NRC Risk Assessment/Management Paradigm (NRC, 1994)



The NAS paradigm is applied in the ORD context through the separation of laboratory and field research from the risk assessment activities planned in the HHRA program. Primary data generation and model development are conducted in the ORD laboratories to address hazard identification and dose-response parameters, exposure variables, and risk management options. Risk assessors in National Center for Environmental Assessment (NCEA) and directly in program offices use this information to prepare a scientific foundation for subsequent decision-making. Research needs identified through the risk assessment process are conveyed to the research laboratories through the ORD planning process and in collaboration with National Program and Laboratory Directors. The principal purpose of HHRA MYP development activities is not to generate new data but to provide direct support to risk assessment needs, such as guidance on model validation procedures, secondary data analysis in the context of a specific risk assessment, or collation of information on exposure factors. In this way, the HHRA program is a client of the ORD laboratories, both receiving data and helping to prioritize research needs in conjunction with the EPA programs.

The principal customers for risk assessment information under many of EPA's implementing statutes are the EPA Programs and Regions. 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 is to include assessment of risks, development of methods and tools for analysis of data, and development of ISAs to serve as the basis for review of the 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** (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.

The HHRA program plays a unique role in serving the needs of the EPA Programs and Regions through incorporating, integrating, and coordinating the use of scientific information as a foundation for regulatory decision-making. IRIS, ISAs, and other assessments are directly responsive to program needs and are primary considerations in Agency actions to protect human health and the environment. In partnership with the ORD laboratories, the HHRA program is at the forefront of applying quantitative methods that advance risk assessment practices, such as the use of physiologically-based pharmacokinetic (PBPK) models to reduce uncertainty in risk

extrapolations and to replace default uncertainty factors. The HHRA program also maintains a leadership role in incorporating mode-of-action (MoA) evaluations to support EPA decision-making, as emphasized in the EPA 2005 *Cancer Guidelines and Early-Life Supplemental Guidance* and used in recent assessments to evaluate the relevance of animal tumors to humans and the associated dose-response relationships. In conducting these cancer assessments, the HHRA program is uniquely responsive to Agency needs by developing and applying quantitative methods and guidance to estimate cancer risks and associated uncertainty parameters. HHRA program activities are characterized by their ability to integrate information within and across scientific disciplines to solve risk assessment questions, whether substance-specific or novel methods development work. These activities are coordinated across EPA research laboratories and program offices, through formal means under the HHRA program, such as the IRIS agency review and Risk Assessment Forum processes, or more informally through leadership in interpreting and applying risk assessment science to inform environmental decision-making.

Beyond EPA, HHRA program's products are widely recognized as the principal environmental health risk assessment benchmarks in the U.S., exemplified by the 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 encourages close relationships with these 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 staff contacts with other federal agencies conducting primary environmental health research, particularly the NIH-NIEHS National Toxicology Program and the CDC-National Center for Environmental Health. Assessment activities are coordinated through interagency working groups and collaborative relationships. Of particular note is the Memorandum of Understanding between EPA-IRIS and the Agency for Toxic Substances and Disease Registry (ATSDR). ATSDR prepares Toxicological Profiles for hazardous substances found at National Priorities List ("Superfund") sites, including quantitative Minimal Risk Levels (MRLs) for non-cancer effects. The EPA-ATSDR memo of understanding emphasizes coordination and sharing of information on substances under evaluation by both organizations. An EPA-ATSDR joint pilot assessment has commenced for 1,1,2,2-tetrachloroethane, where contract resources are leveraged to prepare toxicological materials and summaries for both organizations. 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.

Resources currently allocated to the HHRA program were consolidated in fiscal year 2004 under EPA Government Performance Results Act (GPRA) Goal 4, Healthy Communities and Ecosystems. The FY'08 President's Budget requests 182 full time equivalent work years and $43 million dollars for the HHRA program. Approximately three quarters of these resources are assigned to the preparation of assessments (e.g., IRIS and other major health hazard assessments ~60% and ISAs ~15%), with the remainder to methods and model development (~25%). At any one time, approximately 75 IRIS assessments are underway, plus additional major health hazard

assessments, ISAs, and between 25 and 50 PPRTVs for substances prioritized by the Office of Solid Waste and Emergency Response (OSWER). Although a number of HHRA program activities explore aspects of integrated human health and ecological risk assessment, the HHRA program does not plan ecological risk assessment activities. Theses are addressed under other ORD plans.

Background

Antecedents of the HHRA Program: Efforts at quantifying presumptively safe levels of environmental exposures began in the 1940s through the development of threshold limit values in occupational settings. The concept of acceptable levels was extended to food contaminants in the 1950s (Lehman and Fitzhugh, 1954). Passage of the "Delaney Clause" to the Food Additive Amendments in 1958 focused attention on potential cancer risks by stipulating that no substance found carcinogenic in animals could be added to food. Further impetus toward quantitative risk assessment came from the 1980 Supreme Court decision on occupational standards for benzene. In this decision, several judges opined that OSHA could regulate only if it found that benzene posed a "significant risk of harm," signaling that some form of quantitative risk assessment was necessary as a prelude to regulatory decision-making. These developments led to the now landmark NAS (NRC, 1983) publication *Risk Assessment in the Federal Government*. In this publication, the NAS proposed the four-step paradigm of hazard identification, dose-response assessment, exposure assessment, and risk characterization, separate from, but linked to, risk management decisions. Additional independent reviews of risk assessment in the federal government (NRC, 1994; Presidential/Congressional Commission, 1997) have confirmed the role of quantitative risk assessment as an essential foundation for decision-making.

The risk assessment/risk management paradigm is EPA's organizing principle for generating and using scientific information (EPA Strategic Plan, Cross-Goal Strategy Science; U.S. EPA, 2003). EPA has implemented risk assessment practices through creating specific risk assessment organizations and as a fundamental component of its decision-making processes. Specific organizations include ORD-NCEA, the Risk Assessment Forum, and Program offices such as the Risk Assessment Division of Office of Pollution Prevention and Toxics Substances (OPPTS). The risk assessment paradigm of effects, exposure, assessment, and management has also been extended to the structuring of the ORD laboratories and centers. As a fundamental component in decision-making processes, EPA's Strategic Plan (GPRA Goal 4, Healthy Communities and Ecosystems) directs the Agency to "identify and synthesize the best available scientific information, models, methods and analyses to support Agency guidance and policy decisions related to the health of people, communities and ecosystems." With regard to chemical, organism, and pesticide risks, EPA Strategic Objective 4.1 seeks to "Prevent and reduce pesticide, chemical, and genetically engineered biological organism risks to humans, communities, and ecosystems." ORD's Strategic Plan (U.S. EPA, 2001) further commits to pursuing "science for a purpose," noting that ORD is part of a regulatory Agency and that its scientific products and expertise are critical to supporting Agency decision-making.

To better achieve these risk assessment objectives, the Administration directed in 2003 that ORD consolidate planning for risk assessment to foster a more integrated approach to resource allocation, prioritization, and accountability. This consolidation was necessary because

< Many NCEA assessments supported more than one program office and covered several existing multi-year plans. Prior to consolidation, NCEA had human health risk assessment resources in 25 long-term goals under 14 MYPs;

< Many chemical assessments, such as the perchlorate, trichloroethylene, formaldehyde, and dioxin assessments, did not appear or were inadequately funded in existing MYPs; and

< Research coordination teams had provided funding only for small, incremental risk assessment methods development activities, with the result that there was no coherent, integrated process for improving methods.

The objectives of the consolidation to the risk assessment MYP were to improve the quality and timeliness of assessments; focus development and incorporation of scientific advances into risk assessment methods and products; improve the alignment of ORD laboratory and center research and programs; and increase technical support to Program offices and Regions.

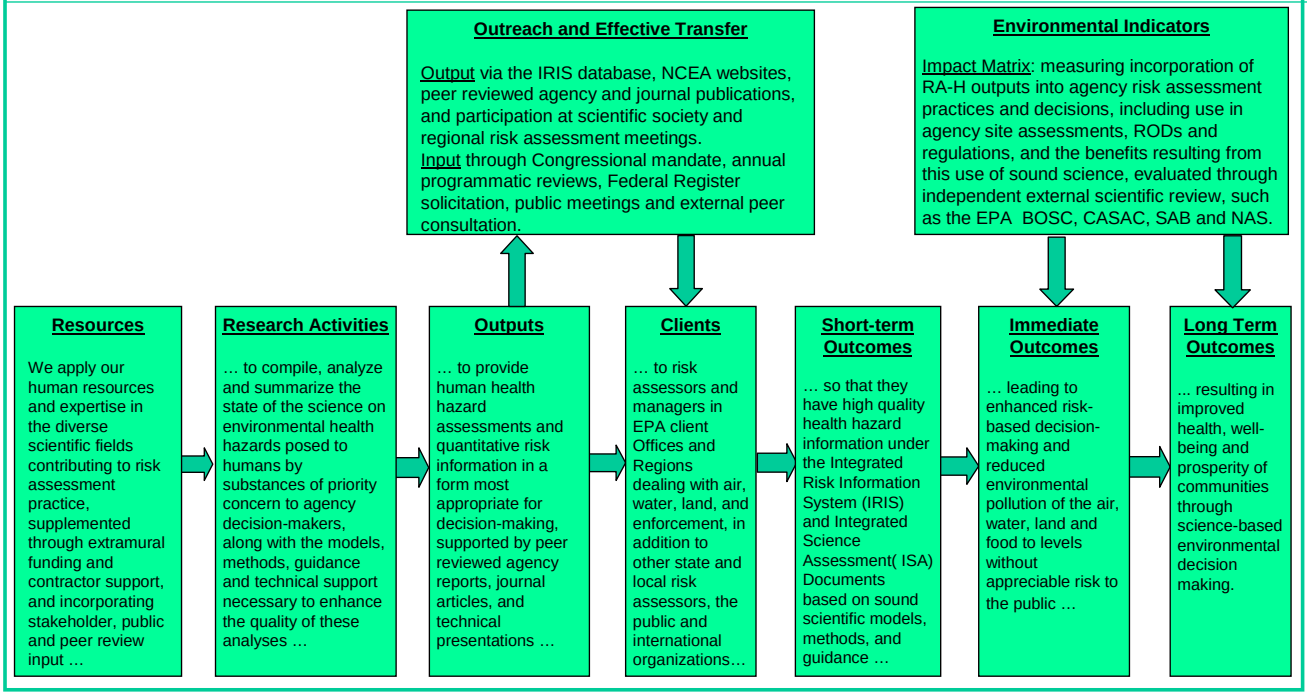
Some confusion arose initially because of the functional ties and similarity in titles and acronyms between the consolidated Human Health Risk Assessment (HHRA) plan and the similarly titled Human Health Research (HHR). As noted, these two plans are distinct in that the HHRA program receives data and methods development science produced under the HHR and other MYPs from the ORD laboratories, as well as from the published literature. The assessments and activities conducted under the auspices of the HHRA program help to prioritize research in the ORD laboratories by identifying critical data gaps and scientific needs, but the HHRA program does not conduct or fund this work itself. In contrast, the HHR plans and coordinates the performance of primary laboratory work on the health effects of environmental pollutants, emphasizing core research to produce a fundamental understanding of the key biological, chemical, and physical processes that underlie environmental systems.

Logic Model: The primary objective of the HHRA program is to provide EPA Programs and Regions with health hazard assessment information on priority substances included in planned Agency decisions and actions. This objective is achieved through the preparation of hazard identification and dose-response assessments under the IRIS program, other major assessments, integrated science assessment documents, and PPRTVs. Methods development and guidance functions are conducted to support this primary objective, thereby ensuring that EPA risk assessment products are consistent with the state-of-the-science and information quality objectives and are considered quality products after undergoing scientific peer review.

Figure 2 displays the logic model for the HHRA program. The intermediate and long-term outcomes on the far right of Figure 2 respond to the Agency's strategic plan to synthesize the best available scientific information to prevent and reduce risks to humans and communities. Through sound science and risk-based decision-making, public health protection can be achieved while facilitating the efficient use of economic resources. The HHRA program supports this Agency strategy through providing health hazard, quantitative risk, and exposure information in the format most appropriate to support decision-making actions. The assessments are based on scientific models, methods, and guidance developed through this and other ORD MYPs and the published literature. Outreach and transfer of HHRA program’s products occurs through the IRIS database and NCEA Web sites; peer reviewed Agency and journal publications; and ongoing

communication, training, and technical support to EPA Program and Regional offices and at scientific conferences.

Figure 2: Logic Model for the Human Health Risk Assessment - Multi-Year Plan



Relevance and the Planning Process: The planning process for the HHRA MYP is closely linked to the needs of program and Regional offices. Planning is conducted on a broad scale through preparation of the HHRA MYP and on a more focused and iterative scale specific to each of the long-term goals, particularly the selection and prioritization of IRIS assessments and PPRTVs, and the timing of ISAs. On a broad scale, HHRA MYP development is conducted through a formal process that involves participation of EPA Programs, Regions, and ORD laboratories in the human health research coordination team (RCT). RCT members are designated by their respective offices to represent their organizational needs and resources. The RCT planning process is supplemented by briefings to senior program managers on proposed MYP activities and outputs. The results of the planning process include revision or prioritization of planned ORD activities over the 5- to 8-year cycle of the MYP, including potential restructuring of the MYP long-term goals. Draft MYPs prepared through this process are subject to internal EPA review by the RCT members and delegated Program, Regional, or laboratory representatives. Designated representatives of the ORD Science Council also internally review the draft MYP. RCT planning is an ongoing activity, recognizing that the MYPs are living documents 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 MYP. Formal planning of the IRIS assessment agenda occurs annually through a call to EPA Programs and Regions for nominations of priority substances for assessment (outline of IRIS process Appendix A). This is supplemented by an IRIS screening process that has been instituted to determine if newly published literature might impact existing, older IRIS assessments, and hence warrant consideration for revision. PPRTVs are prepared on an ongoing basis at the request of OSWER for those substances found at clean-up sites and for which no IRIS value is available. 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 (See Flow chart of NAAQS process in Appendix B).

Due to the extent of this planning and programmatic input on priority needs, the HHRA program has a very close linkage between its outputs and 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. ISAs constitute the scientific basis for review of the NAAQS for criteria air pollutants. 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.

Quality and Peer Review: All HHRA program's products are subject to internal and independent external peer reviews to assure their quality and objectivity. Internal reviews and external peer reviews are conducted consistent with the policies detailed in EPA's *Peer Review Guidelines* (U.S. EPA, 1998) and the White House Office of Management and Budget (OMB)*Peer Review Guidance* (2004). These policies include categorization of all HHRA program products regarding their potential scientific, policy, and economic implications as a determinant of the level of review required. Many HHRA MYP products are considered *influential* or *highly influential* documents under these guidelines, and hence are subject to the most stringent peer review requirements, including independent external peer panels or review by EPA's Science Advisory Board or by NAS. Other documents, such as journal manuscript submissions, undergo internal review prior to submission through normal publication peer-review mechanisms. All EPA external peer reviewers are independently selected by peer review contractors and are required to submit conflict of interest declarations. EPA has contractors who are known as "peer review contractors" whose duty it is to select an appropriate external peer reviewer for a document or report. The conduct of the external peer review is organized and managed by the independent contractor/ science organization. Public comment is solicited on major products undergoing peer review.

HHRA program's products are also subject to the OMB and EPA Information Quality Guidelines (IQGs). These guidelines emphasize the importance of quality and objectivity in information disseminated by the federal government and the benefits of independent peer review. A process is established under the IQGs whereby members of the public can submit a Request for Correction should they believe that information disseminated by the federal government is erroneous. HHRA program's activities are consistent with the IQGs through their emphasis on quality science and pre-dissemination reviews, implementation of the relevant ORD peer review guidelines and policies, and NCEA's responsiveness to Requests for Correction submitted through the Office of Environmental Information.

Technical Support: Technical support to customer Programs and Regions is a key component of all HHRA program's activities, whether assessment production, methods development, guidance, or other outputs. This support is provided through both formal and informal channels. Formal technical support is provided through the IRIS Help Desk and the Superfund Health Risk Technical Support Center and participation in regulatory workgroups. Where necessary, these

support centers can access additional expertise from NCEA and other EPA scientists. NCEA scientists also provide direct technical assistance to EPA Programs and Regions that request regulatory or site-specific support. These efforts are tracked internally through the Programmatic and Regulatory Support Tracking System. More informal channels are also widely used to expedite assistance on less complex issues, testifying to the widespread use of risk assessment products across the Agency and beyond.

Within the purview of the HHRA program, technical expertise is often transferred between projects in order to achieve program objectives. In addition, technical expertise is transferred to Risk Assessment Forum projects, which moved to the Office of the Science advisor in early 2007. These projects represent major Agency consensus documents requiring considerable technical and managerial input. To achieve the Forum objectives, technical support functions allocated to the Forum staff may be supplemented by experts from NCEA Divisions, who may chair or co-chair the Forum work groups alongside representatives of other EPA programs. Transfer of technical expertise also occurs between HHRA MYP long-term goals, and often through specific IRIS assessments serving as vehicles for informing the development of new models and methods. The HHRA MYP proposes continuing and emphasizing the existing formal technical support arrangements and also recognizes the extent and importance of the ad hoc expert assistance provided to customers across EPA.

Performance: HHRA program's performance is tracked through a variety of Agency management systems. Within ORD-NCEA, IRIS outputs and production schedules are tracked through the Internet-accessible IRIS Track System (www.epa.gov/iristrac). As part of the ORD management system, HHRA MYP activities are tracked through the Annual Performance Goal (APG) and Annual Performance Measure (APM) system. Annex 1 provides the APG/M performance measures for this MYP, including products, output goals, and completion dates. These deliverables are tracked by the ORD Office of Resource Management and Administration in the Integrated Resource Management System on a quarterly basis, with annual reporting. Major deliverables are reported to the OMB and Congress.

OMB has also instituted the Performance Appraisal Rating Tool (PART), whereby all federal programs are rated on their performance in achieving identifiable public benefit outcomes. PART evaluation of the HHRA program was completed in FY'07 with a moderately effective rating (the HHRA program received the highest PART score, to date, of any ORD program). The outcome measures for the HHRA MYP are outlined in Figure 2, under the subtitle Environ-mental Indicators. The HHRA MYP outcomes are based on an impact matrix measuring the incorporation of HHRA program's products into Agency risk assessment practice and decisions, including their use in site assessments, records of decision (RODs), and regulations and the benefits to the public from this use of sound science. The impact of risk assessment models, methods, and guidance development under the HHRA program is evaluated through independent external scientific review by outside organizations such as the Clean Air Scientific Advisory Committee (CASAC).

Progress to Date/Changes

Although the HHRA MYP represents the first consolidated risk assessment planning instrument in ORD, assessment activities have been conducted in ORD-NCEA and its predecessor organizations (e.g., Office of Health and Environmental Assessment; Carcinogen Assessment Group,) for many years. These activities continue to be at the forefront of risk assessment science and remain central to EPA actions to protect human health and the environment.

IRIS began over two decades ago as an internal EPA activity to facilitate communication among ORD, Programs, and Regions to harmonize the otherwise disparate reference values prepared for hazardous substances in different parts of the Agency. IRIS first became publicly available in 1988. IRIS has since expanded to become the premier federal database for qualitative and quantitative environmental health hazard assessments. These assessments are widely regarded by regulators and stakeholders as providing a transparent and well-documented resource on substances of central importance to environmental issues. IRIS values are now the primary toxicity values used in preliminary remediation evaluations (OSWER Directive 9285.7-53; 12/5/2003) and in many regulatory reviews conducted by EPA programs, such as the Office of Water and the Office of Air and Radiation. OSWER RODs for superfund sites and EPA regulatory proposals that reference IRIS values are then subject to additional public comment and peer review under the relevant adjudicatory procedures and Administrative Procedures Act. IRIS has been in the forefront of applying scientific advances to substance-specific assessments, such as PBPK modeling and data-derived uncertainty factors for intraspecies and interspecies extrapolation (e.g., boron). IRIS has also been instrumental in advancing and implementing mode-of-action considerations in cancer hazard characterization (e.g., perchlorate).

ISAs, formerly AQCDs, have been prepared under the HHRA program by NCEA or its predecessors since the creation of the EPA in 1970. ISAs and the resulting NAAQS have been pivotal in achieving the air quality standards experienced today in the U.S. and they have influenced regulatory actions worldwide. The AQCD for Particulate Matter, Ozone, and Lead were finalized in 2004, 2006, and 2007, respectively before the new ISA process was implemented. An update of nitrogen oxides and sulfur oxides ISA is going through the new process and is scheduled for finalization in 2008. Through the preparation of ISA, public health protection has been improved by the ongoing, close, collaborative relationships between risk assessors, OAQPS regulators, and research scientists studying criteria air pollutants under other ORD research MYPs.

The ORD-HHRA program has also been responsive to urgent Agency priorities, whether in response to emergency risk assessment needs in the aftermath of the WTC attack and Hurricane Katrina and Rita or in response to immediate program office needs. Following the WTC attacks, HHRA/NCEA was called on to assemble and assess the various data sources on air and dust concentrations of pollutants at Ground Zero and in the surrounding buildings. Experience gained from the WTC assessment has proven valuable in providing expeditious risk assessment support and advice to EPA's remediation and re-entry evaluations in New Orleans following Hurricane Katrina. Urgent program needs have also been supported through expedited re-assignment of staff resources. Platinum and cerium provisional reference concentration assessments were prepared in response to a special request from the Office of Air and Radiation (OAR)-Office of

Transportation and Air Quality regarding their evaluation of proposed diesel fuel additives containing these metals. NCEA scientists prepared independent reviews of the scientific validity of intentional dosing human pesticide studies to assist the Office of Pesticide Programs in their re-registration evaluation of the scientific and ethical attributes of these studies, under intense public and Congressional scrutiny. Assistance was also provided to the Office of Pollution Prevention and Toxics in preparing the science background for a consent agreement on air toxics.

The models, methods, and guidance development work in the HHRA program have been at the forefront of risk assessment science. Model development and application of the integrated exposure and uptake biokinetic model (IEUBK) for lead and other metals has become a standard exposure assessment tool in site evaluations. Collaborative work continues between ORD laboratories and centers [National Health Environmental and Ecological Research Laboratory (NHEERL), National Computational Center for Toxicology (NCCT), and NCEA] on PBPK modeling and its application to risk assessment. Internet-accessible statistical software packages have been well-received by the risk assessment community, including the benchmark dose software and categorical regression software. HHRA program's environmental exposure products are considered a primary reference source in risk assessment practice, including ongoing work collating the *Exposure Factors Handbook* and the *Children's Exposure Factors Handbook.* HHRA's collaborative work with OPPTS on the Dioxin Exposure Initiative (DEI) set national and international quality standards through products such as the dioxin source inventory, coupled with the National Dioxin Air Monitoring Network. The DEI work provides a data framework to link dioxin source emissions to exposure pathways to human dose, informing program office considerations on dioxin risks and potential intervention strategies. Methods guidance work in HHRA program on the derivation of inhalation reference concentrations and the application of inhalation dosimetry, and more recently on less-than-lifetime reference values, have been directly responsive to expressed program needs.

The above-noted activities were conducted under a variety of program and media-specific plans in EPA's GPRA goal structure. The HHRA MYP continues the broad themes apparent above, focusing on enhancing IRIS, ISA, and risk assessment outputs through better alignment of budget resources with planning priorities. In the interim between the consolidation of ORD's risk assessment budget in 2004 and the finalization of this HHRA MYP, health risk assessment planning has been conducted on an annual basis during the President's Budget submission cycle. As such, APGs and APMs have been updated in each successive annual planning cycle, accompanied by the discussion of the resources required and priority given to LTG/APG/APMs under each MYP for that budget period. Through the preparation of this MYP, all current year and out-year NCEA health risk assessment APG/APMs are consolidated into the HHRA MYP. These actions were coordinated with the relevant National Program Directors and ORD Laboratory and Center Directors.

Overview of the Long Term Goals

As noted, the overarching objective of the HHRA program is the production of state-of-the-science health hazard assessments to respond to Program and Regional needs on a timely basis, along with the models, methods, and guidance necessary to maintain the quality of these risk assessment products. To achieve this, there are three long-term goals (LTGs) under the HHRA MYP:

LTG 1: Integrated Risk Information System (IRIS) and other priority health hazard assessments: Agency, state, and local risk assessors use the state-of-the-science health hazard assessment information provided on priority substances in their decisions and actions to protect human health from risks posed by environmental pollutants.

LTG 2: State-of-the-science risk assessment models, methods, and guidance: EPA programs, states, and other risk assessors use the risk assessment models, methods, and guidance provided to enhance, through the incorporation of contemporary scientific advances, the quality and objectivity of their assessments and decision-making on environmental health risks.

LTG 3: Integrated Science Assessments (ISAs; formerly know as Air Quality Criteria Documents): ISAs are updated to reflect the best available scientific information on identifiable effects on public health and the environment from exposure to the criteria pollutants. The EPA Office of Air and Radiation uses this information in its review of the NAAQs to protect public health and the environment with an adequate margin of safety.

Because the LTG 2 work is an essential support to LTG 1 and 3 assessment activities, the level of effort between these goals is maintained at a ratio of approximately 25% LTG 2 development work to 75% assessment effort. With this guidance, Table 1 summarizes the level of effort devoted to the LTGs:

Table 1 Level of support of HHRA LTGs

Table 1: Area	**Emphasis in MYP Planning Window**
LTG 1: IRIS and other priority assessments	Increasing due to realignment of resources
LTG 2: Models, methods and guidance	Decreasing if there are HHRA budget reductions
LTG 3: Integrated Science Assessments	Increasing subject to initiative request

LTG1: Integrated Risk Information System (IRIS) and other priority health hazard assessments

A central feature of the HHRA program's activities is the IRIS. IRIS is an interagency program managed by NCEA with active participation by Program Offices and Regions. Scientists in these Program Offices and Regions nominate chemicals for the annual IRIS agenda, and designated reviewers from these Program Offices and Regions participate in the Agency review of assessments. A typical IRIS output includes a Toxicological Review and Summary of the environmental health hazards posed by a substance to humans. The Toxicological Review provides a hazard characterization of available toxicological information, in addition to quantitative estimates [RfD, RfC, and cancer slope factor (CSF] of human risk

These qualitative and quantitative assessments are summarized and disseminated through the Internet at www.epa.gov/IRIS. Other types of assessment values, such as less-than-lifetime toxicity values, are currently in a pilot development phase and will be incorporated into IRIS documents as they become available. Tools and guidance for conducting new assessments are being developed under LTG 2 of the HHRA MYP. In addition, contemporary chemical-specific data and MoA information provided by the external scientific community and outputs of multiple ORD MYPs are incorporated into these assessments.

Although IRIS values are non-regulatory determinations, quantitative IRIS values do influence many environmental decisions and may serve as a basis for additional regulatory consideration. The hazard characterization and dose-response assessments provided by IRIS constitute the first two steps in the NAS (NRC, 1983) risk assessment paradigm, the other steps being exposure assessment and risk characterization. In the Agency context, IRIS toxicity values resulting from the dose-response assessment (e.g., RfD, RfC, CSF) can be combined with site-specific exposure estimates (e.g., exposure to the chemical in food, in drinking water, in soil at a waste site, in air near an incinerator) to provide a risk estimate for the situation of interest. In doing so, the "health hazard assessment" information provided by IRIS contributes to a fuller "risk assessment" as defined under the NAS paradigm and applied in programmatic and regional actions.

In addition to standard IRIS assessments, the HHRA program also conducts more resource intensive assessments of major chemicals. Major assessments result from such factors as the regulatory scope and priority of the substance, its production volume, potential economic impact, scientific complexity, precedent setting nature, and/or national importance. These highly complex assessments often lead EPA to identify new research needs, apply new methodologies, or conduct multiple high level external scientific peer reviews to ensure the application of sound science. These requirements are generally associated with additional external scrutiny and increased time for completion, potentially impacting NCEA's ability to accurately estimate finalization dates beyond those under its direct control. Many major assessments also go beyond hazard and dose-response information by providing exposure and risk characterization conclusions, such as the WTC assessment and dioxin reassessment.

It should not be construed from the previous summary that IRIS assessments are boilerplate in nature, beyond the standardized outputs for ease of use by risk assessors and

managers (e.g., RfD, RfC, CSF). Each IRIS assessment presents its own unique database, scientific questions, and science-policy judgments. However, these unique characteristics do allow for some grouping of chemical assessments for further consideration and efficiency. These include grouping chemicals based upon mode of action and outcomes of principal interest and by chemical class (e.g., metals, endocrine disruptors). This grouping of assessments based on available scientific information, programmatic importance, and resources required to do the assessment can allow for process efficiencies. These substance-specific factors highlight the importance of the transparent, Agency-wide review process undertaken to develop IRIS values and to maintain this contemporary repository of information. The individual nature of each IRIS assessment is the product of a number of factors, commencing with the quantity, quality, and relevance of available toxicological data. Individual IRIS assessments may also vary due to different opportunities to apply new advances in risk assessment science, such as improved models, methods, and updated Agency guidance. Examples of this progression include methods development for calculation of less-than-lifetime reference doses and application of the supplemental guidance for children's cancer risk in IRIS assessments. In this way, IRIS serves as a dynamic system where substance-specific scientific needs can be identified for research and development, and, conversely, as a vehicle where the results of such scientific advances can be applied for use in decision-making.

The process for developing an IRIS assessment (see appendix A) commences with the solicitation of chemical nominations from EPA Programs and Regions, and, in some years, from other government agencies and the public. The IRIS program uses four general criteria to set priorities: (1) EPA statutory, regulatory, or program-specific implementation needs; (2) availability of new scientific information or methods that might significantly change the current IRIS information; (3) interest to other levels of government or the public; and (4) availability of other scientific assessment documents such that only a modest additional effort would be needed to complete the review and documentation for IRIS. The results of this screening are factored into setting priorities.

Upon selection of a chemical for review, the process for developing assessments is detailed in the IRIS standard operating procedures and consists of (1) an annual Federal Register announcement of EPA's IRIS agenda and call for scientific information from the public on selected chemical substances; (2) a search of the scientific literature; (3) development of IRIS summaries and support documents;(4) Agency review; (5) external peer review and public comment; (6) management review and approval; and (7) entry of IRIS summaries and support documents into the IRIS database. In addition, modifications to this process to incorporate additional interagency and National Academy of Sciences (NAS) review are under consideration.

As outlined in the standard operating procedures, the development of an IRIS summary and toxicological review commences with agreement on the scope of the assessment, a proposed timeline, and major projected milestones. Broad Agency expertise is solicited early on through holding a scoping or problem formulation meeting, including inviting interested NCEA staff and coordinating with scientists from NHEERL. Invitations are also extended to representatives from other EPA Offices and Regions. These invited experts may include staff from ATSDR or other government agencies and the chemical manager's assessment development contractor. The purpose of the scoping meeting is to seek early identification of critical science issues pertinent to

the assessment as well as to facilitate communication of forthcoming laboratory results relevant to the proposed assessment schedule. Additional internal peer consultation is sought in the development phase of the assessment on such matters as advice on the location or interpretation of studies, modeling approaches, interpretation of risk assessment guidelines, identification of issues for Agency review, and other facets of assessment preparation. This is followed by more formal internal review and then interagency review, in advance of the external peer review phase with public comment.

All IRIS assessments undergo independent external peer review, accompanied by a federal register announcement of the public meeting and a request for comments to be submitted approximately 2 weeks beforehand for consideration by the peer reviewers. Each Toxicological Review contains a summary and disposition of these external peer review and major public comments. The progressions of individual chemical assessments through this process, along with estimated future completion dates, are tracked through the publicly available IRIS Track database (http://cfpub.epa.gov/iristrac/index.cfm).

Complementing these major assessments are the PPRTVs. A PPRTV is defined as a toxicity value derived for a substance of potential concern for use in the Superfund Program when such a value is not available in IRIS PPRTVs are developed and peer reviewed on an expeditious basis at the request of OSWER, which uses PPRTVs in its evaluation of Superfund sites.

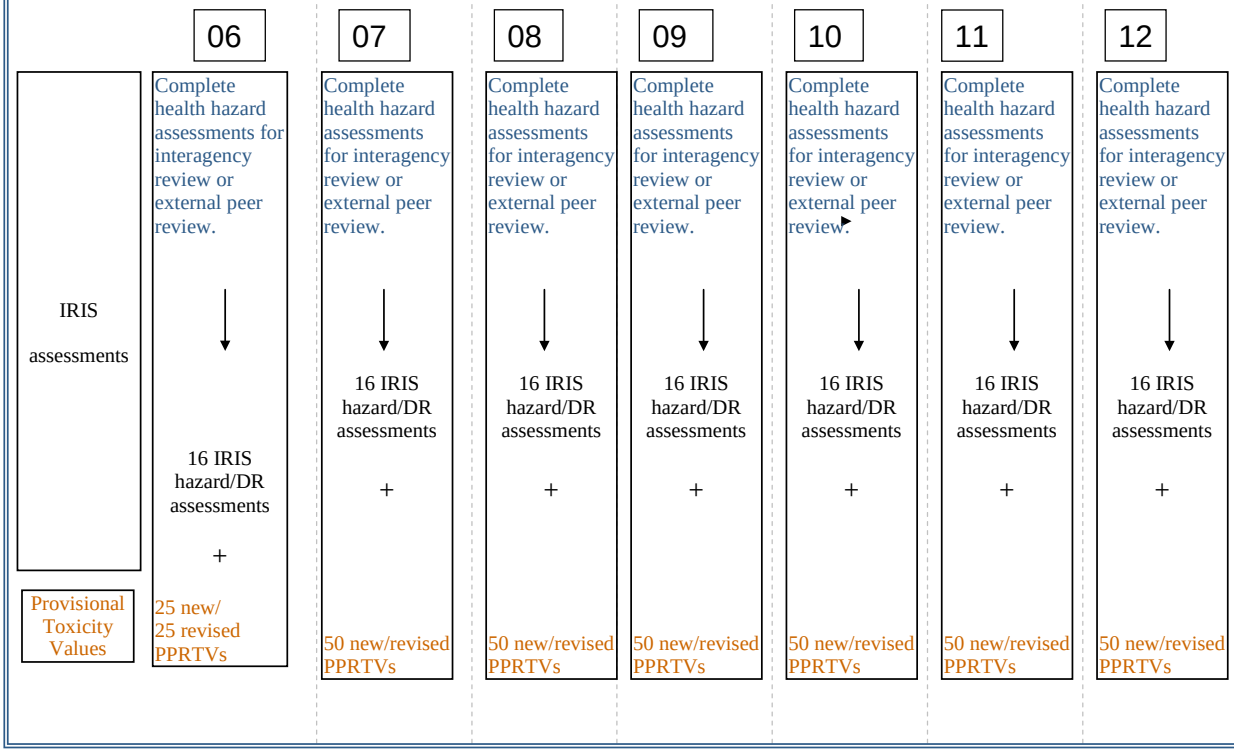
A PPRTV is defined as a toxicity value derived for use in the Superfund Program when such a value is not available in EPA's Integrated Risk Information System (IRIS). PPRTVs are developed according to a standard operating procedure and are derived after a review of the relevant scientific literature using the same methods, sources of data, and Agency guidance for value derivation generally used by the EPA IRIS Program. All provisional toxicity values receive internal review by two EPA scientists and external peer review by three independent scientific experts. PPRTVs differ from IRIS values in that PPRTVs do not receive the Agency review provided for IRIS values. This is because IRIS values are generally intended to be used in all EPA programs, while PPRTVs are developed specifically for the Superfund Program.

Because new information becomes available and scientific methods improve over time, PPRTVs are reviewed on a 5-year basis and updated into the active database. Once an IRIS value for a specific chemical becomes available for Agency review, the analogous PPRTV for that same chemical is retired. It should also be noted that some PPRTV manuscripts conclude that a PPRTV cannot be derived based on inadequate data.

Figure 3 conveys the APG diagram for HHRA LTG 1. The annual IRIS output is a total of 16 or more hazard/dose-response assessments. This number is based on completion dates of assessments commenced since the expansion of IRIS resources in the period 2001 to 2005. It represents a rapid increase in output maintained at a projected annual rate of completion, assuming constant resource allocations while projecting additional review and finalization requirements. To this total are added an annual output of 25 new and 25 revised PPRTVs for OSWER, following the initial completion of 150 PPRTVs.

Figure 3: Human Health Risk Assessment LTG 1 Annual Performance Goals

LTG 1: Integrated Risk Information System (IRIS) and other priority health hazard assessments: Agency, state and local risk assessors are provided state-of-the-science health hazard assessment information on priority substances included in planned Agency decisions and actions.



The APG output for major assessments is defined as "Agency completion for interagency review or external peer review." This is the process stage at which the Agency relinquishes direct control of production dates. The interagency review consists of review by the Executive Office of the President through the Office of Management and Budget, which coordinates these interagency reviews as needed with other federal agencies. Experience has demonstrated that finalization and public dissemination dates for major assessments depend heavily on the path chosen for finalization of the external peer review phase. Delays in finalization are likely to compound due to the ongoing advancement of science in the interim, necessitating additional revisions to the assessments and further peer review.

Decisions on the type and extent of external peer review and finalization procedures are often made late in the assessment process as the science unfolds and areas of controversy become apparent. These late decisions are not amenable to advance planning on a chemical-specific basis in the Agency multi-year planning process. Recognizing, however, the importance of these individual, major assessments, the HHRA program has sought to maximize information on individual substances without compromising its ability to define ambitious, yet realistic, future APG targets. The program recognizes that the posting of final health assessments is a significant milestone. In the interim, estimated specific chemical assessment completion dates are publicly

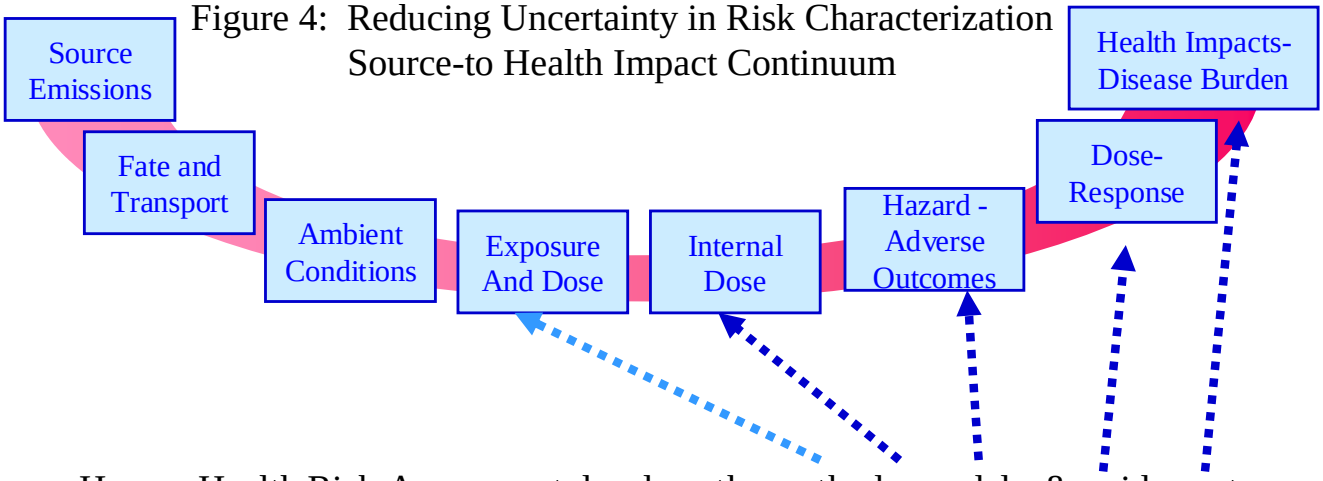
available in IRIS Track (http://cfpub.epa.gov/iristrac/index.cfm). HHRA program's resources have also been retained in out-years for the completion of these priority assessments and, coupled with anticipated new starts, constitute an ambitious out-year plan of increasing output of external review and finalized assessments on a fixed resource base. Included in the resource base are efforts to specifically evaluate IRIS assessments older than 10 years to determine if new data are available to warrant a reassessment of existing values.

LTG 2: State-of-the-science risk assessment models, methods, and guidance

Risk assessment models, methods, and guidance development under the HHRA program is directed toward incorporating scientific advances into risk assessment practice. The LTG 2 outputs support the applied decision-making needs of the EPA programs and Regions, either directly or through HHRA LTG1 (IRIS) and LTG3 (ISA) outputs. These program needs vary from estimating risk levels in exposed people and determining safe levels of environmental pollutants in media such as air and water, to supporting regulatory actions on specific substances and developing clean-up standards for restoring the environment. In making these decisions, risk managers seek information on best estimates of risk, the uncertainty in these estimates. In addition, risk managers/decision makers need to know whether their decisions will be sufficiently protective of potentially sensitive populations, such as children.

Of central importance to these environmental decisions is the need to better quantify risks and characterize uncertainty at the low environmental exposure levels generally experienced in real-world situations by large numbers of people, including susceptible populations. This public health protection objective cannot be achieved through direct testing of people due to ethical, logistical, and statistical constraints. Decisions can be informed, however, through extrapolation from available in vitro, in vivo, epidemiological, and other data. These extrapolations include between animals and humans, from high to low dose, between routes of exposure, and among individual humans, including susceptible populations. Research to inform risk decisions can be broken down along these extrapolation components and the numerous factors that contribute to the variability and uncertainty in each component. For instance, high to low dose extrapolation can be informed by understanding such factors as dose-response model shape and the relevance of the high dose mode of action to low doses. Primary research on these components is undertaken by the ORD laboratories under various MYPs and is a primary consideration of the ORD Human Health Research Program. HHRA MYP LTG 2 acts to incorporate these data and analyses, along with other published literature, into EPA risk assessment practices and risk assessment outputs. These efforts are focused on addressing critical linkages in the risk assessment process between the exposure-to-outcome continuums (Figure 4).

Figure 4: Reducing Uncertainty in Risk Characterization
Source-to Health Impact Continuum



- Human Health Risk Assessment develops the methods, models, & guidance to reduce uncertainty in the 'critical links' across the exposure-to-effect paradigm and to improve risk characterization

HHRA Activities under LTG 2: Risk assessment development activities respond to the diverse array of scientific disciplines informing risk assessment practice and the expanding science base in these fields. Failure to stay current with scientific advances can impact the quality of assessments when evaluated against external peer review standards. This could potentially impugn Agency products and the ability of programs to make appropriate and timely risk management decisions. Given this breadth of science, the HHRA LTG 2 planning process commenced with the identification of risk assessment activity foci by ORD-NCEA science staff and management. These foci were selected taking into consideration programmatic priorities, applied risk assessment needs, the impact of ongoing scientific developments, and the expertise available to incorporate these advances into Agency practice. The risk assessment foci serve to facilitate resource allocation and strategic hiring in NCEA, in addition to conveying priorities for laboratory research elsewhere in ORD. The LTG 2 foci are

< **Exposure assessment:** The aim is to maintain the quality and utility of the *Exposure Factors Handbooks* for use Agency-wide and to maintain the application and refinement of exposure methods to risk assessment.

< **Internal Dosimetry and PBPK modeling**: The aim is to apply advances in pulmonary toxicology inhalation dosimetry methods to interspecies extrapolation and dose-response assessment. In addition, PBPK models use measured biological parameters, such as blood flow and diffusion rates, to mathematically model differences and improve extrapolation between and within animal species, humans, and their lifestages to better estimate dose-response functions in toxicological responses. Whereas primary physiological data and PBPK models are principally developed in the laboratories, the HHRA program's activities are focused on the applicability of these models, their uncertainty parameters, and guidance for use in risk assessment.

< **Hazard Characterization:** Hazard characterization efforts include identifying the susceptibility of sensitive populations (e.g., lifestage and genetic predisposition) and use of MoA in risk assessment. MoA efforts include applying available data to better characterize understanding of the way in which toxicity occurs in order to inform

decisions on the relevance of high dose effects to low level environmental exposures, within and between species, and the quantitative impacts of these factors on dose-response functions used in risk assessment.

< **Dose-Response Analysis:** Quantitative methods have been and are being developed to incorporate state-of-the-science mathematical, probabilistic, and statistical advances into EPA risk assessment practice, particularly dealing with uncertainty and variability analysis in dose-response assessment for low environmental exposures. This includes moving beyond single-chemical assessments to develop and apply novel methods for quantitative health risk assessment of chemical mixtures, accompanied by guidance on chemical mixtures exposure assessment for use in complex, real-world, environmental situations.

< **Risk Characterization:** The development of methods in this topic includes both qualitative and quantitative approaches for describing variability and uncertainty in exposure hazard and dose response. HHRA is addressing characterization of susceptible populations and magnitude of human variability in response and population variability with efforts like the *A Framework for Assessing Health Risk of Environmental Exposures to Children*.

Figure 5 illustrates the linkage in the HHRA MYP between primary research and the application of this information to risk assessment and, ultimately, risk management decisions. The ORD research MYPs (e.g., human health, air, computational toxicology, drinking water) are depicted as examples of focused contributors to the broad body of scientific information that informs risk assessment practice. While the research from specific ORD MYPs is incorporated as it becomes available, example linkage times are illustrated where ORD laboratory research will particularly influence the flow of risk assessment methods development activities planned under LTG 2 and depicted across the center of this figure. The LTG 2 products then inform risk assessment practices under LTG 1 (IRIS) and LTG 3 (ISA). The primary research and LTG 2 products may also be directly incorporated into Program and Regional assessments. Experience from conducting risk assessments feeds back into the identification of priority research needs, and, hence, the iterative development and transfer of new scientific information into risk assessment practice. This feedback and crosstalk between MYP takes place at the National Program Director level, with Lab and Center directors of ORD and clients through the RCT. This active engagement results in collaboration and coordination across MYP.

Figure 5:HHRA-LTG 2 Flow Chart and APG Relationships

LTG 2: State-of-the-science risk assessment models, methods and guidance: EPA programs, states and other risk assessors use the risk assessment guidance, models, and methods provided to enhance the quality and objectivity of assessments through the incorporation of contemporary scientific advances for use in decision-making.

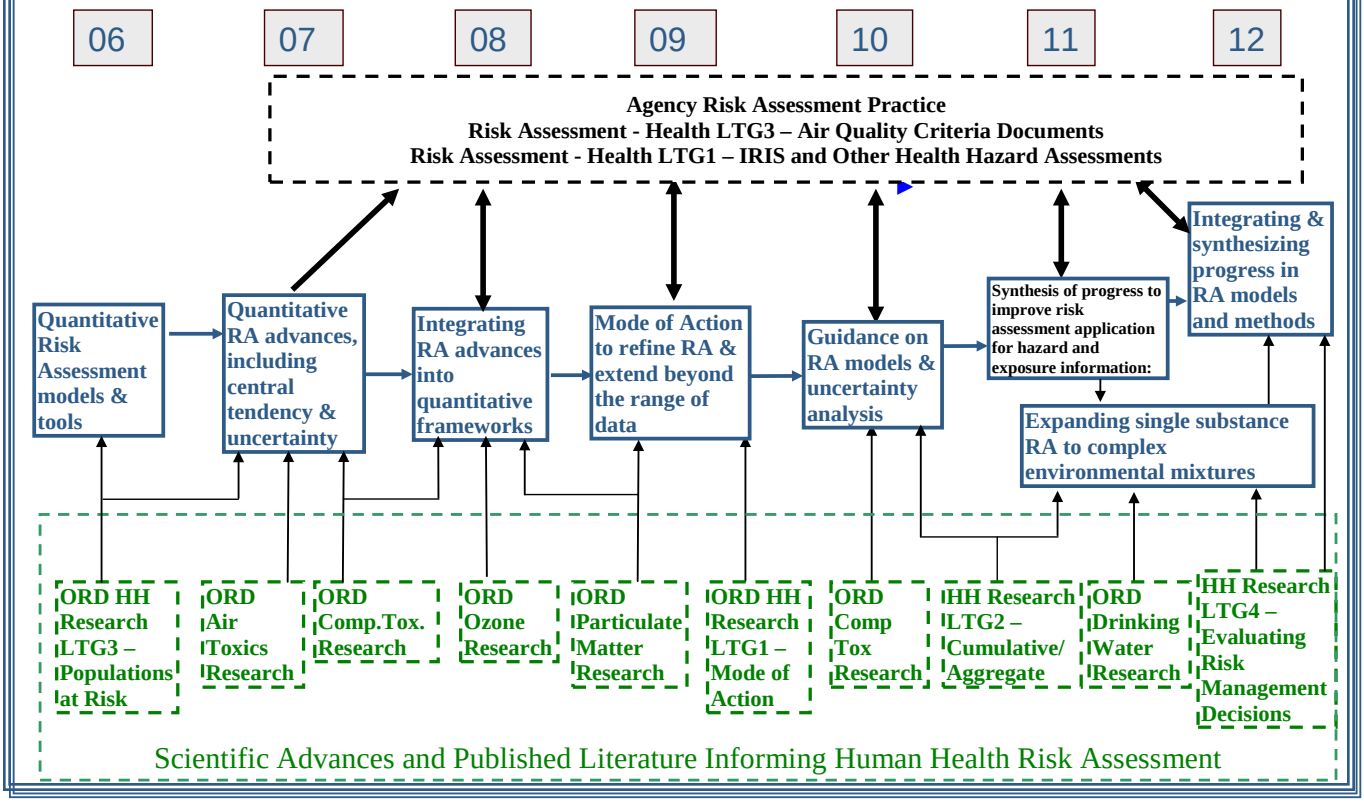
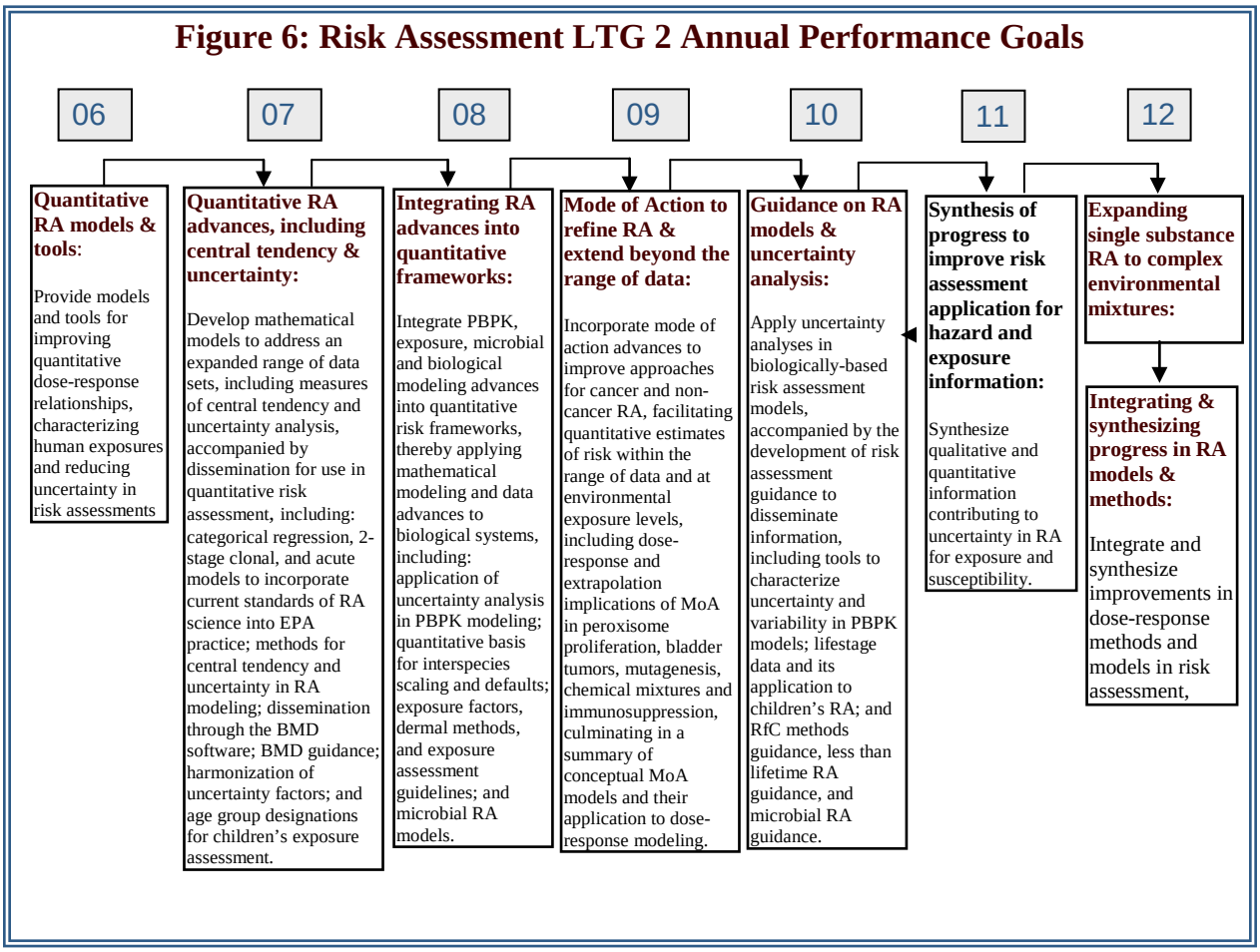


Figure 6 provides details on the LTG 2 APGs. The objective of the LTG 2 APGs is to advance risk assessment science along themes most relevant to EPA's mission needs. In doing so, the APGs serve to maintain the quality and objectivity of HHRA program and other Agency risk assessment products when evaluated against contemporary peer review science standards. Each APG represents the cumulative result of the individual contributing ORD-NCEA APMs and support activities. Each APG also builds on previous APG outputs, demonstrating a progression of risk assessment advances that culminates in synthesis and guidance outputs to support Agency activities and provide a common basis for decision-making. This progression of risk assessment themes occurs in parallel with the incorporation of the individual development activities, as they occur, into substance-specific assessments.

Figure 6: Risk Assessment LTG 2 Annual Performance Goals



The progression of planned risk assessment advances commences in FY'06 and '07 with improved quantitative modeling methods, particularly measures of central tendency and uncertainty analysis, which are of central importance to concerns expressed by EPA programs, stakeholders, and the scientific community. Rather than providing single-point estimates of upper bound risks, the FY'07 APG tracks scientific advances toward estimating risk distributions and providing a fuller characterization of uncertainty and variability. As these quantitative models are developed and experience is gained with their use, opportunities exist to broaden their applicability and integrate these methods into other quantitative assessment frameworks. This is achieved in the FY'08 APG through integrating quantitative advances into PBPK modeling procedures, interspecies scaling defaults, and exposure assessment.

The FY'09 APG reports on actions undertaken to incorporate biological and mode-of-action considerations to refine risk assessment practice and to extend the analysis beyond the range of data. MoA information is critical to determining the relevance of animal data to humans and to informing quantitative estimates of risk within the range of data and at environmental exposure levels. The APGs in fiscal years 10 to 12 of this plan are directed toward developing guidance, integrating findings, and synthesizing the risk assessment advances accomplished under this program and from the scientific literature. These goals consolidate the science, generate a common basis for Agency risk assessment practice, and provide a foundation for future planning activities.

LTG 3: Integrated Science Assessments (ISA)

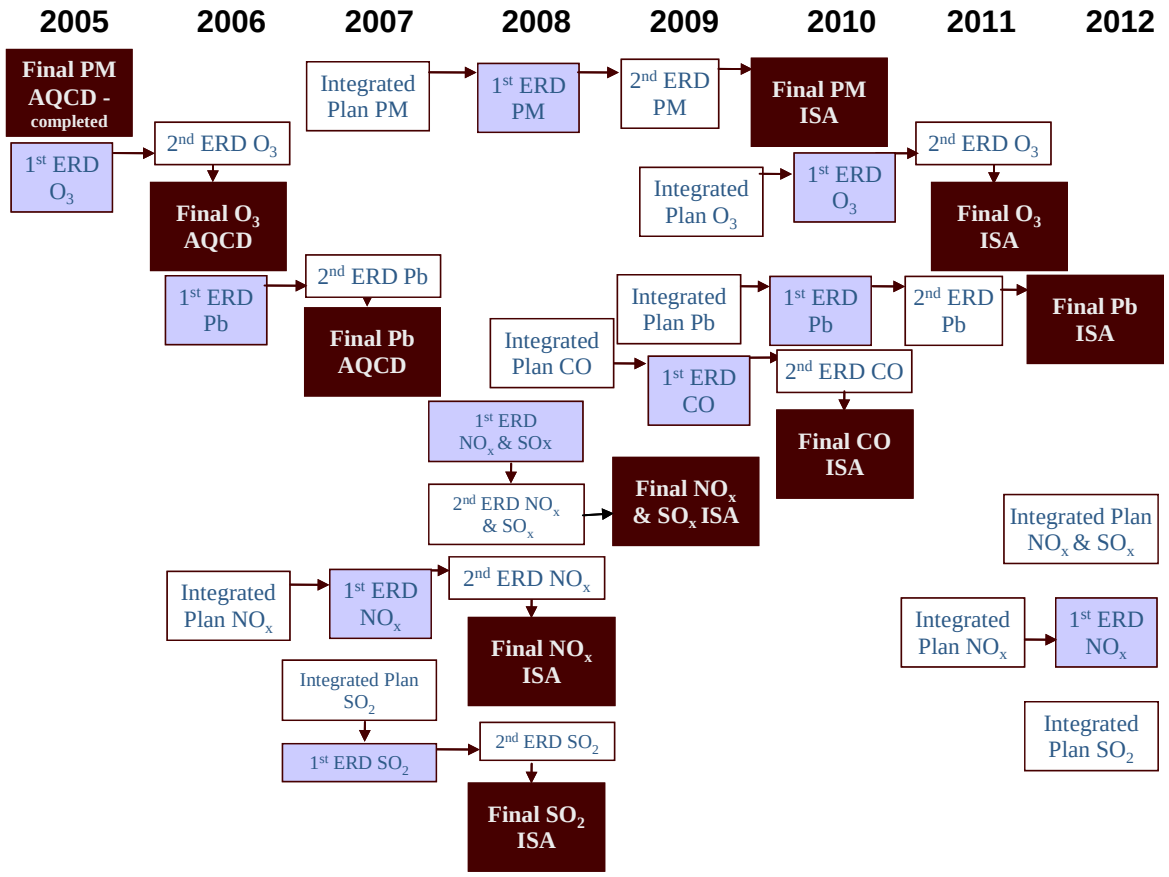
Sections 103, 108, and 109 of the CAA govern the establishment, review, and revision of the NAAQS and direct the Agency to issue air quality criteria for identified pollutants that reasonably may be anticipated to endanger public health or welfare. HHRA MYP LTG 3 produces ISAs that evaluate the latest 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 particulate matter, ozone, and other MYPs. The ISAs incorporate and synthesize research findings from ORD and others into these assessment documents (e.g., Particulate Matter research centers and ORD intramural Particulate Matter research under Air MYP).

For the ISAs, NCEA 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. A close collaboration is maintained in the planning and execution of ISA preparation between NCEA and 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. EPA has set NAAQS for six pollutants: Carbon Monoxide (CO), Lead (Pb), Nitrogen Dioxide (NO_2), Tropospheric Ozone (O_3), Particulate Matter (PM_{10} and $PM_{2.5}$), and Sulfur Dioxide (SO_2).

Specific APGs for LTG 3 are illustrated in Figure 7, with all the ISAs scheduled for revision during this multi-year planning period. This figure also demonstrates the annual operating plan requirements to fulfill these APGs, with each ISA being preceded by a project plan, multiple external review drafts, public comment, and CASAC review, and prior to finalization for delivery to OAQPS. The individual ISA requirements overlap to form a staggered matrix of ongoing activities under HHRA LTG 2.

Figure 7: Risk Assessment LTG 3 Annual Performance Goals

LTG 3: Integrated Science Assessments (ISA; formerly known as Air Quality Criteria Documents): ISA's are updated to reflect the best available scientific information on identifiable effects on public health and the environment outcomes from exposure to the criteria pollutants. This information is used by the EPA Office of Air and Radiation in their review of the National Ambient Air Quality Standards (NAAQs) to protect public health and the environment with an adequate margin of safety.



New Developments and Potential Additional Work

Health hazard assessments conducted under the HHRA program have become increasingly controversial due to their public health and cost implications and the variety of scientific conclusions that can be drawn from toxicity and epidemiology studies. Because these assessments provide the key scientific analyses supporting many critical Agency decisions, the Administrator has directed that ORD institute enhanced development, review and consultation procedures to ensure the highest scientific quality and transparency. In FY2007, the HHRA program received additional resources to support program enhancements through contracts with the National Academy of Sciences (NAS). The NAS created two panels one entitled the *Future of Risk Assessment* and another entitled *Risk Analysis Issues and Reviews*. The NAS panel on the *Future of Risk Assessment* held a series of public meetings in 2007

and the panel is deliberating and preparing a report with their recommendations. The panel on *Risk Analysis Issues* is strictly focused on the NAS convening function to provide the Agency input on contemporary risk analysis issues such as specific topics related to uncertainty analysis in risk assessment. The involvement of the NAS contributes to the identification and resolution of scientific issues and increases confidence and wider acceptance of EPA assessments. Additional resources are also being used by ORD to establish contracts with the NAS for peer reviews of major assessments (e.g., tetrachloroethylene). These reviews are much more costly than current peer reviews and consultations, and former HHRA program's resources were insufficient to support these activities.

Beyond extramural funding for NAS peer reviews, additional resource allocations to the HHRA program are being used to support revisions to the ISA development process, to ensure that CAA mandates for 5-year review are met and to support development of a new data management system to identify and support evaluation of the thousands of studies related to the criteria air pollutants. These activities require a balance between HHRA staff FTE increases and extramural funding for contract and peer review support, and both FTE and extramural resources have been increased.

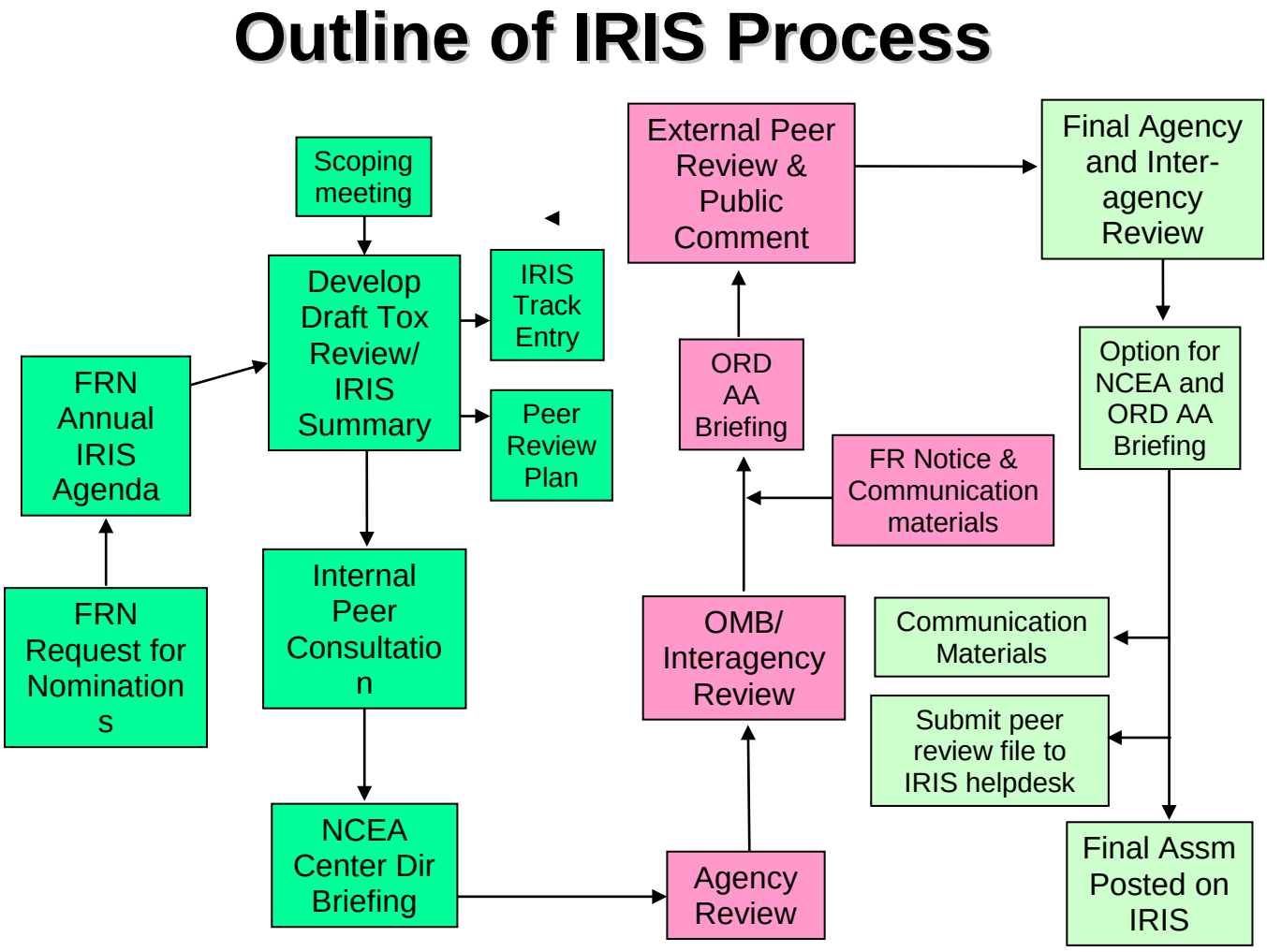
Additional work is also anticipated to incorporate rapidly developing fields of science as tools in risk assessment practice and products. These developing risk assessment tools will be applied directly into IRIS and ISA assessments as available and appropriate under existing LTG 1 and 3 resources. For instance, additional information from the rapidly growing field of "omics" research (genomics, proteomics, and metabolomics) will be incorporated into specific risk assessments based on information from the published literature and developed by the EPA National Center for Computational Toxicology. The experience gained from the applied use of "omics" tools will then contribute to evaluating their broad implications for risk assessment practice under the LTG 2 foci. Bayesian statistics and other decision analysis methods are also increasingly used in risk assessments, and will contribute to methods development case studies under the LTG 2 quantitative risk assessment focus.

Re-prioritization of work under budget constraints is likely in response to emerging concerns, changed agency priorities, and research developments that may expedite or raise new opportunities for risk assessment. This flexibility is tempered by the need to remain focused on those activities most conducive to serving the agency mission and to avoid diluting efforts below a critical level given the finite budget and staff resources available. Timing and coordination are also necessary to ensure that adequate research information is available prior to conducting an assessment, and that time lags be considered when adding or re-scheduling assessment work, such as the planning, document preparation and peer review requirements necessary over several years for IRIS and ISA assessments. Recruitment planning is necessary to adjust staff expertise to changing circumstances.

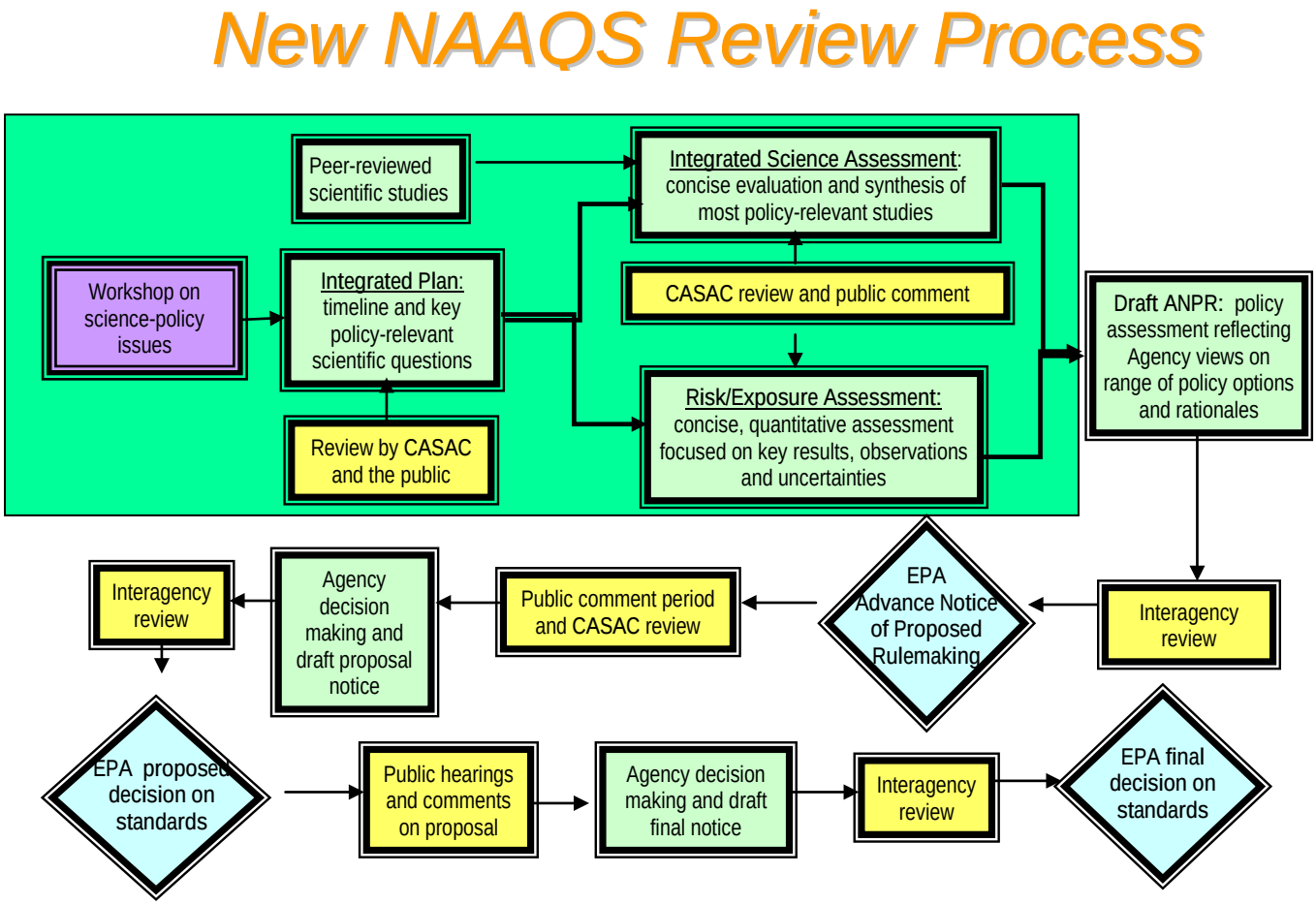
Classification of External Annual Performance Goals and Measures

All HHRA MYP LTG 1 and LTG 3 APGs are recommended for classification as external APGs.

Appendix A: IRIS Process



Appendix B: NAAQS Process



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