Office of Research and Development Health and Environmental Risk Assessment



Looking Closer -Overview of the Research Areas in HERA StRAP

SEPA

Digging Deeper into the HERA RAs

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

Topic I – Science Assessments and Translation SEPA SEPA €PA SEPA ntegrated Re National Aml Ecological Ef Oxides of Inte Assessn **Science Assessments and Translation** Science Assessment Development Science Assessment Translation Res Focused on producing high quality, The range of tailored support Area search activities, modules, and applications transparent, consistent, and scientifically defensible assessment developed to address the requests Are

arch Rese 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.

from EPA program and regional offices, states, and tribes for technical support and consultations.

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 Largely comprised of the portfolio of assessment products developed under wellestablished 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

EPA

Research Area I – Science Assessment Development

The Integrated Science Assessments



- Dig deeper at <u>https://www.epa.gov/isa</u>
- Concise evaluation and synthesis of the most policyrelevant science supporting the primary (healthbased) 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



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 <u>https://www.epa.gov/pprtv</u>
- 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

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

Emma Lavoie CPHEA/IO

Output Lead: Emma Lavoie



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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

Sepa

- 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

			Dashboard	Welcome to the TSCA Support Sharepoint
Project Ge	online Project Sites • Neral Program	pprtv • iris progra n Support	All Tasks Calendar Decisions Documents	 Have questions or comments on this site? Email soto Guidance for Data Extraction of animal studies Guidance for Data Evaluation Distiller Form (An
DashboardAll TasksDocumentsOneNoteSupport Request FormSupport Request Summary	Click HERE for the General P Project Summary	rogram Support SOP	OneNote Restricted Support Request Form TSCA Next 20 Risk Evaluation Support – March 2020	 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 MARCH 2019 - updated Epi QC list HERE LInks to TSCA Problem Formulation Documents
Support Request Summary	Congratulations, We're all done!		EDIT LINKS	 <u>Asbestos</u> <u>1-Bromopropane</u> <u>Carbon Tetrachloride</u> <u>1, 4 Dioxane</u>
	Documents	There are 4 ways a request 1) A request may com particular expertis 2) Program office sta staffer	t could come to CPHEA from the pro ne from senior or division director r e for a chemical and the request is ff knows an expert in CPHEA and se ne from OSAPE (ie, action developm	ogram offices: management when they n directed to CPHEA directo ends a discrete task/reque

Project Online

Project Sites

TSCA Support

•

IRIS Program

PPRTV •

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TSCA Risk Evaluations

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Home

Prioritizing Existing Chemicals for Risk Evaluation

Risk Evaluations for Existing Chemicals Under TSCA

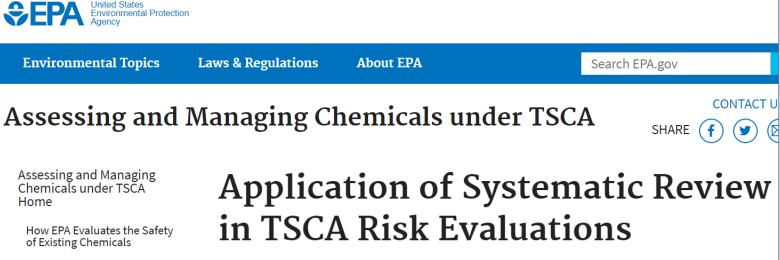
Current Chemical Risk Management Activities

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 first document below, EPA's Application of Systematic Review in TSCA Risk Evaluations, will guid 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.

EPA's initial work on systematic review was described in the supplemental files for each TSCA scope



Participant selection

- Confounding - Analysis

Topic 2 – Advancing the Science and Practice of Risk Assessment

Research Area 3

Advancing the Science and Practice of Risk Assessment

Emerging and Innovative Assessment Methodologies

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 Essential Assessment and Infrastructure Tools

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

Research Area 4



- 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

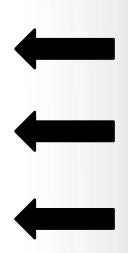
3.1 Advance, translate, and build confidence in the application of new approach methods (NAMs) and data in risk assessment

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





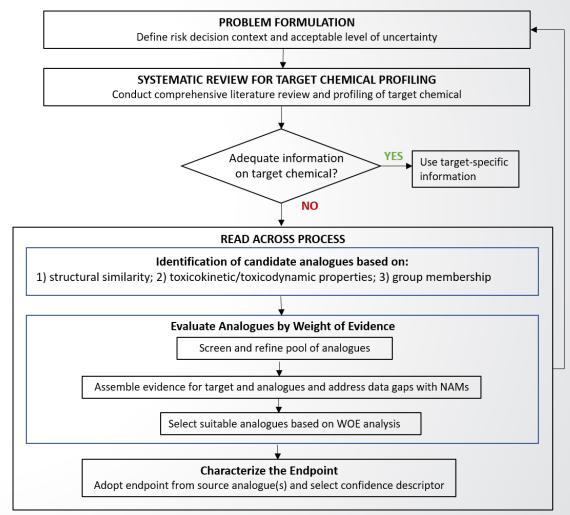
Problem Formulation

- 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-forpurpose 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 datapoor 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





- 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

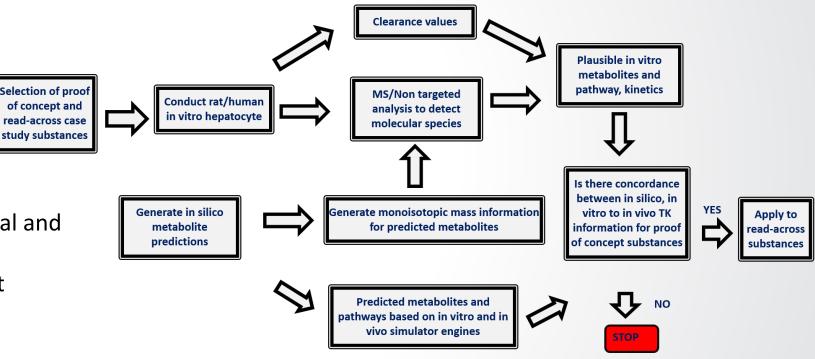
Integrated approach for evaluating metabolism data gaps

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

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

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- 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



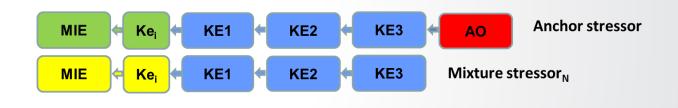


- Ongoing proof-of-concept case studies will explore the use of gene expression data to inform mechanistic insights, qualitative hazard conclusions and dose-response assessment to support HERA-related assessment products:
 - 1. Use Gene Set Enrichment Analysis to identify relevant molecular pathways 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

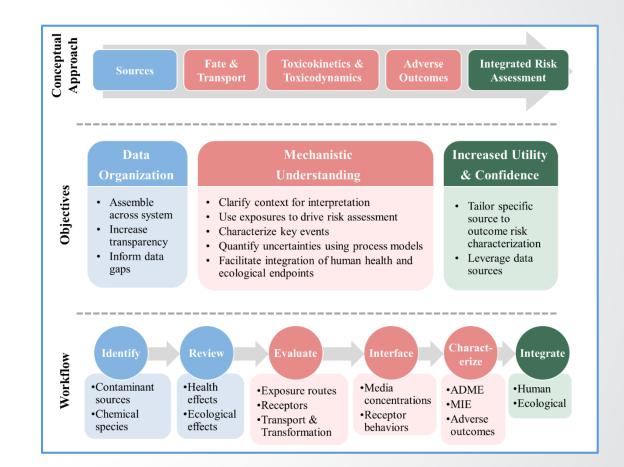


 Case studies will demonstrate how mechanistic information (e.g., AOPs) could be used to inform mixtures assessment applications such as hazard grouping and dose-response analysis



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 sitespecific cumulative risk assessment across multiple species





- 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

CPHEA

SEPA

Jeffry Dean J. Phillip Kaiser Jay Zhao Beth Owens Roman Mezencev Annie Jarabek Matthew Boyce Lucina Lizarraga

CCTE

Jason Lambert 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)

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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
 - Prioritization
 - Need for assessment update?
 - Identifying data gaps
- -Began creating SEMs in 2019, now becoming a routine analysis



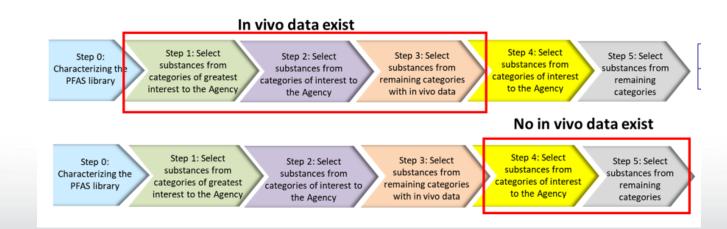
Systematic Evidence Maps (SEM)

- 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
- Tailored to meet decision-making needs
- Results can be disseminated in reports, interactive data interfaces, e.g., EPA CompTox Chemicals Dashboard



- 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").
- PFAS SEM conducted to help identify in vivo data

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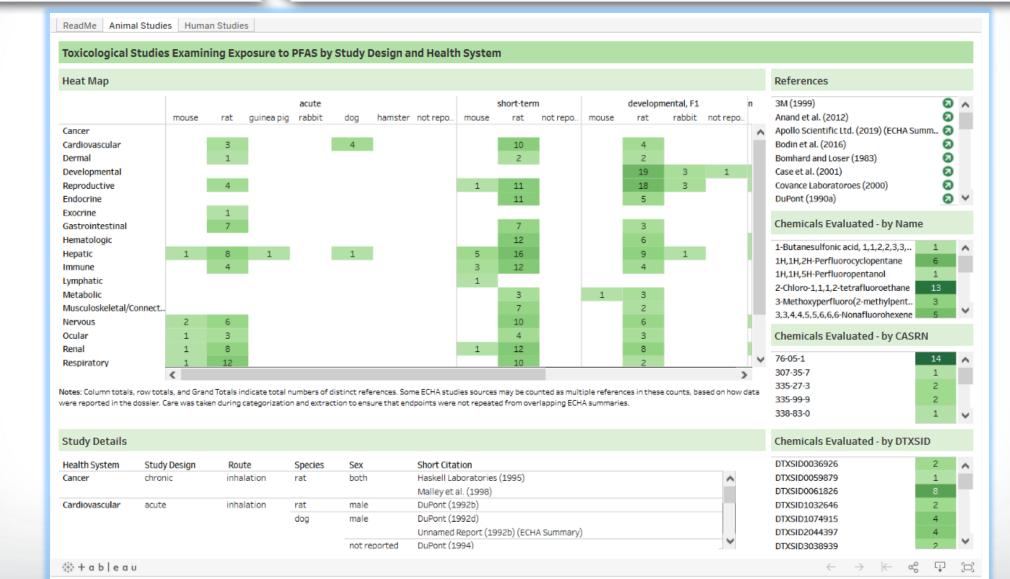




PFAS SEM Methods

- Use information from the Chemicals Dashboard to create higher throughput methods to search for hundreds of chemicals at a time (new semi-automated processes)
- Search journal databases (PubMed, WoS, ProQuest) and grey literature from Chemicals Dashboard ToxVal database and manual searches for additional studies
- Create interactive literature inventories to show landscape of studies
- Conduct full data extraction and study evaluation on animal toxicology studies of repeat dose, developmental or reproductive design
- Publish report + make information accessible via Chemicals Dashboard.
- A related analysis is focusing on the epidemiological data (likely will be journal article)

Example PFAS SEM <u>Literature Inventory</u>: Animal Studies



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Example PFAS SEM <u>Literature Inventory</u>: Human Studies

Epidemiologio	cal Studies B	Examining Expo	sure to PFAS I	by Study D	esign and H	lealth Syst	em						
Heat Map												References	
		case	-control				cohort					3M Company (2000)	8
	preg	infants	children	general population	pregnant women	infants	children	occupational	general population	pregnant women	inf	Aimuzi et al. (2019) Bao et al. (2017)	ର ଜନ ଜନ ଜନ ଜନ ଜନ ଜନ ଜନ ଜନ
Cancer				5				2				Berg et al. (2015)	ĕ
Cardiovascular				1				1		1		Berg et al. (2016)	0
Developmental						6	4					Bjerregaard-Olesen et al. (2019)	ଷ
Reproductive	1			2	3		2	1	3	4		Blake et al. (2018)	0
Endocrine		1			3	2		1	2	2			
Hematologic										1		Chemicals Evaluated - by Nam	e
Hepatic								1	1	1		De flande de la companya de la compa	
Immune			2			2	4	_	2	1		Perfluoroheptanesulfonate Perfluoroheptanesulfonic acid	9
Metabolic Nervous				1			4	1	Z	1		Perfluoroheptanoic acid	22
Other									1			Perfluorooctanesulfonamide	15
Renal								1	1	1		Perfluorooctanesulfonyl fluoride	2
Respiratory		1				1		-	-	-		Perfluoropentanoic acid	7
Systemic/Whole B	lody							1					
Grand Total	1	L 2	2	9	6	10	14	2	8	9	:	Chemicals Evaluated - by CASI	RN
	<										>	307-35-7	2
Notor: Column tota	la routotala a	nd Grand Totals indi	ento total number	- of distinct a	oforoncor							375-85-9	22
Notes: column cote	sis, 1000 cocais, a	ine drane rocais mer	cate cotar number	soreiseneer	ererences.							375-92-8	4
Study Details												376-06-7	12
												422-64-0	з
			Exposure									754-91-6	15
-	Study Design	Population	Measurement	Matrix	Sex	Short Citati						0000.04.0	- 74
Cancer	case-control	ol general population biomonitoring blood female Bonefeld-Jørgensen et al. (2014) Ghisari et al. (2017)			Chemicals Evaluated - by DTXS	SID							
													_
						Hurley et al Wielsøe et i						DTXSID1037303	22
					male	Hardell et a						DTX5ID3038939 DTX5ID3059921	15 12
_	cohort	occupational	occupational		both	3M Compan						DTXSID5027140	2
						Olsen et al.						DTXSID6062599	7

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>

6:2 Fluorotelomer Alcohol and Developmental Effects (Offspring)

	Study	Animal Description	Route		Observation Time									
Body Weight, Fetal	O'Connor et al. 2014	F1 Rat, Sprague-Dawley (Crl:Cd (Sd)) (공일)			GD 21	** *	• • •	O'Connor et al. 2	2014 / Oral One-Ger	neration Repro	oductive Toxicity Study	y / F1 Male and	Female Sprague-D	awley Rat
ead Fetuses	O'Connor et al. 2014	F1 Rat, Sprague-Dawley (Cri:Cd (Sd)) (공일)	oral gavage	GD 6-20	GD 21	**	• • •	Mortality						
ye Opening	Unnamed Report (2013b) (ECHA Summary)	F1 Mouse, CD-1 (යිද)	oral gavage	premating-lactation	LD 21	++		Study Experim	ent Animal Group	Endpoint				
etus Or Pup/Neonate, Small	Unnamed Report (2013b) (ECHA Summary)	F1 Mouse, CD-1 (ವಿಲ್ಲ)	oral gavage	premating-lactation	LD 0-21			Endpoint name		Pup Mortality				
etuses, Live	O'Connor et al. 2014	F1 Rat, Sprague-Dawley (Crl:Cd (Sd)) (공일)	oral gavage	GD 6-20	GD 21		· · · · · ·	System		Developmental	1			
rontal, incomplete Ossification	O'Connor et al. 2014	F1 Rat, Sprague-Dawley (Crl:Cd (Sd)) (공일)	oral gavage	GD 6-20	GD 21		• • • •	Organ		Whole Body				
terparietal, incomplete Ossification	O'Connor et al. 2014	F1 Rat, Sprague-Dawley (Crl:Cd (Sd)) (공일)	oral gavage	GD 6-20	GD 21		• •	Effect		Survival				
actation index	Unnamed Report (2013b) (ECHA Summary)			premating-lactation	LD 4-21		T I	Effect subtype Diagnostic descript	tion	Clinical Obser	umber dead/total number)			
	O'Connor et al. 2014	F1 Rat, Sprague-Dawley (Crl:Cd (Sd)) (공일)			LD 21		_	Observation time		LD 1				
			unan ganage	premating-termination		•••	• •	Data reported?		*				
tters with Fetal Alterations	O'Connor et al. 2014	F1 Rat, Sprague-Dawley (Crl:Cd (Sd)) (공일)	oral gavage	GD 6-20	GD 21		• • •	Data extraoled? Values estimated?		*				
ve Pups Born	Unnamed Report (2013b) (ECHA Summary)	F1 Mouse, CD-1 (공文)	oral gavage	premating-lactation	LD 0			Values estimated?	re	Table 4				
	O'Connor et al. 2014	F1 Rat, Sprague-Dawley (Crl:Cd (Sd)) (승요)	oral gavage	70 d premating-termination	LD 1		·•,	adversity -		Increase from	reference/control group			
ver, Discolored	Unnamed Report (2013b) (ECHA Summary)	E1 Mouse CD-1 (-CO)		premating-lactation	LD 21			NOAEL		25 mg/kg-day				
o. of Pups Born	O'Connor et al. 2014	F1 Rat, Sprague-Dawley (Crl:Cd (Sd)) (SQ)	oral gavage	70 d premating-termination	LD 1			LOAEL <		125 mgikg-day				
instan Data das	Lineared must (2007b) (70114 minuted)	51 54 0400 (00) (00)			DUD (Statistical test desc	oription	One-way ANOV	VA followed by Dunnett's test			
ursing Behavlor	Unnamed report (2005b) (ECHA summary)			14 d (premating-LD 3)				Trend result Results notes		not reported				
arietal, incomplete Ossification	O'Connor et al. 2014	F1 Rat, Sprague-Dawley (Crl:Cd (Sd)) (순오)			GD 21		• ·	Results notes		mg/kg/day, the	atistically significant effects on viability and lactation indices w	vere both statisticall	y significantly reduced comp	pared to the
eMs, Ischlum Incompletely Ossified	O'Connor et al. 2014	F1 Rat, Sprague-Dawley (Crl:Cd (Sd)) (공일)			GD 21	•••	• • ••			approximately	ibility Index was reduced by 12% 27% compared to the control gr	oup. These effects r	effected an increased incld	ience of put
eMs, Publis Incompletely Ossifiled	O'Connor et al. 2014	F1 Rat, Sprague-Dawley (Crl:Cd (Sd)) (공일)	oral gavage	GD 6-20	GD 21					with increased	rved in the 250 mg/kg/day dosag i pup mortality observed through	LD 15 (Table 4). At	125 mg/kg/day, there was all	iso an Incre
up Mortality	O'Connor et al. 2014	F1 Rat, Sprague-Dawley (Crl:Cd (Sd)) (순요)	oral gavage	70 d premating-termination	LD1					remainder of th	up mortality on LD 1, but addition he lactation period (Table 4). In aduced at 125 and 250 mg/kg/da	addition to the effect	s on pup mortality, pup welg	phts were s stistically si
										reduced therein	bout the entire lectedies parled	with an increase in	the manufacte of the scalab	
no apparent trea	tment-related effect				LD 2-5		• •			reduced throug progressed. Or	shout the entire lactation period n LD 1, mean pup weights were	, with an increase in 12% lower than the	the magnitude of the weigh control group. On LD 22, me	ean pup we
no apparent trea treatment-relate				, ,	LD 2-5 LD 6-8		•			reduced throug progressed. Or 58% lower than 23% and 26%	phout the entire lactation period n LD 1, mean pup weights were n the control group. At 125 mg/k compared to the control group o	, with an increase in 12% lower than the g/day, mean pup we on LD 15 and 22, res	the magnitude of the weigh control group. On LD 22, me ights were statistically signi pectively; mean pup weights	ean pup we ificantly red s on LD 1 th
	d Increase			, ,		**		Liller Effects		reduced throug progressed. Or 58% lower than 23% and 26% were similar to	shout the entire lactation period, n LD 1, mean pup weights were n the control group. At 125 mg/k	, with an increase in 12% lower than the g/day, mean pup we on LD 15 and 22, res	the magnitude of the weigh control group. On LD 22, me ights were statistically signi pectively; mean pup weights	ean pup wel ificantly red s on LD 1 th
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treatment-relate	d Increase d decrease Unnamed report (2005b) (ECHA summary) Unnamed Report (2013b) (ECHA summary)		oral gavage oral gavage	14 d (premating-LD 3) premating-lactation	LD 6-8 LD 9-15 LD 16-22 PND 4			Dose (mg/kg-day) 0 5 25 ⁴	222 220 282	reduced throug progressed. Or 58% lower than 23% and 25% were similar to No Pup deaths ex	phout the entire licitation period LD 1, mean pue wights were the control group. At 125 mg/s compared to the control group. The pressed as per total no. pups Percent incidence Offs Offs Offs Offs	, with an Increase in 12% lower than the In LD 15 and 22, res are were no effects o	the magnitude of the weigh control group. On LD 22, me globs were statistically sign pectively; mean pup weights n litter parameters at doses	ean pup we ificantly red s on LD 1 t
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Dose (ma/ka-dav)

SEPA



Moving Forward

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



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

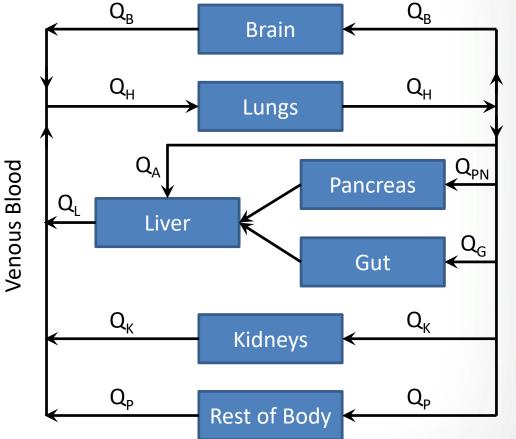
€PA

PBPK Model

Q_BX $Q_{\rm B}^{\rm X}$ \mathcal{P}^{χ} $\mathbf{\hat{k}}^{\mathbf{Q}_{\mathrm{L}}^{\mathrm{X}}}$ Ø Q^X

Chemical engineering applied to a biological organism

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

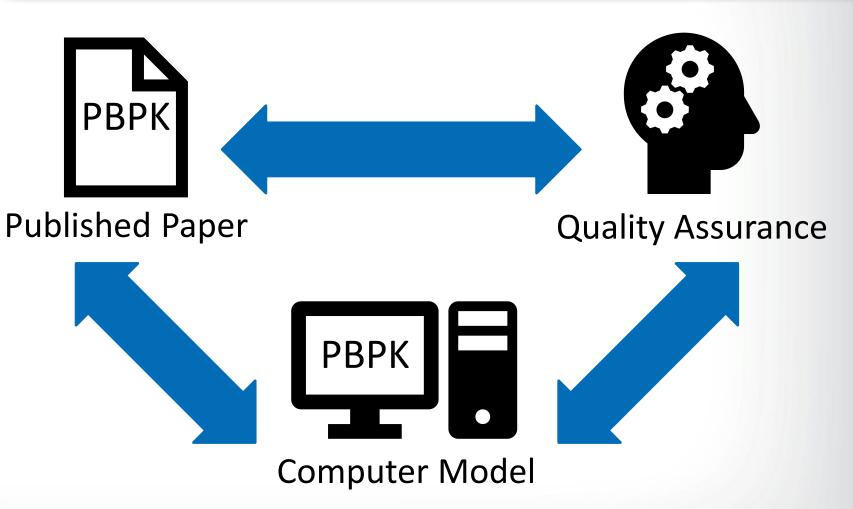


Arterial Blood

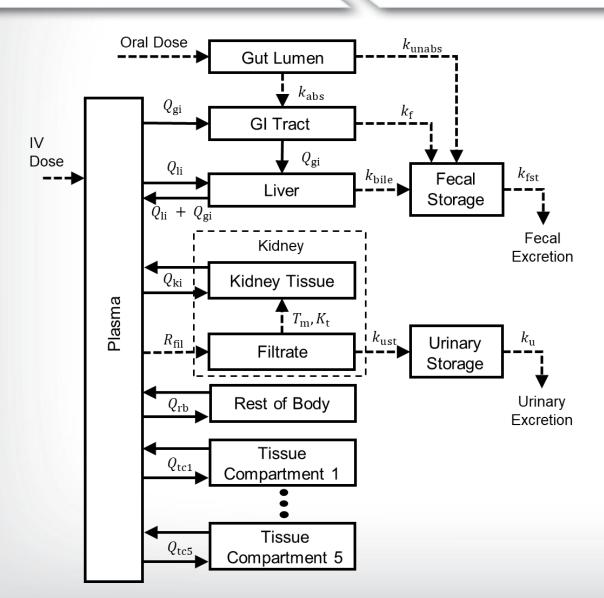


Motivation

- 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



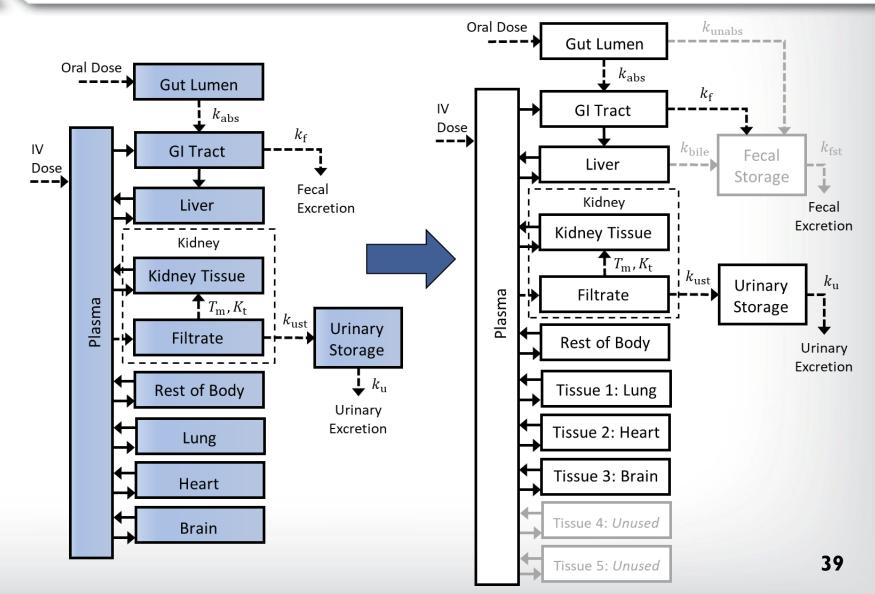
EPA

- 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.

EPA

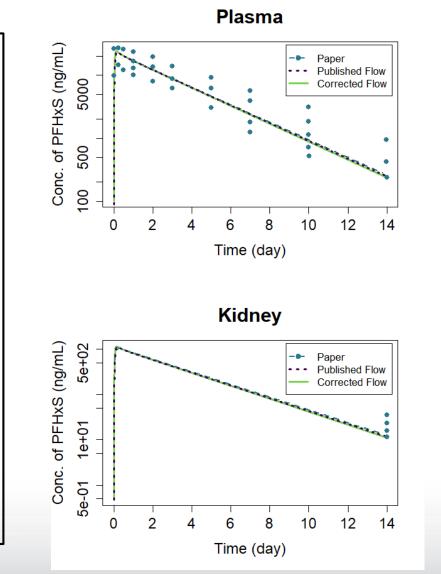


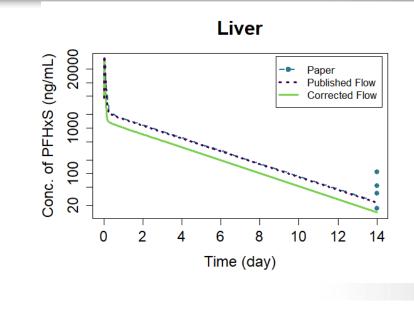
Case Study: PFHxS PBPK Model

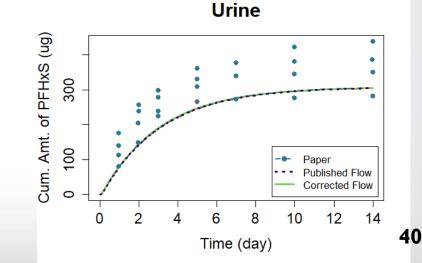
 Using the template, we were able to recreate some of the published results.

EPA

 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

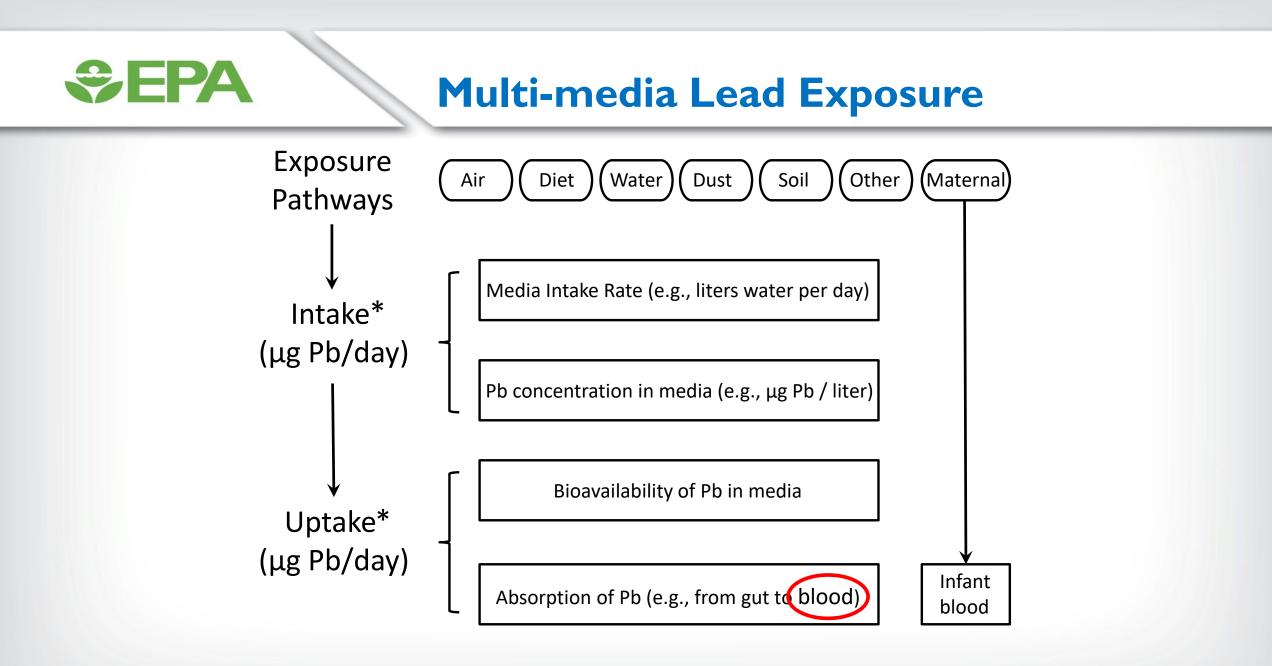
Output Lead: Jennifer Nichols



Sepa

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



* 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

S EPA

- 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.

Sepa

EPA's Pb Biokinetic Models

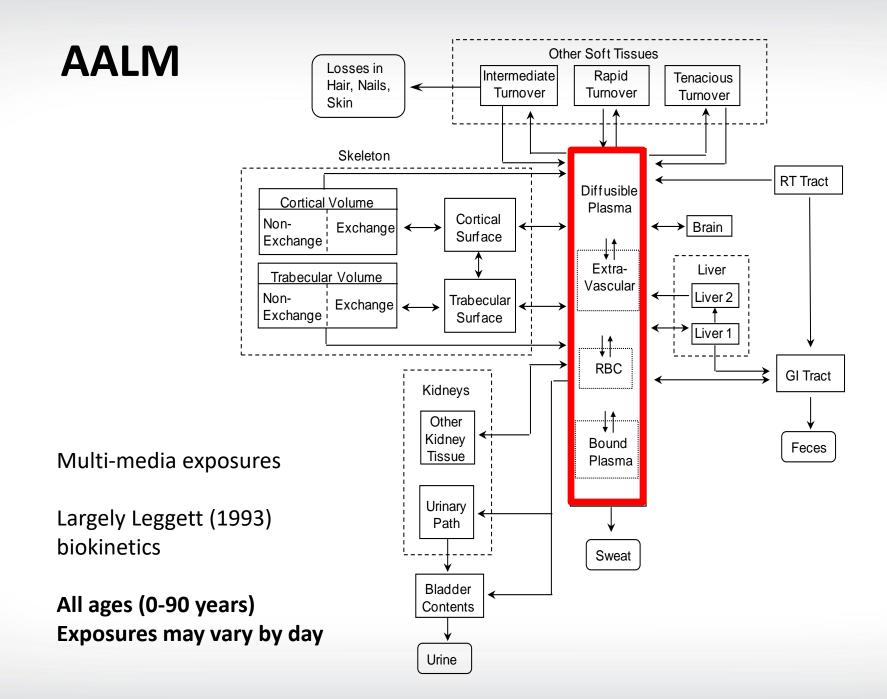
Biokinetic are mathematical descriptions of exposure, uptake, and disposition of a substance in the body. These models allow for multiple exposure pathways for which intake and absorption may vary over time and age of the exposed individual.

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



Recent AALM Development

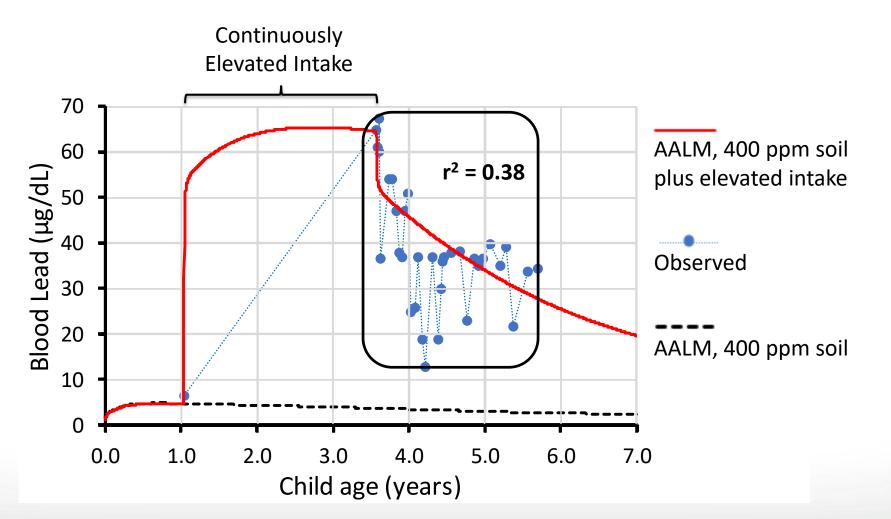
Technical Support Document

- Developed theoretical framework (2017-2019)
 - \circ 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 (acsIX, Fortran) by ORD and OCSPP (Chapter 3)
- Model Evaluation (2016-2017)
 - Assessed predicted blood and bone Pb against human data (Chapters 3 and 4)

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AALM Example of Capabilities

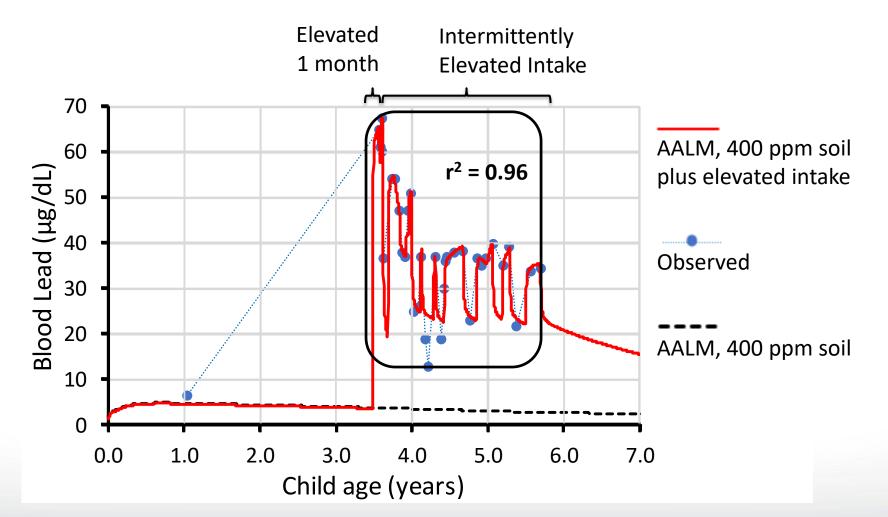
Are elevated BLL due to continued exposure?



AALM Example of Capabilities

Are elevated BLL due to continued exposure?

SEPA



S.FPA **SAB Peer Review of AALM** 中文:简体版 | Tiếng Việt | 한국어 Español 中文:繁體版 | ted States Environmental Protection Agenc Search EPA.gov Laws & Regulations About EPA Learn the Issues Science & Technology EPA Science Advisory Board (SAB) Contact Us You are here: EPA Home >> EPA Science Advisory Board (SAB) >> LookupWebAdvisory ActivitiesCurrentSAB >> All-Ages Lead Model: SAB Home Evaluation of the Theoretical Framework and Mode **Basic Information** All-Ages Lead Model: Evaluation of the Calendar Theoretical Framework and Model Committees, Panels, and

• SAB Review Panel Meeting (Oct 17-18, 2019)

Membership

- 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

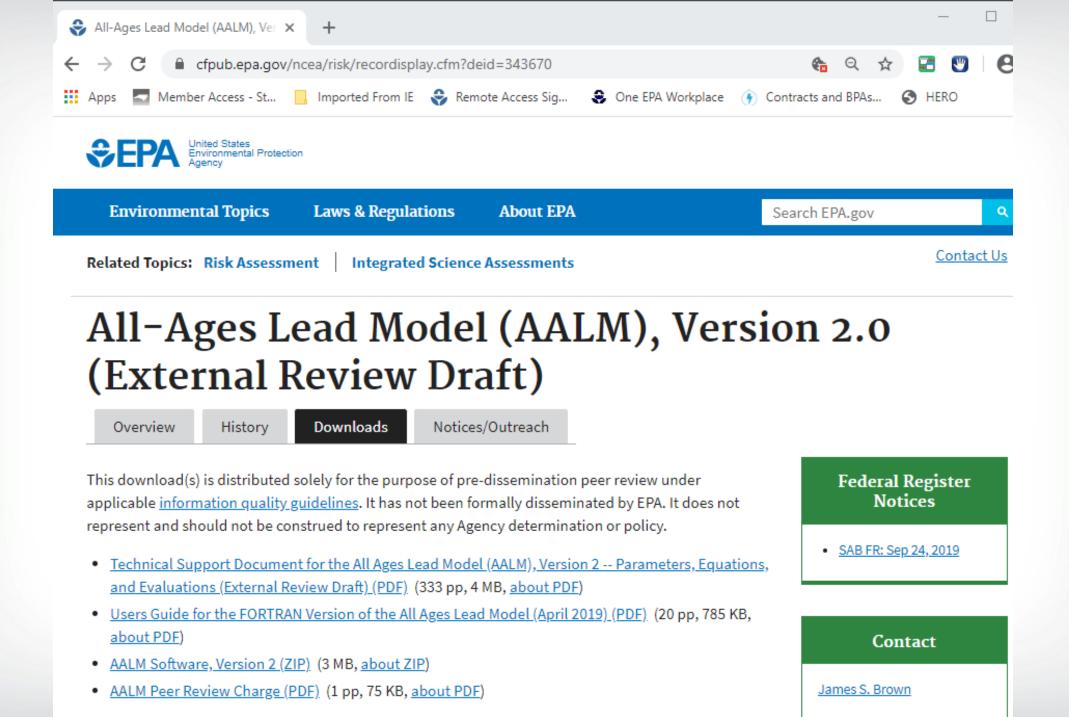
- Developing a new respiratory module

 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
 - $\,\circ\,$ Providing training on request
 - $\,\circ\,$ 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 **Obtaining the AALM** G 🙀 gle epa aalm \times Q 🖾 Images ⊙ Maps News Videos : More Settings Tools About 11,700 results (0.28 seconds) cfpub.epa.gov > ncea > risk > recordisplay -All-Ages Model (AALM), Version 2.0 (External ... - EPA Sep 24, 201 Jised 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 ...





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

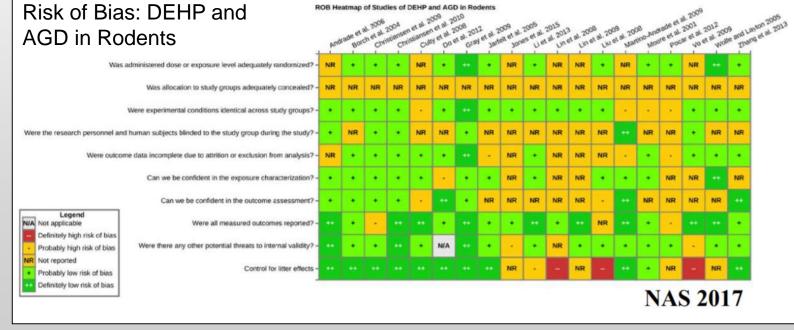
- Office of Chemical Safety and Pollution Prevention (OPPT, OSCP)
- Office of Air and Radiation (OAQPS, OTAQ)
- Office of Children's Health Protection
- Office of General Counsel
- Office of Land and Emergency
 Management
- Office of Water



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.



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

SEPA

Output 4.1 – HERO Innovation and Development

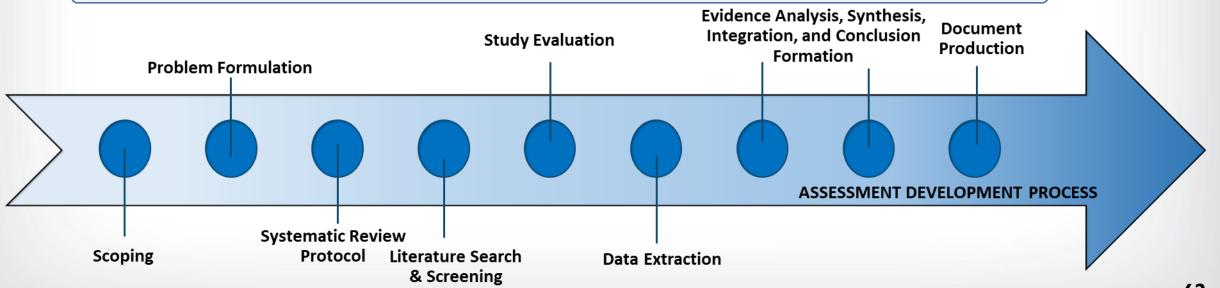
Literature identification – e.g., citation mapping, topic modeling

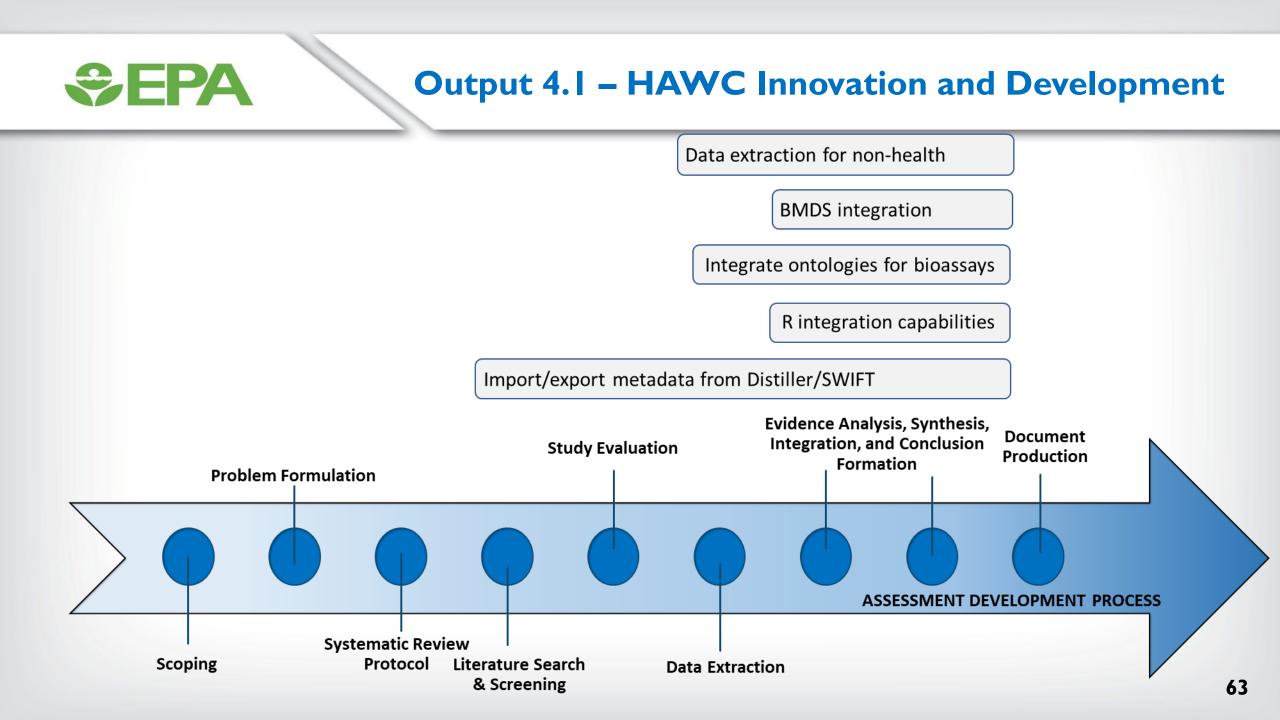
Enable full-text search function in HERO

HERO web services for online assessment

Update LitCiter

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



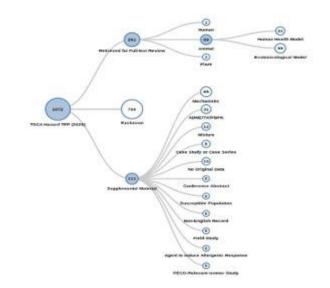




HAWC Visualizations in Development

Literature Identification: Topic Modeling

Interactive Literature Tag Trees



Interactive Data Visualizations

alth Outcome Measure:		Study Year:	Age 0	Group	
Hospital Admissions for Asthma	Department Visits for Asthma	x x 2010 × 2012 × 2017 × 2009 × 2007 × 2013 × 2014 × 2016		All ages × Children × Adults × Older Adults	н
idy Name:		× 2015 × 2016	A w	isure Quartile:	
Silverman and ito × Winguist et al. × Good	nan et al. (2017a) × Zu et al.	Study Type:		40.5-41.9 X NR X 18-4-32.65 X 32.65-40.5 X 41.9-53.9	ж
Goodman et al. (2017b) × Stieb et al. × Vili		× Time series × Case-crossover	× v Lag:		
Sarreit et al. × Sacks et al. × Dany et al.				NR × 0-4 days × 0-1 days × 0-3 days × 0 days × 1 day × 0-2 days	ж
Byers et al. × Alhanti et al. × Sheffield et al		× New York, NY × St. Louis, MO × Str Texas Cities			
Xiao et al. X Szyszkowicz et al.		Houston, Dates, and Austri, TX X Seven Canadian Otes X Atlanta, GA	Sort 8		
		* NC (statewide) * Birmingham, AL * Dallas, TX * Pittsburgh, PA	Stu	dy Name	×
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		* California (statewide) * Georgia (statewide) * Muticity			
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					-
Albarti et al. (65+ years)					
Albanti et al. (19-39 years)					
Albanti et al. (0-4 years)					
Barry et al. (Pittsburgh) (All ages)					
Barry et al. (Birmingham) (All ages)					
Byers et al. (45+ years)		•			
Byers at al. (5-17 years)					
Gleason et al. (2-17 years)					
Goodman et al. (2017a) (19-49 years)					
Goodman et al. (2017a) (<6 years)	+				
Goodman et al. (2017b) (65+ years)		• •			
Goodman et al. (2017b) (5-14 years)		•			
250 et al. (Warm Season) (All ages)					
Maliq et al. (Year Round) (All ages)					
Sacks et al. (Warm Season) (All ages)					
Sarnat et al. (Low Aer) (All ages)					
Sarrat et al. (Overall) (All ages)					
Shuffield at al. (5-17 years)					
Silverman and Ito (19-49 years)		•		•	
Silverman and Ito (<6 years)				-	
Stieb et al. (All ages)					
Szyszkowicz et al. (Females) (0-19 years)					
Villeneuve et al. (Year-Round) (All ages)					
Villencove et al. (Summer) (All ages)					-
Winquist et al. (Warm Season) (5-17 years)				(1
	-			(<



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



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

<u>Librarians</u> Danielle Moore Hillary Hollinger Amanda Haddock Julie Fieldsteel Alexander Thurman

HAWC Team*

Byron Rice Daniel Rabstejnek McKayla Lein



- 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.

Office of Research and Development Health and Environmental Risk Assessment



THANK YOU!