

Office of Research and Development

Health and Environmental Risk Assessment



Looking Closer - Overview of the Research Areas in HERA StRAP

May 13, 2020



Digging Deeper into the HERA RAs

Topic	Research Area
Science Assessments & Translation	1. Science Assessment Development
	2. Science Assessment Translation
Advancing the Science and Practice of Risk Assessment	3. Emerging and Innovative Assessment Methodologies
	4. Essential Assessment and Infrastructure Tools



Topic I – Science Assessments and Translation



Science Assessments and Translation

	Science Assessment Development	Science Assessment Translation	
Research Area 1	<p>Focused on producing high quality, transparent, consistent, and scientifically defensible assessment products to meet EPA’s diverse statutory and policy needs.</p> <p>*Priorities come from Congress and EPA program offices; peer reviewed by groups such as NAS, SAB, CASAC.</p>	<p>The range of tailored support activities, modules, and applications developed to address the requests from EPA program and regional offices, states, and tribes for technical support and consultations.</p>	Research Area 2

- Largely comprised of the portfolio of assessment products developed under well-established product lines yet maintains the agility to produce emerging fit-for-purpose assessment products as requested by Agency programs and regions.

Outputs

1.1 Portfolio of interim assessment products to support decision-making

1.2 Portfolio of final assessment products to support decision-making

The Integrated Science Assessments



- Dig deeper at <https://www.epa.gov/isa>
- Concise evaluation and synthesis of the most policy-relevant science supporting the primary (health-based) and secondary (welfare-based) National Ambient Air Quality Standards

Other Targeted Assessments

- Part of the EPA’s PFAS Action Plan, developing final toxicity assessment for perfluorobutane sulfonic acid (PFBS), a replacement chemical for PFOS



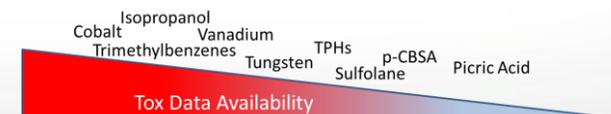
Integrated Risk Information System



- Dig deeper at <https://www.epa.gov/iris>
- Provides scientific evaluation of potential adverse health effects that may result from exposure to substances found in the environment.

Provisional Peer-Reviewed Toxicity Value Assessments

- Dig deeper at <https://www.epa.gov/pprtv>
- Provides hazard and dose-response assessments for priority chemicals for Superfund and RCRA programs





Research Area 2 – Science Assessment Translation

- Includes the range of tailored support activities, modules, and applications developed to address requests for technical support and consultation based on HERA assessment product applications and risk assessment issues, or requests through the ORD Superfund Technical Support Centers (TSCs).

Outputs

2.1 Technical support to EPA regions and states through the STSC and ERASC

2.2 Core translational research modules for expert technical support

Output 2.2

Core translational research modules for expert technical support

Technical support to regions and states and
Translational Research Modules for expert support

Emma Lavoie
CPHEA/IO

Output Lead: Emma Lavoie





Technical Support Centers

- Superfund and IRIS hotlines
 - Address regional questions translating existing assessment science or filling gaps such as:
 - Potential for risks by other exposure routes
 - Understanding if new science influences risk
- Ecological Risk Assessment
 - Provides technical reports to support ecological risk assessors
 - E.g., “Separating Anthropogenic Metals Contamination from Background: A Critical Review of Geochemical Evaluations and Proposal of Alternative Methodology,”





Recent Highlights of Program Office Support

- PCB Exposure Level Estimation Tool
- GenX Chemicals Human Health Assessment
- Lead and Copper Rule
- Hazardous Air Pollutant listing and de-listings
- Risk Technology Reviews
- Bench Mark Dose Modelling Support
- Broad support for TSCA:
 - Toxicology
 - Epidemiology
 - Modelling
 - Statistics
 - Systematic Review

Developing workflows

The screenshot shows the IRIS General Program Support dashboard. At the top, there is a navigation bar with the IRIS logo, 'Project Online', 'Project Sites', 'PPRTV', and 'IRIS Program'. The main heading is 'General Program Support'. A left-hand navigation menu includes 'Dashboard', 'All Tasks', 'Documents', 'OneNote', 'Support Request Form', and 'Support Request Summary'. The 'Dashboard' item is highlighted. The main content area contains a link: 'Click [HERE](#) for the General Program Support SOP'. Below this is a 'Project Summary' section with a grey box that says 'Congratulations, We're all done!'. At the bottom, there is a 'Documents' section.

The screenshot shows the IRIS TSCA Support dashboard. At the top, there is a navigation bar with the IRIS logo, 'Project Online', 'Project Sites', 'PPRTV', and 'IRIS Program'. The main heading is 'TSCA Support'. A left-hand navigation menu includes 'Dashboard', 'All Tasks', 'Calendar', 'Decisions', 'Documents', 'OneNote', 'Restricted', 'Support Request Form', 'TSCA Next 20 Risk Evaluation Support – March 2020', and 'EDIT LINKS'. The 'Dashboard' item is highlighted. The main content area contains a welcome message: 'Welcome to the TSCA Support Sharepoint'. Below this is a link: 'Have questions or comments on this site? Email soto'. A list of links includes: 'Guidance for Data Extraction of animal studies', 'Guidance for Data Evaluation Distiller Form (An', 'Guidance for Data Evaluation of Epi studies ava', 'Epi Extraction Template - example available [HE](#)', 'Epi review additional information available [HER](#)', 'Epi prioritized study list available [HERE](#)', and 'MARCH 2019 - updated Epi QC list [HERE](#)'. Below this is a section titled 'Links to TSCA Problem Formulation Documents' with a list of links: 'Asbestos', '1-Bromopropane', 'Carbon Tetrachloride', '1, 4 Dioxane', and 'Hexachlorobromide Cluster (HBCD)'.

Process for Program Support (including TSCA Requests)

There are 4 ways a request could come to CPHEA from the program offices:

- 1) A request may come from senior or division director management when they need particular expertise for a chemical and the request is directed to CPHEA directly
- 2) Program office staff knows an expert in CPHEA and sends a discrete task/request to a staff member
- 3) Requests that come from OSAPE (ie, action development or agency review)
- 4) CPHEA staff receives a request from a program office



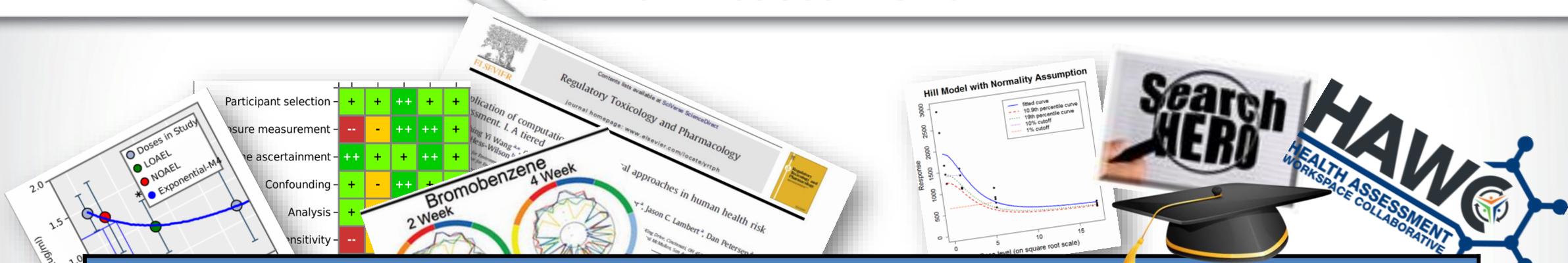
TSCA Risk Evaluations

- Expert support for first ten risk evaluations
- Applying systematic review experience to innovate the workflow for systematic review contributing to TSCA scoping documents.
- There will be ongoing demand and it will require responsive strategies and workflows.
- Reflection on program support activities and modifying approaches for continuing improvement

The screenshot shows the EPA website header with the EPA logo and the text "United States Environmental Protection Agency". The navigation bar includes "Environmental Topics", "Laws & Regulations", and "About EPA", along with a search bar for "Search EPA.gov". The main content area is titled "Assessing and Managing Chemicals under TSCA" and includes a "CONTACT U" link and social media share icons for Facebook, Twitter, and Email. A sidebar on the left lists several related topics: "Assessing and Managing Chemicals under TSCA Home", "How EPA Evaluates the Safety of Existing Chemicals", "Prioritizing Existing Chemicals for Risk Evaluation", "Risk Evaluations for Existing Chemicals Under TSCA", and "Current Chemical Risk Management Activities". The main article is titled "Application of Systematic Review in TSCA Risk Evaluations" and contains the following text: "The first document below, EPA's Application of Systematic Review in TSCA Risk Evaluations, will guide the Agency's selection and review of studies and provide the public with continued transparency regarding how EPA plans to evaluate scientific information. Read the [Federal Register notice](#) announcing the availability of this document. EPA's approach to systematic review will be available for comment until August 16, 2018 in docket EPA-HQ-OPPT-2018-0210." Below the article text, it states: "EPA's initial work on systematic review was described in the supplemental files for each TSCA scope".



Topic 2 – Advancing the Science and Practice of Risk Assessment



Advancing the Science and Practice of Risk Assessment

Research Area 3	Emerging and Innovative Assessment Methodologies	Essential Assessment and Infrastructure Tools	Research Area 4
	Focused on incorporating new and innovative methodologies in predictive toxicology, rapid evidence evaluation, systematic review, and toxicokinetic and dose-response modeling across a landscape of decision contexts and assessment products	Supports maintenance and development of new and existing tools and databases used in the assessment process and provides training on such tools and resources to stakeholders	



RA 3 – Emerging and Innovative Assessment Methodologies

- Focus on increasing transparency and reducing uncertainty in assessment science and conclusions, and accelerating the pace of assessment development
 - enhancing hazard identification,
 - expanding the repertoire of dose-response methods and models,
 - characterizing the utility of emerging data and new computational tools as applied to risk assessment
- Focus on evaluating and optimizing integration of existing, new, and emerging data streams, techniques, models, tools, or other methodologies for practical implementation in assessing human and environmental health.
- Both interpretation of new data streams and improvements in the assessment of traditional data are needed and are complementary in supporting Agency decision making.

Outputs

3.1 Advance, translate, and build confidence in the application of new approach methods (NAMs) and data in risk assessment



3.2 Conduct case study application of rapid assessment methodologies to inform parameters of interest to risk decision contexts



3.3 Evaluate and develop improved methods for dose extrapolation and the related uncertainty characterization in human health risk assessment via classical methods and integration of pharmacokinetic models



3.4 Advance methods for systematic review, including evidence integration

3.5 Advance methods in dose-response modeling with application to risk assessment

Output 3.1

Advance, translate, and build confidence in the application of new approach methods (NAMs) and data in risk assessment

Overview of Strategy and Implementation of New Approach Methods (NAMs) in HERA

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Output Lead: Luci Lizarraga





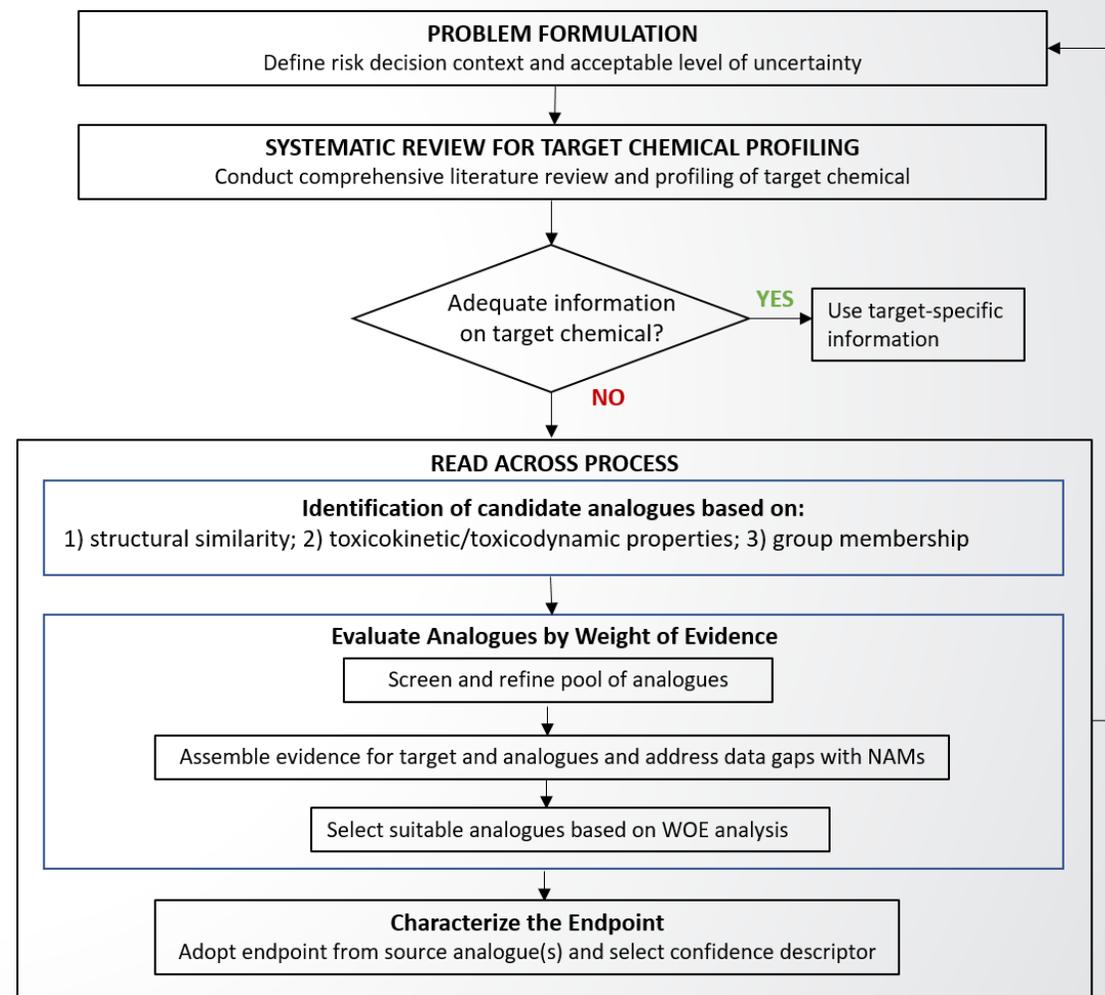
Problem Formulation

- EPA programs and regions are tasked with addressing potential hazard(s) to human health and the environment of chemicals with varying hazard and dose-response databases for several risk decision contexts
- Integration of NAMs in chemical assessments can be useful and should be considered in a fit-for-purpose manner starting with a high level decision gradient:
 - Data-poor chemicals → NAM may be a driver
 - Data-rich chemicals → NAM fills a data gap
- NAMs currently being integrated or evaluated for application in HERA include:
 - Read-across
 - Transcriptomics
 - In vitro bioactivity
- Other NAM-related efforts - transparency principles of systematic review and integration of toxicity pathway (e.g., AOP or MOA) information are also paramount



Advancing the practice and application of read-across in human health risk assessment

- Read-across has been routinely applied to support screening-level quantitative assessment of data-poor chemicals within the Superfund program
- A revised read-across methodology is proposed, incorporating past experiences, scientific advances in the field of read-across and the use of NAM data and tools
- These efforts will continue to address data gaps for chemicals of interest to the Superfund and other Agency-wide activities, and will expand the scope and decision context of read-across applications within HERA





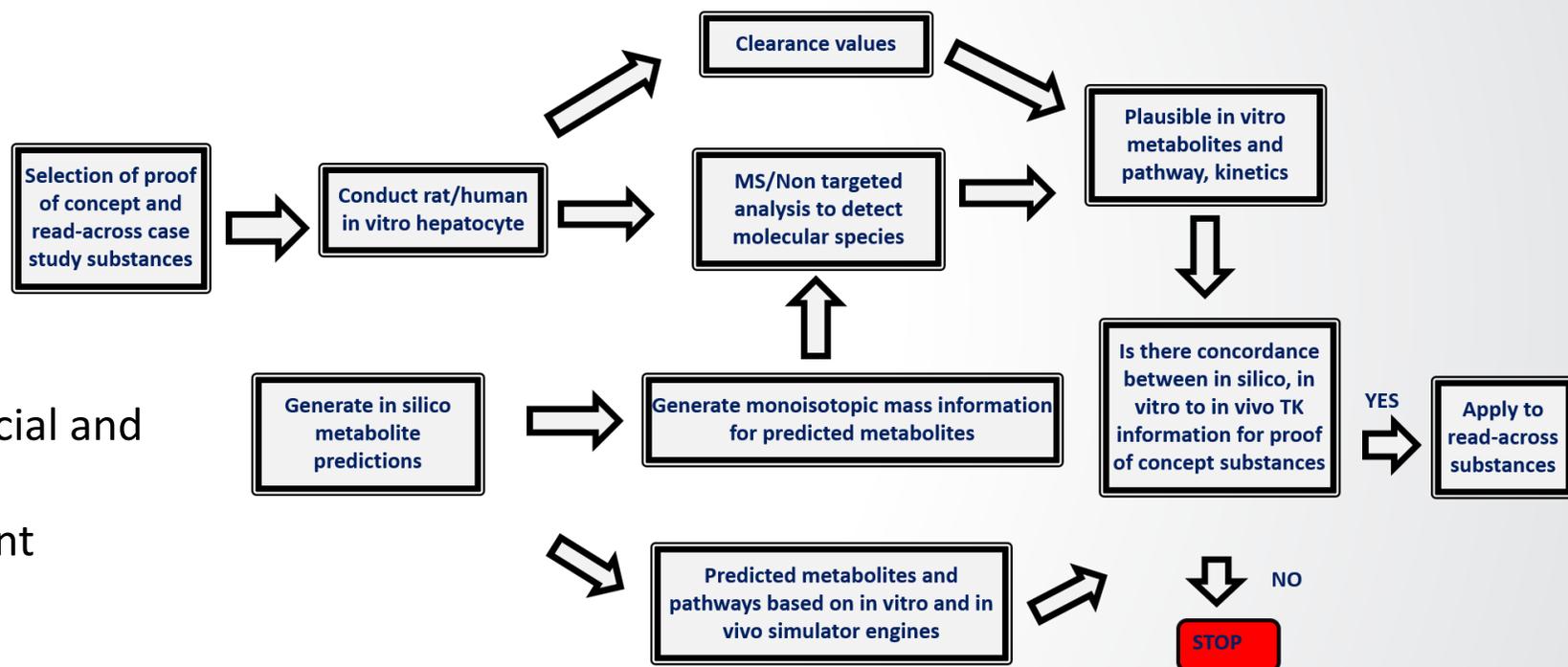
Integrated approach for evaluating metabolism data gaps

- Understanding the potential role of metabolism in the detoxification/bioactivation of xenobiotics is critical for chemical hazard evaluations but information in humans or experimental animal models is only available for a number of well-studied chemicals
- A combination of NAM tools developed under CSS will be explored to characterize metabolism profiles and fill data gaps
- Case studies will demonstrate the utility of these tools to inform chemical assessments, including their potential application in read-across

Workflow incorporating metabolic information to evaluate analogue suitability in read-across

- Metabolism profiles for 32 chemicals (including chemicals being evaluated for read-across) will be determined by aggregating data from multiple sources:

- 1) *In silico* predictions using commercial and publicly available software tools
- 2) *In vitro* metabolism and subsequent analysis via high resolution mass spectrometry (RMS)
- 3) *In vivo* literature review



- This work will be used to enhance the Generalized Read-Across (GenRA) approach developed under CSS

- Previous work has demonstrated concordance between point-of-departure (PODs) derived from transcriptomics data with those derived from apical adverse outcomes

TOXICOLOGICAL SCIENCES **120**(1), 194–205 (2011)
doi:10.1093/toxsci/kfq355
Advance Access publication November 2

TOXICOLOGICAL SCIENCES
doi:10.1093/toxsci/kft
Advance Access publi

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TOXICOLOGICAL SCIENCES, 157(1), 2017, 85–99

Toxicology and Applied Pharmacology 380 (2019) 114706

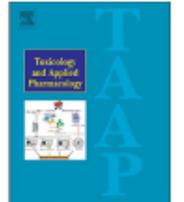
Contents lists available at [ScienceDirect](#)

Toxicology and Applied Pharmacology

journal homepage: www.elsevier.com/locate/taap



ELSEVIER



Applicatio
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The use of evidence from high-throughput screening and transcriptomic data in human health risk assessments

Roman Mezencev*, Ravi Subramaniam

Integrated Risk Information System (IRIS), National Center for Environmental Assessment, Office of Research and Development, U.S. Environmental Protection Agency, Washington DC, United States of America

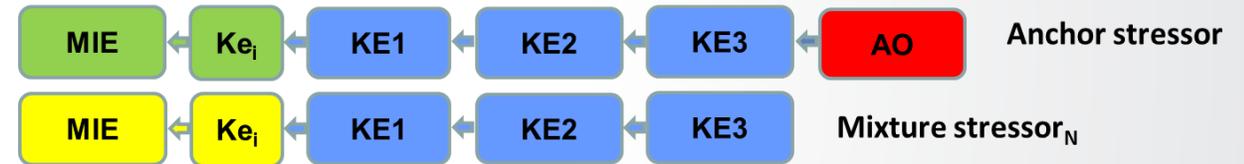




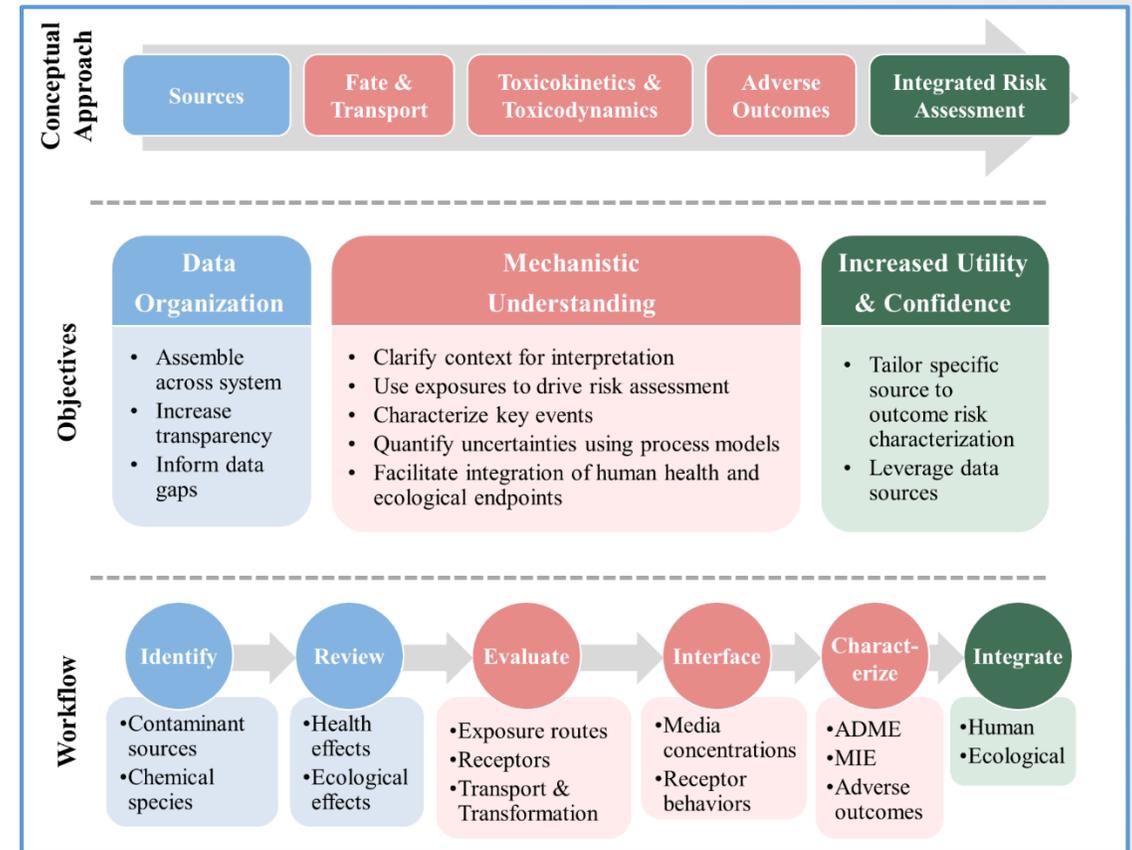
Application of transcriptomic data in qualitative and quantitative risk assessment

- Ongoing proof-of-concept case studies will explore the use of gene expression data to inform mechanistic insights, qualitative hazard conclusions and dose-response assessment to support HERA-related assessment products:
 1. Use Gene Set Enrichment Analysis to identify relevant molecular pathways in the response to chemical mixtures to inform dose-response addition or sufficient similarity in mixtures risk assessment
 2. Development of models for predicting genotoxicity and carcinogenicity integrating gene expression data and bioactivity data from EPA's ToxCast database to inform cancer risk assessment

- The lack of hazard and dose-response data for mixtures of chemicals have limited significant progress in mixtures risk assessment
- The goal of this analysis is to identify key event(s) within an adverse outcome pathway (AOP) at which similarity between mixture chemicals can confidently be determined. These key events are identified as the ‘footprint’ for a given AOP
- Case studies will demonstrate how mechanistic information (e.g., AOPs) could be used to inform mixtures assessment applications such as hazard grouping and dose-response analysis



- HERA has made advancements in the area of risk assessment across species by developing techniques to address challenges of integrating human health and ecological endpoints into risk assessments by combining the Aggregate Exposure Pathway (AEP) and AOP frameworks
- Techniques for integrating mechanistic human health and ecological endpoint data are designed to inform specific use cases or site-specific cumulative risk assessment across multiple species





Closing remarks

- NAMs can assist in accelerating the pace and transparency of chemical assessments across a landscape of decision contexts and hazard/dose-response database needs
- Output 3.1 aims to develop, advance and build confidence in the practical implementation of emerging technologies and data streams, clearly articulating the advantages, limitations and uncertainties in the application of these approaches
- Involves coordination and collaborative research efforts between scientists within the HERA and CSS National Research Programs
- Integration of NAMs to support assessment products and technical support efforts within HERA to meet the chemical assessment needs of EPA partners and stakeholders



Acknowledgements

Output Contributors

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CCTE

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Output 3.2

Conduct case study application of rapid assessment methodologies to inform parameters of interest to risk decision contexts

Systematic Review Tools: Systematic Evidence Maps (SEM)

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- Pre-decisional analysis that uses systematic review methods to compile and summarize evidence but does NOT reach assessment hazard or reference value conclusions
 - Front end compilation of evidence useful for assessment products
 - Publishable in journals
- Used for:
 - Problem formulation and scoping
 - Staff resource allocation, timeframes
 - Prioritization
 - Need for assessment update?
 - Identifying data gaps
- Began creating SEMs in 2019, now becoming a routine analysis



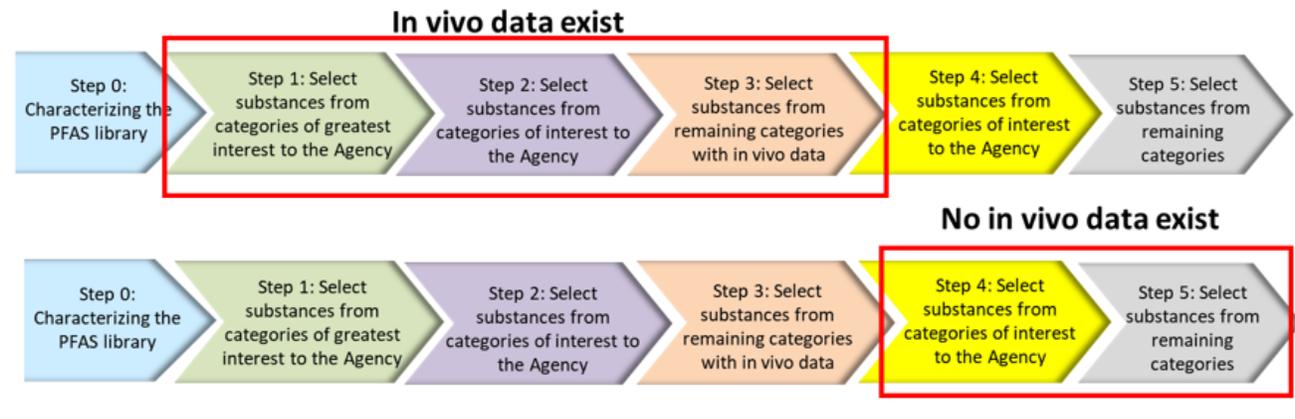
Systematic Evidence Maps (SEM)

- Rapid preparation – weeks to a few months in most cases with experienced teams and use of specialized software
- Use of standardized template format reduces time to prepare and review
- Highly visual with interactive displays and structured data entry that is made available to the public
- Can be tailored to meet decision making needs
- Results can be disseminated in reports, interactive data interfaces, e.g., EPA CompTox Chemicals Dashboard



Per- and Polyfluoroalkyl Substances (PFAS) SEM

- One component of the 2019 EPA PFAS Action Plan involves the use of new approach methods to help fill information gaps. This ongoing work involves tiered toxicity testing of a structurally diverse landscape of PFAS using a suite of in vitro toxicity and toxicokinetic assays
- One goal is to use existing in vivo toxicity data to infer (read-across) missing information for a similar PFAS target (similarity starting point is “structural similarity”).
- SEM conducted to help identify in vivo data for 100+ PFAS



- Use information from the CompTox Chemicals Dashboard to create higher throughput methods to search for many chemicals at a time (can be automated process)
- Search journal databases (PubMed, WoS, ToxLine) and grey literature from CompTox Chemicals Dashboard ToxVal database and manual searches for additional studies
- Used machine-learning tools to reduce screening effort by ~60%
- Create interactive literature inventories to show extent and nature of the evidence
- Conduct full data extraction and study evaluation on animal toxicology studies of repeat dose, developmental or reproductive design
 - A related analysis is focusing on the epidemiological data (likely will be journal article)
- Publish report + make information accessible via CompTox Chemicals Dashboard



Example PFAS SEM Literature Inventory: Animal Studies

ReadMe Animal Studies Human Studies

Toxicological Studies Examining Exposure to PFAS by Study Design and Health System

Heat Map

	acute							short-term			developmental, F1			
	mouse	rat	guinea pig	rabbit	dog	hamster	not repo..	mouse	rat	not repo..	mouse	rat	rabbit	not repo..
Cancer														
Cardiovascular		3			4			10			4			
Dermal		1						2			2			
Developmental											19	3	1	
Reproductive		4					1	11			18	3		
Endocrine								11			5			
Exocrine		1									3			
Gastrointestinal		7						7			3			
Hematologic								12			6			
Hepatic	1	8	1		1		5	16			9	1		
Immune		4					3	12			4			
Lymphatic							1							
Metabolic								3		1	3			
Musculoskeletal/Connect..								7			2			
Nervous	2	6						10			6			
Ocular	1	3						4			3			
Renal	1	8					1	12			8			
Respiratory	1	12						10			2			

Notes: Column totals, row totals, and Grand Totals indicate total numbers of distinct references. Some ECHA studies sources may be counted as multiple references in these counts, based on how data were reported in the dossier. Care was taken during categorization and extraction to ensure that endpoints were not repeated from overlapping ECHA summaries.

References

- 3M (1999)
- Anand et al. (2012)
- Apollo Scientific Ltd. (2019) (ECHA Summ..)
- Bodin et al. (2016)
- Bomhard and Loser (1983)
- Case et al. (2001)
- Covance Laboratores (2000)
- DuPont (1990a)

Chemicals Evaluated - by Name

1-Butanesulfonic acid, 1,1,2,2,3,3,..	1
1H,1H,2H-Perfluorocyclopentane	6
1H,1H,5H-Perfluoropentanol	1
2-Chloro-1,1,1,2-tetrafluoroethane	13
3-Methoxyperfluoro(2-methylpent..	3
3,3,4,4,5,5,6,6,6-Nonafluorohexene	5

Chemicals Evaluated - by CASRN

76-05-1	14
307-35-7	1
335-27-3	2
335-99-9	2
338-83-0	1

Chemicals Evaluated - by DTXSID

DTXSID0036926	2
DTXSID0059879	1
DTXSID0061826	8
DTXSID1032646	2
DTXSID1074915	4
DTXSID2044397	4
DTXSID3038939	2

Study Details

Health System	Study Design	Route	Species	Sex	Short Citation
Cancer	chronic	inhalation	rat	both	Haskell Laboratories (1995) Malley et al. (1998)
Cardiovascular	acute	inhalation	rat	male	DuPont (1992b)
			dog	male	DuPont (1992d)
				not reported	Unnamed Report (1992b) (ECHA Summary) DuPont (1994)

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Example PFAS SEM Literature Inventory: Human Studies

ReadMe Animal Studies Human Studies

Epidemiological Studies Examining Exposure to PFAS by Study Design and Health System

Heat Map

	case-control				cohort				pregnant women	inf
	pregnant women	infants	children	general population	pregnant women	infants	children	occupational		
Cancer				5				2		
Cardiovascular				1				1		1
Developmental						6	4			
Reproductive	1			2	3		2	1	3	4
Endocrine		1			3	2		1	2	2
Hematologic										1
Hepatic								1	1	1
Immune			2			2	4			1
Metabolic				1				1	2	1
Nervous							4			
Other									1	
Renal								1	1	1
Respiratory		1								
Systemic/Whole Body								1		
Grand Total	1	2	2	9	6	10	14	2	8	9

Notes: Column totals, row totals, and Grand Totals indicate total numbers of distinct references.

Study Details

Health System	Study Design	Population	Exposure Measurement	Matrix	Sex	Short Citation
Cancer	case-control	general population	biomonitoring	blood	female	Bonefeld-Jørgensen et al. (2014)
						Ghisari et al. (2017)
						Hurley et al. (2018)
						Wielsøe et al. (2018)
cohort	occupational	occupational	-	both	Hardell et al. (2014)	
					3M Company (2000)	
cross-sectional	general population	biomonitoring	blood	male	Olsen et al. (2004)	
					Christensen et al. (2016a)	

References

- 3M Company (2000)
- Aimuzi et al. (2019)
- Bao et al. (2017)
- Berg et al. (2015)
- Berg et al. (2016)
- Bjerregaard-Olesen et al. (2019)
- Blake et al. (2018)

Chemicals Evaluated - by Name

Perfluoroheptanesulfonate	9
Perfluoroheptanesulfonic acid	4
Perfluoroheptanoic acid	22
Perfluorooctanesulfonamide	15
Perfluorooctanesulfonyl fluoride	2
Perfluoropentanoic acid	7

Chemicals Evaluated - by CASRN

307-35-7	2
375-85-9	22
375-92-8	4
376-06-7	12
422-64-0	3
754-91-6	15

Chemicals Evaluated - by DTXSID

DTXSID1037303	22
DTXSID3038939	15
DTXSID3059921	12
DTXSID5027140	2
DTXSID6062599	7
DTXSID8047553	71



Perfluoroheptanoic Acid

- Human epidemiology studies would be challenging for use to develop an oral or inhalation reference value
 - All studies relied on blood-based biomonitoring and there are significant toxicokinetic data gaps

Health System	infants		children		pregnant women		general population			occupational
	case-control	cohort	case-control	cross-sectional	cohort	cross-sectional	case-control	cohort	cross-sectional	cohort
cardiovascular									2	1
developmental				1						
endocrine	1				1				2	
immune				1				1		
nervous					1					
reproductive							1			
respiratory			1							

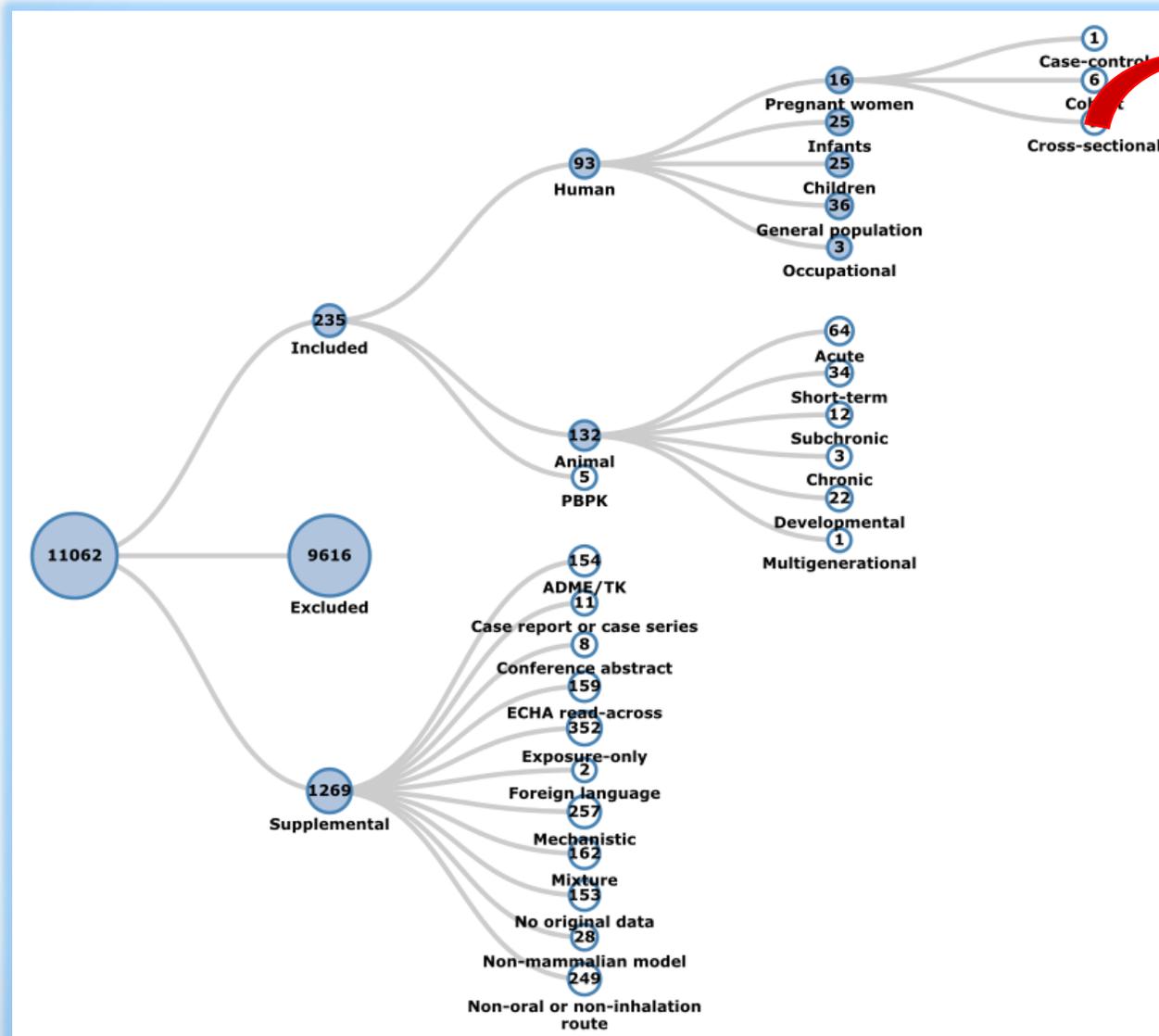
Reference	Population	Health System	case-control	cohort	cross-sectional
Kim et al., 2016	infants	endocrine	■		
Dong et al., 2013	children	respiratory	■		
Lee et al., 2018	children	developmental			■
Smit et al., 2015	children	immune			■
Callan et al., 2016	pregnant women	developmental			■
Hoyer et al., 2017	pregnant women	nervous		■	
Monroy et al., 2008	pregnant women	developmental			■
Rahman et al., 2019	pregnant women	endocrine		■	
Bloom et al., 2010	general population	endocrine			■
Fu et al., 2014	general population	cardiovascular			■
Huang et al., 2018	general population	cardiovascular			■
Kielsen et al., 2017	general population	immune		■	
Lind et al., 2014	general population	endocrine			■
Wang et al., 2017	general population	reproductive	■		
Mattsson et al., 2015	occupational	cardiovascular		■	

■ No association
■ Inverse association with adverse outcome
■ Association with adverse outcome
■ Insufficient samples >LOD

Study Evaluation

	Bloom et al. 2010	Callan et al. 2016	Dong et al. 2013	Fu et al. 2014	Hoyer et al. 2017	Huang et al. 2018	Kielsen et al. 2017	Kim et al. 2016	Lee et al. 2018	Lind et al. 2014	Mattsson et al. 2015	Monroy et al. 2008	Rahman et al. 2019	Smit et al. 2015	Wang et al. 2017
Exposure measurement (all used blood-based biomonitoring)	+	+	+	++	++	-	++	+	-	-	+	++	++	++	-
Study sensitivity (based on % samples >LOD)	--	--	-	++	+	-	++	+	-	++	++	--	-	+	++
Ability to use exposure measure for oral or inhalation toxicity value derivation	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-

Click [here](#) to view the interactive version.



Click to see reference list

References tagged: **Included** > **Human** > **Pregnant women** > **Cross-sectional**

Beig V, Heo Y, Heister KD, Heister S, Yeha AS, Jurek A, Odeh JD, Savage TU 2018
Persistent Organic Pollutants and the Association with Maternal and Infant Thyroid Homeostasis: A Multicohort Assessment
 Environment Health Perspectives 126:10710

BACKGROUND: Disruption of thyroid homeostasis has been indicated in human studies targeting effects of persistent organic pollutants (POPs). Influence on the maternal thyroid system by POPs is of special interest during pregnancy, as such effects could impact infant thyroid homeostasis.

OBJECTIVE: We investigated the association between POPs and thyroid stimulating hormone (TSH) and thyroid hormones (THs) in mother and child pairs from the Northern Norway Mother-and-Child Contaminants Cohort Study (MCC).

METHODS: Nineteen POPs and ten thyroid parameters were analyzed in serum from 381 pregnant women in their second trimester. In addition, TSH concentrations in fetal and cord samples from 194 infants were analyzed by the Norwegian Neonatal Screening program. Association studies with a multicohort approach were performed using multivariate analyses, partial least squares (PLS) regression, hierarchical clustering and principle component analysis (PCA).

RESULTS: Several POPs were significantly associated to TSH and THs. (i) PFOS was positively associated with TSH in POCs, and nonoxarodins were inversely associated to TSH and FT4, and, (ii) PFOS and PFOSDA were inversely associated to TSH and FT3. After mutual adjustments for the other contaminants, only PFOS and PFOSDA remained significantly associated to TSH and FT3, respectively. Infants born to mothers within the highest TSH quartile had 10% higher mean concentration of TSH compared to children born to mothers in the lowest TSH quartile.

CONCLUSION: The present results suggest that background exposures to POPs can alter maternal thyroid homeostasis. This research contributes to the understanding of multicohort studies using multivariate statistical approaches and highlights the complexity of investigating environmental concentrations and outcomes in regards to maternal and infant thyroid function.

HAWC search/imports: Auto-import at 2020-09-04 11:10:07

Grieshammer I, Dornheim G, Gunkler J, Berger U, Rowel R, Beran J, Unger S, Lampa S, Gysin A 2018
Perfluorinated acid levels in first-time mothers in relation to offspring weight gain and growth

We investigated if maternal body burdens of perfluorinated acids (PFASs) at the time of delivery are associated with birth outcome and if early life exposure (in utero/lactation) is associated with early childhood growth and weight gain. Maternal PFASs body burdens were estimated by analysis of serum samples from mothers living in Upper Austria. Susser (PQ)P, sampled three weeks after delivery between 1990 and 2011. Data on child length and weight were collected from medical records and converted into standardized deviation scores (SDS). Multiple linear regression models with appropriate covariates were used to analyze associations between maternal PFASs body burdens and birth outcomes (ln-BMI). After birth Generalized Linear Squares models were used to analyze associations between maternal PFASs and child growth (ln-SDS). Inverse associations were found between maternal levels of perfluorooctanoic acid (PFOS), and perfluorodecanoic acid (PFDA), and perfluoroundecanoic acid (PFUNDA), and birth weight (SDS with a change of -0.10 to -0.18 weight SDS for an inter-quartile range (IQR) increase in ng/g PFAS. After birth, weight and length SDS were not significantly associated with maternal PFASs. However, BMI SDS was significantly associated with PFOS, PFNA, and PFHxS at birth and levels of age, and with PFOS at 1 and 2 years of age. If causal, these associations suggest that PFASs affect fetal and childhood body development in different directions.

HAWC search/imports: Auto-import at 2020-09-04 11:10:07

Huang B, Chen B, Zhang L, Chen L, Sun S, Peng J, Zhang J 2018
Prenatal exposure to perfluorinated and polychlorinated substances and the risk of hypertensive disorders of pregnancy
 Environment Health 4 Case Access Source 163

BACKGROUND: Perfluorinated and polychlorinated substances (PFAS) have been reported to disrupt endocrine system and reproduction. However, epidemiological evidence on the association between PFAS and preeclampsia is inconclusive. We aimed to investigate the association between prenatal PFAS exposure and hypertensive disorders of pregnancy (HDP) in humans.

METHODS: PFAS were measured by liquid chromatography system coupled with tandem mass spectrometry in 687 umbilical cord plasma samples collected between 2011 and 2012 in Shanghai, China. Information on HDP including gestational hypertension and preeclampsia was abstracted from medical records. Multiple logistic regression was used to examine the association of each PFAS with gestational hypertension, preeclampsia, and overall HDP in separate models. Elastic net regression with l1-penalty was used to identify independent associations between exposure and outcomes. Logistic regression was used to obtain the unadjusted estimates of the selected PFAS congeners to the associations with outcomes, adjusting for age, education level, demographic, life style, and mutual adjustment of selected PFAS.

RESULTS: The risk of gestational hypertension and preeclampsia was 2.3% and 2.6% in our subjects, respectively. Perfluorodecanoic sulfonate (PFDS), perfluorooctane sulfonate (PFOS), perfluoroundecanoic acid (PFUNDA) were associated with preeclampsia based on elastic net penalized regression. In the fully adjusted statistical model, women with a higher level of perfluorodecanoic sulfonate (PFDS) had an increased odds of preeclampsia (adjusted odds ratio (AOR): 1.31, 95% confidence interval (CI): 1.025, 1.7) and overall HDP (AOR: 1.64, 95% CI: 1.092, 2.47).

CONCLUSIONS: Prenatal exposure to PFDS was positively associated with the risk of preeclampsia and overall HDP.

HAWC search/imports: Auto-import at 2020-09-04 11:10:07

Jiang H, Zhang J, Du Y, Ding J 2018
Serum levels of perfluorinated acids (PFASs) with cluster analysis and their associations with medical parameters in Chinese pregnant women
 Environment International 114:607

Output 3.3

Evaluate and develop improved methods for dose extrapolation and the related uncertainty characterization in human health risk assessment via classical methods and integration of pharmacokinetic models

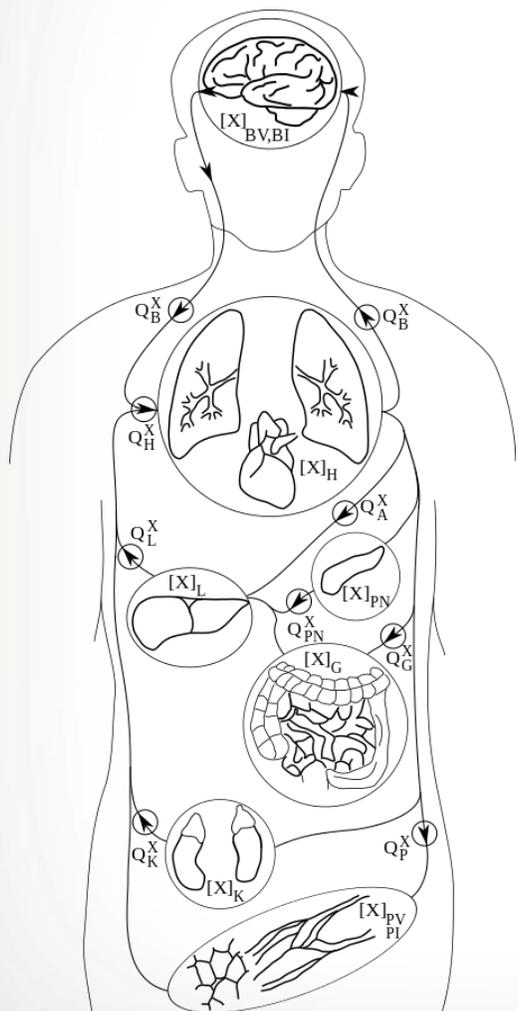
A Template Approach for Rapid Evaluation and Application of PBPK Models

Amanda Bernstein

Oak Ridge Institute for Science and Education (ORISE)
CPHEA

Output Lead: Paul Schlosser

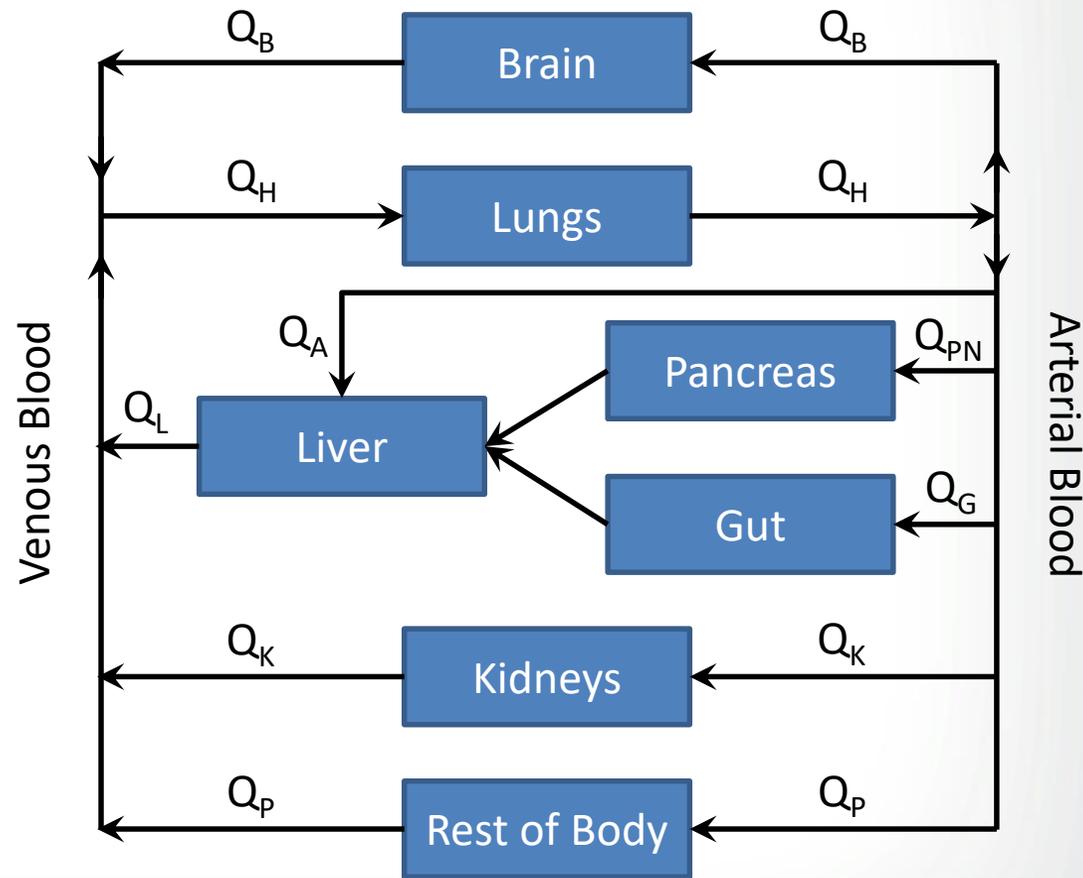




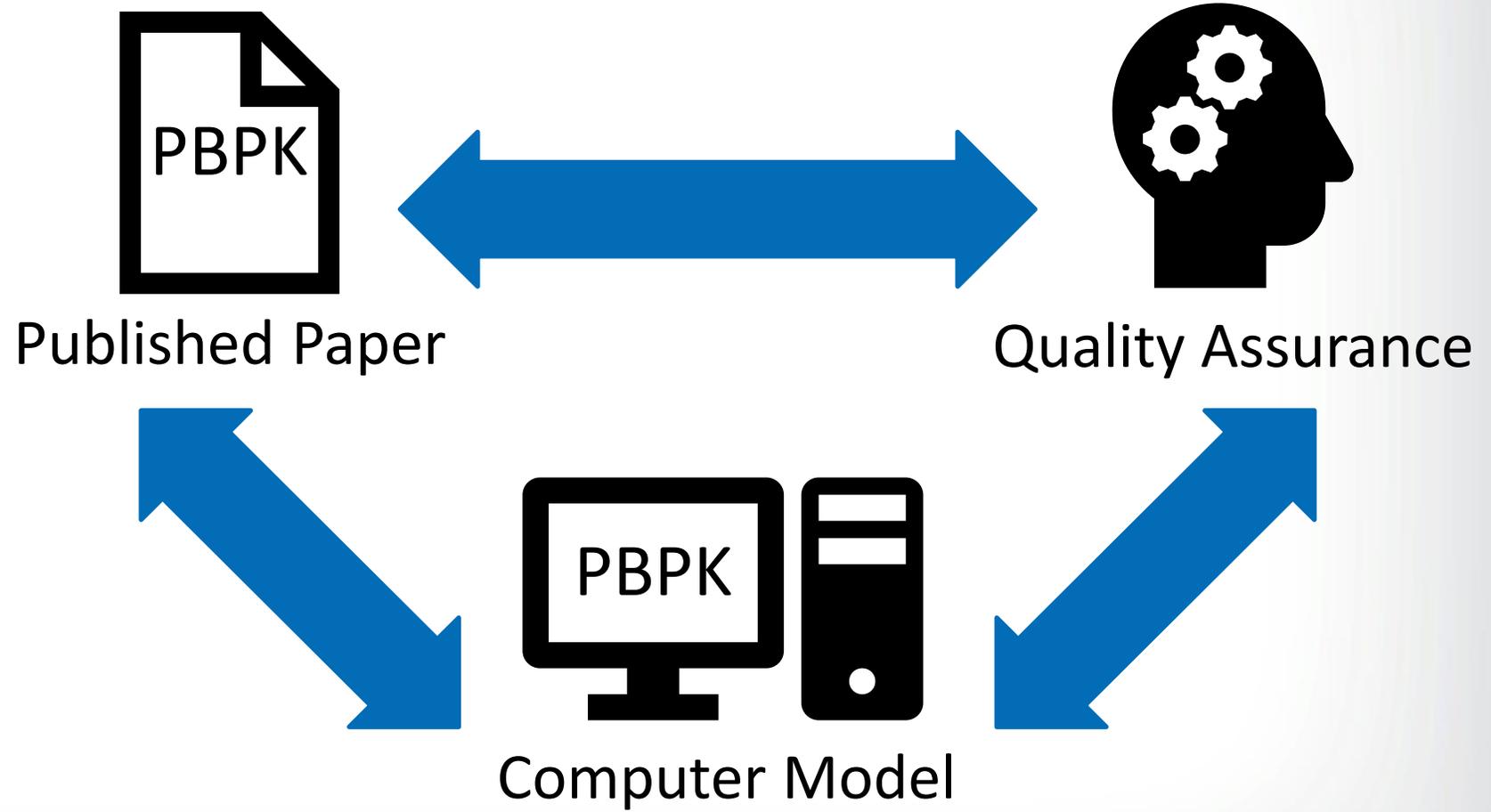
Chemical engineering applied to a biological organism



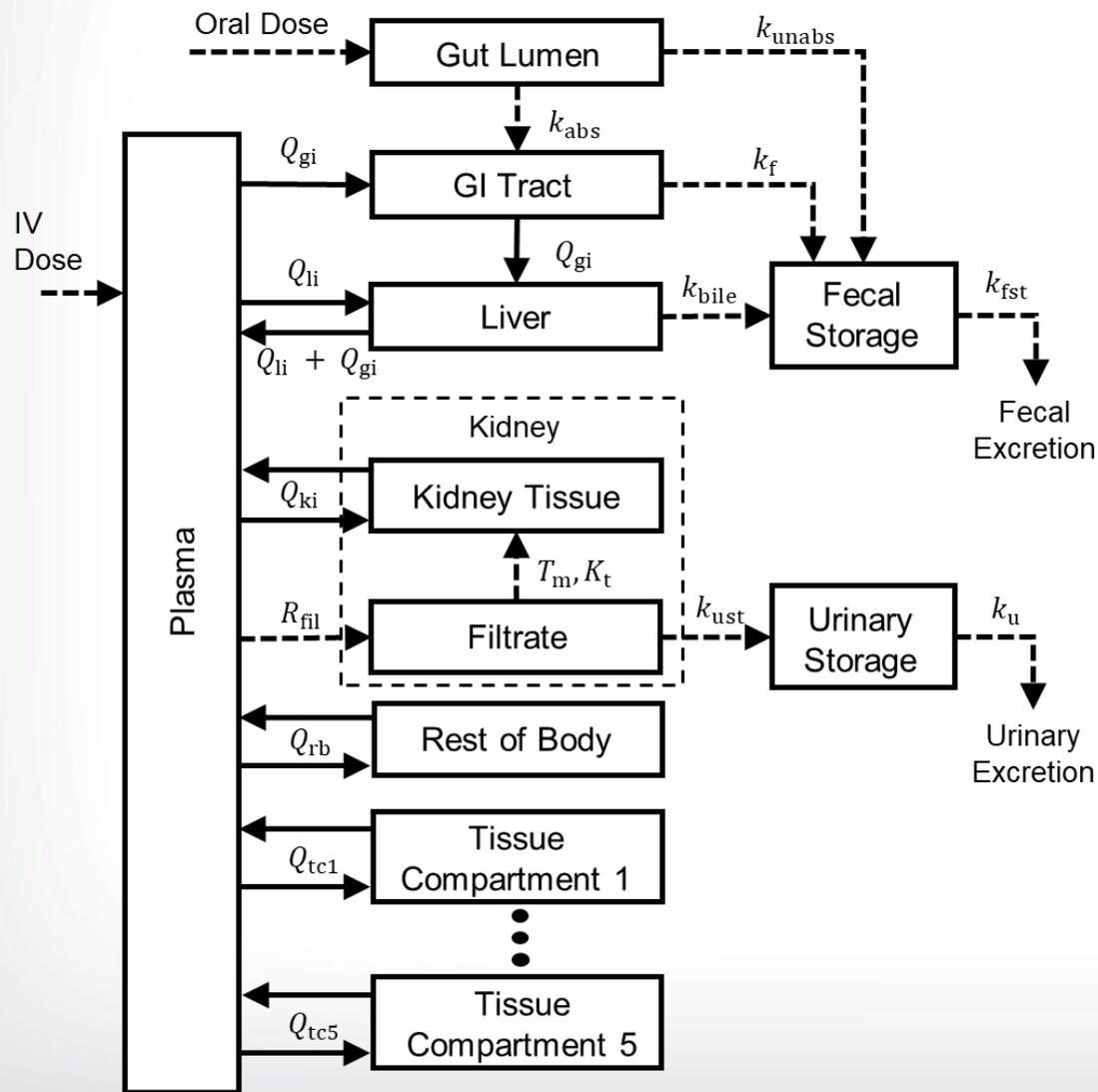
Model parameters are based on anatomy, physiology, and biochemical properties.



- PBPK models reduce the uncertainty in risk assessment.
- Does the computer implementation match the published paper?
- A quality assurance (QA) review is needed.



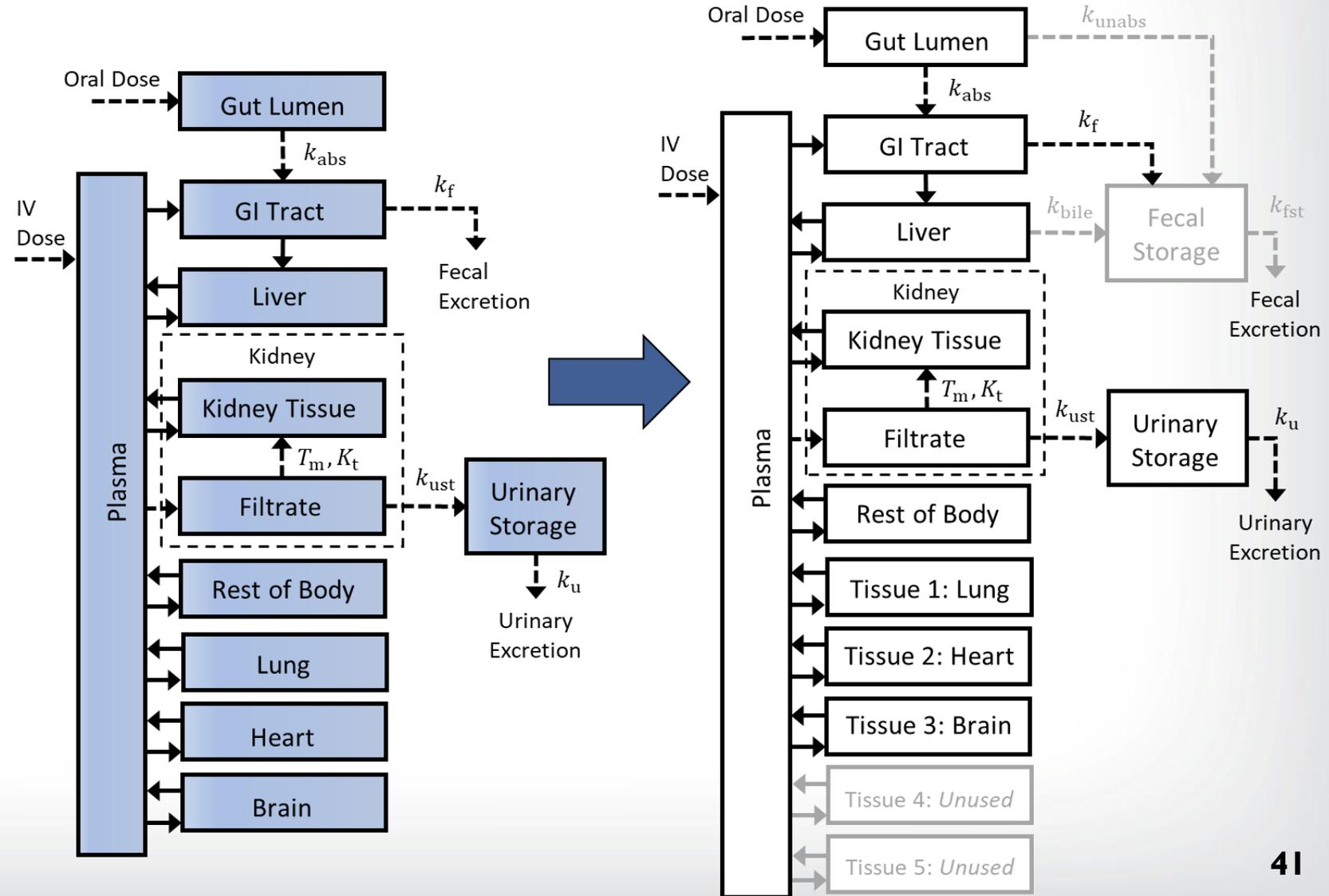
PBPK Model Template



- We developed a template that allows one to quickly implement and review chemical-specific PBPK models.
- Features include:
 - Oral and IV dose exposure routes
 - Saturable resorption in the kidney filtrate
 - Plasma protein binding
 - Multiple basic tissue compartments
 - Fecal elimination from either the GI tract or the liver (bile)
 - The unabsorbed fraction from oral exposures is passed to feces
 - Fecal and urinary storage compartments
 - Constant or changing body weight

Case Study: PFHxS PBPK Model

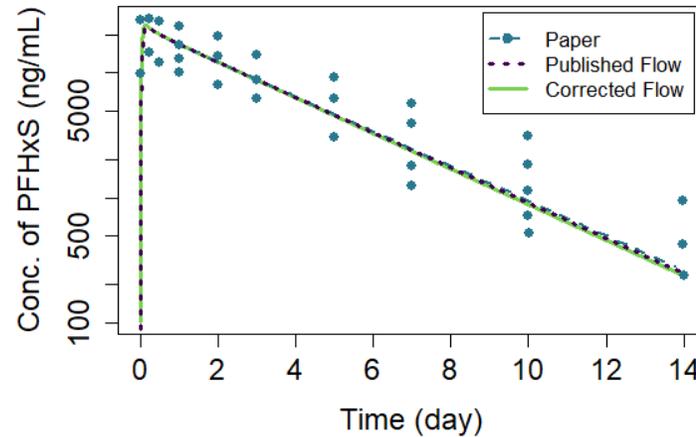
We implemented the PFHxS PBPK model of Kim et al. (2018) using the template and the published parameter values.



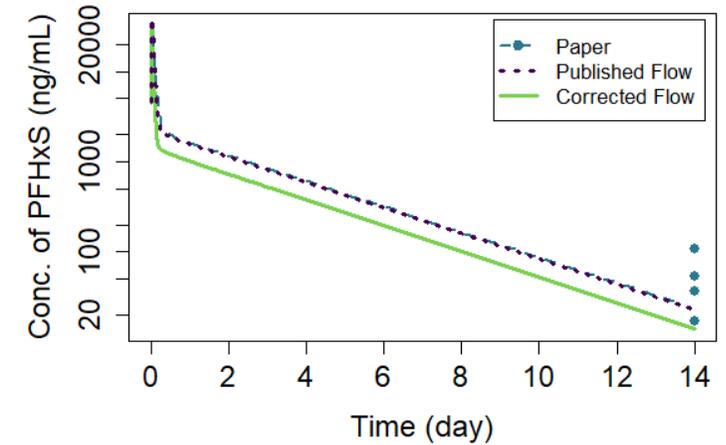
Case Study: PFHxS PBPK Model

- Using the template, we were able to recreate some of the published results.
- However, the model-predicted concentrations of PFHxS in the liver were lower than the published results, leading us to quickly realize that the published model contained an error.

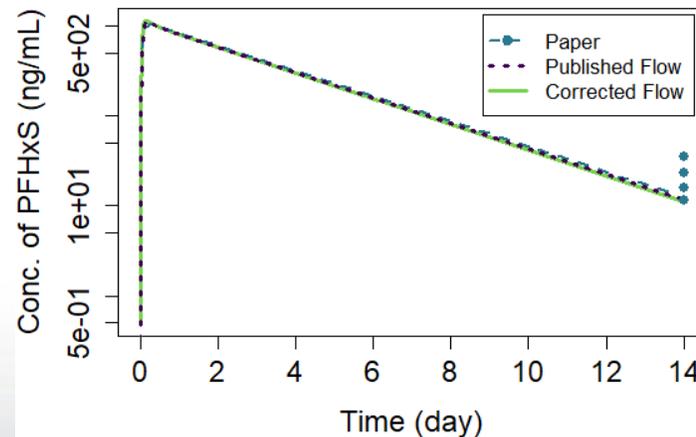
Plasma



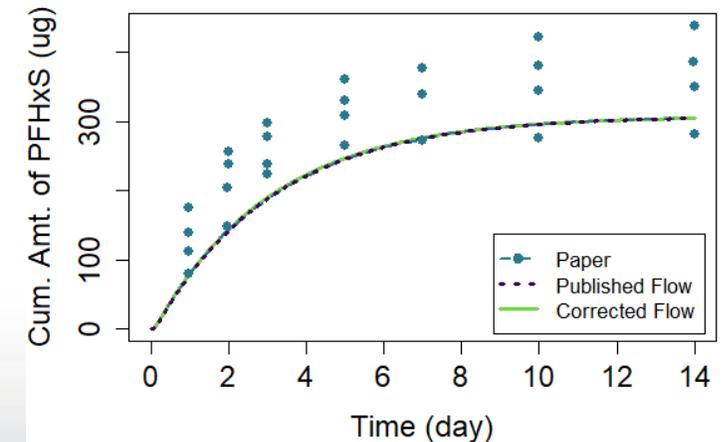
Liver



Kidney



Urine



- **The model template includes sufficient features to allow implementation of a wide range of PBPK models.**
- **Implementation of different models only requires changing parameter values in input files.**
- **Using the template can allow us to quickly identify errors in PBPK models.**
- **To perform QA review of template-implemented models, only the parameter files will require review.**

Acknowledgments

Dustin Kapraun

Paul Schlosser

Viktor Morozov

Thank You!

Amanda Bernstein (bernstein.amanda@epa.gov)

- Will enable the maintenance and development of new or existing tools and databases used in the assessment process and will provide training on these resources and applications

Outputs



4.1 Innovate, develop, and maintain a suite of essential software and support tools for risk assessment

4.2 Innovate, develop, and maintain a training program on the advances in risk assessment and systematic review

Output 4.1

Innovate, develop, and maintain a suite of essential software and support tools for risk assessment

All Ages Lead Model (AALM)

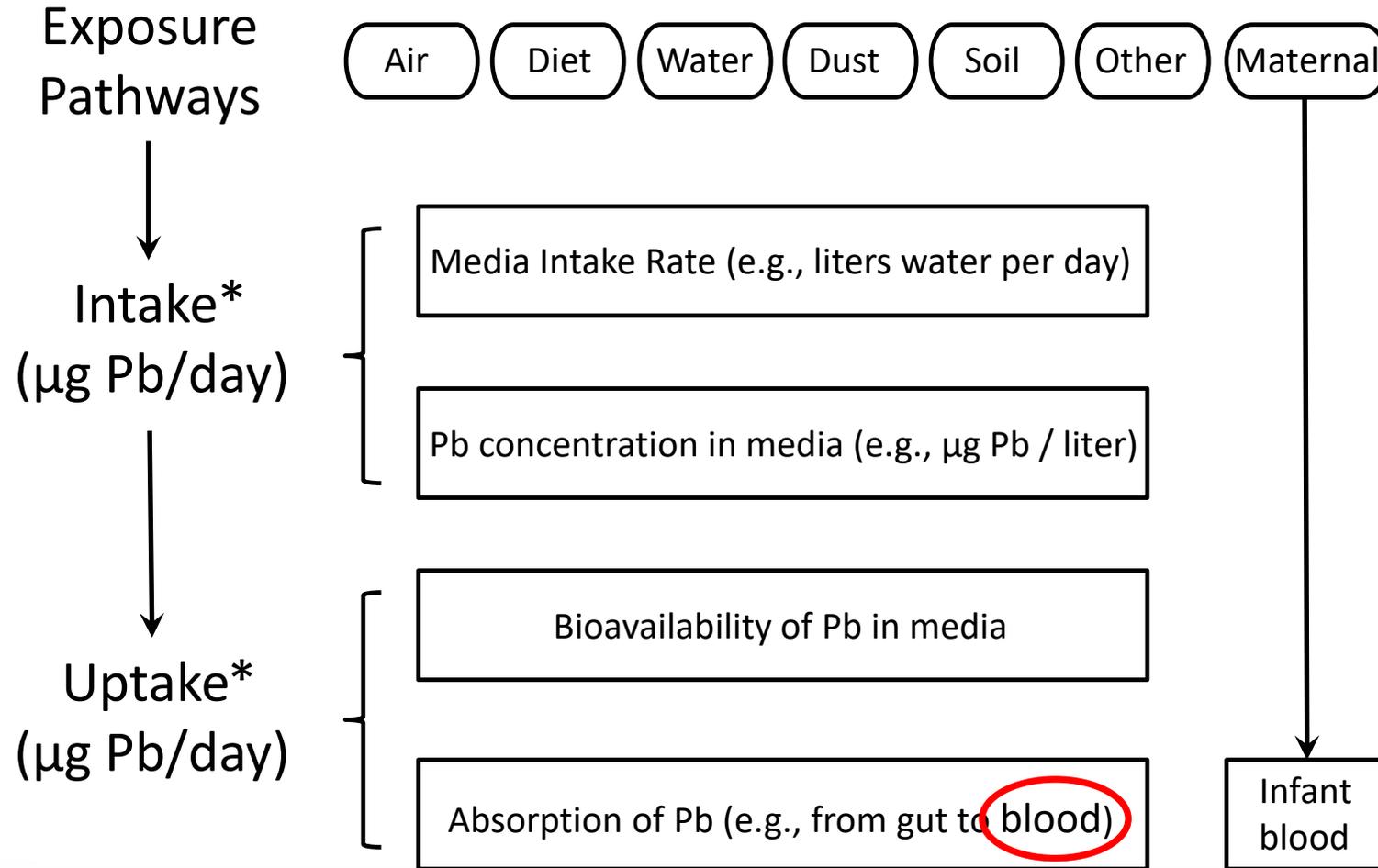
**James Brown
CPHEA/HEEAD**

Output Lead: Jennifer Nichols



- Lead (Pb) exposure and biomarkers
- EPA's Pb biokinetic models
- Recent AALM development
- AALM example of capabilities
- SAB peer review of AALM
- Obtaining the AALM

Multi-media Lead Exposure



* Intake rates and absorption in GI tract all vary with age

Biomarkers of Pb Exposure

- Blood Pb: most common biomarker; ~1% of Pb body burden; >99% bound to RBC, 1% in plasma and extracellular fluid
 - Generally indicates recent exposure
 - Children's blood Pb tends to be greatest in the fall season
 - Half-life of Pb in blood depends on age and exposure history, can range from days to months
- Bone Pb: accounts for ~70% of Pb body burden in children and more than 90% in human adults

Pb is exchanged between blood (via plasma) and compact (Cortical) and spongy (Trabecular) bone.



Bone acts as a source of Pb to blood and other tissues for years following exposure.



EPA's Pb Biokinetic Models

Biokinetic are mathematical descriptions of exposure, uptake, and disposition of a substance in the body. These models allow for multiple exposure pathways for which intake and absorption may vary over time and age of the exposed individual.

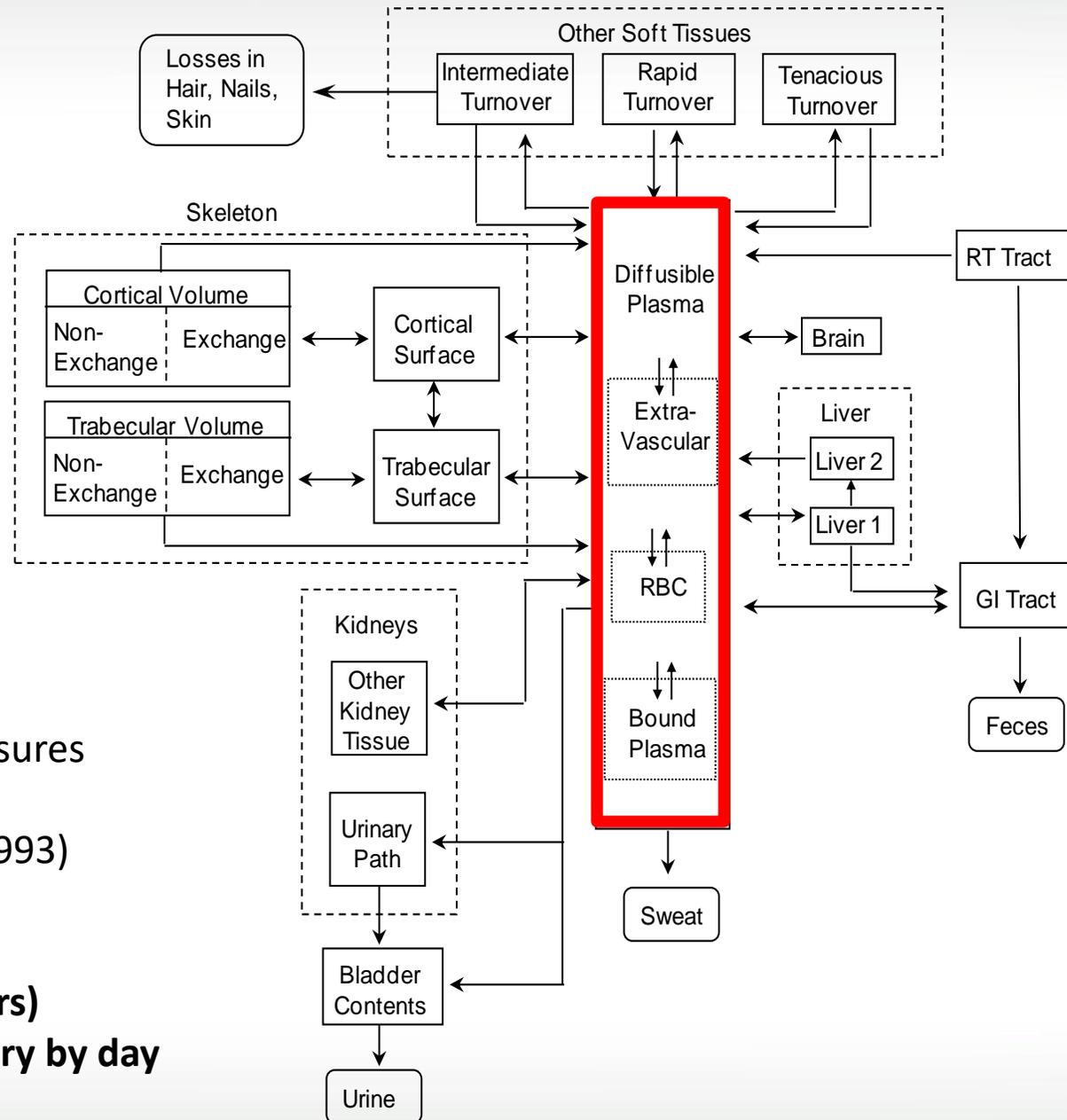
Integrated Exposure Uptake Biokinetic (IEUBK) model

- Estimates Pb in blood of children up to 7 years of age
- Steady state exposure that can vary by year of life
- Recommended risk assessment tool to support residential lead-related site cleanups

All Ages Lead Model (AALM)

- Estimates Pb in blood and other tissues (e.g., bone)
- Extends modeling capabilities for people up to 90 years of age
- Allows acute, transiently reoccurring, and/or chronic exposures

AALM



Multi-media exposures

Largely Leggett (1993)
biokinetics

All ages (0-90 years)
Exposures may vary by day

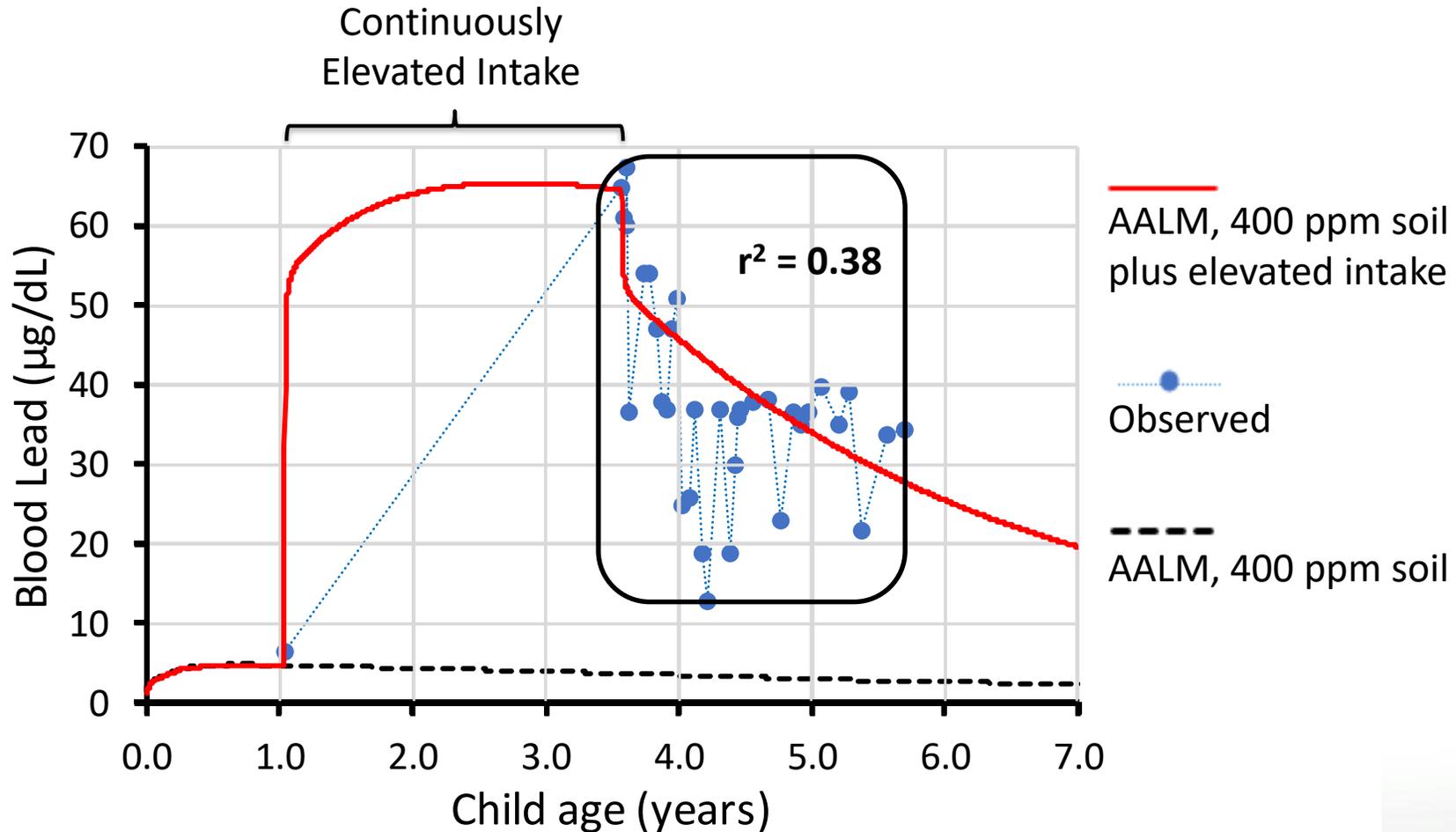
Technical Support Document

- Developed theoretical framework (2017-2019)
 - Basic description of model function (Chapter 2)
 - Detailed equations for exposure and biokinetics (Chapter 2; Tables 2-1 and 2-2; and Appendix A)
- Developed parameter dictionary (2017-2019)
 - Exposure and biokinetic values supported by references (Chapter 2; Table 2-3; and Appendices B-D)
- Software coding and QA (2014-2016)
 - Compared Leggett and O'Flaherty models (Chapter 4)
 - Compared model implemented in two platforms (acslX, Fortran) by ORD and OCSPP (Chapter 3)
- Model Evaluation (2016-2017)
 - Assessed predicted blood and bone Pb against human data (Chapters 3 and 4)



AALM Example of Capabilities

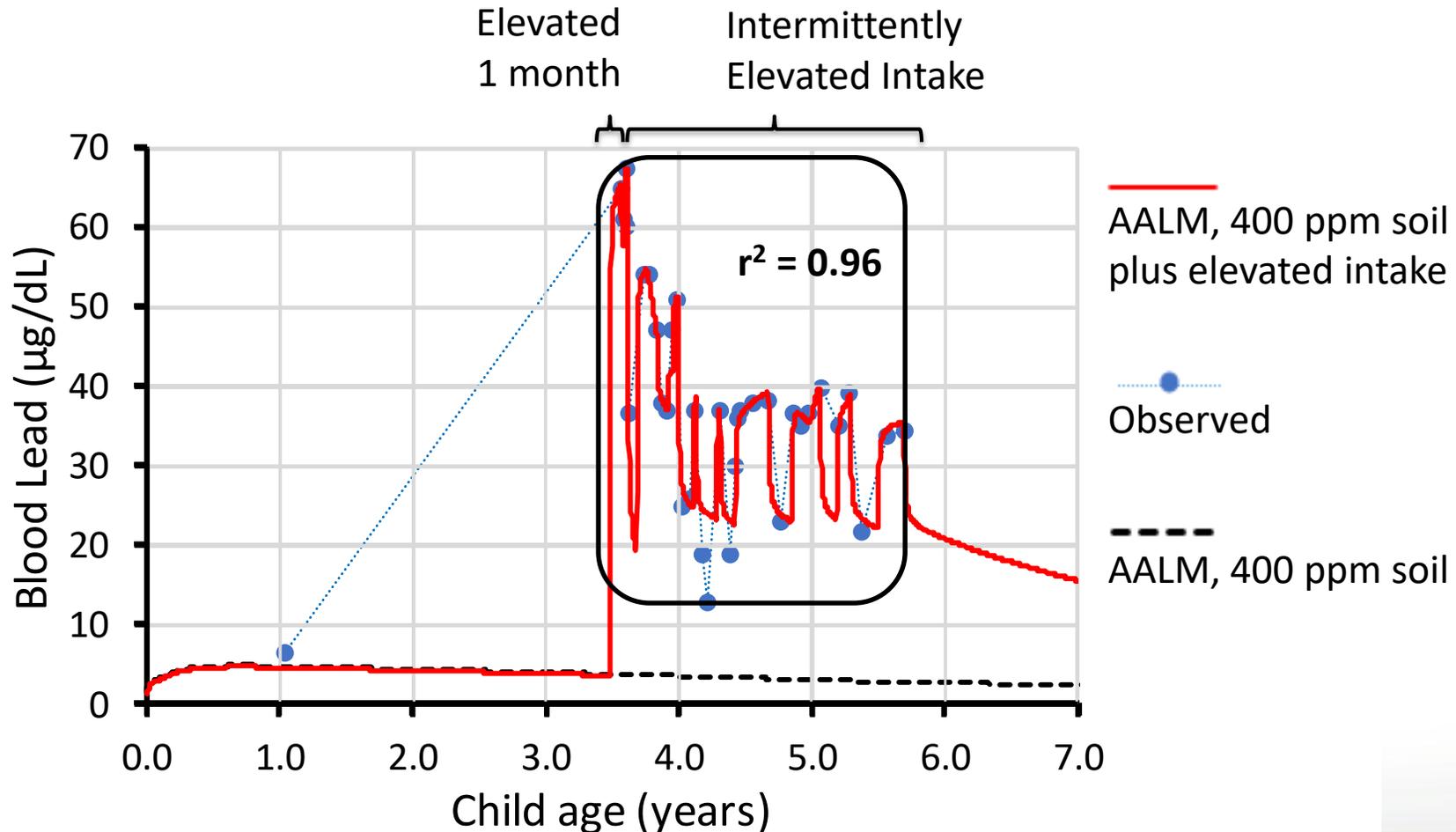
Are elevated BLL due to continued exposure?





AALM Example of Capabilities

Are elevated BLL due to continued exposure?





- SAB Review Panel Meeting (Oct 17-18, 2019)
 - Panelists praised EPA’s work to document the studies and data that underlie the model
 - New version of the AALM as “definitely not black box”
 - Urged clarifying applications and audience, suggesting it may not be well suited to some uses
- SAB Draft Peer Review Report Teleconference (Apr 23, 2020)
 - “Panel recommends that the Agency’s highest priority is to make those changes, clarifications, corrections, and edits to the model and documentation needed to allow use of the AALM 2.0 for research and additional testing”
 - “Panel has described many of these actions in its Tier 1 recommendations” that should be done as soon as possible

Initial Responses to Review

- Developing a new respiratory module
 - Bimodal aerosols between 0.001 and 100 μm
 - Male or female children, adolescents, and adults
 - Three activities (sitting, light and heavy exercise)
- Developing simplified documentation
 - Good for modelers, but not general users
- Developing training materials
 - Providing training on request
 - Considering webinar or video materials
- Considering example runs for users
 - Steady state exposures from multiple pathways
 - Intermittent exposures from multiple pathways
 - Create plausible exposure histories



epa aalm



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About 11,700 results (0.28 seconds)

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[All-Ages Lead Model \(AALM\), Version 2.0 \(External ... - EPA](#)

Sep 24, 2019  ised on the findings of the 2005 SAB Review, the 2019 **AALM** Version 2.0 extends the **EPA's** modeling capabilities to estimate lead in blood ...

yosemite.epa.gov › EPA Science Advisory Board (SAB) ▼

[All-Ages Lead Model: Evaluation of the Theoretical ...](#)

The U.S. **EPA** requested the SAB to conduct a peer review of the All-Ages Lead Model (**AALM**). The Agency's Office of Research and Development (ORD) in ...



Related Topics: [Risk Assessment](#) | [Integrated Science Assessments](#)

[Contact Us](#)

All-Ages Lead Model (AALM), Version 2.0 (External Review Draft)

- Overview
- History
- Downloads**
- Notices/Outreach

This download(s) is distributed solely for the purpose of pre-dissemination peer review under applicable [information quality guidelines](#). It has not been formally disseminated by EPA. It does not represent and should not be construed to represent any Agency determination or policy.

- [Technical Support Document for the All Ages Lead Model \(AALM\), Version 2 -- Parameters, Equations, and Evaluations \(External Review Draft\) \(PDF\)](#) (333 pp, 4 MB, [about PDF](#))
- [Users Guide for the FORTRAN Version of the All Ages Lead Model \(April 2019\) \(PDF\)](#) (20 pp, 785 KB, [about PDF](#))
- [AALM Software, Version 2 \(ZIP\)](#) (3 MB, [about ZIP](#))
- [AALM Peer Review Charge \(PDF\)](#) (1 pp, 75 KB, [about PDF](#))

Federal Register Notices

- [SAB FR: Sep 24, 2019](#)

Contact

[James S. Brown](#)

Output 4.1

**Innovate, develop, and maintain a suite of essential software
and support tools for risk assessment**

**Health and Environmental Research Online (HERO) and
Health Assessment Workplace Collaborative (HAWC)**

**Jennifer Nichols
CPHEA/HEEAD**

Output Lead: Jennifer Nichols



HERO | Health and Environmental Research Online

Database of more than 7 million scientific studies and references used in developing reports and assessments that support critical Agency decision-making.

Assessment teams

- Assistance with literature identification
- Organization of references on Project Pages (customizable tagging to track references)
- Mechanisms for PDF acquisition and storage
- LitCiting to provide accessibility to scientific references via in-text links

Stakeholders (Program offices, panels, public, etc.)

- Access to Project Pages that have been made public
- Universal access to bibliographic details for references cited in a scientific assessment or report
- Limited access directly to PDFs for select internal users and panels (copyright law applies)

HERO | Health and Environmental Research Online

Where is HERO being used?

EPA Products

- Integrated Science Assessments (ISAs)
- IRIS assessments
- PPRTVs

- PFAS
- Lead
- TSCA

- Biofuels
- Enhanced Aquifer Recharge
- Various systematic reviews

Program Offices

- Office of Chemical Safety and Pollution Prevention (OPPT, OSCP)
- Office of Air and Radiation (OAQPS, OTAQ)
- Office of Children's Health Protection

- Office of General Counsel
- Office of Land and Emergency Management
- Office of Water

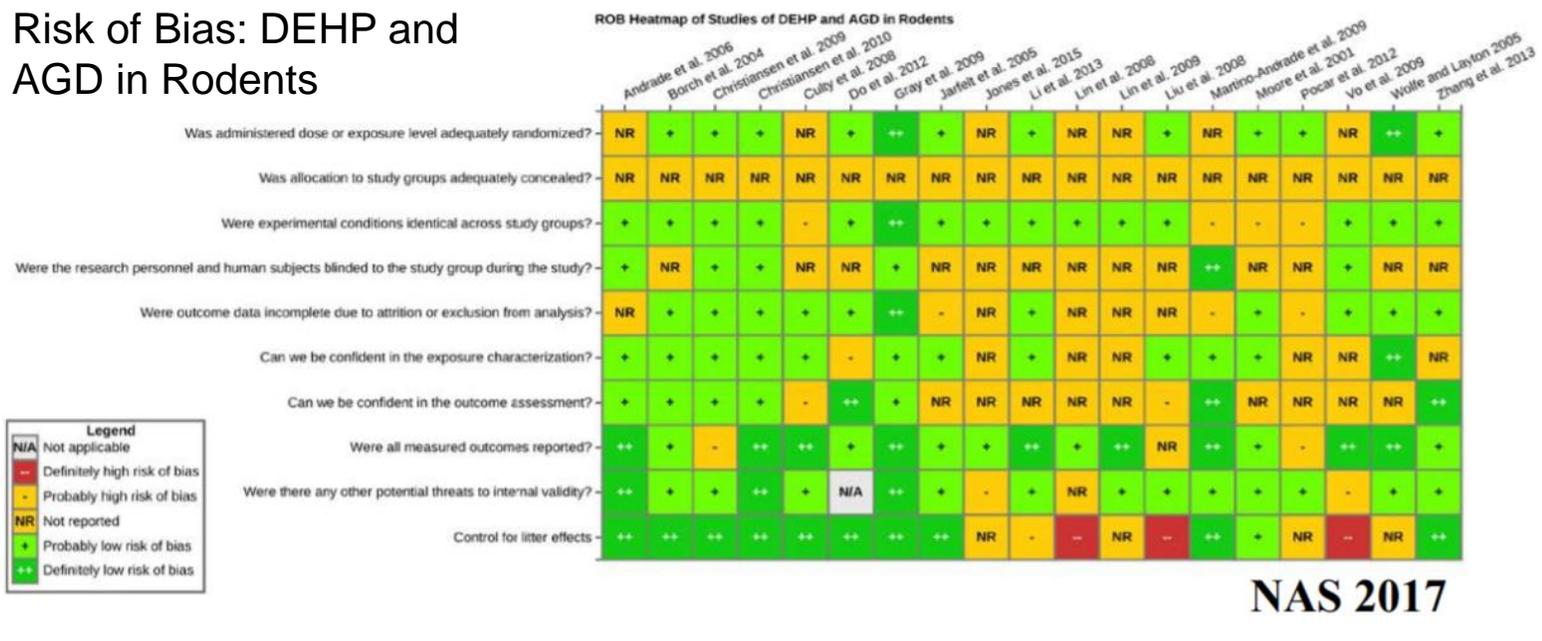


Modular, content management system designed to store, display, and synthesize multiple data sources for the purpose of producing human health assessments of chemicals

Assessment teams (currently Epidemiology and Animal Toxicology)

- Data extraction (static fields)
- Risk of Bias (customizable)
- Data visualization (based on extracted data)
- Level of accessibility can easily be controlled.

Risk of Bias: DEHP and AGD in Rodents



Shapiro et al. https://hawcproject.org/static/docs/posters/2018_NAS_HAWC.pdf



Where is HAWC being used?

Current HAWC Stats (4/20/20)

- Registered HAWC users: 1,258
- Assessments (public and private): 843
- References imported or found from searches: 450,290
- Number of tags applied to references: 235,153
- Tagged references: 198,226 (44%)
- Studies with data extracted: 5,368
- Assessments with studies: 244 (29%)
- Risk of bias scores: 62,613
- Studies with risk of bias: 3,405 (63%)
- Animal bioassay endpoints: 16,686
- Animal bioassay endpoints with data extracted: 15,533 (93%)
- Epidemiology outcomes: 4,913
- Epidemiology results with data: 7,971 (100%)
- In vitro endpoints: 2,239
- In vitro endpoints with data: 1,935 (86%)
- Visualizations: 1,328
- Assessments with visuals: 104 (12%)

ORD/CPHEA

- IRIS assessments
- PPRTVs
- Integrated Science Assessments
- PFAS

Office of Chemical Safety and Pollution Prevention

- TSCA risk evaluations

Outside EPA

- National Toxicology Program
- WHO/IARC
- CalEPA
- TCEQ

Output 4.1 – HERO Innovation and Development

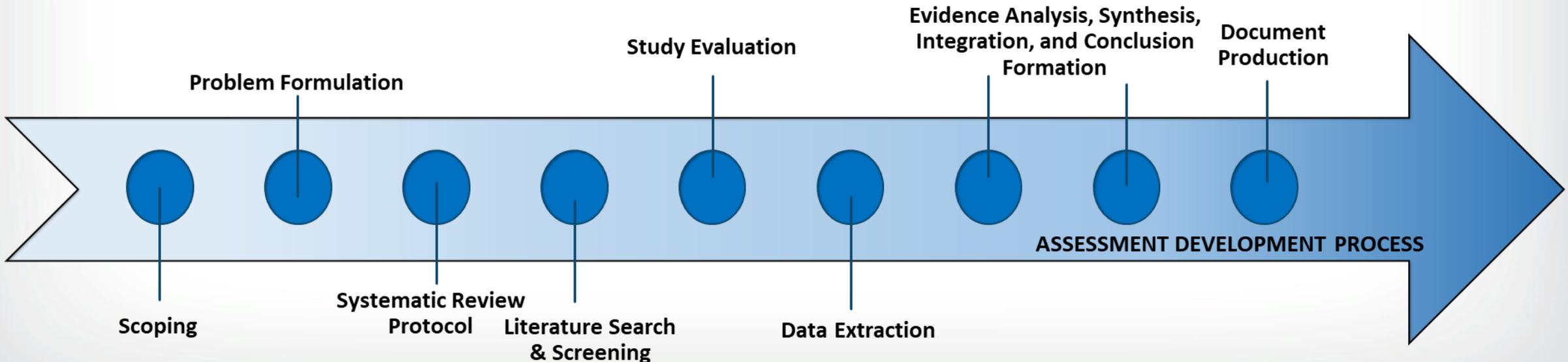
Literature identification – e.g., citation mapping, topic modeling

Enable full-text search function in HERO

HERO web services for online assessment

Update LitCiter

Implement API-driven HERO interface to increase interoperability with other tools



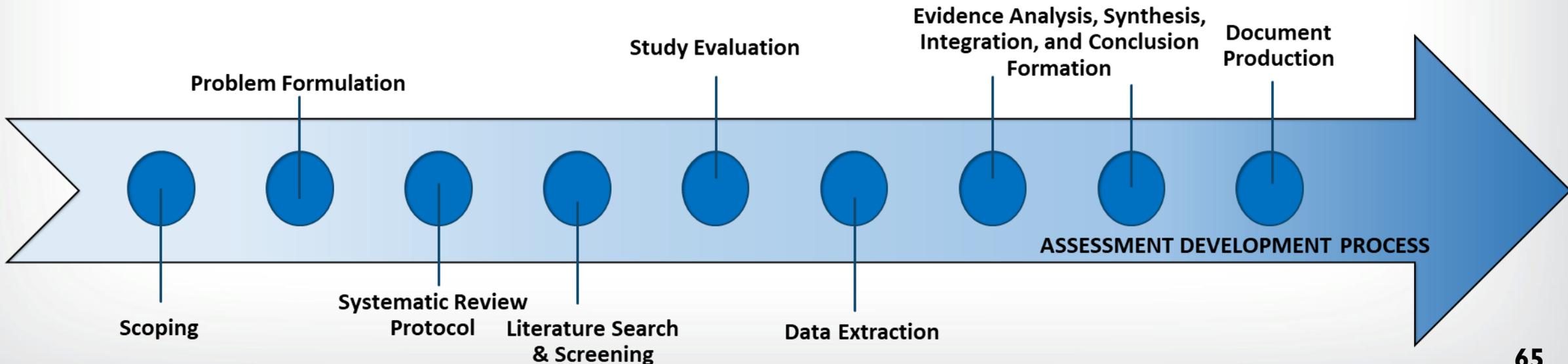
Data extraction for non-health

BMDS integration

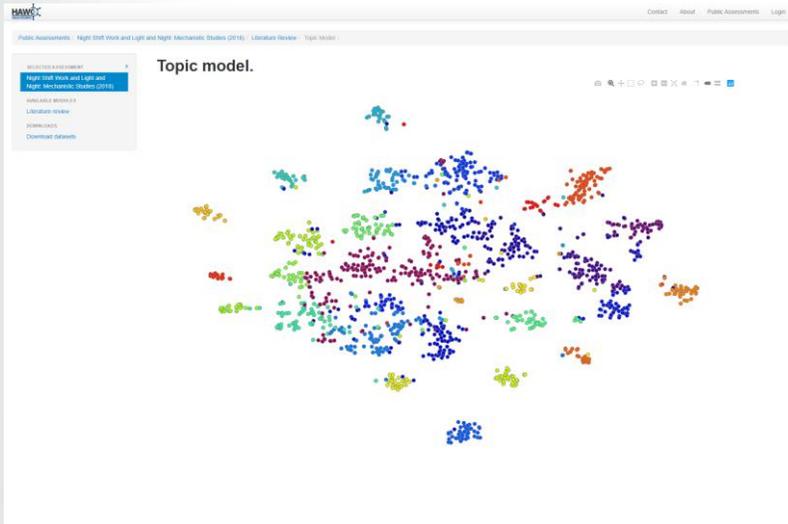
Integrate ontologies for bioassays

R integration capabilities

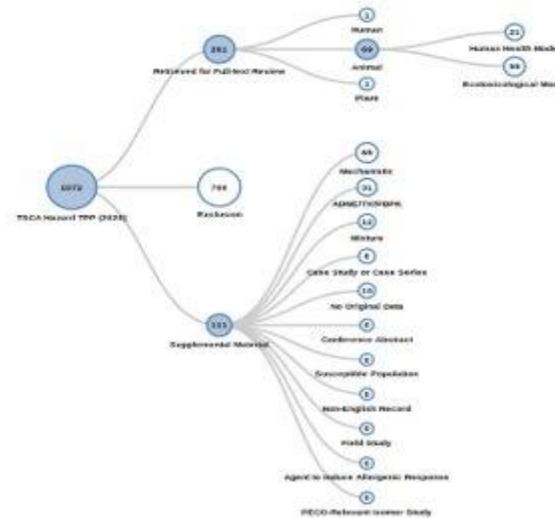
Import/export metadata from Distiller/SWIFT



Literature Identification: Topic Modeling



Interactive Literature Tag Trees



Interactive Data Visualizations



HERO



To innovate, develop, and maintain software and support tools for risk assessment:

- Increased collaboration with scientists
- Increased capacity to plan and strategize
- Increased transparency for users and the public
- Continuing to modernize and streamline how assessments are produced

HERO



Leadership

John Vandenberg
Steve Dutton
Andrew Hotchkiss
Jennifer Nichols
Ryan Jones
Andy Shapiro
Shane Thacker

HERO Team*

Data Specialists
Erin Vining
Brayndon Stafford
Talia Buenrostro
Gabrielle Sullivan

Librarians
Danielle Moore
Hillary Hollinger
Amanda Haddock
Julie Fieldsteel
Alexander Thurman

HAWC Team*

Byron Rice
Daniel Rabstejnek
McKayla Lein

*The HERO/HAWC Team is, in part, comprised of student services contractors through an Oak Ridge Associated Universities contract

- **HERA is committed to advancing the science and practice of assessments, thereby increasing the confidence, transparency, and pace of assessment products.**
- **The approach presented in the HERA StRAP maps out the maintenance and innovation in assessment development and translation science that will be implemented**
- **This best positions the HERA research program to provide assessment products and scientific support to the Agency, while maintaining the leading edge of assessment science.**

Health and Environmental Risk Assessment



THANK YOU!