Human Health Risk Assessment
Multi-Year Plan
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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 plan the direction of ORD's activities and to communicate this program within ORD and with others. Multi-year planning 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." 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 draft Human Health Risk Assessment Multi-Year Plan (RA MYP) has been prepared following 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. Comments received have been reviewed in detail and incorporated as appropriate in this revised internal draft RA MYP, accompanied by a disposition of these internal review comments. The revised draft RA MYP and disposition of comments will be reviewed by the ORD Science Council, followed by the ORD Executive Council. On approval, the draft RA MYP will be submitted for external peer review. Appreciation is extended to all the EPA staff who have contributed to the preparation and review of this draft RA MYP.

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Human Health Risk Assessment (RA) Multi-Year Plan

Introduction

Human health risk assessment is a process in 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 EPA's implementation of its statutory responsibilities and to its mission to protect human health and the environment. The Human Health Risk Assessment Multi-Year Plan (RA 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 RA MYP directs efforts toward:

- Providing qualitative and quantitative health hazard assessments of priority environmental contaminants for incorporation in applied risk assessments, exemplified by the Integrated Risk Information System (IRIS) Toxicological Reviews and Summaries, reference doses (RfDs), reference concentrations (RfCs), oral cancer slope factors and cancer inhalation unit risks;

- Preparing Air Quality Criteria Documents (AQCDs) for criteria air pollutants as a mandated pre-requisite to 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 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;

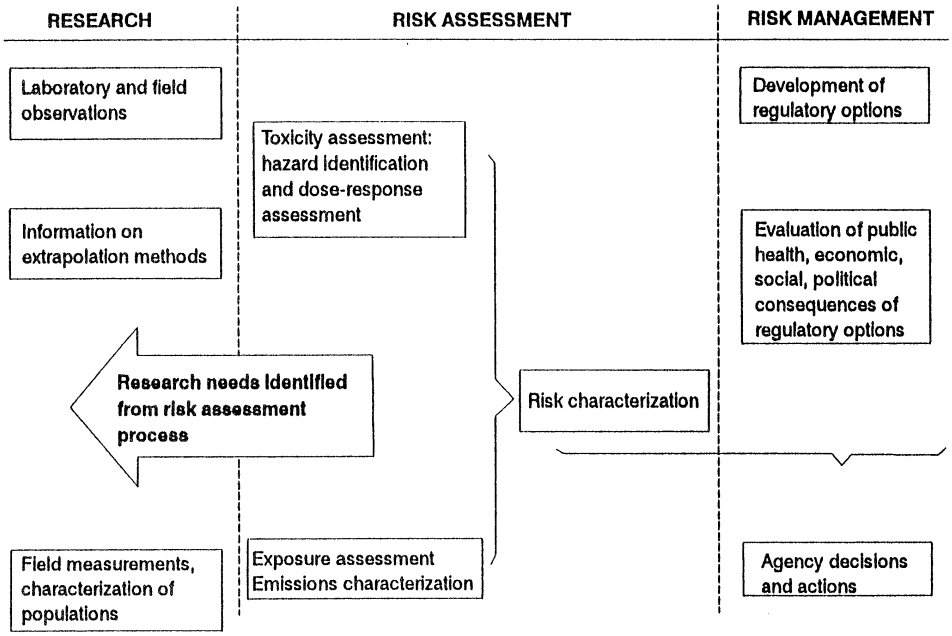
- Identifying, evaluating and conveying to the scientific community key uncertainties and research needed to improve health risk assessments through laboratory, field and methods research; and,

- Supporting the Risk Assessment Forum (Forum), through which risk assessors across the Agency can communicate and harmonize risk assessment practices to facilitate a consistent and predictable framework for EPA activities.

The principal purposes of ORD's multi-year plans 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 RA MYP draws on data and primary methods development science generated under other ORD multi-year plans. Activities under the RA MYP 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.

The flow of information from research, through risk assessment, to risk management is displayed in figure 1 (NAS 1983; revised 1994). Primary data generation refers to laboratory and field observations and measurements, along with information on extrapolation methods. This information is used by risk assessors to evaluate the hazardous properties of environmental agents and the extent of human exposure to these agents. As noted by the NAS (1994), although the conduct of 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 or in relatively qualitative ways. 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 (NAS, 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 RA MYP. Primary data generation and model development are conducted in the ORD laboratories on hazard identification and dose-response parameters, exposure variables, and risk management options. This information is used by risk assessors in NCEA and directly in program offices 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 RA MYP development activities is 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, but not to generate new data. In this way, the RA MYP 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 are the EPA programs and regions 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 is to include assessment of risks, development of methods and tools for analysis of data, and development of AQCDs to serve as the basis for review of the NAAQS on a five 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 *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 RA MYP 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. The core IRIS, AQCD 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 RA MYP is at the forefront of applying quantitative methods advances to risk assessment, such as the use of PBPK models to reduce uncertainty in risk extrapolations and to replace default uncertainty factors. The RA MYP also maintains a leadership role in incorporating mode of action (MoA) evaluations to support EPA decision-making, as emphasized in the Carcinogen Risk Assessment Guidelines 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 RA MYP is uniquely responsive to program needs by developing and applying quantitative methods and guidance to estimate cancer risks and associated uncertainty parameters. RA MYP 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 and program offices, through formal means under the RA MYP, such as the IRIS consensus 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, RA MYP products are widely recognized as the principal environmental health risk assessment benchmarks in the United States, exemplified by the IRIS outputs, AQCDs, and Risk Assessment Forum 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 RA MYP 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 (NPL; "superfund") sites, including quantitative Minimal Risk Levels (MRLs) for non-cancer effects. The EPA-ATSDR MOU 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 (IPCS), the International Agency for Research on Cancer (IARC), and the United Nations Environment Programme (UNEP).

Resources currently allocated to the RA MYP were consolidated in fiscal year 2004 under EPA Government Performance Results Act (GPRA) Goal 4, Healthy Communities and Ecosystems. The FY'07 President's Budget requests 122 full time equivalent (FTE) work years and $13.6 million dollars of extramural funds for the RA MYP. Approximately three quarters of these resources are assigned to the preparation of assessments (e.g., IRIS and other major health hazard assessments ~60% and AQCDs ~15%), with the remainder to methods and guidance development (~25%). At any one time, approximately 80 IRIS assessments are underway, plus additional major health hazard assessments, AQCDs, and between 25 and 50 Provisional Peer Reviewed Toxicity Values (PPRTVs) for substances prioritized by the Office of Solid Waste and Emergency Response (OSWER). The RA MYP does not plan ecological risk assessment activities, which are addressed under other ORD plans, although a number of RA MYP activities explore aspects of integrated human health and ecological risk assessment.

Background

Antecedents of the RA MYP: Modern efforts at quantifying presumptively safe levels of environmental exposures began in the 1940s through the development of threshold limit values (TLVs) 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 (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 (NAS, 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 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 multi-year plans;

  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.

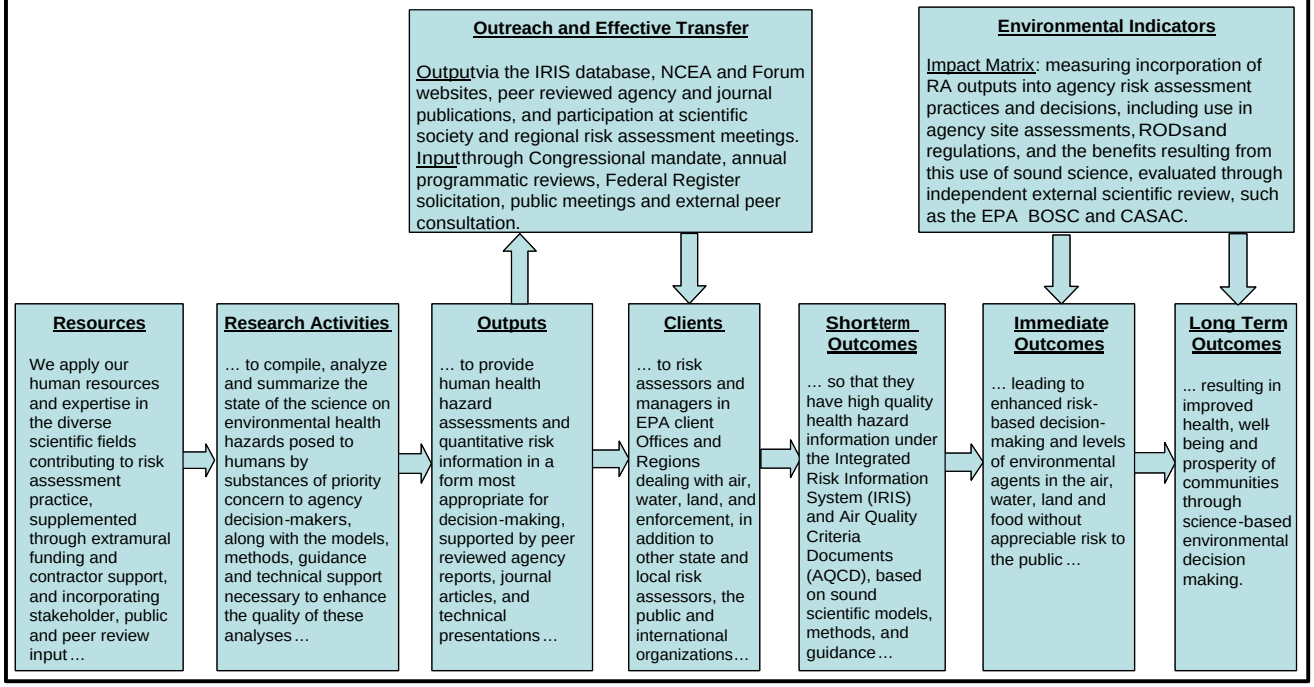
The objectives of the consolidation to the risk assessment MYP were to: improve the quality and timeliness of assessments; focus development and incorporation of scientific advances into risk assessment methods and products; improve the alignment of ORD laboratory and center research and programs; and 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 plan (initial acronym HHRA, now RA) and the similarly titled Human Health Research Plan (HHRP). As noted, these two plans are distinct in that the RA MYP receives data and methods development science produced under the HHRP and other MYPs from the ORD laboratories, as well as from the published literature. The RA MYP helps prioritize research in the ORD laboratories by identifying critical data gaps and scientific needs, but does not conduct or fund this work itself. In contrast, the HHRP 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 RA MYP 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, air quality criteria documents, and provisional peer reviewed toxicity values. 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 RA MYP. 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 RA MYP 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 RA MYP products occurs through the IRIS database, NCEA and Forum websites, 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 RA MYP is closely linked to the needs of program and regional offices. Planning is conducted on a broad scale through preparation of the RA 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 AQCDs. On a broad scale, RA 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 - 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 peer review by the RCT members and delegated program, regional or laboratory representatives. Internal peer review is also undertaken by the ORD Science Council, with approval by the ORD Executive Council prior to independent external peer review. 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 RA 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. 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. Provisional Peer Reviewed Toxicity Values (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. Revisions to the AQCDs are planned every 5 years subject to the requirements of the Clean Air Act, taking into consideration resource constraints, OAQPS priorities, and court deadlines.

Due to the extent of this planning and programmatic input on priority needs, the RA MYP 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 prerequisite consideration in many regulatory determinations. AQCDs constitute the scientific basis for OAQPS staff papers relating to decisions on the National Ambient Air Quality Standards (NAAQS) for criteria air pollutants. RA MYP 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 RA MYP products are subject to internal and independent external peer review to assure their quality and objectivity. Peer reviews are conducted consistent with the policies detailed in EPA's Peer Review Guidelines (U.S. EPA, 1998) and the OMB (2004) peer review guidance. These policies include categorization of all RA MYP products regarding their potential scientific, policy, and economic implications as a determinant of the level of peer review required. Many RA 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 the National Academy of Sciences. Other documents, such as journal manuscript submissions, undergo internal peer 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. The conduct of the external peer review is organized and managed by an independent contractor or science organization. Public comment is solicited on major products undergoing peer review.

RA MYP 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 (RFC) should they believe that information disseminated by the federal government is erroneous. RA MYP activities are consistent with the IQGs through the 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 (OEI).

Technical Support: Technical support to customer programs and regions is a key component of all RA MYP 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. Where necessary, these support centers can access additional expertise from NCEA and other EPA scientists. Direct technical assistance is also provided by NCEA scientists to 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 RA program, technical expertise is often transferred between projects in order to achieve program objectives. For example, Forum projects prepared under this MYP 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 RA MYP long term goals, such as certain IRIS assessments serving as vehicles for informing the development of new models and methods. The RA 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: RA MYP 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, RA 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 (ORMA) in the Integrated Resource Management System (IRMS) on a quarterly basis, with annual reporting. Major deliverables are reported to the White House Office of Management and Budget (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 RA MYP is anticipated in FY'07. The proposed outcome measures for the RA MYP are outlined in Figure 2, under the subtitle Environmental Indicators. The RA MYP outcomes will be based on an impact matrix measuring the incorporation of RA MYP 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 RA MYP will be evaluated through independent external scientific review, such as the ORD Board of Scientific Counselors (BOSC) and the Clean Air Scientific Advisory Committee (CASAC).

Progress to Date/Changes

Although the RA 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, OHEA; Carcinogen Assessment Group, CAG, etc.) 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 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 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 records of decision (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 (APA). IRIS has also 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), and to advancing mode of action considerations in cancer hazard characterization (e.g., perchlorate).

AQCDs have been prepared by NCEA or its predecessors since the creation of the EPA in early 1970s. AQCDs and the resulting NAAQS have been pivotal in achieving the air quality standards experienced today in the United States and they have influenced regulatory actions worldwide. The latest particulate matter AQCD was finalized in 2004, and the Ozone AQCD is scheduled for finalization in early 2006. Through the preparation of AQCDs, public health protection has been furthered by the ongoing, close, collaborative relationships between risk assessors, OAQPS regulators, and research scientists studying criteria air pollutants under other ORD research MYPs.

ORD-NCEA has also been responsive to urgent agency priorities, whether emergency risk assessment needs in the aftermath of the World Trade Center attack and Hurricane Katrina, or in response to immediate program office needs. Following the WTC attacks, 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 assisted through expedited re-assignment of staff resources. Platinum and cerium provisional reference concentration assessments were prepared in response to a special request from the OAR-Office of Transportation and Air Quality (OTAQ) regarding their evaluation of a proposed diesel fuel additive containing both of these metals. Independent reviews of the scientific validity of intentional dosing human pesticide studies were prepared by NCEA scientists to assist the Office of Pesticide Programs (OPP) 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 (OPPT) in preparing the science background for a consent agreement on air toxics.

The models, methods and guidance development work in NCEA 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 (NHEERL, NCEA, NCCT) 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. NCEA 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. NCEA 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 (NDAMN). 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 NCEA 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.

Risk Assessment Forum outputs have included the recent publication of EPA's *Carcinogen Risk Assessment Guidelines* and the related *Supplemental Guidance for Assessing Cancer Susceptibility Resulting from Early-Life Exposure to Carcinogens*. Informed by extensive scientific peer review, these Guidelines advance cancer risk assessment methods by moving beyond alphanumeric cancer classifications to a narrative format with standard descriptors. This facilitates consideration of routes and nature of exposure, and a mode of action evaluation of the relevance to humans of tumors seen in animals. The early-life supplement sets the standard for quantitative evaluations of increased cancer risks from early-life exposure to carcinogens that have a mutagenic mode of action. The Forum has also recently published a *Review of the RfD/C Processes*, recommending modifications and enhancements to Agency practices dealing with non-carcinogenic risks. These activities complement the various Agency risk assessment guidance documents prepared by the Forum, including guidelines on reproductive toxicity, developmental toxicity, neurotoxicity, cumulative risk assessment, mutagenicity assessment, and exposure assessment, to name the most recent (www.epa.gov/ncea/raf).

The above-noted activities were conducted under a variety of program and media-specific plans in EPA's GPRA goal structure. The newly consolidated RA MYP proposes continuing the broad themes apparent above, focusing on enhancing IRIS, AQCD and risk assessment guidance outputs through better aligning budget resources with planning priorities. In the interim between the consolidation of ORD's risk assessment budget in 2004 and the finalization of this RA MYP, health risk assessment planning has been conducted on an annual basis during the President's Budget submission cycle. As such, annual performance goals (APGs) and measures (APMs) have been updated in each successive annual planning cycle, accompanied by the deletion of redundant APG/Ms under other MYPs for that budget period. Through the preparation of this multi-year plan, all current year and out-year NCEA and Forum health risk assessment APG/Ms are consolidated into the RA MYP, or deleted. The objectives of many of the APMs have been retained, such as the movement of AQCDs from the ozone and particulate matter plans to the RA MYP. These actions have been 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 RA MYP 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 RA 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: Air Quality Criteria Documents: As mandated in the Clean Air Act, the ambient air criteria pollutants are reviewed and AQCDs revised to reflect the best available scientific information on identifiable effects on public health and the environment from exposure to the pollutant, and this information is used by the EPA Office of Air and Radiation in their review and promulgation of the National Ambient Air Quality Standards (NAAQSs) to protect public health 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 percent LTG 2 development work to 75 percent assessment effort. With this guidance, table 1 summarizes the level of effort devoted to the LTGs:

Table 1: Area	**Emphasis in MYP Planning Window**
LTG 1: IRIS and other priority assessments	Level, increasing subject to initiative request
LTG 2: Models, methods and guidance	Level, decreasing if RA budget reductions
LTG 3: Air quality criteria documents	Level

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

The core of the RA MYP activities is the Integrated Risk Information System (IRIS). IRIS is an Agency-wide program managed by NCEA with active participation by program offices and regions, who nominate chemicals for the annual IRIS agenda and, through designated reviewers, participate in the Agency consensus 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 of human risk. Quantitative risk values include the IRIS reference dose (RfD; and reference concentration, RfC), which is:

> "An estimate of a daily oral exposure for a given duration to the human population (including susceptible subgroups) that is likely to be without an appreciable risk of adverse health effects over a lifetime. It is derived from a BMDL, a NOAEL, a LOAEL, or another suitable point of departure, with uncertainty/variability factors applied to reflect limitations of the data used."

The cancer slope factor is an upper bound estimate of the increased cancer risk from a lifetime of exposure to an agent, expressed as the proportional increase in cancer risk per mg/kg/day dose. These qualitative and quantitative assessments are summarized and disseminated through the internet at www.epa.gov/IRIS. Other types of assessment values, such as acute and 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 the new assessments are being developed under LTG 2 of the RA MYP.

Although non-regulatory, quantitative IRIS values 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 (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, 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 RA MYP also conducts more resource intensive assessments of major chemicals. Designation as a major assessment takes into consideration 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. A number of major assessments also go beyond hazard and dose-response information by providing

exposure and risk characterization conclusions, such as the World Trade Center assessment and dioxin reassessment. Due to their importance, major assessments are identified on a substance-specific basis in this MYP.

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. These substance-specific factors highlight the importance of the transparent, Agency-wide consensus 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. Specific program requests may also be responded to through a combination of risk assessment guidance development followed by implementation of this guidance in IRIS and AQCD assessments. Examples of this progression include methods development for, and calculation of, acute and 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 commences with the solicitation of chemical nominations from EPA programs and regions, and, in some years, from other government agencies and the public. EPA 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. IRIS also screens the published literature to determine if new information has become available that might alter an existing IRIS toxicity value. The results of this screening are factored into setting priorities.

Upon selection of a substance 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. 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 invitations to interested NCEA staff and coordination with scientists from the ORD effects laboratory (NHEERL). Invitations are also

extended to representatives from EPA Offices and Regions, and may include staff from ATSDR or other government agencies and the chemical manager's assessment development contractor. The scoping meeting seeks 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 peer review and then Agency-wide review, in advance of the external review phase.

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 two weeks beforehand for consideration by the peer reviewers. Each Toxicological Review contains a summary and disposition of these peer review and major public comments. The progression 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 provisional peer-reviewed toxicity values (PPRTVs) for substances of potential concern but where no IRIS value is available. PPRTVs are developed and peer reviewed on an expeditious basis at the request of the Office of Solid Waste and Emergency Response (OSWER), which uses PPRTVs in its evaluation of Superfund sites.

Figure 3 conveys the APG diagram for RA LTG 1. Major risk assessments are identified and contribute to an annual IRIS output total of 16 or more hazard/dose-response assessments. This number is based on estimated 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. These annual performance goals and measures are listed in Appendix 1.

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 process consists of review by the Executive Office of the President, coordinated 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 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 RA MYP has sought to maximize information on individual substances without compromising its ability to define ambitious, yet realistic, future APG targets. This balance is achieved through providing chemical-specific completion dates up to the step of interagency or external peer review. Because of the central importance of finalization and external dissemination of RA assessments, additional APMs are anticipated to track assessment finalization and public dissemination dates as sufficient advance information becomes available. In the interim, estimated completion dates are publicly available in IRIS Track. RA MYP 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.

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 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.

	06	07	08	09	10	11	12
Major Assessments	Complete health hazard assessments for interagency review or external peer review for: acrylamide MTBE naphthalene (ca) perchloroethylene	Complete health hazard assessments for interagency review or external peer review for: acrylonitrile formaldehyde methanol methylene Cl trichloroethylene dioxin	Complete health hazard assessments for interagency review or external peer review for: asbestos (nonCa) ethanol styrene	Complete health hazard assessments for interagency review or external peer review for: asbestos (ca), polycyclic aromatic hydrocarbons	Complete health hazard assessments for interagency review or external peer review for: to be developed, ongoing finalization & new starts	Complete health hazard assessments for interagency review or external peer review for: to be developed, ongoing finalization & new starts	Complete health hazard assessments for interagency review or external peer review for: to be developed, ongoing finalization & new starts
IRIS assessments	16 IRIS hazard/DR assessments +	16 IRIS hazard/DR assessments +	16 IRIS hazard/DR assessments +	16 IRIS hazard/DR assessments +	16 IRIS hazard/DR assessments +	16 IRIS hazard/DR assessments +	16 IRIS hazard/DR assessments +
Provisional Toxicity Values	25 new & 25 revised PPRTVs	25 new & 25 revised PPRTVs	25 new & 25 revised PPRTVs	25 new & 25 revised PPRTVs	25 new & 25 revised PPRTVs	25 new & 25 revised PPRTVs	25 new & 25 revised PPRTVs

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

Risk assessment models, methods and guidance development under the RA MYP is directed toward incorporating scientific advances into risk assessment practice, similar to equipment upgrades to maintain standards of practice. The LTG 2 outputs support the applied decision-making needs of the EPA programs and regions, either directly or through RA LTG 1 (IRIS) and 3 (AQCD) 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, and 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 research 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. RA MYP LTG 2 acts to incorporate these data and analyses, along with other published literature, into EPA risk assessment practices and risk assessment outputs.

Two distinct, yet inter-related, organizational units are supported under RA MYP LTG 2. The first is the models, methods and guidance development work conducted by ORD-NCEA. The second is the Risk Assessment Forum, which is administratively housed in NCEA with support staff and extramural funding under LTG 2, but which is functionally an Agency-wide organization. As an Agency-wide organization, Forum activities are supplemented through additional ORD, program and regional resources provided through committee staffing and extramural funding. Details on these two organizational units are as follows:

ORD-NCEA Activities under LTG 2: Risk assessment development activities in NCEA 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 NCEA LTG 2 planning process commenced with the identification of risk assessment activity foci by ORD-NCEA science staff and management. The selection of foci took 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 resulting 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:

- Physiologically-based pharmacokinetic (PBPK) modeling, using 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 toxicology. Whereas primary physiological data and PBPK models are principally developed in the laboratories, the RA MYP activities are focused on the applicability of these models, their uncertainty parameters, and guidance for use in risk assessment.

- Mode of action (MoA), applying available data to increase 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.

- Quantitative methods 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.

- Inhalation toxicology to apply risk assessment and pulmonary toxicology advances to EPA inhalation methods for interspecies extrapolation and dose-response assessment.

- Exposure assessment, to maintain the quality and utility of the exposure factors handbooks for use Agency-wide, and the application and refinement of exposure methods to risk assessment.

- Mixtures assessment, 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.

- Microbial risk assessment, to extend and apply risk assessment methods, particularly probabilistic approaches and dynamic system analyses, to priority pathogens hitherto inadequately addressed on a quantitative basis, thereby facilitating the assessment of pathogen risks necessary for informed decision-making.

Risk Assessment Forum Activities under LTG 2: The Risk Assessment Forum was established in 1983 to promote consensus on risk assessment issues and to ensure that this consensus is incorporated into appropriate Agency risk assessment documents. The Forum focuses on generic issues fundamental to the risk assessment process and related science-policy issues. Forum activities include reports of Agency colloquia on specific risk assessment topics to inform and communicate among Agency programs, and the development of Agency-wide guidelines, issue

papers, and training on complex risk assessment topics, such as the cancer guidelines, children's risk, cumulative risk, and harmonization of cancer and non-cancer risk assessments. These documents set Agency science-policy for the conduct of risk assessment activities, and provide leadership to other national and international actions. Major Forum guidance documents are developed in accordance with the Agency's regulatory and policy development process, and become Agency policy upon approval by the Administrator or the EPA Science Policy Council.

The Chairperson for the Forum is appointed by the EPA Deputy Administrator. Forum committee members are assembled from throughout the Agency in a formal process to provide scientific and programmatic expertise to study and report on risk assessment issues from an agency-wide perspective. Direct staff, logistical and extramural funding support for the Forum are tracked under RA MYP LTG 2.

Forum activities may be proposed at any time by regions and program offices, and are evaluated by the Forum steering committee. Criteria for choosing projects include: Agency-wide applicability, new or emerging risk assessment issues, opportunity for developing Agency-wide consensus, current project work loads and the availability of scientific staff to serve as panel members. Ongoing and planned Forum activities are listed in Table 2:

Table 2: Planned Activities and Publications of the Risk Assessment Forum

Integrating economics and risk assessment.	Mutagenic mode of action guidance.
Data derived uncertainty factors.	Peroxisome proliferation (PPAR) mode of action.
Metals assessment framework.	Immunosuppression risk assessment guidance.
Benchmark dose technical guidance.	Guidance on bladder tumors.
Children's exposure age-groups.	Cumulative risk assessment issue papers.
Harmonization of uncertainty factors.	Cumulative risk assessment guidance.
Body weight to the three-quarter power.	Microbial risk assessment guidance.
Exposure assessment guidelines update.	

There is a close relationship between the NCEA risk assessment foci and the planned Forum activities. Contemporary Forum documents contribute a science-policy foundation for ongoing risk assessment development work in NCEA. Future Forum documents serve as a locus for the synthesis and output of NCEA foci development activities. Because of this inter-relationship, NCEA and Forum products are included together in the following APG structure and wiring diagrams, with the Agency-wide Forum products labeled in the APG/Ms (appendix A) and distinguished by italics and broken perimeter lines in Figure 5 and Appendix B.

Figure 4 illustrates the linkage provided in the RA 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, 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 (AQCD). 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.

Figure 4: RA LTG 2 Flow Chart and APG Relationships

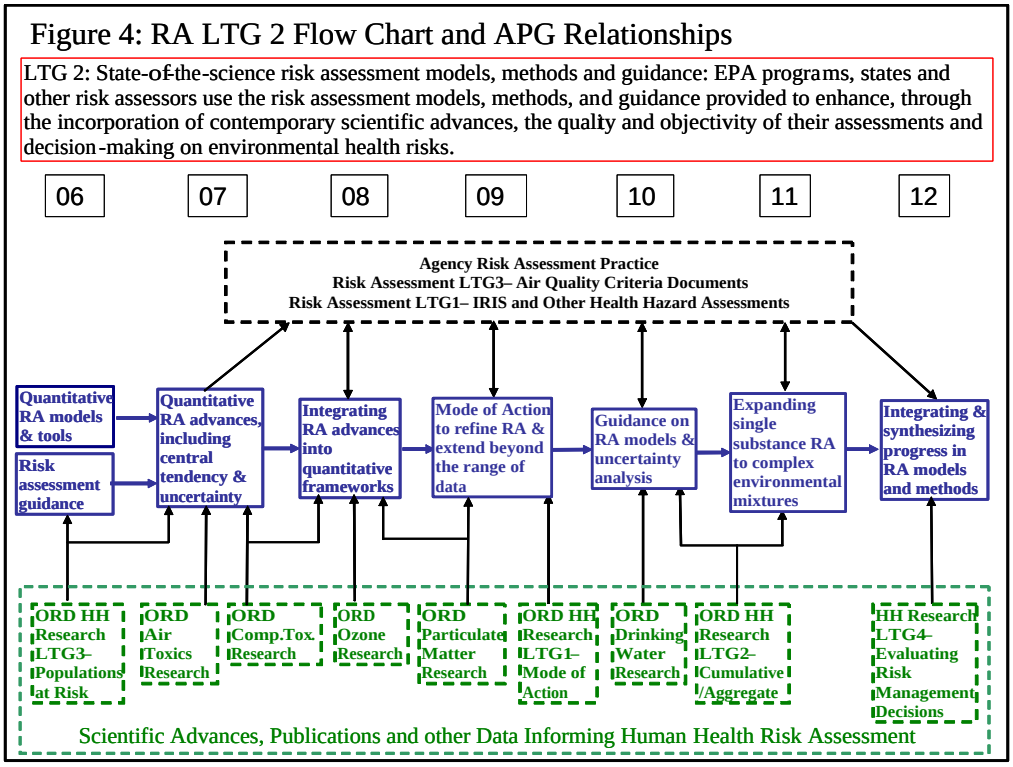
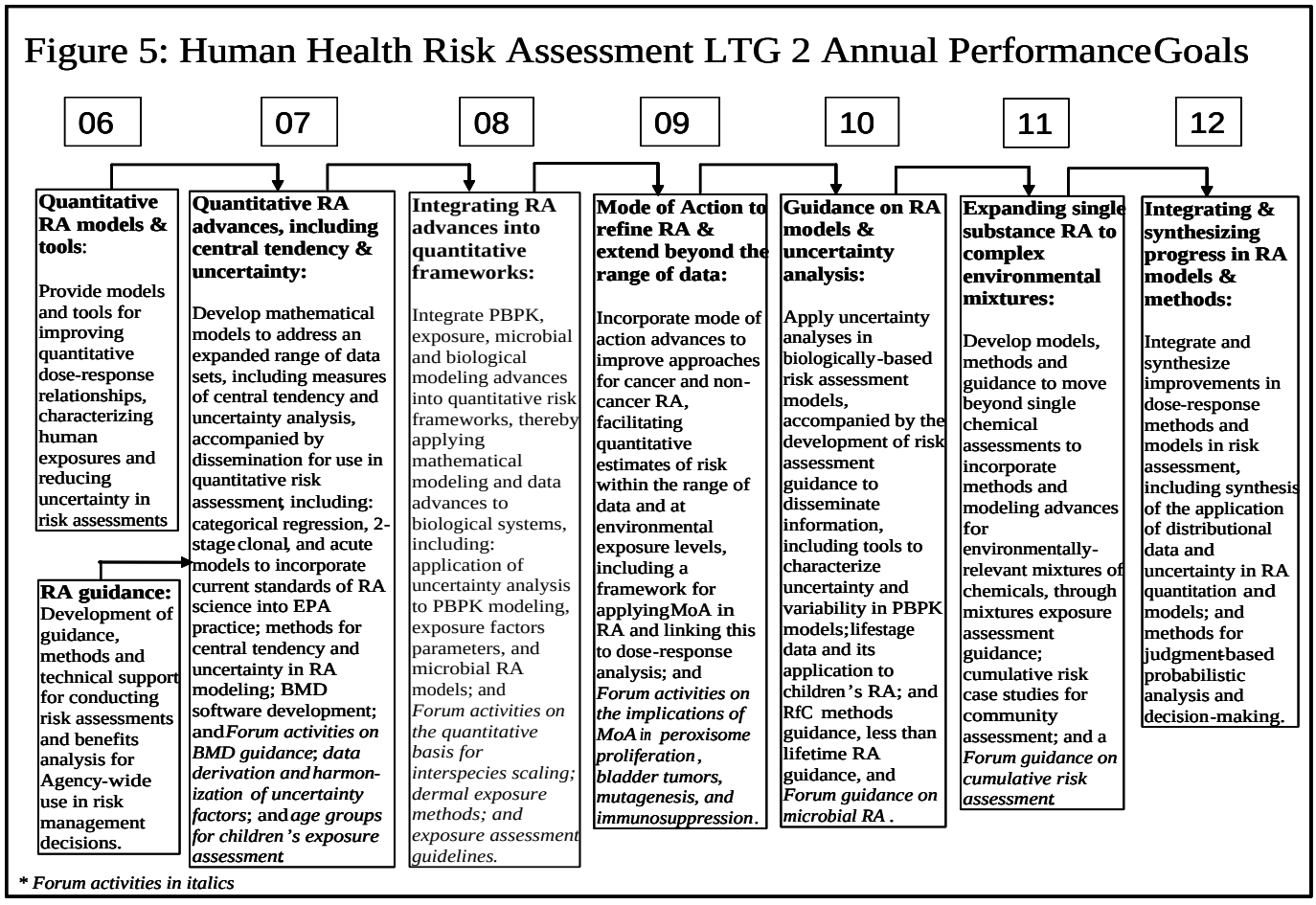


Figure 5 provides details on the LTG 2 annual performance goals. The objective of the LTG 2 APGs is to advance risk assessment science along themes most relevant to EPA's mission needs. In doing so, the APGs serve to maintain the quality and objectivity of RA MYP and other Agency risk assessment products when evaluated against contemporary peer review science standards. Each APG represents the cumulative result of the individual contributing ORD-NCEA and Forum APMs (listed by year in Appendix A) and support activities. Each APG also builds on previous APG outputs, demonstrating a progression of risk assessment advances that culminate 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. Appendix B provides additional detail on the LTG 2 development activities in an annual operating plan structure, grouped and color coded by the risk assessment foci discussed previously.

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 experienced 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, exposure assessment and microbial risk assessment models.



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. Mode of action 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 levels. Early deliverables include Forum products on mutagenic mode of action and peroxisome proliferation guidance. The APGs in fiscal years 10 to 12 of this plan are directed toward developing guidance and synthesizing the risk assessment advances accomplished under this MYP and from the scientific literature. In doing so, these goals consolidate the science, generate a common basis for Agency risk assessment practice, and provide a foundation for future planning activities.

LTG 3: Air Quality Criteria Documents

Sections 103, 108, and 109 of the Clean Air Act govern the establishment, review, and revision of the National Ambient Air Quality Standards (NAAQS) and direct the Agency to issue air quality criteria for identified ubiquitous pollutants that may reasonably be anticipated to endanger public health or welfare. RA MYP LTG 3 produces the mandated ambient Air Quality Criteria Documents (AQCD) which 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. ORD laboratory research is also conducted pursuant to the CAA under the particulate matter, ozone and other MYPs.

For the AQCDs, NCEA scientists and external authors develop chapters on atmospheric chemistry, ecology, toxicology, epidemiology, and exposure sources, ambient concentrations and measurement methods. A close collaboration is maintained in the planning and execution of AQCD preparation between NCEA and the recipient OAR-Office of Air Quality Planning and Standards (OAQPS). Draft AQCDs are reviewed internally and through workshops covering specific areas of the assessment. External review drafts undergo public comment and detailed scrutiny by the Clean Air Scientific Advisory Committee (CASAC). With closure on the final AQCD, NCEA consults with OAR-OAQPS in the development of their Staff Paper risk assessment, which serves as the basis for regulatory review 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). The AQCDs are reviewed and revised on a regular cycle in response to statutory requirements.

Specific APGs for LTG 3 are illustrated in Figure 7, with all the AQCDs scheduled for revision during this multi-year planning period. Figure 8 demonstrates the annual operating plan requirements to fulfil these APGs, with each AQCD being preceded by a project plan, multiple external review drafts, public comment and CASAC review, prior to finalization for delivery to OAQPS. The individual AQCD requirements overlap to form a staggered matrix of ongoing activities under RA LTG 2.

Figure 6: Human Health Risk Assessment LTG 3 Annual Performance Goals

LTG 3: Air Quality Criteria Documents: As mandated in the Clean Air Act, the ambient air criteria pollutants are reviewed and AQCDs revised to reflect the best available scientific information on identifiable effects on public health and the environment from exposure to the pollutant, and this information is used by the EPA Office of Air and Radiation in their review and promulgation of the National Ambient Air Quality Standards (NAAQSs) to protect public health with an adequate margin of safety.

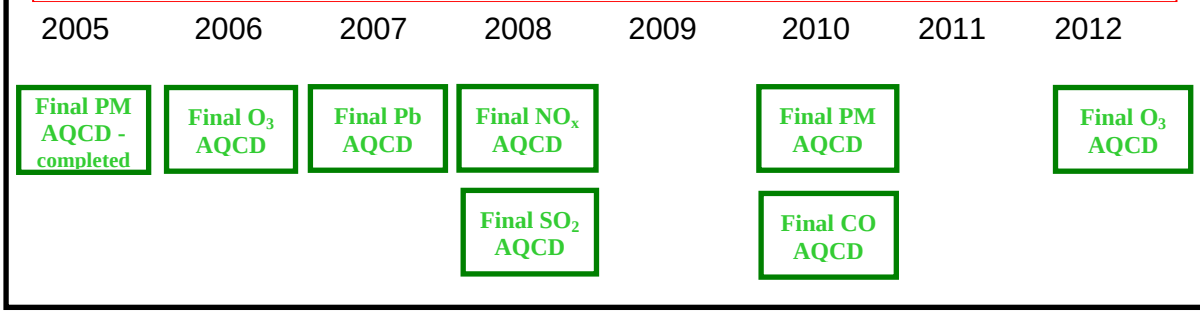
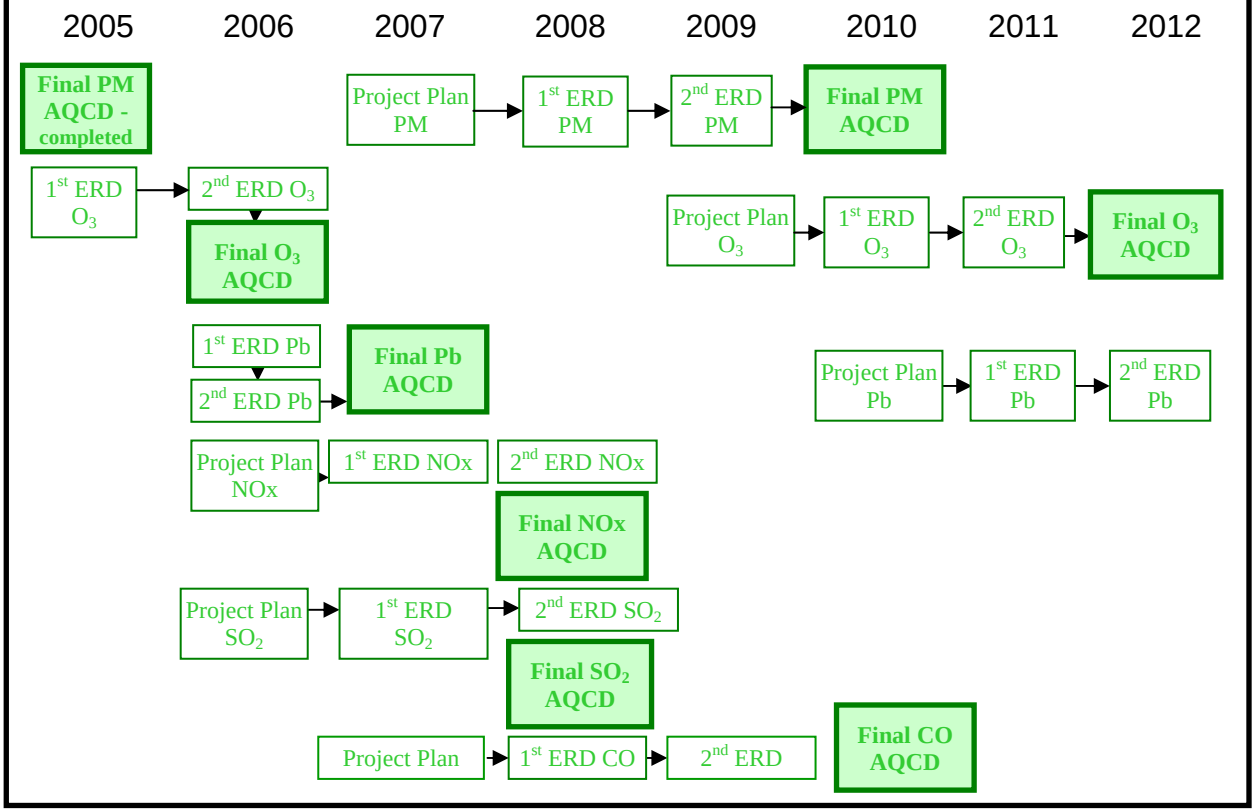


Figure 7: RA LTG 3 Annual Operating Plan APMs and Support Activities



Potential Additional Work

Health hazard assessments conducted under the RA MYP have become increasingly controversial due to their public health and cost implications and the variety of scientific conclusions that can be drawn from toxicity studies. Because these assessments provide the key scientific analyses supporting many critical Agency decisions, the Administrator has directed that ORD institute enhanced review and consultation procedures to ensure the highest scientific quality and transparency. To this end, ORD has proposed new steps in the assessment development process that complement and expand existing review procedures. These steps require additional extramural resources to integrate review and consultation by the National Academy of Sciences (NAS) into the assessment development process. NAS involvement will contribute to the identification and resolution of scientific issues and increased confidence and wide acceptance of EPA assessments. The availability of additional resources would be used by ORD to establish contracts with the NAS for approximately 3 -5 high priority peer consultations on major issues and peer reviews of major assessments. These reviews are much more costly than current peer reviews and consultations, and existing RA MYP resources are insufficient to support these activities. Additional resources will also be used to support early involvement of federal agencies and the public in assessment development, including formal notice of assessment development and the opportunity for input by interested federal agencies and the public.

Beyond extramural funding for NAS peer reviews, additional resource allocations to the RA MYP would be used to support additional assessments of priority chemicals. To do so, however, requires a balance between RA staff FTE increases and extramural funding for contract and peer review support.

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 AQCD 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, 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 mode of action and quantitative methods development 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 a fixed budget is also 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 AQCD assessments. Recruitment planning may also be necessary to adjust staff expertise to changing circumstances.

Classification of External Annual Performance Goals and Measures

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

Appendix A: Long Term Goals and Associated Annual Performance Goals (APG) and Annual Performance Measures (APM)

GPRA Goal 4: Healthy Communities and Ecosystems
Program Project: 84, Human Health Risk Assessment

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.

ANNUAL PERFORMANCE GOALS AND MEASURES		YEAR	LAB/ CENTER
APG 6: IRIS and other priority health hazard assessments: Complete 16 health hazard assessments of high-priority chemicals for interagency review or external peer review and 25 new and 25 revised provisional peer reviewed toxicity values so that EPA program offices, regions, state and local risk assessors have state-of-the-science health hazard assessment information on priority substances included in planned Agency decisions and actions.		**2006**	ORD
APM	Complete 16 health hazard assessments of high priority chemicals for interagency review or external peer review	2006	NCEA
APM	Complete 25 new and 25 revised provisional peer reviewed toxicity values to support OSWER decision-making	2006	NCEA
APG 7: IRIS and other priority health hazard assessments: Complete 16 health hazard assessments of high-priority chemicals for interagency review or external peer review and 25 new and 25 revised provisional peer reviewed toxicity values so that EPA program offices, regions, state and local risk assessors have state-of-the-science health hazard assessment information on priority substances included in planned Agency decisions and actions.		**2007**	ORD
APM	Complete 16 health hazard assessments of high priority chemicals for interagency review or external peer review, including acrylonitrile, methanol, methylene chloride, trichoroethylene and dioxin	2007	NCEA
APM	Complete 25 new and 25 revised provisional peer reviewed toxicity values to support OSWER decision-making	2007	NCEA
APG 8: IRIS and other priority health hazard assessments: Complete 16 health hazard assessments of high-priority chemicals for interagency review or external peer review and 25 new and 25 revised provisional peer reviewed toxicity values so that EPA program offices, regions, state and local risk assessors have state-of-the-science health hazard assessment information on priority substances included in planned Agency decisions and actions.		**2008**	ORD

APM	Complete 16 health hazard assessments of high priority chemicals for interagency review or external peer review, including asbestos (nonCa), ethanol and styrene	2008	NCEA
APM	25 new and 25 revised provisional peer reviewed toxicity values to support OSWER decision-making	2008	NCEA
APG 9: IRIS and other priority health hazard assessments: Complete 16 health hazard assessments of high-priority chemicals for interagency review or external peer review and 25 new and 25 revised provisional peer reviewed toxicity values so that EPA program offices, regions, state and local risk assessors have state-of-the-science health hazard assessment information on priority substances included in planned Agency decisions and actions.		**2009**	ORD
APM	Complete 16 health hazard assessments of high priority chemicals for interagency review or external peer review, including asbestos (cancer) and polycyclic aromatic hydrocarbons	2009	NCEA
APM	25 new and 25 revised provisional peer reviewed toxicity values to support OSWER decision-making	2009	NCEA
APG 10: IRIS and other priority health hazard assessments: Complete 16 health hazard assessments of high-priority chemicals for interagency review or external peer review and 25 new and 25 revised provisional peer reviewed toxicity values so that EPA program offices, regions, state and local risk assessors have state-of-the-science health hazard assessment information on priority substances included in planned Agency decisions and actions.		**2010**	ORD
APM	Complete16 health hazard assessments of high priority chemicals for interagency review or external peer review, including additional nominated priority substances and finalization of assessments for internet dissemination	2010	NCEA
APM	25 new and 25 revised provisional peer reviewed toxicity values to support OSWER decision-making	2010	
APG 11: IRIS and other priority health hazard assessments: Complete 16 health hazard assessments of high-priority chemicals for interagency review or external peer review and 25 new and 25 revised provisional peer reviewed toxicity values so that EPA program offices, regions, state and local risk assessors have state-of-the-science health hazard assessment information on priority substances included in planned Agency decisions and actions.		**2011**	ORD
APM	Complete 16 health hazard assessments of high priority chemicals for interagency review or external peer review, including additional nominated priority substances and finalization of assessments for internet dissemination.	2011	NCEA

APM	25 new and 25 revised provisional peer reviewed toxicity values to support OSWER decision-making	2011	NCEA
APG 12: IRIS and other priority health hazard assessments: Complete 16 health hazard assessments of high-priority chemicals for interagency review or external peer review and 25 new and 25 revised provisional peer reviewed toxicity values so that EPA program offices, regions, state and local risk assessors have state-of-the-science health hazard assessment information on priority substances included in planned Agency decisions and actions.		**2012**	ORD
APM	Complete 16 health hazard assessments of high priority chemicals for interagency review or external peer review, including additional nominated priority substances and finalization of assessments for internet dissemination.	2012	NCEA
APM	25 new and 25 revised provisional peer reviewed toxicity values to support OSWER decision-making	2012	NCEA

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.

ANNUAL PERFORMANCE GOALS AND MEASURES		YEAR	LAB/ CENTER
APG 263: Quantitative risk assessment models and tools: Provide models and tools for improving quantitative dose-response relationships, characterizing human exposures and reducing uncertainty in risk assessments so that by 2010 the Agency will have improved information for estimating human health exposures and risks		**2006**	ORD
APM 53	Models for saturable effects using dichotomous data incorporated in BMD software in support of IRIS dose-response assessment development	2006	NCEA
APM 55	5 final acute reference dose exposure (ARE) assessments of key HAP chemicals to support the residual risk program	2006	NCEA
APM 498	External Review Draft of updated Exposure Factors Handbook for Children to reduce uncertainty in exposure assessments	2006	NCEA
APM 230	External Review Draft of model for estimating human exposure to multiple metal contaminants using biokinetic modeling techniques to reduce uncertainty in exposure assessments	2006	NCEA
APM 357	2 final reports on dose-response models and population exposure methods for assessing microbial risks and defining microbial research needs for OW	2006	NCEA
APG 264: Risk Assessment Guidance: Development of guidance, methods, and technical support for conducting risk assessments and benefits analysis for Agency-wide use in risk management decisions		**2006**	ORD
APM 424	2 draft case studies to demonstrate the potential for quantifying health benefits and risks by integrating methods from toxicology, statistics, epidemiology and economics	2006	NCEA/ RAF
APM 462	Final report supporting development of methodology to guide the replacement of inter/intraspecies default uncertainty factors with factors based on data	2006	NCEA/ RAF
APM	Complete and deliver to the Agency's Science Policy Council a cross-Agency framework for the assessment of metals (moved from 2005 APG129, APM 547)	2006	NCEA/ RAF

APG 7: Quantitative risk assessment advances, including central tendency & uncertainty: Develop mathematical models to address an expanded range of data sets, including measures of central tendency and uncertainty analysis, accompanied by dissemination for use in quantitative risk assessment, including		**2007**	ORD
APM	Benchmark dose technical guidance.	2006	NCEA/ RAF
APM	Report on selecting age groups for evaluating children's exposure to environmental contaminants.	2006	NCEA/ RAF
APM	Approaches to harmonization of uncertainty factors for cancer and non-cancer risk assessment (moved from 06 APG264, APM 458)	2007	NCEA/ RAF
APM	External review draft guidance on replacing default values for uncertainty factors with those based on data.	2007	NCEA/ RAF
APM	Development of three to four additional low dose linear and non-linear models for application in acute and chronic dose-response assessments, incorporating biological and statistical considerations in selection and decision-making recommendations	2007	NCEA
APM	Report on methods for developing central estimates and uncertainty bounds in dose-response analysis – current techniques, alternatives and decision parameters for application to risk assessment. External Review Draft	2007	NCEA
APG 8: Integrating risk assessment advances into quantitative frameworks: Integrate PBPK, exposure, microbial and biological modeling advances into quantitative risk frameworks, thereby applying mathematical modeling and data advances to biological systems, including ...		**2008**	ORD
APM	Use of body weight to the three-quarter power (BW3/4) as a default for interspecies extrapolation	2006	NCEA/ RAF
APM	Final report on Approaches for the Application of Physiologically-Based Pharmacokinetic (PBPK) Models and Supporting Data in Risk Assessment	2006	NCEA
APM	Final report on a Framework for Assessing Health Risks to Children from Environmental Exposures	2006	NCEA
APM	Technical summary of methods for estimating exposure through dermal absorption of contaminants	2007	NCEA
APM	Exposure factors handbook revision for use by programs and regions in modeling exposures - External Review Draft	2008	NCEA
APM	Report on analysis (with workshop input) of uncertainty in PBPK models and application to risk assessment	2008	NCEA

APM	Microbial risk assessment models of exposure, dose response, and population susceptibility	2008	NCEA
APM	Exposure assessment guidelines update	2008	NCEA/ RAF
APG 9: Mode of Action to refine RA & extend beyond the range of data: Incorporate mode of action advances to improve approaches for cancer and non-cancer risk assessment, facilitating quantitative estimates of risk within the range of data and at environmental exposure levels, including ...		**2009**	ORD
APM	Mutagenic mode of action guidance	2006	NCEA/ RAF
APM	Guidance on peroxisome proliferation (PPAR) mode of action	2007	NCEA/ RAF
APM	Immunosuppression risk assessment guidance	2007	NCEA/ RAF
APM	Guidance on bladder tumors	2007	NCEA/ RAF
APM	Develop a mode of action framework for application in chemical risk assessments	2008	NCEA
APM	External review draft report on linking mode of action information in dose-response analysis	2009	NCEA
APG 10: Guidance on risk assessment models & uncertainty analysis: Apply uncertainty analyses in biologically-based risk assessment models, accompanied by the development of risk assessment guidance to disseminate information, including...		**2010**	ORD
APM	Cumulative risk assessment technical issue papers, case studies, and research on methods and priorities	2006	NCEA/ RAF
APM	Revised reference concentration (RfC) methodology for use by the IRIS program to develop dose-response assessments for chronic exposure, external review draft	2008	NCEA
APM	Case studies on the application of the lifestage approach to children's risk assessment for selected chemicals	2008	NCEA
APM	Methods and guidance for use by IRIS in developing less-than-lifetime dose-response assessments for program offices, regions and states, using acute exposure methods and case studies of specific duration	2009	NCEA
APM	Microbial risk assessment guidelines	2009	NCEA/ RAF

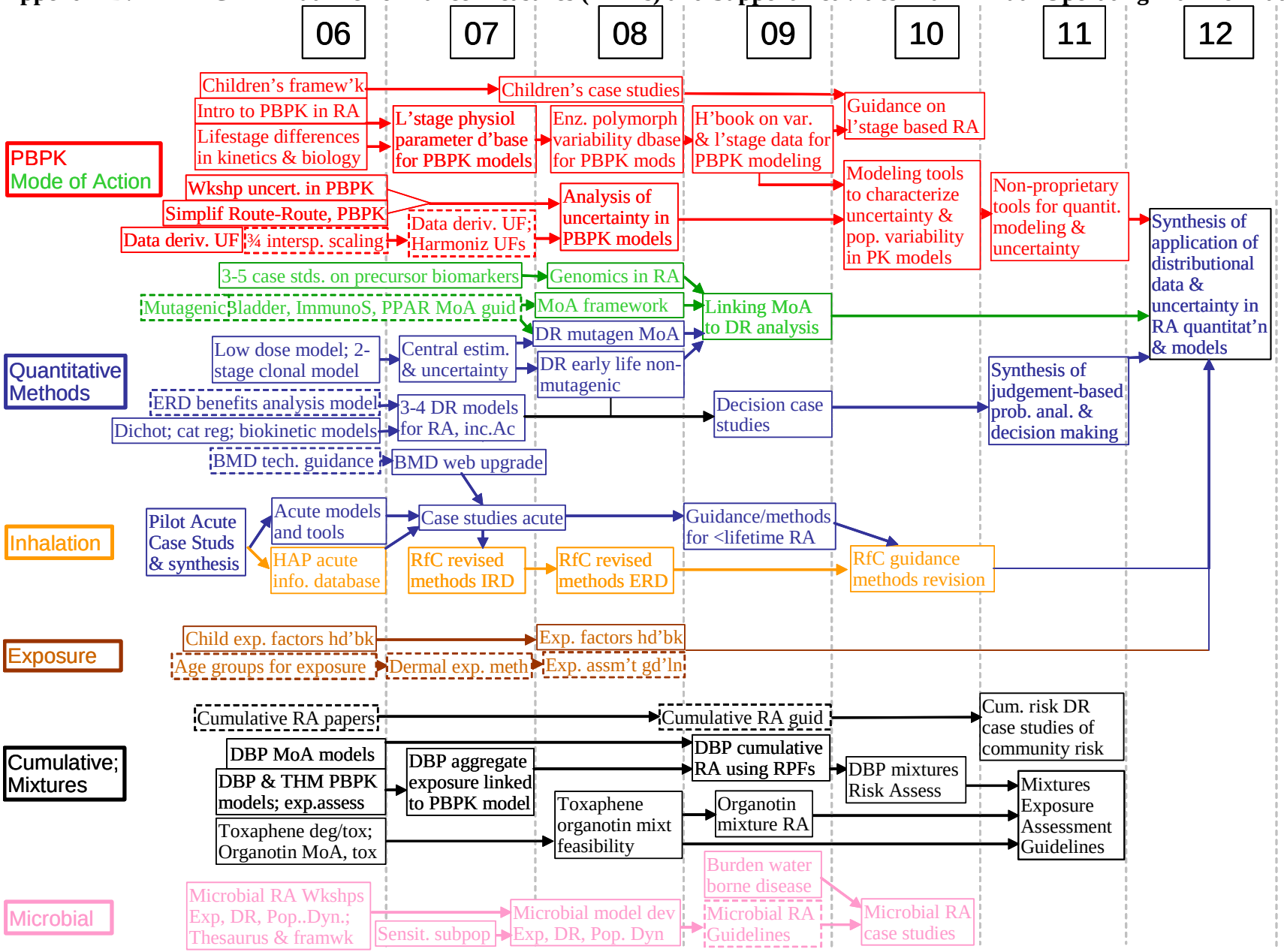
APM	Report on incorporation of variability and lifestage data for PBPK modeling	2009	NCEA
APM	Microbial risk assessment case studies	2010	NCEA
APM	Final revised reference concentration (RfC) methodology for use by the IRIS Program to develop dose-response assessments for chronic exposure	2010	NCEA
APM	Modeling tools to characterize uncertainty and population variability in PBPK models	2010	NCEA
APM	Guidance on lifestage based risk assessment	2010	NCEA
APG 11: Expanding single substance risk assessment to complex environmental mixtures: Develop models, methods, and guidance to move beyond single chemical assessments to incorporate methods and modeling advances for environmentally-relevant mixtures of chemicals, through ...		**2011**	ORD
APM	Cumulative risk assessment guidance	2009	NCEA/ RAF
APM	Mixtures exposure assessment guidance	2011	NCEA
APM	Cumulative risk dose response case studies for community risk assessment	2011	NCEA
APG 12: Integration and synthesis of progress in risk assessment methods & models: Integrate and synthesize improvements in dose-response methods and models in risk assessment, including...		**2012**	ORD
APM	Synthesis of methods and technical guidance for judgment-based probabilistic analysis and decision-making	2011	NCEA
APM	Synthesis of application of distributional data and uncertainty in risk assessment quantitation and models	2012	NCEA

LTG 3: Air Quality Criteria Documents: As mandated in the Clean Air Act, the ambient air criteria pollutants are reviewed and AQCDs revised to reflect the best available scientific information on identifiable effects on public health and the environment from exposure to the pollutant, and this information is used by the EPA Office of Air and Radiation in their review and promulgation of the National Ambient Air Quality Standards (NAAQSs) to protect public health with an adequate margin of safety.

ANNUAL PERFORMANCE GOALS AND MEASURES		YEAR	LAB/ CENTER
APG 6: Complete the Air Quality Criteria Document (AQCD) for Ozone in support of the EPA/OAQPS review and promulgation of the National Ambient Air Quality Standard (NAAQS)		**2006**	ORD
APM	External Review Draft AQCD for Ozone which serves as the basis for the EPA/OAQPS staff paper for the National Ambient Air Quality Standard (NAAQS)	2005	NCEA
APM	Final AQCD for Ozone which serves as the basis for the EPA/OAQPS staff paper for the National Ambient Air Quality Standard (NAAQS)	2006	NCEA
APG 7: Complete the Air Quality Criteria Document (AQCD) for Lead in support of the EPA/OAQPS review and promulgation of the National Ambient Air Quality Standard (NAAQS)		**2007**	ORD
APM	External Review Draft AQCD for Lead which serves as the basis for the EPA/OAQPS staff paper for the National Ambient Air Quality Standard (NAAQS)	2006	NCEA
APM	Final AQCD for Lead which serves as the basis for the EPA/OAQPS staff paper for the National Ambient Air Quality Standard (NAAQS)	2007	NCEA
APG 8: Complete the Air Quality Criteria Document (AQCD) for Nitrogen Oxides in support of the EPA/OAQPS review and promulgation of the National Ambient Air Quality Standard (NAAQS)		**2008**	ORD
APM	External Review Draft AQCD for Nitrogen Oxides which serves as the basis for the EPA/OAQPS staff paper for the National Ambient Air Quality Standard (NAAQS)	2007	NCEA
APM	Final AQCD for Nitrogen Oxides which serves as the basis for the EPA/OAQPS staff paper for the National Ambient Air Quality Standard (NAAQS)	2008	NCEA
APG 9: Complete the Air Quality Criteria Document (AQCD) for Sulfur Dioxide in support of the EPA/OAQPS review and promulgation of the National Ambient Air Quality Standard (NAAQS)		**2008**	ORD

APM	External Review Draft AQCD for Sulfur Dioxide which serves as the basis for the EPA/OAQPS staff paper for the National Ambient Air Quality Standard (NAAQS)	2007	NCEA
APM	Final AQCD for Sulfur Dioxide which serves as the basis for the EPA/OAQPS staff paper for the National Ambient Air Quality Standard (NAAQS)	2008	NCEA
APG 10: Complete the Air Quality Criteria Document (AQCD) for Carbon Monoxide in support of the EPA/OAQPS review and promulgation of the National Ambient Air Quality Standard (NAAQS)		**2010**	ORD
APM	External Review Draft AQCD for Carbon Monoxide which serves as the basis for the EPA/OAQPS staff paper for the National Ambient Air Quality Standard (NAAQS)	2008	NCEA
APM	Final AQCD for Carbon Monoxide which serves as the basis for the EPA/OAQPS staff paper for the National Ambient Air Quality Standard (NAAQS)	2010	NCEA
APG 10: Complete the Air Quality Criteria Document (AQCD) for Particulate Matter in support of the EPA/OAQPS review and promulgation of the National Ambient Air Quality Standard (NAAQS)		**2010**	ORD
APM	External Review Draft AQCD for Particulate Matter which serves as the basis for the EPA/OAQPS staff paper for the National Ambient Air Quality Standard (NAAQS)	2008	NCEA
APM	Final AQCD for Particulate Matter which serves as the basis for the EPA/OAQPS staff paper for the National Ambient Air Quality Standard (NAAQS)	2010	NCEA
APG 12: Complete the Air Quality Criteria Document (AQCD) for Ozone in support of the EPA/OAQPS review and promulgation of the National Ambient Air Quality Standard (NAAQS)		**2012**	ORD
APM	External Review Draft AQCD for Ozone which serves as the basis for the EPA/OAQPS staff paper for the National Ambient Air Quality Standard (NAAQS)	2010	NCEA
APM	Final AQCD for Ozone which serves as the basis for the EPA/OAQPS staff paper for the National Ambient Air Quality Standard (NAAQS)	2012	NCEA

Appendix B: RA LTG 2 Annual Performance Measures (APMs) and Support Activities in an Annual Operating Plan Format



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