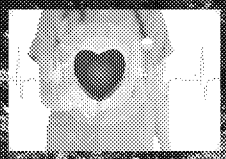
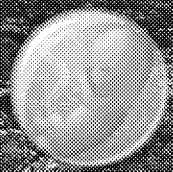
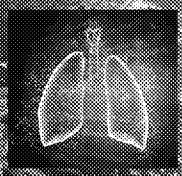
Office of Research and Development

Human Health Risk Assessment Research Program







HHRA FY16 – 19 Program Portfolio: Background for Board of Scientific Councilors (BOSC)

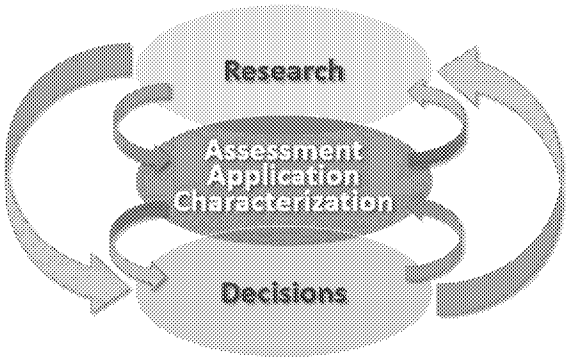
John J. Vandenberg, National Program Director (NPD)
Annie M. Jarabek, Deputy NPD

EPA

Outline

- HHRA Program Overview
  - Role in ORD Portfolio
  - Structure: 9 Projects
  - Partner engagement
- Project status
  - Tasks
  - Accomplishments in FY16
  - Anticipated FY17 progress or products
- Supplemental materials

HHRA: Pivotal Role in ORD Portfolio

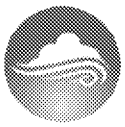


HHRA Vision: *Risk-based decisions by the EPA, State/local/tribal agencies and the public to protect public health and the environment are based on reliable, transparent and high-quality risk assessment methods, models, and data.*

HHRA Addresses all Agency Priorities and Mandates

HHRA

- Clean Air Act (CAA)
- Safe Drinking Water Act (SDWA)
- Food Quality Protection Act (FQPA)
- Comprehensive Environmental Response, Compensation, and Liability Act (CERCLA)
- Resource Conservation and Recovery Act (RCRA)
- Toxic Substances Control Act (TSCA)

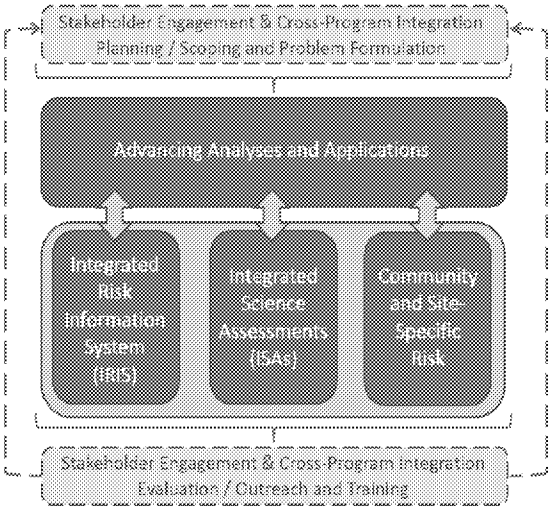


Broad Input to Support

- Agency Strategic Goals
- Children's Health, Environmental Justice, Climate and Nitrogen Roadmaps
- Sustainability

HHRA Program Design

Implemented recommendations for stakeholder engagement in scoping and problem formulation



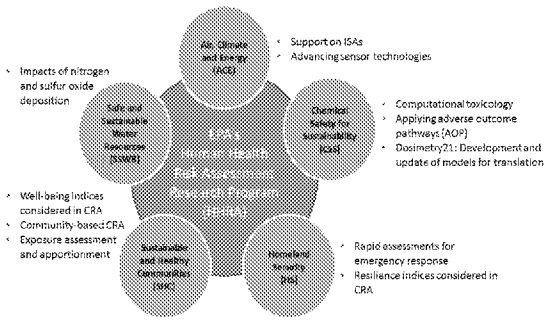
4 Topics and 9 HHRA Projects: Responding to Partner Priorities

- #1) IRIS Assessments
- #2) IRIS Update
- #3) Integrated Science Assessments (ISAs) and Scientific/Regulatory Support
- #4) Provisional Peer-reviewed Toxicity Value (PPRTV) Assessments
- #5) Site-specific and Superfund Regulatory Support
- #6) Cumulative Risk Assessment Methods and Applications
- #7) Advancing Hazard Characterization and Dose-response Methods and Models
- #8) Applying Emerging Science to Inform Risk Screening and Assessment
- #9) Risk Assessment Support and Training

Cross-Cutting Collaborations

HHRA Cross-Cutting National Program Work:

- **Chemical Safety for Sustainability (CSS) –** Application and characterization of new data, tools and concepts in risk screening and assessments; update of dosimetry modeling
- **Air, Climate and Energy (ACE) –** Incorporation of NAAQS research (including climate as a welfare effect) into Integrated Science Assessment (ISA); IRIS assessments of air toxics; interpretation of sensor data
- **Safe and Sustainable Water Resources (SSWR) –** Assessment of deposited oxides of nitrogen and sulfur on surface water quality
- **Sustainable and Healthy Communities (SHC) –** Development of Cumulative Risk Assessment (CRA) methods and decision analytic software to support "place-based" community assessment and to link health and ecology to well-being; evaluating epigenetics data
- **Homeland Security Research Program (HSRP) –** Rapid response assessment and incorporation of resiliency into cumulative risk assessment methods



Implementation: Continued Partner Engagement

- **~ Annual *Risky Business* Program Planning Meetings → StRAP and Project Portfolio**
- **Implementation phase: Cross-ORD discussion devoted to specific topics**
- **Quarterly HHRA Highlights meetings**
  - **All programs and regional partners attend**
  - **High-level status reports on projects or issues of interest**
  - **Spotlight on scientific product: 15-minute presentation**
- **Product release reports or recorded webinars, such as:**
  - April 27, 2016: *Categorical Regression: A New Modeling Tool for Conducting Concentration-time-response and Meta-analyses* https://intranet.ord.epa.gov/events/hhra-risk-assessment-training
  - November 29, 2016: 3:30 to 5:00 pm: *EPA's Exposure Factors Resource for Scenario's Tool (ExpoFIRST) – Support for risk assessors to create custom exposure scenarios based on route of exposure, medium, receptor(s), timeframe, and dose metric for a contaminant of concern*

Implementation: Continued Partner Engagement

- **HHRA FY16-19 Portfolio and PACT launch briefings: 10 in FY16**
- **HHRA Project Alliance and Coordination Team (PACT) meetings**
  - **Project-specific participation**
  - **Meetings held *ad hoc* to ensure success as needed**
  - **New partner opportunities being explored (e.g., development details)**

1) "IRIS" PACT: Projects 1 & 2
2) "ISA" PACT: Project 3
3) "PPRTV and Other Priorities" PACT: Projects 4 & 5
4) "Cumulative Risk Assessment" PACT: Project 6
5) "Advancing Methods & Models" PACT: Project 7
6) "Emerging Science & Exposure Applications" PACT: Project 8
7) "Software, Support & Training" PACT: Project 9

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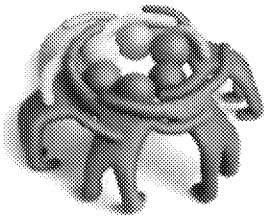
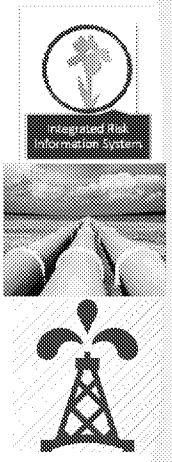
PACTs: Purpose



- Implementing across all ORD research programs to engage partners consistently and effectively
- Leverage Agency expertise and resources
- Strengthen existing relationships and create new collaborations
- Enhance understanding and awareness of HHRA projects
- Opportunity for input and tailoring of tasks
- Increase transparency and clarity regarding project progress and course corrections
- Coordinate communication
- Provide feedback on utility

Topic 1: Integrated Risk Information System (IRIS)

- Topic 1 Lead: Vince Cogliano / Gina Perovich (NCEA-IRIS)
- Project 1 (*RMS HHRA 1.21*) - IRIS Assessments (PLs Vince Cogliano/Gina Perovich)
  - Task 1.211: Developing IRIS Document Components
  - Task 1.212: IRIS Science advancements & technical consultations
  - Task 1.213: Stakeholder engagement & outreach for IRIS Program
  - Task 1.214: IRIS Handbook of Operating Procedures
- Project 2 (*RMS HHRA 1.22*) - IRIS Update (PL Vince Cogliano)
  - Task 1.221: Develop decision strategy
  - Task 1.222: Review and update IRIS Assessments



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Project I: IRIS Accomplishments & Progress

- **FY16 Assessments**
  - Final released to public: Ammonia (inhalation) and trimethylbenzenes
  - External review drafts: ETBE, TBA, RDX
- **IRIS multi-year agenda**
  - Completed: Reflects program and regional priorities to aid planning
  - Scoping/problem formulation on a few top priorities in October 2016
- **Technical support and consultations**
  - IRIS Disciplinary work groups reviewed or wrote sections regarding: Formaldehyde, HBCD, ETBE, TBA, n-butanol, RDX, chromium, and others
  - Other requests: Diesel, Glyphosate, perchlorate, chlorpyrifos, and PFOA/PFOS
- **IRIS Handbook of Operating Procedures**
  - Evergreen and evolving – Some sections under review by ORD IOAA
  - Systematic review and other approaches to ensure scientific credibility, enhance efficiency, and aid transparency

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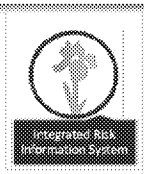
Project 2: IRIS Update



- **Purpose**
  - **Ensure IRIS remains premier risk assessment resource**
  - **Provide timely assessments that are focused on key questions**
  - **Streamline the review process**
  - **Pilot application of new approaches to increase agility for Agency**
- **Status**
  - **Process to identify priorities and criteria developed; under review by IOAA**
  - **Application to new starts delayed until FY17**
  - **Anticipate support to TSCA: Opportunity to expand assessment portfolio**

IRIS PACT Meetings in FY16

- HHRA Portfolio and PACT Launch briefings
- IRIS monthly Agency meetings
- Public Science Meetings (PSM)
  - May 10, 2016, in Arlington VA
    - RDX (Hexahydro-1,3,5-trinitro-1,3,5-triazine): Public comment draft
  - June 29-30, 2016, in Arlington VA
    - Tert-Butyl Alcohol: Public comment draft
    - Benzo[a]pyrene: Modeling approaches for a dermal slope factor
  - October
    - Ethyl tertiary butyl ether (ETBE)
- Specific requests for face-to-face discussions
  - January 27, 2016: Inorganic arsenic stakeholder meeting
  - July 26, 2019: Painesville cohort data on lung cancer
  - August 9, 2016: IRIS Assessment of chloroprene
  - August 10, 2016: Cr6+ Mode of Action research

Topic 2: Integrated Science Assessments (ISA) and Scientific/Regulatory Support

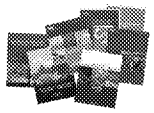
- Topic 2 lead: Steve Dutton (NCEA RTP)
- Project 3 (*RMS HHRA 2.21*) - ISAs and Scientific/Regulatory Support (PL Steve Dutton)
  - Task 2.211: **Development of ISAs**
    - Public science kick-off meetings
    - Public Clean Air Scientific Advisory Committee (CASAC) meetings
  - Task 2.212: **ISA-Related Scientific & Regulatory Support**
  - Task 2.213: **ISA-Related Science Advancements**
- PACT for Project 3: "ISA PACT"
  - Weekly meetings with Office of Air Quality Planning and Standards (OAQPS)
  - Monthly with OTAQ or others as needed

"All NAAQS All the Time"

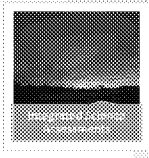
"A five-star process for incorporating science into regulatory policy." Administrative Conference of US (2013)

Project 3: Accomplishments and Anticipated Products

- Task 2.211: Development of ISAs
  - **Final ISA released in FY16**
    - ISA to support Primary (health criteria) NAAQS for Oxides of Sulfur
    - ISA to support Primary (health criteria) NAAQS for Oxides of Nitrogen



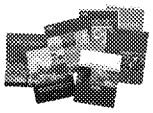
"All NAAQS All the Time"



  - **Anticipated release in FY17**
    - First Draft ISA to support Secondary (ecological criteria) NAAQS for Oxides of Nitrogen and Sulfur (NOx/SOx)
  - **Peer-input workshops (webinars) for PM conducted in FY16:** 1) atmospheric chemistry and exposure; 2) welfare effects; 3) mode of action, dosimetry, and cancer; and 4) health effects
  - **Provided chapters to the Integrated Review Plan (IRP) of OAQPS in FY16**
    - Draft and Final: Secondary NAAQS review for oxides of nitrogen and sulfur
    - Draft: Primary and secondary NAAQS review of PM

Project 3: Accomplishments and Anticipated Products

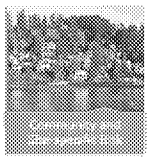
- Task 2.212: **ISA-Related Scientific & Regulatory Support**
  - **Technical support on the Response to Comments Document and Final Rule**
    - **FY16/17:** Primary and secondary NAAQS for lead (Pb)
    - **FY16/17:** Primary and secondary NAAQS for ozone (O_3)
  - **Technical support on the Policy Assessment**
    - **FY16/17:** Primary NAAQS for oxides of nitrogen (NOx)
    - **FY16/17:** Primary NAAQS for oxides of sulfur (SOx)
  - **Technical support on the Risk and Exposure Assessment Planning Document**
    - **FY16/17:** Secondary NAAQS for oxides of nitrogen and sulfur (NOx/SOx)
    - **FY17:** Primary NAAQS for oxides of nitrogen (NOx)
    - **FY17:** Primary NAAQS for PM
  - **Litigation and decision support**
    - **FY16/17:** Primary and secondary NAAQS for ozone (O_3)
- Task 2.213: **ISA-Related Science Advancements**
  - See supplemental material for list of citations



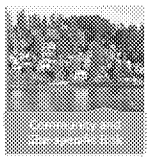
"All NAAQS All the Time"

Topic 3: Community and Site-specific Risk

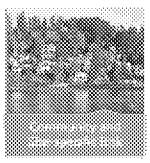
- Topic 3 Lead: Annette Gatchett / Mike Troyer (NCEA CIN)
  - Project 4 (*RMS HHRA 3.21*) - **PPRTV Assessments (PL Teresa Shannon [NCEA CIN])**
  - Project 5 (*RMS HHRA 3.22*) - **Site-specific and Superfund Regulatory Support (PL Teresa Shannon [NCEA CIN])**
  - Project 6 (*RMS HHRA 3.23*) - **Cumulative Risk Assessment (CRA) Methods and Applications (PLs Mike Wright [NCEA CIN] / Deborah Segal [NCEA W])**



Project 4: Accomplishments and Anticipated Products



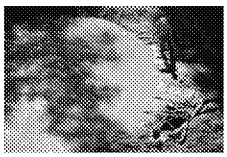
- Task 3.211: Provisional Peer-Reviewed Toxicity Value (PPRTV) Assessments
  - Annually develop ≥ 12 PPRTV assessments as prioritized by OLEM
    - 339 PPRTV assessment documents available online which provide 773 values
    - Derived following a review of the relevant scientific literature using the same methods, sources of data, and guidance used by the IRIS program
    - All PPRTV assessments receive internal review by EPA scientists and external peer review by independent scientific experts.
  - Pilot of new approaches in appendices to derivation as characterization and applications mature (linked to Project 8)
- Task 3.212: PPRTV-related Scientific Analyses and Applications



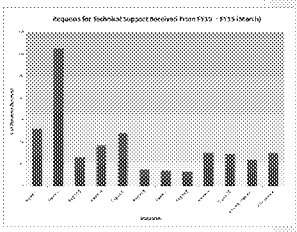
- Task 3.221: Quarterly Reports to Superfund Technical Support Center (STSC) and Ecological Risk Assessment Support Center (ERASC)
  - Distribute PPRTV values developed under Project 4
  - Provide technical consultation on derivation, interpretation or application of PPRTV
  - Respond to requests for reports on specific topics

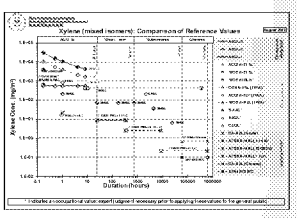
Project 5: Site-specific and Superfund Regulatory Support

- Task 3.222: Technical Support, Consultation and Review for Superfund and other Agency Priorities
  - Rapid risk assessment response to emergent situations provided by multi-disciplinary staff
    - Gold King Mine, CO
    - Flint, MI
    - Tire crumbs



  - Participation on Agency workgroups
    - Soil and dust ingestion collaboration with SHC
  - Visual data array summaries





Project 5: Support on Other Agency Priorities

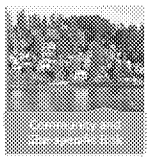
- Integrated Science Assessment (ISA) for Lead (NCEA, 2013) and Integrated Exposure Uptake and Biokinetic Model (IEUBK) and All Ages Lead Model (AALM) development and support
  - Flint, Gold King Mine, other community support
  - Soil Screening Level for Pb (OLEM)
  - National Ambient Air Quality Standards for Pb (OAR)
  - Lead and Copper rule (OW)
  - Tire Weights (OCSPP)
  - Benefits Assessment (OP)

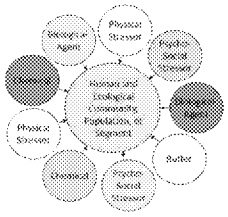
"PPRTV and Other Priorities" PACT

- Combines Projects 4 and 5
- Meetings
  - Bi-monthly meetings with OLEM
  - Bi-monthly meetings with OHHRRAF
- FY16: Standard Operating Procedure (SOP) for chemical selection
  - Developed to codify and clearly define the process
  - More interaction with OLEM HQ and the Regions
    - Includes a scoping team
  - Breaks chemical selection into two categories:
    - Standard annual process
    - "Fast-track" requests from Regions via the STSC
  - 1st draft delivered March 2016 with undergoing continued development by NCEA-CIN and OLEM
- FY17: Anticipate meetings regarding application of new methods

Topic 3: Community and Site-specific Risk (*cont*)

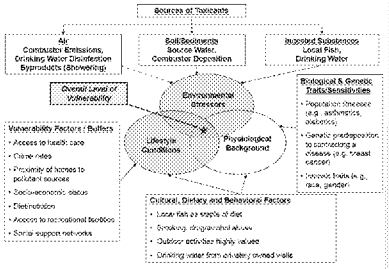
- Project 6 (*RMS HHRA 3.23*) - Cumulative Risk Assessment (CRA) Methods and Applications
  (PLs Mike Wright [NCEA CIN] / Deborah Segal [NCEA W])
  - Task 3.231: Approaches to cross-species data integration to support CRA
  - Task 3.232: Incorporating Multiple Stressors
  - Task 3.233: Applying Genetic and Epigenetic Data to Inform Susceptibility
  - Task 3.234: Apportioning Multimedia Exposure and Risk Across Human and Ecological Receptors





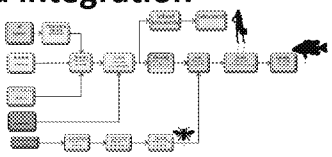
Project 6 (*HHRA 3.23*): Cumulative Risk Assessment Methods and Applications

- **Cumulative risk assessment (CRA) methods**
  http://www.epa.gov/raf/publications/pdfs/frmwrk_cum_risk_assmnt.pdf
  - **Considerable Agency experience**
    - **Guidance for mixtures**
    - **Case studies and publications**
      - Evans et al. (2014). Joint Exposure to Chemical and Nonchemical Neurodevelopmental Stressors in U.S. Women of Reproductive Age in NHANES. *Int. J. Environ. Res. Public Health 11*(4), 4384-4401; doi:10.3390/ijerph110404384http://www.mdpi.com/1660-4601/11/4/4384
    - **Training** NCEA Scientists offer chemical mixtures and cumulative risk assessment training at scientific forums (e.g., SRA Annual Mtg)
- **Well-vetted platform to**
  - **Evolve place-based community assessment**
  - **Address environmental justice issues**
    - *Olden et al. (2014). Epigenome: Biosensor of Cumulative Exposure to Chemical and Non-Chemical Stressors Related to Environmental Justice. J Am Public Health Assoc* Oct;104(10):1816-21. http://www.ncbi.nlm.nih.gov/pubmed/25122010



Project 6 (*HHRA 3.23*): Cumulative Risk Assessment Methods and Applications

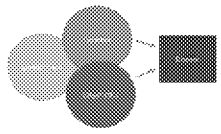
- Task 3.231: **Approaches to cross-species data integration to support CRA**



  - **Collaboration with NHEERL on Case studies**
    - Integrate ecological assessment
    - Application of Aggregate Exposure Pathway:Adverse Outcome Pathway framework with Ecosystem Services-Generic ecological assessment endpoints (ES-GEAE)
  - **Advance multi-criteria decision analysis (MCDA)**
  - **Collaborate with other programs to incorporate and coordinate**
    - Resiliency (HS) and Well-being (SHC)
- Task 3.232: **Incorporating Multiple Stressors**
  - **Expand and characterize additional stressors and interactions**

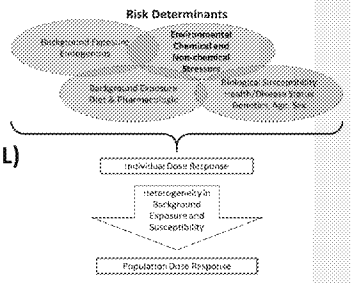
Project 6 (*HHRA 3.23*): Cumulative Risk Assessment Methods and Applications

- Task 3.233: **Applying Genetic and Epigenetic Data to Inform Susceptibility**
  - **Subtask 6.3.1.: Applying Epigenetics Data to Cumulative Risk**
    - **Human Study: Nonchemical Stressors, Epigenetic Changes, Susceptibility to Air Pollution Exposure, and Cardiovascular Disease** ***(HHRA, ACE, and SHC Collaboration with NHEERL on Duke CATHGEN project)***
    - **Case Study: Chemical and Nonchemical Stressors, Epigenetics, and HPA Axis**
    - **Literature Review: Transgenerational Effects, Epigenetics, and Developmental and Reproductive Effects –** ***Implications for Chemical Testing and Risk Assessment***
    - **Epigenetics and Cumulative Risk Assessment Workshop Report**
  - **Subtask 6.3.2.: Applying Polymorphism and Mechanistic Data to Inform Genetic Susceptibility**
    - **Approach and Case Study: Use AOP Framework and Select Relevant and Data Rich AOP for Case Study**

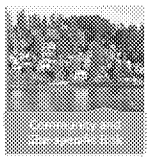


Project 6 (*HHRA 3.23*): Cumulative Risk Assessment Methods and Applications

- Task 3.234: Apportioning Multimedia Exposure and Risk Across Human and Ecological Receptors **(TL Jennifer Richmond-Bryant)**
- **Focus of tasks: multiple stressor, multimedia exposures**
  - Advances in modeling exposure apportionment
    - Modeling dermal and inhalation exposures to phthalates
    - Apportioning chemical stressors for the most affected portions of the populations of human and ecological receptors **(Collaboration with NERL)**
    - Chemical and physical properties of multiple stressors
  - Application of exposure apportionment methods
    - Breastfeeding as a route of exposure for environmental chemicals
    - Cumulative exposures, social determinants, and health **(Collaboration with R3)**
    - Pharmacokinetic modeling of infant body burden from bioaccumulative compounds in mother's milk
    - Residential exposure to pesticide active ingredients and birth defects **(Collaboration with NHEERL)**

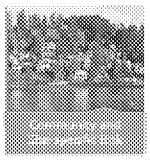


Project 6: Accomplishments and Anticipated Products



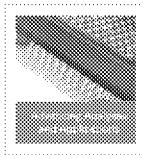
- Task 3.231: **Approaches to cross-species data integration to support CRA**
  - **FY17:** Manuscript on first case study illustrating utility of AEP:AOP frameworks to integrate human and ecological endpoints (e.g., the ES-GEAE) and advance mechanistic considerations
  - **FY17/18:** Second case study and development of MCDA approach
- Task 3.232: **Incorporating Multiple Stressors**
  - **FY16/17:**
    - Revisions to EPA RAF Report *"Dose Addition in Risk Assessment"*
    - Manuscripts:
      - FY16: Brewer LE, Wright JM, Rice G, Neas L, Teuschler L. (In Review). Causal inference in cumulative risk assessment: The roles of directed acyclic graphs. *Environ. Int.*
      - *Characterizing Risk for Cumulative Risk Assessment*

Project 6: Accomplishments and Anticipated Products



- Task 3.233: **Applying Genetic and Epigenetic Data to Inform Susceptibility**
  - FY17: Review manuscript on data sources and approaches for incorporating genetic inter-individual variability information within humans for use in risk assessment
- Task 3.234: **Apportioning Multimedia Exposure and Risk Across Human and Ecological Receptors**
  - FY17: Manuscript applying the maximum cumulative ratio methodology to phthalate biomonitoring data from NHANES

Topic 4: Advancing Analyses and Applications



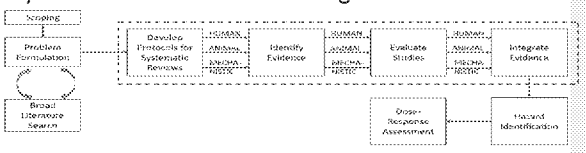
- Topic 4 Lead: David Bussard / Scot Hagerthey (NCEA W)
  - Project 7 (*RMS HHRA 4.21*) – **Advancing Hazard Characterization and Dose-Response Methods**
    (PLs Allen Davis [NCEA RTP] / Andrew Kraft [NCEA W])
  - Project 8 (*RMS HHRA 4.22*) – **Applying Emerging Science to Inform Risk Screening and Assessment**
    (PL John Stanek [NCEA RTP] / Jay Zhao [NCEA CIN])
  - Project 9 (*RMS HHRA 4.23*) – **Risk Assessment Support and Training**
    (PLs Debra Walsh [NCEA RTP] / Maureen Johnson [NCEA IO])

Topic 4: Advancing Analyses and Applications

- Project 7 (*RMS HHRA 4.21*) – Advancing Hazard Characterization and Dose-Response Methods
  (PLs Allen Davis [NCEA RTP] / Andrew Kraft [NCEA W])
  - Task 4.211: Advancing Methods for Systematic Review and Evidence Integration
  - Task 4.212: Advancing Quantitative Methods
  - Task 4.213: Advancing Methods for Benefits and Uncertainty Analyses
  - Task 4.214: Characterizing Determinants of Risk: Concentration, Duration and Timing of Exposure
  - Task 4.215: Science Workshops and Webinars on Major Risk Assessment Methodology Issues

Project 7 (*HHRA 4.21*): Advancing Hazard Characterization and Dose-Response Methods

- Task 4.211: **Advancing Methods for Systematic Review and Evidence Integration**
  - FY16: Workshop on advancements (December 2015) – internal report of approaches presented at workshop to be developed
  - FY16/FY17: Case studies / commentaries for study evaluation and evidence integration for different data types
    - Laboratory animal
    - Epidemiological



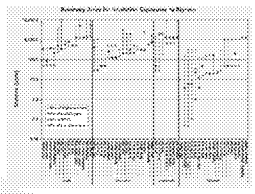
- Task 4.212: **Advancing Quantitative Methods**
  - Evaluate and adopt newer methods to improve the quality and accuracy of risk assessments and advance the quantification of uncertainty and variability
    - Comparison of dose-response analysis methods
    - Best practices for trend and hypothesis testing
    - Multivariate and covariate modeling
    - Quantitative approaches to combining data across studies

Project 7 (*HHRA 4.21*): Advancing Hazard Characterization and Dose-Response Methods

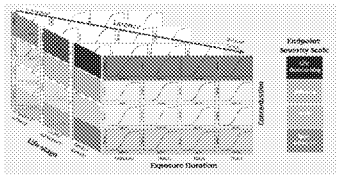
- Task 4.213: **Advancing Methods for Benefits and Uncertainty Analyses**
  - **Collaboration with Office of Policy (OP) and others**
    - Surveys of program office needs for benefits analysis
    - Selection of case studies to develop benefits analysis
  - **Incorporating mechanistic data: Approaches and utility**
    - Systematize MOA analysis to improve consistency and transparency
    - Inform case studies on non-cancer valuation
  - **Uncertainty analyses for toxicological and epidemiological studies**
    - Greater use of quantitative uncertainty analysis throughout assessment process
    - Moving toward a risk-specific dose

Task 4.214: Characterizing Determinants of Risk: Concentration, Duration and Timing of Exposure

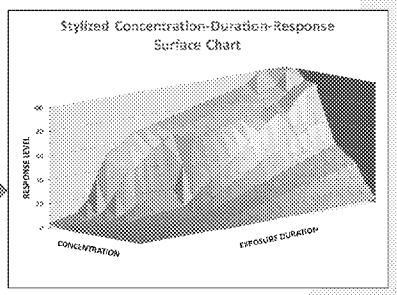
- **Characterization of responses across duration and concentration**
  - **Address trajectory of different lesions**
  - **Create context for evaluating assessment approaches to acute and episodic exposures**
- **Best bridge to systems biology and computational models**
  - **Key events understood as part of pathogenesis**
  - **Aids application of MOA and AOP**
  - **Informs case studies on benefits-cost assessment**



Where we are...



Organizational Construct for Cross-cutting Analyses

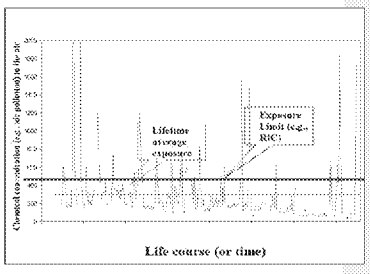


Where we are headed...

Task HHRA 4.214: Accomplishments and Anticipated Products

- *Support to develop acute risk estimates recommended by BOSC*
- *Temporal Exposure Issues Workshop (January 2016)*

- **Approach**
  - **Address different exposure scenarios**
    - Characterize damage accumulation and/or irreversible effects
    - Define dose metrics
  - **Case study approach across chemical categories / endpoints of concern**
    - Reactive gases / solvents / metals
    - Developmental / neurological



- **FY16: Develop set of case studies with programs**
- **FY17: Manuscript on workshop**
- **FY17/18: Compile data on case studies and initiate development of algorithsms**

Draft workshop report will be completed and go into review/clearance in FY2016

Project 7 (*HHRA 4.21*): Advancing Hazard Characterization and Dose-Response Methods

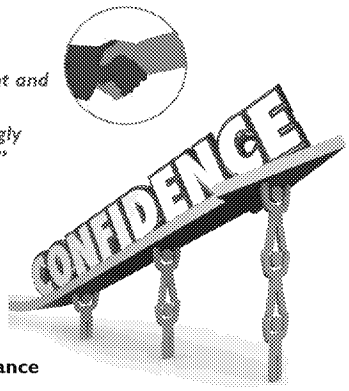
- Task 4.215: **Science Workshops and Webinars on Major Risk Assessment Methodology Issues**
  - Aimed at issues that arise for resolution via assessment activities or challenges emerging in larger public health / scientific community
  - Topics in FY16:
    - December 2015: Advancing systematic review
    - January 2016: Temporal exposure issues
  - Topics in FY17: Likely impacted by resource limitations

Advancing Analyses and Applications (*cont.*)

- Project 8 (*RMS HHRA 4.22*) – Applying Emerging Science to Inform Risk Screening and Assessment
  (PLs John Stanek [NCEA RTP] / Jay Zhao [NCEA CIN])
  - Task 4.221: Disease-based integration of new data types
  - Task 4.222: Characterization and Quantitative Application of High-throughput Screening (HTS) and Other Data-mining Derivations
  - Task 4.223: Dosimetry21: Advancing Multi-scale Dosimetry Models to Incorporate AOP/MOA and Biomarker Data
  - Task 4.224: Evaluation and application of new exposure data and methods

SAB/BOSC Comments and Future Directions

- **Scope of review was limited to <u>application and characterization</u> of CSS-type tools to modernize assessments**
  - SAB/BOSC review found the CSS and HHRA research programs to be scientifically robust and well-aligned to the overarching EPA Strategic Plan…*"considered to be on a path to revolutionize chemical safety assessment and viewed as leading the field"*
  - *"…an iterative approach to tool creation, evaluation, and application is strongly recommended in order to maintain confidence during this period of transition"*
- **Building confidence will require an <u>iterative and integrated</u> approach to foster understanding and trust of new techniques**
- **HHRA characterizations will provide a <u>flexible portfolio</u> and address <u>fit-for-purpose applications</u>:**
  - High-throughput platforms to aid prioritization
  - Multiple platforms and read-across approaches to construct context, enhance evidence integration, and support disease-based evaluations
  - Updated dosimetry models to quantify AOP / MOA key events and biomarkers
  - Response surface analyses to address acute and episodic exposures for various use categories under TSCA



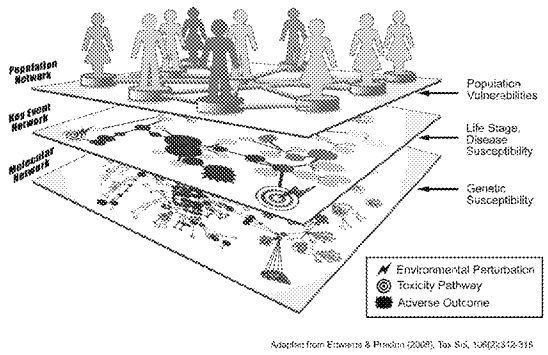
- Task 4.221: Disease-based integration of new data types

— MOAs can be used improve almost every aspect of risk assessment, and they can be built most efficiently and robustly using new methods

— MOA aid understanding of: biomarkers of exposure and effect, susceptible subpops/lifestages, mixtures interactions, hazard ID for data poorer chemicals, and dose-response (potentially)

— Focused on inorganic arsenic (iAs) case study to develop methods. We have used molecular and computational MOA to generate 10 human-based AOPs for cancer (e.g. bladder, lung) and noncancer diseases (atherosclerosis, diabetes).

— These can be used to better understand iAs and other chemical that cause these diseases



Adapted from Edwards & Preston (2008), Tox Sci, 106(2):312-315

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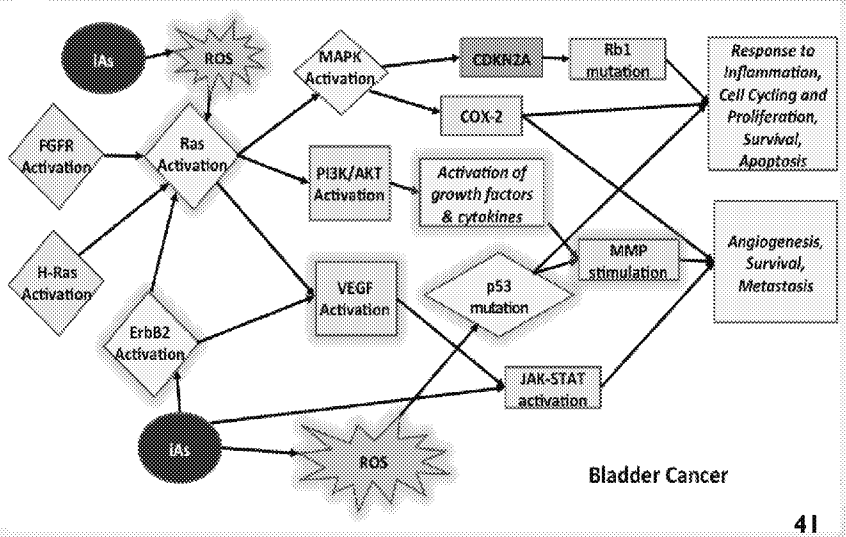
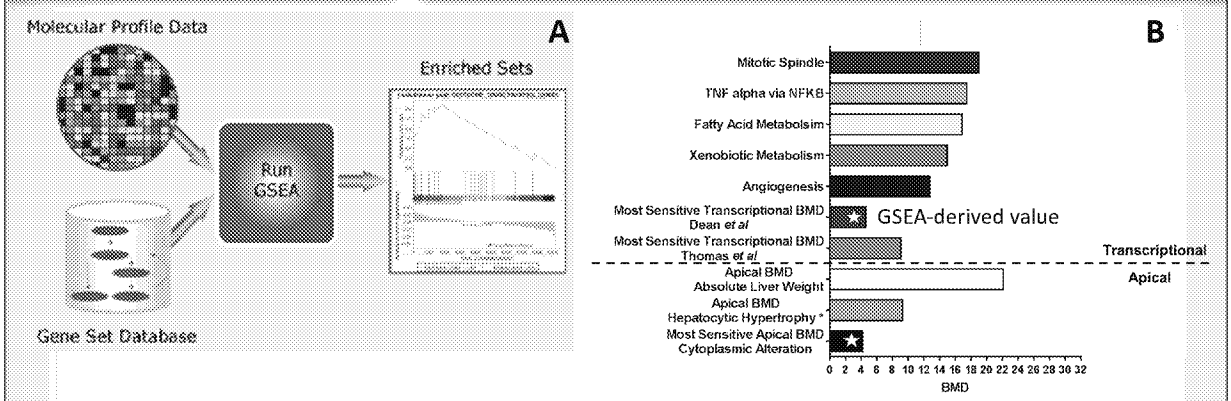
Task 4.221: Disease-based integration of new data types

- Basic AOP network (gray) provided by NIH BioSystems
- Yellow diamonds are iAs-specific gene transcription changes
- Yellow squares are traditional iAs exposure outcomes driven by the identified gene transcription changes
- Green highlights represent events further modified by tobacco smoke
- We understand the dose-response relationships for several genes



- Task 4.222: **Characterization and Quantitative Application of High-throughput Screening (HTS) and Other Data-mining Derivations**
  - **Subtask 4.222.1:** Methods Development: Estimating points of departure (PODs) from transcriptomic data
    - Initial, necessary proof-of-concept step that focusses on well-characterized transcriptomic data sets from several chemicals
    - Applying Gene Set Enrichment Analysis (GSEA) methodology
    - GSEA allows for the identification of cellular signaling pathways that display coordinated deregulation of gene expression following chemical exposure
    - Expression levels for individual gene members of significantly enriched pathways are analyzed to derive BMD values for individual genes, and allows for comparison of "enriched" transcriptional BMD profiles to those obtained for traditional apical endpoints

GSEA Overview



(A) GSEA is a method to identify classes of genes that are over-represented in a large gene dataset, and may have an association with an apical endpoint/phenotype. Unfiltered transcriptomic datasets from individual animals are scored for enrichment of biologically-derived gene expression signatures via a ranked running-sum statistic method. **(B)** Median transcriptional BMD values compared to those of traditional apical endpoints in rat liver after 2 weeks of tribromobenzene exposure.

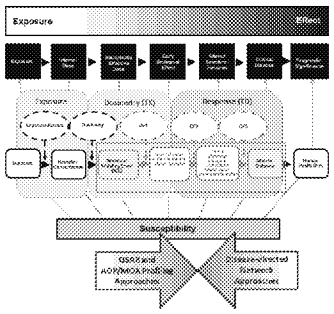
Task 4.222: Accomplishments and Anticipated Products

- **FY16: Manuscript on application of GSEA methods** (Dean J; Zhao J; Lambert JC; Hawkins B; Thomas RS; Wesselkamper S. (In Press). *Application of Gene Set Enrichment Analysis for Identification of Chemically Induced, Biologically Relevant Transcriptomic Networks and Potential Utilization in Human Health Risk Assessment. Toxicol. Sci.*
- **FY17/18: Continue work on additional proof-of-principle subtasks:**
  - **4.222.2:** Characterization of data-derived extrapolation methods for derivation of alternative data-based screening risk estimates based on comparisons to traditional risk estimates
  - **4.222.3:** Adverse outcome pathway (AOP) footprinting: hazard grouping and quantitative analysis for assessment of mixtures of toxicologically uncharacterized stressors

- **Goal is to eventually apply knowledge learned from these subtasks to OLEM-specific case study chemicals**
- **Continue supporting CSS Rapid Tox project**

Project 8 (*HHRA 4.22*) – Applying Emerging Science to Inform Risk Screening and Assessment

- Task 4.223: **Dosimetry21: Advancing Multi-scale Dosimetry Models to Incorporate AOP/MOA and Biomarker Data**
  - **Need:** Define different dose metrics in order to apply and quantify key events of adverse outcome pathways (AOP) and mode of action (MOA) in risk assessment
    - Modernize methods and facilitate consistency across Federal Agencies
    - Support coherent translation, integration, and interpretation of evidence from diverse data sources to support various applications
    - Targeted complement to extant and emerging NRC reports
  - **Approach:** Federal partners develop White paper for review by NRC/BEST to provide perspective on strategic directions
    - Status of current models & necessary measurements
    - Inventory of available tools
    - Strategy for defining dose metrics to fit portfolio of assessments and coherent model implementation
    - NRC/BEST review White Paper to provide perspective on strategic directions

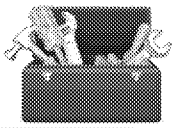


Task 4.223: Accomplishments and Anticipated Products

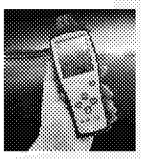
- **FY16/FY17: EPA perspective on dosimetry models**
  - **Manuscript on utility and applications**
  - **Seed resources procured**
- **FY17: Federal participants generate White Paper**
  - **Status of current models & necessary measurements**
  - **Inventory of available tools**
  - **Strategy for defining dose metrics to fit assessment applications and coherent model implementation**
- **FY17/FY18: NRC review with recommendations to implement strategy and vision**
- **FY19+: Agency implementation and anticipated impact**
  - **Provide impetus to modernize methods**
  - **Encourage Federal resource leveraging**
  - **Supports bridging to other public health initiatives**

Project 8 (*HHRA 4.22*) – Applying Emerging Science to Inform Risk Screening and Assessment

- Task 4.224: Evaluation and application of new exposure data and methods
  - **Improving exposure estimates with new and emerging exposure data**
    - **Exposure factors handbook updates**
    - **EcoBox**
    - **ExpoFIRST**
    - **Food consumption rates tool**
    - **Soil ingestion rates (feasibility study and study design under way)**

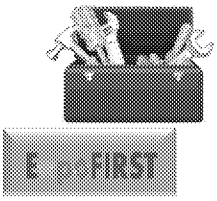


  - **Advancing the Application of Sensor Data for Risk-Informed Decision Making**
    - **Collaboration with ACE, OAQPS, NIOSH Center for Direct Reading and Sensor Technologies**
      - Analytical criteria for characterizing hazards and exposures
      - Approaches for integration of exposure scenarios with dosimetry modeling
      - Guidance on the interpretation of sensor data for risk assessment
      - Good practice recommendations for sensor data management and curation

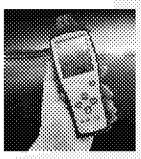


Task *HHRA 4.224* – Accomplishments and Anticipated Products

- **Improving exposure estimates with new and emerging exposure data**
  - **FY16: Release of Exposure Factors Interactive Resource for Scenarios Tool (ExpoFIRST)**
    - Standalone tool that allows users to access data in the *Exposure Factors Handbook: 2011 Edition* to develop user-defined exposure scenarios.
    - Replaces manual calculation and documentation and allows risk assessors to create custom exposure scenarios based on route of exposure, medium, receptor(s), timeframe, and dose metric for a contaminant of concern and use categories
    - Offers a wide range of potential scenarios for various receptor populations and life-stages
  - **FY17: Continued updates**



- **Advancing the Application of Sensor Data for Risk-Informed Decision Making**
  - **FY17:** Development of analytical criteria

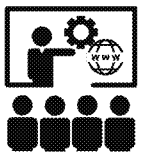


Advancing Analyses and Applications (*cont.*)

- Project 9 (*RMS HHRA 4.23*) – Risk Assessment Support and Training
  (PLs Debra Walsh [NCEA RTP] / Maureen Johnson [NCEA IO])
  - Task 4.231: Development and maintenance of essential software and support tools (e.g, HERO, BMDS, ExpoBox, IRIS website)
  - Task 4.232: Development and application of risk assessment training

HHRA Project 9: Essential Software & Support Tools

- HHRA homepage provides links to all projects: **http://intranet.ord.epa.gov/p2/hhra/home**
  - Integrated Risk Information System (IRIS) Website and database
  - Integrated Science Assessments (ISA) Websites and database
  - Provisional Peer-reviewed Toxicity Value (PPRTV) Website and database
- Health and Environmental Research Online (HERO) database (> 3 million references)
- Benchmark Dose Software (BMDS) Modeling website and training system
- EPA's-Expo-Box Website (EXPO-Box) and database
- Ecological Risk Assessment Support Center (ERASC) website
- Risk Assessment (Risk) Web Portal 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
  - Physiological Information (PID) database.



http://www2.epa.gov/risk

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New landing page for all things risk provides link

Other HHRA Outreach and Technical Support

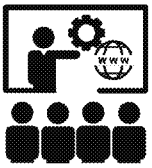
HHRA Bulletin	• Monthly updates about all HHRA program activities • Membership grew from 0 in 2012 to 10,189 in April 2016.
Benchmark Dose Software (BMDS)	• Quarterly updates on new BMDS versions and training opportunities • Membership is 5,519 as of April 2016.
IRIS	• Updates as needed on IRIS Program activities • Membership grew from 700 in 2012 to 3,056 in April 2016.
EPA-Expo-Box	• Periodic messages on updates, new features, and helpful tips • Membership grew from 0 in 2013 to 984 in April 2016

HHRA Project 9: Risk Assessment Training and Experience (RATE) Program

- **Comprehensive training covering critical concepts**
  - Four primary areas of risk assessment.
  - Additional areas: Cumulative risk assessment (CRA), mixtures assessment, microbial risk assessment; Ecological Risk Assessment, risk management, risk communication, and new approaches in human health risk assessment
- **Modular to facilitate tailoring for specific needs**
- **Builds capacity to increase understanding and ensure transparency of assessment activities**
- **Diverse audience and interest indicates impact**
  - **Agency: Program and Region partners**
  - **Scientists working in various sectors around the globe**
    - **Interstate Technology and Regulatory Council (ITRC)-**Currently, all interested risk assessors in the United States and around the globe have free access to this important training material via http://www.itrcweb.org/risk-3/
    - **International** (Ghana, South Africa, Chile, Thailand, Egypt, Saudi Arabia, Dubai, Kuwait, Romania, Switzerland, Singapore, Australia and Canada)
  - **Professional societies: SOT, SRA-** General and specialized training in risk assessment (e.g., BMD)
  - **Academia: University of MD**-Graduate Course in Risk Assessment (MIEH 740: Environmental Risk Assessment)

Project 9 (*RMS HHRA 4.23*): Accomplishments and Anticipated Products

- Task 4.231: Development and maintenance of essential software and support tools (e.g, HERO, BMDS, ExpoBox, IRIS website)
  - FY16:
    - Drupal migration completed
    - Release of Categorical Regression module and training webinars
  - FY17: Webinar training



- Task 4.232: Development and application of risk assessment training
  - **FY16:**
  - **FY17:** Web implementation of 3 RATE modules

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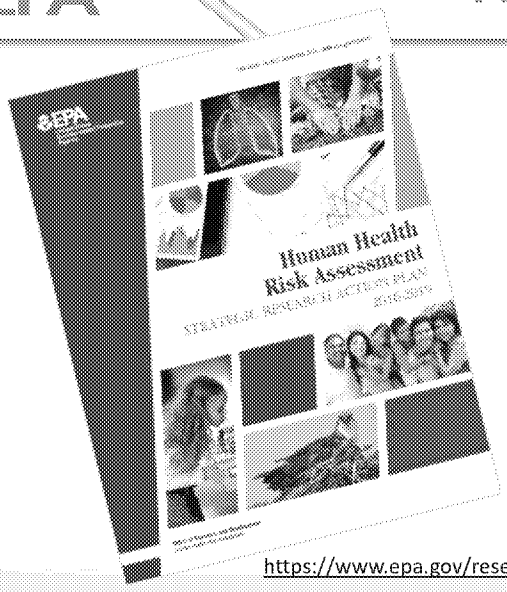
Program Summary



- **Provides a portfolio of assessment products for improved public health**
- **Identifies issues and advances approaches to arrive at solutions**
- **Applies new technologies and data to refine analyses**
- **Supports communities with cumulative risk characterization of multiple stressors on human and ecological health**
- **Educates and engages stakeholders to build capacity**

https://www.epa.gov/research/strategic-research-action-plans-2016-2019