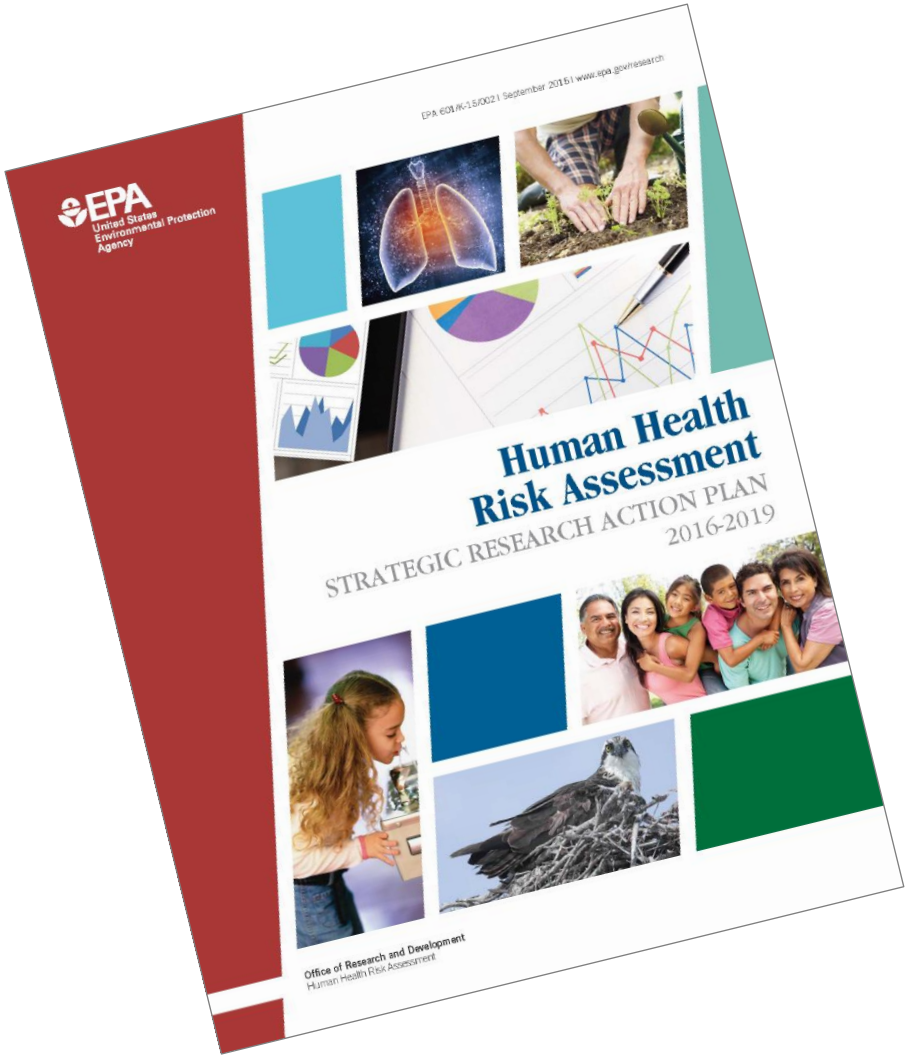

United States

Environmental Protection Agency

Board of Scientific Counselors (BOSC)

Subcommittee

Review

October 6 – 8, 2015

EPA campus

Research Triangle Park, NC

Human Health Risk Assessment (HHRA)

National Research Program

FY16 – 19

Project Plans

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See Appendix for HHRA Topic, Project and Task leads

Human Health Risk Assessment

Project Plans

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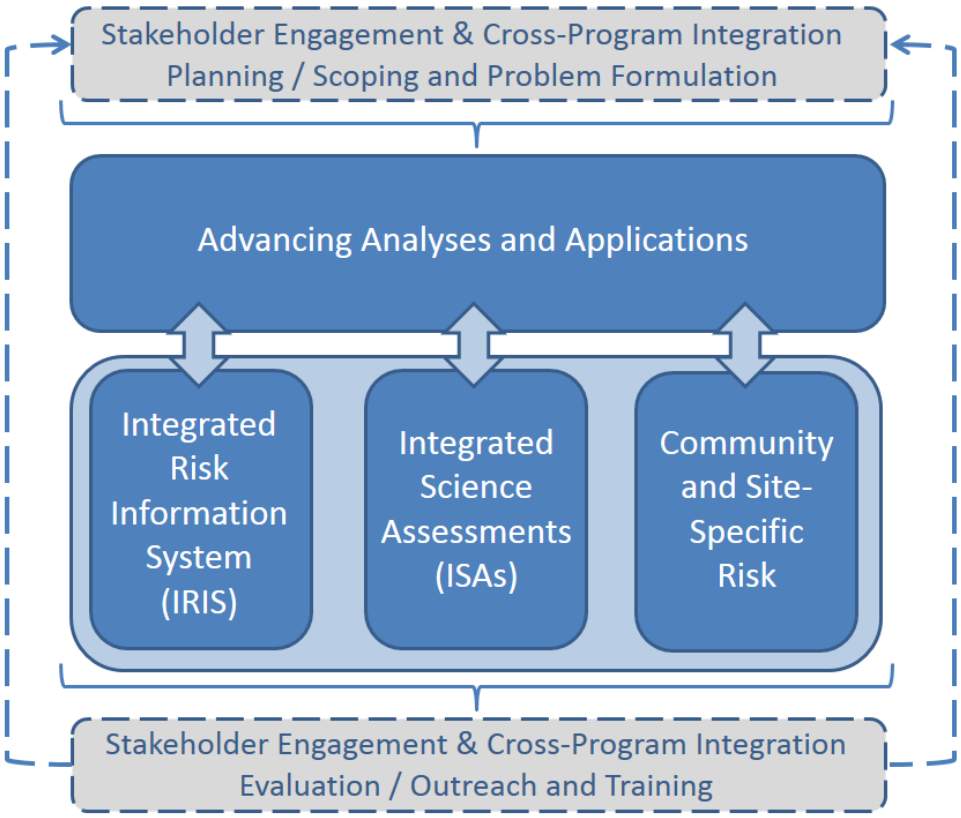
Disclaimer: the views expressed in the following Project Plans are those of the authors and do not necessarily represent the views or policies of the Environmental Protection Agency. The Project Charters and Tasks represent proposed work; the extent to which specific Task and Subtask work is conducted in dependent on budget availability and program priorities.



HHRA program structure (above) and
Relationship among objectives / topics / projects (below)
Red outline denotes focus of BOSC review

Objectives	Topics	Projects
Characterize risks with a portfolio of tailored assessment products	Integrated Risk Information System (IRIS)	1. IRIS Assessments 2. IRIS Update
	Integrated Science Assessments (ISA)	3. ISAs and Scientific/Regulatory Support
Advance new applications and refine risk assessment approaches	Community and Site-specific Risk	4. PPRTV Assessments 5. Site-specific and Superfund Regulatory Support 6. Cumulative Risk Assessment Methods and Applications
Enhance data access and engage stakeholders to support decision making	Advancing Analyses and Applications	7. Advancing Hazard Characterization and Dose-Response Methods 8. Applying Emerging Science to Inform Risk Screening and Assessment 9. Risk Assessment Support and Training

Human Health Risk Assessment (HHRA)

Project Planning Tool

Project Plan

HHRA Project 5 (*RMS ID# HHRA 3.22*): Site-specific and Superfund Regulatory Support

Project Lead (PL): Teresa Shannon (NCEA CIN)

Project Development Team Members: J. Phillip Kaiser (NCEA CIN), Linda Phillips (NCEA W), George Woodall (NCEA RTP)

Project start date: 10/01/2015

Project end date: 09/30/2019

Executive Summary

The HHRA program provides technical support and consultation on both human health and ecological risk assessment to support the Agency and other external stakeholders. The HHRA program supports two of the five EPA technical support centers: the Superfund Technical Support Center (STSC) and the Ecological Risk Assessment Support Center (ERASC)[1]. In addition to support provided via these two technical centers, the HHRA program is often requested to provide technical support and consultations in emergent situations and to address newly arisen Agency priorities. The HHRA program provides direct support to the Homeland Security "Reachback" response program and responds to emerging, often crisis-level, chemical/substance issues with sound science that allows for quick action and, ultimately, quick decisions and effective solutions. HHRA scientists anticipate these types of activities to continue and are developing tools and approaches that will increase readiness to respond efficiently when requests are received.

[1] The other three technical support centers, the Ground Water Technical Support Center (GWTSC); the Engineering Technical Support Center (ETSC); and the Site Characterization and Monitoring Technical Support Center (SCMTSC), are supported by ORD's Sustainable and Health Communities (SHC) research program.

Research Project Description

The HHRA program is often asked to provide its expertise and devote its resources to help with emergent situations such as the Deepwater Horizon Gulf Oil spill or that arise unexpectedly when a new contamination is discovered in a community due to changes in detection capabilities. Communities are also faced with an urgent need for coordinated assistance to assess and address issues of chemical and other environmental contamination, and additionally may now be presented with new sensing or monitoring information that is difficult to interpret. EPA's HHRA program is frequently called upon to quickly assist in these situations, often in the face of large scientific uncertainties due to data gaps. Additionally, the Agency is often tasked to respond on other high-priority problems requiring exposure, human health or ecological risk assessment expertise. HHRA scientists frequently provide technical support, consultation, and review of Superfund and other Agency priorities as a result of "over the transom" requests for assistance or via requests to contribute to high-profile working groups. The HHRA program has constructed this project to respond effectively and rapidly to such requests and is devoted to developing capacities such as databases and visualization tools to further increase its capacity lend anticipated support.

Project Impact

HHRA exposure, human health, and ecological risk assessors serve as an Agency resource and respond to requests by providing evaluations and estimates that serve to guide clean-up criteria and management. Such requests frequently occur and some recent examples (in 2014-2015) of HHRA technical support and consultations include the following responses:

- Response to spill of crude 4-methylcyclohexanemethanol (MCHM) into the Elk River in Charleston, WV.
    - Scientists in the HHRA program input on the drinking water health advisory issued by the Centers for Disease Control to address the spill, and also derived an inhalation screening level. Both assessments supported emergency response actions and guided remediation.
- Request from EPA Region 2 regarding the Reich Farms Superfund site in Toms River, NJ after a higher-than-expected incidence of childhood cancers was found at the location that raised community concerns
    - HHRA scientists developed a Provisional Peer-Reviewed Toxicity Value (PPRTV) assessment for Styrene-Acrylonitrile (SAN) Trimer and subsequently participated in a community meeting on the final risk-based clean-up decision for SAN Trimer (to protect both children and adults) based on the provisional reference dose.
- Request from the NC Division of Water Resources regarding the use of surrogate chemicals
    - HHRA in the assessment of ρ-toluic acid that enabled them to establish new groundwater standards.
- Gold King mine spill in Colorado

- HHRA scientists provided advise to the EPA Science Advisory and helped those in Region 8 respond with human health risk screening criteria

Such technical support is provided on an as-needed basis and varies with regard to nature and complexity of the request.

Project Scope

Project 5 is designed to support the range of requests that the HHRA research program receives for technical support and consultations, as well as position the program to more efficiently respond and anticipate programmatic needs regarding alternative risk assessments or those based on different sources of available data.

Project Structure and Rationale

The types of technical support and consultations on risk assessment products and practices that the HHRA program provides are addressed by the following two tasks which comprise Project 5 (*RMS ID# HHRA 3.222*):

- **Task 5.1 (*RMS ID# HHRA 3.221)* Quarterly Reports to Superfund Technical Support Center (STSC) and Ecological Risk Assessment Support Center (ERASC)**

- **Task 5.2. (*RMS ID# HHRA 3.222*) Technical Support, Consultation and Review for Superfund and other Agency Priorities**

The first task represents the on-going support to the technical centers and typically entails technical consultation on existing assessments or their applications (e.g., clarification on the derivation, interpretation, and application of a PPRTV assessment) or may require *de novo* development or evaluation of an assessment product. Reports on specific topics may also be developed based on partner or stakeholder needs.

The second task provides for responses to the various types of requests that the HHRA program receives for technical support and consultation regarding emergent situations and to address newly arisen Agency priorities. These include a range of activities such as the following: rapid response to spills via direct support to the Homeland Security research program, serving on working groups, specific requested assessments of exposures, or health and ecological impacts, and providing technical oversight or expertise to RARE or other Agency initiatives.

The HHRA program is devoted to developing approaches to respond effectively and rapidly to such requests by developing visualization tools and approaches that will increase readiness to respond efficiently when requests are received. The HHRA program also anticipates developing new assessment approaches by means of an expanded product line to enhance rapid response and screening capabilities and to augment toxicity value derivation procedures for health assessments.

Measures of success

We expect to maintain the high standards of timely expert support in response to Agency priorities, emergent situations and as needed by the EPA STSC and ERASC, and implement improvements or develop visualization and data tools that increase the efficiency and capacity to perform these duties.

Stakeholders (outside ORD)

The technical support and scientific consultations provided by the HHRA program enhance the understanding and application of risk assessment to inform risk-based decisions regarding management of high-profile, often emergency situations, benefitting Agency program offices, regions and communities effected by spills or other contaminations. Such support also provides transparency, technology transfer and translation to build capacity for performing risk assessments or utilizing HHRA assessment products to protect the public health.

Task 5.1

(*RMS ID# 3.221*)

Quarterly Reports to Superfund Technical Support Center (STSC) and Ecological Risk Assessment Support Center (ERASC)

Task Lead (TL): Teresa Shannon (NCEA CIN)

Task Start Date: 10/01/2015

Task End Date: 09/30/2019

Task Description:

Quarterly reports are completed for each of the two technical support centers for which the HHRA program has main responsibility: the Superfund Technical Support Center (STSC) and the Ecological Risk Assessment Support Center (ERASC). Reports are developed and delivered to be compiled into one master quarterly report covering the activities of all five of the ORD technical support centers. The reports serve as an important resource to keep OSWER and the regional risk assessors apprised of activities, developments, and applications with respect to assessments and other technical advice and evaluation. As such they aid efficiency, consistency and communication of assessment information.

Research Approach:

Data on requests for support are compiled and distributed to EPA Regions, OSWER, ORD, and other interested groups.

Task Constraints:

- Possible constraints due to working across all five of the centers to compile accurate and complete information for the reports.

Task Dependencies:

- **Dependency:** Requires human and financial resources

Task Quality Assurance and Data Management Needs:

- Is there an existing IRP/ QAPP(s) that applies to this Task? If so, identify IRP/QAPP. If new IRP/QAPPs are required, provide the status.
  - Yes. NCEA-16-00003: Program Quality Assurance Project Plan (PQAPP) for the Superfund Health Risk Technical Support Center (STSC) and Ecological Risk Assessment Support Center (ERASC).

- Will this Task involve large amounts of data that need a data management plan
  - TBD. The Health and Environmental Research Online (HERO) system is used for systematic literature review and is covered by a separate QAPP: NCEA-16-00005. Quality Assurance Project Plan (QAPP) For Extraction of Scientific Data Into the Health and Environmental Research Online (HERO) Database System.

Task Products:

- **Product 5.2.1 (*RMS ID# HHRA 3.221.1*).**
- **Product Title – Technical Support Centers Summary Report**
- Product Contact (email) – shannon.teresa@epa.gov
- Product's Delivery Date – Quarterly
- Product Description – Report of requests for assistance
- Product's Contribution to Output – Demonstrates ORD support for OSWER, Regional risk assessors, and other stakeholders
- Product's Timeline (with milestones) – delivered quarterly to OSWER
- Product's intended user/customer/audience – ORD IO, OSWER, Regional risk assessors, and other stakeholders
- Is this a key product? Yes
- Does this Product contribute to a Product under another Task? No. An exception would be made if a Region requests the development of a PPRTV (Project 4). This request would be discussed with the Program Office and prioritized with the other chemicals requested.

Task 5.2

(*RMS ID# HHRA 3.222*)

Technical support, consultation, and review for Superfund and other Agency priorities

Task Leads (TLs): J. Phillip Kaiser (NCEA Cin) and Linda Phillips (NCEA W)

Task Start Date: 10/01/2015

Task End Date: 09/30/2019

Task Description:

This task addresses the on-going work that the HHRA program provides in support of the Superfund Technical Support Center (STSC) and the Ecological Risk Assessment Support Center (ERASC). This work entails answering requests for assistance that comes into those centers, and can entail technical consultation on existing assessments or their applications (e.g., clarification on the derivation, interpretation, and application of a PPRTV assessment) or may require *de novo* development or evaluation of an assessment product. Reports on specific topics may also be developed based on partner or stakeholder needs. In addition, the HHRA program is often requested to provide technical support and consultations in emergent situations and to address newly arisen Agency priorities. The HHRA program provides such support on emergency contamination situation directly to the Office of Research and Development's Reachback for Emergency Response (RACER) Program (Homeland Security Research Action Plan). The HHRA program develops approaches to respond to these emerging, often crisis-level, chemical/substance issues with sound science that allows for quick action and, ultimately, quick decisions and effective solutions. A third area captured under this task includes the on-going support and technical consultations, including visualization tools and comparisons of existing reference values, provided in an on-going basis to Agency program offices upon request.

These three general areas of support will be described in subtasks as follows:

Subtask 5.2.1 (*IRMS ID# HHRA 3.222.1*): STSC and ERASC Support

The Superfund Health Risk Technical Support Center (STSC) provides technical assistance to Regional Remedial Project Managers (RPM) and on-site Coordinators of the Superfund Program. The STSC performs three general functions to support the Superfund Program:

- Preparation and distribution of Provisional Peer-Reviewed Toxicity Value (PPRTV) assessments. The development of the PPRTVs occurs via Task 4.1 (*RMS ID# HHRA 3.221*).
- Scientific/technical consultations in support of United States Environmental Protection Agency (U.S. EPA) regional scientists and associates.
- Support for the interpretation of U.S. EPA publications and other guidance, including but not limited to the Risk Assessment Guidance for Superfund (RAGS) Volume I, the Human Health Evaluation Manual (Part A), and the Health Effects Assessment Summary Tables (HEAST).
- Prepared quarterly status reports on STSC and ERASC regional requests to inform senior leadership in the Program Office and Regions.

Examples of additional or specific services include but are not limited to:

- Research and compile available toxicity information from Tier 1, 2, and 3 sources. The toxicity values themselves are not compiled, but hyperlinks to the source reference materials are provided when possible.
- Offer recommendations to help identify preferred Tier 3 sources of toxicity values.
- Perform analyses to identify potential surrogate toxicity values following established STSC methodologies (see Wang et al., *Regul. Toxicol. Pharmacol.* 63:10-19, 2012)
- Offer recommendations and analyses regarding bioconcentration factors.

This support is provided on an as-needed basis and varies with regard to nature and complexity of the request. As a result, NCEA cannot easily predict or develop specific plans for the kind of technical support.

Subtask 5.2.2 (*RMS ID# HHRA 3.222.2*). Rapid Exposure and Risk Assessment Support

The HHRA program is often asked to provide its expertise and devote its resources to help with emergent situations such as the Deepwater Horizon Gulf Oil spill or that arise unexpectedly when a new contamination is discovered in a community due to changes in detection capabilities. Additionally, the Agency is often tasked to respond on other high-priority problems requiring assessment expertise. HHRA exposure assessors often provide technical support, consultation, and review of Superfund and other Agency priorities as a result of “over the transom” requests for assistance. High impact requests are frequently coordinated through the RACER program, to tap into EPA expert capabilities, and this subtask is where such NCEA response activities are located.

Past examples of support on exposure assessment include: comprehensive exposure and risk assessment support following the collapse of the World Trade Center Towers, critical review of the Dow Midland dioxin site, development of a PCB Exposure Estimation Tool for estimating exposures and Public Health Levels for air in schools, and exposure assessment support for the Deepwater Horizon Gulf oil spill.

HHRA human health and ecological risk assessors similarly served as an Agency resource and respond to requests by providing evaluations and estimates that serve to guide clean-up criteria and management. Recent examples (in 2014-2015) include response to the spill of crude 4-methylcyclohexanemethanol (MCHM) into the Elk River in Charleston, WV. Scientists in the HHRA program input on the drinking water health advisory issued by the Centers for Disease Control to address the spill, and also derived an

inhalation screening level. Both assessments supported emergency response actions and guided remediation. HHRA scientists also assisted EPA Region 2 at the Reich Farms Superfund site in Toms River, NJ. HHRA scientists developed a Provisional Peer-Reviewed Toxicity Value (PPRTV) assessment for Styrene-Acrylonitrile (SAN) Trimer and subsequently participated in a community meeting on the final risk-based clean-up decision for SAN Trimer (to protect both children and adults) based on the provisional reference dose. HHRA scientists provided an analysis to a request from the NC Division of Water Resources regarding the use of surrogate chemicals in the assessment of ρ-toluic acid that enabled them to establish new groundwater standards. Most recently, HHRA scientists helped those in Region 8 respond with human health and ecological risk screening criteria in response to the Gold King mine spill in Colorado.

Such technical support is provided on an as-needed basis and varies with regard to nature and complexity of the request. As a result, it is not easy to predict or develop specific plans for the kind of technical support. However, it is important to plan a placeholder and call attention to the potential for significant impact on resources and competing priorities.

Subtask 5.2.3 (*RMS ID# 3.222.3*): Technical Support and Consultation to Program Office Needs

A portion of the support HHRA provides to Program Offices is in the form of recommendations for acceptable levels of exposure to a contaminant. The most desirable advice is in the form of a health effect reference value, such as the IRIS values (RfD, RfC, CSF or IUR) or a regulatory standard (NAAQS, MCL). When those types of values are not readily available or have become suspected of being out of date (e.g., petition comments suggest alternative benchmark values), HHRA Staff may be asked to provide recommendations for alternative values to use in support of regulatory activities across the agency, including the Risk and Technology Reviews (RTRs) for the Office of Air Quality Planning and Standards (OAQPS). The purpose of this subtask is to provide some ready summaries of the available information for those chemicals which are known to be of high interest to the Program Offices, and to develop capacity for derivation of similar types of summaries on short-notice quickly, efficiently and consistently.

Research Approach:

The approach to provide technical support and consultation for each of the three main categories represented by the subtasks will be pursued as follows:

Subtask 5.2.1 (*IRMS ID# HHRA 3.222.1*): STSC and ERASC Support

The approach taken will be dictated by the needs, as they arise. Regarding the STSC, there are currently no projects that are anticipated to overlap into Fiscal year 2016. STSC and ERASC will continue to develop and distribute quarterly report to the Program and Regional Offices.

Subtask 5.2.2 (*IRMS ID# 3.222.2*): Rapid Exposure and Risk Assessment Support

The approach taken will be dictated by the needs, as they arise. NCEA including other ORD organization often support regional projects through technical oversight, review, contract management, data interpretation, write-ups and presentation. General overviews of ongoing products to provide technical support and consultation for exposure issues are as follows:

RARE project on sampling methods for PCBs in indoor air

A Regional Applied Research Effort (RARE) project titled, "Side-by-Side Performance of Passive and Active Air Sampling Methods for PCBs in Indoor Environments" began in FY15. This project has been funded and is being conducted by Region 2, with ORD support in the way of technical input, study design, and data interpretation and dissemination. As well, an HHRA scientist is serving as the Contracting Officer's Representative (COR) to the contractor conducting the sampling. The goal of this project is to evaluate the potential use of passive air samplers to quantify air concentrations of PCBs within schools. These samplers are much less costly and intrusive than active air monitors (which require machinery and electricity, and produce substantial noise in the process of obtaining large volumes of air). Briefly, both monitoring procedures will be running side-by-side and the results from both compared. The active air monitoring procedures are well developed and expected to represent the "actual" air concentrations of PCBs and the question is how well the passive air samplers, which do not include machinery to draw in volumes of air and require many days of passive collection of PCBs in air, match these actual concentrations. The project is expected to conclude in FY16 and final products include a report and one or more peer-reviewed journal articles in FY17.

Workgroup Support

The HHRA program provides scientific support through its participation on technical workgroups aimed at addressing specific exposure and risk assessment needs. HHRA scientists are currently participating on several of these workgroups (e.g., PCBs on indoor surfaces, dioxins and PAH bioavailability in soil). The PCB Science Workgroup is currently exploring the feasibility of developing Exposure Levels for Evaluating (ELE) PCBs on indoor school surfaces that are protective of human health. The Bioavailability Workgroup: Dioxin/PAH Subcommittee is charged to identify, review and validate new methods for assessing bioavailability of dioxins and PAHs, and to develop guidance on how to use bioavailability assessments in human health risk assessments. As noted above, HHRA exposure assessors have also participated in workgroups related to the review of studies involving fish consumption.

Technical Support for the PCBs in Schools and Other Sites

The PCB Exposure Estimation Tool in 2009/2010 in response to a request from OPPT. The Tool provides estimates of exposure for non-school and school exposure pathways (dietary, indoor and outdoor air, soil and dust ingestion and dermal contact). It also calculates maximum PCB levels that could be present in indoor air with exceeding the RfD for PCBs, given background exposures from other pathways. The Tool was used to develop the Public Health Levels for PCBs in Indoor School Air (renamed Exposure Levels for Evaluation of PCBs in Indoor School Air) that are posted on OPPT's website. The HHRA program continues to provide support to OPPT and the regions for updates to the Tool and other issues pertaining to development and use of the Tool.

Review of Guidance and Protocols for Fish Consumption Studies

The HHRA program provides technical support for the development of guidance and protocols of fish consumption studies to EPA program offices and regions, and State agencies, on an 'as needed' basis. For example, HHRA scientists reviewed "Guidance for Conducting Fish Consumption Surveys" for the Office of Water, and a study protocol and survey instrument for the Idaho Fish Consumption Survey and Region 10. Study design reports for estimating fish consumption among various Native American tribes (i.e., Sho Pai, Kootenai, Nez Perce, Shoshone Bannock, Coeur D'Alene) were also reviewed for EPA Region 10, and HHRA scientists have participated in discussions on issues such as fish consumption suppression among Native American tribes. The Office of Water has also requested technical support for the review of "Estimated Fish Consumption Rates for the US Population and Selected Subpopulations (NHANES 2003-2010)." The HHRA program anticipates continued support to the Office of Water, EPA Regions, and states to better refine fish consumption rates for use in exposure and risk assessment.

Dioxin Sources Inventory

The Inventory of Sources of Dioxin-Like Compounds (abbreviated the Inventory) was developed between the mid-1990s and was published in final form in 2006. However, due to concerns raised by the 2005 Peer Review Panel who reviewed the External Review Draft (ERD) of the Inventory, efforts have continued to provide an updated Final Inventory. Another ERD was released for public and Peer Review Panel review in 2013. Efforts are now underway to finalize the Inventory with publication planned for FY '16. Finalization will include a Final Report, an Excel Workbook of the Inventory to be posted along with the Final Report, and a journal manuscript on the Inventory.

Subtask 5.2.3 (*RMS ID# 3.222.3*): Technical Support and Consultation to Program Office Needs

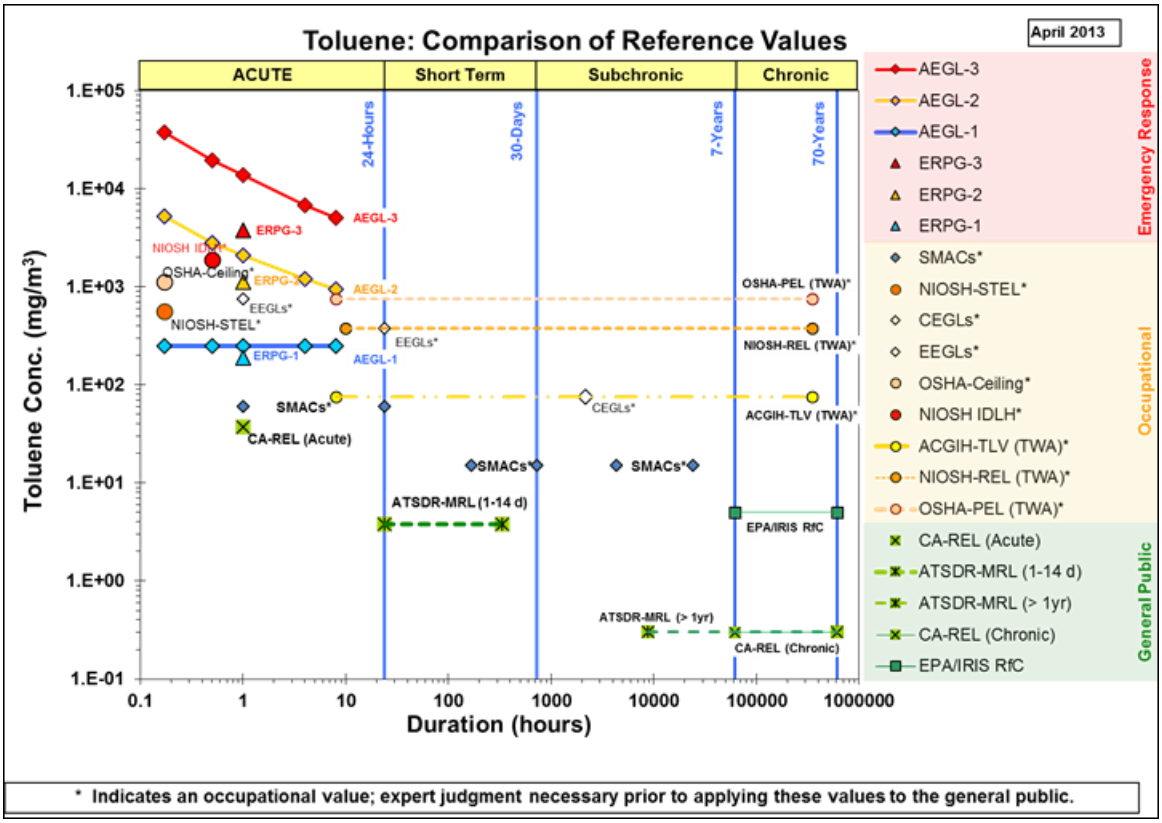
ORD/OSP and HHRA staff have most recently been assisting OAQPS to develop the criteria to allow them to judge the relative merits of the various procedures and methods used by outside organizations (i.e., other health agencies, states, or international health organizations) to produce reference values. A second set of criteria to judge the relative merits of the available reference values for a specific chemical and specific purpose have also been proposed. A review panel consisting of members from various other EPA Program and Regional Offices, ORD, and the OAQPS have been deliberating on these criteria. The recommendations from this panel may prove useful to HHRA in the efforts proposed in this Subtask.

Many of the comments on regulatory proposals presented by the Program Offices typically challenge the reference values they have chosen (most often an IRIS value if one is available) and propose the use of an alternative which was developed differently or more recently. Most often, HHRA staff called upon to assist in providing a response to these petitioner comments is performed in an *ad hoc* manner. An activity proposed in this subtask is to develop a process whereby HHRA is kept aware of the developments regarding updates to reference values being developed by these other reputable organizations. In doing so, HHRA will be better prepared to provide informed recommendations most quickly and with less urgency.

Reference Value Arrays – These graphical arrays help to communicate the options for health effect reference values available to use in a risk assessment. The initial examples were developed to support the work done for the draft *Cleanup Decision-Making Guidance for Chemical Incidents* document which was designed to provide a blueprint for recovery following a major incident involving toxic chemical releases, such as a terrorist event (e.g., September 11, 2001). This effort was overseen by the Subcommittee for Decontamination Standards and Technologies (SDST) which was convened under the auspices of the White House Office of Science and Technology Policy (OSTP).

As these arrays were shared among risk assessment colleagues, their utility in other applications became apparent. A workshop among a number of stakeholders was convened in 2008 to gather input on developing consistent formats, develop standards for presentation and otherwise improve the usefulness of these displays. An EPA report was published in 2009 comparing the available reference values for 24 chemicals (EPA/600/R-09/061; http://cfpub.epa.gov/ncea/cfm/recordisplay.cfm?deid=211003). Many of the chemicals included in the

2009 EPA report are also hazardous air pollutants and this document has proven useful in RTR risk assessments when a preferred reference values may not be available (typical in RTR). A separate series of EPA reports for the chemicals benzene, ethylbenzene, toluene, xylene, and manganese were published in 2013 (EPA/600/R-12/047F [1-5]; http://cfpub.epa.gov/ncea/cfm/recordisplay.cfm?deid=250571) which were largely developed in anticipation of the need for them in upcoming RTR risk assessments. An example array for toluene is shown below along with the accompanying table with derivation details for the reference value included in the document available by following this link: http://oaspub.epa.gov/eims/eimscomm.getfile?p_download_id=512650.



Task Constraints:

Subtask 5.2.1 (*IRMS ID# HHRA 3.222.1*): In the past, a few requests have come through the STSC concerning scientific areas for which NCEA scientists do not have expertise. In those instances, the STSC will locate qualified staff outside of NCEA with the necessary expertise to provide technical assistance to the requestor.

Subtask 5.2.2 (*IRMS ID# HHRA 3.222.2*): The task requires general and chemical-specific expertise on exposure and risk assessment, and proper certifications for contract and/or grant administration.

Subtask 5.2.3 (*IRMS ID# HHRA 3.222.3*): The task requires general and chemical- specific expertise on the derivation procedures used for health risk reference values including science policy across agencies (e.g., application of uncertainty factors), and proper certifications for contract and/or grant administration.

Task Dependencies:

Subtask 5.2.1 (*RMS ID# HHRA 3.222.1*): This task is currently planned to be addressed with NCEA personnel; no extramural funding is currently allocated.

Subtask 5.2.2 (*RMS ID# HHRA 3.222.2*): This task is currently planned to be addressed with NCEA personnel; no extramural funding is currently allocated.

Subtask 5.2.3 (*RMS ID# HHRA 3.222.3*): Most of the effort for this task will be performed by NCEA personnel with additional support anticipated from ORISE Student Fellows and/or Student Services Contractors. Extramural funding is anticipated for letter peer reviews of completed Reference Value Arrays and Derivation Tables prior to posting and use in regulatory decisions.

Task Quality Assurance and Data Management Needs:

Subtask 5.2.1 (*RMS ID# HHRA 3.222.1*):

- Is there an existing IRP/ QAPP(s) that applies to this Task? If so, identify IRP/QAPP. If new IRP/QAPPs are required, provide the status.
    - Yes. NCEA-16-00003: Program Quality Assurance Project Plan (PQAPP) for the Superfund Health Risk Technical Support Center (STSC) and Ecological Risk Assessment Support Center (ERASC)

- Will this Task involve large amounts of data that need a data management plan? If yes, explain.
    - TBD on specific basis of specific response.

Subtask 5.2.2 (*RMS ID# HHRA 3.222.2*):

- Is there an existing IRP/ QAPP(s) that applies to this Task? If so, identify IRP/QAPP. If new IRP/QAPPs are required, provide the status.
    - NCEA-16-00003: Program Quality Assurance Project Plan (PQAPP) for the Superfund Health Risk Technical Support Center (STSC) and Ecological Risk Assessment Support Center (ERASC).

- Will this Task involve large amounts of data that need a data management plan? If yes, explain.
    - Certain products may lead to the generation of data and may need data management plans. It is not expected that the RARE project will require a specific data management plan.

Subtask 5.2.3. (*RMS ID# HHRA 3.222.3*):

- Is there an existing IRP/ QAPP(s) that applies to this Task? If so, identify IRP/QAPP. If new IRP/QAPPs are required, provide the status.

    - NCEA-16-00003: Program Quality Assurance Project Plan (PQAPP) for the Superfund Health Risk Technical Support Center (STSC) and Ecological Risk Assessment Support Center (ERASC).

- Will this Task involve large amounts of data that need a data management plan? If yes, explain.

    - Data will be managed through database and data analysis products being developed in Task 9.1 Subtask 9.1.8. (RMS ID# HHRA 4.231.8): Data Management and Visualization Tools (DMVT) for Risk Assessment

Task Products:

Subtask 5.2.1 (*IRMS ID# HHRA 3.222.1*): STSC and ERASC Support

Because the support is provided on an as-needed basis and varies with regard to nature and complexity of the request, it is not possible to speculate on the types of products that will be delivered in the upcoming years. Products may include but are not limited to PPRTV development, White Papers or EPA documents. For FY12-14, STSC received on average 42 requests per year. As request arise they will be captured under 5.1 in the quarterly reports to the Program Office and Regions.

Subtask 5.2.2 (*RMS ID# HHRA 3.222.2*). Rapid Exposure and Risk Assessment Support

- **Product: 5.2.2.1 (*RMS ID# HHRA 3.222.2.1*)**
- **Product Title: RARE project on Indoor Air Concentrations of PCBs (*"Side-by-Side Performance of Passive and Active Air Sampling Methods for PCBs in Indoor Environments"*)**
- Product Contact (email): lorber.matthew@epa.gov
- Product's Delivery Date: A final report on the project is expected Q4FY '16, and one or more peer review journal articles due in Q1 or Q2 FY '17;
- Product Description: The final report, containing the data generated for the project, is the primary product for this Subtask.
- Product's Contribution to Output:
- Product's Timeline (with milestones): This final report is expected to be available for Internal Review by Q3 FY16, and as noted, will be finalized by Q4 FY16. One or more journal articles should be available for internal review by Q1 FY16 and submitted for publication by Q3 FY16.
- Product's intended user/customer/audience: Given concerns with elevated levels of PCBs found in schools and schoolchildren exposure, this project has a great potential for use should the passive sampling show an acceptable reliability for characterizing air concentrations. As noted, this method is very inexpensive and unobtrusive. As such, the primary users of the information generated in this project will be schools and those responsible for health and safety of schoolchildren. The project also represents HHRA support to the RARE program and regional risk assessors.
- Is this a key product? No
- Does this Product contribute to a Product under another Task? If so, identify other Task.
  No.

- **Product: 5.2.2.2 (*RMS ID# HHRA 3.222.2.2*)**
- **Product Title: HHRA Support to Agency Working Groups**
- Product Contact (email): phillips.linda@epa.gov
- Product's Delivery Date: Various; The PCB Science Workgroup will brief the PCB Steering Committee on its efforts to develop ELEs for PCBs on Indoor School Surfaces in Q1FY16; further efforts will depend on requests by the Steering Committee
- Product Description: Varies depending on need; The PCB Science Workgroup has prepared a memo with its recommendations for surface ELEs for PCBs, and a Q&A document.
- Product's Contribution to Output: No
- Product's Timeline (with milestones): As needed
- Product's intended user/customer/audience: Depends on requestor and topic.
- Is this a key product? No
- Does this Product contribute to a Product under another Task? If so, identify other Task. Yes, some workgroup efforts will contribute to other Tasks (e.g., Soil Ingestion Workgroup will contribute to Task 8.4 (*Evaluation and application of new exposure data and methods*).

- **Product: 5.2.2.3 (*RMS ID# HHRA 3.222.2.3*)**
- **Product Title: Technical Support for the PCBs in Schools and Other Sites**
- Product Contact (email): phillips.linda@epa.gov
- Product's Delivery Date: various
- Product Description: Updates to the PCB Exposure Estimation Tool, assisting OPPT with developing/revising Q&As relevant to the Tool, developing presentations to describe the Tool, reviewing exposure risk assessments, etc.
- Product's Contribution to Output: HHRA
- Product's Timeline (with milestones): As needed
- Product's intended user/customer/audience: Program offices (e.g., OPPT), EPA regions , schools, and/or the general public
- Is this a key product? No
- Does this Product contribute to a Product under another Task? If so, identify other Task. 5.2.2.2

- **Product: 5.2.2.4 (*RMS ID# HHRA 3.222.2.4*)**
- **Product Title: Review of Guidance and Protocols for Fish Consumption Studies**
- Product Contact (email): moya.jacqueline@epa.gov
- Product's Delivery Date: Various
- Product Description: Review of reports and other documents
- Product's Contribution to Output:
- Product's Timeline (with milestones): as needed
- Product's intended user/customer/audience: depends on the request (e.g., program offices, regions, states, other government agencies)
- Is this a key product? No
- Does this Product contribute to a Product under another Task? If so, identify other Task.

- **Product: 5.2.2.5 (*RMS ID# HHRA 3.222.2.5*)**
- **Product Title: Dioxin Sources Inventory**
- Product Contact (email): lorber.matthew@epa.gov
- Product's Delivery Date: Final Inventory scheduled for completion and posting on the internet Q2FY17;
- Product Description: These include a 1) a webpage on the Dioxin Sources Inventory including links to legacy Inventory documents, 2) a Final Report on the Inventory, 3) one or more documents providing response-to-peer review comments, 4) an Excel Workbook containing the Inventory for download and use, and 5) a link to a page providing information on a journal manuscript on the Inventory.
- Product's Contribution to Output: On-going technical expertise and tools to provide technology transfer.
- Product's Timeline (with milestones): All products noted above will be available for Internal EPA review by Q3FY16. No further External Review expected. Final products expected ready for posting Q2 FY17.
- Product's intended user/customer/audience: exposure assessors in the Agency, state, and other government agencies.
- Is this a key product? No
- Does this Product contribute to a Product under another Task? If so, identify other Task.

Subtask 5.2.3 (*RMS ID# 3.222.3*): Technical Support and Consultation to Program Office Needs

- **Product 5.2.3.1 (*RMS ID# 3.222.3.1*)**
- **Product Title: Developing and Maintaining Reference Value Arrays**
- Contact (email): George Woodall (woodall.george@epa.gov)
- Delivery Date: Continuous updates from 2016 - 2019
- Description: In advance of known needs from the client offices, HHRA has developed reference value arrays to assist in deliberations on the most appropriate values to use in specific decision-making contexts. The initial set of reference value arrays were provided in a 2009 EPA Report (http://cfpub.epa.gov/ncea/cfm/recordisplay.cfm?deid=211003) which included a number of chemical agents specifically useful for the Department of Homeland Security, along with a number of industrial chemicals with broader application to HHRA's typical clients (OAQPS, OSWER, Regions and States). A second set of values for the BTEX chemicals (benzene, toluene, ethylbenzene, and xylene) and manganese were published in 2012, in anticipation of the need in a number of OAQPS regulatory actions in the Risk and Technology Review (RTR) program. The continuation of this trend of getting in front of the need to provide comparative context for HHRA's clients and to expand the capacity to develop these types of reports on short notice will enhance the ability of HHRA to provide timely advice in a most consistent manner.
- Contribution to Output: Development of Reference Value Arrays for chemicals of consistent interest to the Program Offices will assist in providing quick, efficient and consistent advice. Development of enhanced techniques for generating these types of analyses will enable HHRA to produce similar reports for other chemicals on short notice, with the advantage of increasing the library of available arrays.
- Timeline (with milestones):
    i. FY2016 – Consult with Program Offices to identify their priority chemicals, beginning with their priorities for the IRIS program. Initiate development of reference value arrays (with accompanying test and tables) for the highest priority chemicals and /or updates to those for which arrays have already been developed. Initiate development of enhanced array development capacity using the existing work effort through the Environmental Modeling and Visibility Lab (EMVL).
    ii. FY2017 – Continue development and updates to reference value arrays for high priority chemicals. Provide prototype examples of products from the EMVL effort.
    iii. FY2018-2019 – Incorporate the EMVL tools into the development and update of arrays for high priority chemicals, and to develop similar capacities to respond on short-notice, high-priority needs.
- Product's intended user/customer/audience: Agency Program Offices, DHS, state and local public health organizations
- Key product? No
- Contributions to a Product under another Task: The development of reference value array products should enhance the review of existing values currently performed as a part of the prioritization of needs for the IRIS development process (Task 1) and lead to greater cooperation between agencies in sharing data resources in their development of values. This task is linked to output from Task 9 (development of supporting databases and software tools) and experience from this task will help inform progress on those related products under Task 9.

- **Product 5.2.3.2 (*RMS ID# 3.222.3.2*)**
- **Product title: Review of Alternate Reference Values and Derivation Methods**
- Contact (email): George Woodall (woodall.george@epa.gov)
- Delivery Date: Continuous updates from 2016 - 2019
- Description: In the absence of preferred reference values to use in their risk assessments and regulatory decisions (e.g., IRIS values), the program offices have identified a number of outside organizations which they use as alternative sources. In this activity, HHRA will actively monitor developments within these organizations, including providing comments when public comment periods open for those new/revised values or methods. In doing so, HHRA will be better prepared to assist client offices when they are faced with decisions on the most appropriate reference values to use.
- Contribution to Output: On-going review process will ensure that HHRA program responds efficiently and effectively with technical support to program offices.
- Timeline (with milestones):
    iv. *FY2016 – Consult with Program Offices to identify the sources they use for alternative reference values and the criteria they use for deciding which values are most appropriate for their needs. Begin to monitor those organizations to keep abreast of upcoming changes in methods and development of updates to their collections of reference values.*
    v. *FY2017 – Develop and/or collaborate on a system to collect information on reference value updates. A potential collaborator may be TERA with their ITER system. Continue to monitor organizations developing/updating reference values.*
    vi. *FY2018-2019 – Continue to monitor and collect information on updates to reference values.*
- Intended user/customer/audience: *Program Offices*
- Key product? No
- Contributions to a Product under another Task: Advanced preparation will also assist in the update of Reference Value Arrays.

References

Wang NC, Jay Zhao Q, Wesselkamper SC, Lambert JC, Petersen D, and Hess-Wilson JK. (2012). Application of computational toxicological approaches in human health risk assessment. I. A tiered surrogate approach. *Regul Toxicol Pharmacol* 63(1):10-9

Human Health Risk Assessment (HHRA)

Project Planning Tool

Project Plan

HHRA Project 6 (*RMS ID# HHRA 3.23*)

Cumulative Risk Assessment (CRA) Methods and Applications

Project Leads (PLs): Michael Wright, NCEA Cin and Deborah Segal, NCEA W

Project Development Team Members: Meredith Lassiter (NCEA RTP), Glenn Rice (NCEA CIN), Susan Euling (NCEA W), Jennifer Richmond-Bryant (NCEA RTP), Jacqueline Moya (NCEA W), Matthew Lorber (NCEA W), Paul Price (NERL IO)

Project start date: 10/01/2015

Project end date: 09/30/2019

Executive Summary

Project 6 in the HHRA portfolio addresses the need to move beyond traditional risk assessment practices by further evolving the state of the science and building capacity to perform CRA. The project pursues further development of CRA methods and case studies to characterize their application. Recent advances in understanding of systems biology, emerging data on epigenetics and genetic polymorphisms, both conceptual and quantitative approaches to characterize the interaction of multiple stressors, and how to best use or interpret multi-media and multi-route cumulative exposure measures

such as biomarkers will be explored. Case studies will help address community-based research needs and concerns and further refine approaches by providing important lessons learned. These efforts promote the general goal of the HHRA program under Topic 3 to provide site-specific and regulatory risk assessment support. Project 6 specifically supports one of the EPA Administrator's themes, "*Making a Visible Difference in Communities Across the Country"* (http://www2.epa.gov/aboutepa/epas-themes-meeting-challenge-ahead).

Research Project Description

Recent recommendations to address cumulative risk by the National Academy of Sciences (NRC, 2009) have reinforced previous guidance in frameworks to consider mixtures (US EPA, 2002) and multiple stressors (US EPA, 2003). This is in recognition that realistic and relevant environmental exposures of regulatory concern are not only to singular chemicals but also concurrent multiple chemical exposures; and the exposed populations may also face social or genetic burdens that may alter their susceptibility to the chemical exposures. Advancing the understanding of the interplay among the various key biological, psychosocial, spatial, and environmental factors shown in Figure 6-1, and of how these factors contribute to disproportionate risk, will support direct application to "place-based" characterizations in overburdened communities and help support environmental justice (EJ).

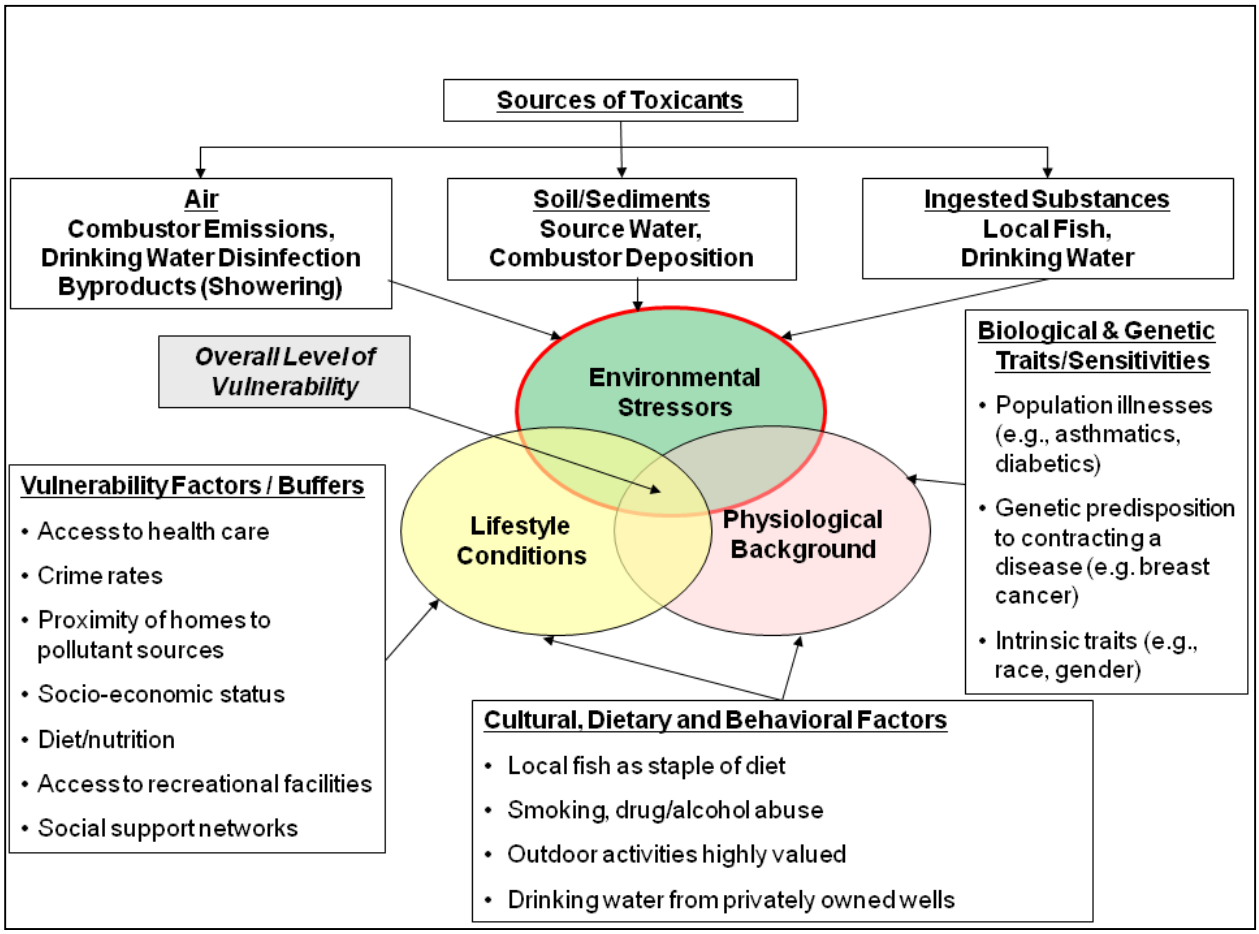


Figure 6-1. CRA framework illustrating various potential roles of chemical and non-chemical stressors and buffers. Current area of emphasis in HHRA is interaction of ecological and human stressors, and active collaboration with the HS and SHC programs to consider resiliency and well-being indices.

CRA is thus viewed as a tool for organizing and analyzing information to examine, characterize, and possibly quantify the combined adverse effects on human health or ecological systems from multiple environmental stressors (Callahan and Sexton, 2007). The need to address this type of problem has been recognized for several decades, but progress has been slow due to insufficient knowledge, inadequate understanding, technologic limitations, and scarce funding (Callan and Sexton, 2007). Advances in biotechnology, for example, analytical capabilities to readily measure biomarkers in various media, computational models to characterize exposures at various scales, and of biologically based dosimetry models to describe key events of pathogenesis leading to different disease states, hold promise to improve CRA. This shift to consider cumulative impacts by receptor-oriented CRA approaches is important as it has resulted in various conceptual models to encourage improvements in characterization of the impact of multiple factors, especially because there is no empirically verified

theory guiding how best to combine and then assess risks from both chemical and nonchemical stressors (Linder and Sexton, 2011). The NRC (2009) proposed a version of the stressor-based paradigm, modified from Menzie et al. (2007), that discriminates among risk-management options, which can be applied to constructing "place-based" approaches to address community concerns.

This project builds on the considerable experience and previous publications of HHRA scientists to advance CRA methods and applications (US EPA 2000; 2003; 2007). The proposed tasks incorporate recent advances in understanding of systems biology such as adverse outcome pathway (AOP) and molecular target sequence similarity developed in the CSS program to help support inclusion of ecological indices such as the general ecological assessment endpoints (US EPA 2004). Multi-criteria decision analysis (MCDA) and other computational models will be explored to inform quantitative data integration. Another task will describe elements and considerations for risk characterization and approaches for integrating multiple stressors. Directed acyclic graphs (DAGs), in collaboration with the Environmental Public Health Division of NHEERL, will be evaluated for potential utility in planning, scoping, analysis and characterization of CRA applications. Case studies and a framework for incorporation of epigenetic or genetic data will be developed to inform data integration to define susceptible populations. Exposure and risk apportionment will advance approaches that address community concerns and support risk mitigation strategies.

Project Impact

Research and work supporting CRA is central to advancing the EPA Risk Assessment Forum's CRA Guidelines, and will position the HHRA program to better address place-based assessment activities and thereby support sustainability, climate change efforts, and goals articulated in the Environmental Justice (EJ) roadmap.

Project Scope

Approaches will be developed to integrate and evaluate impacts of chemical and non-chemical stressors on the environment and health using multi-criteria decision analysis (MCDA) and computational models to assist quantification and visualization of valuation and missing data. Ongoing EPA CRA activities, including strategic coordination and scientific support to the EPA's Risk Assessment Forum Technical Panel on CRA (http://www.epa.gov/raf/) and providing training on CRA methods, will continue to provide advancements in CRA methods and training. HHRA tasks in this project will further advance methods to incorporate multiple stressors and case studies to test CRA applications, including support in response to specific requests from regions and communities. Lessons learned from previous CRA efforts will advance understanding and serve as the basis for further development of more advanced CRA approaches. Additional research will try to broaden the scope of CRA by developing approaches to

evaluate and incorporate epigenetic and genetic polymorphism information to better characterize susceptibility in response to environmental chemical exposures. Evaluation of exposure modeling and guidance on how to apportion exposure and risk from chemical and non-chemical stressors in both human and ecological receptors across various media is another key task anticipated to help advance CRA development. Future work with the HS and SHC programs is expected to consider how to integrate resiliency and well-being indices under development in those programs into the CRA framework.

Project Structure and Rationale

The project is structured into four tasks. Each task area was selected to address important issues in community and cumulative risk assessment (e.g., how to incorporate multiple stressors) or the application of data types that may provide valuable information to advance CRA methods (e.g., epigenetics). The task products, integrated together, comprise a targeted strategy for advancing and applying CRA methods.

- **Task 6.1. (*RMS ID# HHRA 3.231*) Approaches to Cross-species Data Integration to Support CRA**
- **Task 6.2. (*RMS ID# HHRA 3.232*) Incorporating Multiple Stressors**
- **Task 6.3. (*RMS ID# HHRA 3.233*) Applying Genetic and Epigenetic Data to Inform Susceptibility**
- **Task 6.4. (*RMS ID# HHRA 3.234*) Apportioning Multimedia Exposure and Risk across Receptors**

Measures of success

The tasks in this project will advance the science of CRA by incorporating new data, approaches and applications to develop place-based assessments that better address community concerns and complex stressor scenarios.

Stakeholders (outside ORD)

The need for continued advancement and application of CRA methods has long been recognized by the Agency and external stakeholders alike.

References

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Gee GC, Payne-Sturges DC. (2004). Environmental health disparities: a framework integrating psychosocial and environmental concepts. *Environ Health Perspect*. **112(17)**, 1645---1650.

Linder SH, Sexton K. (2011). Conceptual Model for Cumulative Risk Assessment. Am J Public Health 101, S74–S81

Menzie CA, MacDonell MM, Mumtaz M. (2007). A Phased Approach for Assessing Combined Effects from Multiple Stressors. *Environ Health Perspect* **115**, 807–816.

National Research Council. NRC. (2009). Science and Decisions: Advancing Risk Assessment (The Silver Book). National Academy Press. Washington D.C.

U.S. EPA. (2000). Supplementary Guidance for Conducting Health Risk Assessment of Chemical Mixtures. EPA/630/R-00/002. Washington, DC: U.S. Environmental Protection Agency, Risk Assessment Forum, Office of Research and Development.

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U.S. EPA. (2004). Generic Ecological Assessment Endpoints (GEAEs) for Ecological Risk Assessment. EPA/630/P-02/004F. Washington, DC: U.S. Environmental Protection Agency, Risk Assessment Forum, Office of Research and Development.

Task 6.1

(*RMS ID# HHRA 3.231*)

Approaches to Cross-species Data Integration to Support Cumulative Risk Assessment

Task Lead (TL): Meredith Lassiter (NCEA RTP)

Task Start Date: 10/01/2015

Task End Date: 09/30/2019

Task Description:

Advances in the integration of human and ecological data have provided new possibilities for conducting risk assessments that consider the cumulative risks to multiple stressors. In a given environment, humans and non-human biota are exposed to many of the same chemical and non-chemical stressors. In addition to some shared pathways of exposure, it is possible to identify a common mode(s) of action of some chemical stressors in both humans and wildlife. These commonalities can be used to link human and ecological exposures and responses to multiple stressors in new ways. Benefits of this approach include improving the efficiency and predictive capability of risk assessments to humans and wildlife, especially where there is a common underlying modes-of-action (MOA) or adverse outcome pathway (AOP) of effects. Also, characterization of effects of non-chemical stressors may be enhanced by including ecological endpoints, since the role of abiotic stressors in modulation of toxicity is commonly considered in laboratory and field studies with aquatic and terrestrial organisms. Recommendations on cumulative risk assessment (CRA) put forth in the 2009 NRC Science and Decisions: Advancing Risk Assessment report include development of conceptual models and phased approaches to move these types of assessments forward (NRC 2009). Ecological risk assessment already takes into consideration effects of non-chemical stressors and vulnerabilities (e.g. sensitive habitats, species protection status), recommendations included in the NRC report for advancing cumulative risk assessment for human health. However, there is still a lot to be understood in characterizing ecosystem responses to multiple stressors, such as how multiple stressors alter species response and vulnerability and how this can change ecosystem function/services.

This task will explore new methods for integration of human and ecological endpoints and how these techniques may be applied to CRA. The anticipated impact of projects described under this task is improved assessment of ecosystems and human health through methods for cross-species integration. This integration is also anticipated to address community concerns regarding environmental and human health impacts and will facilitate the application of CRA to "place-based" assessments.

HHRA Task 6.1 (*RMS ID# HHRA 3.231*) consists of the following four subtasks described briefly below:

- **Subtask 6.1.1. (*RMS ID# HHRA 3.231.1*): Working group for the integration of ecological receptors into the cumulative risk assessment framework**

  The purpose of this subtask is to establish a working group of 5 to 10 scientists agency-wide with expertise in areas relevant to advancement of cross-species approaches including integration of human and ecological data in cumulative risk assessment (e.g. ecological risk, effects of multiple stressors on aquatic and/or terrestrial biota, toxicology, and tools for integrated assessment). The working group will pursue approaches to advance formal integration of ecological and human health indices and serve as a resource to the Risk Assessment Forum for reviews etc.

- **Subtask 6.1.2. (*RMS ID# HHRA 3.231.2*): Support and application of new tools for integration of human and ecological receptors**

  Several new tools developed at the EPA have potential application to enhance the integration of human and ecological receptors. Examples include EPA-Eco-Box being developed by NCEA as a web-based toolbox to provide links to guidance documents, databases, and other relevant information for ecological risk assessors (see HHRA Topic 4 Task 8.4). The Sequence Alignment to predict Across-Species Susceptibility (SeqAPASS) developed by NHEERL is another example of a web-based tool for addressing the challenges of cross-species extrapolation of chemical toxicity (LaLone et al. 2013). Subtask 6.1.2. is devoted to developing approaches for the application of these tools and characterizing their utility to support CRA. This work will additionally provide support to the other subtasks in Task 6.1 by providing systematic review of evidence in the literature and inferences gained from the tools.

- **Subtask 6.1.3. (*RMS ID# HHRA 3.231.3*): Modeling and multi-criteria decision analysis (MCDA) applications for quantitative integration of human and ecological indicators**

  Multi-criteria decision analysis (MCDA) has proven useful for the prioritization of chemical assessments based on integration of different data streams; and also offers transparent valuation providing great utility for informing community assessment (Mitchell et al., 2013; Kiker et al., 2005). Construction of an MCDA computational model will proceed by formalization of a decision support structure based on the process diagram product of Subtask 6.1.1, consistent with extant models such as NCEA's Causal Analysis and Diagnosis Decision Information System (CADDIS), and which supports transparent and tractable accounting of valuation of ecological and human health indices. Case studies illustrative of data rich examples as well as those with missing data will be pursued to provide indication of feasibility and identification of significant data gaps. In parallel, this subtask will pursue further development of a computational sustainability model that was originally started as a Pathfinder Innovation Project (PIP) by NHEERL scientists. The work leverages and additionally informs data integration and approaches for AOP applications in the IRIS inorganic arsenic assessment. The sustainability model will be applied to more data-rich case studies and evaluated for utility to further inform MCDA. All case studies will serve to advance more formal approaches to ecological and human indices, and serve as fodder for the future workshop planned as part of Subtask 6.1.1.

- **Subtask 6.1.4. (*RMS ID# HHRA 3.231.4*): Multiple stressors in ecological assessments – the case of nitrogen**

  The development of the multipollutant Integrated Science Assessment (ISA) for Oxides of Nitrogen and Sulfur -Ecological Criteria (NOx/SOx ISA) includes consideration of how multiple chemical and non-chemical (e.g. temperature, climate) stressors affect nitrogen impacts to aquatic and terrestrial ecosystems. Dose-response relationships of nitrogen with selected ecological assessment endpoints will be evaluated in freshwater systems considering how multiple stressors affect toxicity. Ecological effects of nitrogen deposition to case study areas such as the Sierra Nevada Mountains, Appalachias, Acadia National Park, and/or Rocky Mountain National Park will be evaluated, and ecosystem services of selected impacted biota will be characterized.

Research Approach:

Systematic review and synthesis of current literature on ecological endpoints affected by chemical and non-chemical stressors and/or integration of human and ecological risk assessment will be conducted for the projects under this task. Task 6.1 builds on recommendations of an HHRA vision paper (in final preparation) on opportunities to integrate ecological considerations in CRA and advances in understanding of systems biology to support new applications for qualitative and quantitative approaches. A quantitative model to support sustainability considerations is included in the quantitative approaches. Opportunities identified include conceptual integration based on common or conserved MOA/AOP, incorporation of the generic ecological assessment endpoints (GEAE) (US EPA 2004) and ecosystem services into CRA, and the use of MCDA to aid problem formulation and transparency of valuation involved when integrating ecological and human health indices.

- **Subtask 6.1.1. (*RMS ID# HHRA 3.231.1*): Working group for the integration of ecological receptors into the cumulative risk assessment framework**

  A working group will be established to develop a standardized working diagram of a conceptual model for use by the EPA that incorporates GEAEs and non-chemical stressors that act on ecological receptors, into the CRA framework. GEAEs have been developed by the EPA for use in risk assessment. This proposed approach will identify receptors and endpoints affected by the stressors while taking into account the effects of non-chemical stressors and needs of stakeholders. This is consistent with the NRC recommendations to develop a conceptual model to advance CRA (NRC 2009). Products under this subtask include formalizing a process diagram for the integration of human and ecological indices and a workshop to convene and consider case studies for application of the tools and approaches developed in other subtasks.

- **Subtask 6.1.2. (*RMS ID# HHRA 3.231.2*): Support and application of new tools for integration of human and ecological receptors**

  Building upon the integration of human health and ecological effects of lead from Lassiter et al (2015), work in this subtask will pursue using SeqAPASS to explore the further integration of human and ecological endpoints by incorporating molecular sequencing data to evaluate cross-species coherence of effects and modes of action. For example, since lead is one of several possible toxicants we may consider for use with SeqAPASS, this subtask could help characterize MOA for ecological effects of lead exposure since there are few such studies. Lead has been demonstrated to affect the IGF-1 pathway in humans and vertebrates and ILS signaling pathway in some invertebrates. Case studies using EPA SeqAPASS tool could be used to predict species that may be susceptible to endocrine disruption by lead by identifying inhibin and IGF-1 like sequences. The feasibility of using EPA-Eco-Box for integration of human and ecological endpoints will be considered once the toolbox is available.

- **Subtask 6.1.3. (*RMS ID# HHRA 3.231.3*): Modeling and multi-criteria decision analysis (MCDA) applications for quantitative integration of human and ecological indicators**
  This subtask will evolve an MCDA computational based on review and recommendations regarding the process diagram product of Subtask 6.1.1. The initial computational structure will utilize that diagram to modify recent work by Igor Linkov at the US Army Corps of Engineers (US ACE) and then refined in the future with review of case study applications planned for use at the future workshop in that subtask. Collaborations will include (US ACE, input from those involved with the GEAE (subtask 6.1.1), and interaction with NHEERL scientists involved with AOP development and the computational sustainability model for optimization. The computational sustainability model is developing visualization software based on a former PIP project. Comparison of the application of both types of models to case studies illustrative of data rich examples such as inorganic arsenic as well as those with missing data will be pursued to provide indication of feasibility and identification of significant data gaps.

- **Subtask 6.1.4. (*RMS ID# HHRA 3.231.4*): Multiple stressors in ecological assessments – the case of nitrogen**

  Dose-response relationships of nitrogen with selected ecological assessment endpoints will be evaluated in freshwater systems considering how multiple stressors affect toxicity. Ecological effects of nitrogen deposition to case study areas such as the Sierra Nevada Mountains, Appalachia, Acadia National Park, and/or Rocky Mountain National Park will be evaluated, and ecosystem services of selected impacted biota will be characterized. At least one peer-reviewed journal article is expected as well as inclusion of dose-response relationships and impacted ecosystem services associated with specific species in case studies within the NOx/SOx ISA.

Task Products:

Subtask 6.1.1. (*RMS ID# HHRA 3.231.1*): Working group for the integration of ecological receptors into the cumulative risk assessment framework

- **Product 6.1.1.1. (*RMS ID# HHRA 3.231.1*)**
- **Product Title: Process diagram for organization of human and ecological data integration**
- **Contact (email)** lassiter.meredith@epa.gov; jarabek.annie@epa.gov; greaver.tara@epa.gov; troyer.michael@epa.gov
- **Product Description:** The current EPA conceptual CRA framework (Figure 6-1) provides for consideration of vulnerability as an integrated function of environmental stressors, physiology and lifestyle; and new advances in understanding of systems biology have elucidated conserved mechanisms resulting in AOPs across species. The purpose of this product is to formalize the previously-developed process diagram for the integration of

human and ecological effects from an HHRA vision paper with additional feedback and discussion to explore refinement and new applications. This process-level diagram will help in organization of additional projects in Task 6.4.

- **Product's Timeline (with milestones):**
  - Q1 FY 2016 Identify agency scientists interested in joining a team focused on integration of ecological receptors in the CRA framework
  - Q3 FY 2016 Draft of the proposed approach including a conceptual diagram based on HHRA Vision paper
  - Q1 FY 2017 Incorporate feedback from scientists and finalize conceptual approach for the integration of ecological endpoints into CRA efforts
- **Product's intended user/customer/audience:** Agency scientists across programs and regions
- **Is this a key product?** No.
- **Does this Product contribute to a Product under another Task?** Yes. Deliberations and process diagrams serve to inform other tasks in Project 6.

- **Product 6.1.1.2 (*RMS ID# HHRA 3.231.1.2*)**
- **Product Title: Workshop to advance incorporation of ecological risk assessment into cumulative risk assessment frameworks**
- **Contact (email)** lassiter.meredith@epa.gov, greaver.tara@epa.gov
- **Product's Delivery Date:** Q1 2018
- **Product Description:** Using tools and approaches developed to date as a starting point, this workshop will explore ways to incorporate ecological endpoints into CRA moving from theoretical approaches to practical applications. Scientists with expertise in integration of human health and ecological risk assessment will be invited to participate in the workshop. The purpose of the workshop will be to (1) plan a case study or studies using a site-specific approach to conduct a CRA that incorporates human and ecological endpoints, and (2) identify ways to incorporate GEAE's to case studies
- **Product's Contribution to Output:** Provide a roadmap to move forward with incorporation of ecological endpoints into CRA
- **Product's Timeline (with milestones):**
  - FY 2017: Develop work assignment through our existing contract with ICF for the workshop
  - FY 2018: Workshop in Q1
  - FY 2019: Report from workshop Q3
- **Product's intended user/customer/audience:** EPA and risk assessors
- **Is this a key product?** TBD
- **Does this Product contribute to a Product under another Task?** Yes, all tasks in Project 6 would be informed by this roadmap.

Subtask 6.1.2. (*RMS ID# HHRA 3.231.2*): Support and application of new tools for integration of human and ecological receptors

- **Product 6.1.2.1.1 (*RMS ID# 3.231.2.1*)**
- **Product Contact:** Meredith Lassiter; lassiter.meredith@epa.gov (NCEA RTP)
- **Product's Delivery Date:** Q4 FY2017
- **Product's Contribution to Output**: Product will demonstrate how new tools could be applied to further cumulative risk assessment. For example, with SeqAPASS species data may be extrapolated from effects in humans and laboratory animals to other organisms.
- **Product's Timeline (with milestones):**
    - 2nd quarter 2016: Scoping meeting with scientists at EPA-Duluth
    - 4th quarter 2016: Training in SeqAPASS for one or more scientists in NCEA-RTP
    - 1st quarter 2017: Results from SeqAPASS analysis, scientists will determine if a peer-reviewed publication is a possible product
    - 4th quarter FY 2017: Feasibility study of this approach using reproductive effects of Pb or another pollutant and endpoint, publication of peer-reviewed journal article, application of EPA-Eco-Box tool as input toCRA efforts.
- **Product's intended user/customer/audience:** Broad scientific audience, especially those interested in tools for cross-species extrapolation
- **Is this a key product?** No.
- **Does this Product contribute to a Product under another Task?** Yes. Results from these analyses could serve as input to Subtask 6.3 tasks.

Subtask 6.1.3. (*RMS ID# HHRA 3.231.3*): Modeling and multi-criteria decision analysis (MCDA) applications for quantitative integration of human and ecological indicators

- **Product 6.1.3.1. (RMS ID# HHRA 3.231.3.1)**
- **Product Title: Multi-criteria decision analysis (MCDA) model and case studies**
- **Product Contact (email)**: Annie Jarabek; jarabek.annie@epa.gov; (NCEA-RTP)
- **Product's Delivery Date:** FY2017

  Product Description: Construction of an MCDA computational model will proceed by formalization of a decision support structure based on the process diagram product of Subtask 6.1.1, in collaboration with Igor Linkov at US ACE, and consistent and utilizing input from extant models such as CADDIS, to support transparent and tractable accounting of valuation of the integration of ecological and human health indices. Case studies illustrative of data rich examples as well as those with missing data will be pursued to provide indication of feasibility and identification of significant data gaps and their impact to decisions. The sustainability model will be applied to more data-rich case studies and evaluated for utility to further inform

MCDA. All case studies will serve to advance more formal approaches to ecological and human indices, and serve as fodder for the future workshop planned as part of Subtask 6.1.1.

- **Product's Contribution to Output:** MCDA computational model will provide formal statistical approach for recommendations regarding integration of human and ecological impact indices.
- **Product's Timeline (with milestones):**
  - Development of computational model for application to case studies and discussion and at workshop: FY2017 Q2
  - Implementation of computational structure and application to case studies
  - Evaluation of application with selected case studies: FY2018
  - Publication of case studies based on feedback (e.g., from workshop planned in Subtask 6.1.1.): FY2019
  - Recommendations and specification for further software development: FY2019
- **Product's intended user/customer/audience:** Support tool for Agency scientist wishing to integrate human and ecological indices into CRA.
- **Is this a key product?** TBD
- **Does this Product contribute to a Product under another Task?** Yes. Provides formal structure for decision analysis application of recommendations developed in other tasks and interface with Product 6.1.3.2 (RMS ID# HRRA 3.231.3.2) and will be reviewed at the workshop planned in Subtask 6.1.1. (RMS ID# HHRA 3.231.1)

- **Product 6.1.3.2. (*RMS ID# HHRA 3.231.3.2*)**
- **Product Title:** Computational Sustainability Models
- **Product Contact (email):** Stephen Edwards, edwards.stephen@epag.gov; Rory Conolly, conolly.rory@epa.gov (NHEERL ISTD)
- **Product's Delivery Date:** FY18
- **Product Description:** This product will consist of a computational model along with software allowing scenario-based interrogation of the model by decision makers. Analysis tools that identify sensitive parameters and potentially optimal values for certain parameters will be developed as time permits. This product will include one or more peer reviewed manuscripts describing the models and analysis tools.
- **Product's Contribution to Output:** Together with the MCDA computational model (Product 6.1.3.1; RMS ID# HHRA 3.231.3.2) this sustainability model will provide formal statistical approach for recommendations regarding integration of human and ecological impact indices and the potential to also incorporate benefit:cost considerations.
- **Product's Timeline (with milestones):**
  - Q4 FY16 – Prototype of computational model for case study 1.
  - Q4 FY17 – Final model and integration with visualization software for case study 1 (Manuscript submitted). Prototype of computational model for case study 2.

  - Q4 FY18 – Use of model and visualization software for case study 2 (manuscript submitted). White paper discussing how this modeling work could be integrated with the other MCDA tools developed within the task.
- **Product's intended user/customer/audience:** This product should support decision makers both inside and outside the Agency by providing a mechanism for translating the results of computational models into a format amenable for making and communicating decisions. This format will be built around the ability to define various scenarios and compare potential outcomes along with mathematical approaches to define sensitive parameters and boundary conditions for those models.
- **Is this a key product?** TBD.
- **Does this Product contribute to a Product under another Task?** Yes. Provides additional visualization and valuation optimization to inform Product 6.1.3.1 (RMS ID# HRRA 3.231.3.1) and will also be reviewed at the workshop planned in Subtask 6.1.1. (RMS ID# HHRA 3.231.1). Insights on data integration and AOP applications will inform the IRIS assessment for inorganic arsenic.

Subtask 6.1.4. (*RMS ID# HHRA 3.231.4*): Multiple stressors in ecological assessments – the case of nitrogen

- **Product Title: Multiple stressors in ecological assessments – the case of nitrogen**
- **Product Contact (email):** greaver.tara@epa.gov, lassiter.meredith@epa.gov
- **Product's Delivery Date:** FY2017 Q4
- **Product Description:** Dose-response relationships of nitrogen with selected ecological assessment endpoints will be evaluated in freshwater systems considering how multiple stressors affect toxicity. Ecological effects of nitrogen deposition to case study areas such as the Sierra Nevada Mountains, Appalachia, Acadia National Park, and/or Rocky Mountain National Park will be evaluated, and ecosystem services of selected impacted biota will be characterized. At least one peer-reviewed journal article is expected as well as inclusion of dose-response relationships and impacted ecosystem services associated with specific species in case studies within the NOx/SOx ISA.
- **Product's Contribution to Output:** Characterization of how dose-response relationships of nitrogen are affected by multiple stressors will provide insights into incorporating ecological endpoints in cumulative risk frameworks. Links between deposition of nitrogen, the role of multiple stressors, and changes to ecosystem services will be demonstrated through impacts to specific species.
- **Product's Timeline (with milestones):**
  - 1st quarter FY 2016 Identify papers with dose-response relationships of nitrogen to ecological endpoints
  - 2nd quarter FY 2016 extract dose-response data from relevant literature
  - 3rd quarter FY 2016 conduct analyses of dose response relationships for NOx/SOx ISA
  - 2nd quarter FY 2017 Prepare draft of one peer-reviewed journal article
  - 4th quarter FY 2017 Peer-reviewed journal article published
- **Product's intended user/customer/audience:** OAQPS and broader scientific audience

- **Is this a key product?** TBD
- **Does this Product contribute to a Product under another Task?** Yes, production of ISAs in Project 3, Task 3.1 (*RMS ID# HHRA 2.211*) as well as inform other subtasks in this task.

Task Dependencies: Work on the models in Subtask 6.1.3. requires establishing an IAG with US ACE and the hire of an R-authority postdoc, both are underway but may result in delays.

Task Constraints:

- **Scientific:**
  - The assessment of cumulative risk for ecological receptors is constrained by the available information on receiving biota. There are many organisms for which no toxicity data exist and assessments rely on extrapolation of effects from other species. The complexity of considering multiple co-occurring stressors is a constraint especially considering multiple environmental compartments (i.e. soil, water, biota) and non-chemical stressors in natural systems
  - **Resources:** Work on all subtasks in this task is constrained by competing priorities and the availability of EPA staff and ORISE support has been included in the budget for this project

Task Quality Assurance and Data Management Needs: All subtasks in Task 6.1 are covered as follows:

- Is there an existing IRP/ QAPP(s) that applies to this Task? If so, identify IRP/QAPP. If new IRP/QAPPs are required, provide the status.
  - NCEA-16-00004. Quality Assurance Project Plan (QAPP) For HHRA Projects 6, 7, & 8 to Develop Methods, Tools, Models and Supporting Analysis.
  - Additionally, Product 6.1.3.2 (*RMS ID# HHRA 3.231.3.2*) is covered as follows: IRP-NHEERL/ISTD/SBB/WL/2012-01-r0 (This QAPP is currently under revision and will be transferred to one of the existing mentors upon the arrival of the new postdoc)

- Will this Task involve large amounts of data that need a data management plan? If yes, explain.
  - TBD. The Health and Environmental Research Online (HERO) system is used for systematic literature review and is covered by a separate QAPP: NCEA-16-00005. Quality Assurance Project Plan (QAPP) For Extraction of Scientific Data Into the Health and Environmental Research Online (HERO) Database System

- Additionally, Product 6.1.3.2 (*RMS ID# HHRA 3.231.3.2*) is covered as follows: This will be dependent on the specific case studies chosen for the product to be determined after the postdoc has arrived and will likely also use the HERO resource per above.

References:

Kiker GA, Bridges TS, Varghese A, Seager PT, Linkov I. (2005). Application of multicriteria decision analysis in environmental decision making. *Integr Environ Assess Manag*. Apr;1(2):95-108.

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Lassiter MG, Owens EO, Patel MM, Kirrane E, Madden M, Richmond-Bryant J, Hines EP, Davis JA, Vinikoor-Imler L, Dubois JJ. (2015). Cross-species coherence in effects and modes of action in support of causality determinations in the U.S. Environmental Protection Agency's Integrated Science Assessment for Lead. *Toxicol* 1;330, 19 – 40

Mitchell J, Pabon N, Collier ZA, Egeghy PP, Cohen-Hubal E, Linkov I, Vallero DA. (2013). A decision analytic approach to exposure-based chemical prioritization. *PLoS One*, Aug 5; 8(8):e70911.

NRC (2009). Science and decisions: Advancing risk assessment. Chapter 7. Implementing cumulative risk assessment. Committee on improving risk analysis approaches used by the US EPA; Board on Environmental Studies and Toxicology; Division on Earth and Life Studies. National Academies Press: Washington, DC. http://dels.nas.edu/dels/rpt_briefs/IRA_brief_final.pdf.

U.S. EPA. (2004). Generic Ecological Assessment Endpoints (GEAEs) for Ecological Risk Assessment. EPA/630/P-02/004F. Washington, DC: U.S. Environmental Protection Agency, Risk Assessment Forum, Office of Research and Development.

Task 6.2

(*RMS ID# HHRA 3.232*)

Incorporating Multiple Stressors

Task Leads (TL): Glenn Rice (NCEA CIN) and Deborah Segal (NCEA W)

Task Start Date: 10/01/2015

Task End Date: 09/30/2019

Task Description:

Under Task 6.2, the HHRA Program will continue to develop Cumulative Risk Assessment (CRA) methods and case studies that evaluate exposures, assess dose-response, and characterize risks posed by multiple chemical and non-chemical stressors to human health. The types of stressors envisioned for consideration in CRAs include biological agents, physical entities such as temperature, and psychosocial stressors, in addition to hazardous environmental chemicals. Expert panels have encouraged EPA to expand the focus of human health risk assessment, moving from analyses of human health risks posed by individual environmental stressors toward CRA (NAS, 2008; 2009; USEPA, 2003); however, progress in this area of risk assessment is limited by the lack of methods to support such comprehensive investigations that examine health outcomes associated with the combined effects of multiple stressors.

To accomplish this work of methods development and then application in case studies, Task 6.2. (*RMS ID# HHRA 2.232.2*) is composed of two subtasks as follows:

- **Subtask 6.2.1 (*RMS ID# HHRA 3.232.1*): Cumulative Risk Assessment Methods for Integrating Stressors**
  Under this subtask, HHRA scientists will continue to lead the development of cumulative risk assessment (CRA) methods that 1) inform hazard assessment/characterization; 2) evaluate exposures; 3) assess dose-response; and 4) characterize risks posed by multiple chemical and non-chemical stressors to human health.

- **Subtask 6.2.2 (*RMS ID# HHRA 3.232.2*): Cumulative Risk Assessment – Multiple Stressor Case Studies**
  Research indicates that nonchemical stressors can interact and modify the response to chemical toxicants. However, the extent to which nonchemical stressors modify toxic responses is not known. In addition, the mechanisms involved in their interaction is only beginning to be understood. This subtask presents case studies of chemical and nonchemical stressors in an attempt to better understand how nonchemical stressors may increase vulnerability of individuals or communities to toxicant exposures. Ultimately, these case studies should improve our ability to assess multiple stressors in cumulative risk assessment.

Research Approach:

Work under the two subtasks will work in concert to advance CRA methods and illustrate their application in case studies. Methods will mature with additional research and benefit from lessons learned in the case studies. Existing epidemiological and toxicological study data will be accessed for the purpose of developing CRA methods and case study applications. Case studies will explore specific interactions among established stressors. The development of case studies that include disparate types of stressors (e.g., chemical and non-chemical) will be emphasized. Nonchemical stressors with similar health endpoints and mechanisms of action with chemical stressors will be prioritized for case studies. As needed, experts will be convened in workshops to inform issues relevant to CRA approaches.

- **Subtask 6.2.1 (*RMS ID# HHRA 3.232.1*): Cumulative Risk Assessment Methods for Integrating Stressors**

- **Subtask 6.2.2 (*RMS ID# HHRA 3.232.2*): Cumulative Risk Assessment – Multiple Stressor Case Studies**

Task Constraints:

- **Subtask 6.2.1 (*RMS ID# HHRA 3.232.1*): Cumulative Risk Assessment Methods for Integrating Stressors.** Specific products developed under this subtask will be of interest to select EPA program offices, so their timely review of these relevant products will be needed. Sufficient funding of vehicle for external scientists' contributions to workshop. Sufficient funding for ASPPH and ORISE Fellows. Commitment of FTE and availability of EPA staff given multiple and sometimes competing priorities.

- **Subtask 6.2.2 (*RMS ID# HHRA 3.232.2*): Cumulative Risk Assessment – Multiple Stressor Case Studies.** Specific products developed under this subtask will be of interest to select EPA program offices; their timely review of these relevant products will be needed. Sufficient funding of vehicle for external scientists' contributions to workshop. Sufficient funding for ASPPH and ORISE Fellows. Commitment of FTE and availability of EPA staff given multiple and sometimes competing priorities.

Task Dependencies:

Subtask 6.2.1 (*RMS ID# HHRA 3.232.1*): Cumulative Risk Assessment Methods for Integrating Stressors. Efficient Internal Review and Clearance processes. The completion of the manuscript titled "A Review of STAR Research Grants Exploring the Role of Nonchemical Stressors in Cumulative Risk Assessments" will be dependent on the completion of the grants themselves. At this time, the closing date is mid-2016.

Subtask 6.2.2 (*RMS ID# HHRA 3.232.2*): Cumulative Risk Assessment – Multiple Stressor Case Studies. Efficient Internal Review and Clearance processes.

Task Quality Assurance and Data Management Needs:

Subtask 6.2.1 (*RMS ID# HHRA 3.232.1*): Cumulative Risk Assessment Methods for Integrating Stressors

- Is there an existing IRP/ QAPP(s) that applies to this Task? If so, identify IRP/QAPP. If new IRP/QAPPs are required, provide the status. Yes. NCEA-16-00004. Quality Assurance Project Plan (QAPP) For HHRA Projects 6, 7, & 8 To Develop Methods, Tools, Models and Supporting Analysis

- Will this Task involve large amounts of data that need a data management plan? If yes, explain TBD.

Subtask 6.2.2 (*RMS ID# HHRA 3.232.2*): Cumulative Risk Assessment – Multiple Stressor Case Studies

- Is there an existing IRP/ QAPP(s) that applies to this Task? If so, identify IRP/QAPP. If new IRP/QAPPs are required, provide the status. Yes. NCEA-16-00004. Quality

Assurance Project Plan (QAPP) For HHRA Projects 6, 7, & 8 To Develop Methods, Tools, Models and Supporting Analysis

- Will this Task involve large amounts of data that need a data management plan? If yes, explain TBD.

Task Products:

Subtask 6.2.1 (*RMS ID# HHRA 3.232.1*): Cumulative Risk Assessment Methods for Integrating Stressors

- **Product 6.2.1.1 (*RMS ID# HHRA 3.232.1.1*)**
- **Product Title: Characterizing Risk for Cumulative Risk Assessment (CRA)**
- Product Contact (email): Glenn Rice (rice.glenn@epa.gov)
- Product's Delivery Date: 7/29/16
- Product Description: Journal Manuscript Submission
  This manuscript describes elements of and considerations for the risk characterization step for CRAs. The risk characterization step of a CRA can be much more difficult than its counterpart in "conventional" single stressor risk assessments. The manuscript will utilize a series of examples to illustrate some of these difficulties (e.g., development of dose-response functions for joint stressor exposure) and identify some methods for scientifically addressing these difficulties in the risk characterization step of a CRA.
- Product's Contribution to Output: This manuscript describes elements of and considerations for the risk characterization step for CRAs that can be used by regional and program office risk assessors in the EPA.
- Product's Timeline (with milestones):
  - Final Draft Journal Manuscript to Coauthors: 12/30/15
  - Journal Manuscript Internal Review and EPA Clearance: 4/1/16
  - Journal Manuscript Submission: 7/29/16
- Product's intended user/customer/audience: Regional and Program office Risk Assessors (accessible to scientists and managers)
- Is this a key product? No.
- Does this Product contribute to a Product under another Task? If so, identify other Task. No.

- **Product 6.2.1.2 (*RMS ID# HHRA 3.232.1.2*)**
- **Product Title: Grouping stressors for human health cumulative risk assessments: A simplifying approach for inclusion of non-chemical stressors and vulnerabilities**
- Product Contact (email): Glenn Rice (rice.glenn@epa.gov)
- Product's Delivery Date: 12/20/17
- Product Description: Journal Manuscript Submission
  Consensus is growing on the need to assess some environmental health risks with cumulative risk assessment (CRA) approaches that examine health outcomes associated with the combined effects of multiple stressors and consider vulnerabilities. This manuscript extends an earlier grouping approach focused on grouping of chemical stressors based on exposure and health effects information. The extended CRA groupings approach provides methods for grouping and integrating chemical and non-chemical stressors including potential vulnerabilities due to immutable factors, diseases and physiologic states affecting health risks. Development of the manuscript will entail secondary data analyses of epidemiology and toxicology data and refinement of an existing EPA approach described in EPA's (2007) "Concepts, Methods, and Data Sources for Cumulative Health Risk Assessment of Multiple Chemicals, Exposures and Effects: A Resource Document." Product's Contribution to Output: Approaches are needed to efficiently evaluate CRA information.
- Product's Timeline (with milestones):
  - Final Draft Journal Manuscript to Coauthors: 11/21/16
  - Journal Manuscript Internal Review and EPA Clearance: 9/15/17
  - Journal Manuscript Submission: 12/20/17
- Product's intended user/customer/audience: Regional and Program office Risk Assessors (accessible to scientists and managers)
- Is this a key product? No.
- Does this Product contribute to a Product under another Task? If so, identify other Task. No.

- **Product 6.2.1.3 (*RMS ID# HHRA 3.232.1.3*)**
- **Product Title: Causal Inference in Cumulative Risk Assessment: The Role of Directed Acyclic Graphs**
- Product Contact (email): Beth Brewer (brewer.beth@epa.gov)
- Product's Delivery Date: 9/1/2016
- Product Description: Journal Manuscript Submission
  As noted in the National Academy of Science's Science and Decisions (2009), one of the challenges EPA is grappling with is the ability to examine multiple exposures (including complex mixtures) and vulnerability of exposed populations in a cumulative risk assessment (CRA) perspective. They also noted a distinct need in CRA to develop methods to address the integration of non-chemical stressors into cumulative risk assessment. This task focuses on challenges to address these needs including development of case studies and methodology to integrate multiple (chemical and non-chemical) stressors into CRA.

This manuscript addresses the potential use of directed acyclic graphs (DAGs) for CRA applications. It focuses on DAGs as a tool for planning and scoping, risk analysis and risk characterization phases of a CRA. The manuscript describes the theoretical underpinnings of DAGs and provides useful guidance on their consideration for CRAs. The relationship between conceptual models and DAGs was explored for each phase of a hypothetical CRA. DAGitty.net software was used to develop a DAG for comparison with a conceptual model and to better delineate causal pathways. This tool should help inform causal assessment and improve weight of evidence considerations.

- Product's Contribution to Output: This manuscript will offer some guidance on how to use DAGs to inform the CRA process which can be used by regional and program office risk assessors in the EPA and beyond
- Product's Timeline (with milestones):
  - Final Draft Journal Manuscript to Coauthors: 3/28/16
  - Journal Manuscript Internal Review and EPA Clearance: 6/1/16
  - Journal Manuscript Submission: 9/1/16
- Product's intended user/customer/audience: Regional and Program office Risk Assessors (accessible to scientists and managers)
- Is this a key product? No.
- Does this Product contribute to a Product under another Task? If so, identify other Task. No.

- **Product 6.2.1.4 (*RMS ID# HHRA 3.232.1.4*)**
- **Product Title: A Review of STAR Research Grants Exploring the Role of Nonchemical Stressors in Cumulative Risk Assessments**.
- Product Contact (email): Deborah Segal (segal.deborah@epa.gov)
- Product's Delivery Date: 9/30/18
- Product Description: Journal Manuscript Submission

  This manuscript synthesizes the research results for grants funded through the EPA STAR RFA "Understanding the Role of Nonchemical Stressors and Developing Analytic Methods for Cumulative Risk Assessments." It will also discuss the implications of the findings to cumulative risk assessments and lessons learned on utilizing a community participatory approach. Seven grants were initially funded in 2010 to explore the biological underpinning of the interaction of nonchemical stressors with toxic chemicals and also to develop statistical methods for the incorporation of nonchemical stressors into cumulative risk assessments. Some of the subsequent publications of the grantees will be reviewed, as well their annual progress reports. This project will be conducted in collaboration with the NCER Project Officer for the grants as well as with the grantees.

- Product's Contribution to Output: This manuscript will highlight how nonchemical stressors can exacerbate chemical toxicity and how this information can be considered in cumulative risk assessments.

- Product's Timeline (with milestones):
  - Final Draft Journal Manuscript to Coauthors: 5/1/18
  - Journal Manuscript Internal Review and EPA Clearance: 7/1/18
  - Journal Manuscript Submission: 9/30/18
- Product's intended user/customer/audience: Regional and Program office Risk Assessors (accessible to scientists and managers)
- Is this a key product? No.
- Does this Product contribute to a Product under another Task? If so, identify other Task. No.

Subtask 6.2.2 (RMS ID# HHRA 3.232.2): Cumulative Risk Assessment – Multiple Stressor Case Studies

- **Product 6.2.2.1 (*RMS ID# HHRA 3.232.2.1*):**
- **Product Title: Analyzing greenspace and asthma and allergy occurrence from a Cumulative Risk Assessment (CRA) perspective**
- Product Contact (email): Glenn Rice (rice.glenn@epa.gov)
- Product's Delivery Date: 1/4/2018
- Product Description: Journal Manuscript Submission
  Greenspace is defined as publicly accessible land that is at least partially vegetated. In children and adults, greenspace has been associated with health effects related to improved air quality, increased physical activity, and psychosocial improvements. Health benefits or risks of greenspace on asthma and allergy development in children have not been thoroughly investigated. This product entails the development of a manuscript that investigates the incorporation of greenspace measures into analyses of environmental exposure and potential asthma health impacts in an epidemiologic cohort study of children.
  Development of the manuscript will entail analyses of cohort data (asthma and allergy; residential locations), and development of spatial analytic methods to derive greenspace exposure estimates.
- Product's Contribution to Output: This manuscript describes an analysis of access to green space, exposure to motor vehicle exhaust and asthma and allergy occurrence from a CRA perspective.
- Product's Timeline (with milestones):
  - Final Draft Journal Manuscript to Coauthors: 4/21/17
  - Journal Manuscript Internal Review and EPA Clearance: 7/31/17
  - Journal Manuscript Submission: 1/4/18
- Product's intended user/customer/audience: Regional and Program office Risk Assessors (accessible to scientists and managers)
- Is this a key product? No.

- Does this Product contribute to a Product under another Task? If so, identify other Task. No.

- **Product 6.2.2.2. (*RMS ID# HHRA 3.232.2.2*):**
- **Product Title: Workgroup Report: Greenspace (GS) exposure and health effect occurrence from a Cumulative Risk Assessment (CRA) perspective**
- Product Contact (email): Glenn Rice (rice.glenn@epa.gov)
- Product's Delivery Date: 10/15/16
- Product Description: EPA Workgroup Report
  Product's Contribution to Output: The product represents a report of a workshop that explored the various greenspace measures and the epidemiologic evidence of associations between greenspace exposures and various health outcomes and 2) developing an EPA summary of the workshop findings. This workshop report will summarize the results of an EPA-led workshop that will address greenspace exposure measures, associations with health outcomes and consider these interactions as opportunities for CRA methods to be developed.
- Product's Timeline (with milestones):
  - Final Draft WS Report to Coauthors: 12/15/15
  - Internal Review and EPA Clearance: 4/16/16
  - Submission of Workshop Report for posting on EPA website: 10/15/16
- Product's intended user/customer/audience: Regional and Program office risk assessors, risk managers, city planners, etc (accessible to scientists and managers);
- Is this a key product? No
- Does this Product contribute to a Product under another Task? If so, identify other Task. No.

- **Product 6.2.2.3. (*RMS ID# HHRA 3.232.2.3*):**
- **Product Title: Cumulative risk assessment considerations for chronic kidney disease**
- Product Contact (email): Lin.Yu-Sheng@epa.gov
- Product's Delivery Date: June 30, 2017
- Product Description: Peer-reviewed Journal submission
  The goal of the proposed project is to develop predictive models for the interaction of chemical and other non-chemical stressors, illustrated by a specific example of chemical nephrotoxicity. Chronic kidney disease is associated with exposure to multiple metals (e.g., cadmium, lead, and mercury) and non-chemical (e.g., diabetes), but limited epidemiological studies to date have assessed the combined effects of both chemical and non-chemical stressors on chronic health in the context of cumulative risk assessment. The approach developed in this proposal (e.g., statistical models, see below) has potential to be applied to other U.S. populations exposed to these multiple stressors in order to identify high-risk populations and

inform regulatory policy.
The proposed project will develop conceptual data models (e.g., structural equation models with directed acyclic graph) using the data from national databases (e.g., NHANES datasets) to evaluate the combined impact of metal stressors (lead, cadmium, and mercury) and non-chemical risk factors (e.g., socioeconomic status and diabetes, elevated BMI, and other risk factors) on two major prognostic indicators of kidney disease (e.g., reduced glomerular filtration rate and albuminuria), and later renal-relevant mortality (e.g., renal cancer). For example, structural equation models will be applied to investigate complex associations among predictors of stressors as well as adverse health outcomes (e.g., albuminuria prevalence using cross-sectional analysis).

- Product's Timeline (with milestones):
  - Manuscript to coauthors 12/31/2016 for initial review;
  - Manuscript to Management 3/31/2017;
  - Manuscript ready for submission to peer-reviewed journal 6/30/2017
- Product's Contribution to Output:
  The USEPA has been increasingly considering other non-chemical stressors that may be risk factors for adverse health outcomes or effect measure modifiers. A better understanding of the interactions between the chemical of interest and those stressors could help elucidate the key sources of variability in susceptibility in dose-response analyses.
- Product's intended user/customer/audience: (i) NCEA assessments; (ii) Office of Children's Health Protection and other EPA program offices; (iii) Public at large
- Is this a key product? No
- Does this Product contribute to a Product under another Task? If so, identify other Task. No.

- **Product 6.2.2.4. (*RMS ID# HHRA 3.232.2.4*)**
- **Product Title: The Interaction of Psychosocial Stress with Chemicals that Alter the HPA Axis**
- Product Contact (email): segal.deborah@epa.gov
- Product's Delivery Date: 6/30/2018
- Product Description: Journal manuscript
  This will be a follow-up to a FY2014 HHRA product in which we publishing a paper that evaluated the interaction of lead (Pb^{+}) and psychosocial stress and postulated that their interaction is based, at least partly, on their mutual effects to the HPA axis. We plan to extend this line of research to determine if an interaction with psychosocial stress exists for other chemicals that alter the HPA axis. First, we will survey the literature to determine which other chemical pollutants interact with the HPA axis. Second, we will analyze NHANES data to see if low-SES communities or other vulnerable communities are disproportionately exposed to those chemicals that interact with the HPA axis. Then, we will determine if there is any evidence in the literature (either animal or human) for an interaction between

exposures to chemicals with psychosocial stress. Last, we will determine how this information might be used in a cumulative risk assessment.

- Product's Contribution to Output: The Product will help the risk assessment community to identify chemicals that may interact with psychosocial stress. It will also provide suggestions for how this information might be considered in cumulative risk assessments. It will also help inform CRA guideline efforts.
- Product's Timeline (with milestones):
  - All data acquired and analyzed 7/30/2017
  - Manuscript to coauthors 12/1/2017
  - Manuscript to Management 3/30/2018
  - Manuscript submission to Journal 6/30/2018
- Product's intended user/customer/audience: Advances in understanding how to characterize cumulative risk will benefit all assessment products of the HHRA program (Tasks 1.1, 2.1, 3.1 and 4.1), and inform risk assessment practice across the Agency and at the community level.
- Is this a key product? No
- Does this Product contribute to a Product under another Task? If so, identify other Task. No

References

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NAS (National Academy of Science). 2009. Science and Decisions: Advancing Risk Assessment. Washington, DC: National Academy of Sciences. http://dels.nas.edu/dels/rpt_briefs/IRA_brief_final.pdf.

USEPA. 2003. Framework for Cumulative Risk Assessment. EPA/630/P-02/001F. Washington, D.C.: USEPA. http://nepis.epa.gov/, http://www.epa.gov/raf/publications/framework-cra.htm.

Task 6.3

(*RMS ID# HHRA 3.233*)

Applying Genetic and Epigenetic Data to Inform Susceptibility

Task Lead (TL): Susan Y. Euling (NCEA W)

Task Start Date: 10/01/2015

Task End Date: 09/30/2019

Task Description: The National Research Council's *Science and Decisions: Advancing Risk Assessment* (NRC, 2009) report stated that "Variability in human susceptibility has not received sufficient or consistent attention in many EPA health risk assessments..." Susceptibility is defined by the NRC (2009) as the capacity to be affected. A person can be at greater or less risk relative to population median risk because of susceptibility factors including life stage, sex, genetics, socioeconomic status, prior exposure to environmental chemicals and/or pharmaceuticals, and stress. Improving our understanding of susceptibility in response to environmental chemical exposure and applying this knowledge to risk assessment will improve EPA risk assessments, at the community, single chemical, and cumulative levels.

Two important policy drivers that have required EPA to use susceptibility information environmental chemical decision-making are the Food Quality Protection Act (FQPA, 1996) and the Safe Drinking Water Act amendments (SDWA, 1996). The FQPA (1996) mandated that EPA consider possible increased susceptibility of infants and children in the risk assessments of food use pesticides; and the SDWA amendments (1996) required EPA to consider susceptible populations in risk assessments used in support of drinking water contaminant regulations. Approaches to address life-stage susceptibility have been described, for example, EPA's Supplemental Guidance for Assessing Susceptibility for Early-Life Exposures to Carcinogens (EPA, 2005). However, approaches to incorporate new types of information to inform susceptibility are needed. The goal of Task 6.3. is to apply emerging molecular data to inform susceptibility for risk assessment.

Epigenetic, genomic, DNA sequencing, and polymorphism data are molecular data types that can be used to inform susceptibility and variability. These data have the potential to define susceptible populations and in turn, increase our knowledge of variability in response to a chemical exposure. The

application of the knowledge gained from these molecular data types can enhance our community, single chemical and cumulative risk assessments. EPA, faced with the challenge of evaluating and synthesizing these new data types in risk assessment, can borrow approaches (e.g., Adverse Outcome Framework) for integrating the mechanistic data at different levels of biological organization into risk assessment. EPA also needs to understand the study design requirements for identifying transgenerational effects, which could be mediated by an epigenetic mechanism, in chemical testing. Task 6.3. (*RMS ID# HHRA 3.233*) products have developed innovative science to use new data streams and analysis approaches to inform susceptibility.

Task is separated into two subtasks, one utilizing epigenetic data (i.e., DNA methylation, microRNA expression, and histone modification) and one utilizing genetic susceptibility data (i.e., polymorphism, microarray, DNA sequence) to inform community risk assessment. Task 6.3. (*RMS ID# HHRA 3.233*) intersects with and may inform other HHRA efforts to develop approaches for using new data types, e.g., epigenetics; HHRA Project 8 (*RMS ID# HHRA 4.22*, "Applying Emerging Science to Inform Risk Screening and Assessment", especially Task 8.1.(RMS ID# HHRA 4.221, "Disease-based Integration of New Data Types"). Subtask 6.3.1. is informed by an HHRA workshop on epigenetics and cumulative risk (http://cfpub.epa.gov/ncea/risk/recordisplay.cfm?deid=308271) held in August 2015. Workshops are conducted on critical challenges as part of Task 7.5 (*RMS ID# HHRA 4.215*). The output of the task will support the EPA programs (OW, Children's Office) and regions as well as risk assessors inside and outside of the Agency.

- **Subtask 6.3.1. (*RMS ID# HHRA 3.233.1*): Applying Epigenetics Data to Cumulative Risk**
  Twin studies have shown that expression of diseases is not completely concordant between monozygotic twins and thus, arise in part from differences in environmental factors. Epidemiological and laboratory studies suggest that some environmental chemicals as well as some nonchemical stressors are capable of affecting human health through a variety of epigenetic mechanisms. Epigenetic changes include DNA methylation (hypo or hypermethylation), histone modifications (e.g., acetylation, methylation, glycosylation) and microRNA expression (down or up regulations of specific microRNAs). Evidence suggests that various stressors can influence disease outcomes through the accumulation of epigenetic modifications. Complex interactions among genes, the environment, and disease require the examination of how epigenetic changes regulate susceptibility to environmental stressors.

  Data on epigenetics (heritable phenotypic traits due to chromatin changes without DNA sequence changes) are not routinely evaluated in risk assessment. To address this need, approaches, including literature reviews, case studies, and workshop findings, will increase our ability to interpret these data for cumulative risk assessment.

Science questions that are addressed in Subtask 6.3.1. include the following:

- What are the issues regarding interpretation of epigenetic data (for each of the different markers) and transgenerational effects data for risk assessment? (Products 1,2, 3, and 5)
- Are there approaches to evaluate the quality of publicly available epigenetic data? (Product 1,2, and 5)
- Are there approaches for determining whether there is a causal relationship between an identified epigenetic marker and a disease outcome? (Products 1-5)
- How can nonchemical stressors, which may modulate epigenetic effects after exposure to environmental chemicals, be considered in risk assessment? (Products 1, 3, and 5)
- What is the adequacy of current test methods to identify transgenerational effects? (Product 4)
- What evidence is necessary to support the conclusion that an epigenetic mechanism of action underlies transgenerational effects? (Product 4)

The impact of the work performed in Subtask 6.3.1 (*RMS ID# HHRA 3.233*) will be increased knowledge, experience, and expertise in evaluating and interpreting epigenetic data and transgenerational effect data for application to EPA risk assessment, particularly regarding interindividual variability and susceptibility to environmental chemicals.

- **Subtask 6.3.2. (*RMS ID# HHRA 3.233.2*): Applying Polymorphism and Mechanistic Data to Inform Genetic Susceptibility**

✓ Defining genetic susceptibility, or inter-individual genetic variation, that impacts response to environmental chemicals across human populations is an area of interest to EPA regions and programs that must evaluate susceptibility for their community or for a chemical risk assessment. Molecular data streams including polymorphism data, DNA sequencing data, and genomic data can inform intraspecies variability, due to genetics, in response to chemical exposure. Lessons learned from the 6.3.2. products will improve EPA expertise in reviewing, evaluating and interpreting genetic susceptibility data for the purpose of risk assessment and develop enhanced approaches for defining genetic variability that influence response to chemical exposures.

Science questions that are addressed in Subtask 6.3.2. (*RMS ID# HHRA 3.233.2*) include the following:

- Can an approach be developed for utilizing polymorphism, genomics, and other mechanistic data to inform susceptibility for risk assessment (at the community, single and multi-chemical level)? Can the AOP Framework

enhance our ability to integrate these different data types? (Products 1 and 2)
- What are the issues regarding interpretation of polymorphism data, DNA sequence, and mechanistic data for informing genetic susceptibility that impacts human response to environmental chemical exposures? (Product 2)
- Are there approaches for evaluating the quality of publicly available polymorphism, DNA sequence, and genomic data? (Product 2)

The impact of the work performed in Task 6.3. (*RMS ID# HHRA 3.233*) will be the establishment of EPA expertise in reviewing, evaluating and interpreting genetic and epigenetic data for the purpose of improving our understanding of susceptibility information for risk assessment. The products within Task 6.3. (*RMS ID# HHRA 3.233*) are designed to support risk assessments within EPA, the Programs, Regions and EPA's Children's Office, and outside of EPA. Utilizing molecular data to gain knowledge about susceptibility also supports one of the EPA Administrator's themes, *Making a Visible Difference in Communities across the Country*.

Task Approach:
Details regarding the approaches taken in each of the two subtask areas, the first aimed at the use of epigenetic information and the second aimed at genetic data to inform susceptibility considerations, can be found in the subtask descriptions (above) as well as in the product descriptions for each subtask that follow.

Task Products:

- **Subtask 6.3.1. (*RMS ID# HHRA 3.233.1*): Applying Epigenetics Data to Cumulative Risk**

- **Product 6.3.1.1. (*RMS ID# HHRA 3.233.1.1*)**
- **Product Title: Report from the Epigenetics and Cumulative Risk Assessment Workshop**
- **Product Co-Leads (emails):** Kenneth Olden (olden.kenneth@epa.gov), Paul White (white.paul@epa.gov), and Teneille Walker (walker.teneille@epa.gov)
- **Product Description:** This workshop (held Sept. 2-3, 2015) brought together experts to examine the role that data on epigenetic changes can play in assessing cumulative risks in human populations exposed to multiple stressors. Attention was given to needs of neighborhood level health assessment, with consideration of the joint effects of traditional environmental stressors and social stressors contributing to adverse health outcomes.
  The Workshop on Epigenetics and Cumulative Risk Assessment (convened in September 2015; (http://cfpub.epa.gov/ncea/risk/recordisplay.cfm?deid=308271) had two main components: 1) examination the state of science on the role of epigenetic changes in

mediating the relationship between environmental stressors and disease processes and the role of neighborhood context; and 2) examination of opportunities and developmental needs for practical application of epigenetic measures to address cumulative risks from environmental stressors. This workshop report will include the perspectives from multiple sectors, including academia and the environmental community, interested in the role of epigenetics in exposure to environmental stressors. The workshop participants will discuss the following science questions:

- *What are the developmental origins of disease as it relates to environmental exposures?*
- *Can the epigenome be used as a biomarker for exposure?*
- *How does the potential reversibility of environmental epigenetic changes play a role in risk assessment or the larger paradigm of diseases?*

The workshop report will be prepared for journal publication. During workshop planning, we will consider whether joint publication(s) authored by workshop participants are feasible and desirable.

- **Product's Delivery Date:** 6/30/16 (Submission to journal)
- **Product's Contribution to Output:** This workshop report will contribute to the overall understanding of how to utilize epigenetics information in cumulative risk and community-based risk assessment.
- **Product Type:** Workshop report in the form of a manuscript submitted to a peer-reviewed journal
- **Product's Timeline (with milestones):** Workshop held, Sept 2-3 2015; Journal submission of manuscript reporting on workshop 6/30/2016
- **Product's intended user/customer/audience:** Risk assessment community; EPA programs addressing chemical contamination, environmental justice and childrens' health.
- **Is this a key product?** No.
- **Related products:** This would coordinate with the efforts in other tasks related to epigenetics (in Subtask 6.3.1.) as well as a recently convened workshop in Task 7.5. (HHRA Workshop held September 2-3, 2015; http://cfpub.epa.gov/ncea/risk/recordisplay.cfm?deid=308271)

- **Product 6.3.1.2. (*RMS ID# HHRA 3.233.1.2*)**
- **Product Title: Human Epigenetic-Disease Case Study of Metals and Cardiovascular Disease**
- **Product Contact (email):** Raghu G Nath (nath.raghu@epa.gov)
- **Product's Delivery Date:** 9/30/17
- **Product Description:** The overall goal of this product is to identify and compile the available literature on epigenetics, identify a subset of literature specifically targeting epigenetic changes as a result of chemical stressors, and prepare one case study relevant to a specific disease outcome. This information will be useful to the IRIS program (HHRA Topic 1) as its multi-year agenda for this planning period includes several metals. Program offices and all the regions of EPA will also be supported. The case study report will also be made available to the outside scientific community.
- **Product Approach:** An epigenetic-human disease case study will be developed. The selection process for selecting the case study scenarios (i.e., epigenetic marker, disease, and chemical) will consider data availability and quantity, interest/relevance to IRIS, EPA programs, and/or EPA regions. A potential case study example scenario of toxicologically relevant metals and epigenetic regulation (reviewed in Ryu et al., 2015; Ho et al., 2012) is –
    - *MicroRNA alterations in cardiovascular diseases from exposure to heavy metals.* This case study would focus on microRNA expression effects after mercury exposure from various sources. Other heavy metals and their mixtures as well as nonchemical stressors will be reviewed and resulting contributions to cardiovascular diseases in different subgroups (e.g., socioeconomic groups) within the population will be analyzed.

  Published articles and reports will be identified using EPA's Health and Environmental Research Online (HERO) database which allows for a systematic review of the literature including searching PubMed, Web of Science, and Toxline, sorting, and accessing articles. An initial list of search terms has been prepared and submitted to HERO. Human disease relationships at the community level will also be gathered using a variety of methods including surveys and the National Health and Nutrition Examination Survey (NHANES) database.

- **Product Type:** Submission of manuscript in a peer-reviewed journal
- **Product's Timeline (with milestones):**
    - 1st Case Study Final Draft Manuscript to Coauthors: 3/30/17
    - 1st Case Study Manuscript Internal Review and EPA Clearance: 5/1/17
    - 1st Case Study Manuscript submission to journal: 9/30/17
- **Product's intended user/customer/audience:** Regional and Program office Risk Assessors. The case study information will be useful to EPA research laboratories (e.g., NHEERL) as they design studies to study epigenetic mechanisms.
- **Is this a key product?** No.
- **Does this Product contribute to a Product under another Task? If so, identify other Task.** Yes. This product could be utilized across the HHRA assessment product portfolio

in the development of ISAs, PPRTVs, and several IRIS assessments for metals on its multi-year agenda.

- **Product 6.3.1.3. (RMS ID# HHRA 3.233.1.3)**
- **Product Title: Epigenetic Alterations: A Mechanism Through Which Nonchemical Stressors Increase Susceptibility to Chemical Stressors**
- **Product Contact (email):** Deborah Segal (segal.deborah@epa.gov)
- **Product's Delivery Date:** 9/30/19
- **Product Description:** Research has demonstrated that psychosocial stress, a nonchemical stressor, results in epigenetic changes. Many of these epigenetic changes affect the functioning of the Hypothalamic-Pituitary-Adrenal axis. For this product, we will investigate whether such epigenetic changes resulting from psychosocial stress can help to explain the interaction of psychosocial stress with chemical stressors, such that individuals who are exposed to higher levels of psychosocial stress may face greater developmental neurotoxicity following exposure to toxic chemicals. As low-socioeconomic status (SES) communities are believed to confront higher levels of psychosocial stress and chemical exposures than higher SES communities, this research will have important implications for community-based risk assessments in lower-income and environmental justice communities.
- **Product Type:** Journal Manuscript Submission
- **Product's Contribution to Output:** This case study will help to elucidate one mechanism by which nonchemical stressors exacerbate the response to chemical exposures. The results of the case study will have broad application to understanding potential interactions between nonchemical stressors and responses to chemical exposures, which could in turn lead to improved community health protection.
- **Product's Timeline (with milestones):**
    - Final Draft Journal Manuscript to Coauthors: 3/30/19
    - Journal Manuscript Internal Review and EPA Clearance: 5/1/19
    - Journal Manuscript Submission: 9/30/19
- **Product's intended user/customer/audience:** Regional and Program office Risk Assessors (accessible to scientists and managers). This product will build on efforts underway in Task 6.2 to understand interactions of chemical/nonchemical stressors. Further, this product may help to develop future methods for considering chemical/non-chemical stressor interactions in risk assessments.
- **Is this a key product?** No.
- **Does this Product contribute to a Product under another Task?** No.

- **Product 6.3.1.4. (*RMS ID# HHRA 3.233.1.4*)**
- **Product Title: Incorporating Transgenerational Testing and Epigenetic Mechanisms into Chemical Testing and Risk Assessment: A Literature Survey of Transgenerational Responses in Environmental Chemical Studies**
- **Product Contact (email):** Susan Makris (makris.susan@epa.gov)
- **Product's Delivery Date:** June 2017

  Product Description: A number of environmental chemicals have been shown to alter epigenetic markers. Some published multi-generation rodent studies have identified effects on F2 and later generations after chemical exposures solely to F0 dams, but these studies were not focused on chemical safety. A question of interest is -What is the adequacy of current test methods to identify transgenerational effects? To address the specific question of how could outcomes related to epigenetic changes be identified and incorporated into chemical testing and risk assessment, a systematic literature review to identify transgenerational studies in rodents will be conducted. The studies will be evaluated to characterize the methods and observed outcomes, and to identify strengths, limitations, and biases.
  A preliminary evaluation of a subset of the literature found that many of the studies identify chemicals or combinations of chemicals that produce transgenerational effects and/or adult-onset diseases, but there appears to be a paucity of published studies indicating a lack of transgenerational effects, perhaps due to publication bias. A number of study design issues were identified including the numbers of litters assigned to control and test groups are not always transparently reported, nested statistical analyses of data are not always utilized to address litter effects, and "blind" testing is seldom performed.

- **Product Type:** A draft manuscript will be prepared for publication in a peer-reviewed journal.
- **Product's Contribution to Output:** This effort will be focused on identifying ways in which potential hazards identified in transgenerational epigenetic research studies might be applied to the traditional toxicity testing and risk assessment paradigm for environmental chemicals.
- **Product's Timeline (with milestones):**
  - Oct 2015 - HERO literature search
  - Dec 2015 - Identify and download pdfs for transgenerational epigenetic studies
  - Feb 2016 - Evaluate studies
  - April 2016 - Analyze results
  - Aug 2016 - Draft manuscript
  - Oct 2016 – Team review and literature update
  - Feb 2017 - Initiate EPA review and clearance process
  - June 2017 - Submit manuscript for publication
- **Product's intended user/customer/audience:** There is interest in this topic in the broad scientific and risk assessment community. The manuscript will address the evaluation and use of transgenerational studies for risk evaluation in ORD/NCEA (IRIS assessments), Program Offices such as OSCPP, OW, OSWER, and OCHP, and Regional Offices. In addition, it will provide

information useful to EPA research laboratories (e.g., NHEERL) as they design studies to study transgenerational epigenetic effects.

- **Is this a key product?** No.
- **Does this Product contribute to a Product under another Task?** If so, identify other Task. This product will support assessments in the HHRA program.

- **Product 6.3.1.5. (*RMS ID# HHRA 3.233.1.5*)**
- **Product Title: Interpreting Epigenetic Data for Risk Assessment: A Framework**
- **Product Contact (email):** Susan Euling (euling.susan@epa.gov)
- **Product's Delivery Date:** September 2019
- **Product Description:** EPA needs to carefully review epigenetics data of all types to determine the appropriate methods for and issues in data interpretation for single and multiple chemical risk assessment. A framework for risk assessors to structure their searches, review and interpret epigenetic data for risk assessment is needed. Components of the report will include: 1) Data quality issues; 2) Lessons learned from the from completion of Products 1-4, above; and 3) Issues involved in establishing whether there is a causal relationship between the various epigenetic markers and later life disease.
- **Product Contributors:** Anu Mudipalli (NCEA W); Janice Lee, (NCEA IRIS); Susan Makris, (NCEA W); Deb Segal (NCEA W).
- **Product Type:** EPA Report
- **Product's Contribution to Output:** A framework that provides risk assessors with a method to structure their searches, review, quality assessment, and interpretation of epigenetic data for risk assessment. This is one of the key outputs of Subtask 6.3.1.
- **Product's Timeline (with milestones):**
    - December 2015 - Initiate HERO literature search; identify publicly available human epigenetic data sources
    - August 2016 – Evaluate studies: Identify study quality issues
    - December 2016 - Evaluate epigenetic data sources: Identify study quality issues
    - August 2017 – Expert review of data: causal relationship issue
    - December 2018 – Compile lessons learned from Products 1-4
    - August 2018 - Draft manuscript
    - October 2018 – Revisions based on team review
    - February 2019 – Incorporate newly completed Task 6.3.1. product findings into the framework
    - March 2019 - Initiate EPA review and clearance process
    - September 2019 – Submit manuscript to journal
- **Product's intended user/customer/audience:** There is interest in evaluating epigenetic data in the broad scientific and risk assessment community. The manuscript will address the evaluation and use of epigenetics data for risk evaluation in ORD/NCEA (IRIS assessments), Program Offices such as OSCPP, OW, OSWER, and OCHP, and Regional Offices.
- **Is this a key product?** TBD.
- **Does this Product contribute to a Product under another Task?** If so, identify other Task. No

Subtask 6.3.2. (*RMS ID# HHRA 3.233.2*): Applying Polymorphism and Mechanistic Data to Inform Genetic Susceptibility

- **Product 6.3.2.1. (*RMS ID# HHRA 3.233.2.1*) Product Title: Use of the Adverse Outcome Pathway (AOP) Framework for the Incorporation of Intraspecies Genetic Susceptibility Information in Community Risk Assessment**
- **Product contact (email):** Susan Euling, NCEA W (euling.susan@epa.gov); Contributors: Holly Mortensen, NHEERL; Bonnie Joubert, NIEHS; Janice Lee, IRIS.
- **Product's Delivery Date:** February 2017
- **Product Description:** An approach to integrating mechanistic and polymorphism data to characterize genetic susceptibility to chemical exposure was previously described (Mortensen and Euling, 2013). In human health risk assessment, data on susceptibility can be derived based on a study of a susceptible population and/or an intraspecies uncertainty factor may be applied to account for the lack of information about susceptibility. Defining genetic susceptibility in response to environmental chemicals across human populations is an area of interest in the NAS' new paradigm of toxicity pathway-based risk assessment (NRC, 2010). This draft manuscript for publication will develop an approach for the incorporation of human genetic susceptibility information from publically available sources (e.g., Tox21 s1500, NIEHS Environmental Genome Project). The approach will adapt the previously defined Adverse Outcome Pathway (AOP) construct (Ankley et al., 2010) to organize and integrate genetic susceptibility information. This project will explore the utility of new genomic data streams in addressing issues of susceptibility to adverse outcomes at the population and community levels, and the utility of this information for application to community, single chemical and cumulative risk assessment.
- **Product Type:** Manuscript
- **Product's Contribution to Output:** The first manuscript will describe the approach for incorporating genetic inter-individual variability information within humans using the AOP construct (Ankley et al., 2010) for use in risk assessment.
- **Product's Timeline (with milestones):**
    - Sept 2015: Initiate approach development and literature search
    - June 2016: Draft manuscript for inclusion of intraspecies genetic susceptibility information using AOP framework
    - August 2016: Revisions based on team input
    - Sept. 2016: Internal Review of manuscript
    - November 2016: Clearance of manuscript
    - February 2017: Submission to peer-reviewed journal
- **Product's intended user/customer/audience:** Regional and Program office Risk Assessors. In particular, Region 3 is interested in this approach and case study in risk assessment for environmental chemicals (Gross-Davis et al., 2015). This product will build capacity in utilizing publically available polymorphism data derived from large, genomic re-sequencing projects in risk assessment, making it useful to new chemical assessments at EPA.

- **Is this a key product?** No.
- **Does this Product contribute to a Product under another Task? If so, identify other Task.** Yes. HHRA 6.1. (*RMS ID# 3.231*) is considering AOP as basios for integration of ecological and human data so this product will contribute to that task. A related manuscript has been proposed as a Milestone for CSS Task 1.1c: Taxonomic Relevance of AOPs, for specifically between species relevance of AOPs.

- **Subtask 6.3.2. (*RMS ID# HHRA 3.233.2*): Applying Polymorphism and Mechanistic Data to Inform Genetic Susceptibility**
- **Product 6.3.2.2 (*RMS ID# HHRA 3.233.2.2*). Application of the AOP Framework for the Incorporation of Intraspecies Genetic Susceptibility Information: Case Study Applied to Community Risk Assessment**
- **Product contact (email):** Holly Mortensen, NHEERL (mortensen.holly@epa.gov); Contributors: Janice Lee, (NCEA IRIS); Bonnie Joubert, NIEHS; Susan Euling (NCEA W).
- **Product's Delivery Date:** January 2018
- **Product Description:** This product is a collaboration with EPA NHEERL, EPA NCEA, and NIEHS.
- A case study will test the approach described in Product 6.3.2.1 (*RMS ID# HHRA 2.233.1*). A well-characterized AOP and publicly available human genetic variation data sources will be utilized to characterize genetic variation at loci associated with an adverse outcome. The case study will allow us to examine the utility of publically available human genomic and polymorphism data for addressing the role of genetic variation in adverse outcome across individuals and populations. A number of environmentally responsive gene targets have been identified in human populations (*e.g.*, Tox21 s1500 [http:// ntp.niehs.nih.gov/go/S1500]), NIEHS Environmental Genome Project [(http://egp.gs.washington.edu/]), and these targets have been characterized across populations and for functional relevance. For each case study, single nucleotide polymorphism (SNP) information for each locus implicated in the adverse outcome, along with population frequency information for the molecular initiating event (MIE) and subsequent key events (KEs), will be investigated. The relevance of allelic and haplotypic differences at these gene targets between individuals, and the consequence for variation in adverse outcome at the population level, will be explored.
- **Product's Contribution to Output:** This manuscript will implement the framework using established AOPs as case studies, examining their utility in risk assessment.
- **Product's Timeline (with milestones):**
    - June 2016- Review of approach developed and selection of candidate AOPs for case study
    - August 2016 -Select AOP for case study
    - March 2016 - Compilation of available data sources
    - May 2016-Begin consolidation of data sources and analyses
    - April 2017- Draft manuscript
    - June 2017 – Team Review of Manuscript
    - September 2017 – Initiate clearance
    - January 2018 – Submission to peer reviewed journal(s)

- **Product's intended user/customer/audience:** Regional and Program office Risk Assessors. In particular, Region 3 is interested in this approach and case study in risk assessment for environmental chemicals (Gross-Davis et al., 2015). This product will build capacity in utilizing publically available polymorphism data derived from large, genomic re-sequencing projects in risk assessment, making it useful to new chemical assessments at EPA.
- **Is this a key product?** No.
- **Does this Product contribute to a Product under another Task? If so, identify other Task.** Yes, Task 6.1.

Overall Task Constraints:

Define scientific, logistical, and technical constraints associated with completing the Task

- ✓ **Scientific**: Janice Lee, Raghu Nath, Deb Segal, Anu Mudipalli, Nagu Keshava, Yu-Sheng Lin, Susan Euling, Susan Makris, and Teneille Walker work on IRIS chemicals. They may have a change in their availability due to high priority chemical assignments. Holly Mortensen works at NHEERL's genomics core and thus, has incoming work requests that may be of higher priority.
- ✓ **Logistical**: There may be a lag in the time to award of a contract and work order on an existing contract.
- ✓ **Technical**: Need for specific data and analyses (products 6.3.1.2, 6.3.1.3, and 6.3.2.2).
- ✓ **Resources**: Time to award of contracts and hiring are potential constraints.

Task Dependencies:

- ✓ **Dependency:** Product 6.3.1.5 is only partially dependent on the completion of products 6.3.1.1-4. Product 6.3.2.2 is dependent on the completion of product 6.3.2.1.

Task Resources: *Please see funding and FTE tables, below.*

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Task 6.4

(*RMS ID# HHRA 3.234*)

Apportioning Multimedia Exposure and Risk Across Human and Ecological Receptors

Task Leads (TLs): Jennifer Richmond-Bryant (NCEA RTP) and Jacqueline Moya (NCEA W)

Task Start Date: 10/01/2015

Task End Date: 09/30/2019

Task Description:

The National Academy of Sciences stated that to address community concerns about exposure to stressors, "as the number and types of stressors and endpoints under consideration increase, decisions must be made about which dimensions should be considered as components of risk assessment as defined and used by EPA." (National Research Council, 2008). This Task will focus on relationships among multiple stressors and their sources to human and ecologic receptors for the purpose of apportioning risk. Hence, the overall objectives of this task are 1) to address scientific challenges regarding integration of exposure assessment considerations for multiple stressors into cumulative risk applications and 2) to explore stressors that may modify exposures and may influence dose-response relationships for cumulative risk applications.

The impact of this task will be to expand NCEA's and the Agency's knowledge base regarding the application of multimedia, multiple stressor exposure data in cumulative risk assessment.

Examples of research questions to be explored through this task include:

Integration of Cumulative Exposure Assessment Measures within Human Health and Ecological Effects Studies:

- How do scientists rectify differences in exposure measurement error among multiple stressors in cumulative risk studies of different focus (i.e., epidemiology, ecology)? How do the following issues influence exposure measurement error for different stressors and media: differences in spatial and temporal variability of the concentration profile; differences among media in delivering stressors to the receptors with respect to transport, chemistry, and fate; and differences among sampling methodologies for each specific medium-stressor combinations?
- How can results be compared across epidemiologic studies of health or ecological effects related to exposure to stressors for different exposure scenarios? If results can be compared across epidemiologic studies, can toxicology studies be designed in a complementary manner to address research questions about common exposures/mixtures of exposures to inform multiple events along an adverse outcome pathway? If so, how can exposures be generated for toxicology studies to best represent exposures to stressors in epidemiology studies? How does chemical stability of multiple stressors influence such differences?

Integrating Evidence of Human Health and Ecological Effects of Pollution Exposure among Different Media:

- How can risk be apportioned for specific exposures to or sources of multiple stressors when the EPA regulates pollution by medium?
- How (or to what degree) can risk be quantified for non-chemical stressors and other factors not regulated by EPA?
- How should risk be apportioned among different media (e.g., when based on biomonitoring data integrated across multiple sources and routes of exposure)?
- What is the best way for information on different routes of exposure (e.g., inhalation, ingestion, dermal), including information on uncertainties in different media and routes, to be integrated?

Factors Influencing Exposure or Leading to Modification of Health Effects:

- How do diet and behavioral factors influence multiple stressor, multimedia exposures? How do such factors modify effects associated with exposures to stressors via multiple media?
- What behavioral, social, demographic, economic, and other external factors influence multiple stressor, multimedia exposures and modify health effects? Similarly, what factors influence multiple stressor, multimedia exposures and modify ecological effects?

Research Approach:

Researchers will engage in ongoing analyses of multiple stressor and/or multimedia exposures that influence cumulative risk assessment. The results of these analyses will be presented in the peer-reviewed literature, so that they are available for reference in NCEA assessments. Two distinct subtasks focus on advancing NCEA's multiple stressor, multimedia knowledge base through model development and application. Details on products from each are described in the next section.

- **Subtask 6.4.1. (*RMS ID# HHRA 2.234.1*): Advances in modeling for exposure apportionment in the study of multiple stressor exposure via multiple media:** This subtask expands NCEA's and the Agency's ability to model multiple stressors by developing and testing three approaches: multiple pathway exposure modeling (using phthalates as a test case), apportionment of exposure via multiple pathway modeling, and apportionment of exposure and risk via modeling of multiple stressors' physical and chemical properties.

  Product 6.4.1.1. (*RMS ID# HHRA 3.234.1.1*) Modeling dermal and inhalation exposures to diethyl- and di(1 n-butyl) phthalate: The EPA will investigate the two main pathways for phthalate exposure (consumer products and diet), focusing on two phthalates with the potential to extrapolate the results to other phthalates. The objective of this work is to model the full pathway of air-skin/lung-bladder to predict urine concentrations for comparison with experimentally measured concentrations of DEP and DnBP metabolites. While the experimental data provides a "proof of concept" for the importance and differences in dermal and inhalation intakes, the modeling provides a predictive tool that can then be extrapolated to the general population, occupational, or other settings to characterize the exposures resulting from air concentrations of DnBP and DEP.

  Product 6.4.1.2. (*RMS ID# HHRA 2.234.1.2*) Apportioning chemical stressors for the most affected portions of exposed populations of humans and ecological receptors: This study will review the published studies of cumulative exposures to mixtures and investigate how new research can be applied to the task of apportionment for specific populations. The project will also analyze the predictions of cumulative exposures that will be generated by several modeling approaches. The work would seek to determine when the upper bound of a population is driven by one or two stressors and when groups of stressors drive risk and to develop ways of identifying the specific drivers of the impacts in the upper bound.

  Product 6.4.1.3. (*RMS ID# HHRA 2.234.1.3*) Chemical and physical properties of multiple stressors and cardiovascular effects: NCEA exposure assessment scientists have been participating in a collaboration with scientists from academia to study the impact of multiple stressors on cardiovascular disease (CVD) risk factors. The study will

continue this work by identifying the physicochemical properties of a wider set of air pollutants contributing to CVD risk factors using quantitative structure activity relationship (QSAR) models and estimate epidemiologic associations between CVD risk factors and multiple stressors using an epidemiologic model that includes the physicochemical properties of pollutants identified by the QSAR models.

- **Subtask 6.4.2 (*RMS ID# HHRA 2.234.2*): Application of exposure apportionment in the study of multiple stressor exposure via multiple media:** The methodologies developed above will be applied to investigate how exposures can be apportioned for two specific cases. First, pathway analysis will be applied to study breast milk as a route of exposure for multiple stressors and nutrients. Second, exposures to multiple stressors will be apportioned for multiple media in a test city (Philadelphia) for which the Agency holds a substantial amount of data.

  Product 6.4.2.1. (*RMS ID# HHRA 2.234.2.1*) Breastfeeding as a route of exposure for environmental chemicals as well as nutrients: The purpose of this study is to provide a comprehensive literature evaluation on the potential for the reduction in optimal benefits of breastfeeding that may arise due to infant exposure to one or more chemicals in breast milk. The core goal of the health outcome evaluation will be on the epidemiological literature that has evaluated the benefits of breast milk.

  Product 6.4.2.2. (*RMS ID# HHRA 2.234.2.2*) Cumulative exposures, social determinants, and health in Philadelphia: This study will combine ambient concentration data for criteria air pollutants and benzene with survey data on health, fast food consumption, sugary beverage consumption, tobacco usage, number of servings of fruits and vegetables, sodium intake, access and quality to fresh produce, and availability of green space to analyze associations between ambient pollutants and other determinants of health.

Task Products:

- **Subtask 6.4.1. (*RMS ID# HHRA 2.234.1*): Advances in modeling for exposure apportionment in the study of multiple stressor exposure via multiple media**

  - **Product 6.4.1.1. (*RMS ID# HHRA 2.234.1.1*)**
  - **Product Title: Modeling of dermal and inhalation exposures to diethyl- and di(1 n-butyl) phthalate**
  - Product Contact (email): lorber.matthew@epa.gov
  - Product's Delivery Date: September 30, 2017
  - Product Description: One or more peer-reviewed journal articles
  - Product's Contribution to Output: This peer-reviewed article will inform cumulative risk assessment efforts related to consideration of phthalate exposure mixtures.
  - Product's Timeline (with milestones): Draft of journal article for internal clearance anticipated 1st Quarter FY17
  - Product's intended user/customer/audience: IRIS and Program Office (particularly OPPT) who are conducting assessments on phthalates.
    Is this a key product? No
    Does this Product contribute to a Product under another Task? Yes. This project will be useful to IRIS assessments on phthalates and of interest to OCSPP.

  - **Product 6.4.1.2. (*RMS ID# HHRA 2.234.1.2*)**
  - **Product Title: Apportioning chemical stressors for the most affected portions of exposed human populations and ecological receptors**
  - Product Contact (email): price.pauls@epa.gov
  - Product's Delivery Date: September 30, 2018
  - Product Description: Two or more peer-reviewed journal articles
  - Product's Contribution to Output: These peer-reviewed articles will inform cumulative risk assessment efforts in the apportionment of chemicals in exposed populations of humans and ecological receptors.
  - Product's Timeline (with milestones): Draft of first journal article for internal clearance anticipated 2st Quarter FY17 and additional article(s) by 2nd quarter of FY18
  - Product's intended user/customer/audience: Program Offices (particularly OPPT). This work will also support other projects in the HHRA program, as well as the CSS and SHC research programs.
  - Is this a key product? TBD
  - Does this Product contribute to a Product under another Task. Yes. These products will support work in Subtasks 6.1 and 6.2.

- **Product 6.4.1.3. (RMS ID# HHRA 2.234.1.3)**
- **Product Title: Chemical and physical properties of multiple pollutants and cardiovascular effects**
- Product Contact (email): richmond-bryant.jennifer@epa.gov
- Product's Delivery Date: September 30, 2019
- Product Description: One peer-reviewed journal article
- Product's Contribution to Output: This peer-reviewed article will be available for citation in government reports on cumulative risk assessment and in the Integrated Science Assessments.
- Product's Timeline (with milestones): Draft of journal article for internal clearance anticipated 1st Quarter FY19
- Product's intended user/customer/audience: NCEA and OAQPS
- Is this a key product? No
- Does this Product contribute to a Product under another Task? Yes. This contributes to Tasks under Project 2, Integrated Science Assessments.

- **Subtask 6.4.2. (*RMS ID# HHRA 2.234.2*): Application of exposure apportionment in the study of multiple stressor exposure via multiple media**

  - **Product 6.4.2.1. (*RMS ID# HHRA 2.234.2.1*)**
  - **Product Title: Breastfeeding as a route of exposure for environmental chemicals as well as nutrients**
  - Product Contact (email): lorber.matthew@epa.gov
  - Product's Delivery Date: September 30, 2016
  - Product Description: One peer-reviewed journal article
  - Product's Contribution to Output: This peer-reviewed article will be available for citation in government reports on cumulative risk assessment and in the Integrated Science Assessments.
  - Product's Timeline (with milestones): August 2015: Draft suitable for internal EPA review; February 2016: Submission of manuscript to a peer-reviewed journal
  - Product's intended user/customer/audience: NCEA, Office of Children's Health Protection (OCHP)
  - Is this a key product? No.
  - Does this Product contribute to a Product under another Task? This product will likely inform exposure considerations for CRA case studies in Task 6.2 (*RMS ID# HHRA 2.232*).

  - **Product 6.4.2.2. (*RMS ID# HHRA 2.234.2.2*)**
  - **Product Title: Cumulative exposures, social determinants, and health in Philadelphia**
  - Product Contact (email): richmond-bryant.jennifer@epa.gov
  - Product's Delivery Date: March 30, 2019
  - Product Description: One or more peer-reviewed journal articles

- Product's Contribution to Output: One peer-reviewed article will inform urban cumulative risk assessment efforts in the apportionment of chemicals for human exposure.
- Product's Timeline (with milestones): Draft of first journal article for internal clearance anticipated 2st Quarter FY18 and additional article(s) by 2nd quarter of FY19
- Product's intended user/customer/audience: Program Offices (particularly OPPT). This work will also support work across the HHRA program as well as the CSS, and SHC research programs. It is also of keen interest to Region 3.
- Is this a key product? No.
- Does this Product contribute to a Product under another Task? Yes. This products will help to inform case studies in Task 6.2.

References:

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Silva E, Cerejeira M, 2015. Concentration addition-based approach for aquatic risk assessment of realistic pesticide mixtures in Portuguese river basins. Environmental Science and Pollution Research May 2015, Volume 22, Issue 9, pp 6756-6765

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Young, B and Price P. Application of the Maximum Cumulative Ratio (MCR) Approach Using Residue Data from Pesticide Data Program and the Cumulative and Aggregate Risk Evaluation System (CARES) Model; ISES 2014 Annual meeting.

Task Constraints:

For all of the research activities in the five subtasks, inferences from the study results are constrained by the quality and availability of exposure and health data used in the studies. Execution of each of the sub-tasks is also constrained by the availability of funding and FTEs for EPA staff.

Task Dependencies:

Successful implementation of the research described in Sub-tasks 6.4.1-6.4.5 is contingent upon availability of data and of staff time to complete the studies. Release of any published reports for either government or peer-reviewed publications depends on efficient internal review and clearance processes.

Task Quality Assurance and Data Management Needs:

- Is there an existing IRP/ QAPP(s) that applies to this Task? If so, identify IRP/QAPP. If new IRP/QAPPs are required, provide the status.
    - Yes. NCEA-16-00004. Quality Assurance Project Plan (QAPP) For HHRA Projects 6, 7, & 8 To Develop Methods, Tools, Models and Supporting Analysis

- Will this Task involve large amounts of data that need a data management plan? If yes, explain.
    - TBD. The Health and Environmental Research Online (HERO) system is used for systematic literature review and is covered by a separate QAPP: NCEA-16-00005. Quality Assurance Project Plan (QAPP) For Extraction of Scientific Data Into the Health and Environmental Research Online (HERO) Database System

Human Health Risk Assessment (HHRA)

Project Planning Tool

Project Plan

HHRA Project 7 (*RMS ID# HHRA 4.21*): *Advancing Hazard Characterization and Dose-response Methods*

Project Leads (PLs): Allen Davis (NCEA RTP) and Andrew Kraft (NCEA W)

Project Development Team Members: Glinda Cooper (NCEA IRIS), Molini Patel (NCEA RTP), Beth Owens (NCEA CIN), John Fox (NCEA W), Karen Hogan (NCEA IRIS), Tom Bateson (NCEA W), Todd Blessinger (NCEA W), Jason Fritz (NCEA IRIS), Catherine Gibbons (NCEA IRIS), Andrew Hotchkiss (NCEA IRIS), George Woodall (NCEA RTP), Susan Makris (NCEA IRIS), David Bussard (NCEA W), and Lynn Flowers (NCEA IO)

Project start date: 10/01/2015

Project end date: 09/30/2019

Executive Summary

Project 7 addresses the on-going need to modernize and refine risk assessment methodologies by identifying critical challenges and advancing new analytical approaches and applications to incorporate new science, methods and technologies to address them. This project will address how best to advance systematic review for the HHRA assessment product portfolio and develop methods to identify,

evaluate, and integrate evidence streams, including mechanistic information, into hazard and causal determinations for both cancer and non-cancer endpoints. Other work will continue to improve approaches for dose-response analysis and to explore new methods for quantifying health benefits of exposure reductions. A critical challenge of how best to characterize risk from real-world exposures, including acute and episodic or fluctuating scenarios, will be investigated using case studies and visualization tools to advance understanding and motivate more accurate risk characterizations.

Research Project Description

Numerous decisions made by the Agency require reliable risk assessments as their scientific foundation. Tasks in this project advance new approaches and refine procedures to address specific challenges that arise across HHRA assessment activities. Systematic review methods were recommended by the NRC (NRC, 2009; 2011; 2014) and aid transparency of assessment activities and inform evidence integration for determination of hazard. Steps include identifying relevant studies and evaluating their quality, identifying relevant endpoints for human health risk evaluation, evaluating mechanistic information, synthesizing study results within an evidence stream for a health effect (e.g., human, animal, mechanistic), and integrating qualitative and quantitative information across evidence streams (Figure 7-1). Work in this project will further refine approaches for systematic review across all HHRA assessment products, incorporate data from various types of studies including mechanistic, and develop advanced methods for quantifying human health risks (as well as the associated uncertainties) from real-world exposure scenarios in a manner that is most useful to Agency partners, thereby facilitating stakeholder input into the development of approaches to solve critical and often controversial HHRA scientific issues.

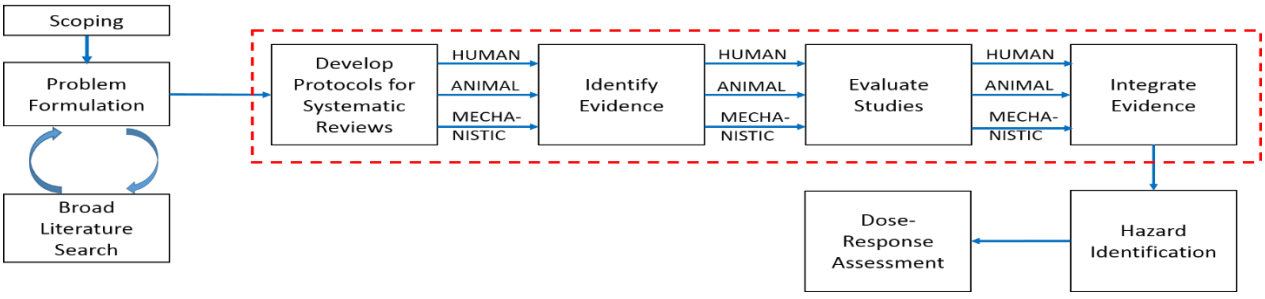

Figure 7-1. Systematic Review as applied in the IRS process. Adapted from *Review of EPA's Integrated Risk Information System (IRIS) Process.* Washington DC: The National Academies Press, 2014

Project Impact

Risk assessment is a dynamic application. In order to remain credible as the foundation for decision making, risk assessment must keep contemporary with current scientific concepts and emerging understanding of disease processes resulting from exposures to contaminants. Assessments that include an integration of the full spectrum of relevant evidence and information on key events involved with disease due to contaminant exposures will expand the basis for decision making and ensure that they are public health protective. Advancing systematic review and quantitative methods will additionally ensure that the nature of the response to these exposures is well characterized. Together the tasks facilitate decision making and advance the supporting science.

Project Scope

The reliance on HHRA products across a large landscape of decision making, from priority-setting or screening to supporting the setting of National Ambient Air Quality Standards, requires comprehensive coverage of cutting-edge issues across several critical challenge areas and a dedication to continued improvement. Enhancing hazard characterization, expanding the repertoire of quantitative dose-response methods and models, addressing and characterizing the utility of emerging data and new computational tools as applied to risk assessment, will all ensure that such Agency decisions continue to be based on sound science and incorporate the latest technologies to protect the public health and environment. This requires identification of contemporary concepts and issues based on evaluation of their relevance to the problem formulation of the given assessment, production of HHRA products that are most translatable to Agency decision-making efforts, and consistent application of these features across the assessments. Issues to be addressed in this project include how best to identify and evaluate studies, how to integrate evidence across various type of studies and scientific disciplines, advance approaches for quantitative analysis, and consideration of critical issues challenging the interpretation, analysis, and economic valuation of different types of disease endpoints.

Project Structure and Rationale

Project 7 addresses the on-going need to update and refine methods used in development of HHRA risk assessment products. The project is designed to identify critical issues and advance approaches to address them in an iterative fashion, building capacity based on lessons learned, and employing new methods when mature after thorough evaluation, development, and implementation. To adequately cover and continue to improve the large landscape of risk assessments developed by the HHRA program, and ensure scientifically sound supporting applications, this project is comprised of the following five integrated tasks:

- **Task 7.1 (*RMS ID# HHRA 4.211*): Advancing methods for systematic review and evidence integration**
- **Task 7.2 (*RMS ID# HHRA 4.212*): Advancing quantitative methods**
- **Task 7.3 (*RMS ID# HHRA 4.213*): Advancing methods for benefits and uncertainty analyses**
- **Task 7.4 (*RMS ID# HHRA 4.214*): Characterizing determinants of risk: Concentration, duration and timing of exposure**
- **Task 7.5 (*RMS ID# HHRA 4.215*): Science workshops on major risk assessment methodology issues**

The first task will continue work to enhance and tailor advances in systematic review to address specific application to HHRA assessments. This will involve improving methods to identify and evaluate studies and to develop approaches to evidence integration for both cancer and non-cancer endpoints from various disciplines. The task on advancing quantitative methods represents on-going work to improve the quality and accuracy of HHRA risk assessments with new methods and models for evaluation of health evidence. Quantitative approaches will be advanced in the next tasks as well, with special emphasis on key areas. Benefit-cost analysis is widely employed and accepted for evaluating environmental policies and is required by Executive Order and certain statutes, yet there are few a tools with which to valuate non-cancer outcomes. Task 7.3 is devoted to developing approaches for quantifying those health risks and thereby support future decision making. Task 7.3 also focuses on methodologies with which to characterize uncertainties as they arise in risk assessments, including quantitatively evaluating uncertainty in epidemiologic and toxicological data and developing probabilistic dose-response approaches. A challenge for EPA is to determine the best approaches for considering risk from real-world exposures based on concentration, duration, and timing of exposure. Concerns are linked to adverse health outcomes from: early-life exposures (e.g., in utero) at critical stages of development; acute and episodic exposures; and the relationship of exposure concentration, duration, and timing of exposure and how that influences responses across different levels of biological complexity. Task 7.4 has products that will increase our understanding and result in approaches to address those concerns. Finally, Task 7.5 represents a mechanism for on-going dialogue and engagement to find solutions to issues that arise in assessment activities or that are identified as

emerging major scientific concepts or challenges that could be addressed or incorporated into HHRA methods.

Measures of success

Refinements and continued improvement to current approaches are expected to improve the accuracy, efficiency, flexibility, consistency, and utility of applications across the large landscape of assessment activities served by the HHRA program and position it to be both more agile and better able to identify issues and support characterization of risks.

Stakeholders (outside ORD)

Risk assessors and decision makers across the Agency, as well as external stakeholders in states and community level organizations interested in protecting public health and the environment, all rely upon the hazard characterization and dose-response methods developed by the HHRA program.

References

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Task 7.1

(RMS ID# *HHRA 4.211*)

Advancing Methods for Systematic Review and Evidence Integration

Task Leads (TLs): Glinda Cooper (NCEA IRIS) and Molini Patel (NCEA RTP)

Task Start Date: 10/1/2015

Task End Date: 09/30/2019

Task Description:

Systematic review methods were recommended by the NRC (NRC, 2009; 2011; 2014) and aid transparency of assessment activities and inform evidence integration for determination of hazard. A key priority of the HHRA program is to develop more systematic and transparent processes for hazard identification in HHRA assessments of cancer and non-cancer health effects and apply them consistently across its risk assessment products (i.e., PPRTV, IRIS and ISA). The two subtasks and their products under Task 7.1 (*RMS ID# HHRA 4.211*) address that priority by aiming to improve methods for multiple steps taken in HHRA assessments to draw conclusions about the health risks of a chemical, air pollutant, mixture, or other hazards. Steps include identifying relevant studies and evaluating their quality, identifying relevant endpoints for human health risk evaluation, evaluating mechanistic information, synthesizing study results within an evidence stream for a health effect (e.g., human, animal, mechanistic), and integrating qualitative and quantitative information across evidence streams. This task is also heavily leveraged with case study development described in Task 7.3. (*RMS ID# HHRA 4.213*) and insights on key events and utility of mechanistic data will be used to inform Subtask 7.1.3 herein.

By targeting multiple steps in the development of HHRA assessments and multiple levels of scientific information from individual studies to the evidence base overall, two subtasks in this project plan together aim to improve the methods being used and developed by the IRIS and ISA programs to systematically consider all of the relevant evidence and its strengths and limitations in hazard and causal determinations for both cancer and non-cancer health effects. By improving the transparency and consistency of hazard identification, the products developed under this task to advance methods for systematic review and evidence integration have the potential impact of better informing assessments

of the public health impact of environmental toxicants and improving the defensibility of EPA's policy decisions to protect human health.

- **Subtask 7.1.1. (*RMS ID# HHRA 4.211.1*) Systematic Review: Evidence Identification, Evaluation, and Analytic Summary**

Subtask 7.1.1 (*RMS ID# HHRA 4.211.1*) covers initial systematic review steps involving literature searching, screening, study quality evaluation, and presentation of study data. NCEA has made substantial progress in incorporating aspects of systematic review in HHRA assessments; however, the full implementation of these methods into HHRA assessments is an ongoing process. The goal of this subtask is to continue to advance the development and adaptation of systematic review in HHRA products and to ensure that the methods and principles that are being adopted are well implemented and refined.

The products of subtask 7.1.1 (*RMS ID# HHRA 4.211.1*) also will improve the transparency of decisions involved in developing assessment products and communication across NCEA scientists and management on the methods being used by various assessment teams to adopt aspects of systematic review. The products are expected to discuss the different challenges and thus appropriate approaches to adopting systematic review methods based on the size and complexity of the evidence base and assessment needs. The products will also provide much needed guidance in implementation for the proposed methodology. Continued refinement, development, and coordination of tools to efficiently apply the methods developed within this subtask are implemented in Task 9.1 (*RMS ID# HHRA 4.23*). Task 9.1 (*RMS ID# HHRA 4.23*) is devoted to software to support such critical applications. By continuing to advance the incorporation of aspects of systematic review in HHRA assessments, the HHRA program ensures that EPA decisions are based on the best available scientific information and that the assessments supporting these decisions are transparent, systematic, and defensible.

- **Subtask 7.1.2. (*RMS ID# HHRA 4.211.2*) Advancing Evidence Integration for Determination of Hazard and Causality**

Subtask 7.1.2. (*RMS ID# HHRA 4.211.2*) addresses the importance of applying a systematic and transparent process for evidence integration to a sound weight-of- evidence approach to hazard and causal determination. Drawing on the systematic evaluation of results from individual studies and application of mechanistic information, subtask 7.1.2. (*RMS ID# HHRA 4.211.2*) covers the steps of a systematic review that involve synthesizing study results within an evidence stream for a health effect (human, animal, mechanistic) and integration across evidence streams to draw conclusions about

the health effects of a chemical, air pollutant, mixture or other hazard. The products under this subtask will improve the schemes and frameworks under development by the PPRTV, IRIS, and ISA programs to systematically consider all available evidence as a whole to draw hazard conclusions and to transparently characterize the conclusions, describing the amount and quality of evidence that supports the conclusions. Further, the products will contribute to efforts to harmonize approaches used for cancer and noncancer effects, which is identified as a critical need in IRIS assessments. The products under this subtask will provide examples and highlight lessons learned regarding the application of evidence integration methods to NCEA's scientific assessments with the aim of providing a consistent, transparent basis for assessing causality of health effects associated with exposure to environmental toxicants.

Research Approach:

- **Subtask 7.1.1. (*RMS ID# HHRA 4.211.1*): Systematic Review – Evidence Integration, Evaluation, and Analytic Summary.** This task will evaluate selected case studies, consider comparisons of approaches across HHRA assessment products, develop tools, and analyze discussion/recommendations from the 2016 workshop "Advancing Systematic Review" (see Task 7.5, RMS ID# HHRA 4.211.5).

- **Subtask 7.1.2. (*RMS ID# HHRA 4.211.2*)**: **Advancing Evidence Integration for Determination of Hazard and Causality.** This task involves evaluation and testing of proposed frameworks for two case studies and consideration of lessons learned and insights from Task 7.3.

Task Products:

Subtask 7.1.1. Systematic Review: Evidence Identification, Evaluation, and Analytic Summary

- **Product 7.1.1.1. Comparison of Systematic Review Processes across HHRA Assessments**
- **Product Contact (email):** owens.beth@epa.gov, cooper.glinda@epa.gov
- **Product's Delivery Date:** FY17
- **Product Description:** Major HHRA assessments (i.e., IRIS, ISA, PPRTV) vary in the size and complexity of evidence available and assessment purpose. Product 7.1.1.1 will compare and contrast the processes, methods, frameworks, or tools used by the various major HHRA assessments (i.e., IRIS, ISA, PPRTV) in adopting aspects of systematic review and increasing transparency. This product will take the form of an internal report for use

in the HHRA program as a means to ensure that the systematic review approach pursued is appropriately tailored to its assessment products. This report will also survey and present the various methods such as those being developed by the NIEHS and elsewhere, used for literature searching, screening, and study quality evaluation steps of systematic review, methods used to synthesize and integrate evidence within and across evidence streams, discuss the strengths and limitations of these approaches, and allow for greater conversation across HHRA.
Product's Contribution to Output: This internal report will help to understand the various methods being used to adopt systematic review principles and will serve as a bridge among HHRA assessments.

- **Product's Timeline (with milestones):**

Survey of systematic review methods being used across NCEA,	FY16
Develop writing team from the various assessments/methods being discussed,	
Rough draft with distribution to NCEA teams for comment	
(milestone – FY16)	
Distribute final report	FY17

- **Product's intended user/customer/audience: HHRA scientists and management, program partners and external stakeholders.**
- **Is this a key product?** No.
- **Does this Product contribute to a Product under another Task? If so, identify other Task:** This product will contribute to Product 7.1.1.4 below and methods used in assessment products, i.e., Tasks 1.1 (IRIS), 3.1 (ISA) and 4.1 (PPRTV).

- **Product 7.1.1.2. Testing and Refining Methods for Study Quality Evaluation**
- **Product Contact (email):** kraft.andrew@epa.gov, luke.april@epa.gov, cooper.glinda@epa.gov, fritz.jason@epa.gov, gibbons.catherine@epa.gov, makris.susan@epa.gov
- **Product's Delivery Date:** FY16, FY17
- **Product Description:**
  Evaluation of attributes of study quality, specifically attributes that could influence the interpretation and confidence in a study's results, is an essential component of all systematic review approaches. Several methods for use with observational epidemiology, controlled exposure, and experimental toxicology studies, have been proposed or are in use by the HHRA program and other environmental health organizations. Development of these approaches continues based on lessons learned as they are applied and evaluated and will notably be informed by the case studies

developed under Task 7.3 (*RMS ID# HHRA 4.2113*). Additionally, specific endpoints (e.g., immunotoxicity, genotoxicity, imaging) may require specialized methods for evaluation. This product includes several components:

- Article submitted for publication discussing the organizing concepts and rationale for evaluating the quality of animal toxicology studies, including comparison of commonly used tools with an IRIS-developed approach, as well as a brief case study of the use of this newly developed tool
- Case studies of application to IRIS-developed approach to evaluating animal toxicology studies using several sets of studies of a variety of toxicities (to be presented at public workshops, professional meetings, or peer-reviewed journal publication)
- Case studies of application of IRIS-developed approach to evaluating observational epidemiology studies using several sets of studies drawn from reproductive health, neurodevelopment, and common chronic diseases (e.g., asthma, diabetes) (to be presented at public workshops, professional meetings, or peer-reviewed journal publication).
- Development of evaluation measures for quality, utility, and informativeness of data supporting the identification of mechanistic events. This will be informed by the case studies in Task 7.3 and by application to IRIS and PPRTV assessments.
- Approaches will be developed to evaluate specific study types (e.g., immunotoxicity, genotoxicity). Case studies may be used to consider the utility of the developed approaches.
    - A report will be developed that systematically addresses the evaluation of mutagenic/genotoxic data for assessing the risk of a chemical in support of the IRIS Program. This report may build off of a draft U.S. EPA's Risk Assessment Forum document, *Framework for determining a mutagenic mode of action for carcinogenicity* (External Peer Review draft, Sept 2007 with an External Peer Review Public meeting April 2008). The approach will provide a framework for (a) organizing data, (b) categorizing the data followed by reviewing the methodological information, (c) determining the strength, weakness and human relevance of the data for mode of action (MOA) analysis, and (d) interpreting the data for a mutagenic MOA for cancer. This report will have direct impact on how genotoxicity data will be evaluated and incorporated in chemical risk assessment.
    - A workshop (fully funded and facilitated by ILSI/HESI) and draft manuscript for publication in a peer reviewed journal will focus on the use of imaging data to support or replace developmental toxicity testing for hazard assessment and dose response. This workshop aims to: introduce and discuss image capture technology relative to existing fetal evaluation methodology; understand the regulatory community's perspective and path for acceptance of results using imaging technology; discuss minimal acceptable criteria for imaging to comply with Good Laboratory Practices and Computer Validation requirements, and develop criteria to demonstrate concordance between new and existing

examination methods and between testing results. It will provide information to support consideration of imaging data in developmental toxicology assessment for IRIS documents. The work contributing to this product is ongoing. Based on this work, additional products may be developed.

- **Product's Contribution to Output:** These reports, publications and workshop will be available to risk assessment scientists and environmental health researchers, and will advance this field of research. This work will directly address recommendations from the National Research Council committee and will support the IRIS process. This product will result in more efficient and effective approaches for study evaluation that have been tested and validated. Results of this product will be used to inform the development and refinement of tools under Task 9.1.

- **Product's Timeline (with milestones):**

Initial animal toxicology evaluation method Publication submitted to journal	FY16
Report of epidemiology case studies submitted to clearance	FY16
Developmental toxicity imaging workshop and report	FY16 (continued from FY15)
Report of case studies using animal toxicology evaluation approach submitted to clearance. Analysis of animal toxicology case studies prepared for presentation	FY17
Evaluation measures for mechanistic studies developed (milestone) Case studies conducted and submitted to clearance	FY16 FY17
Report of methods to evaluate mutagenic/genotoxic data Case studies conducted and submitted to clearance	FY16 FY17

- **Product's intended user/customer/audience:** HHRA program scientists, other parts of EPA, other organizations, academia, NGOs, other public organizations responsible for interpreting health effects data
- **Is this a key product?** No.
- **Does this Product contribute to a Product under another Task? If so, identify other Task:** This product may contribute to methods used in assessment products, i.e., Tasks

1.1 (IRIS), 3.1 (ISA) and 4.1 (PPRTV).Additionally, these products will be used to direct development and refinement of tools in Task 9.1.

- **Product 7.1.1.3. Human relevance of Chronic Progressive Nephropathy (CPN)**
- **Product Contact (email):** Raghu Nath (NCEA IRIS)
- **Product's Delivery Date:** FY16
- **Product Description:** Decisions made regarding human hazard are often primarily based on laboratory animal evidence. Human relevance may be questioned due to mechanistic information (i.e., when the mode of action in animals is not known or if there is some evidence that it may not be operative in humans) or lack of site concordance (i.e., if the affected tissue in rodents differs from that in humans or does not have a direct equivalent in humans). This product will update assessment approaches for chronic progressive nephropathy (CPN). CPN is a common age-related disease of the kidney in rats. It has been debated whether chemically-enhanced CPN is a mode of action for renal tubular tumors (RTTs), especially in male rats. It is not clear whether RTTs are induced by chemicals that concomitantly exacerbate CPN and are relevant for human cancer risk assessments. The objective of this research project is to conduct a comprehensive review of all relevant information related to the renal carcinogenicity of environmental agents, validity of hypotheses regarding possible modes of action evidence in support of them and their relevance to CPN and kidney tumors.
- **Product's Contribution to Output:** This work will result in a manuscript(s) detailing the review of evidence either as a series of case studies with chemical-specific datasets, or on a series of tissue comparisons across numerous chemicals. The longer term impact of this work could result in proposals to modify existing MOA guidance, or provide support to statements of default assumptions regarding human relevance.
- **Product's Timeline (with milestones):**

Concurrently, conduct analyses on CPN which have been identified as current IRIS priority issues. These analyses will rely, not only on existing environmental health literature, but also outputs from the CSS program and outputs from Task 8.1, in particular (Milestone years 1 and 2). Contract is in place and work has already commenced.	FY16

- **Product's intended user/customer/audience:** Scientists involved with evaluating rodent bioassay data for the purposes of estimating potential human hazards: specifically EPA, FDA, NTP and NCI scientists, and interested academic and industry scientists.
- **Is this a key product?** No.
- **Does this product contribute to a Product under another Task? If so, identify other Task.** This product will inform assessments for chemicals under Tasks 1.1 (IRIS) and 4.1 (PPRTV) for which CPN may be an endpoint.

- **Product 7.1.1.4. Advancing Systematic Review Workshop Report**

- **Product Contact (email):** owens.beth@epa.gov, cooper.glinda@epa.gov
- **Product's Delivery Date:** FY17
- **Product Description:** A scientific workshop is being held in December 2016 to discuss advancing the incorporation of aspects of systematic review in HHRA assessments. A report will be developed to evaluate and summarize observations and recommendations resulting from the workshop. A peer-reviewed publications may also result.
- **Product's Contribution to Output:** The report will serve as a record of the workshop discussion or conclusions and allow for further conversation across HHRA, EPA, and the outside systematic review scientific community.
- **Product's Timeline (with milestones):** Report development following workshops
- **Product's intended user/customer/audience:** HHRA scientists, program partners and external stakeholders, especially those such as the NIEHS interested in systematic review.
- **Is this a key product?** No.
- **Does this Product contribute to a Product under another Task? If so, identify other Task:** This product will contribute to methods used in assessment products, i.e., Tasks 1.1 (IRIS), 3.1 (ISA) and 4.1 (PPRTV).

Subtask 7.1.2: Advancing Evidence Integration for Determination of Hazard and Causality

- **Product 7.1.2.1. Development and Refinement of an Integrated Approach to Synthesizing Health Effects Research and Characterizing Hazards using Multiple Evidence Streams**
- **Product Contact (email):** glenn.barbara@epa.gov, patel.molini@epa.gov (with other epidemiologists, toxicologists, and statisticians)
- **Product's Delivery Date:** FY17, FY18
- **Product Description:** Multiple reports and journal articles. This product addresses a critical need identified in IRIS assessments to develop weight-of-evidence evaluation processes for both cancer and noncancer health effects. The analyses under this product will evaluate approaches for evidence integration currently used in ISAs and IRIS assessments as well as those described in the peer-reviewed literature. A framework is under development for IRIS chemical assessments. The IRIS framework for integration is a two-step process that first synthesizes evidence within disciplines (e.g., epidemiology, toxicology and mechanistic studies) and then weighs the totality of evidence to characterize the hazard for health effects. In the first step, a descriptor regarding a chemical's hazard is applied based on the each of the human and animal evidence streams. In the second step, the descriptors from the syntheses of evidence in humans and animals are weighed with an evaluation of relevance and coherence using

mechanistic information to arrive at a conclusion regarding causality. The approach is intended to harmonize weight-of-evidence evaluation for both cancer and non-cancer endpoints.

Similar to IRIS, the ISA causal framework provides a consistent basis for evaluating evidence integrated within and across disciplines and characterizing causality for health effects, considering the cumulative evidence base. Recent ISAs have improved the integration of information on exposure assessment, dosimetry, toxicokinetics, and mode of action with health effects evidence. The ISA and IRIS frameworks will be compared to each other, and to other weight-of-evidence frameworks for cancer endpoints and other health effects. Similarities and differences will be highlighted and appropriate changes to the existing frameworks will be proposed. The framework or approaches developed aim to provide a consistent, transparent process for evaluating the strengths, limitations, and uncertainties of individual lines of evidence and types of scientific data, and characterize how information from one line of evidence can inform uncertainties in another. The framework and approaches developed will be tested using a variety of datasets that encompass a range of study number, comprehensiveness, completeness and quality, and conclusions may be compared with those that used other approaches. Reports and manuscripts will describe the application of the framework to assessments for forming hazard or causal determinations to user communities and communicate the framework to the broader scientific community. Guidance also will be provided to the user communities on the documentation of evidence integration in HHRA assessments.

This product will also be informed by the mechanistic information developed and evaluated for the case studies in Task 7.3.

- **Product's Contribution to Output:** Application to ISAs, IRIS Toxicological Reviews, and PPRTVs for improved consistency, rigor, and transparency of evidence integration for hazard and causal determinations.

- **Product's Timeline (with milestones):**

Consider the case studies in Task 7.3. or select one other air pollutant/chemical and health effects to evaluate for evidence integration (ideally a pollutant for which an ISA is currently being developed and a chemical for which the IRIS systematic process for literature identification and study evaluation has been completed for one or more health effects)	FY16
Organize the evidence and describe methodology used to integrate evidence in the ISA and IRIS assessments	
Hold discussions with NCEA-RTP-EMAG, IRIS, Office of Air Quality Planning and Standards, on the strengths and limitations of process	
Develop and apply approaches for evidence integration and compare approaches used in the ISAs and IRIS	
Develop and apply approaches for evidence integration and compare approaches used in the ISAs and IRIS	FY16-FY17
Develop reports and manuscripts, submit for clearance and publication	FY17-FY18

- **Product's intended user/customer/audience:** NCEA, EPA
- **Is this a key product?**
- **Does this Product contribute to a Product under another Task? If so, identify other Task.** This product will draw upon methods developed for systematic review in subtask 7.1.1 and processes for the application of mechanistic data developed in subtask 7.1.2 and may be informed by products developed under subtask 7.2.5 and task 8.3. The framework for evidence integration may contribute to products under tasks 1.4, 3.1, 4.1, and 6.1. This product also is related to Task 7.3.1 for application in benefits analyses.

References:

National Research Council. (2009). Science and Decisions: Advancing Risk Assessment. Committee on Improving Risk Analysis Approaches Used by the U.S. EPA; Board on Environmental Studies and Toxicology; Division on Earth and Life Studies. National Academies of Science. http://www.nap.edu/catalog/12209/science-and-decisions-advancing-risk-assessment

National Research Council. (2011). Review of the Environmental Protection Agency's Draft IRIS Assessment of Formaldehyde. Committee to Review EPA's Draft IRIS Assessment of Formaldehyde; Board on Environmental Studies and Toxicology; Division on Earth and Life Studies. National Academies of Science. http://www.nap.edu/openbook.php?record_id=13142

National Research Council. (2014). Review of EPA's Integrated Risk Information System (IRIS) Process. Committee to Review the IRIS Process; Board on Environmental Studies and Toxicology. National Academies of Science. http://www.nap.edu/catalog.php?record_id=18764

Task Constraints: Similar constraints apply to both of the subtasks.

- **Scientific:** Work by NCEA staff on IRIS, ISA, and PPRTV assessments may delay completion of products and interim milestones.
- **Logistical:** For some products, time to award work assignments/contracts and time to organize and conduct workshops in order to prepare reports may impact progress on products.
- **Technical:** Elements of products depend on development of tools or generation of data.
- **Resources:** Many products require extramural resources including contracts, ORISE grantees, and possibly student service contractors.

Task Dependencies: Some products proposed in the various subtasks are partially dependent on each other. Elements of products depend on development of tools for implementation (e.g., tools under Task 9.1) or generation of data.

Task Quality Assurance and Data Management Needs:

- Is there an existing IRP/ QAPP(s) that applies to this Task? If so, identify IRP/QAPP.
    - Yes. NCEA-16-00004. Quality Assurance Project Plan (QAPP) For HHRA Projects 6, 7, & 8 to Develop Methods, Tools, Models and Supporting Analysis.

- Will this Task involve large amounts of data that need a data management plan? If yes, explain.
    - TBD. The Health and Environmental Research Online (HERO) system is used for systematic literature review and is covered by a separate QAPP: NCEA-16-00005. Quality Assurance Project Plan (QAPP) For Extraction of Scientific Data Into the Health and Environmental Research Online (HERO) Database System. Some products may generate a limited amount of data or metadata during case study or method development and refinement.

Task 7.2

(*RMS ID# HHRA 4.212*)

Advancing Quantitative Methods

Task Leads (TLs): John Fox (NCEA W) and Karen Hogan (NCEA IRIS)

Task Start Date: 10/1/2015

Task End Date: 09/30/2019

Task Description:

Methods for quantitative dose-response analysis continue to evolve steadily and NCEA needs to evaluate and adopt newer methods when these can improve the quality and accuracy of risk assessments and advance the quantification of uncertainty and variability:

1) More robust methods for dose-response modeling may improve the quantification of model uncertainty, can simplify modeling decisions; these methods include Bayesian and frequentist methods for model averaging and non- or semi-parametric modeling and adoption of more flexible model functions. These methods need to be evaluated in relation to one another and older methods of fitting multiple parametric models, and BMDL coverage needs to be validated.
2) More powerful statistical methods of testing for a dose response or a trend have been identified in recent years. Some rely on approximations, so evaluation is needed with small samples and data types typical of NCEA risk assessments.
3) Health effects often consist of a multivariate response (i.e. set of related responses). Published studies have shown that modeling each separately may over-estimate a BMD and be less health-protective than estimating a multivariate or joint BMD. There are challenges to overcome in computing a BMDL with accurate coverage.

The NCEA Statistical Workgroup (SWG) promotes application of the best science in the fields of statistical analysis and modeling as applied in human health hazard and dose-response assessment of chemicals, in NCEA assessments and in particular in those developed for EPA's Integrated Risk Information System (IRIS). To support this goal, SWG develops methods and tools for statistical modeling and analysis in risk assessment and provides documentation and instruction on the application

of these tools. SWG identifies research necessary for the improvement of quantitative dose-response assessment and epidemiological analysis and assessment, and works with NCEA, ORD, and other sponsors to promote research to meet these needs**.** Quantitative dose-response analysis includes identification of a credible response, detection of a trend (increase or decrease), and dose-response modeling; it also includes synthesis of information from multiple studies using statistical meta-analysis.

Research Approach:

The approaches will include literature review, development of case studies as examples, and implementation, evaluation, and comparison of statistical methods and other quantitative or qualitative tools using real and simulated data. Simulated datasets can be used to efficiently examine how the developed methods (in 7.2.1 and 7.2.2) perform from a variety of perspectives, including computational burden, convergence performance, and method performance with a wide range of dose-response patterns and sample sizes (e.g., West et al. 2012; Ringblom et al. 2014; Kopylev & Fox 2009). Real datasets obtained from a variety of sources (i.e., IRIS documents) can be used to further validate methods in a "real world" setting.

The research in this task will be a combination of ORD intramural research and contract support. Academic expertise will be sought out where appropriate. We will prioritize recurring issues and methods, for example recurring issues relating to model selection procedures and characterization of model uncertainty. We will also perform necessary research and method evaluations, and draft manuscripts and reports that review or synthesize available literature and summarize results of methods evaluations and comparisons. Results would also be communicated within NCEA as presentations and as SOPS (standard operating procedures) for statistical and dose-response analysis, with supporting materials based on research.

Task Products:

- **Product 7.2.1. (*RMS ID# HHRA 4.212.1*)**
- **Product title: Comparison of non-parametric, semi-parametric, and parametric dose-response modeling methods**
- Product Contact (email): blessinger.todd@epa.gov, kopylev.leonid@epa.gov, gift.jeff@epa.gov, spassova.maria@epa.gov, fox.john@epa.gov
- Product's Delivery Date: June, 2019
- Product Description: Recent years have seen an acceleration in the publication and testing of new non-parametric and semi-parametric dose-response modeling methods (including Bayesian and frequentist methods). There are several proposed advantages of these methods (Piegorsch et al. 2014; Gerschman & Blei 2011), such as greater flexibility and reduction of model uncertainty, and they have a wide range of applications. They need to

be compared to and tested against competing approaches such as model averaging (Shao et al. 2012; Wheeler & Bailer 2009), use of a single, flexible parametric model like the Hill model (Slob and Setzer 2014) and similar for dichotomous data, and the current NCEA approach of selecting a 'best-fitting' model from a limited set of parametric models (USEPA 2012; Filipsson et al. 2005). Methods of quantifying model uncertainty also must be evaluated in the context of each modeling approach. For a flexible parametric model, small-sample asymptotic methods for more accurate and simpler BMD inference can be developed. The final product will consist of a report and publications that will compare and evaluate dose-response methods with worked examples for users to follow.

- Product's Contribution to Output: Dose-response modeling is vital to multiple areas of the HHRA research program, including IRIS and PPRTV assessments, benefits-analysis, and cumulative risk, and is used throughout the agency. It is essential to be using the best dose-response modeling practices when doing risk assessment. These methods will better quantify model uncertainty and can reduce disagreements over choice of models, small model differences in goodness of fit, and model differences in BMDs and BMDLs.
- Product's Timeline (with milestones): Delivery of results by June, 2019; continued investigation of newly developed methods afterward.

Literature survey of modeling methods Develop, document and test program code Acquire and document data Select Comparison Measures and Uncertainty Metrics Conduct modeling runs with data	FY 2016 FY 2016 FY 2016 FY 2016 FY 2017
Write manuscript & presentations Write and QA programs for users & user manuals Publication	FY 2017 FY 2017 FY 2018-19

- Product's intended user/customer/audience: EPA Risk assessors and dose-response modelers. Agency and external reviewers of risk assessments.
- Is this a key product? No.
- Does this Product contribute to a Product under another Task? If so, identify other Task. *Yes.* This product will contribute to IRIS chemical assessments (Project 1), PPRTV assessments (Project 4), and may contribute to cumulative risk tasks (Project 4), Community and Site-Specific Risk tasks (Project 3), and benefits-analysis (Project 7.3). However, completion of this task is not expected to impact completion of other tasks. Some of the results of this research could be included in the IRIS Handbook for chemical assessments.
- **Product 7.2.2. (*RMS ID# HHRA 4.212.2*)**
- **Product title: Advancing Best Practices for Trend and Hypothesis Testing of Dose Response** Product Contacts (emails): blessinger.todd@epa.gov, farrar.david@epa.gov, fox.john@epa.gov
- Product's Delivery Date: FY18
- Product Description: More powerful statistical methods of testing for a dose response or a trend have been identified in recent years. Some rely on approximations, so evaluation is

needed with small samples and data types typical of NCEA risk assessments. Different methods apply to binary and continuous (interval scale) data. Rank-ordered (e.g. severity) data can be evaluated using methods for continuous data or exact methods for counts. Newer methods will be contrasted with older methods frequently used in publications and assessments. The final product will consist of a report and publications comparing methods using real data examples and evaluating coverage and small-sample performance using simulations. Worked examples for users to follow will be included (using Agency supported software).

- Product's Contribution to Output: Supplies information gaps in evaluating published results and synthesizing them for hazard ID. Provides more powerful methods (with authoritative references) for comparing current and historical data.
- Product's Timeline (with milestones): Delivery of all products by 2019

Literature survey of methods and software Acquire and document data Conduct comparisons with data Evaluate coverage with simulations	FY 2016 FY 2016 FY 2016 FY 2017
Write manuscript & presentations Write and QA programs & instructions for users Publication	FY 2017-18 FY 2017-18 FY 2018-19

- Product's intended user/customer/audience: EPA Risk assessors and dose-response modelers. Agency and external reviewers of risk assessments.
- Is this a key product? TBD
- Does this Product contribute to a Product under another Task? Yes. This product will contribute to IRIS chemical assessments (Project 1), PPRTV assessments (Project 4), and may contribute to cumulative risk tasks (Project 4). However, completion of this task is not expected to impact completion of other tasks. Results of this research will be included in the IRIS Handbook for chemical assessments.

- **Product 7.2.3. (*RMS ID# HHRA 4.212.3*)**
- **Product title: Multivariate Benchmark Dose Modeling**
- Product Contacts (emails):): gift.jeff@epa.gov, spassova.maria@epa.gov, blessinger.todd@epa.gov, hogan.karen@epa.gov, farrar.david@epa.gov,
- Product's Delivery Date: FY19
- Product Description: Health effects often consist of a multivariate response (i.e. sets of related responses). Published studies (Catalano and Ryan, 1992; Regan and Catalano, 1999) have shown that modeling each response separately may over-estimate a BMD and be less health-protective than estimating a multivariate or joint BMD. There are challenges to overcome in computing a BMDL with accurate coverage. Methods will be implemented for independent animal units and for offspring in litters from developmental studies. Published

methods will be reviewed and compared, including GEE estimation for parametric models, Bayesian hierarchical models, and other methods. The final product will consist of a report and publications comparing performance of joint/multivariate BMD approach to one-at-a-time and combined-data (current) approaches. Worked examples for users to follow will be included (using Agency supported software).

- Product's Contribution to Output: Products will allow more accurate and comprehensive risk estimation in IRIS and other programs.
- Product's Timeline (with milestones): Delivery of results by June, 2019; continued investigation of newly developed methods afterward

Literature survey of modeling methods	FY 2016
Investigate, implement alternate methods for BMDL	FY 2016
Develop, document and test program code	FY 2016-17
Acquire and document data	FY 2016-17
Conduct modeling runs with data	FY 2017-18
Evaluate coverage by simulations	FY 2017-18
Write manuscript & presentations	FY 2017-18
Write and QA programs & examples for users	FY 2017-18
Publication	FY 2019

- Product's intended user/customer/audience: EPA Risk assessors and dose-response modelers. Agency and external reviewers of risk assessments.
- Is this a key product? TBD
- Does this Product contribute to a Product under another Task? Yes. This product will contribute to IRIS chemical assessments (Project 1), PPRTV assessments (Project 4), and may contribute to cumulative risk tasks (Project 4) and Community and Site-Specific Risk tasks (Project 3). However, completion of this task is not expected to impact completion of other tasks. Some of the results of this research could be included in the IRIS Handbook (Task 1.4) for chemical assessments.

- **Product 7.2.4. (*RMS ID# HHRA 4.212.4*)**
- **Product title: Incorporating covariates into BMD modeling**
- Product Contact (email): blessinger.todd@epa.gov; gift.jeff@epa.gov, , hogan.karen@epa.gov,
- Product's Delivery Date: Sept., 2018
- Product Description: Covariates often arise in dose-response modeling of toxicity data and their use can offer a more complete analysis of the dose-response relationship. Methods exist for incorporating covariates in dose-response modeling, and NRC (2014) has recommended their use in human health risk assessments. For example, incorporation of covariates, such as the number of implantation sites or dam weight, into the modelling of nested dichotomous data is already possible when using EPA's BMDS. However, the ability

to use covariates when modeling other types of data such as quantal or continuous endpoints would improve the rigor of Agency dose-response analyses by incorporating additional information important in describing the dose-response relationship between exposure and disease formation. These methods will be evaluated using appropriate software and once sufficiently mature, implemented and documented on the BMDS platform.

- Product's Contribution to Output: Incorporating covariates into dose-response modeling with provide a more complete and accurate analysis of dose-response relationships.
- Product's Timeline (with milestones):

Literature survey and evaluation of methods Incorporate into software	FY 2016-2017 FY 2017-2019

- Product's intended user/customer/audience: *EPA Risk assessors and dose-response modelers. Agency and external reviewers of risk assessments.*
- Is this a key product? N/A
  Does this Product contribute to a Product under another Task? Yes. This product will contribute to IRIS chemical assessments (Project 1)), PPRTV assessments (Project 4), and may contribute to cumulative risk tasks (Project 4) and Community and Site-Specific Risk tasks (Project 3). However, completion of this task is not expected to impact completion of other tasks. Some of the results of this research could be included in the IRIS Handbook for chemical assessments.

- **Product 7.2.5. (*RMS ID# HHRA 2.412.5*):**
- **Product title: Development of methods to quantitatively combine results across studies and evidence streams**
- Product Contact (email): fox.john@epa.gov, kopylev.leonid@epa.gov, blessinger.todd@epa.gov, bateson.tom@epa.gov, spassova.maria@epa.gov
- Product's Delivery Date: 2017-19
- Product Description: (A) Combining information within one evidence stream. Meta-analyses of epidemiological results have been conducted rarely in IRIS assessments (e.g., TCE/Libby), and even more rarely for toxicological data. More experience is needed to develop good practices for evidence integration using data from multiple epidemiological or toxicological studies. Good practices would encompass not only quantitative methodology, but also an understanding of the appropriate homogeneity of individual study methods (i.e., study designs, exposure measurement methods, outcome measures, etc.) for which a formal quantitative meta-analysis would add critical value to a chemical assessment (e.g., for derivation of toxicity values), and when a combined effect estimates might not be statistically appropriate for quantitative risk assessment. (B) Combining information across evidence streams. Quantitative Bayesian methods for combining results across evidence streams/scientific disciplines will also be investigated and developed. This endeavor is more

difficult and requires a longer time frame and greater involvement of academic experts. The final products will consist of publications or contributions to IRIS assessments using specific chemicals for case studies.

- Product's Contribution to Output: Product will provide methods for applying meta-analytical approaches to synthesize results for evidence integration and hazard identification. The quantitative methods developed here will complement the qualitative evidence integration methods identified and developed in Project 7.1 (Advancing Methods for Systematic Review and Evidence Integration). This product addresses NRC recommendations for improvements to IRIS methods.
- Product's Timeline (with milestones):

Identify chemical case studies, hire post-doc(s) or ORISE faculty fellow, initiate work assignment(s), identify methods available	FY 2016
Identify case-studies; develop & revise methods	FY 2017
Implement methods	FY 2017-18
Submit (assessment, manuscript, or both)	FY 2018-19

- Product's intended user/customer/audience: *EPA Risk assessors and dose-response modelers. Agency and external reviewers of risk assessments.*
- Is this a key product? N/A
- Does this Product contribute to a Product under another Task? Yes. Relates and builds upon Task 7.1 (quantitative methods developed herein will complement the qualitative methods developed in 7.1). This product will contribute to IRIS chemical assessments (Project 1). Some of the results of this research could be included in the IRIS Handbook for chemical assessments. Relates to Task 7.4 for application to benefits analyses.

Task Constraints:

- **Scientific**: SWG members and other collaborating NCEA scientists are working on IRIS, ISA, or PPRTV assessments that may delay progress on task products.
- **Logistical**: Contract support is essential to accomplish work on case studies, method evaluations, data acquisition, data management, some statistical programming, and publications will require contract support.
- **Technical**: Some academic consultations will be needed (also requires extramural support). Expert, extramural assistance on a continuing basis may be needed to implement some of the methods. This assistance can best be provided by an ORISE faculty fellow.
- **Resources**: Extramural funding is essential, for postdoctoral and faculty fellows and contractor support.

Task Dependencies: None

Task Quality Assurance and Data Management Needs:

- Is there an existing IRP/ QAPP(s) that applies to this Task?
    - Yes. NCEA-16-00004. Quality Assurance Project Plan (QAPP) For HHRA Projects 6, 7, & 8 to Develop Methods, Tools, Models and Supporting Analysis.

- Will this Task involve large amounts of data that need a data management plan?
    - TBD. The Health and Environmental Research Online (HERO) system is used for systematic literature review and is covered by a separate QAPP: NCEA-16-00005. Quality Assurance Project Plan (QAPP) For Extraction of Scientific Data Into the Health and Environmental Research Online (HERO) Database System.

Task 7.3

(RMS ID# *HHRA 4.213*)

Advancing Methods for Benefits and Uncertainty Analysis

Task Leads (TLs): Thomas Bateson (NCEA W) and Todd Blesssinger (NCEA W)

Task Start Date: 10/1/2015

Task End Date: 09/30/2019

Task Description:

This task consists of three subtasks to advance methods needed for benefits and uncertainty analysis. Task 7.3 is also highly integrated with Task 7.1 on systematic review and evidence integration, and lessons learned from the work herein will be used as input to products in that task.

- **Subtask 7.3.1. (*RMS ID# HHRA 4.213.1*) Case studies to Develop Benefit-cost Analysis for Non-cancer Outcomes.** Benefit-Cost Analysis is widely employed in evaluating environmental policies, enjoys widespread acceptance, and is required by Executive Order and certain statutes. While some environmental policies, particularly those involving development of National Ambient Air Quality Standards (NAAQS) for criteria air pollutants and control of some toxics (e.g., mercury) have well-developed tools for human health benefits analysis, for most other contaminants there are fewer tools with which to evaluate the benefits of exposure reductions. Without an investment in new methods for quantifying health risks and outcomes, and for valuating changes in these risks and outcomes, EPA will not have the information needed to make sound decisions on regulating contaminants. EPA needs risk assessment methods and economic valuation estimates to evaluate policies and actions to reduce exposures to toxic chemicals.

- **Subtask 7.3.2. (*RMS ID# HHRA 4.213.2*) Mechanistic Data: Approach and Utility for Informing Benefit-cost Analysis and Evidence Integration.** Mechanistic data are emerging as essential information to understand a chemical's mode of action (MOA). As more evidence for key events and adverse outcome pathways (AOP) emerges for different apical endpoints or disease outcomes, consideration of the utility of those key events to refine benefit-cost analysis become critical. For example, the mechanistic and clinical data considered in the evaluation of evidence for the ISA of ozone continue to inform interpretation of effects on the respiratory tract observed in epidemiological studies. Consideration of mechanistic data in this subtask will thus additionally be featured in the case studies chosen. Lessons learned also will inform evidence integration efforts under Task 7.1.

- **Subtask 7.3.3. (*RMS ID# HHRA 4.213.3*) Scoping Uncertainty Analyses for Epidemiologic and Toxicological Data**

Uncertainty exists at all stages of hazard identification and dose-response analysis; sources include interspecies extrapolation and database insufficiencies, among others. In the past, EPA has relied mostly on qualitative methods of characterizing uncertainty and the use of default factors for calculating a deterministic reference dose/concentration (RfD/RfC). Such methods can be useful and are sometimes necessary when the database is not robust. However, it is often preferable to characterize uncertainty quantitatively to allow the calculating of a probabilistic RfD/RfC. These methods increase transparency, yield more justifiable conclusions, and allows more flexibility in decision-making. Furthermore, NRC has recommended that EPA conduct quantitative uncertainty analysis more frequently in assessments, as discussed in several EPA evaluations (e.g., NRC 2009; 2014). EPA must evaluate and compare methods of characterizing uncertainty to determine their applicability and utility.

Research Approach:

- **Subtask 7.3.1. (*RMS ID# HHRA 4.213.1*): Case studies to Develop Benefit-cost Analysis for Non-cancer Outcomes.** For evaluation of benefit-cost analysis, we will gather information on current and near-term needs of the EPA Program offices for rulemaking as well as outcomes that they consider critical to evaluate. Detailed information on the relevant exposure routes, levels and durations will be evaluated. Additional considerations in selecting case studies may include, for example, the degree of population exposure, the prevalence of the health condition in the population and the severity of the effect. We may also inventory the IRIS database of health outcomes and the ISA assessments to standardize nomenclature for key endpoints. Collaboration is anticipated with economists from the Office of Policy's National Center for Environmental Economics to identify outcomes with existing valuations and those which would benefit from valuation (valuation efforts are anticipated to be the focus of OP activities). Mechanistic insights on the mode of action (MOA) for potential candidates from Subtask 7.3.2. will also help in the selection of case studies. Case-studies of

benefits monetization based on exposure-response relationships from recent completed IRIS assessment or ongoing assessments will provide additional expertise and build capacity for further cross-disciplinary and cross-office work.

Methods of qualitatively and quantitatively characterizing uncertainty will be evaluated and compared through a review of literature, evaluation of available methods, demonstration through case studies, and use and possible development of software. We will also develop scoping recommendations for determining what level of uncertainty analysis is feasible given available data.

- **Subtask 7.3.2. (*RMS ID# HHRA 4.213.2*): Mechanistic Data: Approach and Utility for Informing Benefit-cost Analysis and Evidence Integration.** The purpose of Subtask 7.3.2. is to collect and characterize mechanistic data that may be available on the case studies chosen for benefits-cost analysis. Products collected under subtask 7.3.2 are designed to facilitate the systematic, reproducible and transparent categorization of information relevant to mechanistic events applied to human health hazard characterization. These products seek to evaluate and update both specific modes of action (MOA) that have been proposed to operate in only model systems or in both humans and lower mammals, as well as refine various MOA analytical frameworks and descriptions for these case studies to facilitate the organization of mechanistic information into disease pathways, and inform the human relevance and/or dose-response characteristics of adverse effects attributed to agent exposure. This process is envisioned to be iterative with the process of both choosing the case study and that of evaluation of the key events for possible benefit-cost analysis. Utilization of tools such as the ToxRef Database to inform taxonomy considerations, and population of the AOP Wiki and Effectopedia for organizing and evaluating potential AOP for the case studies will help inform the case studies and provide lessons learned on the utility of current constructs for AOP and MOA data. Feedback provided on these tools will be mutually informative to both the HHRA and CSS program.

- **Subtask 7.3.3. (*RMS ID# HHRA 4.213.3*): Scoping Uncertainty Analyses for Epidemiologic and Toxicological Data**
  The NRC (2009) recommended a four tiered system for uncertainty analyses: Tier 0: Default assumptions—single value of result. Tier 1: Qualitative but systematic identification and characterization of uncertainty. Tier 2: Quantitative evaluation of uncertainty making use of bounding values, interval analysis, and sensitivity analysis. Tier 3: Probabilistic assessment with single or multiple outcome distributions reflecting uncertainty and variability. This sub- task would develop scoping recommendations for future uncertainty analyses of exposure-response relationships derived from epidemiologic and toxicological data based on characterization from the case studies in Subtask 7.3.1. or possibly recent IRIS assessments (e.g., Libby amphibole asbestos, tetrachloroethylene). The data and assumptions will be fully described and provide a reference base for further analyses.

Task Products:

Subtask 7.3.1. (*RMS ID# HHRA 4.213.1*): Case studies to Develop Benefit-cost Analysis for Non-cancer Outcomes.

- **Product 7.3.1.1. (*RMS ID# HHRA 4.213.1.1*)**
- **Product Title: Selection of Case Studies Based on Assessment of EPA Program Needs for Chemical- or Endpoint-specific Benefits Analysis**
- Product Contact (email): birchfield.norman@epa.gov, bateson.thomas@epa.gov
- Product's Delivery Date: 2016-2017.
- Product Description: Use a formal process to consult across EPA programs on potential or planned rulemakings with regard to what chemicals they plan on trying to assess the benefits of exposure reductions and which health outcomes they consider as economic drivers. [*NOTE: It is important to build upon, and not duplicate, HHRA program efforts to obtain priority information regarding which chemicals to assess under IRIS.]* An understanding of the relevant range of exposures for potential benefits analysis is a key step to scoping such analyses because even when an exposure-response relationship can be derived, it may not be well-informed across the entire range of potential human exposures. NCEA needs to better understand at the onset of any benefits project what the relevant exposure range is for rule-making or other applications.
- Product's Contribution to Output: Identifies needs of Program Offices for benefits analyses to allow NCEA/IRIS scope future work involving benefits analyses
- Product's Timeline (with milestones): First draft by Q1 FY2016; revised draft report to NPD by Q2 FY2016; choice of case studies by Q3 FY2016.
- Product's intended user/customer/audience: EPA Program Offices, ORD/NCEA, OP/NCEE
- Is this a key product? Yes, this will identify the environmental agents most in need of benefits analysis to support rulemaking. Investing in a fuller understanding of the specific needs for benefits, the specific available exposure, and the specific epidemiologic or animal data available will better synchronize coordination in benefits analyses.
- Does this Product contribute to a Product under another Task? Yes, this will inform Product 7.3.1.2 (Inventory) and Product 7.3.1.3 (Analytic methods)

- **Product 7.3.1.2. (*RMS ID# HHRA 4.213.1.2*)**
- **Product Title: Inventory of IRIS Non-cancer Outcomes for Selected Case Studies**
- Product Contact (email): bateson.thomas@epa.gov; contractor to review IRIS database; subject-matter experts from with NCEA and IRIS (disciplinary workgroups + supplemental experts)
- Product's Delivery Date: Q4 FY 2016 to NPD.
  Product Description: Naming conventions and non-cancer health outcome definitions are not currently standardized, and non-cancer health outcomes do not yet have formal hazard

descriptors. Product would develop, with input from Task 7.3.2. regarding the biological plausibility, a compilation of all endpoints for both human and animal data used in IRIS assessments and ISA for the chosen case studies. The Program Offices and the OP/NCEE can identify which levels of hazard (e.g., 'causal', 'likely','suggestive') and which endpoints may be directly suitable for monetization and which may need biological or other linkages to other more easily monetized endpoints. Product can be extended to include information on relevant exposure paradigms, valuations, and specific uncertainties relevant to IPCS methodology.

- Product's Contribution to Output: Increase transparency and improve consistency of IRIS products. Provide for standardized description/definition of all IRIS non-cancer endpoint for internal use and a product that can be shared with OP economists to review for valuation information.
- Product's Timeline (with milestones): Q4 FY2016 to NPD; possible refinement and further work after that.
- Product's intended user/customer/audience: HHRA program risk assessors, OP economists, and program office partners.
- Is this a key product? TBD
- Does this Product contribute to a Product under another Task? If so, identify other Task. Yes. This will ultimately identify which endpoints can be directly valued and which would require a relational understanding with other endpoints or additional economic work to identify valuations for both the ISA (Task 3.1) and IRIS (Task 1.1) assessments.

- **Product 7.3.1.3. (*RMS ID# HHRA 4.213.1.3*)**
- **Product Title: 7.3.1.3 Case Studies of Dose-response Analysis to Support Benefits Analysis**
- Product Contact (email): bateson.thomas@epa.gov; blessinger.todd@epa.gov
- Product's Delivery Date: Pilot in near-term. By end of March 2017 (Q2 FY2017) to NPD if case study is based on an effect relevant to the ISA process or previously completed IRIS assessment. If the case study is done in collaboration with an on-going assessment, timing may be based on schedule for that assessment; possible further work after that.
- Product Description: Experience from work on the formaldehyde benefits analysis strongly recommends that health effects utilized for benefit analysis have already been recognized/peer-reviewed by an authoritative body. Examine recently completed assessments and evaluate if available data supports dose-response conclusions suitable for benefits analysis and proceed to develop an EPA analysis to support rulemaking. Practical examples exploring the challenges of human non-cancer exposure-response derivation for the purposes of benefits analysis should begin with those endpoints already under evaluation in the ISA program, for which clinical profiles exist, and which may be relevant to the IRIS program. Additional considerations will come from Subtask 7.3.2. with respect to which health effects have sufficient mechanistic underpinning to consider AOP key events and other intermediate outcomes along disease pathogenesis continuum. Plan on collecting "lessons learned" as this work is done, and developing a

report at least for internal use and for cross-office education, potentially for external publication as well. Consider adding analysis in support of benefits assessment into IRIS assessments due for External Review within the period of 2016-2019.

- Product's Contribution to Output: Supports Program Offices
- Product's Timeline (with milestones): Pilot in near-term. By end of March 2017 to NPD if based on a previously completed IRIS assessment – if done in collaboration with an on-going assessment timing will be based on schedule for that assessment; possible further work after that.
- Product's intended user/customer/audience: HHRA program risk assessors, OP economists, and program office partners.
- Is this a key product? TBD.
- Does this Product contribute to a Product under another Task? These case studies are likely to advance approaches for both IRIS and ISA assessments.

Subtask 7.3.2. (*RMS ID# HHRA 4.213.2*): Mechanistic Data: Approach and Utility for Informing Benefit-cost Analysis and Evidence Integration

- **Product 7.3.2.1. (*RMS ID# HHRA 4.213.2.1*) Analysis Strategy for Mechanistic Data.**
- **Product Contact (email):** fritz.jason@epa.gov, gibbons.catherine@epa.gov
- **Product's Delivery Date:** FY19 (with milestones in FY16, FY17, FY18)
- **Product Description:** The evaluation of evidence pertaining to the effects or key events assembled as part of a mode of action (MOA) analysis (e.g. organized into an adverse outcome pathway [AOP]) is difficult due to the vast heterogeneity commonly encountered in a database of information relevant to cellular responses following molecular interactions to an exogenous agent. This heterogeneity exists both in the dimension of model systems employed (e.g. biochemical evaluations, prokaryotes, low to high eukaryotic cells or tissue systems in vitro, various non-mammalian and mammalian species in vivo, including multiple routes and durations of agent exposure), as well as the techniques used to measure and report experimental observations (e.g. direct evaluation of cell cycle progression and physical measurement of cellular proliferation versus indirect measurements of labeled nucleoside incorporation into DNA, or mitochondrial reduction of a chromagen and colorimetric output: all techniques reported to inform cellular "growth" or "viability"). Desirable descriptive characteristics for assays/model systems should include:
    - Methodological quality:
        i. Do standard conditions exist for the exposure system?
        ii. Do standard conditions exist for the endpoint measurement?
        iii. Is dosing to cytotoxicity expected?
    - Informativeness:
        i. Level of biological complexity (relevance to humans)
        ii. Related adverse outcomes

iii. Sensitivity and specificity, and how these attributes may impact the ability of this assay to predict each related adverse outcome

- **Product's Contribution to Output:** A systematic process utilizing existing guidance will enable MOA analyses to become more consistent and transparent. This product will directly address NAS recommendations for the IRIS program (NRC, 2014). In addition to aiding IRIS toxicological review work, this is likely to result in manuscripts detailing the results of the case study evaluation. This will also keep agency MOA analysis methods up-to-date, as "best-practices" methodology has been continually evolving since the 2005 finalization of the EPA Cancer Guidelines and MOA analysis framework. This product will become more important with increasing age of EPA Cancer Guidelines (2005), and with the continued deployment of different MOA/AOP analytical frameworks by other agencies interested in human health hazards.
- **Product's Timeline (with milestones):**

Establish a community of practice for application of MOA and AOP mechanistic data. Group will be comprised of HHRA assessors across PPRTV, IRIS and ISA program working on MOA, and with CSS scientists working on AOP Wiki.	FY16
For the selected case studies, develop a succinct and clear description of the analysis process and critical decision points for analyzing mechanistic support (i.e. the "how to" nuts and bolts for performing a mode-of-action analysis) for hazard characterization.	FY16
Populate the AOP Wiki and Effectopedia with mechanistic data for selected case studies. Evaluate issues of taxonomy and performance attributes of Wiki and Effectopedia for elucidating MOA / AOP for the chosen case studies.	FY16
Using the selected case studies, compile and evaluate evidence for key events and the description of MOA. Evaluate the utility of the mechanistic data to inform consideration of defining adversity and for informing benefits analysis.	FY17

- **Product's intended user/customer/audience:** ORD scientists performing or interested in MOA analysis, and interested scientists in the MOA community.
- **Is this a key product?** TBD.
- **Does this product contribute to a Product under another Task? If so, identify other Task.** Yes. Lessons learned on the use of mechanistic data in these case studies will inform evidence integration approaches of Subtask 7.1.3.

Subtask 7.3.3. (*RMS ID# HHRA 4.213.3*)Scoping Uncertainty Analyses for Epidemiologic and Toxicological Data

- **Product 7.3.3.1. (*RMS ID# HHRA 4.213.3.1*)**
- **Product title: Scoping Uncertainty Analyses for Epidemiologic and Toxicological Data**
- Product Contact (email): bateson.thomas@epa.gov; blessinger.todd@epa.gov; epi group; stat group; tox group
- Product's Delivery Date: Q4 FY2018

- Product Description: Scoping recommendations for future uncertainty analyses of exposure-response relationships derived from epidemiologic and toxicological data based on characterization from the case studies in Subtask 7.3.1. or possibly recent IRIS assessments (e.g., Libby, tetrachloroethylene). The data and assumptions that would be needed to pursue higher levels of uncertainty analyses will be determined.
- Product's Contribution to Output: Advances analysis and characterization of uncertainty
- Product's Timeline (with milestones): First draft by September 2017; revised draft report to NPD by Q2 FY2018; then determine further work
- Product's intended user/customer/audience: ORD/NCEA; EPA Program Offices
- Is this a key product? Yes. In order to be responsive to NRC, NCEA/IRIS needs to describe the practical limits of uncertainty analyses and when investments in greater efforts are warranted.
- Does this Product contribute to a Product under another Task? No.

- **Product (*RMS ID# HHRA 4.213.3.2*)**
- **Product title: Evaluation of probabilistic methods to compute risk with quantified uncertainty**
- Product Contact (email): blessinger.todd@epa.gov; swartout.jeff@epa.gov
- Product's Delivery Date: near-term; Dec., 2015
- Product Description: Currently, to account for uncertainty and extrapolation in assessments, default adjustment factors are applied to PODs to derive a reference dose or reference concentration (RfD/RfC), which is subsequently used as a threshold for risk. The adjustment factors typically can attain one of only a small set of values (such as 1, 3, or 10), and their value is determined qualitatively. More robust and flexible methods are available for quantitatively characterizing uncertainty and computing risk. One method, APROBA, is a more probabilistic approach to using adjustment factors. In this method, adjustment factors representing uncertainty and variability are assumed to follow the independent lognormal distributions and subsequently applied to PODs. Parameters of these distributions (median, 95th percentile, etc) are estimated empirically using real toxicological data, taken primarily from publications. Another quantitative method estimates the distribution of adjustment factors without the independent lognormal assumption using Monte Carlo methods. These methods can be used to estimate the probabilities bounded by risk values, as opposed to defining a single-value threshold for risk. Various probabilistic methods of characterizing uncertainty will be evaluated and applied to recent and possibly ongoing IRIS assessments and compared to the traditional default method.
- Product's Contribution to Output: Provides a vital tool for estimating risk.
- Product's Timeline (with milestones): long-term; Q4 FY2019
- Product's intended user/customer/audience: Risk assessors in EPA
- Is this a key product? TBD. A thorough evaluation of quantitative analysis of uncertainty and estimation of risk across dose is essential to estimating of risk above the reference dose and evaluating confidence in risk estimation.

- Does this Product contribute to a Product under another Task? This task may inform approaches under development in Task 7.4 and IRIS assessments (Task 1.1).

- **Product 7.3.3.3. (*RMS ID# HHRA 4.213.3.3*)**
- **Product title: Characterizing Uncertainty in Developmental and Reproductive Toxicity Studies**
- Product Contact (email): hotchkiss.andrew@epa.gov
- Product's Delivery Date: Sept, 2017
- Product Description: The developmental and reproductive toxicity data that are currently available for chemical risk assessments are seldom ideal in terms of adequately characterizing hazard and dose response for every target toxicity in these systems and processes. It is standard practice to assume that one or two guideline developmental toxicology studies and a guideline two-generation reproduction study will adequately address any concerns regarding developmental and reproductive toxicity, and that there is no remaining uncertainty in this regard. Yet these studies do not address most functional development (including but not limited to developmental neurotoxicity and developmental immunotoxicity), they do not focus meaningfully on postnatal development, and they do not necessarily evaluate the most critical endpoints relative to the chemical toxicity. Often, the information that defines a level of confidence in the developmental and reproductive toxicity assessment is contained in non-guideline data: structure-activity data, genomic profiles, in vitro data, toxicokinetic studies, alternative in vivo study designs, etc. A framework is needed for considering the overall database for developmental and reproductive toxicology data, for assessing and quantifying uncertainties, and for defining research needs to address residual uncertainties for environmental toxicants.
- Product's Contribution to Output: Addresses the database uncertainty factor.
- Product's Timeline (with milestones): Sept, 2017
- Product's intended user/customer/audience:
- Is this a key product? TBD.
- Does this Product contribute to a Product under another Task? Yes. This task will inform Subtasks 7.3.1. and 7.3.2., especially if this reproductive or developmental effects are selected; and will also inform approaches under development in Task 7.4 and IRIS assessments (Task 1.1).

Task Constraints: Work on HHRA assessments may delay completion of products and interim milestones for all of the subtasks.

Task Dependencies: Subtasks 7.3.1. and 7.3.2. depends on ongoing assessments and program office participation; and work in Topic 1 to provide data and examples for some applications.

Task Quality Assurance and Data Management Needs:

- Is there an existing IRP/ QAPP(s) that applies to this Task? If so, identify IRP/QAPP.
    - Yes. NCEA-16-00004. Quality Assurance Project Plan (QAPP) For HHRA Projects 6, 7, & 8 to Develop Methods, Tools, Models and Supporting Analysis.

- Will this Task involve large amounts of data that need a data management plan? If yes, explain.
    - TBD. The Health and Environmental Research Online (HERO) system is used for systematic literature review and is covered by a separate QAPP: NCEA-16-00005. Quality Assurance Project Plan (QAPP) For Extraction of Scientific Data Into the Health and Environmental Research Online (HERO) Database System. Some products may generate a limited amount of data or metadata during case study or method development and refinement.

Task 7.4

(*RMS ID# HHRA 4.214*)

Characterizing Determinants of Risk:

Concentration, Duration, and Timing of Exposure

Task Leads (TL): George Woodall (NCEA RTP) and Andrew Hotchkiss (NCEA IRIS)

Task Start Date: Q1 2016

Task End Date: Q4 2019

Task Description:

An ongoing challenge for EPA is to determine the best approaches for consideration of risk from real-world exposures. Exposures leading to adverse health outcomes (responses) are most fully characterized by concentration, duration, as well as the critical timing of exposure. In this task, we will investigate the relationship of adverse health outcomes (responses) as a function of these three elements of exposure: concentration (how much), duration (how long), and critical timing of exposures (when). Challenges in linking adverse health outcomes to specific exposure scenarios include (but are not limited to): (1) single acute duration increases in exposure; (2) fluctuations in exposure levels (including repeated episodic increases); (3) accumulation of effects from a long-term, low-level averages and/or episodic increases in exposure; and (4) exposures during susceptible life-stages or windows of vulnerability.

Emerging technologies and systems-based characterizations of pathogenesis provide more comprehensive understanding of disease progression as represented by measurements of key events early in an adverse outcome pathway (AOP). Understanding the prognostic value of key events in an APO to predict apical disease states and their relationship to the critical elements of exposure will allow endpoints which occur earlier and/or at lower doses on the concentration/duration/response continuum to be included in cost-benefit analyses. Developing approaches to identify and incorporate the most relevant elements of an exposure characterization which lead to these key events in AOPs will advance their application into agency risk assessments, and build better bridges with computational models to ensure our assessments are based on the most contemporary methods using sound scientific evidence. The capacity to effectively communicate these complex evaluations in a clear and transparent

fashion is another challenge to be addressed with visualization tools being developed under Project 9 (*RMS ID# HHRA 4.23*). This project thereby supports development of a flexible array of response estimates characterizing dose from various real-world exposure scenarios, across durations spanning from acute to chronic, and builds capacity for the application of computational approaches such as adverse outcome pathways (AOPs).

Research Approach:

This task builds upon several ongoing efforts within HHRA, other research programs (ACE and CSS) and Program Offices within EPA (OAQPS, OCHP, OCSPP, OSWER, and OW), and leverages resources and expertise with key Federal partner agencies (FDA, NTP, and NIOSH). It is comprised of two general areas of work in subtasks as follows:

- **Subtask 7.4.1 (*RMS ID# HHRA 4.214.1*): Evaluation of early life exposure for lifetime cancer and noncancer outcomes**
  An ongoing challenge for EPA is to determine the best approaches for consideration of life-stage susceptibilities/windows of vulnerability. A number of emerging technologies and systems-based characterizations of pathogenesis provides a more comprehensive understanding of disease progression that an early, reversible measurement represents.
  Currently, an area of significant interest and concern are health effects resulting from early-life exposures (e.g., in utero) in which effects may occur due to exposure during a critical stage of development. Health effects observed from early life exposures may result in categories commonly identified as developmental and reproductive effects, but may also contribute to effects (e.g., cancer) usually thought to occur from chronic low-dose exposures.

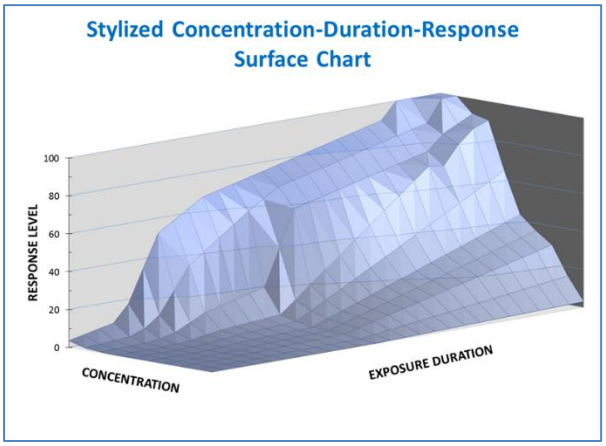
  Characterization of the range of exposure scenarios, mechanistic information contributing to mode of action (MOA) / adverse outcome pathways (AOPs), and resulting health effects (cancer and noncancer endpoints) across groups of chemicals will inform the use or development of risk assessment methodologies. Building upon the findings from the investigations of early-life exposures, case studies will be used to examine other types of effects in other life stages to more fully explore the relationship of episodic exposure scenarios to affect dose-response relationships.

  This sub-task builds upon several ongoing efforts within HHRA, other research programs (CSS – Kevin Crofton, John Cowden, NCCT; Mary Gilbert, Tim Wade, Earl Gray, David Thomas, NHEERL) and Program Offices (OCHP – Michael Firestone; OW - Santhini Ramasamy) within EPA, and partner agencies (FDA – Suzy Fitzpatrick; NIEHS – Paul Foster; NTP – Andrew Rooney, Abee Boyles). Within this effort the outcomes will be highly dependent upon existing literature. For example, based upon a brief literature search, epidemiological studies have characterized relationships between neurological health effects and early life exposures to environmental pollutants including polybrominated diphenyl ether (Chen et al., 2013; Eskenazi, et al., 2013;), polyaromatic hydrocarbons (PAHs; Perera et al., 2012; 2009), arsenic (Graziano et al., 2014; Nadeau et al., 2014; Recio-Vega et al., 2014;

Steinmaus et al., 2014), lead (Nye et al., 2014), methylmercury (Yorifuji, et al., 2014; Zeilmaker et al., 2011; Ryan, 2008), perfluorooctanoic acid (Chen et al., 2013;) and organochlorines (Vested et al., 2014; Eskenazi et al., 2008). Although this brief literature search was performed to scope the focus of this subtask and a complete literature search will be conducted in this subtask focused to identify information on multiple health effects, cancer and noncancer, that have been associated with early life exposures. This effort will characterize the state of the science, describe exposure characterization for women of reproductive age, evaluate potential hazards, and contribute to possible qualitative and quantitative AOPs. Culmination of this health effects information will inform and set the stage to explore current and future risk assessment methodologies for exposure to environmental pollutants during early life.

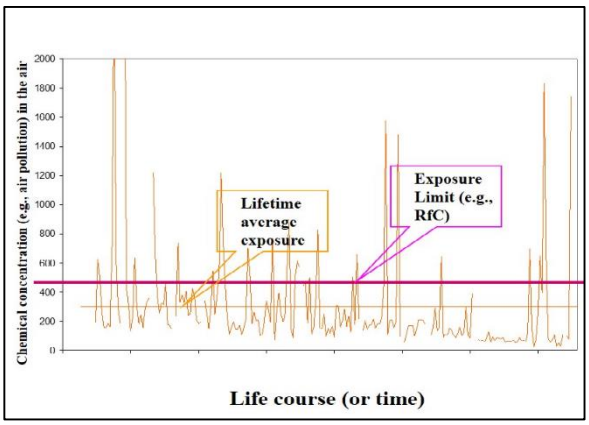
- **Subtask 7.4.2. (*RMS ID# HHRA 4.214.2*) Concentration-duration-response surface analysis and interpretation**

The overall goal of this subtask is to better understand which combination of factors are the most critical to eliciting an adverse outcome: exposure level, duration of exposure, and timing of those exposures. A key tool to perform these investigations will be use of the concentration-duration-response surface concept to help analyze the biological evidence, to better visualize and communicate those relationships, and to incorporate all these factors into better risk assessments.



The simplest representation of toxicity in a graphical form is the classic, two-dimensional dose-response curve which typically represents increasing dose/concentration levels on the x-axis and increasing response levels on the y-axis. Other factors can affect this relationship, such as duration of exposure, intermittent or fluctuating exposures, consideration of adequate recovery time between exposures, etc. When taking any one of these other factors into account, the two-dimensional dose-response relationship will change into a multi-dimensional relationship. These more complex, multi-dimensional relationships cannot be communicated in a simple two-dimensional graphical display (i.e., a dose-response curve), but are more appropriately rendered as a three-dimensional surface, hence the term surface analysis. The concept of a concentration-duration-response surface will be applied in this subtask to the analysis and interpretation of toxicological data. The capacity to effectively communicate these complex relationships in a clear and transparent fashion is a challenge to be addressed with visualization tools being developed under Project 9 (*RMS ID# HHRA 4.24*).

The risk-based estimate (i.e., RfD or RfC) for a single chemical and single exposure route assumes a threshold dose (or concentration) below which there is no adverse non-cancer effects. The implicit assumption underlying the current practice in estimating an RfD/RfC is that chemical exposure remains relatively constant over a life-span of 70 years. Nevertheless, the interpretation of single RfD/RfC values is complicated by day-to-day real-life exposure variability. As shown in the graphic example, even when the lifetime average is below estimated RfD/RfC, individuals or communities may not be protected from exposure to environmental hazards. In some cases, such as developmental and neurological endpoints, risk is specifically associated with peak blood or tissue levels. In these cases inter- and even intra-day variability in exposure may be significant. This possibility presents a major challenge in interpreting RfD/RfC toxicity values without considering real-life exposure scenarios.



Understanding the relationship of key events in AOPs to the most relevant exposure characterization elements (how much, how long, and when) will ensure that our assessments are based on the most contemporary methods and sound scientific evidence, and help identify the real-world exposure scenarios most important for risk assessment/risk management. In this subtask, investigations will focus on the relative contributions from each dimension (exposure/duration/timing) on adverse outcomes from: (1) single acute peak exposures; (2) fluctuations in exposure levels (including repeated episodic increases); (3) long-term, low-level exposures to ambient stressors leading to an accumulation effects; and (4) known examples where critical timing of exposure leads to adverse outcomes and how those examples are translatable to other scenarios. We will also examine some of the assumptions made in the extrapolation of data across durations and/or exposure scenarios.

The field of industrial hygiene has long recognized the hazard from short-term, elevated exposures to chemicals. Time-weighted averages for a standard workday (e.g., 8-hours) are protective overall, however, those protections are irrelevant if the bulk of the exposure occurs in a shorter time frame (e.g., 15 minutes). As such, short-term exposure limits were designed to ensure that chemical exposures did not exceed certain thresholds at any time during the workday. The current RfC/RfD framework used in IRIS is consistent with low-level average exposure levels over years (similar to a time-weighted average for long-term exposures), such as years of exposure. In addition, recent findings coming from occupational exposures for some chemicals are showing indications of increases in adverse effects more strongly associated with repeated episodic exposures (hours to days) than those predicted from long-term averages. Further elucidation of the effects of fluctuating exposure levels on adverse health outcomes will improve the capability of risk assessors to accurately predict risks from realistic exposure profiles. In this

subtask, we will also review existing toxicity/reference values and investigate opportunities to develop values most appropriate to characterize risk from acute or episodic fluctuations in exposure.

Task Products:

Subtask 7.4.1 (*RMS ID# HHRA 4.214.1*): Evaluation of early life exposure for lifetime cancer and noncancer outcomes. It is noted that the EPA Science and Technology Policy Council (STPC) has initiated a project to address NRC *Science and Decisions* recommendations regarding "methods for explicitly considering in cancer risk assessment *in utero* exposure and chemicals that do not meet the threshold of evidence that the agency is considering for judging whether a chemical has a mutagenic mode of action." Opportunities for parallel efforts may be available through coordination with the STPC project on cancer risks following early life exposures. This product will be developed in a stepwise manner with three interim deliverables anticipated.

- **Product 7.4.1.1. (*RMS ID# HHRA 4.214.1.1*)**
- **Product title: Literature search and systematic review of mechanistic and health effects data for early life exposures resulting in cancer and noncancer outcomes later in life**
- Contact (email): Reeder Sams (sams.reeder@epa.gov)
- Delivery Date: FY16 (1st Qtr)
- Description: This product can result in a series of review articles focused on multiple health effects categories as well as hypothesis manuscripts focused on MOA and AOP development.
- Contribution to Output: Characterization of the state of the science will set the stage and is the first step for potential development of future risk assessment methodologies for early life exposures
- Timeline (with milestones): Draft an document systematic review protocol, develop search strategy, conduct literature search, document results on HERO project page; all completed within FY16 (1st Qtr)
- Intended user/customer/audience: Retrieved literature will be curated in HERO for current task and future assessment development.
- Key product? No.
- Contributions to a Product under another Task: Task 1.1; Task 3.1; Task 4.1;Task 7.1, 7.5

- **Product 7.4.1.2. (*RMS ID# HHRA 4.214.1.2*)**
- **Product title: Evaluation of potential AOPs related to early life exposure.**
- Contact (email): Reeder Sams (sams.reeder@epa.gov)
- Delivery Date: Q2 FY2017
- Description: Based upon results from the broad literature search and systematic review of health effects data, it is likely that numerous environmental pollutants will be identified having significant data to suggest causal relationships. For endpoints with sufficient data to merit a hazard concern, mechanistic data will be evaluated to hypothesize potential AOPs and compare against existing AOPs (e.g., OECD, etc.). Multiple manuscripts may be generated based upon endpoints and availability of mechanistic data.

- Contribution to Output: Characterization of the state of the science will set the stage and is the first step for potential development of future risk assessment methodologies for early life exposures
- Timeline (with milestones): Evaluation of AOPs relevant to health effects identified through literature search product, FY16 (2nd Qtr); generation of hypothesized AOPs FY16 (3rd Qtr); Report synthesizing evidence for hypothesized AOPs FY17 (2nd Qtr)
- Intended user/customer/audience: Retrieved literature will be curated in HERO for future assessment development. Report and possible manuscripts published on AOPs for health effects with sufficient information will provide information relevant for hazard identification.
- Key product?
- Contributions to a Product under another Task: Task 1.1; Task 3.1; Task 4.1;Task 7.6

- **Product 7.4.1.3. (*RMS ID# HHRA 4.214.1.3*)**
- **Product title: Report evaluating the state of the science for health effects due to early life exposures, including current and future risk assessment methodologies for exposure to environmental pollutants during early life.**
- Contact (email): Reeder Sams (sams.reeder@epa.gov)
- Delivery Date: 2017
- Description: Products from 7.4.1 will set the stage for evaluating the available scientific information with respect to health effects due to early life exposure. Based upon this information a list of pollutants will be identified and in Subtask 8.4.1 exposure datasets (e.g., NHANES) will be utilized to characterize the range of exposure for women of reproductive age within the US. Levels of concern can be evaluated based upon the consideration of health effects data in epidemiological and toxicology studies. Lastly, current and future risk assessment methodologies for exposure to environmental pollutants during early life. These products will culminate in a comprehensive report (output). Products in development will in part support a workshop focused on temporal exposure characteristics (e.g., less-than-lifetime duration, fluctuating patterns of exposure, and critical windows of susceptibility) planned for FY16 (1st Qtr). Multiple manuscripts may be generated based upon evaluation of information characterized in this subtask.
- Contribution to Output: Characterization of the state of the science provide relevant information with respect to hazard for multiple chemicals and set the stage for potential development of future risk assessment methodologies due to early life exposures
- Timeline (with milestones): Products generated under Tasks 7.4.1, 8.4.1, and 7.5 (see corresponding timelines) will provide the basis for an report on the state of the science for health effects due to early life exposures and risk assessment methodologies, FY17 (4th Qtr)
- Intended user/customer/audience: Retrieved literature will be curated in HERO for future assessment development. Reports and manuscripts published on health effects with sufficient information will provide information directly relevant for hazard identification and inform risk assessment methodologies.
- Key product? TBD.
- Contributions to a Product under another Task: This report will be informative to all HHRA assessment products, i.e., IRIS (Task 1.1), ISA (Task 3.1) and PPRTV (Task 4.1).

- **Product 7.4.1.4. (*RMS ID# HHRA 4.214.1.4*)**
- **Product title: Summary Report of the "Temporal Exposure Issues for Environmental Pollutants: Health Effects and Methodologies for Estimating Risk" Workshop**
- Contact (email): Reeder Sams (sams.reeder@epa.gov)
- Delivery Date: FY16 (4^{th} Qtr)
- Description: This report will provide the evaluation and documentation of the proceeding of the workshop which is planned to be held in early FY2016.
- Contribution to Output: Consideration of options in the development of other products in this task are anticipated.
- Timeline (with milestones):
- 1Q, FY2016 – Compilation of notes from the workshop (contractor, session chairs, EPA staff and student contractors)
- 2Q, FY2016 – Draft summary developed from compiled notes and sent to session chairs and presenters to ensure accuracy.
- 3Q, FY2016 – Review draft of summary enters clearance process.
- 4Q, FY2016 – Final summary report posted on NCEA web site.
- Intended user/customer/audience: Risk assessment community and EPA staff working to better incorporate considerations of less-than-lifetime issues in risk assessments.
- Key product? No.
- Contributions to a Product under another Task: Lessons learned from the workshop and captured in this report will be informative to all HHRA assessment products, i.e., IRIS (Task 1.1), ISA (Task 3.1) and PPRTV (Task 4.1).

Subtask 7.4.2. (*RMS ID# HHRA 4.214.2*) Concentration-duration-response surface analysis and interpretation. In this subtask, dose-response data will be used to analyze, model and interpret the relationship of concentration-duration and response across multiple types of adverse health effects. The collection of these types of data are occurring across a number of activities within HHRA, across the Agency (CSS and NCCT; TSCA; etc.), and with other agencies performing risk assessments (ATSDR, FDA, NIOSH, DHS, and others). Several products planned for development in this subtask leverage capabilities being developed in a visualization project already underway at the Environmental Modeling and Visibility Lab (EMVL) and builds upon several ongoing efforts within NCEA/HHRA, other research programs (ACE – TBD; CSS – Richard Judson and Matt Martin, NCCT) and Program Offices (OAQPS – Ines Pagan) within EPA.

The end product of this effort will be a white paper and set of recommendations for the application of Concentration-Duration-Response Surface Analysis into human health risk assessment. It is anticipated that this product and the interim deliverables will lead to advances in all of the major products from HHRA Projects 1, 2 and 3. Listed below are the three major deliverables which will lead to the development of this product.

- **Product 7.4.2.1 (*RMS ID# HHRA 4.214.2.1*)**
- **Product title: Categorical case studies to evaluate determinants of concentration-duration-response surfaces**
- Contact (email): George Woodall (woodall.george@epa.gov), Allen Davis (davis.allen@epa.gov), and Annie Jarabek (jarabek.annie@epa.gov)
- Start Date: Q2FY16;
- Delivery Date: End Q4 FY18
- Description: Chemicals to be used in these case studies will be selected to represent a range of health effects and mechanisms known to cause an apical adverse effect. It is anticipated that these chemical case studies will be discussion items for the workshop to be convened under Task 7.7, and that those discussions will help inform selection of representative chemicals.
- Work being performed in the current EMVL work effort under Task 9.1 will provide data analysis/management and graphical tools allowing greater potential to evaluate the complex relationships between concentration, duration and response, and how to best represent the dependencies of the most critical factors to causing apical effects important to HHRA risk assessments (IRIS, ISAs, and PPRTVs). These EMVL visualization tools will be applied to different key chemicals in case studies to evaluate determinants of response and identify prognostic significance of key events.
- Timeline (with milestones):
  - FY2016 – Identify set of case studies (n ≤ 5) that illustrate mechanistic considerations (e.g., inhaled irritant; parent versus metabolite toxicity; other physicochemical property or specific IRIS or programmatic priority).
  - FY2017 – Develop case studies with reports for 1 or more of the identified classes of effects, using the prototype data visualization tools being developed under Task 9.1. Feedback from this pilot test case will help inform the further development of the visualization tools and the types of analyses which may be most appropriate in later case studies.
  - FY2018 – Develop case studies with reports for the remaining examples. Identify additional types of analyses where the developed tools may be appropriate.
  - FY2019 – Dependent on success with the case studies, apply similar analyses to key, priority-need chemicals.
- Intended user/customer/audience: Risk assessment community and EPA staff working to better incorporate considerations of less-than-lifetime issues in risk assessments.
- Key product?
- Contributions to a Product under another Task: Workshop being conducted under Task 7.5. The work in this task will also provide support for work done in Task 7.3.

- **Product 7.4.2.2 (*RMS ID# HHRA 4.214.2.2*)**
- **Case Study: duration of exposure for male reproductive toxicology testing in rodents**
- Contact (email): makris.susan@epa.gov
- Delivery Date: Q2 2017
- Description: This product will be one of the case studies investigating duration and timing of exposure leading to a known, measurable adverse health outcome. A manuscript will be written for publication in a peer reviewed journal by a group of experts assembled to evaluate duration of treatment in male rodents used for male reproductive toxicity testing. For environmental chemicals, male reproductive toxicity is assessed in 2-generation reproduction studies, in which the males are exposed to the test substance for the entire duration of male spermatogenesis

(approximately 70 days). For nonclinical data supporting pharmaceutical development, a limited exposure period (14-28 days) is considered acceptable for screening male reproductive toxicity, with reliance on pathology and some fertility assessment to indicate the need for additional testing. The limited exposure approach has also been incorporated into the OECD extended one-generation reproductive toxicity study protocol, which is accepted by EPA. By serendipity, several researchers have identified situations indicating that for some chemicals, the short term screening of male rodents may not identify male reproductive toxicity that will be apparent after longer exposures. (This problem may be related to the MOA of male reproductive toxicity.) Comparative data (i.e., short vs. longer term exposures to the same test substance, with assessment of structural and function male reproductive outcomes) are not typically available. A more rigorous data search and evaluation of this topic is warranted. Several interested US and European collaborators from pharmaceutical and CRO organizations have already been identified; this group will be expanded to include EPA experts in male reproductive toxicology and risk assessment.

- Contribution to Output: This project will evaluate and characterize uncertainties linked to abbreviated exposures of male rodents in toxicology studies. Such information would be valuable in the assessment of hazard and risk, for IRIS and Program Offices.
- Timeline (with milestones): Initiate collaborative activities in late 2015; workgroup systematic research and discussions through 2016; draft manuscript completed for submission to peer reviewed journal in Q2 2017.
- Intended user/customer/audience: This topic would be of interest to inter- and intra-Agency researchers and hazard/risk assessors.
- Does this product contribute to a Product under another Task: This ties to projects on AOP/MOA products for reproductive toxicology, Task 7.1, Subtask 2.

- **Product 7.4.2.3. (*RMS ID# HHRA 4.214.2.3*)**
- **Product title: Evaluation of Mechanisms via Concentration-Duration-Response Surface Analysis**
- Contact (email): George Woodall (woodall.george@epa.gov) and Annie Jarabek (jarabek.annie@epa.gov)
- Start Date: FY2018
- Delivery Date: FY2019
- Description: The "Categorical Case Study" deliverable within this subtask will provide analysis on a chemical-by-chemical basis with an intent to better understand the relation between effects of toxicants on mechanisms leading to an apical disease state. In this deliverable, the emphasis will be on the mechanisms across multiple chemicals which lead to a common (or very similar) apical disease state. The objective will be to look for both commonalities and anomalies in those relationships as an analysis tool and to potentially lead to establishing potential linkages in mechanisms beyond QSAR.
- Timeline (with milestones):
  - Q1 FY2018 – Identify candidate mechanisms based on the anticipated priority needs for HHRA and outcomes from the Categorical Case Studies work.
  - Q2 FY2018 – Initiate searches and consolidate existing searches for chemicals with information related to the previously identified mechanisms. Collect and organize the relevant data streams and perform initial analyses to create an analytical strategy and protocol.

  - Q4 FY2018 – Produce an analytical strategy and protocol report; review and seek comments prior to initiation of analysis.
  - FY2019 – Develop report of the results with potential for peer-review publication; revise as needed; clear and publish.
- Intended user/customer/audience: Risk assessment community and EPA staff working to better incorporate a better understanding of underlying mechanisms in chemical toxicity risk assessments.
- Key product? TBD.
- Contributions to a Product under another Task: Anticipate this analytical approach will prove useful in developing assessments in HHRA Projects 1, 2 and 3.

- **Product 7.4.2.4. (*RMS ID# HHRA 4.214.2.4*)**
- **Product title: Approach to Concentration-Duration-Response Surface Analysis from Exposure to Specific Toxicants**
- Contact (email): George Woodall (woodall.george@epa.gov), Allen Davis (davis.allen@epa.gov), and Annie Jarabek (jarabek.annie@epa.gov)
- Start Date: FY2018
- Delivery Date: FY2019
- Description: This document will incorporate the lessons from the "Categorical Case Studies" and "Exposure Variability" products in this subtask, combine them with the graphical data visualizations being develop in Task 9.1 to provide recommendations in how to best apply surface response into risk assessments. It is anticipated that this work will provide indicators for a number of stakeholders:
- Risk assessors in better characterizing potential risk from evidence provided in human, animal and in vitro studies;
- Risk managers in being able to discriminate potential risks from varying durations and exposure levels in lieu of a single point estimate of risk;
- Researchers in developing studies to better fill missing portions of the topography in a concentration-duration-response surface.
- Timeline (with milestones):
  - FY2018 – Initiate drafting of the white paper; develop preliminary draft for internal HHRA review; provide draft to research partners within ORD.
  - FY2019 – Develop final draft of white paper; provide final draft to program offices for review and comments; revise as needed; clear and post.
- Intended user/customer/audience: Risk assessment community and EPA staff working to better incorporate considerations of concentration-duration-response surface analysis into risk assessments.
- Key product?
- Contributions to a Product under another Task: Anticipate this document will be useful in developing assessments in HHRA Projects 1, 2 and 3.

- **Product 7.4.2.5. (*RMS ID# HHRA 4.214.2.5*)**
- **Product title: Toxicity values to assess less-than-lifetime and time-varying exposures**
- Product Contact (email): George Woodall (woodall.george@epa.gov) and Annie Jarabek (jarabek.annie@epa.gov)
- Product's Delivery Date: FY2019
- Product Description: The field of industrial hygiene has long recognized the hazard from short-term, elevated exposures to chemicals. Time-weighted averages for a standard workday (e.g., 8-hours) are protective overall, however, those protections are irrelevant if the bulk of the exposure occurs in a shorter time frame (e.g., 15 minutes); therefore short-term exposure limits were designed to ensure that chemical exposures did not exceed certain thresholds at any time during the workday. The current chronic RfC/RfD framework is consistent with a time-weighted average over years of exposure but does not address potential short-duration peaks. In addition, recent findings from occupational exposures for some chemicals are showing indications of increases in adverse outcomes more strongly associated with repeated episodic exposures (hours to days) than those predicted from long-term averages. Further elucidation of the effects of fluctuating exposure levels on adverse health outcomes will improve the capability of risk assessors to accurately predict risks from realistic exposure profiles.
- Not all hazards of chemical exposure are associated with long-term average exposure levels. Defining safe exposure levels for shorter-term excursions, episodic spikes in exposure, or similar exposures which occur in many real world situations has been adopted in occupational settings; defining similar protections for the general public is logical. This effort will seek out existing reference values to meet those needs for risk assessors, using criteria which are being developed in a cross-Agency review panel to assess the adequacy of the derivation methods used in deriving values, along with criteria to determine the appropriateness of specific reference values for use in Agency risk assessments. In addition, the capacity to develop values for less-than-lifetime durations (and episodic fluctuations in exposures) into IRIS will be investigated.
- Product's Contribution to Output: For chemicals where short-term exposures can be expected to occur, and pose a risk of health-related effects from such exposures, appropriate values can be either derived for inclusion in the IRIS Assessments for those chemicals, or appropriate values from other sources of reference values can be identified which meet specific criteria for appropriateness.
- Product's Timeline (with milestones):
    - Q1 FY2016 –
      Identify candidate outside sources of less-than-lifetime reference values for evaluation.
    - Q3 FY2016 –
      a) Apply derivation method criteria to assess which sources of values provide values which may be candidates to use in agency risk assessment (with reference to those values by HHRA through the IRIS Program).
      b) Scope which chemicals in the MYP and those with existing IRIS Assessments are candidates for development of additional, less-than-lifetime values and begin the process of developing values for up to 5 of those chemicals. Prime candidates are the 5 which were examples used in the development of the EPA/OECD acute method (acrolein, ethylene oxide, hexachlorocyclopentadiene, hydrogen sulfide, and phosgene).
    - FY2017 – 2019
      a) Apply chemical specific criteria to reference values originating from those

organizations with derivation methods meeting the prior criteria. Focus will be on chemicals identified as high-priority, high-need by consultation with the Regional and Program Offices.
b) Incorporate development of less-than-lifetime values into new IRIS assessment starts, dependent on the needs of the MYP.
c) Develop up to 3 additional less-than-lifetime reference values for inclusion in existing IRIS assessments for high-priority, high-need chemicals as determined by consultation with the Regional and Program Offices, with a focus on those chemicals without an appropriate existing reference value from another organization.

- Product's intended user/customer/audience: OSWER, Regions, Program Offices
- Is this a key product?
- Contribution to a Product under another Task: This would enhance the capabilities to provide a more complete portfolio of reference values for inclusion in the IRIS Assessments being developed in both Task 1 and Task 2 in Program 1.

- **Product 7.4.2.6. (*RMS ID# HHRA 4.214.2.6*)**
- **Product title: Characterization of environmental exposure variability and application to internal dosimetry models for chemical risk assessments**
  - Product Contact (email): Lin.Yu-Sheng@epa.gov; Schlosser.paul@Epa.gov
  - Start Date: Q1 FY2016
  - Delivery Date: Q4 2018
  - Product Description: The proposed product will refine and utilize existing algorithms, or develop novel ones to investigate the impact of exposure variability on internal doses estimation in support of IRIS chemical assessments. The objective is to generate computational modules which generate simulated exposure patterns for each type of media (water, food, air) that can be used as inputs to pharmacokinetic (PK) models. Then, using those modules linked to a specific set of PK models, selected to illustrate a range of PK half-lives and behavior, to investigate the degree to which exposure variability impacts internal dose and hence risk. It is expected that for long half-life materials, short-term variability will be shown not to be important, for intermediate half-life materials day-to-day variability will be important, and for short half-life materials intra-day variability may be significant. Ultimately we seek to identify the variability time-scale that should be incorporated into a risk assessment for a chemical, depending on its PK properties.
    - Characterization of chemical exposure patterns (both trend and variation) and identification of potential contributing sources (interim milestones) for selected chemicals.
    - Two (one for ingestion and the other is for inhalation for selected chemicals [to be determined]) or more peer-reviewed journal articles Handbooks (long term milestone).
    - Draft of materials for inclusion into the IRIS/ISA Assessment Handbooks (long term milestone).
  - Contribution to Output:

As compared to relatively homogeneous and constant exposure scenarios in experimental animal studies, human chemical exposures often vary over time. It is increasingly apparent that better characterization of such variability could improve the understanding of the exposure-response relationships. The goal of the proposed project is to apply probabilistic statistical approaches and physiologically based pharmacokinetic (PBPK) modeling to investigate the impact of exposure variability on the internal doses of chemical exposures.
The efforts will combine existing (previously developed) PBPK models with the use of realistic

uncertainty / variability exposure estimates based on national data (e.g.., U.S. National Health and Nutrition Examination Survey (NHANES) data, and the EPA Physiological Information Database). Hence an intermediary step will be development of probabilistic exposure models or sampling methods to use as inputs to the PBPK models. Ideally several chemicals/PBPK models with a range of half-lives will be used in the evaluation. For chemicals with longer half-lives, very short-term fluctuations in exposure will be of less consequence than for chemicals with shorter half-lives. So part of the effort will be to determine the sampling or simulation time-scale over which variation needs to be evaluated to characterize the range of human dosimetry. The project should result in at least two reports or publications, describing the findings for inhalation and water ingestion, respectively. If additional research is conducted to identify rates of water/beverage consumption, this could be described in a third paper.

It will improve our understanding of how different exposure scenarios (low- and high-variability) may impact the external-internal dose relationship. Different types of internal dose metrics including the target organ (i.e., liver) concentration-time curve (AUCL), the area under the metabolic rate-time curve (AURC), and peak concentration (Cmax) will be examined and compared to the dosimetry values generated in the current IRIS practice. As such, this proposed work will enhance the interpretation of RfD/RfC in the complex exposure scenarios in human populations. The proposed project will be exemplified with case studies of chemical(s).

- Timeline (with milestones):
    i. Q1 FY 2016: Scoping of the work
    ii. Q4 FY2018: Product completion and delivery
- Intended user/customer/audience:
    i. NCEA/RTP lead assessment (Integrated Science Assessments, ISA);
    ii. Office of Children's Health Protection and other EPA program offices;
    iii. Public at large
- Is this a key product?
- Contributions to a Product under another Task: If so, identify other Task. Yes. Task 8.3, Advancing Multi-scale Dosimetry Models to incorporate AOP and biomarker data, and Task 8.4: Evaluation and application of new exposure data and methods. For task 8.3 the results can be used as an adjustment to default inter-species scaling methods for oral and inhalation exposures that are inputs to the dosimetry models to be employed there.
- Contingencies: Initial work on analysis of NHANES data and other data sources to identify intra-day and inter-individual variability in exposure pattern (e.g., inhalation exposure and water ingestion) was performed in collaboration with Kristin Isaacs (NERL) and Jianping Xue (NERL), who extracted the water/dietary ingestion amounts from the NHANES dietary recall studies. A small contribution of their time would be helpful with further analyses. The effort would also benefit from input from statistician(s) on characterizing the ingestion/inhalation patterns. Finally, while the available data provided amounts ingested at particular times of the day, it's clear that ingesting a cup of coffee or bottle of water takes some time, but the amount of time taken was not recorded. Hence additional data on how quickly beverages are consumed could be useful.

Task Constraints:

- **Scientific**: Work on several products within this task will require the participation of scientists also involved in development of primary HHRA products under Projects 1, 2 and 3. Timing of their participation in relation to needs on those other projects will need to be defined as the timelines for production are better delineated.
- **Logistical**: Research topics covered in Subtasks 7.4.1 and 7.4.2 may be affected by discussions in a workshop convened under Task 7.7 with potential for changes to the direction taken based on the outcome of that workshop.
- **Technical**: Much of the work in Subtask 7.4.2 may be constrained based on the progress made in the Enhanced Arrays subtask under Task 9.1; work that is being conducted by the EMVL contractor. Other constraints on data availability and translation may also affect progress, and will be dependent on activities under Task 9.1.
- **Resources**: Successful completion of the case studies product within Subtask 7.4.2. is dependent on resources for the development of data visualization and analysis capabilities through work conducted in Task 9.1. Progress will be enhanced by addition of Student Services Contract and/or ORISE Fellow support. Lack of such supporting resources will delay implementation and may increase costs through the need to procure support through task orders on existing contract mechanisms.

Task Dependencies:

- The data visualization and data management aspects of this task are linked to and partially dependent on a project funded through the Environmental Modeling and Visibility Lab (EMVL) initiated in FY2015; continuation of funding in future years is favorable dependent upon a successful proposal for continued support.

- This task depends heavily on the availability of existent data and the manner in which dose-response data are organized and stored. The capacity to enable seamless movement of the required information with all relevant associated aspects will be a challenge to negotiate as this Task progresses.

Task Quality Assurance and Data Management Needs:

- Is there an existing IRP/ QAPP(s) that applies to this Task? If so, identify IRP/QAPP.
    - Yes. NCEA-16-00004. Quality Assurance Project Plan (QAPP) For HHRA Projects 6, 7, & 8 to Develop Methods, Tools, Models and Supporting Analysis.

- Will this Task involve large amounts of data that need a data management plan? If yes, explain.
    - TBD. The Health and Environmental Research Online (HERO) system is used for systematic literature review and is covered by a separate QAPP: NCEA-16-00005. Quality Assurance Project Plan (QAPP) For Extraction of Scientific Data Into the Health and Environmental Research Online (HERO) Database System. Some products may generate a limited amount of data or metadata during case study or method development and refinement.

Task 7.5

(*RMS ID# HHRA 4.215*)

Science Workshops on Major Risk Assessment Methodology Issues

Task Leads (TLs): Lynn Flowers (NCEA IO) and David Bussard (NCEA W)

Task Start Date: 10/01/2015

Task End Date: 09/30/2019

Task Description:

HHRA anticipates hosting between 2 and 4 major scientific workshops each year. The purpose will be to advance the scientific dialogue on major issues that arise as HHRA implements the other goals of HHRA. Workshops are expected to cover topics that are cross-cutting, may affect multiple chemical assessments, and may concern forward-thinking issues that are expected to impact future assessments. HHRA anticipates that for several years it will annually hold a workshop on advances in systematic review methodologies. Systematic review is a major focus for improvements to how IRIS chemical assessments are conducted; it is also an active area of research and change in the scientific community. HHRA anticipates the major scientific workshops for each year will otherwise tentatively be determined by the end of the preceding fiscal year based on what scientific issues at that time are most important

and most ready for a major public workshop. (In addition to major workshops hosted by HHRA, scientists working under HHRA will also often participate in symposium, workshops and presentations in other venues, such as professional society meetings, and may as the need arises hold small scientific dialogues as useful to advance the Projects and Tasks under HHRA.)

Research Approach:

For some topics, HHRA may use an existing report to frame the issue for discussion. For example, on systematic review HHRA could use recent NRC reports on the IRIS program and draw from participants in the NRC panels that did those reports as a core set of expert participants familiar with the topic. For other topics, HHRA will draw from work done by scientists working under HHRA to frame the nature of the scientific issues, the risk assessment context, and the needs of the program.

Task Products:

HHRA will annually develop a list of workshops based on critical issues and challenge that arise in its assessment activities or which emerge as critical issues for risk assessment in general. The following three workshops are planned in FY16.

- Advancing systematic review (December 2015)
- Temporal issues for Environmental Pollutants: Health Effects and Methodologies for Estimating Risk (January 2016)
- Characterizing and communicating uncertainty in human health risk assessment

Each of these topics contributes to other HHRA tasks. Topics in future years also will both arise out of work on other HHRA Tasks and will contribute to the completion of other HHRA Tasks, whether contributing to major on-going tasks such as the completion of IRIS or ISA assessments, or contributing to resolving methodological tasks under Topic 3 or 4.

- **Product 7.5.1. (*RMS ID# 4.214.1*)**
- **Product title: Advancing Systematic Review**
- Product Contact (email): Vince Cogliano (NCEA IRIS); coglinio.vince@epa.gov
- Product's Delivery Date: Q1 FY16
- Product Description: Convene a workshop to continue evaluation of systematic review for tailored application to HHRA assessment products.

- Product's Contribution to Output: Refinement of systematic review approaches will enhance efficiency and credibility of HHRA assessment products.
- Product's Timeline (with milestones): Workshop in December 2015. Evaluation of discussion and recommendations will inform a report as a product under Task 7.1.
- Product's intended user/customer/audience: HHRA scientists, Agency partners and external stakeholders
- Is this a key product? No
- Does this Product contribute to a Product under another Task? Yes. This workshop will continue to advance the application of systematic review in support of HHRA assessment products.
- **Product 7.5.2. (*RMS ID# 4.214.2*)**
- **Product title: Temporal Exposure Issues**
- **Product Contact (email):** Reeder Sams (NCEA RTP); sams.reeder@epa.gov
- Product's Delivery Date: Q2 FY16
- Product Description: Workshop (http://cfpub.epa.gov/ncea/risk/recordisplay.cfm?deid=307738)
- Product's Contribution to Output: Advance understanding of critical issues regarding the impact of early life exposures and timing of exposures to inform development of approaches.
- Product's Timeline (with milestones): Convene workshop Q2 FY2016
- Product's intended user/customer/audience: HHRA scientists, Agency partners and external stakeholders
- Is this a key product? No.
- Does this Product contribute to a Product under another Task? Yes. This workshop is serving all the subtasks in Task 7.4 and will inform IRIS (Task 1.1) and PPRTV (Task 2.1) assessments.

- **Product 7.5.3. (*RMS ID# 4.214.3*)**
- **Product title: Characterizing and Communicating Uncertainty in Risk Assessment**
- Product Contact (email): David Bussard (NCEA W); bussard.david@epa.gov
- Product's Delivery Date: Q4 FY16
- Product Description: Workshop
- Product's Contribution to Output: Dialogue on how characterizing uncertainty in risk hazard and dose-response can be done in a practical manner useful to risk management decision-making
- Product's Timeline (with milestones): Workshop Q4 fy16 or Q1 fy17
- Product's intended user/customer/audience: HHRA scientists, Agency partners and external stakeholders
- Is this a key product? No
- Does this Product contribute to a Product under another Task? Yes. Insights from the workshop will contribute to work on methods for hazard id and dose-response (Task

7.1) and to how uncertainty is characterized in IRIS assessments (Task 1.1), PPRTVs (task 2.1), and other assessments as appropriate.

Task Constraints:

Organizing a major workshop can be resource intensive in terms of requiring time from HHRA scientists, even if the topic is one on which scientists have been working. Identifying appropriate external scientists with the right knowledge and balancing perspectives takes research and time. Experts in the topic are often very busy with multiple demands upon their time, and sufficient lead time and key experts in the field may need at least 6 months' notice with some flexibility about dates to accommodate other commitments from key participants. A final constraint is keeping the total cost (conference space if not in EPA space, travel, *per diem*) at a reasonable level and to obtain the needed prior approval of conference expenses. Work on a major workshop can impact schedules for other HHRA deliverables if the preparation draws from staff working on other products.

Task Dependencies:

Initial workshops on an issue can sometimes be organized building on the work of others, such as building on a recent NRC Report. Typically, however, a major scientific workshop on a topic may be dependent on work done under another project or task within HHRA in which scientists have evaluated the assessment context in which the issue arises, the range of scientific views, the current state of scientific practice, and key experts who would most effectively contribute in a workshop.

Task Quality Assurance and Data Management Needs:

- Is there an existing IRP/ QAPP(s) that applies to this Task?
  - Yes. NCEA-16-00004. Quality Assurance Project Plan (QAPP) For HHRA Projects 6, 7, & 8 to Develop Methods, Tools, Models and Supporting Analysis.

- Will this Task involve large amounts of data that need a data management plan? If yes, explain.
  - No.

Human Health Risk Assessment (HHRA)

Project Planning Tool

Project Plan

HHRA Project 8 (*RMS ID# HHRA 4.22*): Applying Emerging Science to Inform Risk Screening and Assessment

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Project start date: 10/01/2015

Project end date: 09/30/2019

Executive Summary

This project is devoted to characterizing the utility of emerging data streams and new computational tools, such as those developed by the CSS program and from other sources such as the NIH, university consortiums, and in the clinical arena. The HHRA program plans to build confidence in the application of this emerging science by characterizing its utility for different chemical classes over a broad range of disease outcomes (e.g., cardiovascular, respiratory, etc), and for different types of data (e.g., QSAR, HTS, molecular epidemiology, clinical profiling, alternate animal models, quantitative adverse outcome pathways). The project will also advance updates to dosimetry modeling and methods to be able to describe the dose-response for key events in mode of action (MOA) and adverse outcome pathways

(AOP), thereby facilitating the quantitative use of these concepts and mechanistic data in assessments. Updates to the repertoire of the HHRA program's exposure assessment tools are also planned, including developing best practices to address interpretation of new sensor data. Together the tasks in this project will be the basis for building confidence in and building capacity for employing emerging technologies across the risk assessment landscape covered by the HHRA program.

Research Project Description

The rapid pace of new product development and the global need to assess the safety of chemicals and alternatives is increasing the number of chemicals and exposure scenarios that need to be evaluated. Meanwhile, with biotechnology advances, the generation of toxicological data is moving from a relatively small number of standard *in vivo* tests (with 2-3 dose levels) to >500 *in vitro* tests (with 5-12 dose levels) for many chemicals under programs such as ToxCast and Tox21. The interpretation of very large amounts of diverse new toxicity-related data on industry products and other potential contaminants represents a significant challenge. Computational chemistry is advancing new approaches to identify active properties or to apply methods for read-across and structure-activity analysis to more rapidly address categories of chemicals and endpoints. Exposure models are able to refine estimates to the personal level. Risk assessments are evolving to incorporate information on mechanism of action (MOA) in humans rather than a simple point of departure in mammalian systems. The public has greater expectations of transparency for risk management decisions and the data on which such decisions are based. Together these developments have resulted in a deluge of information that has potential application to various risk assessment-related decision contexts. In addition, development of new environmental sensing and monitoring capabilities will increasingly provide the need to assess exposures for chemicals not yet characterized and to interpret data from new types of sensors.

Initially, to understand their relevance to diverse risk-based decision making, these new types of data must be evaluated in the context of traditional outcome measures used in risk assessment. The utility of these new data and computation tools for a range of risk assessment applications (e.g., screening or priority setting, hazard identification, and dose-response analysis) must be characterized. Characterizing the utility for such a large range of potential applications in a "fit-for-purpose" sense requires an awareness of context and includes: proper problem formulation; careful construction of evaluation criteria and case studies to analyze the impact on hazard or risk predictions due to differences in underlying data sources, relevant chemical properties, types of endpoint data, mining or modeling algorithms; and attention to extrapolation assumptions.

The HHRA program plans to approach this characterization of high-throughput screening and other data mining outputs to informing and improving HHRA risk assessment products in a step-wise fashion. Emerging data will be evaluated within the conceptual model of exposure-dose-response to provide context for risk assessment and in order to understand what key biological, spatial or temporal features the new measures or computational tool output may replace or represent. This understanding is the basis for building confidence in and building capacity for employing emerging technologies across the

assessment landscape spanning from research prioritization to risk screening, and ultimately quantitative dose-response analysis.

Project Impact

As new technologies and types of data emerge, the risk assessment community across the Agency as well as external stakeholder that use HHRA risk assessments, need to understand the scope, limitations, and advantages of this emerging science to apply the information with confidence to various types of decision making. This project is targeted to accelerate application of these innovative approaches by thorough characterization of their utility in the context of risk-based decision making.

Project Scope

The HHRA program anticipates that in order to advance and achieve the vision proposed by the NRC for exposure science and toxicology testing, these concepts must be applied in risk assessment approaches. As understanding of systems biology advances, mechanistic insights should help to incorporate other measures such as biomarkers and effects at different levels of biological organization into risk assessment for a fuller characterization of the spectrum of a disease outcome and the key events of pathogenesis. For example, how do new data mining tools for *in vitro* measures at the genomic level inform dose-response? As our understanding of the key events for different endpoints or diseases evolves, building bridges to systems biology requires construction of methods that can incorporate data on biomarkers from various disease dimensions (e.g., early or late-stage) in various tissues (e.g., blood or liver) of different species, and the ability to incorporate high-throughput data and adverse outcome pathways (AOP) with different degrees of verification. The prognostic significance of various key events relative to more traditional endpoints and disease outcomes need to be established to employ AOP and MOA in risk assessment. Strategies to integrate evidence from these diverse data types must be conceptually consistent and attempt to describe the pathogenesis as a continuum.

A fuller characterization of disease pathogenesis also necessitates consideration of the nature of toxicity and how this relates to the various exposure scenarios that may require assessment. Real-world exposures include single acute duration increases in exposure and fluctuations in exposure levels (including repeated episodic increases). To best address these variables, accumulation of effects or the chemical must be characterized, and consideration given to susceptible life-stages or windows of vulnerability. Determinants such as the concentration, duration, and timing of exposures for different classes of chemicals based on physicochemical characteristics (e.g., aldehydes versus volatile organic chemicals) and specific endpoints of interest across HHRA risk assessment products will be evaluated by targeted case studies aimed at developing new assessment products to characterize risks for different

diseases and various data types spanning the range from MIE to apical outcomes across chemical classes, different endpoints, and varying degrees of supporting data.

Figure 8-1 provides a conceptual construct for the project and illustrates the relationships among biomarkers, AOP, and MOA, with the types of computational approaches that can inform and improve the accuracy of descriptions for those relationships, and where considerations of susceptibility (e.g., due to life stage or disease) may modify those relationships.

Tasks in this project are targeted to address the various components illustrated in this figure. Development of a disease-based data integration approach will begin by case study of specific disease outcomes of interest to HHRA assessment priorities such as that underway for inorganic arsenic. The approach will build on lessons learned in the report *"Next Generation Risk Assessment: Incorporation of Recent Advances in Molecular, Computational, and Systems Biology"* (U.S. EPA 2014). This report was a collaborative effort by the CSS and HHRA programs and points to future directions for stronger collaboration and innovative applications of new data streams and computational approaches in risk assessment. Collaboration with the CSS program for developing screening and read-across applications is ensured by having HHRA scientists participate on the Demonstration and Evaluation project within CSS; these same scientists are involved in tasks that then apply the tools developed directly into informing PPRTV assessments or for developing new assessment products. Other components of the project that address additional features of this construct are described below.

Project Structure and Rationale

Project 8 is comprised of four tasks to evaluate new data streams and develop or revise computational tools and models to characterize their utility and accelerate their application in risk assessment approaches. The four tasks in Project 8 include the following:

- **Task 8.1 (*RMS ID# HHRA 4.221*) Disease-based Data Integration of New Data Types**
- **Task 8.2 (*RMS ID# HHRA 4.222*) Characterization and Quantitative Application of High-throughput Screening and Other Data-mining Derivations**
- **Task 8.3. (*RMS ID# HHRA 4.223*) Dosimetry 21: Advancing Multi-scale Dosimetry Models to Incorporate AOP/MOA and Biomarker Data**
- **Task 8.4. (*RMS ID# HHRA 4.224*) Evaluation and Application of New Exposure Data and Methods**

Task 8.1 approaches the exposure-dose-continuum from the “right-hand side”, i.e., evaluating diseases associated with an exposure and constructing MOA or AOP based on those data, whereas Task 8.2 is constructing approaches based on data mining using chemical properties and MIE (Thomas et al., 2014) extended to a larger array of data including read-across QSAR, additional endpoints, and other data sources. The two approaches of course are not mutually exclusive and HHRA program scientists working on each will strive to ensure that they remain consistent within this general conceptual context.

Task 8.3 is targeting multi-scale dosimetry modeling to update current approaches to facilitate the application of mechanistic data. Current models and guidance on choice of dosimetry models will be updated to describe potential dose metrics for key events at different levels of organization for portal-of-entry effects in the respiratory tract and other critical target tissues. These updates are necessary to inform both evidence integration approaches and to facilitate quantitative dose-response analyses in keeping with the NRC vision represented by Exposure21 and Tox21 recommendations (NRC 2007; 2012). The updates will support that application with guidance and model suites for prediction of internal dose for various levels of biological organization at which key events of an AOP or MOA are observed. This task and others on exposure will also evaluate how best to integrate with exposure modeling platforms.

Exposure assessment is also a key component integral to characterizing hazard and risk and an area of rapidly emerging scientific advances. There is broad recognition that the risk estimates used to protect human health and ecosystems would be improved with better exposure data (NRC 2012). Task 8.4 has several products to enhance exposure modeling and predictions including development of analytical considerations and interpretation guidance for sensors.

With the recent development of large environmental and chemical databases and personal and environmental sensors, there is great opportunity to improve methods to more accurately characterize exposure (e.g., intensity, frequency, duration, and route). However, to utilize the diverse array of newly available data for exposure assessments, methods are required to translate and adapt data into well-established exposure protocols.

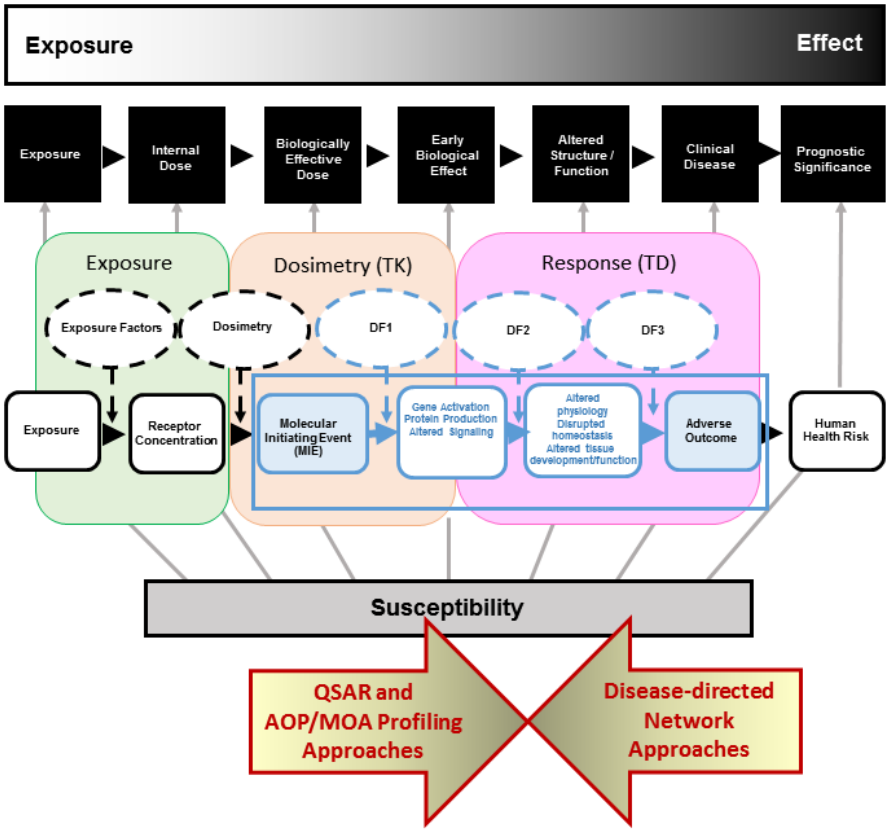

Figure 8-1. Conceptual construct showing the relationships of computational approaches in Project 8 and schematics developed for biomarkers, AOP and MOA applied to risk assessment. Yellow arrows depict the general direction of two types of strategies to emerging data in Tasks 8.1 (right-hand side) and Task 8.2 (left-hand side). Dosimetry and exposure models to improve and refine those descriptions are also included in Project 8. The scheme of key events along the exposure-dose-response continuum is based on that of Schulte (1989) as proposed for biomarkers and modified by Jarabek et al (2009) for mode of action (MOA). The blue box and blue-bordered key events outline elements of an adverse outcome pathway (AOP) described by Villeneuve et al (2014). Key events of pathogenesis are depicted as solid border nodes, key event relationships are depicted are shown as solid directed arrows between key events, and determining factors (DF) that control or may modify those relationships (e.g., ventilation rate; absorption, distribution, metabolism or elimination; repair, etc.) are depicted as dashed ovals and arrows. The areas covered by components of a biologically-based (BBDR) model structure to support quantitative dose-response analysis are shown as the following: exposure models (green); dosimetry or physiologically-based pharmacokinetic (PBPK) models of toxicokinetics (TK) to describe tissue delivery (orange); and tissue response or toxicodynamics (TD) models (pink). Markers or considerations of susceptibility inform all components of the continuum. For example, life stage or disease state factors may influence parameter values for exposure, dose and response.

Measures of success

We hope to achieve capacity building for the use of innovative technologies, computational tools, emerging data and new approaches for risk assessment both within the HHRA program and across the Agency, and to transfer this technology and understanding to external stakeholders, thereby accelerating the acceptance and application of these new data and approaches in the context of risk-based decision making.

Stakeholders (outside ORD)

Risk assessors and decision makers within the HHRA program, in partner programs across the Agency, and external stakeholders in academia, industry and the public interested in protecting the public health and environment.

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Task 8.1

(*RMS ID# HHRA 4.221*)

Disease-based Data Integration to Develop Multi-scale Risk Assessment Methods

Task Leads (TL): Ila Cote (NCEA IO)

Task Start Date: 10/1/2015

Task End Date: 06/30/2019

Task Description:

This task addresses the need (1) to understand new types of biologic data (e.g., omics) in the context of human disorders and disease, and (2) to have methods for integrating the effects of disease pathogenesis, for describing the influence of multiple stressors, and for better characterizing human susceptibility to these stressors. The task will develop human disease-based risk assessment that integrate a broad array of advanced biological data and traditional data, using computer-based identification and analyses of datasets from large, public databases.[2] Advanced biologic data considered will range from molecular epidemiological and clinical data to medium throughput in vitro data. This task is a companion to Task 8.2 (*RMS ID# HHRA 4.222*) which is focused on the application of high-throughput screening (HTS) *in vitro* data. These data have not been previously extensively used by EPA.

Diseases of interest will be determined in conjunction with program and regional office clients, but are likely to include several types of cancer, respiratory and cardiovascular diseases, and diabetes. Greater

[2] We will integrate current knowledge of disease mechanisms and causation (primarily develop by NIH and their grantees) and chemical specific toxicity data to develop human disease based assessments. Chemical specific data is extracted from the published literature and stored monthly by the NIEHS funded Comparative Toxicogenomics Database.

efficiencies in assessment will be achieved by focusing on major health outcomes (vs. all effects), and by taking full advantage of computerized data mining of large databases.

These disease-based assessments will augment NCEA assessments as follows:

- Strengthen the evidence base by articulating underlying mechanisms of action
- Identify biomarkers that can be quantitatively related to apical outcomes
- Facilitate cumulative risk assessment for multiple chemical exposures and nonchemical stressors, and impacts of covariates in modifying risks.
- Help characterize community risks including evaluation of impacts on disadvantaged communities, multiple stressor exposures, and differential effects by race, ethnicity and age.
- Enable benefits analyses by extending knowledge of the effects associated with exposures.

Research Approach:

Over the last ten year governments around the world have been developing extensive, searchable, databases that compile most of the world's published biological data. Examples include the NIEHS-funded Comparative Toxicogenomic Database (molecular, disease and chemical effects data), NIH's PubChem (compound and bioactivity information) BioSystems (mechanistic data), Gene Expression Omnibus (omics data), and the Database of Genotypes and Phenotypes (dbGaP). These databases contain new types of data that are not systematically analyzed nor currently well integrated into risk assessment. Now, bioinformatic and refined Bayesian methods have emerged that allow computer assisted searching, organizing and meta-analyses of "big" data. These techniques allow integration of evidence in unprecedented ways and on an unprecedented scale, and facilitate probabilistic description of risks. The databases of interest are intended to capture most of the world's literature, hence, meta-analyses across multiple studies and conditions can be utilized for characterizing variability and uncertainty.

Using these new data and methods, we will: (a) compile existing data on chemical and nonchemical stressors that contribute to selected disease; (b) refine existing descriptions of underlying mechanisms; (c) quantitatively and quantitatively characterize potential risk factor impacts; (d) characterize cumulative risks for selected diseases; (e) articulate criteria for study selection, evidence integration, and confidence descriptions; and (f) illustrate use of new knowledge in assessing national and community level risks including impacts on at risk populations using Geographic Information System mapping. For example in the Advancing the Next Generation of Risk Assessment Report (2014) prevalence of genetic and dietary risk factors for diabetes in the US Mexican population, and coexposures to multiple pollutants associated with diabetes were mapped in Los Angeles California to illustrate the overlap of multiple risk factors in the community.

Task Products:

- **Product 8.1.1. (*RMS ID# HHRA 4.221.1*)**
- **Product Titles: Disease-Specific Assessments for [*add specific disease*] of Multiple Environmental Risk Factors in General and Susceptible Populations: New Data, Methods and Results**
- Product Contact: Ila Cote (cote.ila@epa.gov)
- Product Delivery Dates: 2016, 2017, 2018, and 2019.
- Product Description: We will develop 4 disease-specific assessments of multiple environmental risk factors in general and susceptible populations, with associated methods documents. Product will illustrate integrated use of multiple, new advanced biological data types in both national and community assessments. Details are provided in the milestones
- Product's Contribution to Output: New methods refined by expert consultation will support novel and highly efficient chemical and community risk assessment development, significantly improving our understanding of contributions from multiple risk factors and risks incurred by sensitive subpopulations. This effort will allow more nuanced risk evaluation than previously possible.
- Product's Timeline (with milestones)
  a. 2016 - Develop workshop plan and workshop materials for proposed approaches for refinement by external experts. Proposed approaches to include:
     i. Identify multiple chemical and nonchemical stressors that contribute to risks for selected diseases (e.g. common respiratory diseases) using the PubChem, Comparative Toxicogenomics Database and other sources.
     ii. Update existing descriptions of disease mechanisms, building on NIH BioSystems, Reactome, and other sources as needed, and provide input into the EPA/OECD AOPs database.
     iii. Overlay risk factors onto disease mechanism using data from the NIH's Gene Expression Omnibus, Epigenomics, Database of Genotypes and Phenotypes (dbGaP), and other sources.
     iv. Review criteria for hand curated data and articulate weight of evidence for various risk factors using criteria developed in the NexGen report (EPA 2014) and McConnell et al. (2014).
     v. Develop relative risk rankings using traditional and Bayesian approaches
     vi. Describe risk factors and susceptible subpopulations considering characteristics such as socioeconomic status, preexisting health conditions, age, gender etc.
     vii. Use GIS to develop illustrative community level assessment of potential exposures and at-risk populations.
     viii. Hold workshop and refine methods based on workshop feedback; begin application to selected diseases (determined in conjunction with program offices.
  b. 2016-17 – Develop workshop report describing refined methods and begin to apply refined methods to an expanded set of diseases and risk factors.

c. 2017 – Develop draft final reports on new methods and results for multiple diseases and risk factors i.e. probabilistic description of risks and uncertainties for general and at risk populations at large (described above #a)
d. 2018 – Develop draft report on new methods and results for community level risk assessment applications including impacts on disadvantaged subpopulations in selected communities (described above #a)
e. 2019 – Externally peer review both draft documents and finalize.

- Product's intended user/customer/audience. Program offices, regions, states, communities, the general public
- Is this a key product? TBD.
- Does this Product contribute to a Product under another Task? Yes. This is a companion to Project 7: Advancing hazard characterization and dose-response methods and models, the other Project 8 tasks and Project 6: Cumulative risk assessment methods. In total the project provides all of the tools necessary to develop more rapid, robust and efficient risk assessments. This is a collaborative project with NHEERL, NIEHS, NCATs, CDC/NIOSH, FDA, and US ACE.

Task Constraints:

Knowledge mining identifies associations only. Hand curation with disciplinary expertise will be necessary to increase confidence in the data. Evidence integration and quantitative evaluation schemes for this type of work are emerging science, and will be associated with some uncertainties. Additionally, discussion in and refinement by the scientific community will be needed for general acceptance of approaches.

Task Dependencies:

Each milestone and associated product components builds one upon another. Problems in any one will slow or obviate subsequent accomplishments.

Task Quality Assurance and Data Management Needs:

- Is there an existing IRP/ QAPP(s) that applies to this Task? If so, identify IRP/QAPP.
    - Yes. NCEA-16-00004. Quality Assurance Project Plan (QAPP) For HHRA Projects 6, 7, & 8 to Develop Methods, Tools, Models and Supporting Analysis.

- Will this Task involve large amounts of data that need a data management plan? If yes, explain.
    - TBD. The Health and Environmental Research Online (HERO) system is used for systematic literature review and is covered by a separate QAPP: NCEA-16-00005. Quality Assurance Project Plan (QAPP) For Extraction of Scientific Data Into the Health and Environmental Research Online (HERO) Database System. Some products may generate a limited amount of data or metadata during case study or method development and refinement.

Task 8.2.

(*RMS ID# HHRA 4.222*)

Characterization and Quantitative Application of High-throughput Screening (HTS) and Other Data-mining Derivations

Task Lead: Scott Wesselkamper (NCEA CIN)

Task Start Date: 10/1/2016

Task End Date: 09/30/2019

Task Description:

This task addresses the need to develop approaches for interpreting and applying non-traditional, higher-throughput data to human health risk assessment and technical support efforts conducted within the HHRA Program. Initially, the development of these approaches will focus on chemicals with inadequate or non-existent hazard databases. This task addresses data from alternative, high-throughput screening (HTS) platforms or approaches such as structural read-across/(quantitative) structure-activity relationship ([Q]SAR), in vitro biological activity assays (e.g., ToxCast), and toxicogenomics. Many of these higher-throughput data and approaches will be developed by the Chemical Safety for Sustainability (CSS) Program, who will also be coordinating external peer review of these data and approaches, and generating acceptance of and willingness to support these data and approaches by the Regions and Program Offices. Task 8.2 in the HHRA StRAP is designed to help facilitate the interpretation/characterization and application of higher-throughput data to various quantitative fit-for-purpose risk assessment needs within the Regions and Program Offices.

This task is comprised of four major subtasks designed to sequentially characterize the use of HTS data and develop applications of these data in risk assessment.

- **Subtask 8.2.1. (*RMS ID# HHRA 4.222.1*): Methods development for estimating points-of-departure (PODs) from transcriptomic data**

- **Subtask 8.2.2. (RMS ID# *HHRA 4.222.2*): Characterization of uncertainties in high-throughput data-derived extrapolation methods for derivation of alternative data-based screening risk estimates**

- **Subtask 8.2.3. (*RMS ID# HHRA 4.222.3*): Adverse outcome pathway (AOP) footprinting: hazard grouping and quantitative analysis for assessment of mixtures of toxicologically uncharacterized stressors**

- **Subtask 8.2.4. (RMS ID# HHRA 4.222.4): Incorporation and application of high-throughput screening estimates into HHRA products**

Research Approach:

Over the past four decades, the U.S. EPA has made significant progress in protecting human health and the environment from the adverse effects of chemical exposures. Nonetheless, several EPA programs and regions are often tasked with addressing the potential hazard(s) to human health and the environment of chemicals for which little-to-no data exist (for example, OSWER/OSRTI's assessment of Superfund sites and OW's UCMR efforts). The shared problem formulation in this context warrants basic identification of hazard and associated quantitative dose-response assessment for screening and prioritization purposes. Considering the lack of repeat-dose toxicity data for a significant number of potentially hazardous chemicals of interest to EPA client offices, the proposed research in Task 8.2 is highly relevant because alternative methods and data may fill a critical need and be used to be directly responsive to decision maker needs across EPA programs and regions.

This task represents part of a continuum of collaborative research efforts between scientists within the HHRA and CSS Programs on the integration of new technologies into chemical safety and risk assessment. Four subtasks are proposed, and the anticipated products generated from these subtasks primarily encompass white papers and/or scientific publications on methods development and proof-of-concept evaluations that will inform and facilitate the interpretation/characterization of how data from alternative platforms may ultimately be used in the identification of quantitative screening estimates and other fit-for-purpose risk assessment applications. The long-term (FY19) objective of this task will yield application of such screening estimates into HHRA technical support and assessment products delivered to end-users.

Approaches specifically within each subtask are described briefly below.

- **Subtask 8.2.1. (*RMS ID# HHRA 4.222.1*): Methods development for estimating points-of-departure (PODs) from transcriptomic data**

Use of transcriptomic data in HHRA is promising, but a lack of good tools and methods limits its use, which is especially true for quantitative risk assessment. This subtask is unique in that it incorporates considerations of molecular mechanism and toxicological/pathological adversity into the analysis of transcriptomic data for HHRA application purposes. In lieu of applying the most-sensitive perturbed pathway approach to determine transcriptional PODs (as described by Thomas et al., 2011, 2013), this subtask is a proof-of-concept demonstration that aims to use tissue-specific gene signatures that represent critical signaling pathways from which to determine PODs based on

differential transcriptomic changes. The differential expression of each gene signature will be converted into a quantifiable score, and these scores will be used to determine a POD for each gene signature. For validation and method refinement purposes, these PODs will be compared to apical in vivo PODs as well as transcriptomic PODs based on the most sensitive gene expression pathway changes derived in the same study.

- **Subtask 8.2.2. (RMS ID# *HHRA 4.222.2*): Characterization of uncertainties in high-throughput data-derived extrapolation methods for derivation of alternative data-based screening risk estimates**

A major obstacle in the application of high-throughput data in human health risk assessment is the significant uncertainties associated with the quantitative relationship between high-throughput PODs and PODs based on traditional in vivo toxicity studies. This subtask will focus on the analysis of uncertainties associated with quantitative relationships between currently available high-throughput data, and existing dose-response data associated with toxicity values in HHRA databases such as IRIS and PPRTV. Approaches characterizing this quantitative relationship will be explored to further inform the potential use of high-throughput-based PODs in derivation of screening risk estimates. Case studies will be developed to demonstrate the application of these approaches in human health risk assessment settings.

- **Subtask 8.2.3. (*RMS ID# HHRA 4.222.3*): Adverse outcome pathway (AOP) footprinting: hazard grouping and quantitative analysis for assessment of mixtures of toxicologically uncharacterized stressors**

Lack of adverse health outcome data for chemical and non-chemical stressors limits hazard and dose-response evaluations for mixtures risk assessment. Current U.S. EPA mixtures risk assessment practice affords flexibility in the level of biological organization at which determinations of "like" toxicity are made for hazard grouping purposes (e.g., MOA-based). Additionally, determinations in the grouping of "like" hazards can have a significant impact on subsequent mixtures dose-response analyses (e.g., dose-addition versus response-addition). The paucity of hazard and dose-response data for mixtures of stressors, as well as a general lack of characterization and understanding of the causal relationship(s) between MOA/mechanistic perturbations and apical effects, have limited progress in mixtures risk assessment applications. Tremendous strides have been made in advancing our understanding of causal relationships between molecular/cellular perturbations and adverse outcomes of interest (e.g., liver injury; developmental/reproductive toxicity).

This subtask will focus on demonstrating how mechanistic information (e.g., AOPs) could be used to inform mixtures assessment applications such as hazard grouping and dose-response analysis for data-poor stressors. This subtask will include proof-of-concept demonstrations using data-rich stressors, identification of relative potency factor distributions within an adverse outcome class using a footprinting approach; 'footprinting' will entail qualitative WOE evaluation of each key event node within an AOP, working backward from the AO to the molecular initiating event. Data-

permitting, 'footprinting' will also include methods development on probability or confidence descriptions in relation to different exposure paradigms (e.g., differences in exposure duration, frequency, or levels) for each AOP event node.

- **Subtask 8.2.4. (RMS ID# HHRA 4.222.4): Incorporation and application of high-throughput screening estimates into HHRA products**

This subtask will facilitate the characterization/interpretation of higher-throughput data (e.g., from read-across/SAR, QSAR, ToxCast, toxicogenomics data, etc.), as well as information gleaned from the other three subtasks listed under this Task, to derive quantitative screening estimates for chemicals for which little-to-no data exist. The multiple lines of alternative data- based evidence from sources such as the CSS Demonstration and Evaluation (D&E) and RapidTox projects, as well as HHRA Task 8.2, will be integrated into technical support documents and/or other HHRA assessment products. It is anticipated that these technical support documents will provide gradations of information relevant to hazard identification and dose-response assessment, facilitating a broad range of assessment foci from basic hazard screening/prioritization to derivation of quantitative risk estimates.

Task Products:

- **Product 8.2.1. (*RMS ID# HHRA 4.222.1*)**
- **Product title: Methods development for estimating points-of-departure (PODs) from transcriptomic data**
- Contact (email): Scott Wesselkamper (wesselkamper.scott@epa.gov)
- Product's Delivery Date: FY17
- Product Description: White paper and/or scientific journal publication
- Product's Contribution to Output: The proof-of-concept demonstration within this product represents one of the necessary initial steps in understanding the potential utility of alternative data in quantitative HHRA applications. It will likely also inform Subtask 8.2.4
- Product's Timeline (with milestones): FY16 – External review draft; FY17 – Final draft (for submission to journal or EPA release)
- Product's intended user/customer/audience: HHRA risk assessors, Regions and Program Offices
- Is this a key product? TBD
- Does this Product contribute to a Product under another Task? Yes. This demonstration will Subtasks 8.2.2 and 8.2.4 as well as other tasks in the HHRA StRAP (7.1, 7.3 7.4, 8.1, 8.3) that evaluate application of AOPs and modes-of-action mechanistic data.
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- **Product 8.2.2. (*RMS ID# HHRA 4.222.2*)**
- **Product title: Characterization of uncertainties in high-throughput data-derived extrapolation methods for derivation of alternative data-based screening risk estimates**
- Subtask Contacts (emails): Jay Zhao (zhao.jay@epa.gov); Scott Wesselkamper (wesselkamper.scott@epa.gov); Jason Lambert (lambert.jason@epa.gov)
- Product's Delivery Date: FY17
- Product Description: White paper and/or scientific journal publication
- Product's Contribution to Output: The proof-of-concept demonstration and case studies generated from this subtask may significantly advance our understanding of the uncertainties associated with the quantitative relationship between high-throughput PODs and traditional in vivo PODs.
- Product's Timeline (with milestones): FY16 – External review draft; FY17 – Final draft (for submission to journal or EPA release)
- Product's intended user/customer/audience: Regions and Program Offices; will also inform Subtask 8.2.4
- Is this a key product? TBD
- Does this Product contribute to a Product under another Task? Yes. This work will inform Subtask 8.2.4 as well as other tasks in the HHRA StRAP (7.1, 7.4, 8.1, 8.3) that evaluate AOPs and modes of action.

- **Product 8.2.3 (RMS ID# HHRA 4.222.3)**
- **Product title**: **Adverse outcome pathway (AOP) footprinting: hazard grouping and quantitative analysis for assessment of mixtures of toxicologically uncharacterized stressors**
- Contact (email): Jason Lambert (lambert.jason@epa.gov)
- Product's Delivery Date: FY18
- Product Description: White paper and/or scientific journal publication
- Product's Contribution to Output: Proof-of-concept publication(s) demonstrating application of AOP data in a mixtures context may significantly advance approaches in stressor (hazard) grouping and mixtures dose-response analyses using non-apical effect data/metrics.
- Product's Timeline (with milestones): FY18 – External review draft; FY19 – Final draft (for submission to journal or EPA release)
- Product's intended user/customer/audience: HHRA risk assessors, Regions and Program Offices
- Is this a key product? TBD
- Does this Product contribute to a Product under another Task? Yes. This work will inform Subtask 8.2.4 as well as other tasks in the HHRA StRAP (7.1, 7.4, 8.1, 8.3) that evaluate AOPs and modes-of-action.

- **Product 8.2.4. (RMS ID# HHRA 4.222.4)**
- **Product title: Incorporation and application of high-throughput screening estimates into HHRA products**
- Contacts (emails): Scott Wesselkamper (wesselkamper.scott@epa.gov); Jason Lambert (lambert.jason@epa.gov); Jay Zhao (zhao.jay@epa.gov)
- Product's Delivery Date: FY19
- Product Description: White paper and/or scientific journal publication on case studies; integrated hazard and quantitative technical support documents for fit-for-purpose applications
- Product's Contribution to Output: It is envisioned that the technical support documents developed within this subtask will significantly advance fit-for-purpose application of alternative data streams across multiple partner Program Offices and Regions.
- Product's Timeline (with milestones): For white paper/journal publication: FY18 – External review draft; FY19 – Final draft (for submission to journal or EPA release); For HHRA products (i.e., technical support documents) – FY19
- Product's intended user/customer/audience: Regions and Program Offices
- Is this a key product? TBD
- Does this Product contribute to a Product under another Task? Yes. It is anticipated that the technical support documents for fit-for-purpose applications could contribute to products generated under Topic 3, Project 5, Task 5.2 – Technical Support, Consultation and Review for Superfund and other Agency Priorities.

Task Constraints:

- Scientific: Potential constraints include limitations associated with in silico, in vitro and transcriptomic data, transitioning the basis for screening estimate derivation from traditional apical effects to cellular and molecular responses, limitations for testing of deviations from dose-additivity, and the acceptability of the application of alternative data streams to human health risk assessment products within intended end-user offices.

- Logistical: This task relies heavily on efforts supplied by postdoctoral participants within the ORISE program, which currently has a 3-year participation limit. Completion of long-term products will likely require repletion of ORISE participants.

- Technical: There are no significant technical constraints envisioned for this task.

- Resources: Need continued support to hire ORISE participants and/or other postdoctoral fellows.

Task Dependencies:

This task depends heavily on the availability of extant data and the manner in which dose-response was evaluated. Specifically, risk assessment practice across labs/centers/offices within EPA and other agencies outside of EPA differ in some respects, particularly quantitative dose-response assessment.

Task Quality Assurance and Data Management Needs:

- Is there an existing IRP/ QAPP(s) that applies to this Task? If so, identify IRP/QAPP.
    - Yes. NCEA-16-00004. Quality Assurance Project Plan (QAPP) For HHRA Projects 6, 7, & 8 to Develop Methods, Tools, Models and Supporting Analysis.

- Will this Task involve large amounts of data that need a data management plan? If yes, explain.
    - TBD. The Health and Environmental Research Online (HERO) system is used for systematic literature review and is covered by a separate QAPP: NCEA-16-00005. Quality Assurance Project Plan (QAPP) For Extraction of Scientific Data Into the Health and Environmental Research Online (HERO) Database System. Some products may generate a limited amount of data or metadata during case study or method development and refinement.

Task 8.3.

(*RMS ID# HHRA 4.223*)

Dosimetry21: Advancing Multi-scale Dosimetry Modeling for Quantitative Application of AOP/MOA and Biomarker Data

Task Leads (TL): Annie Jarabek (NCEA RTP IO) with IWG/PKWG and key planning partners for collaboration and coordination

Task Start Date: Q1 2016

Task End Date: Q3/2016

Task Description:

Various dose metrics are needed to accurately translate internal dose across the experimental designs underlying diverse data used in risk assessment, including: epidemiological (including biomonitoring), clinical evaluations, *in vitro* and *in vivo* toxicological studies, and *in silico* simulations. Further, as the understanding of key events in the pathogenesis of various diseases rapidly evolves via the development of adverse outcome pathways (AOP) or mode of action (MOA) for chemicals and other mechanistic measurements such as specific biomarkers of exposure and bioindicators of disease, multi-scale dosimetry models that predict dose metrics for different levels of biological organization (e.g., genomic to community) become requisite to be able to incorporate such markers into quantitative response analysis. Guidance on how to best choose a dose metric and match a model structure to describe it has not been updated and has hindered broader application of dosimetry in derivations of risk estimates. Users are also often confused by applications that were dictated by differing mandates of offices or Agencies doing the derivation (e.g., occupational versus ambient applications). Federal collaboration on the development of such guidance and facilitated sharing of available model templates will best leverage experience and provide expertise to educate end users.

A suite of model structures for each route of exposure and which ranges from simple algorithms to well-stirred compartments or single-path mass transfer to physiologically-based empirical models and more mechanistic and complex computational fluid dynamics (CFD) models capable of estimating local flux to specific epithelia in the portal of entry becomes necessary in order to provide the needed flexibility to predict internal dose metrics with the precision commensurate with these various internal responses or endpoints. Detailed portal-of-entry dose descriptions are necessary to characterize effects in the respiratory tract for a large number of inhaled chemicals, as well as for chemicals with reactive or corrosive properties by both ingestion and dermal routes. As part of implementation of the anticipated NRC recommendations, the suites will be constructed in parallel so that the conceptual approach for each route will be the same (e.g., detailed portal-of-entry description linked to systemic model) to facilitate quantitative route-to-route extrapolation and will also serve to update the current dosimetry defaults algorithms. The suites will support the needed application of AOP/MOA and biomarker data in all HHRA product lines: ISA, IRIS and PPRTV.

This work focuses on portal of entry (POE) model structures as an important complement to efforts in CSS on reverse exposure and dosimetry. Over 70% of the inhalation risk assessment values on IRIS are based on or consider POE effects, and occupational concerns for dermal POE effects are typically coupled with inhalation. Likewise, there have been some significant assessments that had to characterize POE in the GI tract.

Research Approach:

This task aims to convene a Federal consortium of dosimetry practitioners (both modelers and experimentalists who employ or support modeling) to develop an issue paper that identifies the challenges posed by the need for multi-scale models to advance other NRC vision recommendations including Tox21 and Exposure21. This issue paper would also address recommendations for models and enhanced interoperability from the SOT Current Concepts in Toxicology (CCT) workshop on “Multiscale Modeling to Support Decision Making” held at the EPA in 2012, and recent publications on updating dosimetry methods employed in development of IRIS RfC values (EPA, 2002). The issue paper will serve as the basis to convene an NRC workshop to provide recommendations on how to implement the multi-scale vision. Associated subtasks include development of a suite of model structures for each route and implementation via development of methods and case studies to serve as training. The task will leverage internal EPA expertise in NCEA, NCCT, NERL and NHEERL and complement CSS ExpoCast modeling efforts employing simple models for reverse dosimetry to support screening with a suite of structures with the capability of describing detailed dose metrics to support quantitative response analyses in the portal of entry and for various levels of organization associated with AOP/MOA and biomarker work.

Several Federal partners are already engaged, are willing to contribute to the issue paper, and endorse the need for the NRC workshop as follows:

- ATSDR
- DoD and DARPA
- DoE PNNL
- FDA NCTR
- ICRP and NCRP (pending)

Work to engage a Federal Community of Practice and develop a consensus conceptual construct will proceed with the following steps as major subtasks. Some work such as the model construction can take advantage of established structures whereas description for other metrics associated with potential key events will require new methods.

Subtask 8.3.1. Issue Paper to Provide Conceptual Construct of Multi-scale Dosimetry Modeling Applications to Support Decision Making

- **Product 8.3.1. (RMS ID# HHRA 4.223.1)**
- **Product title: Issue Paper to Provide Conceptual Construct of Multi-scale Dosimetry Modeling Applications to Support Decision Making**
- Product Contact (email): Annie Jarabek (Jarabek.annie@epa.gov); interested members of Inhalation Working Group (IWG; John Stanek, John Whalen) and Pharmocokinetic Working Group (PKWG; John Lipscomb, Allen Sasso, Elaina Kenyon, Hisham El-Masri, Marina Evans), Rory Conolly (NHEERL), and other laboratories involved with CSS RED (NERL, NCCT, NHEERL) as competing priorities allow.
- Product's Delivery Date: Q4FY16
- Product Description: The involved internal and other Federal partners have agreed to construct an issue paper to tee up the vision for a NRC workshop that will complement the Tox21 and Exposure21 recommendations. The resultant framework should provide the needed credibility and momentum to initiate implementation in various risk assessment activities and sustain the required modeling application development and software support.
- Product's Contribution to Output: Issue paper will serve as foundation to build Federal community of practice and as a vehicle to submit issues to the NRC for recommendations; subsequent implementation will advance applications needed for dose translation across various experimental designs and to incorporate AOP/MOA and biomarker data in quantitative analyses.

- Product's Timeline (with milestones): Q4 2016: Manuscript describing lessons learned and identifying approaches needed to advance application of dosimetry modeling to best achieve proper dose translation and integration of measurements and models to support Exposure21 and Tox21 initiatives.
- Product's intended user/customer/audience: Research scientists and risk assessors across various Federal agencies.
- Is this a key product? TBD. Designation of key product is an annual negotiation between the IOAA and the NPD.
- Does this Product contribute to a Product under another Task? If so, identify other Task. Yes, this issue paper will provide problem formulation for NRC recommendations (subtask 8.3.2. below) and serve as a template for partners and the subsequent subtasks/products below. Concepts will also inform Task 7.1 and 8.1, 8.2 and 8.4.

Subtask 8.3.2. NRC Workshop on Multi-scale Dosimetry Modeling Applications to Support Decision Making

- **Product 8.3.2. (RMS ID# HHRA 4.223.2)**
- **Product title: NRC Workshop on Multi-scale Dosimetry Modeling Applications to Support Decision Making**
- Product Contact (email): Annie Jarabek (Jarabek.annie@epa.gov)
- Product's Delivery Date: Q2FY17
- Product Description: Conversation with the NRC has begun with a proposal in August 2015 to develop the problem formulation and scope of the envisioned NRC report. The report will serve to highlight the requisite role of dosimetry modeling as integral to linking exposure modeling with response modeling in a seamless fashion for accurate exposure-dose-response characterization. The need to quantitatively describe and link key events to dose metrics to advance AOP/MOA constructs and to bridge to biomarkers used in clinical and molecular epidemiology will be emphasized.
- Product's Contribution to Output: The NRC report is envisioned as serving to provide focus and momentum to bring these practices and expertise to bear as part of advancing Tox21 and Exposure21 applications.
- Product's Timeline (with milestones): The NRC workshop will be convened by Q4 2017 and an associated report either by then or by Q2 2018.
- Product's intended user/customer/audience: Research scientists and risk assessors across various Federal agencies.
- Is this a key product? TBD. Designation of key product is an annual negotiation between the IOAA and the NPD.
- Does this Product contribute to a Product under another Task? If so, identify other Task. Yes, the NRC report and recommendations will help provide momentum for Federal

implementation and serve as a template for partners and the subsequent subtasks/products below. Concepts will also inform Task 7.1 and 8.1, 8.2 and 8.4.

Subtask 8.3.3. Construction of Model Suites for Inhalation, Oral and Dermal Routes

- **Product 8.3.3. (RMS ID# HHRA 4.223.3)**
- **Product title: Construction of Model Suites for Inhalation, Oral and Dermal Routes**
- Product Contact (email): Annie Jarabek (Jarabek.annie@epa.gov); interested members of Inhalation Working Group (IWG; John Stanek, John Whalen) and Pharmocokinetic Working Group (PKWG; John Lipscomb, Allen Sasso, Elaina Kenyon, Hisham El-Masri, Marina Evans), Rory Conolly, and other laboratories involved with CSS RED (NERL, NCCT, NHEERL) as competing priorities allow.
- Product's Delivery Date: Q4 FY2019
- Product Description: This product will provide guidance on construction and availability of extant model structures to describe a range of dosimetry models from the update of default algorithms for the inhalation route to sophisticated CFD models that can describe local estimates to specific epithelial types. This range is necessary to support the application of dosimetry models in a fashion commensurate with available data. When limited data are available, a rudimentary structure based on reduced forms can be employed whereas to describe more refined metrics (e.g., specific epithelial concentrations of metabolite) a detailed structure is necessary. Developing a suite of structures will best position the users to take advantage of the most recent and sufficiently mature innovations in this type of modeling. The envisioned suites for inhalation will build on templates (e.g., ATSDR metals and VOC toolboxes), previous model suites and recommended updates to current default structures made internally at EPA (e.g., per IWG request and EPA, 2002); leverage on-going work on specific models (e.g., IEUBK and MPPD, metals) and integrate with reverse exposure and dosimetry (RED) systemic models used in CSS.
- Product's Contribution to Output: Suite of structures shared across the Federal consortium will leverage capacity and expertise currently somewhat isolated in various institutions; thereby enhancing opportunities for informed application and facilitating education of end users.
- Product's Timeline (with milestones): Q42019; these structures will continue to evolve as partners in the Federal consortium advance models and measurements.
- Product's intended user/customer/audience: Research scientists and risk assessors across various Federal agencies.
- Is this a key product? TBD. Designation of key product is an annual negotiation between the IOAA and the NPD.

- Does this Product contribute to a Product under another Task? If so, identify other Task. Yes. The concepts and suites of shared model structures will inform will also inform Task 7.1 and 8.1, 8.2 and 8.4.

Subtask 8.3.4. Conceptual Considerations for Application of Dosimetry to Different Experimental Data

- **Product 8.3.4. (*RMS ID# HHRA 4.223.4*)**
- **Product title: Conceptual Considerations for Application of Dosimetry to Different Experimental Data**
- Product Contact (email): Annie Jarabek, (jarabek.annie@epa.gov); Ellen Kirrane (Kirrane.ellen@epa.gov); Barbara Buckley (buckley.barbara@epa.gov); interested members of Inhalation Working Group (IWG; John Stanek, John Whalen) and Pharmocokinetic Working Group (PKWG; John Lipscomb, Allen Sasso, Elaina Kenyon, Hisham El-Masri, Marina Evans), and Rory Conolly, as competing priorities allow.
- Product's Delivery Date: Q2FY2019
- Product Description: This task is envisioned as a complement to the construction of the modeling suites and will be a manuscript and guidance on how to identify and apply different model structures to define different key events to describe AOP/MOA, utilize biomarker data from clinical and ecological epidemiological studies, and ultimately provide interpretation and integration of various data types.
- Product's Contribution to Output: This manuscript will provide the qualitative considerations to employ and inform choice of model structure from the suite described under subtask 8.3.3.
- Product's Timeline (with milestones): Q2 2019 manuscript to incorporate into case study applications and general guidance.
- Product's intended user/customer/audience: Research scientists and risk assessors across various Federal agencies.
- Is this a key product? Designation of key product is an annual negotiation between the IOAA and the NPD.
- Does this Product contribute to a Product under another Task? Yes. The conceptual considerations will inform the construction of the models under subtask 8.3.3. and also inform Tasks 7., 7.3, 7.4 and Tasks 8.1, 8.2 and 8.4.

Subtask 8.3.5. Implementation: Development of Approach Using Integrated Case Study Applications

- **Product 8.3.5. (RMS ID# HHRA 4.223.5)**
- **Product title: Implementation: Development of Approach Using Integrated Case Study Applications**
- Product Contact (email): Annie Jarabek (Jarabek.annie@epa.gov); interested members of Inhalation Working Group (IWG; John Stanek, John Whalen) and Pharmocokinetic Working Group (PKWG; John Lipscomb, Allen Sasso, Elaina Kenyon, Hisham El-Masri, Marina Evans), Rory Conolly (NHEERL), and other laboratories involved with CSS RED (NERL, NCCT, NHEERL) as competing priorities allow.
- Product's Delivery Date: Q4FY19
- Product Description: This product will utilize outputs from 8.3.2 through 8.3.4. and illustrate minimal to robust datasets across varying levels of biological complexity to serve as general guidance for the application of dosimetry modeling to quantitatively describe key events of AOP/MOA or biomarkers to support their use in dose-response analysis and risk assessment.
- Product's Contribution to Output: The case studies and resultant guidance will serve as educational tool to provide translation of concepts and illustrate application of quantitative structures developed in the preceding subtasks. It is envisioned to host this guidance on-line to facilitate engagement and enhance consistent application of concepts across Agency partners and participating Federal consortium.
- Product's Timeline (with milestones): Q4 2019 illustrative case studies and guidance available on-line.
- Product's intended user/customer/audience: Research scientists and risk assessors across various Federal agencies.
- Is this a key product? TBD. Designation of key product is an annual negotiation between the IOAA and the NPD.
- Does this Product contribute to a Product under another Task? The case studies and guidance considerations will inform the construction of the models under subtask 8.3.3. as well as Tasks 7., 7.3, 7.4 and Tasks 8.1, 8.2 and 8.4.

Task Constraints:

  - **Scientific: Competing priorities of the scientists with this expertise**
  - **Logistical**: Time to negotiate a contract with NRC.
  - **Technical:** Software and administrative privileges or relaxation of restrictions to allow open access to computational tools in other Federal Agencies; data sharing and management
  - **Resources**: Will depend on ability of interested Federal partners to contribute.

Task Dependencies:

- **Dependency:** Requires participation of several key Federal players (commitments confirmed)

Task Quality Assurance and Data Management Needs:

- Is there an existing IRP/ QAPP(s) that applies to this Task? If so, identify IRP/QAPP.
  - Yes. NCEA-16-00004. Quality Assurance Project Plan (QAPP) For HHRA Projects 6, 7, & 8 to Develop Methods, Tools, Models and Supporting Analysis.

- Will this Task involve large amounts of data that need a data management plan? If yes, explain.
  - TBD. The Health and Environmental Research Online (HERO) system is used for systematic literature review and is covered by a separate QAPP: NCEA-16-00005. Quality Assurance Project Plan (QAPP) For Extraction of Scientific Data Into the Health and Environmental Research Online (HERO) Database System. Some products may generate a limited amount of data or metadata during case study or method development and refinement.

Task 8.4.

(*RMS ID# HHRA 4.224*)

Evaluation and Application of New Exposure Data and Methods

Task Leads (TLs): Scot Hagerthey (NCEA W) and Tom Long (NCEA RTP)

Task Start Date: FY16

Task End Date: FY19

Task Description:

This task aims to evaluate and apply new forms of exposure data and methods to better quantify exposure to an environmental contaminant across a variety of life stages or risk for exposure. There is broad recognition that the risk estimates used to protect human health and ecosystems would be improved with better exposure data (NRC 2012; Lioy 2014). With the recent development of large environmental and chemical databases and personal and environmental sensors, there is great opportunity to improve the ability to accurately characterize the actual exposure (e.g., intensity, frequency, duration, and route) and activity and behavior patterns. However, to utilize the diverse array of newly available data for exposure assessments, methods are required to translate and adapt data into well-established exposure protocols. The two subtasks divide the work into improving the currently applied exposure factors and supporting the tools associated with them, and then recognizing the rapidly emerging sensor data arena that will bring new analytical capabilities and data sources (including citizen science) to characterize exposures. The resultant products will enable risk assessors in EPA program offices and regions to take advantage of the increasingly available amount of exposure related information to develop more precise exposure estimates.

- **Subtask 8.4.1 (*RMS ID# HHRA 4.224.1*): Improving exposure estimates with new and emerging exposure data.**

  This subtask addresses the evaluation and application of new forms of exposure data and methods to better quantify exposure to an environmental contaminant across a variety of life stages or risk for exposure. The primary goal is improve exposure estimates by applying

state-of-the-art technologies to more accurately assess exposure and activity and behavior. This subtask couples new data sources and methods with existing well-established sources of exposure information for the purposes of developing exposure estimates in a timely manner that are relevant and pertinent to the exposed population.

- **Subtask 8.4.2 (*RMS ID# HHRA 4.224.2*): Advancing the Application of Sensor Data for Risk-Informed Decision Making.**

As exposure science and analytical measurement capabilities rapidly progress, development of an understanding of the applications and limitation of such sampling devices and approaches for the interpretation of resultant measurements in a risk assessment context become critical. This includes understanding the analytical considerations such as operating constraints and detection limits as well as issues for translation of readings to internal dose and interpretation of dose-response. Data access, curation and management concerns are also raised.

The HHRA program is partnering with the NIOSH Center for Direct Reading and Sensor Technologies to advance the application of sensor data to support decision making, and continue collaborative efforts with the ACE national program and the cross-agency Air Sensors Health Group (ASHG). Focal areas include developing criteria on analytical methods, understanding how to interface such measurements with dosimetry models to predict internal metrics more analogous to those used in risk assessment, guidance on the interpretation of sensor data applied to risk assessment, and articulation of best practices for sensor data curation and management. It is expected that the advances in Subtask 8.4.2 will also inform citizen science and aid communities in applying cumulative risk assessment methods (HHRA Project 6).

Research Approach:

To achieve the broad goal of evaluating and applying new forms of exposure data and methods, the following research approaches will be used.

- **Subtask 8.4.1 (*RMS ID# HHRA 4.224.1*): Improving exposure estimates with new and emerging exposure data.**

Three approaches will be used to evaluate and apply new forms of exposure data and methods. The first approach evaluates and applies new forms of exposure data to available exposure resources. The amount of digital information available to assess exposure intensity, frequency,

duration and route as well as human activity and behavior patterns continues to grow at a rapid rate. The goal is to shift existing exposure resources (e.g., Exposure Factors Handbook) from a static to dynamic. The foundation of how to do this will be established through the continued improvements to the Food Commodity Intake Tool and development of the Exposure Factors Interactive Resource for Scenarios Tool (ExpoFIRST). Although not specific to human-health, EPA-Eco-Box will continue to be developed as an addendum to the popular EPA-Expo-Box as an online toolbox that will provide links to databases, models, guidance documents and other resources. This work, along with traditional efforts, will form the basis for updating the Exposure Factors Handbook that will provide assessors with ready access to a broad array of exposure information and greater flexibility in selecting parameters and analyzing status and trends.

The second approach evaluates and applies methods for improving estimates of exposure to soil and dust, Bisphenol A (BPA), exposure in women of reproductive age, and trends in IRIS chemical background levels. Improving estimates of soil and ingestion rates for standard age groups of children and adults will be accomplished via consultation and collaboration with other ORD scientists to develop a study utilizing state-of-the-art tracer and video technology. To further our understanding human exposure to BPA, a new collaborative study with Emory University will be conducted that focuses on BPA and several analogues including, but not limited to, Bisphenol F (BPF) and Bisphenol S (BPS). For women of reproductive age, results from a broad literature search and systematic review of health effects data will be conducted to identify environmental pollutants having significant data to suggest levels of causal relationships. Based upon this list of pollutants, exposure datasets (e.g., NHANES) will be utilized to characterize the range of exposure for women of reproductive age within the US. Levels of concern can be evaluated based upon the consideration of health effects data in epidemiological and toxicology studies. Finally, we will investigate the exposure trend of selected IRIS chemicals (metals), including elemental mercury, methyl mercury, cadmium, and uranium. We will take advantage of existing U.S. national health databases (e.g., NHANES and the available biomonitoring databases), to quantitatively assess chemical distributions and to identify important contributing sources of chemical exposures.

The third approach centers on bi-annual workshops with EPA staff with a strong interest and need for improving exposure information. The goal of is to ensure that exposure science in EPA remains at the forefront by identifying and utilizing emerging data and technology. These 2 to 3 day workshops will 1) identify new and emerging exposure data streams, 2) prioritize which data streams would have an immediate and strong impact for risk assessors in EPA Offices and Regions, and 3) develop strategies to rapidly incorporate this information for use by risk-assessors.

- **Subtask 8.4.2 (*RMS ID# HHRA 4.224.2*): Advancing the Application of Sensor Data for Risk-Informed Decision Making.**

  Products under this subtask will be provided as part of an established collaborative effort with ACE and the cross-agency Air Sensors Health Group (ASHG) and the work will be conducted in a combination of in-house FTE; from collaborative contributions from other Programs, the Regions and Program Offices; and from selective contractor support. Linkages will also be made to other ongoing work to develop visualizations of key risk assessment data streams being performed by the Environmental Modeling and Visibility Lab (EMVL) under Project 7 / Task 7.4, and in work being done to curate those data streams. Data management and curation collaborations include the following:

  - *NIOSH Center for Direct Reading and Sensor Technology*
  - *CSS Program through collaboration with NCCT (Richard Judson and Matt Martin)*
  - *IRIS and ISA data extractions (HHRA Projects 1 and 2)*
  - *HERO management of study data (HHRA Project 4, Task 9).*

Task Products:

- **Subtask 8.4.1 (*RMS ID# HHRA 4.224.1*): Improving exposure estimates with new and emerging exposure data.**

  - **Product 8.4.1.1. (*RMS ID# HHRA 4.224.1.1*)**
  - **Product title: Age-specific Soil and Dust Ingestion Rates**
  - Product Contact (email): geller.andrew@epa.gov, Phillips.linda@epa.gov
  - Product's Delivery Date: Q4FY18
  - Product Description: Report
  - Product's Contribution to Output: The report is the fourth phase of a project intended to develop age-specific soil and dust ingestion rates.
  - Product's Timeline (with milestones):
    - Milestone 1: QAFY15 Feasibility Report
    - Milestone 2: Q3FY16 Study Design Report
    - Milestone 3: Q4FY17 Pilot Study Report
    - Milestone 4: Q2F19 Exposure Factors Handbook-Revisions and Recommendations
  - Product's intended user/customer/audience: Information used to develop soil and dust ingestion rates for specific ages of children and adults.
  - Is this a key product?

- Does this Product contribute to a Product under another Task? Yes. It will contribute to the work being led by SHC on soil and dust ingestion. HHRA's role is as collaborators.

- **Product 8.4.1.2. (*RMS ID# HHRA 4.224.1.2*)**
- **Product title: Food Commodity Database (FCID) Interactive Tool**
- Product Contact (email): moya.jacqueline@epa.gov
- Product's Delivery Date: final version Q2FY16; improvements/additions FY17. As new NHANES data on exposure factors become available, there will be need for updates.
- Product Description: Standalone interactive tool kept and maintained by JIFSAN
- Product's Contribution to Output: The tool will improve the usability of the Exposure Factors Handbook; provide a quick, easy, and flexible way for users to develop obtain up-to-date food consumption data
- Product's Timeline (with milestones): A beta version for internal review in Q3FY15; a beta version for external review in Q1FY16; final version Q2FY16; improvements/additions FY17
- Product's intended user/customer/audience: exposure assessors in the Agency, state, and outside the Agency.
- Is this a key product?
- Does this Product contribute to a Product under another Task? If so, identify other Task. This product will be linked from EPA-Expo-Box.

- **Product 8.4.1.3. (*RMS ID# HHRA 4.224.1.3*)**
  Product title: ExpoFIRST
- Product Contact (email): moya.jacqueline@epa.gov and Phillips.linda@epa.gov
- Product's Delivery Date: final version Q4 FY16; other improvements/additions FY17. As new data on exposure factors become available, there will be need for updates.
- Product Description: Standalone interactive tool downloadable from the NCEA homepage
- Product's Contribution to Output: The tool will improve the usability of the Exposure Factors Handbook; provide a quick, easy, and flexible way for users to develop exposure scenarios.
- Product's Timeline (with milestones): A beta version for internal review in Q2FY15; a beta version for external review in Q4FY15; final version Q2FY16; improvements/additions FY17
- Product's intended user/customer/audience: exposure assessors in the Agency, state, and outside the Agency.
- Is this a key product? Yes

- Does this Product contribute to a Product under another Task? If so, identify other Task. This product will be added as another tool in EPA-Expo-Box.
- **Product 8.4.1.4. (*RMS ID# HHRA 4.224.1.4*)**
  Product title: EPA-Eco-Box
- Product Contact (email): Phillips.linda@epa.gov
- Product's Delivery Date: final version Q4FY16; improvements/updates FY17-FY19.
- Product Description: Online toolbox on NCEA homepage
- Product's Contribution to Output: The tool will provide a quick, easy, and flexible way for users to access information and resources for conducting ecological risk assessments.
- Product's Timeline (with milestones): A draft version for internal review in Q1FY16; final version Q4FY16; additional improvements/updates FY17-FY19
- Product's intended user/customer/audience: ecological risk assessors in the Agency, state, and outside the Agency.
- Is this a key product?
- Does this Product contribute to a Product under another Task? If so, identify other Task. This product will be linked to EPA-Expo-Box.

- **Product 8.4.1.5. (*RMS ID# HHRA 4.224.1.5*)**
- **Product title: Assessing Exposure to BPA and BPA Analogues in Beverage**
- Product Contact (email): Lorber.Matthew@epa.gov
- Product's Delivery Date:
- Product Description: Manuscript
- Product's Contribution to Output:
- Product's Timeline (with milestones):
- Product's intended user/customer/audience: exposure assessors in the Agency, state, and outside the Agency.
- Is this a key product? TBD
- Does this Product contribute to a Product under another Task?

- **Product 8.1.1.6. (*RMS ID# HHRA 4.224.1.6*)**
- **Product title: Exposure Factors Handbook Updates**
- Product Contact (email): moya.jacqueline@epa.gov
- Product's Delivery Date: updated food chapters by Q3FY16. Other chapters as needed.
- Product Description: Produce new chapters to replace individual chapters in EFH.
- Product's Contribution to Output: The updates will reduce uncertainty in exposure assessments by providing the most up-to-date information on exposure factors.
- Product's Timeline (with milestones): Draft food intake chapters by Q3FY16; improvements/additions to other chapters FY17

- Product's intended user/customer/audience: exposure assessors in the Agency, state, and outside the Agency.
- Is this a key product? TBD.
- Does this Product contribute to a Product under another Task? If so, identify other Task. This product will be linked to EPA-Expo-Box.

- **Subtask 8.4.2 (*RMS ID# HHRA 4.224.2*): Advancing the Application of Sensor Data for Risk-Informed Decision Making.**

  - **Product 8.4.2.1. (*RMS ID# HHRA 4.224.2.1*)**
  - **Product title: Analytical Criteria for Characterizing Hazards and Exposures**
  - Contact (email): Mark Hoover, NIOSH (mark.hoover@cdc.hhs.gov) and Annie Jarabek (jarabek.annie@epa.gov)
  - Start Date: 1Q 2016
  - Delivery Date: 3Q 2017
  - Description: Based on the long-standing experience with developing monitoring for the occupational environment at NIOSH, the NIOSH Center for Direct Reading and Sensor Technologies has embarked on a life-cycle assessment approach to the development and validation of novel sensors as they emerge to determine their operating parameters and applicability to characterizing different exposure scenarios (Hoover and DeBord, *in press*). HHRA scientists will work with NIOSH experts to extend this work to environmental applications and cumulative risk characterizations.
  - Contribution to Output: This is envisioned as the first in a series of products that will help in a key need to provide context for an anticipated proliferation of distributed sensor technologies in the hands of both researchers and citizen scientists.
  - Timeline (with milestones): Manuscript on occupational applications 1Q 2017; and possible update to NIOSH guidance; manuscript on ambient applications with considerations for cumulative characterization 3Q2017
  - Intended user/customer/audience: Scientific staff seeking to apply the developed criteria to the utility of various sensor technologies to define potential health hazards based on their ability to characterize exposures.
  - Key product? *TBD*
  - Contributions to a Product under another Task: Likely to inform EPA ExpoBox in out years.

  - **Product 8.4.2.2. (*RMS ID# HHRA 4.224.2.2*)**
  - **Product title: Approaches for integration of exposure scenarios with dosimetry modeling**

- Contact (email): *Annie Jarabek (jarabek.annie@epa.gov),* Mark Hoover (NIOSH)
- *Start Date: 1Q 2016*
- Delivery Date: *2Q 2018*
- Description: Dosimetry is necessary bridge between exposure data and response analysis. Understanding restrictions based on operating characteristics of sensors will facilitate the translation of sensor data to application in risk assessment. Considerations of the operating parameters of different types of sensors will be incorporated into approaches for integrating exposure data with dosimetry modeling. For example, extensive NIOSH testing has demonstrated that the personal dust monitor (PDM), a real-time dust monitor, is an accurate dust sampler (http://www.cdc.gov/niosh/mining/topics/RespirableDust.html) and the U.S. Mine Safety and Health Administration (MSHA) has specified that the PDM will be used for compliance dust sampling in its new respirable dust regulations. Approaches and limitations on inputing these data into the multipath particle dosimetry model (MPPD) used in inhalation dosimetry will be developed. Similar approaches for other samples will also be developed.
- Contribution to Output: These approaches will be integral to the development of guidance on the interpretation of sensor data for use in various exposure settings; the target context for NIOSH is occupational whereas that for the EPA is ambient. Ultimately, an understanding of the 24-hour day and influences of activity pattern; all sources including both occupational and environmental; and quantification of influencing factors is needed to be able to inform cumulative risk assessment.
- Timeline (with milestones): Manuscript on recommendations regarding particle samplers 2Q 2017; manuscript on gas samplers 2Q 2018.
- Intended user/customer/audience:
- Key product: TBD
- Contributions to a Product under another Task: Yes – see product below. Also likely to inform Task 8.3.

- **Product 8.4.2.3. (*RMS ID# HHRA 4.224.2.3*)**
- **Product title: Guidance on the interpretation of sensor data for risk assessment**
- Contact (email): George Woodall (woodall.george@epa.gov), Annie Jarabek (Jarabek.Annie@epa.gov), and Tom Long (long.tom@epa.gov); Mark Hoover and Gayle DeBord (NIOSH)
- Start Date: 1Q 2017
- Delivery Date: 3Q 2019
- Description: This product will be a joint effort between HHRA and NIOSH, with heavy involvement by the multi-agency Air Sensors Health Group (ASHG). The intention is to capture the lessons learned from the development of the first two

products in this Subtask as well as work done by the ASHG to support OAQPS and NERL (ACE Program) to properly place distributed sensor readings into context when comparing to compliance monitors, reference values, other air quality tools (e.g., AirNow) and/or air quality standards. A review of published literature on sensor applications and performance will document the potential for sensors to inform exposure and dose characterization through combining concentration and activity data.

- Contribution to Output: This guidance will facilitate the translation of emerging sensor data to exposure and risk assessment.
- Timeline (with milestones): 1Q 2017 – conduct literature review; 4Q 2017 – complete draft manuscript; 1Q 2018 – submit manuscript to peer-reviewed journal
- Intended user/customer/audience: Various program offices and regions that will be receiving and requiring interpretation of more and more sensor data as the technologies advance. The review paper will be useful for Agency staff in HHRA/NCEA, ACE/NERL, and OAQPS as well as the broader scientific community in characterizing the extent to which emerging concentration and activity sensors are able to inform exposure, dose, and risk assessment.
- Key product? TBD
- Contributions to a Product under another Task: Contributions to a Product under another Task: This product will inform other tasks in the project area.

- **Product 8.4.2.4. (*RMS ID# HHRA 4.224.2.4*)**
- **Product title: Good practice recommendations for sensor data management and curation**
- Contact (email): George Woodall (woodall.george@epa.gov), Annie Jarabek (Jarabek.Annie@epa.gov), and Tom Long (long.tom@epa.gov); Mark Hoover and Gayle DeBord (NIOSH)
- Delivery Date: *Q4 2019*
  - Description: Guidance and recommendations will be garnered through the work done in managing, manipulating, and analyzing data for products 8.4.2.1 through 8.4.2.3.
  - Contribution to Output: Lessons learned reflected as recommendations will highlight the need for this area often overlooked in projects and critical to the credibility and integrity of the data for applications.
  - Timeline (with milestones): *Manuscript in Q4 2019.*
  - Intended user/customer/audience: Scientist in both agencies as well as citizen scientists.
  - Key product? TBD
  - Contributions to a Product under another Task: Likely to be implemented in out year efforts of Task 7.4 and 9.2.

Task Constraints:

Subtask 8.4.1:

- Scientific: Potential constraints associated with evaluating new methods include obtaining approval by the Human Subjects Review Board.
- Logistical: There are no significant logistical constraints envisioned for this task.
- Technical: There are no significant technical constraints envisioned for this task.
- Resources: Need for extramural support to continue development of the Food Commodity Intake Tool Enhancements, Exposure Factors Interactive Resources for Scenarios Tools (ExpoFIRST), EPA-Eco-Box, and Exposure Factors Handbook Updates. All of these projects were funded in FY15 and are well on the way to completion.

Subtask 8.4.2:

- Scientific: Potentially, competing priorities of both NIOSH and NCEA staff.
- Logistical: Contract support on literature review. Coordination of data with NIOSH.
- Technical: Rapidly emerging area; we will need to coordinate with both NIOSH and NERL, collaborate with ACE scientists.
- Resources: Dependent on commitment from NIOSH (still being determined); possibly others.

Task Dependencies:

Subtask 8.4.1:

Implementation of the soil and dust ingestion study will require approval by the Human Subjects Review Board as well as participant consent. The feasibility of obtaining such consent and approval will be assessed in the first phase of the project. There are no dependencies associated with the other components of the subtask.

Subtask 8.4.2: Scope will depend on resource commitments. A phased approach with specific types of sensors (e.g., particle versus gas, which gas category) will be considered based on both Agency needs.

Task Quality Assurance and Data Management Needs:

Subtask 8.4.1: Soil Ingestion Study

- Is there an existing IRP/ QAPP(s) that applies to this Subtask?
    - There is an existing QAPP for ExpoFIRST, signed 5/14/14.

- A QAPP will need to be developed for the Food Intake Tool.
- For EPA-Eco-Box, a QAPP is not been required for the work being conducted by EPA's technical support contractor for the toolboxes (i.e., for developing toolbox content). However, quality assurance is conducted by the contractor designing and implementing the website, and maintaining the database that houses the Master Tool Lists for the toolboxes.
- For Exposure Factors Handbook, QAPP on the use of secondary data may be necessary.
- For the Soil and Dust Ingestion study, the Sustainable and Healthy Communities program has the lead and would likely prepare and oversee all elements of the QAPP.
- A QAPP will need to be developed for the BPA, women of reproductive age, and background level trend study.

- Will this Subtask involve large amounts of data that need a data management plan?
  - Only the Exposure Factors Interactive Resource Scenarios Tool will require a data management plan as it uses data from the Exposure Factors Handbook.

Subtask 8.4.2:

- Is there an existing IRP/ QAPP(s) that applies to this Task? If so, identify IRP/QAPP.
  - Yes. NCEA-16-00004. Quality Assurance Project Plan (QAPP) For HHRA Projects 6, 7, & 8 to Develop Methods, Tools, Models and Supporting Analysis.

- Will this Task involve large amounts of data that need a data management plan? If yes, explain.
  - TBD. The Health and Environmental Research Online (HERO) system is used for systematic literature review and is covered by a separate QAPP: NCEA-16-00005. Quality Assurance Project Plan (QAPP) For Extraction of Scientific Data Into the Health and Environmental Research Online (HERO) Database System. Some products may generate a limited amount of data or metadata during case study or method development and refinement.

References

Hoover MD; DeBord DG. (2015). Turning numbers into knowledge. Sensors for safety, health, well-being and productivity. The Synergist. March. www.AIHA.org

Lioy, P.J. 2015. Exposure science and its places in environmental health sciences and risk assessment: why is its application still an ongoing struggle in 2014. *J. Exposure Sci. Environ. Epidemiol.* 25: 1-3.

NRC. 2012. *Exposure Science in the 21st Century: A Vision and a Strategy*. The National Aca**demies** Press.

Human Health Risk Assessment (HHRA)

Project Planning Tool

Project Plan

HHRA Project 9 (*RMS ID# HHRA 4.23*):

Risk Assessment Support and Training

Project Leads (PLs): Debra Walsh (NCEA RTP) and Maureen Johnson (NCEA IO)

Project start date: 10/01/2015

Project end date: 09/30/2019

Executive Summary

Increasing the efficiency of operational derivations, providing for transparency and documentation including reference citations, ensuring the clear communication of methods or results, and maintaining current scientific standards and credibility of the risk assessments developed by the HHRA risk program all include the need for support by data access and management software, computational tools, and training. The project is devoted to maintaining current scientific standards and credibility of the risk assessments developed by the HHRA. The project is implementing upgrades to ensure the clear communication of methods and risk program by improving data access and management software, computational tools, and training to widely-used websites, guidance, databases, tools, and training used both across the HHRA program and by its external stakeholders; such as the EPA Risk Assessment website which includes all EPA Risk Guidelines, tools and databases plus instructions on conducting risk assessments, the IRIS website of chemical assessments, a collection of over 800 tools for exposure assessors provided by the EPA-Expo-Box, the Health and Environmental Research Online (HERO) database, and the Benchmark Dose Software (BMDS). The project is also designed to implement advances in approaches and applications that are developed via other tasks in the HHRA portfolio, such as additional modules for BMDS to provide new approaches

for quantitative dose-response model averaging. Training aids communication and understanding of the state-of-the science methods employed in the HHRA program to derive its assessments, and thereby results in more engaged and informed stakeholders which helps to ensure more consistent understanding and application of current risk assessment procedures by the larger public health community. The access to databases, development of tools, and reference management provided by this project serve as a valuable resource for the HHRA program's partners and stakeholders and help HHRA scientists perform assessments under HHRA more efficiently.

Research Project Description

Providing easy access regarding the underlying science, relevant references, operational procedures, and resultant quantitative estimates for risk assessments produced by the HHRA program is necessary to maintain its scientific credibility and provide the transparency required to engage stakeholders in a meaningful manner. Webcasts of important public science meetings allow for more attendance at meetings and opportunities for input. The HHRA program has also upgraded its website presence to recent Agency security and open-access standards to provide a more seamless and efficient navigation experience to its important resources. For example, the RISK website and database contains the guidelines, handbooks, models, tools and databases that the Agency has developed to perform risk assessments. RISK contains links to each risk assessment product in the HHRA portfolio, i.e., the Integrated Risk Information System (IRIS), the Integrated Science Assessments (ISAs) and the Peer-reviewed Toxicity Value (PPRTV) assessments that have dedicated websites to aid communication and dissemination of these important documents. The Health and Environmental Research Online (HERO) database contains the key studies that the HHRA program uses to develop health and environmental assessments for the public, including the references used for ISAs, PPRTV, IRIS and other health assessments. The HERO database is publically accessible so anyone is able to review the scientific literature behind EPA science assessments, and thus provides transparency regarding the foundation for key regulatory decisions.

Computational tools help implement advances in systematic review, exposure assessment, and dose-response assessment developed in other tasks of the HHRA Program portfolio, and accelerate end-user understanding and application in a consistent fashion. For example, the benchmark dose methodology is EPA's preferred methodology and is fast becoming the world's standard for dose-response analysis, which in turn drives risk estimates for the majority of chemicals evaluated and regulated by EPA. Maintenance and further additions to the Benchmark Dose Software (BMDS) platform is critical to health assessments developed within HHRA and other organizations. EPA's EXPOsure toolBOX (EPA-Expo-Box) is a website and database that contains a toolbox created to assist individuals from within government, industry, academia, and the general public with assessing exposure resources in a one-stop location.

Training modules developed on key concepts and procedures for risk assessment enhance the communication regarding assessments and approaches. This supports uptake by stakeholders, providing transparency, increased understanding, and engagement.

Project Impact

This project serves as a resource for external stakeholder to provide understanding and transparency regarding the HHRA program's research approaches and assessment products, and provides training to enhance understanding and build capacity for new applications. Project 9 advances program efficiency and transparency, provides software for use of new approaches in the public domain, and supports the Agency and external risk assessment training efforts. The significant impact on stakeholder engagement is evidenced by the number of subscribers to the various mailing lists associated with these activities that the HHRA program supports. Many thousands subscribe to the HHRA Bulletin and over 500 to the EPA-Expo-Box Bulletin. Thousands more also subscribe to receive important updates for the IRIS Program as meetings/workshops are announced or as new assessments are available. BMDS has approximately 4,000 registered users in over 90 countries of which 30% of users are international and 70% from the United States. The HHRA program components on the Agency's website receive tens of thousands of web page 'hits' annually by users, and substantial outreach occurs using email list serves.

Also included in HHRA outreach supported by Project 9 is its risk assessment training and experience (RATE) program comprised of over 30 specific modules covering hazard identification, exposure assessment, dose-response assessment, benchmark dose modeling, PBPK modeling, mixtures guidance and cumulative risk assessment. These training modules have been provided internally to EPA program and regional offices, to various states, and internationally. A portion of the RATE training, dealing with exposure assessment, is publically available through the EPA-Expo-Box toolbox as well. Further, the HHRA program has worked with the Environmental Council of the State's (ECOS) Interstate Technology and Regulatory Council to develop a risk assessment training program that targets state risk assessors, increasing capabilities and consistency in risk assessments conducted by federal, state and tribal organizations.

Project Scope

Tasks under this project involve transforming our websites to the new EPA Drupal Web Content Management System (WCMS) and updating critical software infrastructure with enhanced features including data access, interoperability with other ORD models and databases, and transparency of assessments, such as the Health and Environmental Research Online (HERO) database (http://hero.epa.gov/) of studies used in assessments and benchmark dose software (BMDS) for dose-response modeling (http://www.epa.gov/bmds). New software modules to support advances in

evidence integration and extend dose-response methods developed in other HHRA projects will be implemented in additional modules to accelerate application. A second task is focused on training for human health and ecological risk assessment. The program is comprised of over 35 specific modules covering hazard identification, exposure assessment, dose-response assessment, benchmark dose modeling, PBPK modeling, mixtures guidance and cumulative risk assessment. These training modules have been provided internally to EPA program and regional offices, to various states, and internationally. The module for exposure assessment, however, was made available to the public via EPA-Expo-Box in 2014. Training conducted under this task provides communication to the risk assessment community of methods and advances in risk analysis, and supports consistency in risk assessment development.

Overall, this project increases the efficiency and availability of developing health assessments by providing transparency and documentation including reference citations, ensuring the clear communication of methods or results, maintaining current scientific standards, and scientific credibility in the HHRA program. Project 9 supports the overall goals of HHRA by providing data access and management software, computational tools, and training.

Project Structure and Rationale

The project is designed to provide two major categories of support to benefit the HHRA program, risk assessors across the Agency in ORD, Program Offices or Regions, and external stakeholders as follows:

- **Task 9.1. Development and Maintenance of Essential Software and Support Tools**
- **Task 9.2. Development and Application of Risk Assessment Training**

The first, Task 9.1, ensures efficient access on EPA websites and databases, including but not limited to: Health and Environmental Research Online (HERO), EPA's EXPOsure-toolBOX (EPA-Expo-Box), Integrated Science Assessments (ISA), Integrated Risk Information System (IRIS), Benchmark Dose Software (BMDS), Risk Assessments (RISK), and Ecological Risk Assessment Support Center (ERASC).

Task 9.2 provides training on risk assessment procedures including general concepts, approaches for cumulative risk assessment, how to use the BMDS for dosed-response analysis, exposure assessment and foundational scientific concepts. Training resources are currently delivered in the form of classroom-based courses and provide an opportunity for face-to-face interactions. The set of training modules allows the flexibility to be tailored to various user needs. Alternative methods of delivery (webinars and web based presentations) have already been made available from the BMSD, RISK, and EPA-Expo-Box websites.

Measures of success

We hope to improve and refine websites, guidance, databases, computational tools, and software to meet Agency cyber security standards and provide efficient access to data and health assessment products across EPA and to external stakeholders. Together with training modules, these resources will facilitate a comprehensive understanding of the state-of-the science for risk assessment approaches and build capacity in the larger public health community to apply new methods in the interest of human health protection.

Stakeholders (outside ORD)

Risk assessors and other disciplinary scientists across the Agency that are either interested in understanding risk assessments produced by the HHRA program or in how to apply their scientific expertise to inform risk assessments benefit by the easy access and transparency that this project targets to maintain and support. External stakeholders also gain understanding and the feeling of partnership by access to public training opportunities, online training, and by participation in the development of tools, databases and other products provided by this project.

Task 9.1

(*RMS ID# HHRA 4.231*)

Development and maintenance of essential

Software and support tools

Task Leads (TLs): Maureen Johnson (NCEA IO) and Reeder Sams (NCEA RTP)

Task Start Date: 10/01/2015

Task End Date: 09/30/2019

Task Description:

This task focuses on a collection of efforts to develop and maintain tools that are essential to the development of human health assessment, ecological assessments, and many of the research products developed under the HHRA program. These efforts include the development and on-going maintenance of HHRA databases, models (or tools), and websites. The work related to this task also includes the migration of existing HHRA websites to the Agency's new open-source web content management software, referred to as "Drupal." In addition, all HHRA Oracle applications will be moving to the newest EPA web template and will require an overhaul to integrate with these Drupal websites seamlessly. These tools aid transparency and communication of risk assessment products and implement science advances such as dose-response models developed by the HHRA program. They additionally enhance stakeholder engagement and build capacity for understanding assessment methods and approaches. Access to databases, tools, and references is a valuable resource for HHRA scientists, the HHRA program's partners and stakeholders.

The list of applicable websites, models and database, includes but is not limited to the following:

1) Integrated Risk Information System (IRIS) Website and database,
2) Integrated Science Assessments (ISA) Websites and database,
3) Peer-reviewed Toxicity Value (PPRTV) Website and database
4) Health and Environmental Research Online (HERO) database,
5) Benchmark Dose Software (BMDS) Modeling website and training system,
6) EPA's-Expo-Box Website (EXPO-Box) and database,
7) Systematic review tool

8) Data Management and Visualization Tool (DMVT),
9) Ecological Risk Assessment Support Center (ERASC) website,
10) Enzyme Ontogeny (EOD) database,
11) Risk Assessment (Risk) Web Portal which is founded on the work of the National Center for Environmental Assessment. It is a collection of human health risk assessments website and databases, including:

    - All-Ages Lead Model (AALM) Website,
    - BioMarkers database,
    - Database of Sources of Dioxin-like Compounds in the US,
    - Dioxin Website and database,
    - Epigenetics reference compilation,
    - Next Generation of Risk Assessment (NexGen) website,
    - Physiologically Based Pharmacokinetic (PBPK) modeling Website, and the
    - Physiological Information (PID) database.

The databases and tools described within this task house essential components of daily work activities within HHRA and across the EPA. These all in one way or another provide direct stakeholder support either in the form of databases to provide the scientific foundation for decisions made within assessment products or to specific risk assessment tools for defined applications (e.g., BMDS for derivation of toxicity values). Each will be described more fully in each of the subtasks below.

Subtask 9.1.1. (*RMS ID# HHRA 4.231.1.*): Integrated Risk Information System (IRIS) Website and Database

Description: EPA's Integrated Risk Information System (IRIS) is a human health assessment program that evaluates information on health effects that may result from exposure to environmental contaminants. Through the IRIS Program, EPA provides the highest quality science-based human health assessments to support the Agency's regulatory activities. IRIS has been undergoing a transformation in the development of assessments engaging the public earlier on in the process, hosting public bimonthly meetings with stakeholders and inviting the public to submit comments on both preliminary draft materials and draft reports prior to peer review. These enhancements will be more evident in the redesigned IRIS website and database. However, IRIS has several enhancements in planning to implement in FY16 and beyond as the site evolves to further meet end-user needs. Activities related to development of IRIS assessments and associated products are described in Projects 1 and 2.

Subtask 9.1.2. (*RMS ID# HHRA 4.231.2*): Integrated Science Assessments (ISA) Website and database

Description: The ISA website and database contains links to assessments that accurately reflects "the latest scientific knowledge useful in indicating the kind and extent of identifiable effects on public health which may be expected from the presence of a pollutant in ambient air". The ISA communicates critical science judgments relevant to the scientific foundation for the review of the NAAQS standards. Every 5 years, the NCEA-RTP Division staff undergoes steps to update and revise the collection of scientific evidence available at the time of the previous review and includes this with the newest studies and information available to generate a new revision of these reports. All Integrated Science Assessments are then vetted through a rigorous peer review process, including review by the Clean Air Scientific Advisory Committee with public comment periods to improve the quality of the science. Activities related to development of ISAs and associated products are described in Project 3.

Subtask 9.1.3. (*RMS ID# HHRA 4.231.3.*): Peer-reviewed Toxicity Value (PPRTV) Website and database

Description: The PPRTV website and database contains links to assessments that provide toxicity values for use in the Superfund Program when such values are not available from EPA's IRIS database. PPRTVs are derived after a review of the relevant scientific literature using the methods, sources of data and guidance for value derivation used by the EPA IRIS Program. The PPRTV assessment informs the hazard and dose response assessment pertaining to chronic and subchronic exposures to substances of concern, presents the major conclusions reached in the hazard identification and derivation of the PPRTVs, and characterizes the overall confidence in these conclusions and derived values. All PPRTVs receive internal review by EPA scientists and external peer review by independent scientific experts. Activities related to development of PPRTV assessments and associated products are described in Project 4.

Subtask 9.1.4. (*RMS ID# HHRA 4.231.4*): Health and Environmental Research Online (HERO)

Description: The Health and Environmental Research Online (HERO) contains the key studies the HHRA program uses to develop health and environmental assessments for the public, including references used for ISAs, PPRTVs and IRIS assessments. HERO facilitates public access to the scientific studies that underpin key regulatory decisions. The HHRA program has continued to develop and implement improvements in HERO. The HERO database is publically accessible so anyone is able to review the scientific literature behind EPA science assessments. All assessments developed under the Human Health Risk Assessment (HHRA) program utilize

HERO which has been recognized by the National Research Council (NRC) as proactive addition to human health assessments. The HERO database strengthens the transparency of the science supporting agency decisions. HERO has transformed into a valuable asset to the Agency and has been utilized by multiple national programs including Air, Climate, and Energy (ACE), Chemical Safety and Sustainability (CSS), and HHRA.

Subtask 9.1.5. (*RMS ID# HHRA 4.231.5*): Benchmark Dose Software (BMDS) Modeling and Website

Description: The Benchmark Dose (BMD) methodology and the accompanying Benchmark Dose Software (BMDS) are available at both the national and international level via the website and training component. The BMD methodology is EPA's preferred methodology and is fast becoming the world's standard for dose-response analysis, which in turn drives risk estimates for the majority of chemicals evaluated and regulated by EPA. BMDS has approximately 4,000 registered users in over 90 countries of which 30% of users are international and 70% from the United States. The development and use of the BMD and BMDS may represent the most significant advancement in risk assessment within the Agency. Maintenance and further development of BMDS is critical to health assessments developed within HHRA and other organizations.

Subtask 9.1.6. (*RMS ID# HHRA 4.231.6*): EPA's-Expo-Box Website (EXPO-Box) and database

Description: EPA's EXPOsure toolBOX (EPA-Expo-Box) is a website and database that contains a toolbox created to assist individuals from within government, industry, academia, and the general public with assess to exposure resources in a one-stop location. EPA-Expo-Box was developed to serve as a web-based compendium of exposure assessment tools. It is comprised of a series of Tool Sets, each containing modules that address exposure assessment topics. Toolbox modules contain descriptions of the topics, based on the 1992 Guidelines for Exposure Assessment, and links to exposure assessment resources including databases, models, guidance documents, and other resources for exposure assessors. There are currently link to more than 800 exposure assessment resources (developed in Access and maintained in an Oracle database), organized by topic areas relevant to human exposure assessment. A search interface allows users to identify resources using keywords or topics. EPA-Expo-Box was released in 2013, but requires periodic maintenance to ensure that its content and tool links remain current, and to update it after release of the revised Guidelines for Human Exposure Assessment. EPA-Expo-Box is available at http://www.epa.gov/ncea/risk/expobox/.

A major component of EPA-Expo-Box is an online version of the 2011 update of the Exposure Factors Handbook including tables and spreadsheets used in the report. It is anticipated that future updates to portions of the Exposure Factors Handbook will be provided to the public via EPA-Expo-Box in lieu of updating the full report. There are also plans to link EPA-Expo-Box to another new tool under development called EPA-Eco-Box (see below) in 2016.

Other new products under this task include development of the Exposure Factors Interactive Resource for Scenarios Tool (ExpoFIRST) and EPA –Eco-Box. ExpoFIRST is a standalone tool that draws from data in the EPA's Exposure Factors Handbook for quick, easy, and flexible development of human exposure scenarios. EPA-Eco-Box is being developed as a web-based toolbox providing links to guidance documents, databases, and other relevant information for ecological risk assessors.

Subtask 9.1.7. (*RMS ID# HHRA 4.231.7*): Systematic Review Tool

Description: To more efficiently implement the newly developed methods for incorporating aspects of systematic review, tools need to be developed/refined to meet both the immediate and long term goals. An inventory and needs assessment will highlight the available tools and identify the gaps between the capabilities of currently available tools and the capabilities needed to efficiently and successfully implement the principles of systematic review in HHRA assessments. Currently available tools/software need to be made available to NCEA scientists for use in ongoing assessments. One product (Phase I) will address the short term need to more fully implement and refine currently available tools. In the long term, flexible tools must be developed that can be used sustainably across HHRA assessments (e.g., IRIS, ISAs). Another product (Phase II) will address the long term development of a set of modular tools that can interface with one another, and that provide the flexibility needed to modify and adapt tools to meet diverse and changing needs within NCEA.

Subtask 9.1.8. (RMS ID# HHRA 4.231.8): Data Management and Visualization Tools (DMVT) for Risk Assessment

Description: Work in this subtask is being performed largely by the Environmental Modeling and Visibility Lab (EMVL) under a successful proposal to gain support in FY 2015 and 2016. There are two product lines anticipated for this subtask which are aimed at providing technical support to Program Offices (Task 5.2, *RMS ID# HHRA 3.222.3*) and at analyzing concentration/duration/response relationships to develop methods to derive assessments for acute and episodic exposures (Task 7.4, *RMS ID# HHRA 4.21.4*).

Subtask 9.1.9. (*RMS ID# HHRA 4.231.9*): Ecological Risk Assessment Support Center (ERASC) Website

Description: The ERASC website provides access to the technical information and addresses scientific questions of concern or interest on topics relevant to ecological risk assessment at hazardous waste sites for EPA's Office of Solid Waste and Emergency Response (OSWER) personnel and the Office of Resource Conservation and Recovery (ORCR) staff provided by the HHRA program under Task 5.2. ERASC also addresses requests for information or answers to scientific questions through coordination of members in the Ecological Risk Assessment Forum (ERAF). To assess emerging and complex scientific issues that require expert judgment, the ERASC relies on the expertise of scientists and engineers located throughout EPA's ORD labs and centers. ERASC develops responses that reflect the state of the science for ecological risk assessment and also provides a communication point for the distribution of these responses to other interested parties.

Subtask 9.1.10. (*RMS ID# HHRA 4.231.10*: Enzyme Ontogeny Database (EOD) and Website

Description: The EOD database is intended to inform physiologically-based toxicokinetic (PBTK) modelers and risk assessors in the scoping, assessment and the PBTK modeling phases. Furthermore, this database provides necessary information for a qualitative or semi-quantitative assessment for PBTK modelers. While there are cross-species differences in specific enzyme development, evaluation of the ontogeny of metabolizing enzymes in rodents relative to humans can aid in understanding the potential differences in xenobiotic metabolism across different lifestages. This further helps in making potential adjustments for life-stage in risk evaluation.

The EOD is a searchable database built in Microsoft Access with in-built capability to export the results into different file formats available in a user-friendly way. The data can be accessed based on the location, nature, and extent of the enzyme ontogeny across species for metabolic pathways specific to particular substrates. This database gives a better understanding of whether metabolic windows of vulnerability may exist across species and helps to scope the manner in which a health risk assessment of xenobiotics might incorporate developmental profiles of enzymes in assessing population variability and uncertainty across the lifestages.

Subtask 9.1.11 (*RMS ID# HHRA 4.231.11*: Risk Assessment (RISK) Website and Database

Description: The RISK website and database contains basic information for performing both human health risk assessments and ecological risk assessments. It contains the guidelines, handbooks, models, tools and databases that the Agency has developed to perform risk assessments. It is the umbrella from which all of HHRA, ERA and NCEA products, reports and outputs are linked.

The RISK portal which is built on top of the National Center for Environmental Assessment's collection of human health risk assessments website and database, includes the following:

- All-Ages Lead Model (AALM) Website,
- BioMarkers database,
- Database of Sources of Dioxin-like Compounds in the US,
- Dioxin Website and database, Epigenetics reference compilation,
- Next Generation of Risk Assessment (NexGen) website,
- Physiologically Based Pharmacokinetic (PBPK) modeling Website, and the
- Physiological Information (PID) database.

Research Approach:

Subtask 9.1.1. (*RMS ID# HHRA 4.231.1.*): Integrated Risk Information System (IRIS) Website and Database

The IRIS Program is redesigning its website to comply with the new EPA website standards that require transformation to the Drupal for launch of the implementation of the HHRA FY16 – 19.

The timing of this Drupal migration gave the IRIS Program the opportunity to provide a more user-friendly interface for IRIS users, easier navigation, and access to background information on the IRIS Program and steps to performing assessment development. Improvements to the description of the IRIS Program and to the IRIS process will increase the transparency and clarity of IRIS assessment development. In addition, this effort supports the public outreach tasks described above with announcing new draft assessments, meeting/workshop opportunities, blog discussions, public comment periods, and providing easier access to meeting materials after the bimonthly meetings.

The most notable improvements to the functionality of the redesigned website include:

1) a new quick-access dashboard to get risk assessors to the latest cutting edge IRIS assessments, event schedule, and searching;

2) new chemical-specific "landing" pages (over 550 of these) that include evergreen links to meetings, drafts, schedules, key IRIS values, HERO project information (where applicable) and related historical supporting documents;

enhanced search capabilities that will support filtering for critical effects by target organ and includes a more robust keyword searching taxonomy linked to outside chemical applications; and

4) tracking system updates to improve upkeep of development schedules and public expectations of assessment development.

A rollout/outreach plan will be developed on stakeholder engagement and outreach for the IRIS program (Task 1.33 (RMS ID# 1.213.4)), and integrated and implemented here in Project 9. The plan will communicate website enhancements with IRIS program stakeholders and the public.

Subtask 9.1.2. (*RMS ID# HHRA 4.231.2.*): Integrated Science Assessments (ISA) Website and database

The objective under this subtask is keep the ISA website compliant with the agency web standards by migrating it to Drupal in 2015. Future updates will mainly take place in the application/database side of this website and new reports are generated.

Subtask 9.1.3. (*RMS ID# HHRA 4.231.3.*): Peer-reviewed Toxicity Value (PPRTV) Website and database

The objective of this subtask is to migrate the current electronic library of assessments to the ORD/NCEA website under the new Drupal platform in order to maintain compliance with the new EPA web standards.

Subtask 9.1.4. (*RMS ID# HHRA 4.231.4*): Health and Environmental Research Online (HERO)

The HERO database is continually updating the software and methodologies to meet the current needs within HHRA. Multiple methodologies are currently being developed to improve the approach and reduce the resource needs for literature searching, identification, retrieval and curation within the database to support all levels (e.g., peer-review) of assessment development. Advances in data mining and data extraction are currently in development.

Subtask 9.1.5. (*RMS ID# HHRA 4.21.5*): Benchmark Dose Software (BMDS) Modeling and Website

BMDS is maintained on EPA servers and updated on a yearly basis including the implementation of new risk assessment methodologies for dose-response analysis. As assessments are developed within HHRA, the need for new dose-response tools in BMDS become evident. The development efforts are in Project 7.

Subtask 9.1.6. (*RMS ID# HHRA 4.231.6*): EPA's-Expo-Box Website (EXPO-Box) and database

The objective of this subtask is to add enhancements/updates to EPA-Expo-Box since its release in 2013. Maintenance and updates will be needed to keep the toolbox current with EPA web standards and changing web links and locations. For example, EPA's Guidelines for Human Exposure Assessment are currently being revised by the Risk Assessment Forum and will replace the site currently linked in the toolbox. Because EPA-Expo-Box was developed to be consistent with the 1992 Guidelines, it will need to be updated when the revised guidelines are released. Additional revisions may be needed to reflect updated EPA policies or procedures. Also, toolbox users are encouraged to provide comments and suggestions for adding new topics or tools to EPA-Expo-Box through an online form.

Subtask 9.1.7. (*RMS ID# HHRA 4.231.7*): Systematic Review Tool

The objective of the subtask is to provide tools to more efficiently implement the newly developed methods for incorporating aspects of systematic review into HHRA assessments. Several tools are currently being used or developed that may address some of the needs or steps for incorporating systematic review methods to HHRA assessments. An inventory of these tools and needs assessment will be conducted. Two phases of tool refinement and development will be completed to meet the immediate and long term goals of the subtask

Subtask 9.1.8. (RMS ID# HHRA 4.231.8): Data Management and Visualization Tools (DMVT) for Risk Assessment

The overarching goal in this subtask is to enable greater flexibility and interactivity for authors/experts and end-users to generate two separate product lines, both of which are heavily reliant on data analysis and graphical depictions of data: Exposure Response (ER) arrays and Reference Value (RefVal) Arrays. Migration of ER Array development to a more robust and customizable platform occurred in the first year of this project. The work going forward will add capabilities to support the products for Tasks 5.2 and 7.4 via development of more complex displays and data analyses; develop tools in support of developing enhanced Reference Value Arrays; and to develop partial automation of array development.

Objectives and Activities:

1. Refine graphic generation platforms – Generate more complex visualizations for ER Arrays and migrate RefVal Array development to a complementary platform. Incorporate data being stored and managed in other software (e.g., ToxRefDB, DRAGON, HAWC, etc.) into array graphics.
2. Enhance data management platform capabilities – Generation of more complex data analysis within the platform (e.g., queries) and via linking to analytical tools (e.g., calls to R scripts and BMDS).
3. User Tools – Develop GUIs to integrate graphic generation, data management, and data entry. Incorporate Revision Logging for QA activities of the underlying data bases.
4. Automated data integration capabilities – Develop capacity to search for and link to data from multiple existing data sources from partner organizations for incorporation into arrays.

Benefits and Relevance: Exposure Response arrays have been used in NCEA risk assessments (IRIS and ISAs), and by other federal agencies and states. Reference Value Arrays have been used by Program Offices (e.g., OAR) for risk management decisions. Improvements in the capabilities to generate these data displays will enhance consistency, interoperability, and productivity in developing risk assessments. Creating new databases and enhancing existing databases to house these data will allow the sharing of these resources for risk assessments across the agency and with partner organizations.

Subtask 9.1.9. (*RMS ID# HHRA 4.231.9*): Ecological Risk Assessment Support Center (ERASC) Website

The objective under this subtask is keep the ERASC website compliant with the agency web standards by migrating it to Drupal in 2015. Future updates will mainly take place in the application/database side of this website.

Subtask 9.1.10. (*RMS ID# HHRA 4.231.10*: Enzyme Ontogeny Database (EOD) and Website

The objective is to use suitable key words and conduct a comprehensive systematic review the literature (e.g., PubMed, Web of Science or other search engines) and add the new references to the database and will independently perform QA/QC on the module.

Subtask 9.1.11. (*RMS ID# HHRA 4.231.11*): Risk Assessment (RISK) Website and Database

The objective in this subtask is to integrate the RISK Portal with the NCEA website as these are both migrated to Drupal by September 2015. NCEA will continue to launch reports and products that will be linked to the risk site or from other topical Drupal sites as applicable.

Task Constraints:

Resources:

Work on all subtasks is constrained by competing priorities and available funding. All subtasks require varying levels of FTE and extramural resources (see Task Resources section) in order to maintain minimum requirements to support products developed within the HHRA program. To advance current capabilities and capacity additional FTE and extramural funds are required. Development of advanced capabilities for some subtasks (i.e., 9.1.3, 9.1.5, 9.1.6, 9.1.7) are covered in other projects

Task Dependencies:

Subtasks 9.1.1, 9.1.2, 9.1.3, and 9.1.11 are dependent upon major product lines (e.g., PPRTVs, ISAs, IRIS) developed under other projects to update these subtasks (i.e., websites). Subtasks 9.1.5, 9.1.7, and 9.1.8 require products produced from other projects to advance capabilities for human health risk assessment. Subtask 9.1.4, provides support to essentially all science assessment products produced in Projects 1-8, and requires communication / requests to provide support from the HERO system. During periods of high demand, support requests are dependent upon prioritization by the HHRA program.

Task Quality Assurance and Data Management Needs: All subtasks in Task 9.1 are covered as follows:

- Is there an existing IRP/ QAPP(s) that applies to this Task? Yes. The following QAPP apply to specific subtasks in Project 9.1.
    - HERO. NCEA-16-00005. Quality Assurance Project Plan (QAPP) For Extraction of Scientific Data Into the Health and Environmental Research Online (HERO) Database System
    - BMDS. NCEA-16-00006. Quality Assurance Project Plan (QAPP) For Enhancements to Benchmark Dose Software
- Will this Task involve large amounts of data that need a data management plan? If yes, explain.
    - TBD. The Health and Environmental Research Online (HERO) system is used for systematic literature review and is covered by a separate QAPP: NCEA-16-00005. Quality Assurance Project Plan (QAPP) For Extraction of Scientific Data into the Health and Environmental Research Online (HERO) Database System. Specific scientific data management plans (SDMP) may be included for some products if determined to be necessary.

Task Products:

Subtask 9.1.1. (*RMS ID# HHRA 4.231.1.*): Integrated Risk Information System (IRIS) Website and Database

- **Product 9.1.1.1. (*RMS ID# HHRA 4.231.1.1.*):**
- **Product Title: Integrated Risk Information System (IRIS) Website and Database**
- Product Contact (email): Susan Rieth (rieth.susan@epa.gov) and Maureen Johnson (johnson.maureen@epa.gov)
- Product's Delivery Date: Maintenance and improvements annually in FY16 - 19
- Product Description: Redesigned website that provides a more user-friendly interface for IRIS users, easier navigation, more content on the IRIS Program and assessment development, and enhanced search capabilities.
- Product's Contribution to Output: Website landing pages for each IRIS chemical assessment that will provide all information related to a chemical with only 1–2 clicks from the landing page, increased transparency of the IRIS process in general and the status of a specific assessment in the development process, and improved search capabilities.
- Product's Timeline (with milestones): The site was upgraded and migrated to comply with Drupal for the launch of the HHRA StRAP on October 1 2015. Annual upgrades and maintenance are necessary to support the IRIS program.
- Product's intended user/customer/audience: EPA program offices and regions, other federal agencies, state and local governments, international organizations, risk assessors in the private sector, and the general public.
- Is this a key product? No
- Does this Product contribute to a Product under another Task? If so, identify other Task. Relates to Task 1.3 (*IRIS Website and Database Improvements*).

Subtask 9.1.2. (*RMS ID# HHRA 4.231.2.*): Integrated Science Assessments (ISA) Website and database

- **Product 9.1.2.1. (*RMS ID# HHRA 4.231.2.1*)**
- **Product Title: Integrated Science Assessments (ISA) Website and database**
- Product Contact (email): John Vandenberg (vandenberg.john@epa.gov)
- Product's Delivery Date: website updated Q4 FY15
- Product Description: Website and database that contains the ISAs with links to the HERO database.
- Product's Contribution to Output: The reports on the ISA website represent a concise evaluation and synthesis of the most policy-relevant science for reviewing

the National Ambient Air Quality Standards (NAAQS). This is important piece in the writing of these standards and providing sound science to back these up.

- Product's Timeline (with milestones): ISA will be transformed to a Drupal website by Sept 2015. It will be updated periodically as needed throughout FY16-19.
- Product's intended user/customer/audience: human exposure assessors in the Agency, state, and outside the Agency.
- Is this a key product? No
- Does this Product contribute to a Product under another Task? Yes. This product is linked and serves as a communication vehicle for Project 2, Task 2.1 (*RMS ID# HHRA 2.21*).

Subtask 9.1.3. (*RMS ID# HHRA 4.231.3.*): Peer-reviewed Toxicity Value (PPRTV) Website and database

- **Product 9.1.3.1. (*RMS ID# HHRA 4.231.3.1*)**
- **Product Title: Peer-reviewed Toxicity Value (PPRTV) Website and database**
- Product Contact (email): Annette Gatchett (Gatchett.Annette@epa.gov)
- Product's Delivery Date: FY16
- Product Description: Website and database that contains links to the PPRTVs
- Product's Contribution to Output: The PPRTV website and database contains links to assessments that provide toxicity values for use in the Superfund Program when such values are not available from EPA's IRIS database.
- Product's Timeline (with milestones): The electronic library of assessments will be migrated to Drupal by FY16 and will be updated periodically as needed through FY16-19.
- Product's intended user/customer/audience: EPA program offices and regions, specifically Office of Superfund Remediation and Technology Innovation, other federal agencies, state and local governments, risk assessors in the private sector, and the general public.
- Is this a key product? No
- Does this Product contribute to a Product under another Task? Yes. This product is linked and serves as a communication vehicle for Project 4.

Subtask 9.1.4. (*RMS ID# HHRA 4.231.4*): Health and Environmental Research Online (HERO)

- **Product 9.1.4.1. (RMS ID# HHRA 4.231.4.1)**
- **Product Title: Maintenance and development / yearly updates for HERO**
- Product Contact (email): Debra Walsh (Walsh.Debra@epa.gov)
- Product's Delivery Date: FY16-FY19
- Product Description: HERO annual update
- Product's Contribution to Output: Provides a literature database for development of human health and ecological risk assessments
- Product's Timeline (with milestones): continual updates
- Product's intended user/customer/audience: Risk assessors inside and outside the Agency
- Is this a key product? No.
- Does this Product contribute to a Product under another Task? Yes. ISA assessments contribute to advances in approaches to evidence integration and response analyses. For example, Task 6.1 (*RMS ID# HHRA 3.23.1*, *Approaches to Cross-species Data Integration to Support CRA*)) is being informed by the example integration of ecological and human endpoints based on mode of action that was used in the ISA for lead.

Subtask 9.1.5. (*RMS ID# HHRA 4.231.5*): Benchmark Dose Software (BMDS) Modeling and Website

- **Product 9.1.5.1. (*RMS ID# HHRA 4.231.5.1*):**
- **Product Title: Development of new modules for BMDS**
- Product Contact (email): Jeff Gift (Gift.Jeff@epa.gov)
- Product's Delivery Date: FY16
- Product Description: Advancing BMDS software modules
- Product's Contribution to Output: Provides new dose-response tools for quantitative analyses in HHRA
- Product's Timeline (with milestones): Migration to Drupal by Sep 2015. Future improvements starting in FY16.
- Product's intended user/customer/audience: Risk assessors inside and outside the Agency
- Is this a key product? No
- Does this Product contribute to a Product under another Task? Yes. BMDS software serves as the platform for all quantitative dose-response modeling performed in the IRIS (Project 1, Tasks 1) and Project 2, Task 2 and PPRTV (Project 4, Task 1)

assessment products of the HHRA program, and additionally provides such support to Agency program offices and array of external stakeholders.

Subtask 9.1.6. (*RMS ID# HHRA 4.231.6*): EPA's-Expo-Box Website (EXPO-Box) and database

- **Product 9.1.6.1 (*RMS ID# HHRA 4.231.6.1*):**
- **Product Title: EPA-Expo-Box**
- Product Contact (email): Linda Phillips (Phillips.linda@epa.gov)
- Product's Delivery Date: final version Q4 FY15; improvements/additions FY16, FY17, FY18, and FY19. Periodic maintenance will be required to fix broken links and update based on new guidelines/policies. As new tools become available, there will be need for updates.
- Product Description: Online toolbox on the EPA Risk Portal
- Product's Contribution to Output: The tool provides a quick, easy, and flexible way for users to access information and resources for conducting human exposure assessments.
- Product's Timeline (with milestones): EPA-Expo-Box will be transformed to a Drupal website by Sept 2015. It will be updated periodically as needed throughout FY16-19.
- Product's intended user/customer/audience: human exposure assessors in the Agency, state, and outside the Agency.
- Is this a key product? Yes
- Does this Product contribute to a Product under another Task? If so, identify other Task. The ExpoFIRST tool also being developed under HHRA will be added as a link in EPA-Expo-Box when complete. In addition, EPA-Expo-Box includes a portion of the RATE training covering courses on exposure assessment. There are also plans to link the site to EPA-Eco-Box (see below).

Subtask 9.1.7. (*RMS ID# HHRA 4.231.7*): Systematic Review Tool

- **Product 9.1.6.7 (*RMS ID# HHRA 4.231.7.1*):**
- **Product Title:** Needs Assessment and Inventory of Currently Available Tools to Improve Efficiency of Systematic Review
- **Product Contact (email):** owens.beth@epa.gov; cooper.glinda@epa.gov
- **Product's Delivery Date:** FY16
- **Product Description:**

A number of tools and software supporting aspects of systematic review are already in use by NCEA, while other tools are being developed by NCEA or being used by other Agencies. An inventory of these tools is required to fully judge the applicability and relative strengths and weaknesses for implementing systematic review in HHRA assessments. Information collected will include the cost and cost-

effectiveness of particular tools, optimal uses of the tool, and ease of use and training requirements. Additionally, a needs assessment will be conducted to determine the different needs of various HHRA products (e.g., IRIS, ISAs). This assessment will serve to better understand the most important needs for successful implementation of each component of systematic review (e.g., literature screening, study quality evaluation, abstraction of results, data display and data analysis) for each HHRA product. The needs assessment and inventory will identify the gaps between the capabilities of currently available tools and the desired capabilities in order to efficiently and successfully implement the principles of systematic review in HHRA assessments.

- **Product's Contribution to Output:** An inventory and needs assessment of tools required for implementing systematic review in HHRA assessments is required to set priorities for continued development of tools.
- **Product's Timeline (with milestones):** FY16
- **Product's intended user/customer/audience:** NCEA
- Is this a key product? Yes
- Does this Product contribute to a Product under another Task? Yes. This product implements development of approaches in Task 7.1 on systematic review and evidence integration.

Subtask 9.1.8. (RMS ID# HHRA 4.231.8): Data Management and Visualization Tools (DMVT) for Risk Assessment

- **Product 9.1.8.1 (*RMS ID# HHRA 4.231.8.1*)**
- **Product Title: Data Visualization Tools to Enhance Analysis and Generate Graphical Representations of Dose/Response/Duration Relationships for Risk Assessments**
- Product Contact (email): George Woodall (Woodall.george@epa.gov)
- Product's Delivery Date: 3QFY17
- Product Description: This product will consist of a graphical user interface (potentially web-based) to manage and manipulate dose-response and other study data, and apply those data into pre-formatted graphics options and allow the user to customize graphic designs using the visualization tool. The initial prototypes will use the already established conventions used for Exposure-Response Arrays, Forest Plots, and dose-response curves. Later iterations will expand upon those with additional templates and formats, including the development of interactive capacity which will allow the innovative user to develop their own analyses and graphical designs
- Product's Contribution to Output: Work on this product is anticipated to provide tools that will enhance the ability of researchers and risk assessors to evaluate data from multiple studies across multiple endpoints, allowing for trend analysis and a

better understanding of dose-response relationships within datasets. Consideration of duration as another dimension in the dose-response relationship is also a key attribute in this product. Development of these tools will enable a better understanding of the dose-response relationship across endpoints and how variations in exposure duration/frequency may affect that relationship. These tools will also be useful in developing and communicating the risk assessments being developed by major HHRA Product lines: IRIS (Projects 1 and 2), ISAs (Project 3), and PPRTVs (Project 4), and the major research and support initiatives in Projects 5-8. In addition, these products are anticipated to help meet the OSTP Initiative for Federal Agencies to share the data they generate (see OSTP Memo of February 22, 2013 - http://www.whitehouse.gov/blog/2013/02/22/expanding-public-access-results-federally-funded-research). EPA is among the agencies included in this initiative. Development of these data storage and display resources, and making them available to the public and to other agencies performing risk assessments, will demonstrate how HHRA is contributing to this effort.

- Product's Timeline (with milestones):
  - FY2016 – Distribution of beta version of the graphical interface and tools for use in HHRA risk assessment product development (prototype being developed in FY2015). Capacity to tap into data streams from DRAGON and HAWC (Project 9). Cooperative interaction with CSS products (ToxRefDB and others) will also be initiated.
  - FY2017 – Incorporation of and seamless linkage to HERO data repository (also being developed under Project 9)
  - FY2019 – Incorporation and seamless linkage to NCCT data streams for incorporation into analysis for risk assessment products using high-throughput data streams (in collaboration with Task 8.2).
- Product's intended user/customer/audience: Risk assessment community; EPA staff developing risk assessment documents; and EPA Staff working to better incorporate considerations of less-than-lifetime issues in risk assessments.
- Is this a key product? No
- Does this Product contribute to a Product under another Task? This will enable the development of graphical data visualizations to enhance analysis of multiple data streams, and incorporation of improved graphical elements into HHRA risk assessment products (Tasks 1.1, 1.2, 3.1, and 4.1). Creation of linkages to other data management products being developed under Tasks 8 and 9 will also contribute. Interaction with other Research Programs (CSS) and outside organizations (NTP for access to CEBS and UNC for HAWC) are also planned.

- **Product 9.1.8.2 (*RMS ID# HHRA 4.231.8.2*)**
- **Product Title: Advanced Graphical and Data Management Software Tools to Create Reference Value Arrays**
- Product Contact (email): George Woodall (woodall.george@epa.gov)
- Product Delivery Date: Continuous updates from 2016 - 2019

- Product Description: HHRA has developed reference value arrays to assist in deliberations on the most appropriate values to use in specific decision-making contexts. The initial set of reference value arrays were provided in a 2009 EPA Report (http://cfpub.epa.gov/ncea/cfm/recordisplay.cfm?deid=211003) which included a number of chemical agents specifically useful for the Department of Homeland Security, along with a number of industrial chemicals with broader application to HHRA's typical clients (OAQPS, OSWER, Regions and States). The focus of this subtask is to expand the capacity to manage the information used in developing the graphical and tabular summaries used for these types of reports and to provide graphical software to generate the arrays more quickly and efficiently. Capacity to develop reports on short notice will enhance the ability of HHRA to provide timely advice in a most consistent manner. The work in this subtask will be highly coordinated with the needs being identified in Task 5.2.
- Product's Contribution to Output: Preparation of Reference Value Arrays graphical and tabular summaries for chemicals will assist in providing quick, efficient and consistent advice to the Program Offices. Development of enhanced techniques for generating these types of summaries will enable HHRA to produce quickly produce reports on short notice, with the advantage of increasing the library of available arrays for later use.
- Product's Timeline (with milestones):
  - FY2016 –Initiate development of enhanced array development capacity using the existing work effort through the Environmental Modeling and Visibility Lab (EMVL).
  - FY2017 – Provide prototype examples of products from the EMVL effort using data from the existing reference value arrays.
  - FY2018-2019 – Incorporate the EMVL tools into the development and update of arrays for high priority chemicals, and to develop similar capacities to respond on short-notice, high-priority needs.
- Product's Intended user/customer/audience: Program Offices, DHS, Agency Administration
- Key product? No
- Contributions to a Product under another Task: Development of these software and data management tools will allow the development of chemical-specific reports comparing reference values to support the Program Offices when making risk-based decisions, a key activity under Task 5.2.

Subtask 9.1.9. (*RMS ID# HHRA 4.231.9*): Ecological Risk Assessment Support Center (ERASC) Website

- **Product 9.1.9. (*RMS ID# HHRA 4.231.9*):**
- **Product Title: Ecological Risk Assessment Support Center (ERASC) Website**
- Product Contact (email): Michael Kravitz (kravitz.michael@epa.gov)
- Product's Delivery Date: Website updated for start of FY16
- Product Description: Response site to ecological risk assessment requests.
- Product's Contribution to Output: The tool provides the answers to specific ecological questions leveraging the expertise of scientists across EPA to assist users who may use these responses to perform assessments that are ecological in nature.

- Product's Timeline (with milestones): ERASC will be transformed to a Drupal website by Sept 2015. It will be updated periodically as needed throughout FY16-19.
- Product's intended user/customer/audience: human exposure assessors in the Agency, state, and outside the Agency.
- Is this a key product? No
- Does this Product contribute to a Product under another Task? If so, identify other Task. Yes this website provides support and access to work performed and data from the ERASC described in Task 5.2 (*RMS ID# HHRA 3.222, Technical Support, Consultation and Review for Superfund and Other Agency Priorities*).

Subtask 9.1.10 (*RMS ID# HHRA 4.23.10)* Enzyme Ontogeny Database (EOD) and Website

- **Product 9.1.10. (*RMS ID# HHRA 4.231.10*):**
- **Product Title: Updating the Enzyme Ontogeny Database Module**
- Product Contact (email): Sury Vulimiri (Vulimiri.sury@epa.gov)
- Product's Delivery Date: Q2FY17
- Product Description: In 2013 we developed an Enzyme Ontogeny Database (EOD) containing relevant information on selected Phase I and Phase II xenobiotic metabolizing enzymes. As part of the HHRA deliverable in RMS which was completed and posted on NCEA intranet. The EOD is located at the following link: http://cfint.rtpnc.epa.gov/ncea/recordisplay.cfm?deid=260543
  - The database includes 5 case studies :(i) Acetaminophen, (ii) Chlorpyrifos, (iii) Toluene, (iv) Aromatic amines, and (v) Trichloroethylene.
  - Three of the case studies (e.g., toluene, chlorpyrifos, and acetaminophen) have already been modeled or extensively tested in early life providing a proof of concept that they can provide a reasonable projection of these age groups, while the other two case studies (aromatic amine and trichloroethylene) are examples of how one can scope an early life toxicokinetic assessment based solely on the types of enzyme ontogeny data available in the database.
  - The utility of this EOD can be enhanced by adding newly published enzyme ontogeny information to the existing module and by performing QA/QC.
- Product's Contribution to Output: The understanding about the developmental variability acros species will help better evaluation of life-stage susceptibility.
- Product's Timeline (with milestones):
  i. Scoping of the work by August 31st, 2015
  ii. Product completion and deliver by March 2017.
- Product's intended user/customer/audience: It has both internal and external users - (i) IRIS program (ii) PBPK modelers across ORD, specifically NHEERL expressed interest in continuing the project and EPA, and (iii) Public at large
- Is this a key product? No.

- Does this Product contribute to a Product under another Task? If so, identify other Task. This task will serve as a resource for IRIS (Task 1.1) and PPRTV (Task 4.1) assessments.

Subtask 9.1.11 (*RMS ID# HHRA 4.231.11*): Risk Assessment (RISK) Website and Database

- **Product 9.1.11. (*RMS ID# HHRA 4.231.11*: Risk Assessment (RISK) Website and Database**
- **Product Title: Risk Assessment (RISK) Website and Database**
- Product Contact (email): Maureen Johnson (Johnson.maureen@epa.gov)
- Product's Delivery Date: Website updated to support launch on October 1 of HHRA StRAP and the associated FY16-19 implementation period.
- Product Description: Website and database that supports the RISK Microsite with links to the Human Health Risk Assessment (HHRA) and Ecological Risk Assessment (ERA) resource directories.
- Product's Contribution to Output: The RISK portal is the single one-stop shop for everything to do with risk assessment. It is linked from the Home page Science and Technology website.
- Product's Timeline (with milestones): RISK was transformed to a Drupal website for launch on October 1, 2015. It will be updated periodically as needed throughout FY16-19.
- Product's intended user/customer/audience: Human, ecological, and exposure assessors in the Agency, state, and outside the Agency.
- Is this a key product? No
- Does this Product contribute to a Product under another Task? This product will serve as a resource to inform assessments in IRIS (Task 1), ISA (Task 2) and PPRTV (Task 3), other risk assessors across the Agency in Program Offices and Regions, and external stakeholders.

Task 9.2

(*RMS ID# HHRA 4.232*)

Development and Application of Risk Assessment Training

Task Leads (TLs): Abdel Kadry (NCEA IO) and Reeder Sams (NCEA RTP)

Task Start Date: 10/01/2015

Task End Date: 09/30/2019

Task Description:

The overall goal of this task is to develop, improve, and provide risk assessment training resources to NCEA stakeholders, inside and outside of United States Environmental Protection Agency's (USEPA's) Office of Research and Development (ORD) on current state-of-the-science approaches for risk assessment as used and implemented by the US EPA.

Risk assessment plays a unique role in serving the needs of various state, tribal, national and international programs through incorporating, integrating, and coordinating the use of scientific information as a foundation for regulatory decision-making. Risk assessment is an ever-evolving process that significantly impacts human health, food safety, economics, ecological systems, and social decision-making. The HHRA research program is a global leader in conducting state-of-the-science risk assessments, and its approaches and documents are often the first to apply new Agency risk assessment guidelines, scientific methods, and data.

Risk assessment training results in more engaged, informed stakeholders, provides capacity building and ensures more consistent understanding and application of state-of-the-science methods employed by the EPA and others. More knowledgeable stakeholders improves effectiveness of communications and aids both transparency and technology transfer, supporting better informed risk managers and resultant decisions. The training efforts internally also position the HHRA program to incorporate state-of-the-science methods as they become available, and maintain high quality through the rigorous peer review process for its assessment products. Overall this will improve the performance, quality, and transparency of risk assessments produced by EPA and others.

Research Approach:

Training resources are delivered in the form of classroom-based courses that include a Microsoft Power Point presentation with notes, a reading packet of comprehensive supporting course material, and a reference list for each course described. The training provides an opportunity for face to face interactions between EPA risk assessors and EPA and other stakeholders. The set of training modules allows the flexibility to be tailored to specific user needs. Alternative methods of delivery (webinars and web based presentations) may also be utilized.

Specific task goals:

- Updating the current risk assessment training and experience (RATE) training database based on the new developments in the risk assessment science and the verbal classroom and management feedback received from presentations
- Developing new training modules such as application of risk assessment in food matrices, microbial risk assessment, implementation and use of computational toxicology methods in risk assessment, cumulative risk assessment to support sustainability and environmental justice, and risk management
- Providing risk assessment to interested divisions in various USEPA's program offices and regions
- Providing risk assessment training to state, tribal, national and international audience as resources permit.

Task Constraints:

- Availability of time for HHRA or other ORD scientists to review and to provide feedback on the updating of these courses.
- Logistics and travel resources for training in various USEPA's program offices and regions.
- Resources to update and develop new course materials.

Task Dependencies:

- Logistics for the arrangement of the training

Task Quality Assurance and Data Management Needs:

- Is there an existing IRP/ QAPP(s) that applies to this Task? If so, identify IRP/QAPP. If new IRP/QAPPs are required, provide the status.
    - Yes. NCEA-16-00007: Quality Assurance Project Plan (QAPP) For The Development of Risk Assessment Training and Experience (RATE)
- Will this Task involve large amounts of data that need a data management plan? If yes, explain No

Task Products:

- **Product 9.2.1. (*RMS ID# HHRA 4.232*)**
- **Product Title: Providing risk assessment training to interested scientists from various EPA offices and regions:**
- Product Contact (email): kadry.abdel@epa.gov; sams.reeder@epa.gov
- Product's Delivery Date: Q1 2016 – Q4, 2019
- Product Description: The product is in the form of targeted training sessions on the basic and advanced methods of risk assessment. The product will be delivered in classroom setting or via webinars
- Product's Contribution to Output: The training efforts are important to communicate to various internal and external stakeholders the state of the science regarding risk assessment methods and models. This supports effective and timely risk assessment and management decisions, provides important engagement, and is an important opportunity for feedback on the utility of various HHRA approaches. This training additionally builds stakeholder capacity.
- Product's Timeline (with milestones): EPA offices and regions and other external stakeholders such as the states will be provided targeted training as requested and as resources permit.
- Product's intended user/customer/audience: This training supports scientists within the HHRA program and supports Program Office partners and external stakeholders.
- Is this a key product? No.
- Does this Product contribute to a Product under another Task? If so, identify other Task. Risk assessment training indirectly contributes to all tasks within the HHRA program. The opportunity for staff to train others and receive training provides important career development and supports application activities across the HHRA program, its Program Office partners and external stakeholders.

Appendix

Note: the October 2015 BOSC review is focused on Projects 5-9

HHRA Topic, Project (PAL) and Task Leads (TL)

Topic 1 – Integrated Risk Information System (IRIS) **Vincent Cogliano, NCEA IRIS**

- **Project 1: IRIS Assessments**
- PALs: Vincent Cogliano, NCEA IRIS and Gina Perovich, NCEA IRIS
    - **Task 1.1.** Developing IRIS Document Components (TL: Samantha Jones, NCEA IRIS)
    - **Task 1.2.** IRIS Scientific and Technical Consultations (TL: Samantha Jones, NCEA IRIS)
    - **Task 1.3.** Stakeholder Engagement and Outreach for IRIS Program (TL: Joe DeSantis, NCEA IRIS)
    - **Task 1.4.** IRIS Handbook of Operating Procedures (TL: Glinda Cooper, NCEA IRIS)

- **Project 2: IRIS Updates**
- PAL: Vincent Cogliano, NCEA IRIS
    - **Task 2.1.** Develop Decision Strategy (TL: Vincent Cogliano, NCEA IRIS)
    - **Task 2.2.** Review and Update IRIS Files (TL: Vincent Cogliano, NCEA IRIS)

Topic 2 – Integrated Science Assessments (ISAs) **Debra Walsh, NCEA RTP**

- **Project 3: ISAs and Science/Regulatory Support**
- PALs: Debra Walsh, NCEA RTP and Ellen Kirrane, NCEA RTP
    - **Task 3.1.** Development of ISAs (TLs: Debra Walsh, NCEA RTP and Ellen Kirrane, NCEA, RTP)
    - **Task 3.2.** ISA-related Scientific and Regulatory Support (TL: James Brown, NCEA RTP)
    - **Task 3.3.** ISA-related Science Advancements and Support (TLs: Steve Dutton, NCEA RTP and Jennifer Richmond-Bryant, NCEA RTP)

Topic 3 – Community and Site-specific Risk **Annette Gatchett, NCEA CIN**

- **Project 4: Provisional Peer-Reviewed Toxicity (PPRTV) Assessments**
- PAL: Teresa Shannon, NCEA CIN
    - **Task 4.1** PPRTV Assessments (TL: Jay Zhao, NCEA CIN)

Topic 3 – Community and Site-specific Risk (*continued*)

- **Project 5: Site-specific and Superfund Regulatory Support**
- PAL: Teresa Shannon, NCEA CIN
    - **Task 5.1.** Quarterly Reports to Superfund Technical Support Center (STSC) and Ecological Risk Assessment Support Center (ERASC) (TL: Teresa Shannon, NCEA CIN)
    - **Task 5.2.** Technical Support, Consultation and Review for Superfund and Other Agency Priorities (TLs: J. Phillip Kaiser, NCEA CIN and Linda Phillips, NCEA W)

- **Project 6: Cumulative Risk Assessment Methods and Applications**
- PALs: Michael Wright, NCEA CIN and Deborah Segal, NCEA W
    - **Task 6.1.** Approaches to cross-species data integration to support CRA (TL: Meredith Lassiter, NCEA RTP)
    - **Task 6.2.** Incorporating Multiple Stressors (TL: Glenn Rice, NCEA CIN)
    - **Task 6.3.** Applying Genetic and Epigenetic Data to Inform Susceptibility (TL: Susan Euling, NCEA W)
    - **Task 6.4.** Apportioning Multimedia Exposure and Risk across Receptors (TLs: Jennifer Richmond-Bryant, NCEA RTP and Jacqueline Moya, NCEA W)

Topic 4 – Advancing Analyses and Applications **David Bussard, NCEA W**

- **Project 7: Advancing Hazard Characterization and Dose-response Methods and Models**
- PALs: Allen Davis, NCEA RTP and Andrew Kraft, NCEA W
    - **Task 7.1.** Advancing Methods for Systematic Review and Evidence Integration (TLs Glinda Cooper, NCEA IRIS and Molini Patel, NCEA RTP)
    - **Task 7.2.** Advancing Quantitative Methods (TLs John Fox, NCEA W and Karen Hogan, NCEA IRIS)
    - **Task 7.3.** Advancing Methods for Benefits and Uncertainty Analysis (TLs Tom Bateson, NCEA W and Todd Blessinger, NCEA W)
    - **Task 7.4.** Characterizing Determinants of Risk: Concentration, Duration and Timing of Exposure (TLs Andrew Hotchkiss, NCEA IRIS and George Woodall, NCEA RTP)
    - **Task 7.5.** Science Workshops on Major Risk Assessment Methodology Issues (TLs Lynn Flowers, NCEA IO and David Bussard, NCEA W)

- **Project 8: Applying Emerging Science to Inform Risk Screening and Assessment**
- PALs: Ila Cote, NCEA IO and Bob Sonawane, NCEA W
    - **Task 8.1.** Disease-based Integration of New Data Types (TL: Ila Cote, NCEA IO)
    - **Task 8.2.** Characterization and Quantitative Application of High-throughput Screening (HTS) and Other Data-mining Derivations (TL: Scott Wesselkamper, NCEA CIN)

Topic 4 – Advancing Analyses and Applications (*continued*)

- **Task 8.3.** Dosimetry 21: Advancing Multiscale Dosimetry Models to Incorporate AOP/MOA and Biomarker Data (TL: Annie Jarabek, NCEA RTP with IRIS Inhalation Work Group (IWG), and Pharmacokinetics Work Group (PKWG)
- **Task 8.4.** Evaluation and Application of New Exposure Data and Methods (TLs: Scot Hagerthey, NCEA W and Tom Long, NCEA RTP)

- **Project 9: Risk Assessment Support and Training**
- PALs: Debra Walsh, NCEA RTP and Maureen Johnson, NCEA IO
  - **Task 9.1.** Development and Maintenance of Essential Software and Support Tools (TLs: Maureen Johnson, NCEA IO and Reeder Sams, NCEA RTP)
  - **Task 9.1.** Development and Application of Risk Assessment Training (TLs: Abdel Kadry, NCEA IO and Reeder Sams, NCEA RTP)