

Human Health Risk Assessment Program (HHRA)

1. Program Context

The HHRA program plays a unique role in serving the needs of the EPA programs and regions through incorporating, integrating and coordinating the use of scientific information as a foundation for regulatory decision-making. The products of the program i.e., Integrated Risk Information System (IRIS) assessments, Integrated Science Assessments (ISA) for major air pollutants, and other assessments (e.g., World Trade Center) 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, and benefiting from the research products from many other ORD multi-year plans (MYP), the HHRA program 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 HHRA program also maintains a leadership role in incorporating mode of action (MoA) evaluations to support EPA decision-making, as emphasized in the EPA 2005 Cancer Guidelines and Early-Life Supplemental Guidance and used in recent assessments to evaluate the relevance of animal tumors to humans and the associated dose-response relationships.

EPA's National Center for Environmental Assessment (NCEA) consolidated its program in 2004 to focus on health risk assessment activities in support of the core mission of the agency to protect public health and the environment. The Human Health Risk Assessment Program (HHRA) was formed to develop and apply new methods in state-of-the-art health risk assessments through a more integrated and focused program. The HHRA Multi-Year Plan was recently developed to serve as the strategic plan for implementing the new annual and longer-term performance goals of the program.

2. Strategic Directions, Science Challenges, and Research Needs

The program is strategically designed around three long-term goals (LTG) which together represent the development and application of state-of-the-science information in health risk assessments.

LTG1: Integrated Risk Information System (IRIS) and other priority health hazard assessments: Agency, state and local risk assessors use the state-of-the-science health hazard assessment information provided on priority substances in their decisions and actions to protect human health from risks posed by environmental pollutants.

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

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

What are the scientific challenges for the research program in the next 5-10 years?

Of central importance to environmental health decision making is the need to better quantify risks and characterize uncertainty at the exposure levels generally experienced in real world situations by large numbers of people, including susceptible populations. This public health protection objective cannot be fully achieved based on evidence from humans, due in part to ethical, logistical and statistical constraints. Decisions can be informed, however, through extrapolation from available *in vitro*, *in vivo*, epidemiological and other data, including emerging evidence from new approaches such as genomics analyses. 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 the relevance of high dose mode of action to low doses. Primary research on these components is undertaken by the ORD laboratories under various MYPs, and is a primary consideration of the ORD Human Health Research Program. HHRA MYP LTG 2 acts to incorporate these data and analyses, along with other published literature, into EPA risk assessment practices and outputs. These efforts are focused on addressing critical linkages in the risk assessment process between the exposure-to-outcome continuum.

Relevance:

What are the drivers prompting these challenges?

Although non-regulatory, IRIS and other assessments developed under LTG 1 support environmental decision making and may serve as a basis for other activities such as resource prioritization. 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., reference values, cancer slope factors) 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.

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. HHRA MYP LTG 3 produces the mandated ambient ISAs 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 Air MYP. The ISA’s incorporate and synthesize research of ORD and others into these assessments documents (e.g., NCER particulate matter (PM) research centers and ORD intramural PM research under Air MYP).

Risk assessment methods, models, and guidance development under the HHRA MYP are directed toward incorporating scientific advances into risk assessment practice. The LTG 2 outputs support the applied decision-making needs of the EPA programs and regions, either directly or through HHRA LTG1 (IRIS) and LTG3 (ISA) outputs. These program needs vary from estimating risk levels in exposed people and determining acceptable 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.

What are the associated research questions that need to be addressed?

Illustrative questions include:

- How to use often limited information on one or more hypothesized modes of action in risk assessments?
- How to characterize risks to susceptible population with available data?
- What are the latest exposure factors, including distributional data and variation across lifestages?
- How do we efficiently and appropriately use PBPK modeling in risk analysis?
- How can we improve dose-response quantification (e.g., BBDR modeling, Categorical Regression, meta analysis approaches)?
- When do we qualitatively characterize uncertainty versus quantitatively characterize uncertainty in risk estimates and how do we do this in the most transparent fashion?
- What lessons can we learn from applying cumulative risk assessment principles to health assessments?

3. Leadership and Quality- HHRA's Past, Present and Future Directions

The program has provided leadership in the area of risk assessment science in numerous ways. The scientific expertise of the staff in the HHRA program is illustrated by their credentials with eighty-two PhD or Equivalent Degrees (MD, D Sc, and DVM), thirty-four Post Doc Fellows, and sixteen Diplomates of the American Board of Toxicology.

The HHRA staff demonstrates leadership both internally and externally through a number of venues. These include as members of and leaders of Agency Regulatory Workgroup Members (115). External recognition of HHRA staff scientific leadership is also recognized in the number of Adjunct and University Appointments (27), Membership on Editorial Boards (14), Journal Reviewers (51) and the number of times (175) they have been invited to give Talks/Lecturers (2002-2007). These lectures and talks are independent of recent (2006 and 2007) presentations at National Society Meetings-(146 and 110, respectively) and presentations at International Society Meetings (25 and 15, respectively).

This scientific acumen is also shared with the broader risk assessment community through numerous publications [(2002-2007)-Peer –Review Journal (365), Books and Book Chapters (43), EPA Technical Reports (91)].

Evidence of the recognition of HHRA program's leadership is also exemplified by number of Agency Award (2002-2007) for HHRA staff.

Gold 5

Silver 9

Bronze 64

Scientific and Technological Achievement Awards (STAA) 15

Superior Accomplishments/Performance Awards 82

Administrator Award for Excellence 5

President's Award for Meritorious Service 3

What is the HHRA program currently doing?

Research under HHRA program is addressing the following major areas along the source to outcome continuum.

(1) **Approaches for Assessing Environmental Exposures:** Exposure work is done by the HHRA program in support of the needs of multiple risk assessors across EPA and States, with particular focus on information for which there are multiple clients such that a common centralized database or approach is of the greatest value. The HHRA program has developed targeted state-of-the-science exposure methods and provided critically important exposure factors data used in innumerable risk assessments.

(2) **Internal dose and Physiologically-based pharmacokinetic (PBPK) modeling:** More complex chemical assessments conducted under the HHRA program frequently include evaluation of PBPK models. This includes evaluation of how differences in metabolism affect risk estimation, either in considering when data is available from only one route-of-exposure, to evaluate if PBPK explains differences across species, and for high-to-low-dose extrapolation. The HHRA program is at the forefront of advancing and applying these methods, which results in reduced uncertainty in extrapolations and quantitative risk estimation.

(3) **Hazard Characterization:** Hazard characterization efforts include identifying likely human health effects to a chemical including consideration of susceptible populations (e.g., lifestage and genetic predisposition) and use of mode of action (MOA) in risk assessment. MOA efforts include applying available data to better inform decisions on the relevance of high dose effects to low level environmental exposures, within and between species, impact on susceptible populations (e.g., lifestage and genetic predisposition) and the quantitative impacts of these factors on dose-response functions used in risk assessment. As demonstrated in many IRIS assessments, the HHRA program has a leadership role in evaluating newest scientific data on MOA and using the insights gained to directly support qualitative and quantitative risk assessments.

(4) **Dose-Response Analysis:** Quantitatively relating exposure or dose to likely effect has received increased interest for nongenotoxic modes of action. There is a renewed need to consider appropriate dose-response models in the range of observed data and the underlying reasons for the default linear low-dose extrapolation for carcinogens and potential alternatives to that. The HHRA program is responding to that need by activities such as including efforts to evaluate low-dose extrapolation/biologically-based dose response models and through the development of versions of existing dose-response models that can take into account potential additivity to background doses or background processes.

(5) **Risk Characterization:** Quantitative analysis of uncertainty, derivation of central estimates and confidence limits on estimates of risk is another need driven in part by those who wish to use risk assessment results in the context of formal decision analysis or in cost-benefit analysis. These efforts also inform the relationship between adverse outcomes and the impact of environmentally-induced burden of disease on human health. The HHRA program has developed new ways to transparently represent uncertainty with numerous new assessments presenting creative approaches to qualitative and quantitatively represent uncertainty, thereby improving the understanding of risk assessments by the user community.

What research should be done in future years, and what are the critical paths to getting there?

The HHRA MYP includes in FY'09 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 exposure levels. In fiscal years FY10 to 12 activities of this MYP are directed toward developing guidance, integrating findings and synthesizing the risk assessment advances accomplished under this HHRA program 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.

Why is ORD the right place to do this research (our niche), and how will we collaborate with/complement the work of others?

ORD is the right place to do develop methods and create state-of-the-science health risk assessments because we can capitalize on lessons learned from assessments activities and feed that back through our research planning and implementation to improve the scientific basis for future assessments. The HHRA 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 in support of regulatory decision-making. The IRIS, ISA and other assessments are directly responsive to program needs and are primary considerations in Agency actions to protect human health and the environment. A key advantage of HHRA program is that the experience in developing health assessments and synthesizing and integrating data for methods, models and guidance for the agency results in the identification of data gaps, data needs and priority research needs to reduce or better characterize existing science assessments. These include methods, models and refinement of existing tools. NCEA communicates these needs to partners within ORD, and to outside collaborators, and develops collaborations on priority areas.

The HHRA program encourages close relationships with other parts of ORD, 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 within ORD and other federal agencies conducting primary environmental health research, particularly NHEERL and NERL, and 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. 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).

Performance: Making a Difference

HHRA program has designed ambitious performance measures into the program. These performance measures are described in the performance facts sheet section of the background material. Since the initiation of the program there has been significant progress in completing annual performance measures. This progress can be seen across all 3 long-term goals since 2004 where annual performance was at it lowest for LTG3. Since 2004, a revised multiyear plan, significant redirection of resources and management oversight has provided assurance that we complete our products in timely fashion and produce outputs that make a difference. The program now operates at or near 100% completion for annual measures and is making significant progress on completing long-term measures of success (see performance factsheet).

What are our planned research products?

The HHRA Program has numerous outputs under 3 long-term goals (LTG)s. In 2008 LTG 1 is on schedule to deliver 16 Integrated Risk Information System (IRIS) assessments to interagency or independent external peer review, to complete 50 new or revised Provisional Peer Reviewed Toxicity Values (PPRTVs), and to post 6 final IRIS Health assessment documents.

In 2008, efforts under LTG 2 will result in a posting of a final Exposure Factors Handbook for Children to reduce uncertainty in exposure assessments, release an external review draft of improvements to BMD software enabling extrapolation across exposure durations and evaluation of peak responses as a function of exposure magnitude and/or duration, publish information regarding analysis of the sensitivity and uncertainty in 2-stage clonal growth models for formaldehyde with relevance to other biologically-based dose response models and post on website a report summarizing findings from workshop on uncertainty and variability in PBPK models including case example approaches for chemical-specific analyses (TCE applications).

In 2008, efforts under LTG 3 the first Integrated Science Assessments for Nitrogen Oxide and Sulfur Oxides will be finalized under the newly implemented process in support of NAAQS.

How will our clients—the programs, regions, and others—use our research?

Beyond EPA, **HHRA products are widely recognized as the principal environmental health risk assessment benchmarks in the United States**, exemplified by the IRIS outputs, ISAs, and guidance documents. Although non-regulatory and non-binding in nature, these health assessment products and the scientific analyses therein are referenced in many federal, state, local, and stakeholder environmental decisions.

How will the results of our research contribute to environmental outcomes that protect human health and safeguard the environment?

ORD's science 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 independent 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).

ISAs have been prepared by NCEA or its predecessors since the creation of the EPA in early 1970s. ISAs 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 AQCDs for Airborne Particulate Matter, Ozone, and Lead were finalized in 2004, 2006, and 2007, respectively before the new ISA process was implemented. The NO_x and SO_x ISAs are being developed utilizing new procedures and are scheduled for finalization in 2008. Through the preparation of ISAs, 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.