Office of Research and Development

Health and Environmental Risk Assessment

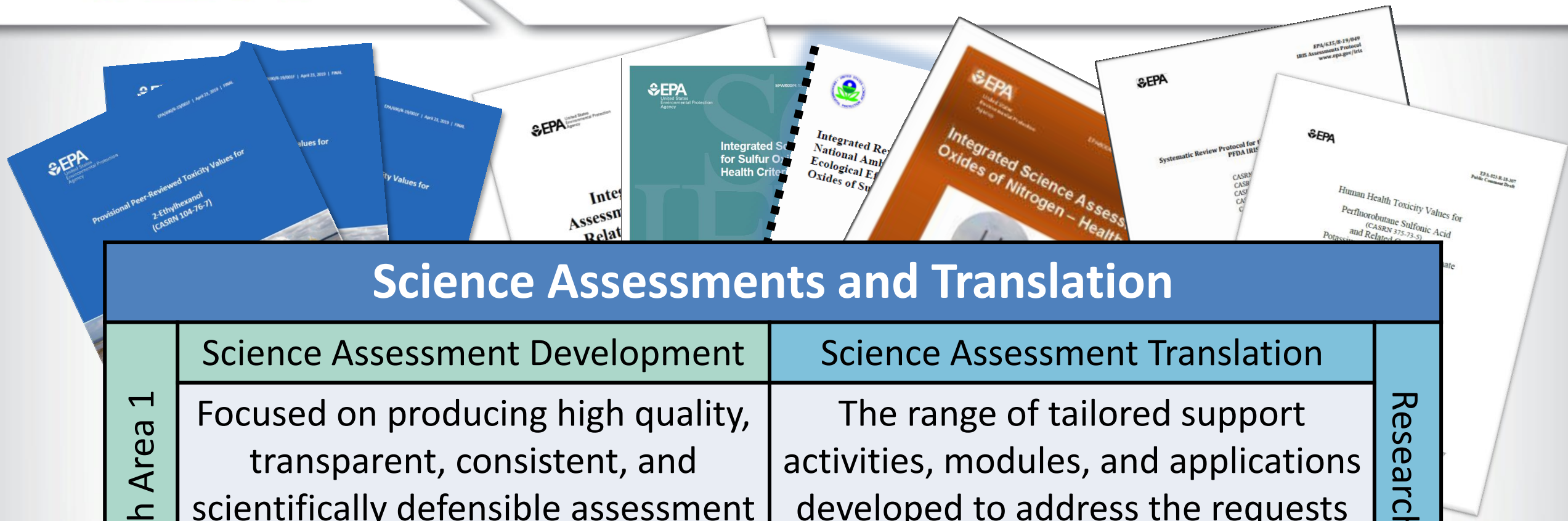
Looking Closer - Overview of the Research Areas in HERA StRAP

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 1 – Science Assessments and Translation



Science Assessments and Translation

Research Area 1	Science Assessment Development	Science Assessment Translation	Research Area 2
	Focused on producing high quality, transparent, consistent, and scientifically defensible assessment products to meet EPA's diverse statutory and policy needs. *Priorities come from Congress and EPA program offices; peer reviewed by groups such as NAS, SAB, CASAC.	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.	

Research Area 1 – Science Assessment Development

- 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.

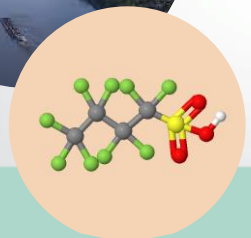
Outputs
1.1 Portfolio of interim assessment products to support decision-making
1.2 Portfolio of final assessment products to support decision-making

Research Area 1 – Science Assessment Development

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

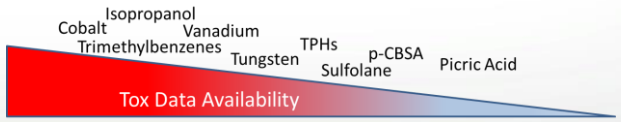
Integrated Risk Information System

IRIS
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

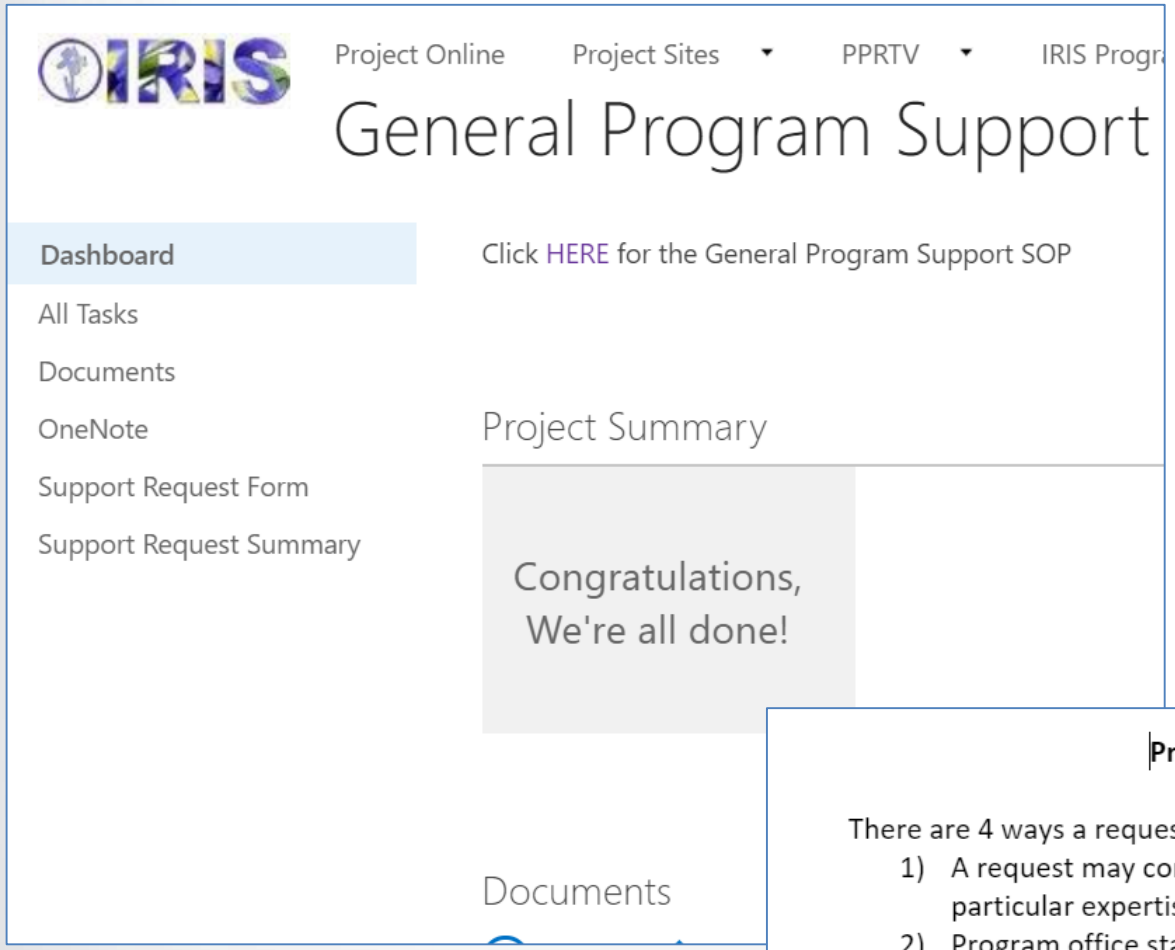
Technical Support Centers

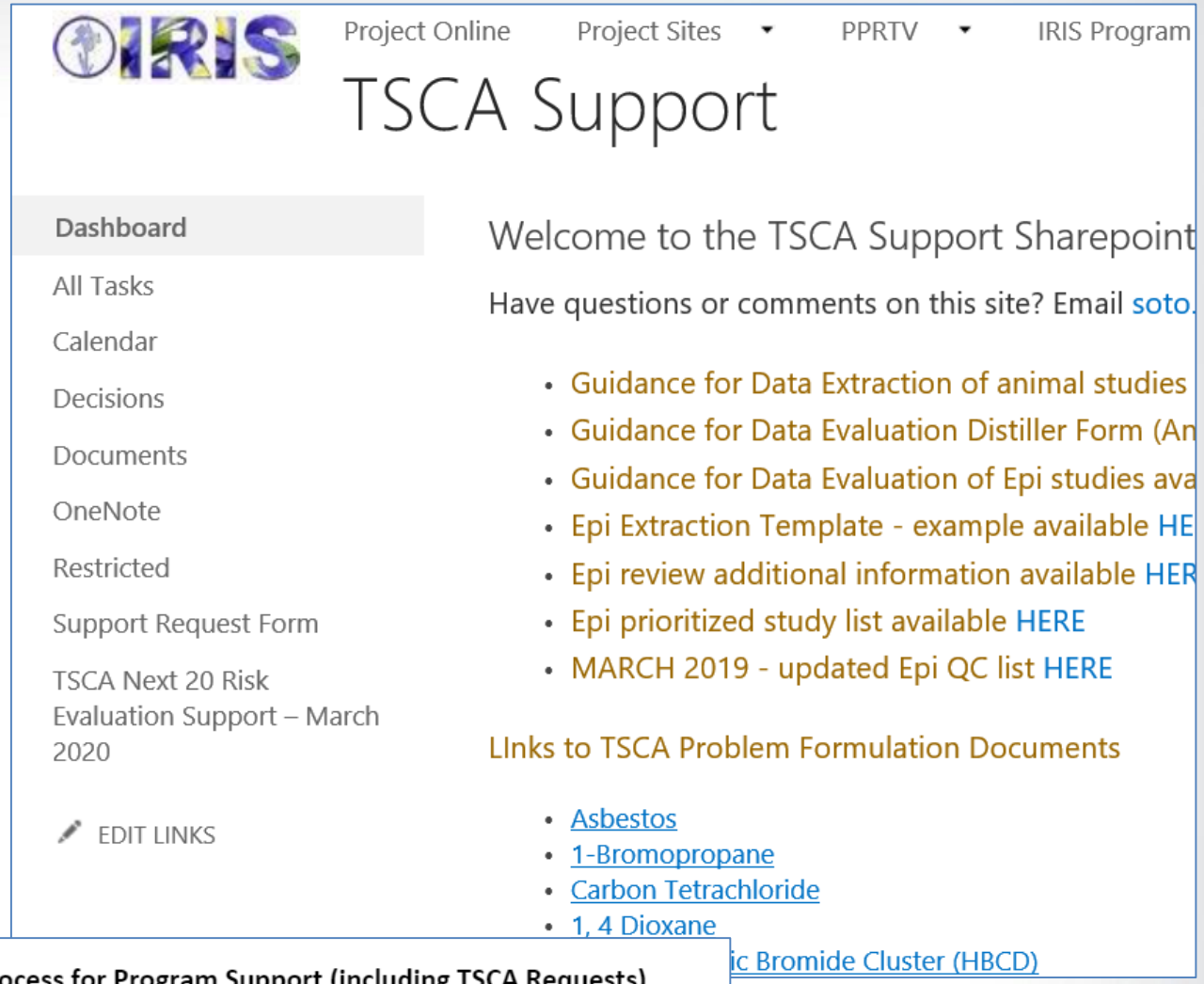
- Superfund and IRIS hotlines
  - Address regional questions translating existing assessment science or filling gaps such as:
    - Potential for risks by other exposure routes
    - Understanding if new science influences risk
- Ecological Risk Assessment
  - Provides technical reports to support ecological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

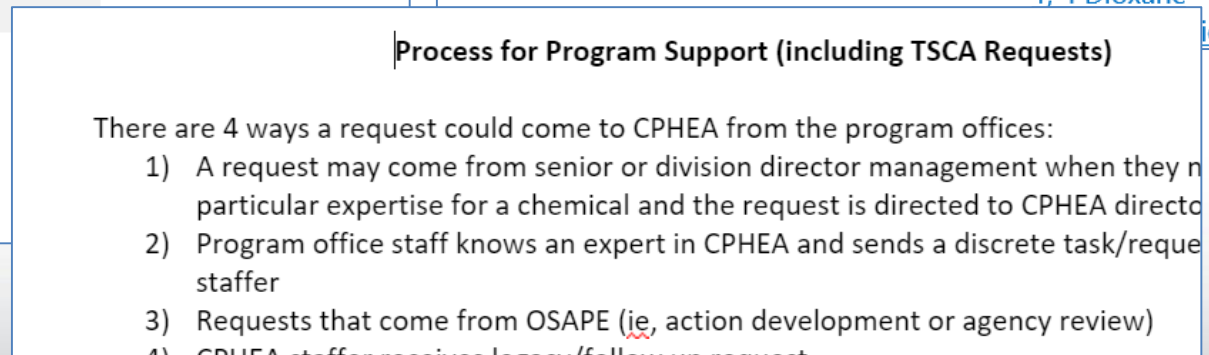
Recent Highlights of Program Office Support

- 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







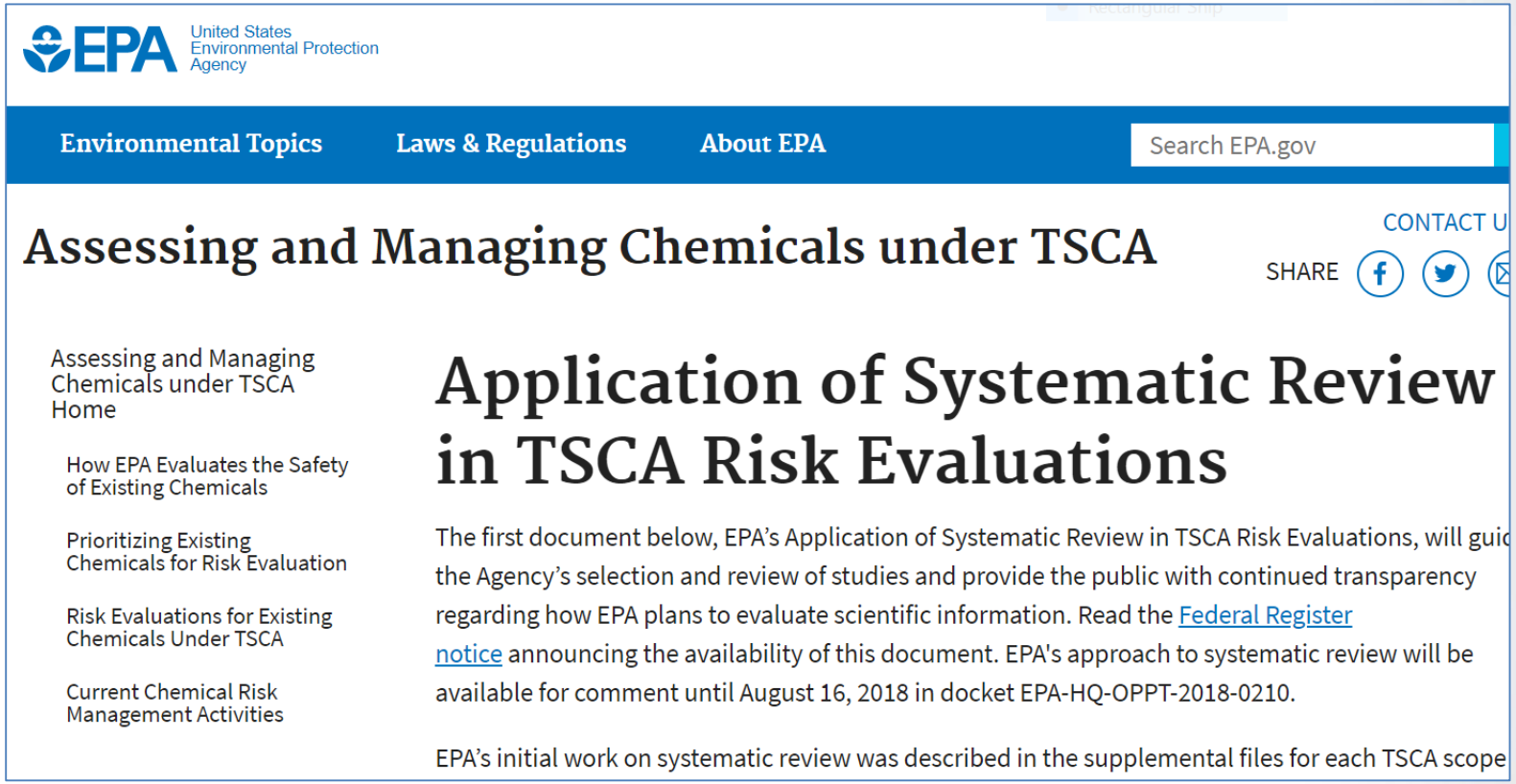
Process for Program Support (including TSCA Requests)

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 n particular expertise for a chemical and the request is directed to CPHEA directo
2) Program office staff knows an expert in CPHEA and sends a discrete task/reque staffer
3) Requests that come from OSAPE (ie, action development or agency review)

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



Topic 2 – Advancing the Science and Practice of Risk Assessment

Advancing the Science and Practice of Risk Assessment

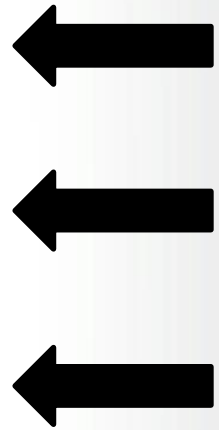
Research Area 3	Emerging and Innovative Assessment Methodologies	Essential Assessment and Infrastructure Tools	Research Area 4
	Focused on incorporating new and innovative methodologies in predictive toxicology, rapid evidence evaluation, systematic review, and toxicokinetic and dose-response modeling 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.

RA 3 – Emerging and Innovative Assessment Methodologies

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

Luci Lizarraga
CPHEA/CPAD

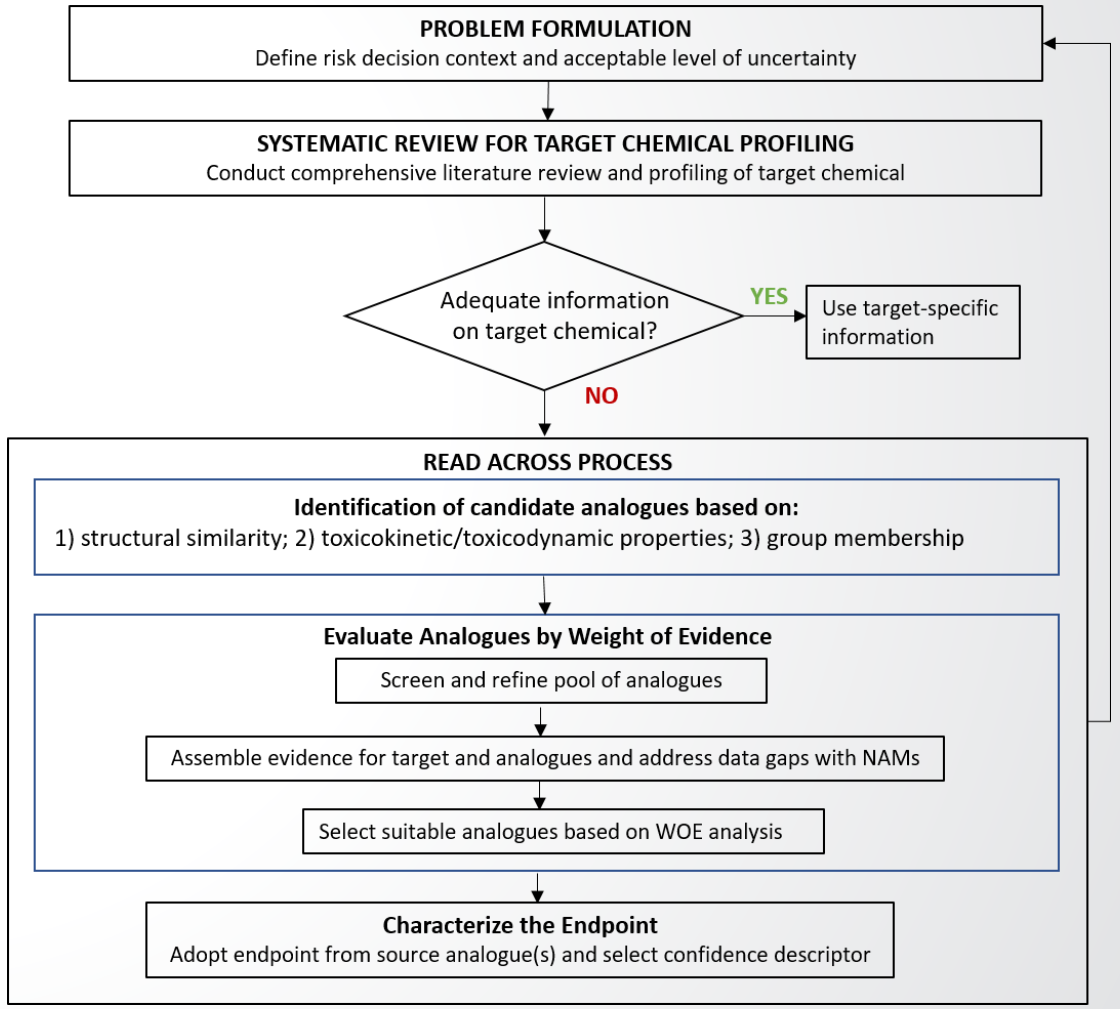
Output Lead: Luci Lizarraga

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

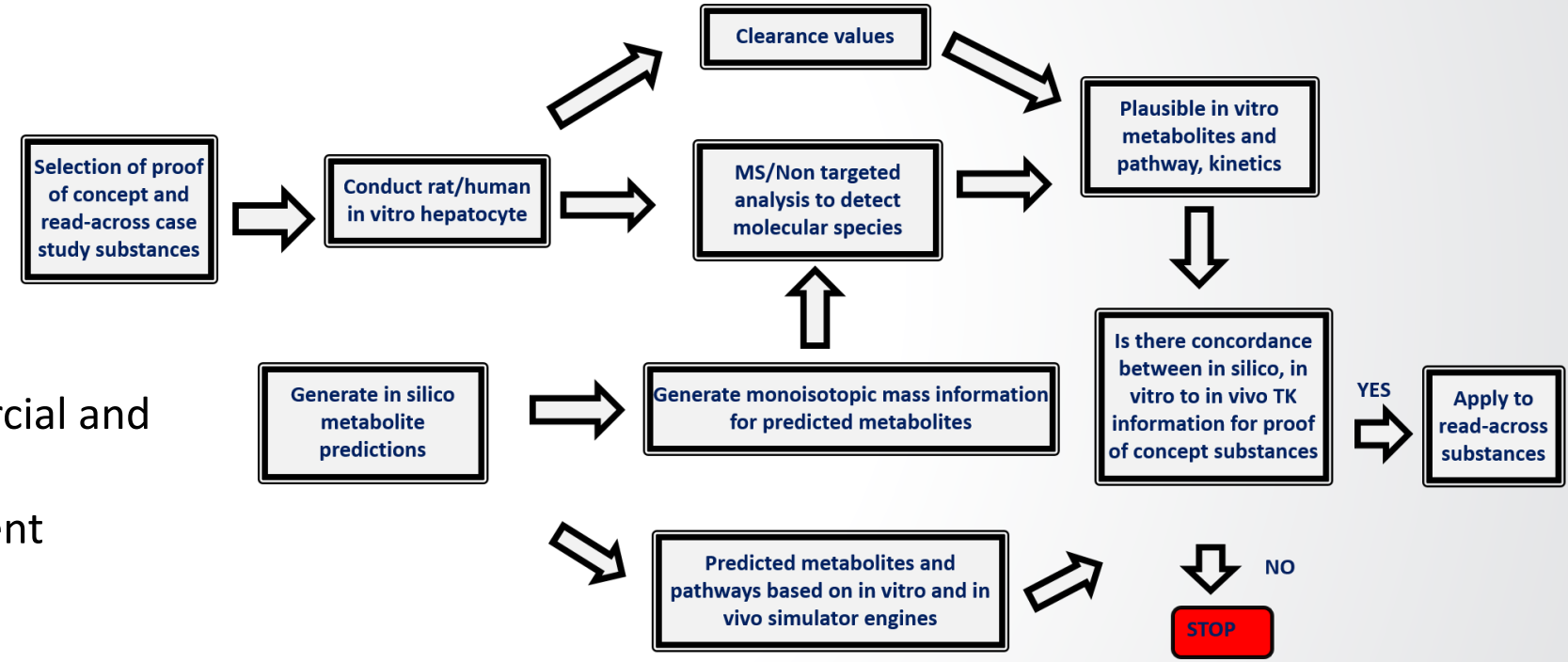
- A combination of NAM tools developed under CSS will be explored to characterize metabolism profiles and fill data gaps

- Case studies will demonstrate the utility of these tools to inform chemical assessments, including their potential application in read-across

Integrated approach for evaluating metabolism data gaps

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

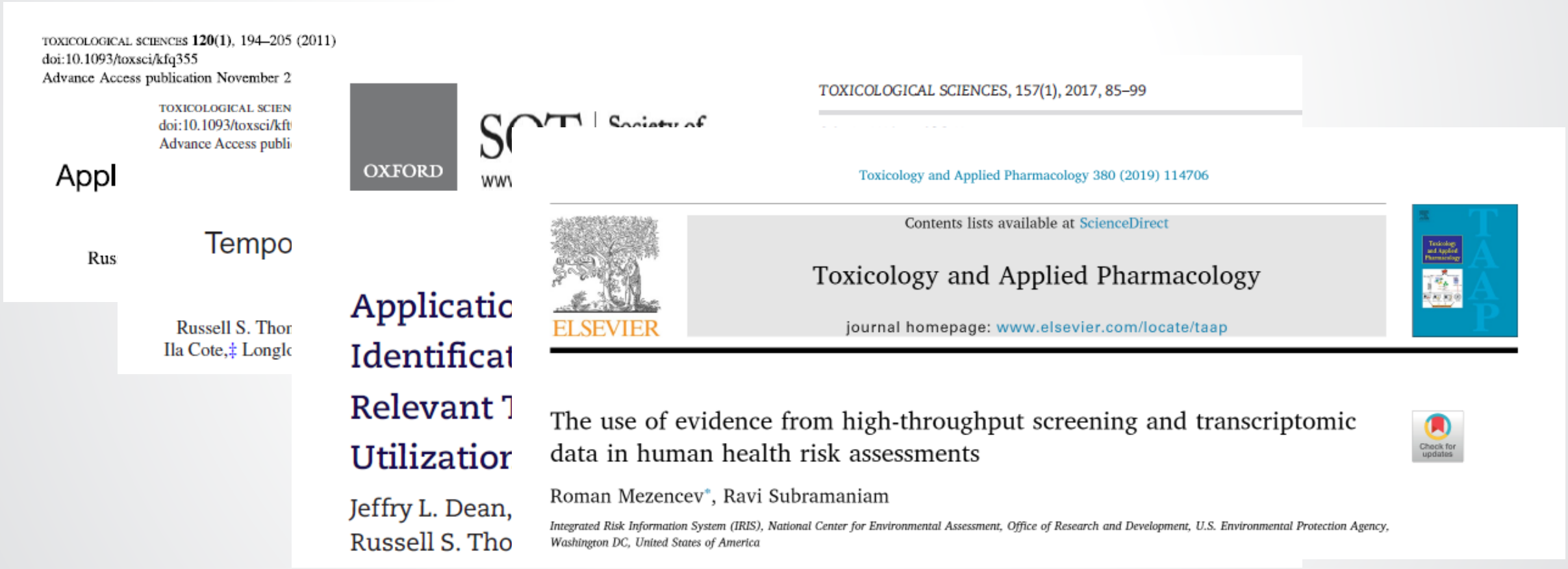
- Metabolism profiles for 32 chemicals (including chemicals being evaluated for read-across) will be determined by aggregating data from multiple sources:
  1) *In silico* predictions using commercial and publicly available software tools
  2) *In vitro* metabolism and subsequent analysis via high resolution mass spectrometry (RMS)
  3) *In vivo* literature review



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

Application of transcriptomic data in qualitative and quantitative risk assessment

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



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:

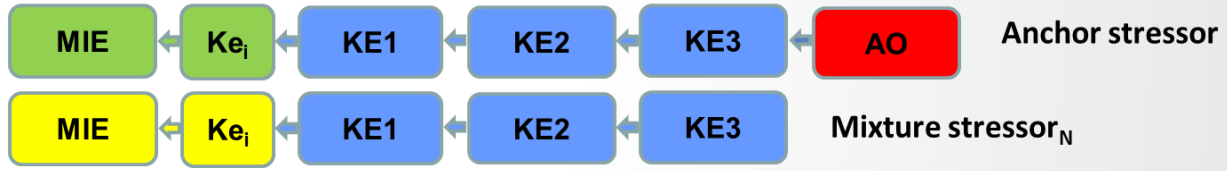
1. Use Gene Set Enrichment Analysis to identify relevant molecular pathways in the response to chemical mixtures to inform dose-response addition or sufficient similarity in mixtures risk assessment

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

Application of an AOP footprint approach to mixtures 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

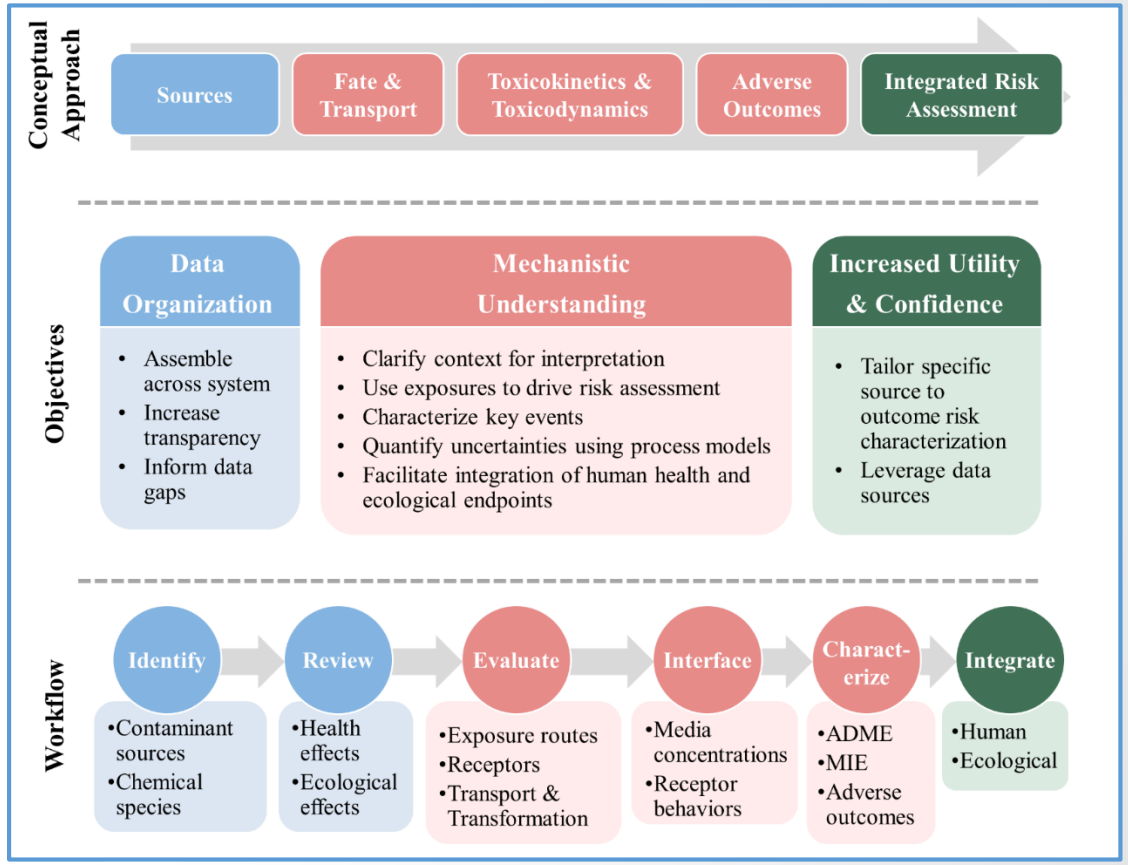


- Case studies will demonstrate how mechanistic information (e.g., AOPs) could be used to inform mixtures assessment applications such as hazard grouping and dose-response analysis

Advances in cumulative risk assessment across species

- 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



Jarabek and Hines, 2019, Current Opinion in Toxicology, 16:83-92

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 Contributers

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Grace Patlewicz

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)

Kris Thayer
CPHEA/CPAD

Output Lead: Luci Lizarraga

Systematic Evidence Maps (SEM)

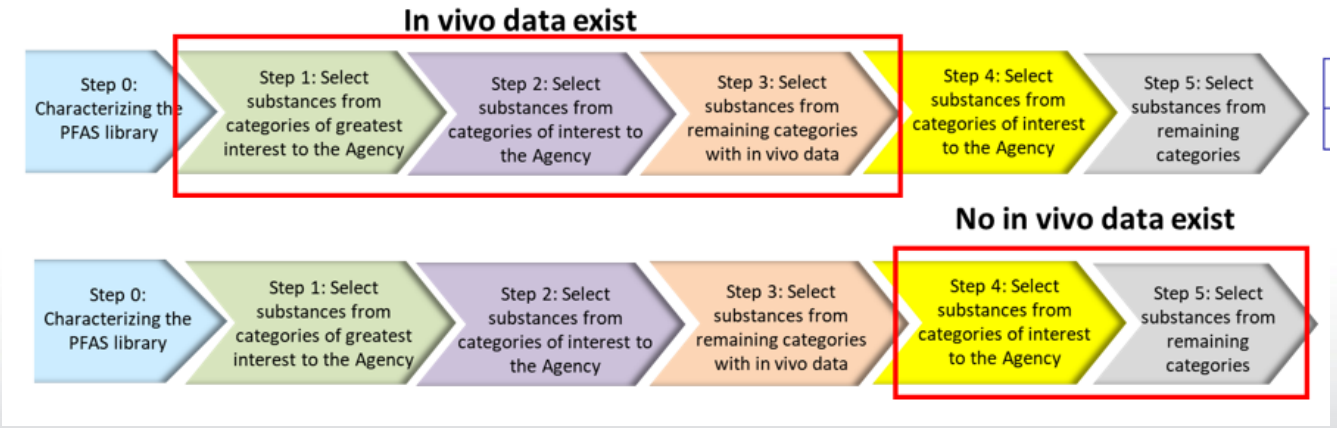
- Pre-decisional analysis that uses systematic review methods to compile and summarize evidence but does NOT reach assessment hazard or reference value conclusions
  - Front end compilation of evidence useful for assessment products
  - Publishable in journals
- Used for:
  - Problem formulation and 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

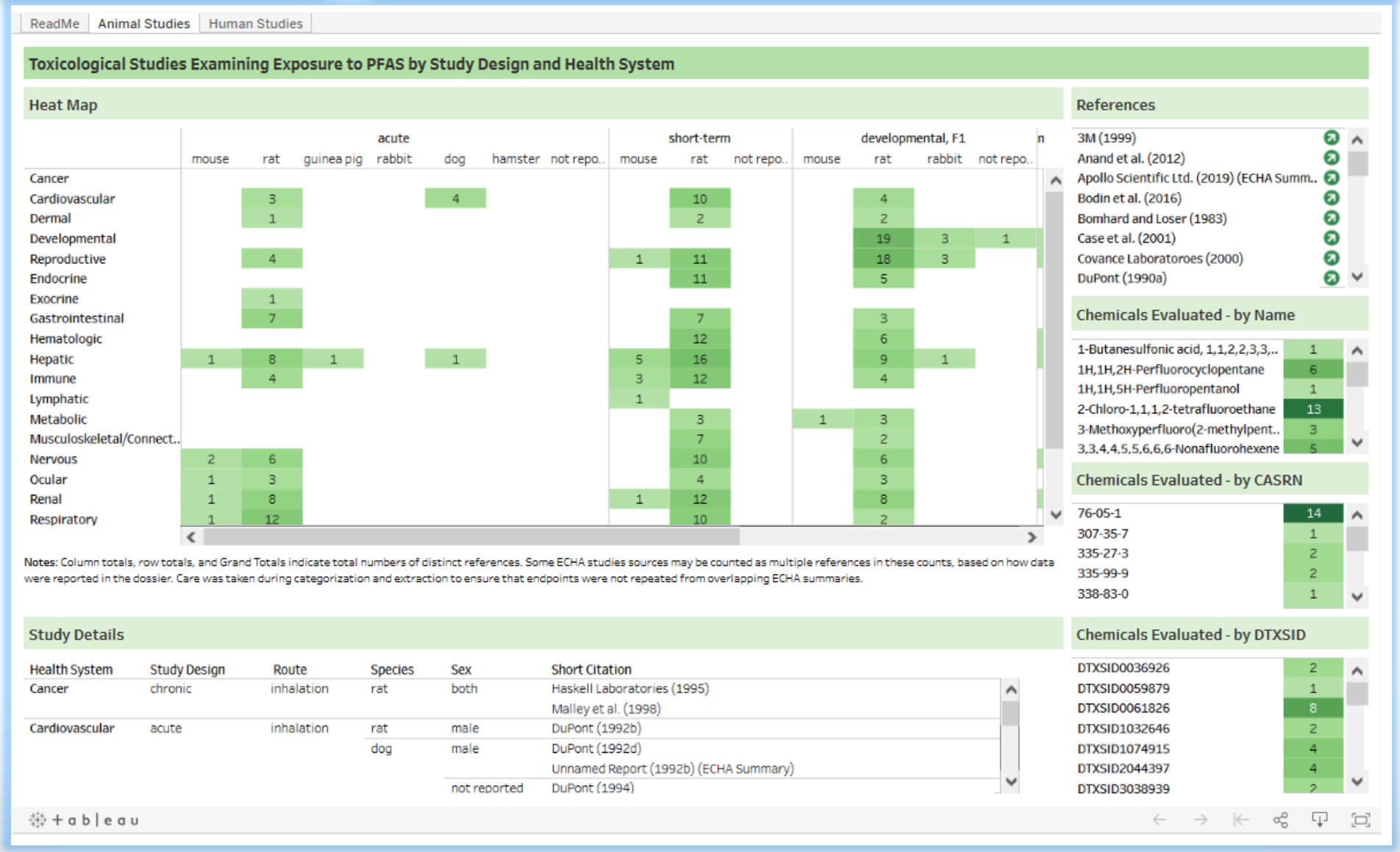
- One component of the 2019 EPA PFAS Action Plan involves the use of new approach methods to help fill information gaps. This ongoing work involves tiered toxicity testing of a structurally diverse landscape of PFAS using a suite of in vitro toxicity and toxicokinetic assays
- One goal is to use existing 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



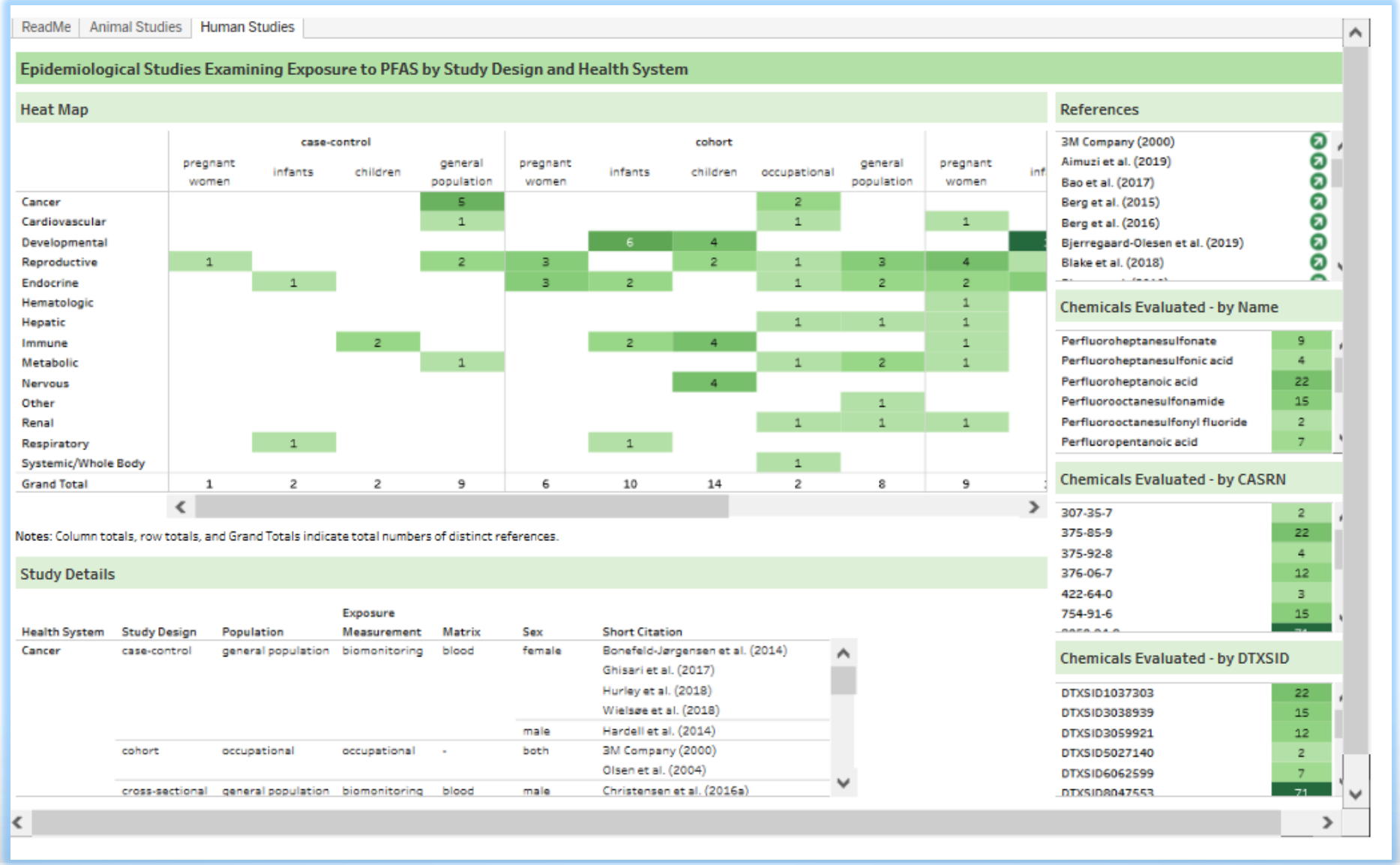
PFAS SEM Methods

- 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



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	infants	children	general population	pregnant women	infants	children	occupational	general population	pregnant women	inf
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				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.

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

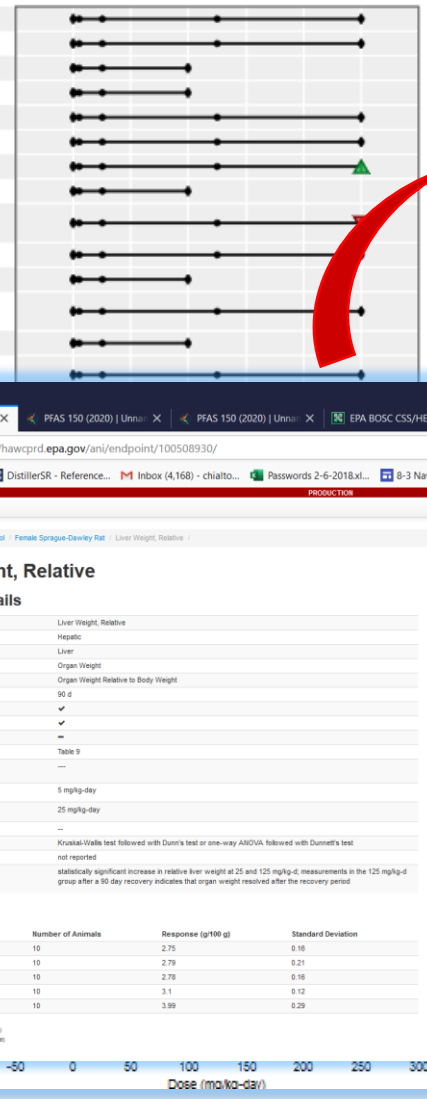
Study Details

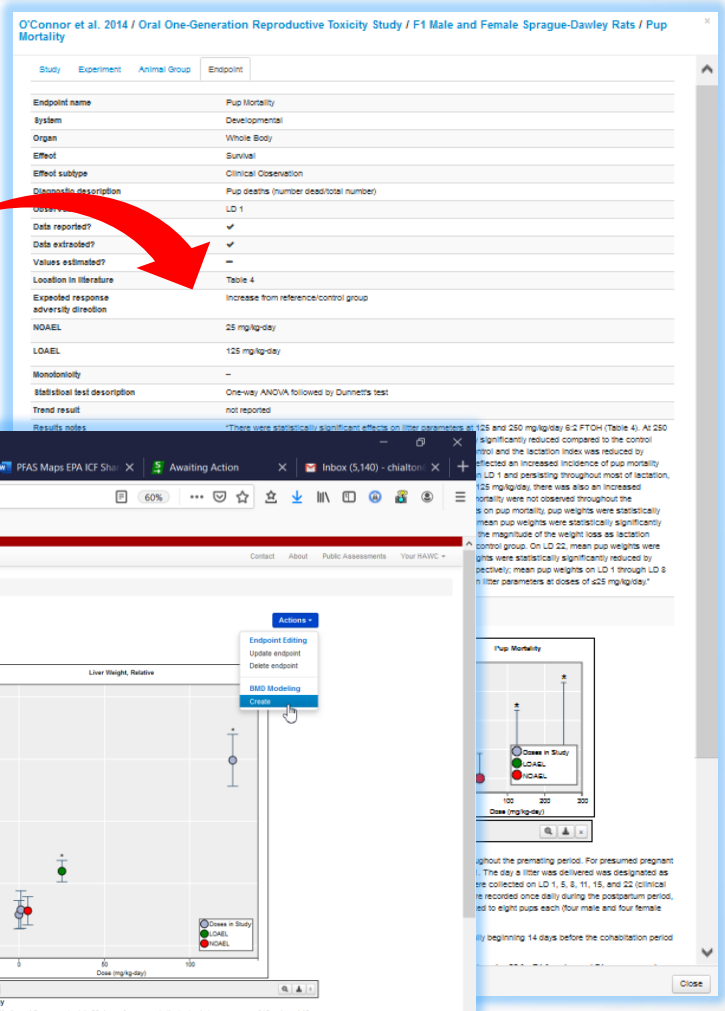
Health System	Study Design	Population	Exposure Measurement	Matrix	Sex	Short Citation
Cancer	case-control	general population	biomonitoring	blood	female	Bonefeld-Jørgensen et al. (2014)
						Ghisari et al. (2017)
						Hurley et al. (2018)
						Wielsøe et al. (2018)
					male	Hardell et al. (2014)
	cohort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

6:2 Fluorotelomer Alcohol and Developmental Effects in HAWC

Endpoint	Study	Animal Description	Route	Exposure Duration	Observation Time
Body Weight, Fetal	O'Connor et al. 2014	F1 Rat, Sprague-Dawley (Crl:Cd (Sd)) (♂♀)	oral gavage	GD 6-20	GD 21
Dead Fetuses	O'Connor et al. 2014	F1 Rat, Sprague-Dawley (Crl:Cd (Sd)) (♂♀)	oral gavage	GD 6-20	GD 21
Eye Opening	Unnamed Report (2013b) (ECHA Summary)	F1 Mouse, CD-1 (♂♀)	oral gavage	premating-lactation	LD 21
Fetus Or Pup/Neonate, Small	Unnamed Report (2013b) (ECHA Summary)	F1 Mouse, CD-1 (♂♀)	oral gavage	premating-lactation	LD 0-21
Fetuses, Live	O'Connor et al. 2014	F1 Rat, Sprague-Dawley (Crl:Cd (Sd)) (♂♀)	oral gavage	GD 6-20	GD 21
Frontal, Incomplete Ossification	O'Connor et al. 2014	F1 Rat, Sprague-Dawley (Crl:Cd (Sd)) (♂♀)	oral gavage	GD 6-20	GD 21
Interparietal, Incomplete Ossification	O'Connor et al. 2014	F1 Rat, Sprague-Dawley (Crl:Cd (Sd)) (♂♀)	oral gavage	GD 6-20	GD 21
Lactation Index	Unnamed Report (2013b) (ECHA Summary)	F1 Mouse, CD-1 (♂♀)	oral gavage	premating-lactation	LD 4-21
	O'Connor et al. 2014	F1 Rat, Sprague-Dawley (Crl:Cd (Sd)) (♂♀)	oral gavage	70 d premating-termination	LD 21
Litters with Fetal Alterations	O'Connor et al. 2014	F1 Rat, Sprague-Dawley (Crl:Cd (Sd)) (♂♀)	oral gavage	GD 6-20	GD 21
Live Pups Born	Unnamed Report (2013b) (ECHA Summary)	F1 Mouse, CD-1 (♂♀)	oral gavage	premating-lactation	LD 0
	O'Connor et al. 2014	F1 Rat, Sprague-Dawley (Crl:Cd (Sd)) (♂♀)	oral gavage	70 d premating-termination	LD 1
Liver, Discolored	Unnamed Report (2013b) (ECHA Summary)	F1 Mouse, CD-1 (♂♀)	oral gavage	premating-lactation	LD 21
No. of Pups Born	O'Connor et al. 2014	F1 Rat, Sprague-Dawley (Crl:Cd (Sd)) (♂♀)	oral gavage	70 d premating-termination	LD 1
Nursing Behavior	Unnamed report (2005b) (ECHA summary)	F1 Rat, Crl:CD(SD) (♂♀)	oral gavage		
Parietal, Incomplete Ossification	O'Connor et al. 2014	F1 Rat, Sprague-Dawley (Crl:Cd (Sd)) (♂♀)	oral gavage		
Pelvis, Ischium Incompletely Ossified	O'Connor et al. 2014	F1 Rat, Sprague-Dawley (Crl:Cd (Sd)) (♂♀)	oral gavage		
Pelvis, Pubis Incompletely Ossified	O'Connor et al. 2014	F1 Rat, Sprague-Dawley (Crl:Cd (Sd)) (♂♀)	oral gavage		
Pup Mortality	O'Connor et al. 2014	F1 Rat, Sprague-Dawley (Crl:Cd (Sd)) (♂♀)	oral gavage		
Pup Weight	Unnamed report (2005b) (ECHA summary)	F1 Rat, Crl:CD(SD) (♂♀)	oral gavage		
Pup Weight Relative to Litter	Unnamed Report (2013b) (ECHA Summary)	F1 Mouse, CD-1 (♂♀)	oral gavage		
	O'Connor et al. 2014	F1 Rat, Sprague-Dawley (Crl:Cd (Sd)) (♂♀)	oral gavage		
Skeletal Malformation	Unnamed report (2005b) (ECHA summary)	F1 Rat, Crl:CD(SD) (♂♀)	oral gavage		
Supraoccipital, Incomplete Ossification	O'Connor et al. 2014	F1 Rat, Sprague-Dawley (Crl:Cd (Sd)) (♂♀)	oral gavage		
Survival	Unnamed Report (2013b) (ECHA Summary)	F1 Mouse, CD-1 (♂♀)	oral gavage		
Viability Index	Unnamed Report (2013b) (ECHA Summary)	F1 Mouse, CD-1 (♂♀)	oral gavage		
	Unnamed report (2005b) (ECHA summary)	F1 Rat, Crl:CD(SD) (♂♀)	oral gavage		
	O'Connor et al. 2014	F1 Rat, Sprague-Dawley (Crl:Cd (Sd)) (♂♀)	oral gavage		
Weaning Body Weight	Unnamed Report (2013b) (ECHA Summary)	F1 Mouse, CD-1 (♂♀)	oral gavage		
Zygomatic Arch, Incomplete Ossification	O'Connor et al. 2014	F1 Rat, Sprague-Dawley (Crl:Cd (Sd)) (♂♀)	oral gavage		

- no apparent treatment-related effect
- treatment-related increase
- treatment-related decrease





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	case-control	cross-sectional	cohort	cross-sectional	case-control	cohort	cross-sectional	cohort
cardiovascular								2	1
developmental			1		2				
endocrine	1			1				2	
immune			1				1		
nervous				1					
reproductive						1			
respiratory		1							

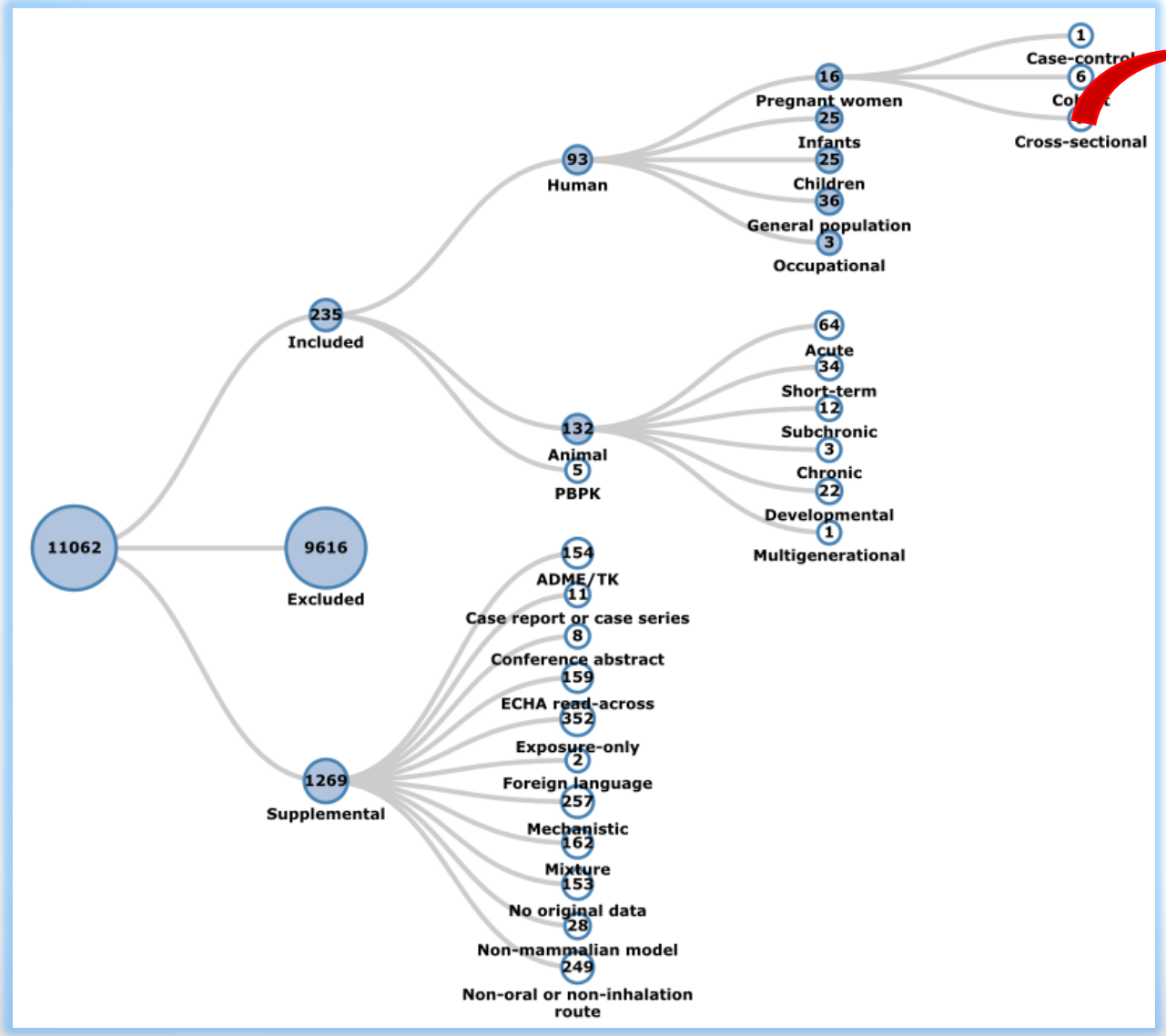
Reference	Population	Health System	case-control	cohort	cross-sectional
Kim et al, 2016	infants	endocrine			
Dong et al., 2013	children	respiratory			
Lee et al., 2018	children	developmental			
Smit et al, 2015	children	immune			
Callan et al., 2016	pregnant women	developmental			
Hoyer et al., 2017	pregnant 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

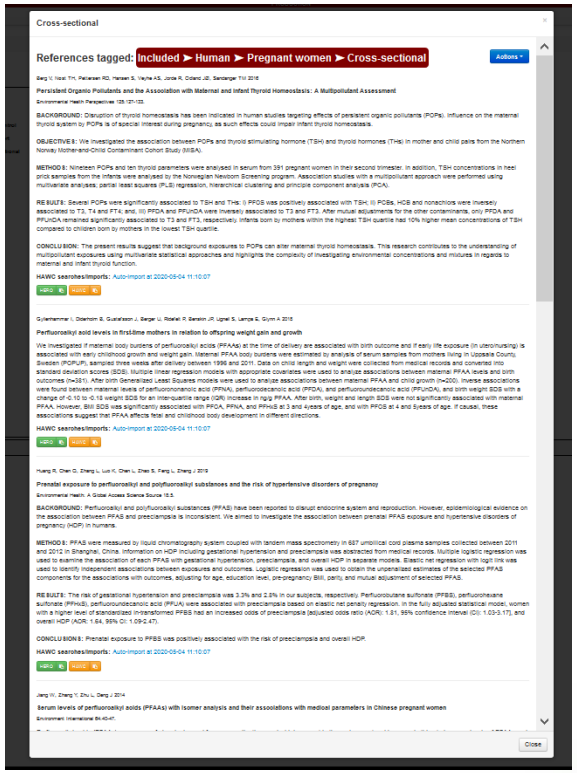
Click here to view the interactive version.

Study Evaluation

Interactive Literature Trees in HAWC



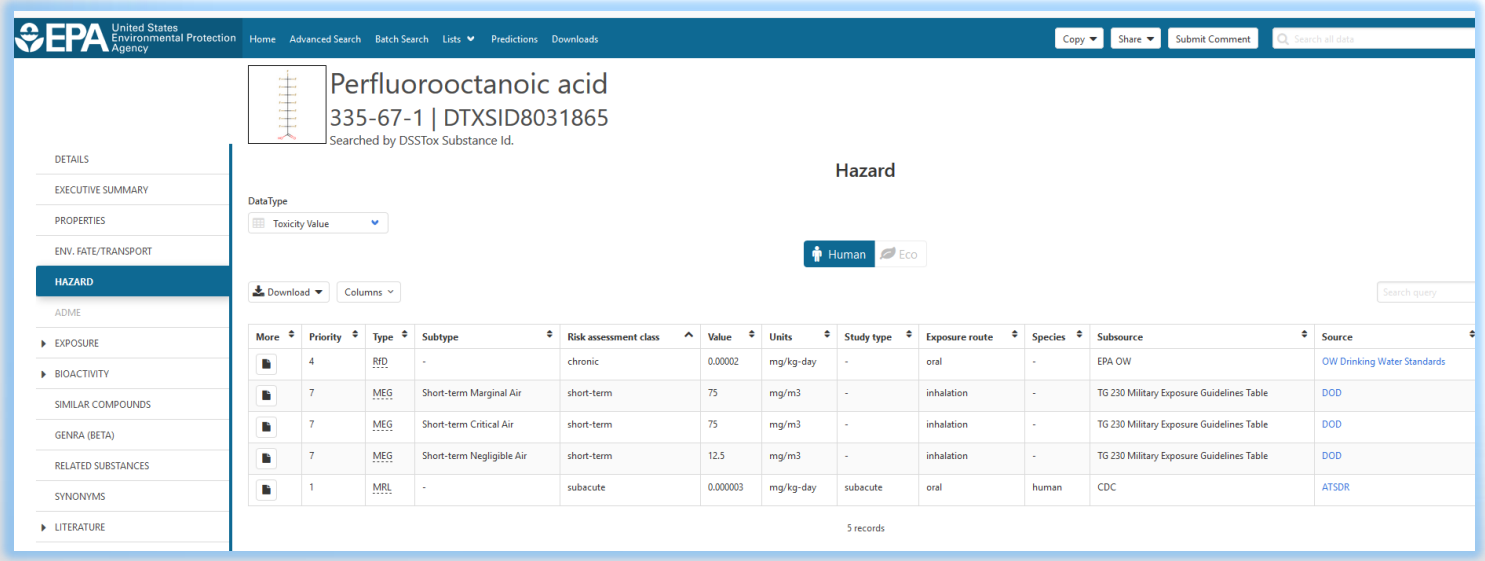
Click to see reference list



Moving Forward

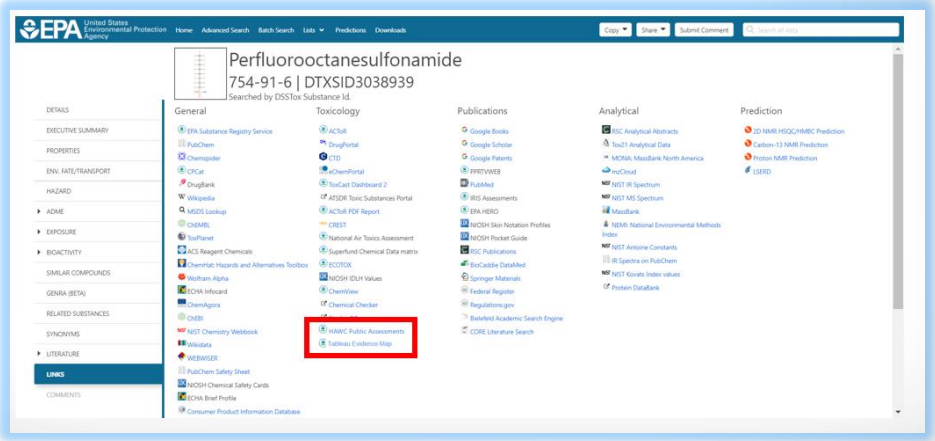
- Experience with SEM for 100+ PFAS was encouraging, pursuing efforts with a larger set of PFAS.
- SEMs have become a routine component for IRIS and PPRTV assessments
- Make findings available in CompTox Chemicals Dashboard via ToxVal module and links to the SEM report and HAWC page

EPA CompTox Chemicals Dashboard Hazard Module



More	Priority	Type	Subtype	Risk assessment class	Value	Units	Study type	Exposure route	Species	Subsource	Source
	4	RfD	-	chronic	0.00002	mg/kg-day	-	oral	-	EPA OW	OW Drinking Water Standards
	7	MEG	Short-term Marginal Air	short-term	75	mg/m3	-	inhalation	-	TG 230 Military Exposure Guidelines Table	DOD
	7	MEG	Short-term Critical Air	short-term	75	mg/m3	-	inhalation	-	TG 230 Military Exposure Guidelines Table	DOD
	7	MEG	Short-term Negligible Air	short-term	12.5	mg/m3	-	inhalation	-	TG 230 Military Exposure Guidelines Table	DOD
	1	MRL	-	subacute	0.000003	mg/kg-day	subacute	oral	human	CDC	ATSDR

EPA CompTox Chemicals Dashboard Links



Output 3.3

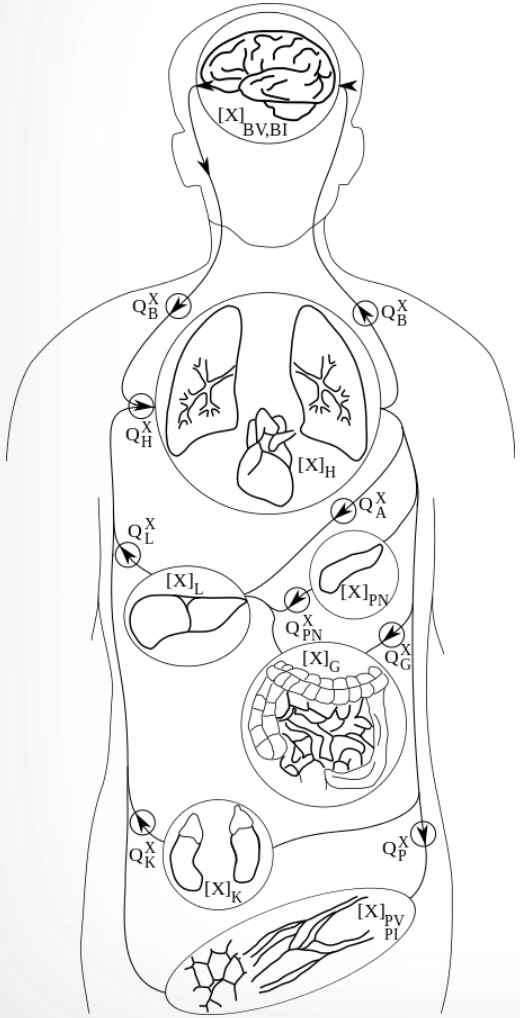
Evaluate and develop improved methods for dose extrapolation and the related uncertainty characterization in human health risk assessment via classical methods and integration of pharmacokinetic models

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

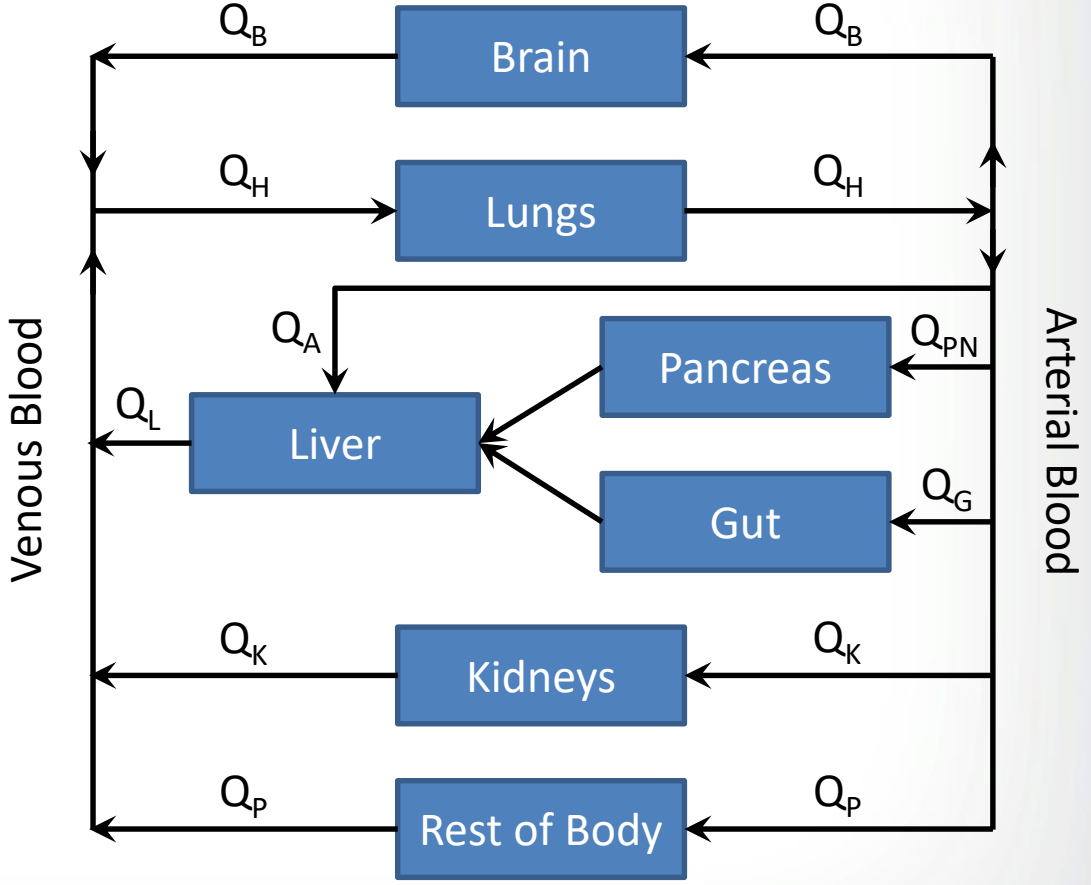
PBPK Model



(Wikimedia Commons)

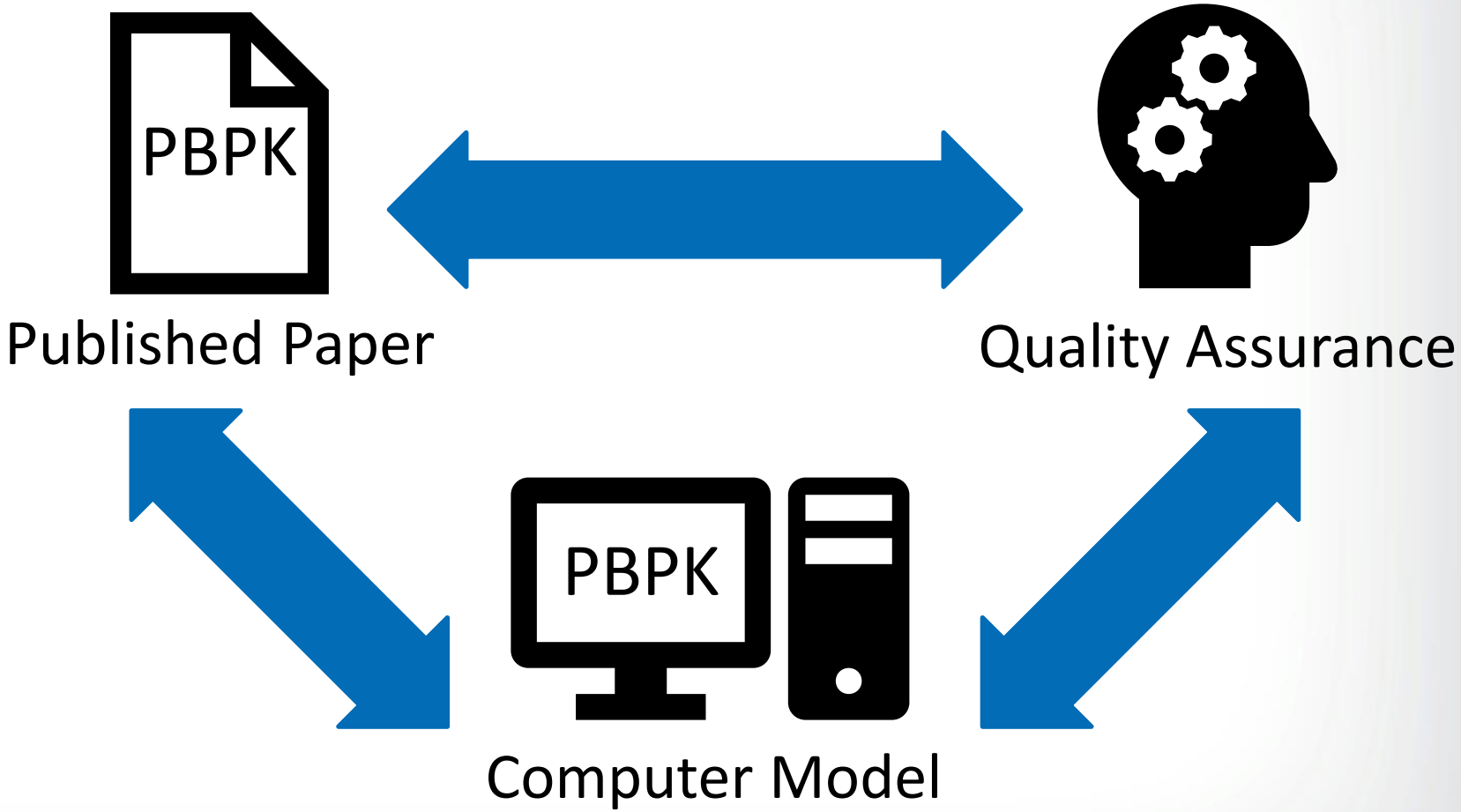
Chemical engineering applied to a **biological organism**

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

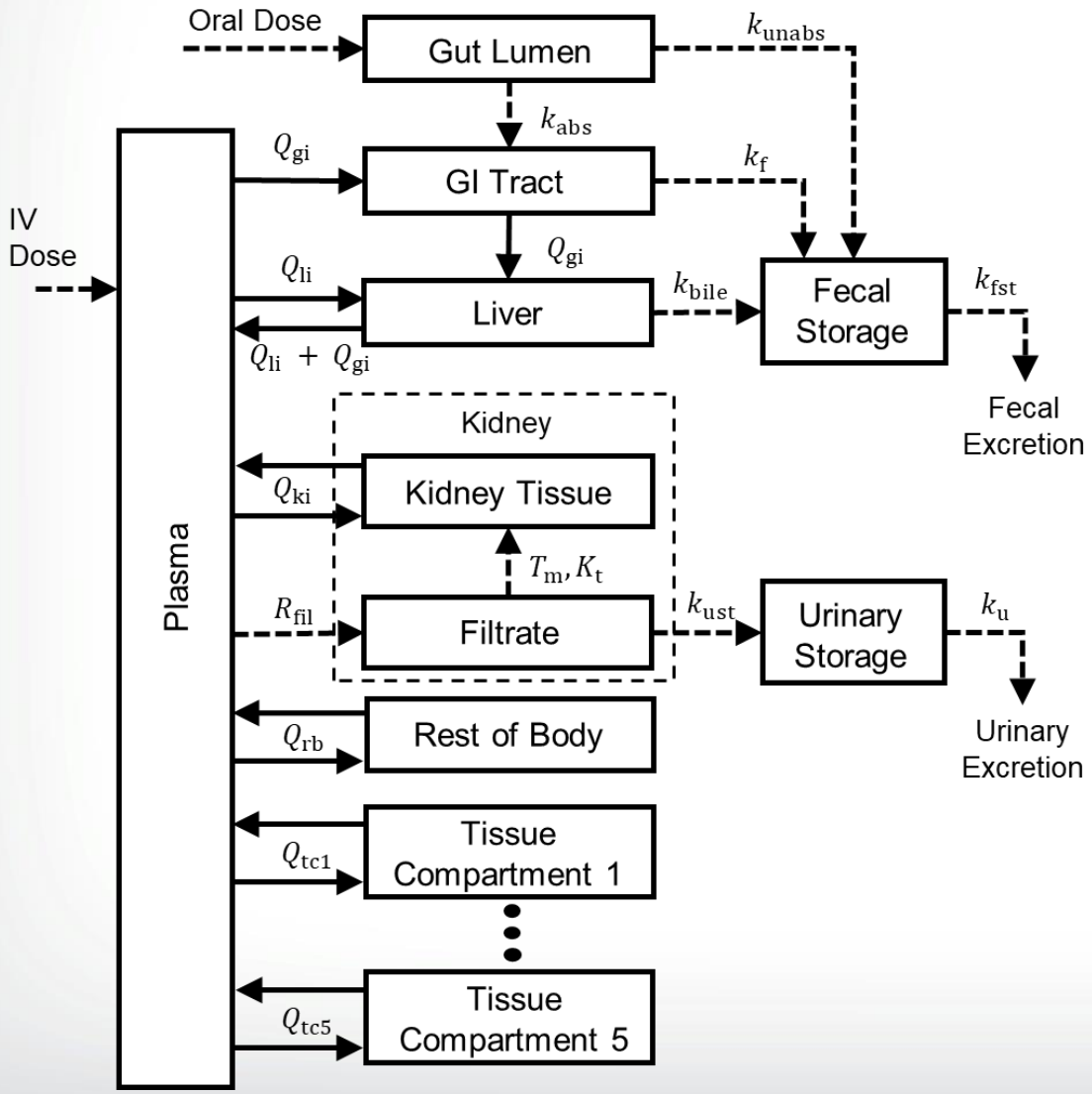


Motivation

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



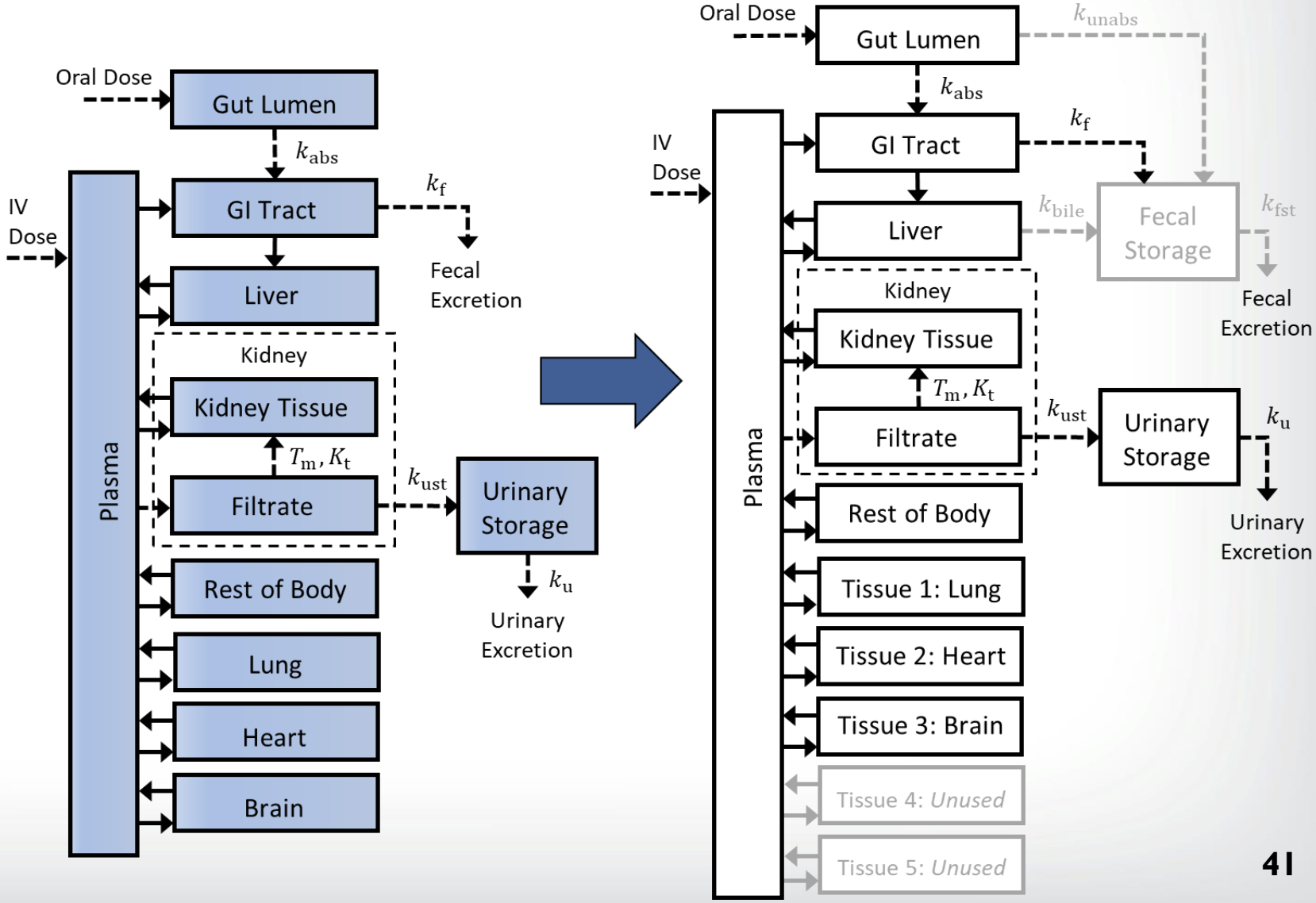
PBPK Model Template



- **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**

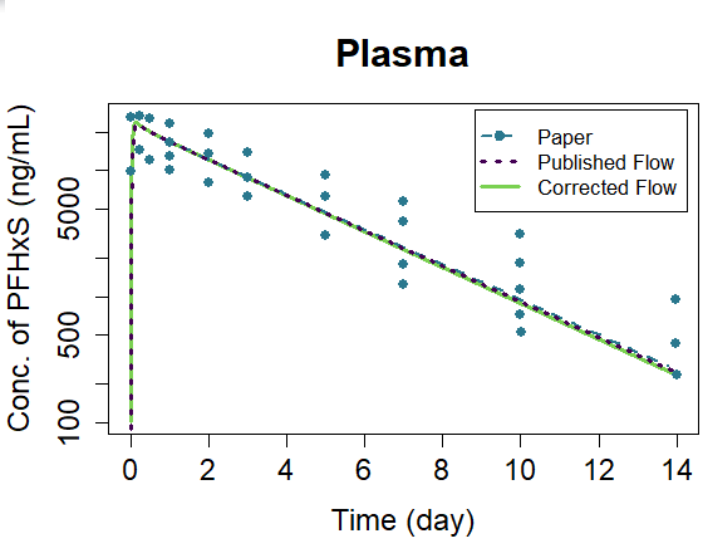
Case Study: PFHxS PBPK Model

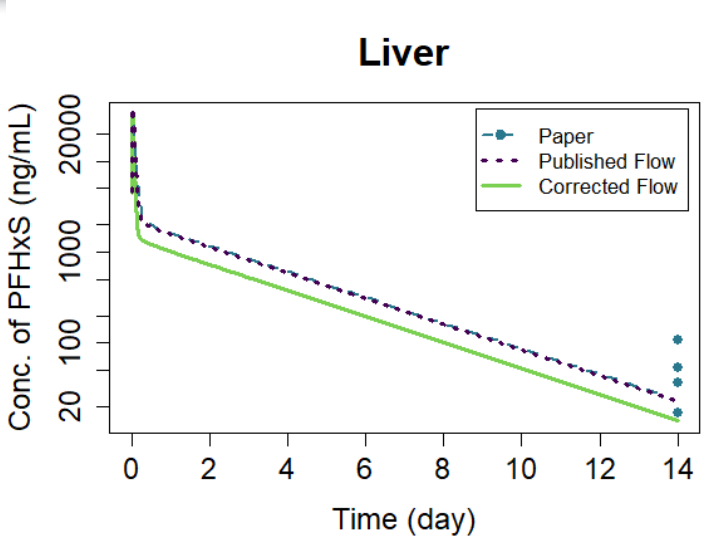
We implemented the PFHxS PBPK model of Kim et al. (2018) using the template and the published parameter values.

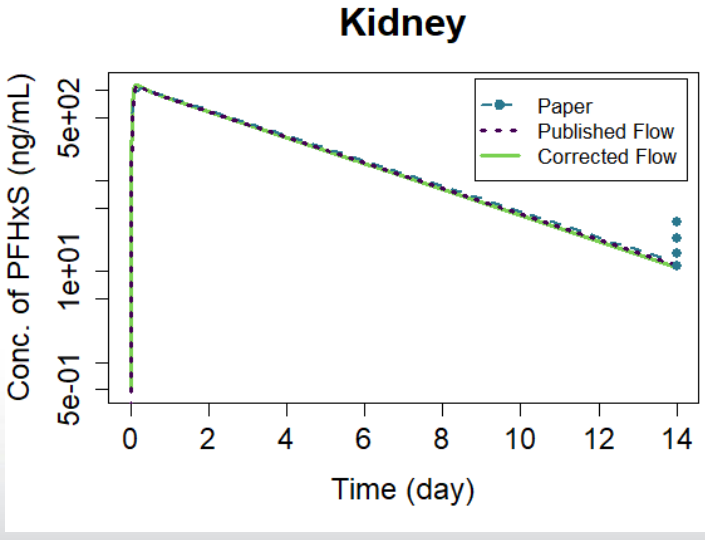


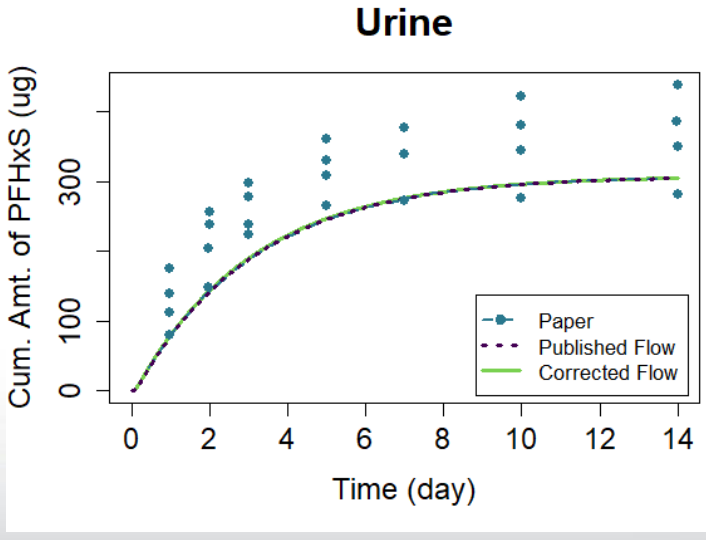
Case Study: PFHxS PBPK Model

- 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.









Conclusions

- 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)

RA4 – Essential Assessment and Infrastructure Tools

- 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)

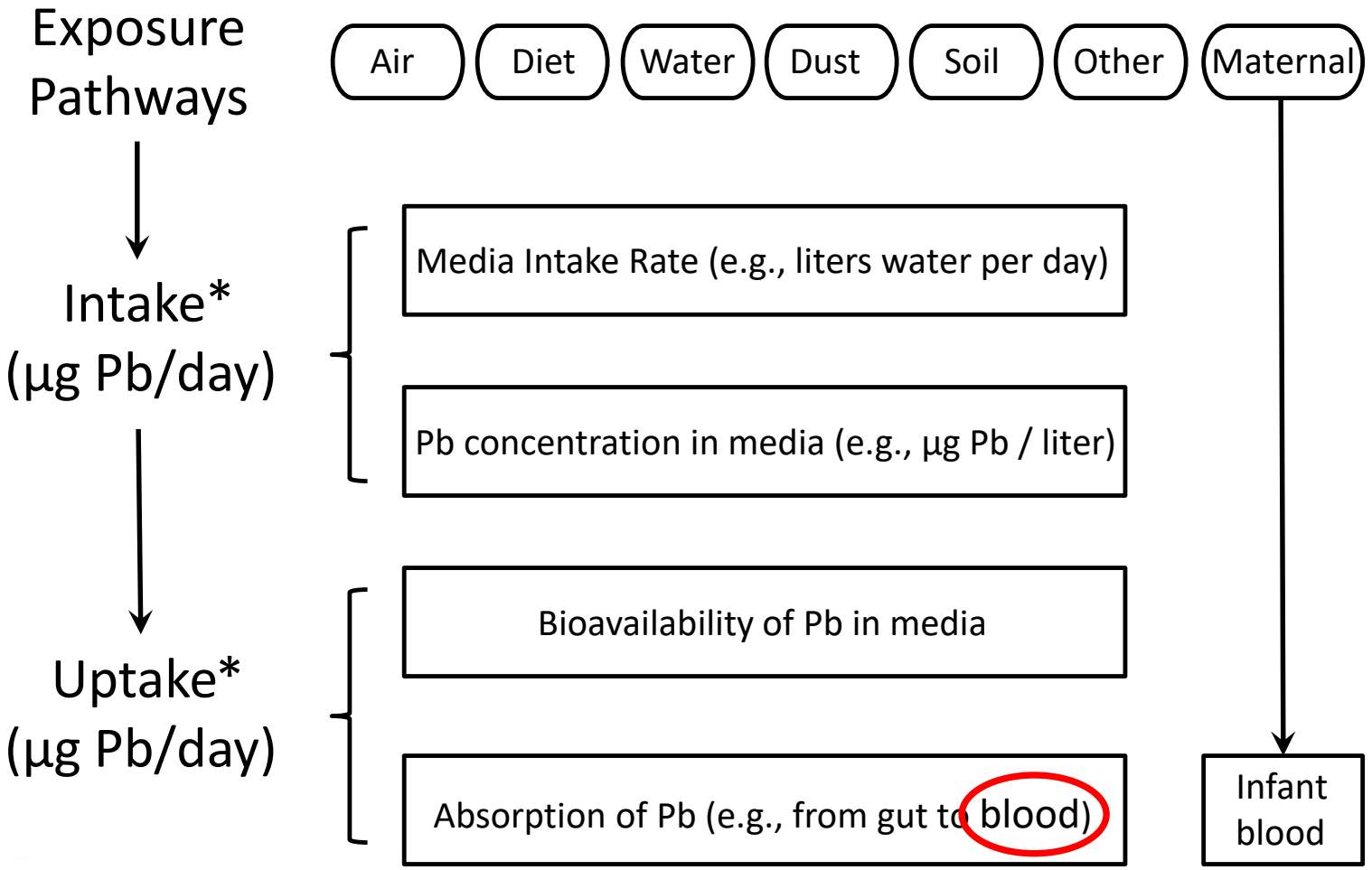
James Brown
CPHEA/HEEAD

Output Lead: Jennifer Nichols

Outline

- 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

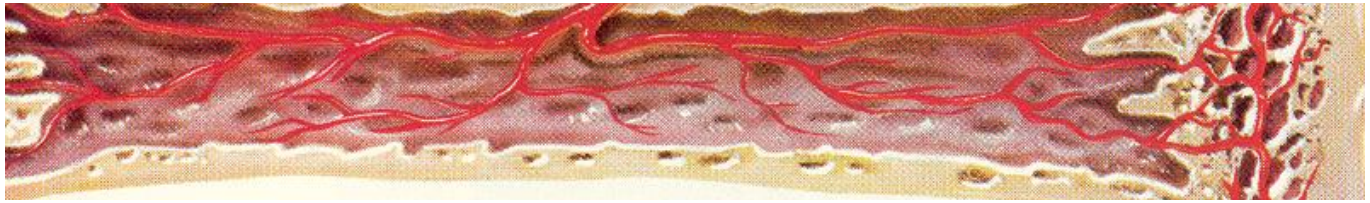


* Intake rates and absorption in GI tract all vary with age

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.

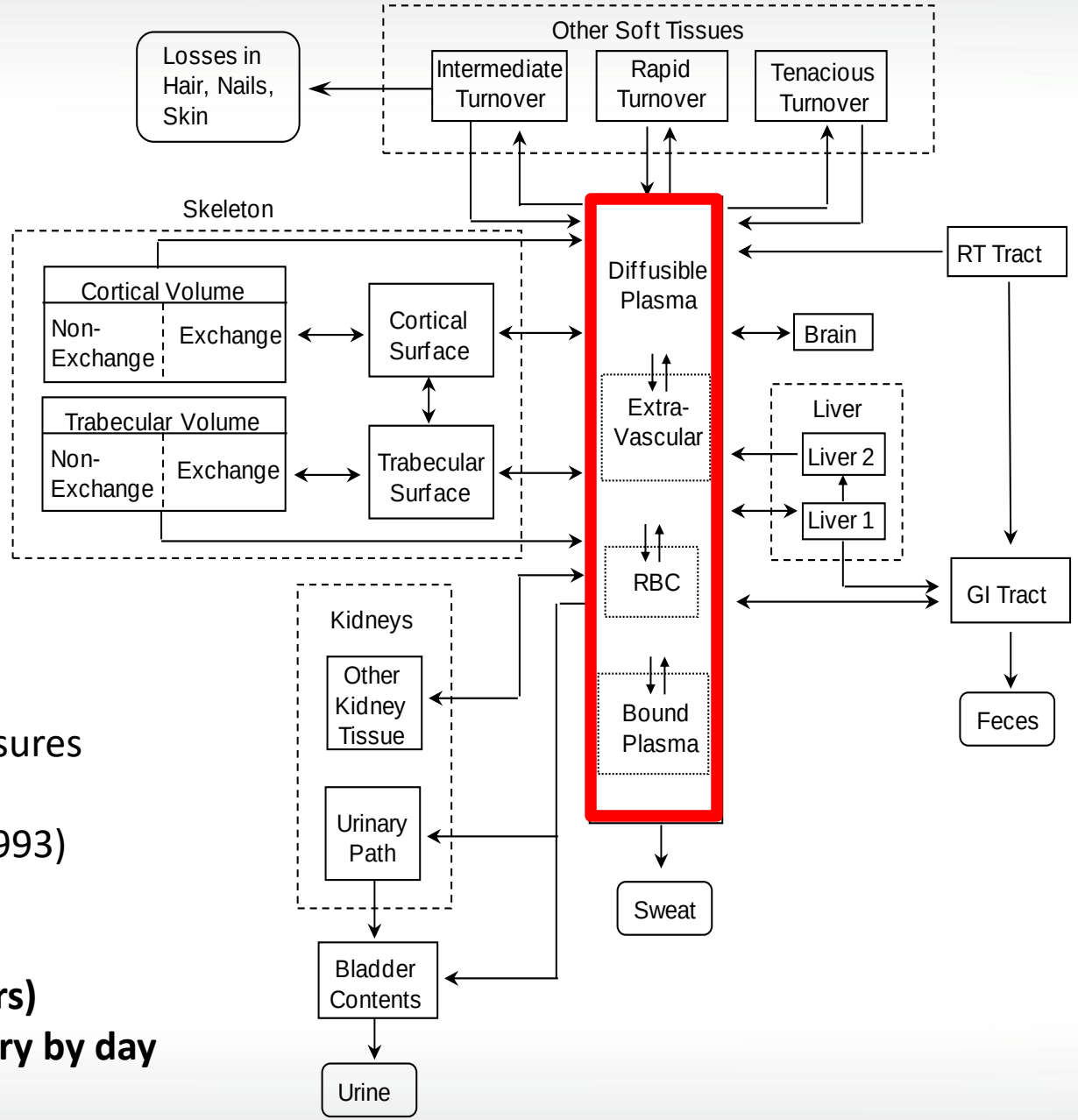
Integrated Exposure Uptake Biokinetic (IEUBK) model

- 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

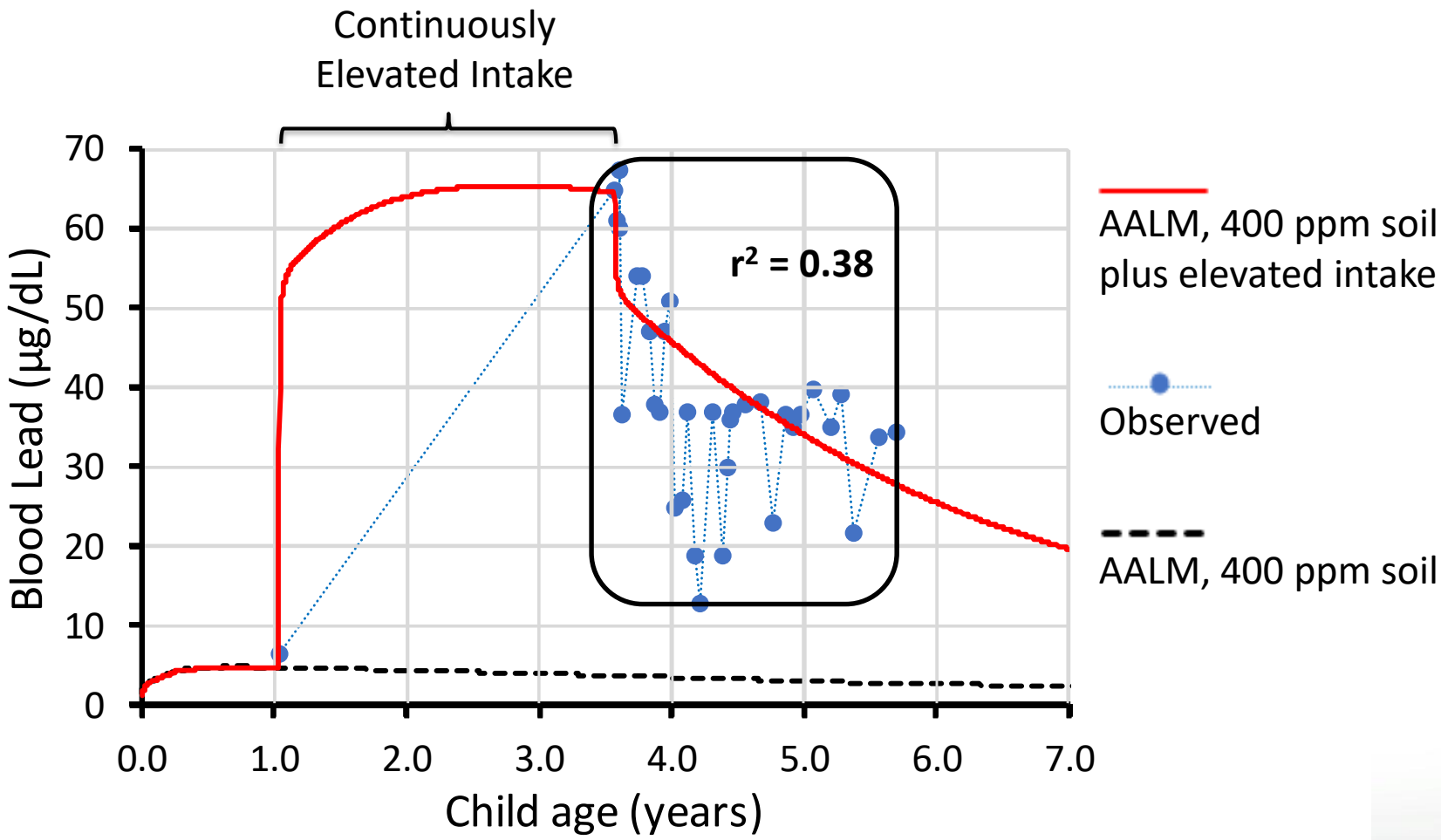
Recent AALM Development

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)

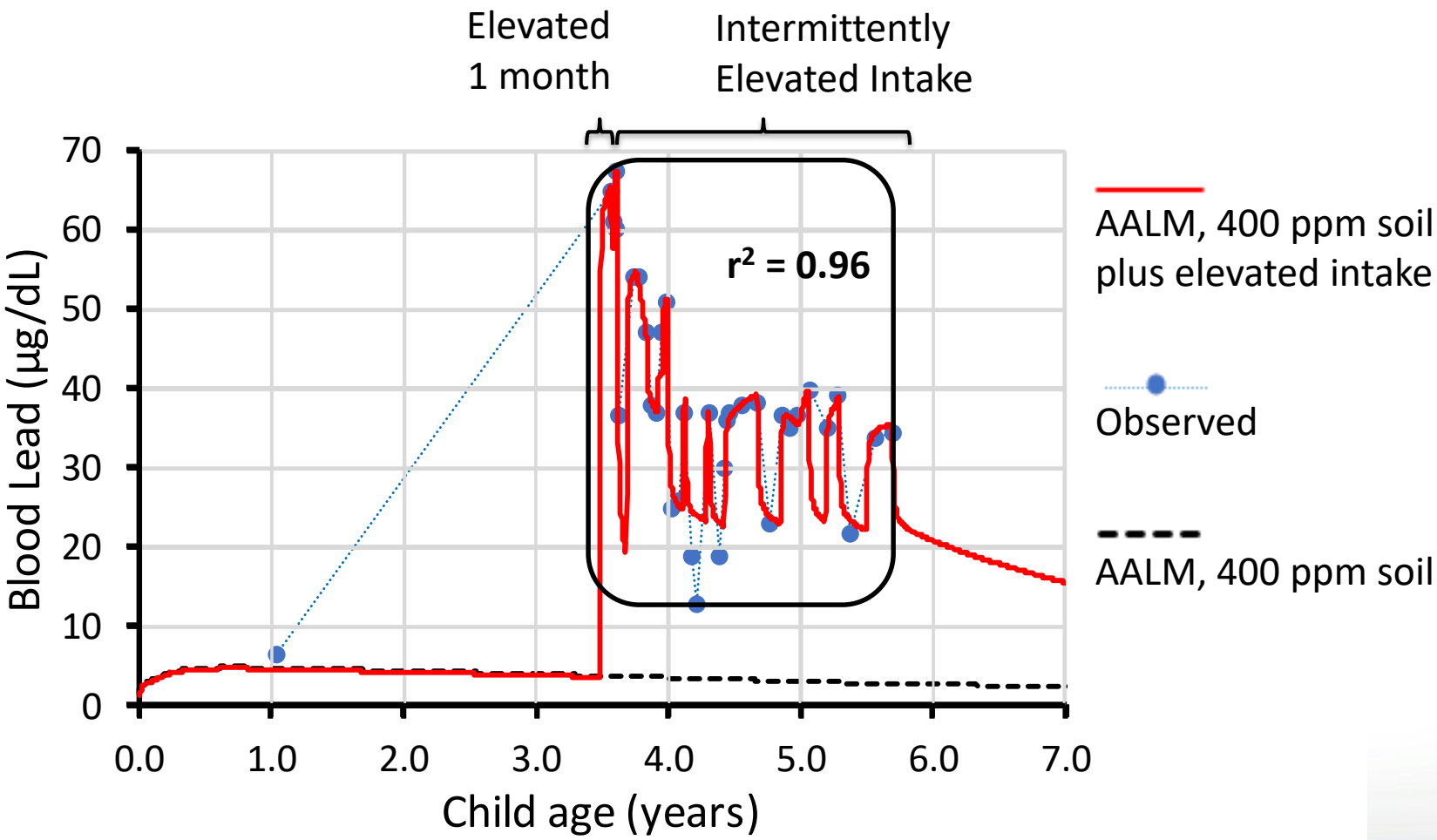
AALM Example of Capabilities

Are elevated BLL due to continued exposure?

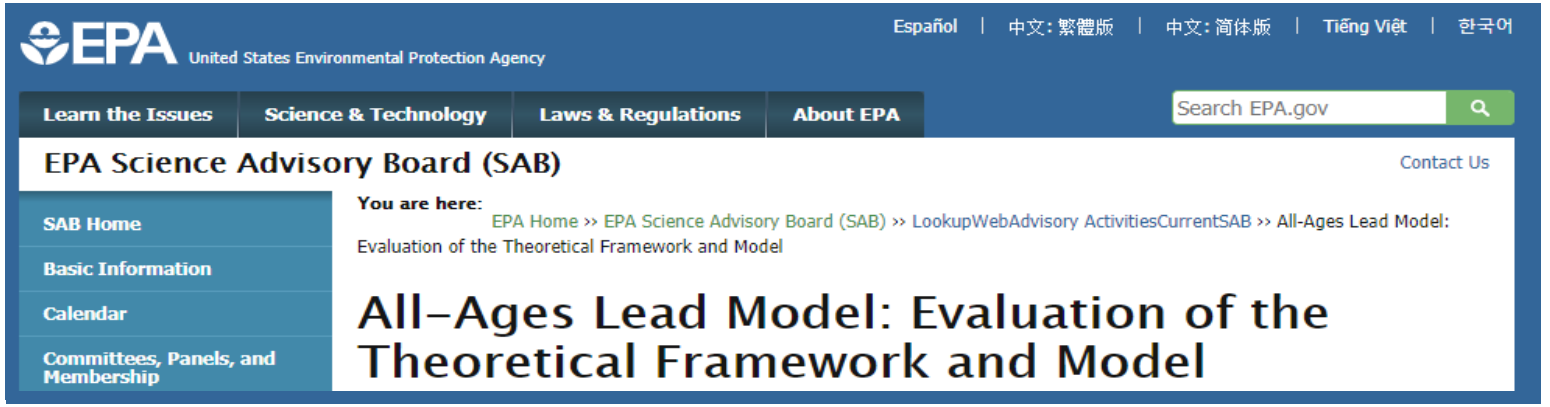


AALM Example of Capabilities

Are elevated BLL due to continued exposure?



SAB Peer Review of AALM



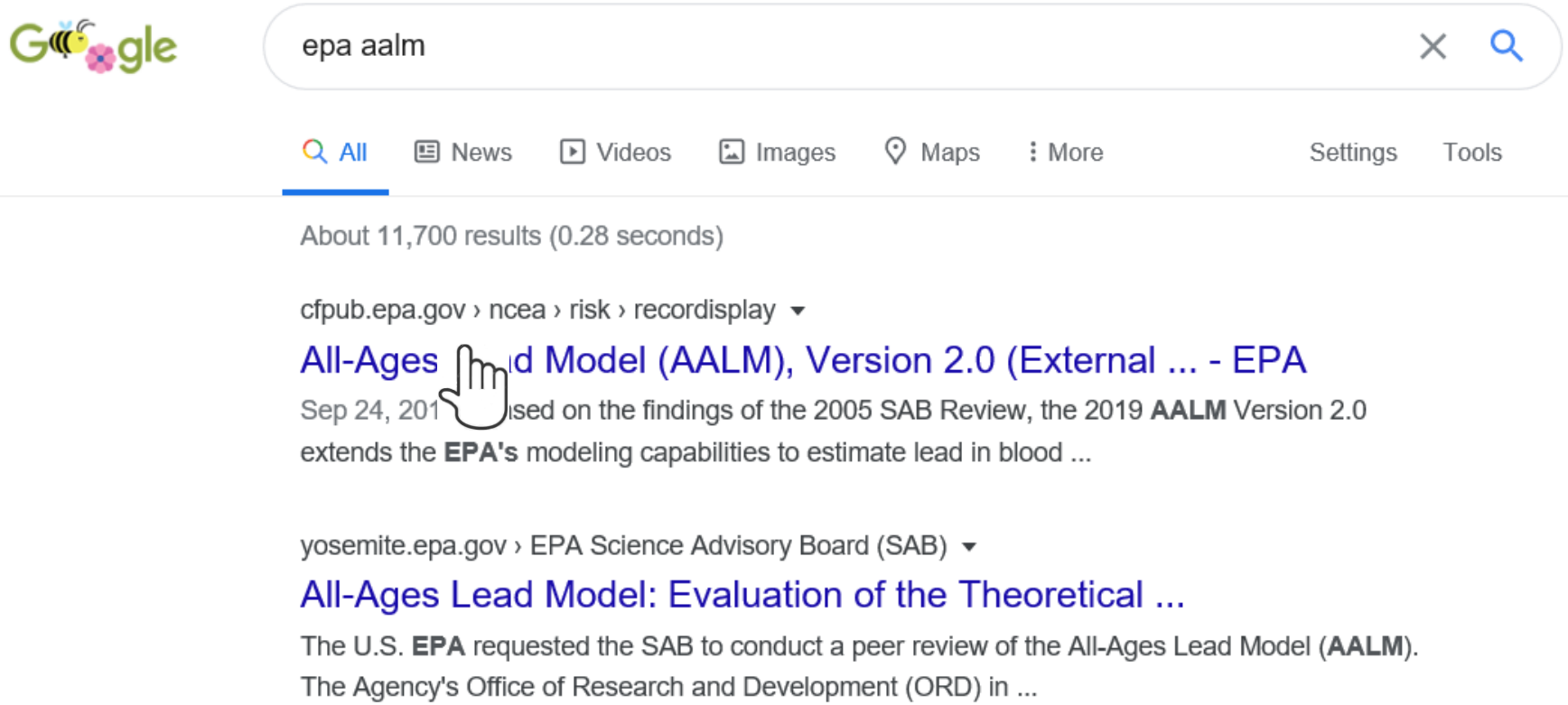
- SAB Review Panel Meeting (Oct 17-18, 2019)
  - Panelists praised EPA's work to document the studies and data that underlie the model
  - New version of the AALM as "definitely not black box"
  - Urged clarifying applications and audience, suggesting it may not be well suited to some uses
- SAB Draft 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

SAB Peer Review of AALM

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

Obtaining the AALM



All-Ages Lead Model (AALM), Ver

cfpub.epa.gov/ncea/risk/recordisplay.cfm?deid=343670

Apps | Member Access - St... | Imported From IE | Remote Access Sig... | One EPA Workplace | Contracts and BPAs... | HERO

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

HAWC
HEALTH ASSESSMENT WORKSPACE COLLABORATIVE

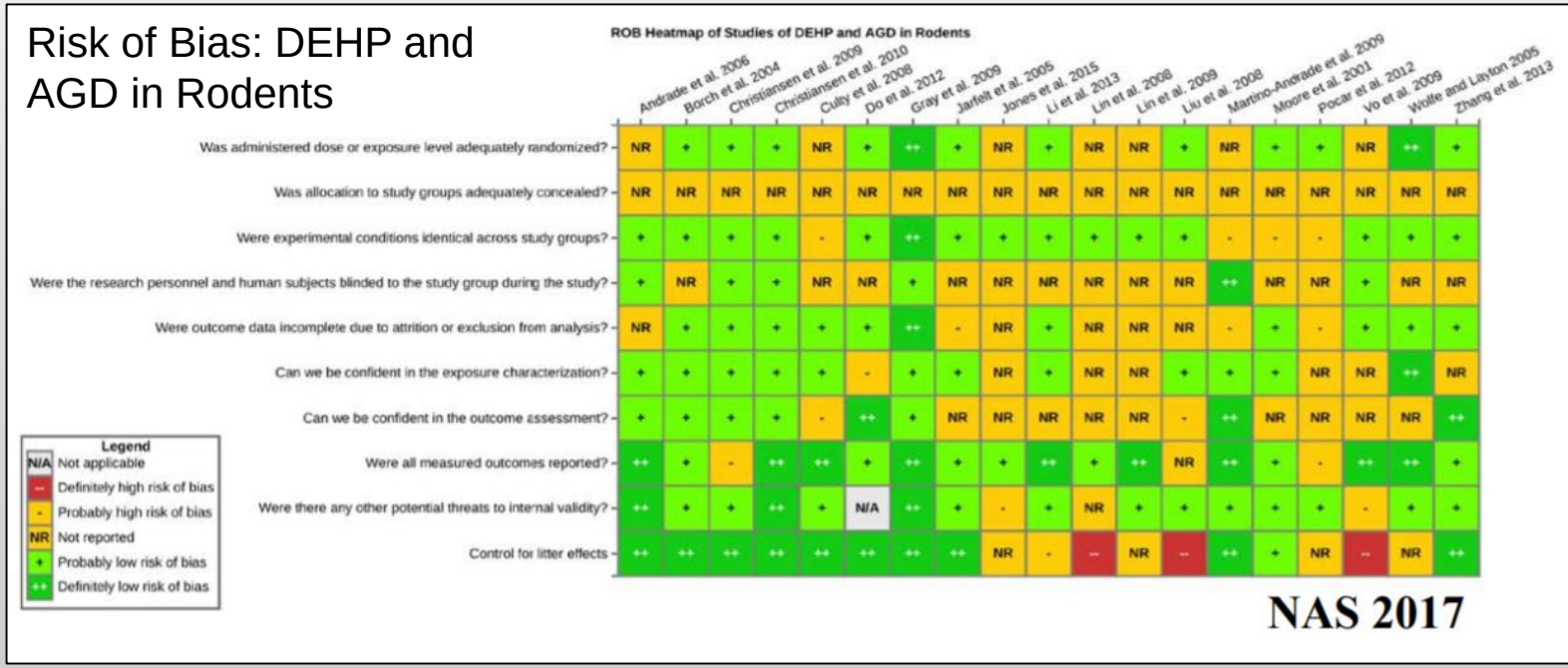
Modular, content management system designed to store, display, and synthesize multiple data sources for the purpose of producing human health assessments of chemicals

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

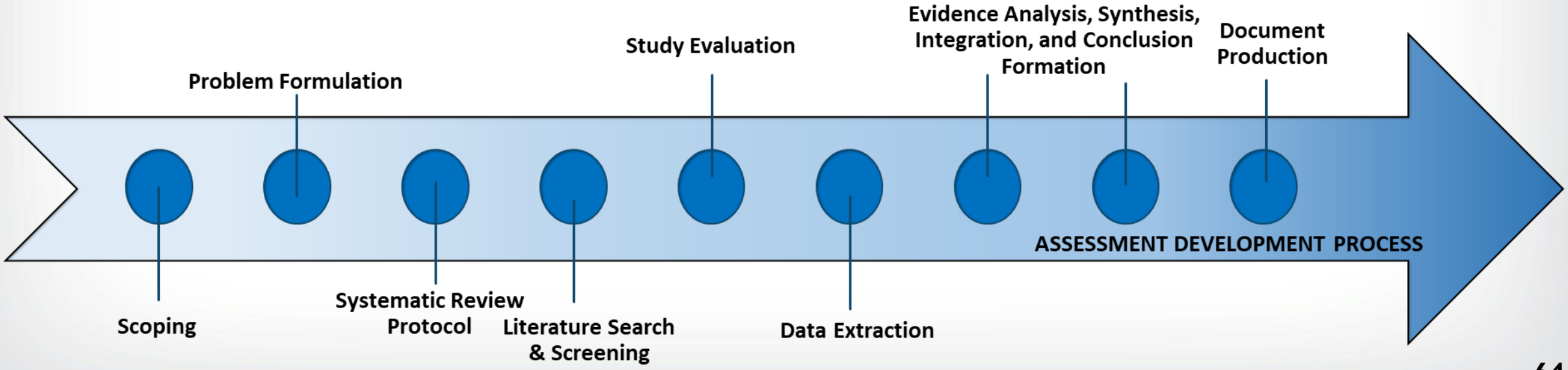
Literature identification – e.g., citation mapping, topic modeling

Enable full-text search function in HERO

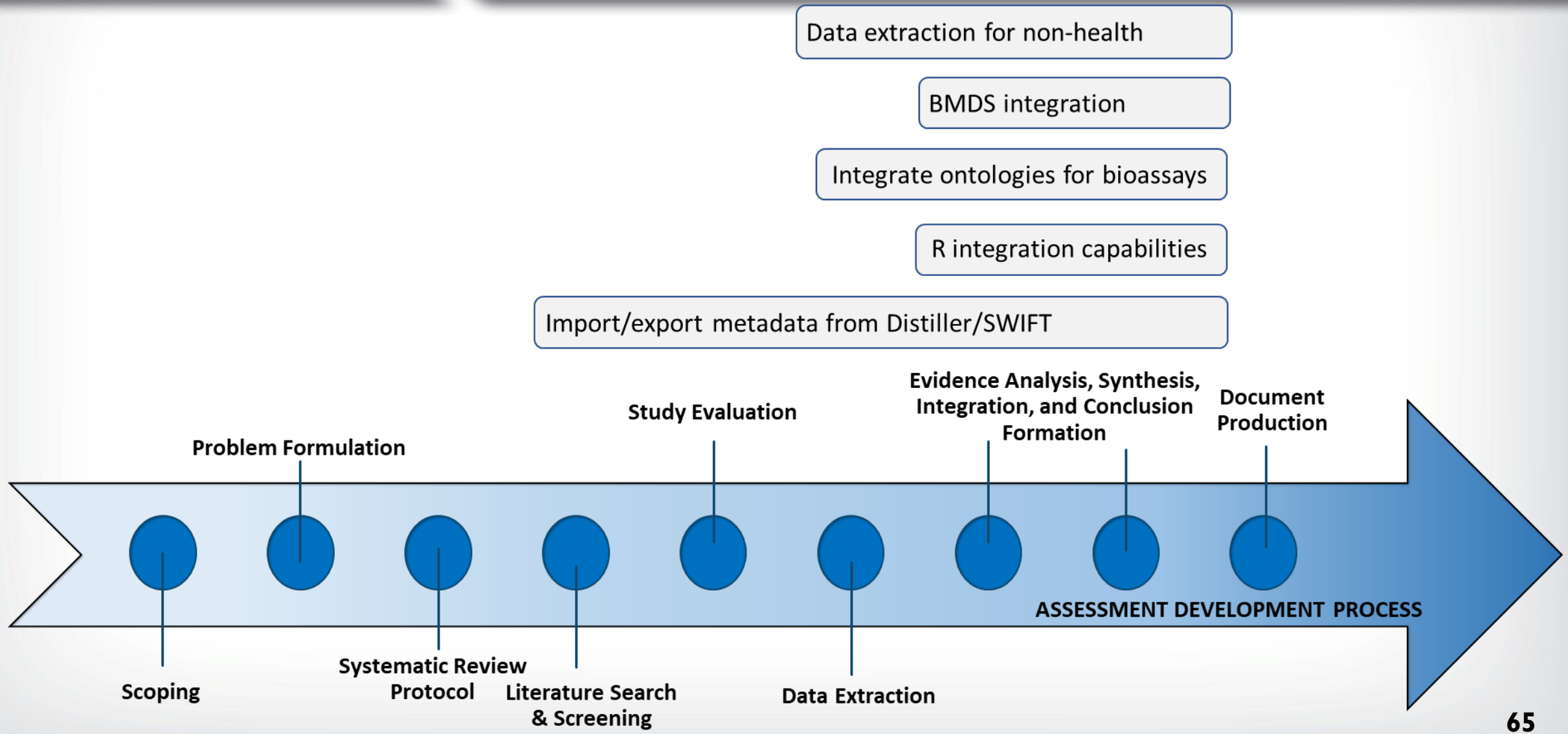
HERO web services for online assessment

Update LitCiter

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

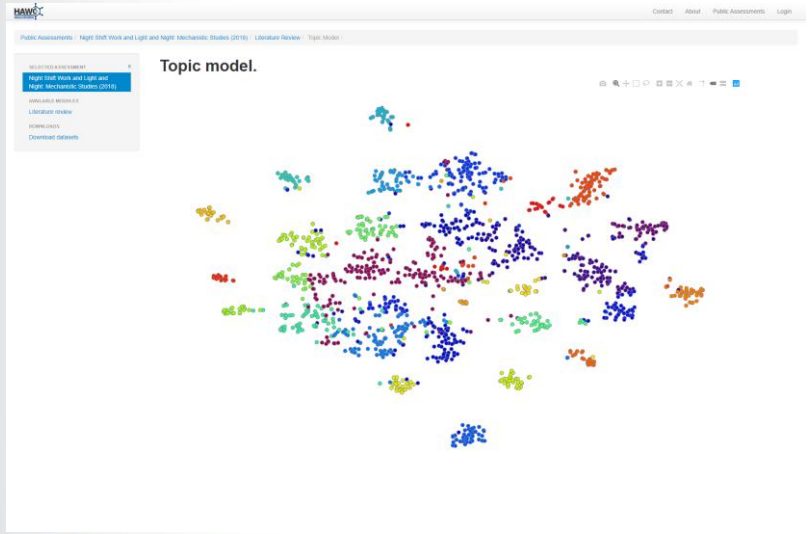


Output 4.1 – HAWC Innovation and Development

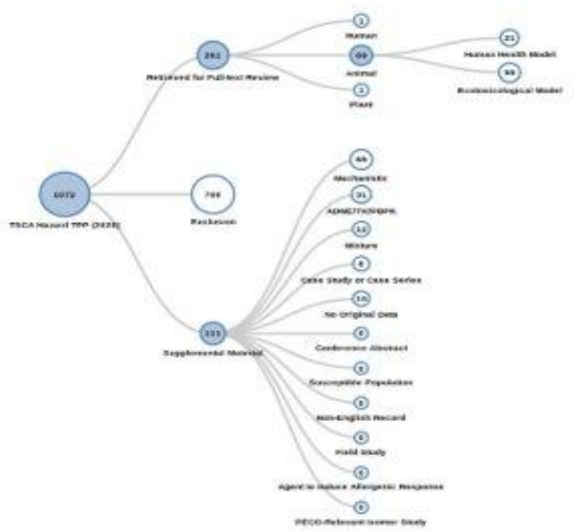


HAWC Visualizations in Development

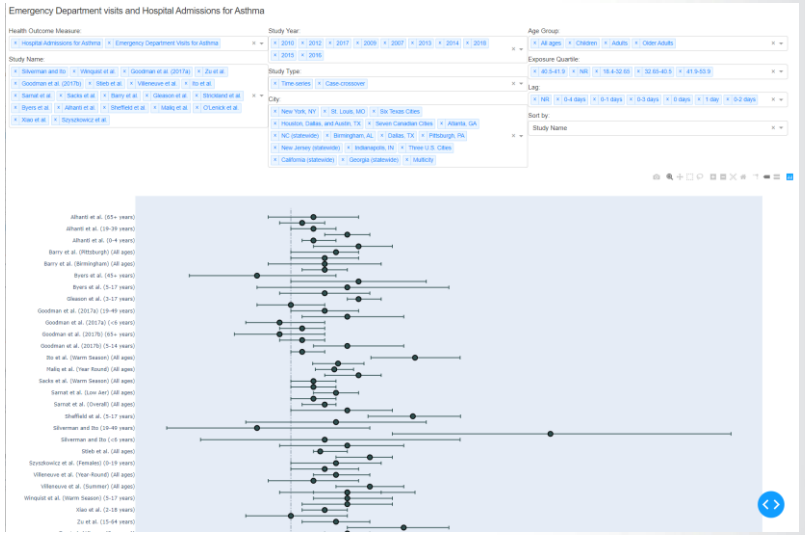
Literature Identification: Topic Modeling



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 HAWC

HEALTH ASSESSMENT WORKSPACE COLLABORATIVE

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

Summary

- **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!