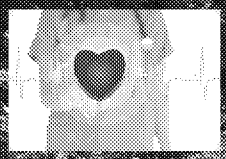
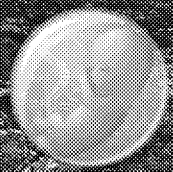
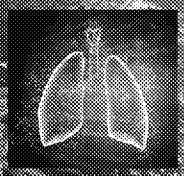
Office of Research and Development

Human Health Risk Assessment Research Program







HHRA Research Program Highlights Briefing: FY17 Q2
February 14, 2017

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

EPA

EPA

Today's Topics

Office of Research and Development

EPA HHRA Research Program Highlights

- **Welcome**
- **Science Spotlight: Dr. Paul S. Price (NERL) "*New Findings on Cumulative Phthalate Exposure Using NHANES Biomonitoring Data*"**
- **Important transitions: Parts 1 & 2**
- **Project progress reports**
- **PACT Status**
- **Partner feedback**

New Findings on Cumulative Phthalate Exposures Using NHANES Biomonitoring Data

Paul Price[1] and Jeanette Reyes[2]
[1]US EPA, RTP, NC; [2]ORISE Research Participant hosted at US EPA, RTP, NC

Science Spotlight
FY17 Q2 HHRA Highlights Briefing
February 14, 2017

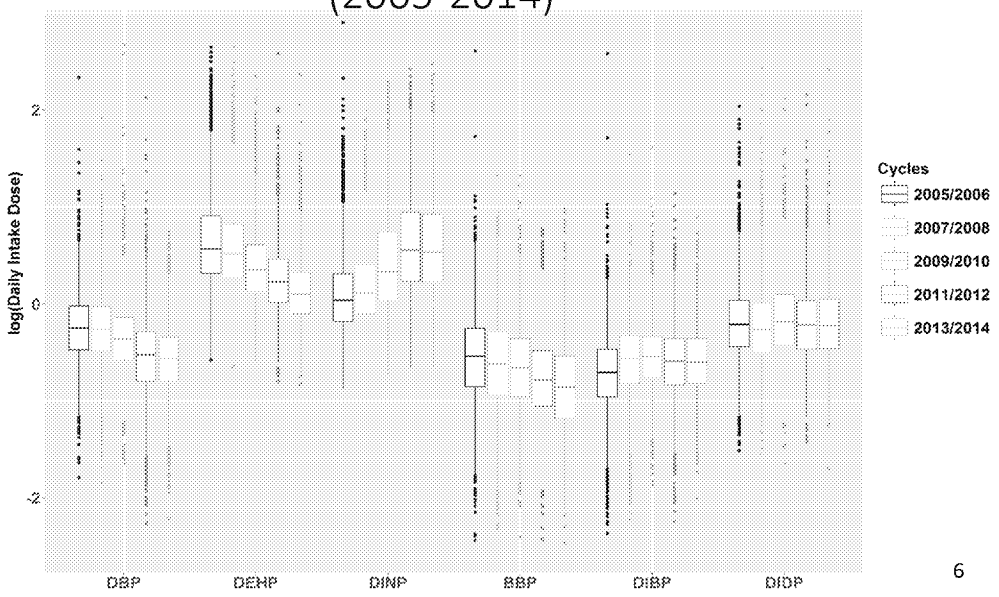
Phthalates

- History of concern over cumulative effects of phthalates (NAS, 2008)
  - Cumulative risk assessment investigating common adverse outcome pathway for reproductive effects
  - Five phthalates (DBP, DiBP, BBP, DiNP, DEHP) associated with a "phthalate syndrome"
- Exposure data
  - Biomonitoring data available from the National Health and Nutrition Examination Survey (NHANES) over the last 14 years
    - Will focus on the 10 most recent years
  - Methodology of converting biomontoring to doses developed by EPA (Christensen et al. 2014) for five phthalates DBP, DiBP, BBP, DiNP, DEHP
    - Estimates of doses are conservative for the most exposed individuals

Today's presentation

- New work
  - Apply the Christensen et al. methodology do three additional cycles of NHANES data
  - Add a sixth phthalate
  - Apply the Maximum Cumulative Ratio technique to determine the pattern of relative contribution of individual phthalates to cumulative risk
- Two findings
  1. A significant decline in estimates of cumulative risk over 2005-2014
  2. Elevated risks are not associated with combined exposures but are due to high levels of one of four phthalates.

Changes in Hazard Quotients and Hazard Indices of phthalates (2005-2014)

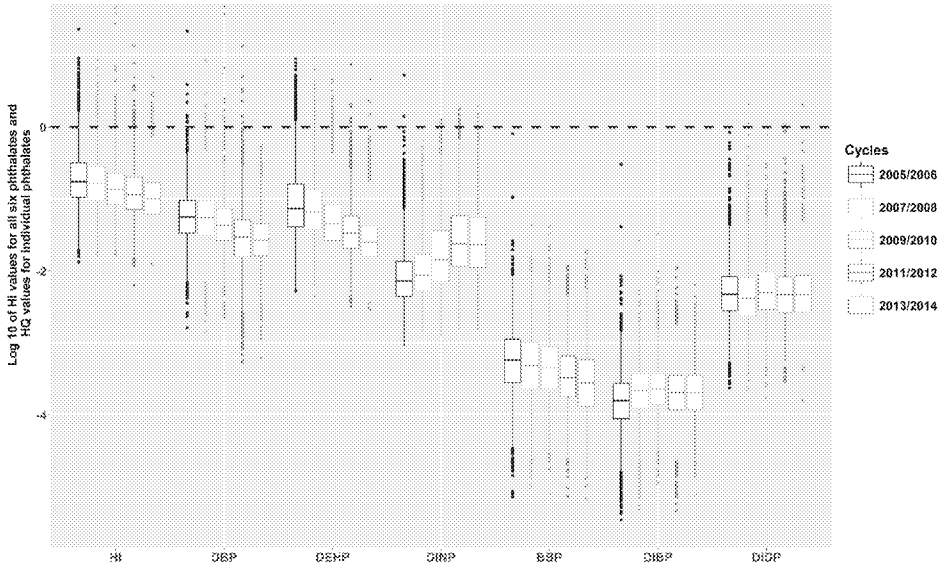


Calculation of the Hazard Quotient and Hazard Index for monitored individuals

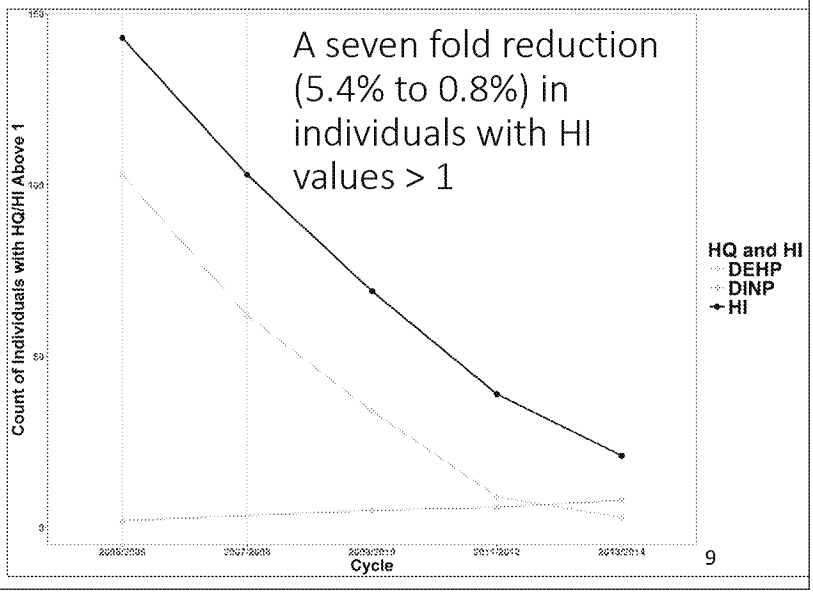
Metric	Description	Equation
HQ	Hazard Quotient	$HQ_i = DI_i / PD_i$
HI	Hazard Index	$HI = \sum_{i=1}^{n} HQ_i$

- Based on dose additivity
- Toxicity values taken from Christensen et al. 2016 and CPSC, 2010

Changes in short-term doses of phthalates 2005-2014



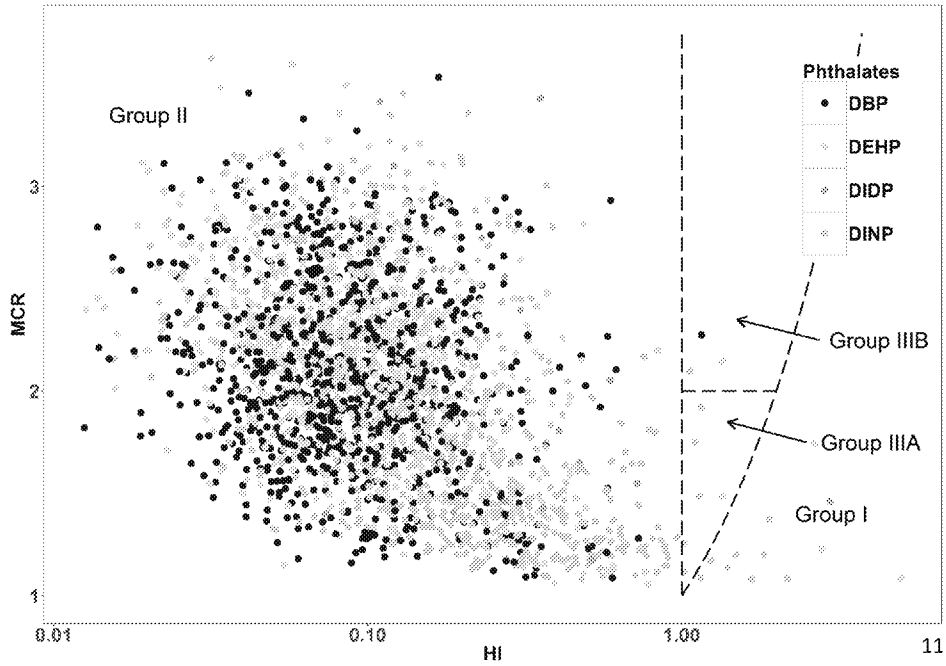
Number of individuals with values >1 for HI, HQ for DEHP, and HQ for DINP



Second finding

- Maximum Cumulative Ratio
  - Not a measure of hazard
  - A measure of the degree that the impact of an individuals combined exposure is driven by one chemical
    - A value close to 1 → one chemical contributes close to 100% of HI
    - A value of 2 → one chemical contributes 50% of HI
- MCR is plotted against HI to show how:
  - Cumulative risk varies over the population
  - The importance of combined exposures varies over the population
  - Phthalates with the largest HQ values varies

HI vs. MCR


Group II
Phthalates
DBP
DEHP
DIDP
DINP
Group IIIB
Group IIIA
Group I
MCR
3
2
1
0.01
0.10
1.00
HI

What does this MCR finding mean?

- A phthalate-by-phthalate approach would have found:
  - 12 of the 2663 individuals had an HQ value>1
  - Range (average) of HQ are 1 – 4.6 (1.8)
- A cumulative assessment would have found
  - An additional 9 individuals with HI values >1
  - Range (average) of HI values in the additional 9 individuals 1 - 1.4 (1.1)
- Conclusion: Performing a cumulative assessment had a measurable but modest impact in the evaluation of phthalates
  - Four phthalates had elevated exposures in small non-overlapping fractions of the population possibly due to rare sources
  - These elevated exposures added to background exposures of the six phthalates that was modest in size (average HI of 0.1).
  - If the phthalate was close to 1, the background exposures could push the total HI slightly over 1

Caveats

- Data are dependent on the toxicity values used in the analyses
  - Standards were based on common endpoints
  - Other standards could change estimates of HI and which phthalates are drivers
- The findings of low values of MCR are not likely to change since they are a function of exposure
- NHANES data has limitations:
  - Does not monitor phthalate metabolites in children under the age of six
    - If infants and small children have sources of exposure that differ from older children then the observed trend may not be relevant
  - Local populations with unique exposure sources would not be captured
- The dose estimation methodology will tend to over estimate doses are the upper tail thus the true fraction of the population HI values greater than 1 could be lower than the values presented here.

Next steps

- Additional research areas
  - Expanded time series to earlier periods
  - Explore including other phthalates
  - Investigate subpopulations based on age and ethnicity
  - Common characteristics of those highly exposed
- Presentation of mixture findings at SOT
- Two publications planned for 2017

Questions?

Back up slides

HI by group and group/age

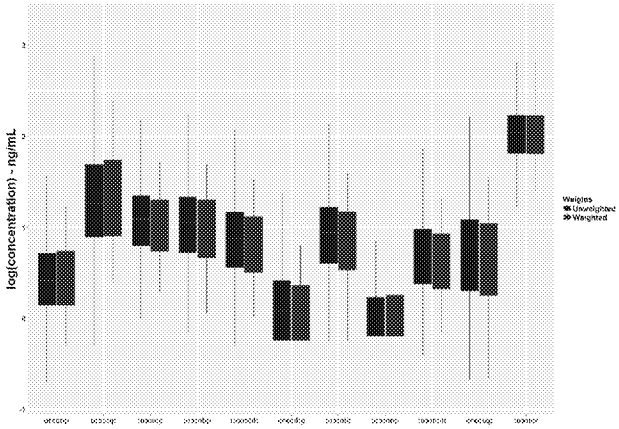
Group	Count	Percent	HI Mean	HI Min	HI Max
I	12	0.5	2.2	1.1	5.0
II	2642	99.2	0.1	0.0	1.0
IIIA	6	0.2	1.1	1.0	1.3
IIIB	3	0.1	1.2	1.1	1.4

		Count		Percent	
		< 18	≥ 18	< 18	≥ 18
Group	I	3	9	0.4	0.5
	II	741	1901	98.9	99.3
	III	5	4	0.7	0.2
	Total	749	1914	100.0	100.0
	I or III	8	13	1.1	0.7

Count of max HQ by Cycle

	2005/2006	2007/2008	2009/2010	2011/2012	2013/2014
DBP	958	1047	1188	754	959
DEHP	1517	1454	1150	895	717
DINP	37	53	351	773	961
BBP	0	0	0	0	0
DIBP	0	0	0	0	0
DIDP	18	25	36	32	26

Weighted vs Unweighted



Data Defaults

- One NHANES cycle – 2013/2014
- 6 phthalates (DBP, DiBP, BBP, DEHP, DiNP, DiDP*)
- DiNP has two metabolites (i.e. MCOP and MiNP*)
- Creatinine excretion correction (instead of using urinary volume)
- Creatinine excretion correction from Mage et al.
- $BD = LOD/\sqrt{2}$
- Permitted dose = Tolerable Daily Intake (TDI)

*In Qian but not in Christensen

Table 2
Reference values (µg/kg-day) used in derivation of hazard quotients and hazard indices

Phthalate, source	EU: (EFSA, 2005a,b,c,d) Tolerable Daily Intake	Denmark EPA: (Toxning et al., 2006)[^] Derived No Effect Level
DEHP	TDI = 50 µg/kg-day (Testis related parameters: ↓ testicular weight, small or aplastic testes, seminiferous tubular atrophy, infertility) (EFSA, 2005c) NOAEL = 5 mg/kg-day (5000 µg/kg-day) Total UF = 100	DNEL = 50 µg/kg-day (effects on gametes and ↓ testicular weight) (Wolfe and Layton, 2003) NOAEL = 5 mg/kg-day (5000 µg/kg-day) AF1 = 4, AF2 = 2.5, AF3 = 10, AF4 = 1 Total UF = 100
DBP	TDI = 10 µg/kg-day (↓ Number of spermatocytes) (EFSA, 2005b) LOAEL = 2 mg/kg-day (2000 µg/kg-day) Total UF = 200	DNEL = 6.7 µg/kg-day (effects on gamete development and development of mammary tissue) (Lee et al., 2004) LOAEL = 2 mg/kg-day (2000 µg/kg-day) AF1 = 4, AF2 = 2.5, AF3 = 10, AF4 = 3 Total UF = 300
BBP	TDI = 500 µg/kg-day (↓ Anogenital distance) (EFSA, 2005d) NOAEL = 50 mg/kg-day (50,000 µg/kg-day) Total UF = 100	DNEL = 500 µg/kg-day (↓ AGD) (Tyl et al., 2004) NOAEL = 50 mg/kg-day (50,000 µg/kg-day) AF1 = 4, AF2 = 2.5, AF3 = 10, AF4 = 1 Total UF = 100
DINP	TDI = 150 µg/kg-day (↑ Incidence of spongiosis hepatis, accompanied by ↑ serum levels of liver enzymes and absolute and relative liver and kidney weights in both sexes) (EFSA, 2005e) NOAEL = 15 mg/kg-day (15,000 µg/kg-day) Total UF = 100	DNEL = 1600 µg/kg-day (↓ testicular weight) (Aristech, 1994) NOAEL = 276 mg/kg-day (276,000 µg/kg-day) AF1 = 7, AF2 = 2.5, AF3 = 10, AF4 = 1 Total UF = 175
DIBP	--	DNEL = 1.250 µg/kg-day (↓ AGD and ↑ nipple retention) (Saillenfait et al., 2008) NOAEL = 125 mg/kg-day (125,000 µg/kg-day) AF1 = 4, AF2 = 2.5, AF3 = 10, AF4 = 1 Total UF = 100

[^] Note: Focus on animal studies of ED effects. Assessment factors (AFs) are (1) interspecies (4 for rats, 7 for mice), (2) interspecies (2.5 for 'remaining interspecies differences'), (3) intraspecies (10), (4) dose response (3 for LOAEL to NOAEL).

CPSC set ADI for DiDP of 130 ug/kg/d

4 Topics and 9 HHRA Projects: Responding to Partner Priorities

- #1) IRIS Assessments
- #2) IRIS Update

See separate Q2 update file

- #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

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

Topic 2 lead: Steve Dutton (NCEA RTP)

- Project 3 (*HHRA 2.21*) - ISAs and Scientific/Regulatory Support (PL Steve Dutton, NCEA RTP)
  - **Task 3.1 (*HHRA 2.211*):** Development of ISAs (TL Steve Dutton, NCEA RTP)
    - Public science workshops
    - Draft and final Integrated Review Plans (IRPs) and ISAs
    - Public Clean Air Scientific Advisory Committee (CASAC) meetings
  - **Task 3.2 (*HHRA 2.212*):** ISA-Related Scientific & Regulatory Support (TL James Brown, NCEA RTP)
  - **Task 3.3 (*HHRA 2.213*):** ISA-Related Science Advancements (TL Jennifer Richmond-Bryant, NCEA RTP)
- **HHRA PACT #2: "ISA PACT"**
  - Weekly meetings with OAQPS; monthly with others as needed

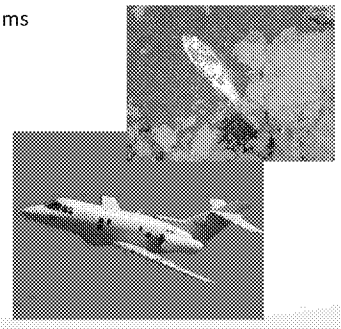
"A five-star process for incorporating science into regulatory policy." Administrative Conference of US (2013)

Task 3.1 (*HHRA 2.211*) Development of ISAs

- FY17 Q1
  - Second draft ISA to support primary (health criteria) NAAQS for oxides of sulfur
    - Released Dec 2016
    - CASAC review scheduled for Mar 20-21, 2017
  - Final IRP to support primary and secondary (welfare criteria) NAAQS for particulate matter
    - Released Dec 2016 by OAQPS with ISA chapter developed by NCEA
    - Working on first draft ISA
- FY17 Q2
  - Final IRP to support secondary (ecological criteria) NAAQS for oxides of nitrogen, oxides of sulfur, and particulate matter
    - Released Jan 2017 by OAQPS with ISA chapter developed by NCEA
  - First draft ISA to support secondary (ecological criteria) NAAQS for oxides of nitrogen, oxides of sulfur, and particulate matter
    - Release scheduled for Feb 23, 2017
    - CASAC review scheduled for May 24-25, 2017

Task 3.2 (*HHRA 2.212*) ISA-Related Scientific and Regulatory Support

- FY17 Q1 and Q2
  - Subtask 3.2.1 (2.212.1) Scientific and Regulatory Support for the NAAQS
    - Support to OAR/OAQPS on the Risk and Exposure Assessment (REA) for the Oxides of Sulfur NAAQS
    - Support to OAR/OAQPS on the Policy Assessment (PA) for the Oxides of Nitrogen NAAQS
    - Litigation and decision support to OGC for Oxides of Nitrogen and Oxides of Sulfur NAAQS
  - Subtask 3.2.2 (2.212.2) Regulatory and Policy Support for Other Programs
    - OAR/OAQPS (ecosystem critical loads; multipollutant science; health messaging)
    - EPA Roadmaps (nitrogen, children's health, climate)
    - SERDP/ESTCP (climate change proposal reviews)
    - NCCT (advancing risk assessment methodology)
    - S. Australia EPA & Taiwan EPA (presentations)
    - Health Effects Institute (liaison committee)
    - ORD/OSP (aircraft GHG and Pb emissions)
    - OAR/OTAQ (rulemaking support)
    - OPPT/OCSPP (azo dye transport)
    - NIEHS (exposure science)
    - OPP (systematic review)
    - OW (Pb support)
    - Regions (RARE)
    - ACE (PACTs)

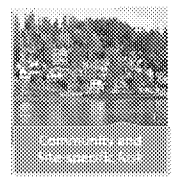


Task 3.3 (*HHRA 2.213*) ISA-Related Science Advancements

- FY17 Q1 and Q2
  - Subtask 3.3.1 (2.213.1) Publications and Scientific Analyses
    - Sparks, A., A. Smith, A. Talhelm, C. Kolden, K. Yedinak, and D. Johnson. Impacts of fire radiative flux on mature Pinus ponderosa growth and vulnerability to secondary mortality agents (International Journal of Wildland Fire. DOI:10.1071/WF16139)
    - Owens, B., M. Patel, E. Kirrane, T. Long, J. Brown, I. Cote, M. Ross, and S. Dutton. Framework for assessing causality of air pollution-related health effects for reviews of the National Ambient Air quality Standards (submitted)
    - Xia, M., A. Talhelm, and K. Pregitzer. Long-term simulated atmospheric nitrogen deposition alters leaf and fine root decomposition (submitted)
    - Deener, K., J. Sacks, E. Kirrane, B. Glenn, M. Gwinn, T. Bateson, and T. Burke. Epidemiology: A Foundation of Environmental Decision-Making (submitted)
    - Chan, E., and J. Currier. Zinc and zinc-dependent proteins in cancer and chemotherapeutics. Molecular and Cellular Toxicology (submitted)
    - Richmond-Bryant, J., M. Snyder, C. Owen, and S. Kimbrough. Factors associated with near-road NO2 concentration gradient size (in clearance)
  - Presentations
    - 16 presentations at national and international conferences

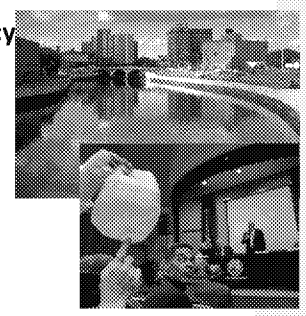
Project 4 (*HHRA 3.2.1*): Provisional Peer-reviewed Toxicity (PPRTV) Assessments

- Project 4 PL: Teresa Shannon, NCEA CIN
- Provisional Peer-Reviewed Toxicity Value (PPRTV) Assessments (TL J. Phillip Kaiser, NCEA CIN)
  - Annually develop ≥ 12 PPRTV assessments as prioritized by OLEM.
    - 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.
  - Status FY17 Q2
    - pCBSA (para-chloro benzene sulfonic acid)
      - Chronic and subchronic oral RfD
    - Now 335 PPRTV assessment documents available online which provide 799 values
    - On target to deliver all in FY17 and FY18 already in process
  - FY17: Continued application of new approaches in appendices as characterization and understanding matures



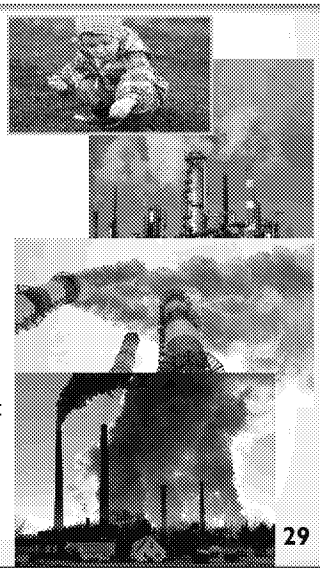
HHRA Project 5 (*HHRA 3.22*): Site-specific and Superfund Regulatory Support

- Project 5 PL: Teresa Shannon, NCEA CIN
- **Provides technical support, consultation and reviews for Superfund and other Agency priorities**
  - Task 5.1 (*HHRA 3.221*) **Quarterly reports to Superfund Technical Support Center (STSC) and Ecological Risk Assessment Support Center (ERASC)** (TL Teresa Shannon, NCEA CIN)
    - FY17Q1 delivered
  - Task 5.2 (*HHRA 3.222*) **Technical consultation and support on Agency priorities** (TL Beth Owens, NCEA CIN and Linda Phillips, NCEA W)
    - Denka facility in LA: Chloroprene
    - Region 5, Manganese: Consultation to Region 5 regarding best exposure levels (reference values) to use for an enforcement action under consent decree that mandated fence-line monitoring at a facility in East Liverpool, OH
      - NCEA RTP helped to develop a "Preventative Action Level" (as measured in PM-10)
    - Tire crumbs
    - Health and education outcomes in R7 near former Pb refinery / smelter

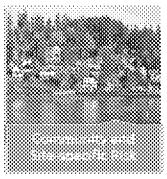


HHRA Project 5 (*HHRA 3.22*): Site-specific and Superfund Regulatory Support (cont)

- **Participation on Agency workgroups**
  - Soil and dust ingestion collaboration with SHC
  - OAQPS, n-Propyl Bromide (nPB): NCEA RTP Staff participated as a member of the nPB HAP-Listing Work Group convened by OAQPS
    - n-PB will be the first chemical to be added to the list of Hazardous Air Pollutants (HAPs) since the Clean Air Act 1990 amendments
    - On December 28, 2016, the US EPA issued a draft notice of the Agency's rationale for granting petitions to add nPB to the list of HAPs
  - OAQPS, Risk and Technology Review (RTR) Program: NCEA RTP staff participates as work group members on a number of RTR, source-category specific regulatory actions, working collaboratively with ORD/OSP to provide an ORD-wide perspective.
    - Brick and Clay Manufacturing: Assist on review of court briefs to support the findings of an adequate margin of safety
    - Serve on workgroups for several other active RTR Source Categories: Pulp & Paper Manufacturing; Asphalt Manufacturing; Ferroalloys Manufacturing; and Portland Cement;



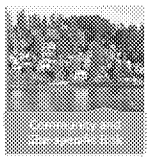
HHRA PACT #3 – PPRTV and Other Priorities: Meetings

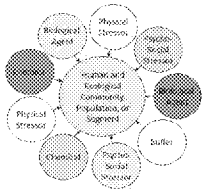


- **PACT Meetings**
  - Bi-monthly meetings with OLEM
  - Bi-monthly meetings with OHHRRAF
- **Standard Operating Procedure (SOP) for chemical selection**
  - Finalized October 2016 and delivered to OLEM
  - Developed to codify and clearly define the process
  - Increases interaction with OLEM HQ and the Regions to include scoping team
  - Breaks chemical selection into two categories:
    - Standard annual process
    - "Fast-track" requests from Regions via the STSC
- **Status FY17 Q2:**
  - 1st Call for chemicals (January 2017) to OLEM, OSRTI and ORD STL
  - Scoping team will meet in March 2017 to identify and prioritize FY19 candidates

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

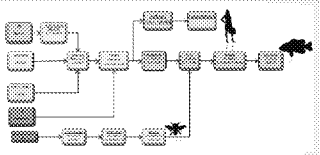
- Project 6 (*HHRA 3.23*) - Cumulative Risk Assessment (CRA) Methods and Applications [PLs Mike Wright (NCEA CIN) / Deborah Segal (NCEA W)]
  - Task 6.1 (*HHRA 3.231*): **Approaches to cross-species data integration to support CRA** (TL Meredith Lassiter, NCEA RTP)
  - Task 6.2 (*HHRA 3.232*): **Incorporating Multiple Stressors** (TL Glenn Rice, NCEA CIN)
  - Task 6.3 (*HHRA 3.233*): **Applying Genetic and Epigenetic Data to Inform Susceptibility** (TL Sue Euling, NCEA W)
  - Task 6.4 (*HHRA 3.234*): **Apportioning Multimedia Exposure and Risk Across Human and Ecological Receptors** (TL Jennifer Richmond-Bryant, NCEA RTP)



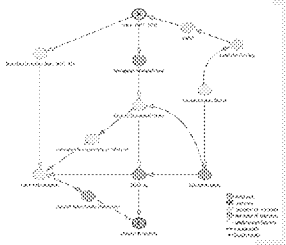


Project 6 (*HHRA 3.23*): Cumulative Risk Assessment Methods and Applications

- Task 6.1 (HHRA 3.231) Approaches to cross-species data integration (collaboration with NHEERL)
  - FY17: Case study illustrating utility of AEP:AOP frameworks to integrate human and ecological endpoints (e.g., the ES-GEAE) and advance mechanistic considerations
  - SOT 2017 RASS Best Abstract Award – Poster (Abstract # /Poster #: 2827/P229) on Wednesday March 15: David Hines et al. *Cross-species integration of human health and ecological endpoints using the Aggregate Exposure Pathway (AEP) and Adverse Outcome Pathway (AOP) frameworks to advance risk assessment*

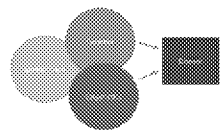


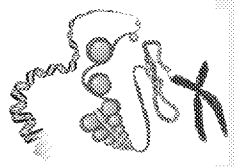
- Task 6.2 (HHRA 3.232) Incorporating multiple stressors
  - Completed early (FY16): Workshop report: Greenspace (GS) exposure and health effects occurrence from a CRA perspective. https://cfpub.epa.gov/ncea/risk/recordisplay.cfm?deid=314417
  - FY16 Q4: Brewer LE, Wright JM, Rice G, Neas L, Teuschler L. (Accepted – galley proof stage). Causal inference in cumulative risk assessment: The roles of directed acyclic graphs. *Environ. Int.*
  - FY17/18: Additional case studies, including: Gernes R, Rice G, Wright JM, et al (In Preparation) Evaluation of Multiple Measures of Residential Greenspace Exposure and Early and Late-onset Allergy Outcomes in the Cincinnati Childhood Allergy and Air Pollution Study (CCAAPS) cohort.



Project 6 (HHRA 3.23) CRA (*continued*): Creating Context for Communities

- Task 6.3 (*HHRA 3.223*) Applying Genetic and Epigenetic Data to Inform Susceptibility (TL Sue Euling, NCEA W)
  - **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)*
      - *Currently running DNA methylation chips and anticipate completion of data collection in Spring*
      - *Analysis thereafter with results in summer*
    - **Literature Review:** Transgenerational Effects, Epigenetics, and Developmental and Reproductive Effects – *Implications for Chemical Testing and Risk Assessment*
      - *Updated draft manuscript with new search; 2 presentations provided by co-author*
    - **Epigenetics and Cumulative Risk Assessment Workshop Report**
  - **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
      - On track; developing different approaches depending on available data with comparisons and advantages / disadvantages





Project 6 (HHRA 3.23) CRA (*continued*): Creating Context for Communities

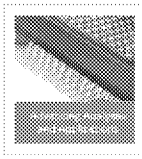
- Task 6.4 (HHRA 3.234) **Apportioning Multimedia Exposure and Risk Across Human and Ecological Receptors (TL Jen Richmond-Bryant)**
  - Targeted to advance and apply methodologies for studying multiple stressor, multimedia exposures
  - **Today's Science spotlight:** *Apportioning chemical stressors for the most affected portions of the populations of human and ecological receptors*
    - SOT 2017 Poster (Abstract # / Poster #: 3536/P511) on March 16: Reyes J and Price P. *An analysis of cumulative risks indicated by biomonitoring data of six phthalates using the maximum cumulative ratio.*
  - Two papers in progress:
    - Modeling cumulative risk from multiple phthalates exposures using the maximum cumulative ratio
    - Trends in NHANES phthalate data

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

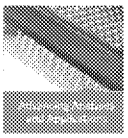
- Task 6.4 (*HHRA 3.234*) *continued*: Cumulative exposures, social determinants, and health in Philadelphia (Richmond-Bryant, Reyes, Gross-Davis)
  - Collaboration with R3 (Gross-Davis)
  - Study addresses how to integrate non-chemical stressors in a community-level cumulative risk assessment (CRA), specifically by testing:
    - What social factors modify associations of health effects with chemical/non-chemical stressors
    - Why exposures to stressors may disproportionately burden vulnerable populations
  - Selected as one of four pilot studies of ORD Social-Environmental Science Exchange (SESE) and thereby receive assistance to
    - Design and implement focus groups related to perceptions of surrounding environment and factors that influence neighborhood environments
    - Address questions related to combining social and environmental data
    - Interpret results from focus groups in a larger context

Topic 4: Advancing Analyses and Applications

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



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



- Task 7.1 (*HHRA 4.211*) **Advancing Methods for Systematic Review and Evidence Integration** (TL Molini Patel, NCEA RTP)
  - No update for FY17 Q2
- Task 7.2 (*HHRA 4.212*) **Advancing Quantitative Methods** (TLs John Fox (NCEA W) / Karen Hogan (NCEA IRIS)
  - Bayesian epi meta-regression software
    - Developed in 2016 and finalized in FY17 Q1/Q2 to support arsenic assessment for evaluation of multiple epidemiological (e.g., case control and cohort) studies in a single meta-analysis.
    - Significant software development as it represents a method that goes beyond existing published methods in several respects, but particularly with respect to an expansion of the types of studies that can be combined in a meta-regression analysis.
  - Model averaging methods – methods currently under development for model averaging (frequentist and Bayesian methods for continuous and dichotomous endpoints)
    - To be presented and discussed at a BMD workshop hosted by the European Food Safety Authority in Brussels, Belgium, March 1st and 2nd.

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

- Task 7.3 (HHRA 4.213): **Advancing Methods for Benefits and Uncertainty Analyses** (TLs Todd Blessinger, NCEA W / Tom Bateson, NCEA W)
  - Case study of exposure-response functions from epidemiology studies that illustrates methodologies showing how those functions can be presented to inform benefits analyses was drafted and shared with OP
  - These same methodological materials are currently intended as part of the appendix materials for the IRIS formaldehyde assessment
  - For completion of the HHRA product in 7.3, explanatory materials and text regarding potential implications of the methodologies are being drafted
- Task 7.4 (HHRA 4.214): **Characterizing Determinants of Risk: Concentration, Duration and Timing of Exposure** (TLs Andrew Hotchkiss, NCEA RTP / George Woodall, NCEA RTP)
  - No FY17 Q2 update
- Task 7.5 (HHRA 4.215): **Science Workshops and Webinars on Major Risk Assessment Methodology Issues (2-4 per year)** (TL David Bussard, NCEA W)
  - On hold due to budget impact

Advancing Analyses and Applications (*cont.*)

- Project 8 (*HHRA 4.22*) – Applying Emerging Science to Inform Risk Screening and Assessment [PLs John Stanek (NCEA RTP) / Jay Zhao (NCEA CIN)]
  - Task 8.1 (*HHRA 4.221*) **Disease-based integration of new data types** (TL Ila Cote, NCEA IO)
  - Task 8.2 (*HHRA 4.222*) **Characterization and Quantitative Application of High-throughput Screening (HTS) and Other Data-mining Derivations** (TL Scott Wesselkamper, NCEA CIN)
  - Task 8.3 (*HHRA 4.223*) **Dosimetry21: Advancing Multi-scale Dosimetry Models to Incorporate AOP/MOA and Biomarker Data** (TL Annie Jarabek, NCEA RTP with IWG/PKWG)
  - Task 8.4 (*HHRA 4.224*) **Evaluation and application of new exposure data and methods** (TLs Jacqueline Moya, NCEA W / Tom Long, NCEA RTP)

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

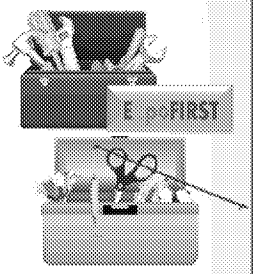
- **Task 8.1 (*HHRA 4.221*) Disease-based Data Integration** (TL Ila Cote)
  - Focus has been inorganic arsenic assessment
    - Manuscripts in preparation on various disease outcomes
    - SOT 2017 Poster (Abstract # /Poster #: 2808 / P210) on March 15 : Druwe et al. Using Data Science to Identify at-Risk Subpopulations Exposed to Ground Water Contaminants: A Case Study of AS3MT in US-Mexican Mestizos and Arsenic Exposure
  - Future work will expand on above approaches and explore other applications of AOP
    - SOT 2017 Poster (Abstract # 2825 / Poster # P227): Jarabek and Harkema. Adverse Outcome Pathway (AOP) for ICL2-mediated Respiratory Epithelial Dysregulation and Remodeling Demonstrated by Inhaled Ozone and Chlorine
    - SOT 2017 Poster (Abstract # 2826 / Poster # P228): Clippinger et al. A Mechanistic Approach Using Adverse Outcome Pathways (AOPs) to Aid Design of *In Vitro* Inhalation Testing

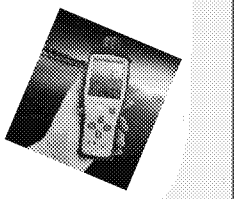
Project 8 (HHRA 4.22): Applying Emerging Science to Inform Risk Screening and Assessment

- **Task 8.2 (*HHRA 4.222*) Characterization and Quantitative Application of High-throughput Screening (HTS) and Other Data-mining Derivations** (TL Scott Wesselkamper, NCEA CIN)
  - Subtask 8.2.1 (RMS ID# HHRA 4.222.1): Manuscript accepted for publication and available electronically ahead of print:
    - Dean JL, Jay Zhao Q, Lambert JC, Hawkins BS, Thomas RS, Wesselkamper SC et al. (2017). 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.* [Epub ahead of print] https://academic.oup.com/toxsci/article-lookup/doi/10.1093/toxsci/kfx021
- **Task 8.3 (*HHRA 4.223*) Dosimetry21: Advancing Multi-scale Dosimetry Models to Incorporate AOP/MOA and Biomarker Data** (TL Annie Jarabek, NCEA RTP with IWG/PKWG)
  - On hold with NRC due to budget impact

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

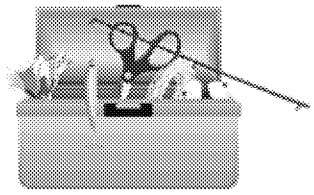
- **Task 8.4 (*HHRA 4.224*) Evaluation and application of new exposure data and methods (TLs Jackie Moya, NCEA W and Tom Long, NCEA RTP)**
  - The updated Chapter 5 -Soil and Dust Ingestion of the Exposure Factors Handbook was released for internal review on 2/7.
  - Eco-Box will be released for internal review on 2/9.
  - Food Consumption tool is expected to be released for internal review in March.
- **Advancing the Application of Sensor Data for Risk-Informed Decision Making**





What is EPA-Eco-Box?

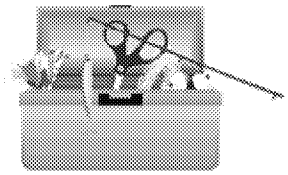
- Web-based compendium of links to ecological risk assessment tools
- One-stop shopping for ecological risk assessors
- Organized by Topic Areas
- User-friendly format
- Companion to EPA-Expo-Box
- Currently under development



To view draft website:
Login using your LAN/Wan ID and password at: https://wcms.epa.gov/user/login
Use the following link to access the draft website: https://wcms.epa.gov/ecobox

EPA-Eco-Box Features

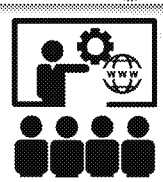
- Annotated Links to Over 400 Tools
  - Databases
  - Models
  - Guidance documents
  - References
- Organized into 4 Tool Sets
  - Stressors
  - Exposure Pathways
  - Receptors and Exposure Factors
  - Effects
- Search Interface
- Additional Resources
  - Basic information
  - Frequently asked questions
  - Join mailing list
  - Contact us / provide suggestions



Advancing Analyses and Applications (*cont.*)

- Project 9 (*RMS HHRA 4.23*) – Risk Assessment Support and Training (PLs Maureen Johnson, NCEA IO / Reeder Sams, NCEA RTP)
  - Task 9.1 (*HHRA 4.231*): **Development and maintenance of essential software and support tools (e.g, HERO, BMDS, ExpoBox, IRIS website)** (TLs Maureen Johnson, NCEA IO / Reeder Sams, NCEA RTP)
  - Task 9.2 (*HHRA 4.232*): **Development and application of risk assessment training** (TL Abdel Kadry, NCEA IO)

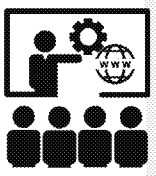
Project 9 (HHRA 4.23): Risk Assessment Support and Training



- **Task 9.1 (*HHRA 4.231*) Development and maintenance of essential software and support tools (e.g, HERO, BMDS, ExpoBox, IRIS website)**
  - EPA updated the OneEPA website template in mid-December based on recommendations from user evaluations and a Government-wide workgroup
    - New design is easier to read, a larger font, and more friendly on mobile devices.
    - This update was made on the Drupal part of the website and replicated to the standalone portions of our site which impacted IRIS, ISA's, Expo-Box, RISK, ERASC, and the exposure factors program pages with minimal changes made to the way the web pages are displayed.

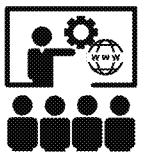
Project 9 (HHRA 4.23): Risk Assessment Support and Training

- **Task 9.2 (*HHRA 4.232*) Development and application of risk assessment training**
- **Risk Assessment training to scientists from the Chinese Environmental Protection Agency. Beijing China, November 21-25, 2016.**
  - NCEA team provided full four day's course consists of fifteen modules, and includes cases of application of risk assessment in various challenges throughout the course. Instructors: Mary Ross, Jason Fritz and Teneille Walker
- **NCEA provided training at the Society for Risk Analysis (SRA) Annual Meeting, California, USA December 11-15, December 2016.**
  - **Categorical Regression Modeling**. Course Instructors: J. Allen Davis; Jeff Gift, and Jay Zhao
  - **Exposure-Response Array Training.** Course Instructors: George Woodall, and Ingrid Druwe.
- Full semester (fall 2016) of graduate course work on **Environmental Health Risk Assessment** to the graduate students at University of Maryland, College Park, MD. NCEA instructors: Abdel Kadry, Jason Fritz, Mathew Lorber, Barbra Glenn Meredith Lassiter, Allen Davis, Jeff Gift and Yu-Sheng Lin
- FY17: Work in progress on **web implementation of three basic modules** of the rate program: 1) Risk Assessment Basics (RAB) 101: Introduction to Risk Assessment; 2) RAB 102: Laws and Regulatory Foundation for Risk Assessment; and 3) RAB 103: Overview of Human Health and Ecological Reference Values



Software, Support and Training PACT: Project 9 (HHRA 4.23) cont.

- 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

48

New landing page for all things risk provides link

Other HHRA Outreach and Technical Support

HHRA Bulletin	• Monthly to bi-monthly updates about all HHRA program activities • Membership grew from 0 in 2012 to 12,854 in November 2016
Benchmark Dose Software (BMDS)	• Periodic updates on new BMDS versions; including new categorical regression (CatReg) module, new developments activities such as model averaging, and training opportunities • Membership is 5,519 as of November 2016
IRIS	• Updates as needed on IRIS Program activities • Membership grew from 700 in 2012 to 3,287 in November 2016
EPA-Expo-Box	• Periodic messages on updates, new features and helpful tips; most recent message sent September 2016 to announce release of ExpoFIRST • Membership grew from 0 in 2013 to 1,215 in November 2016

EPA

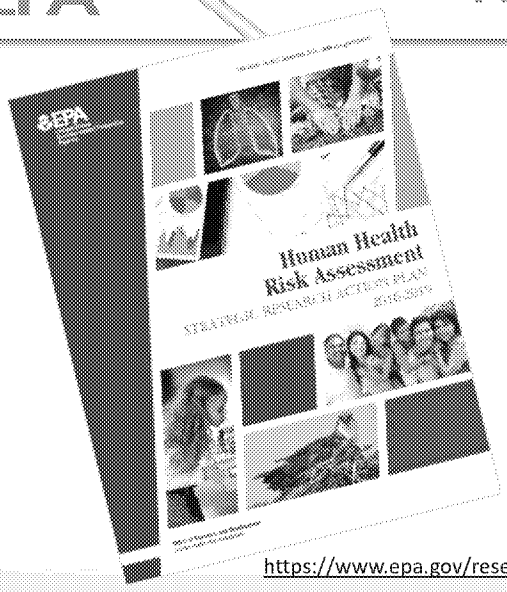
Project and PACT Updates: Continued Partner Engagement

- **Quarterly HHRA Highlights briefings: Q3 on May 9 and Q4 on July 11, 2017**
- **HHRA Project Alliance and Coordination Team (PACT) meetings**
  - **Project-specific participation: IRIS Public Science meetings, Bi-monthly PPRTV meetings, other**
  - **Other PACT Meetings to be 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

EPA

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