



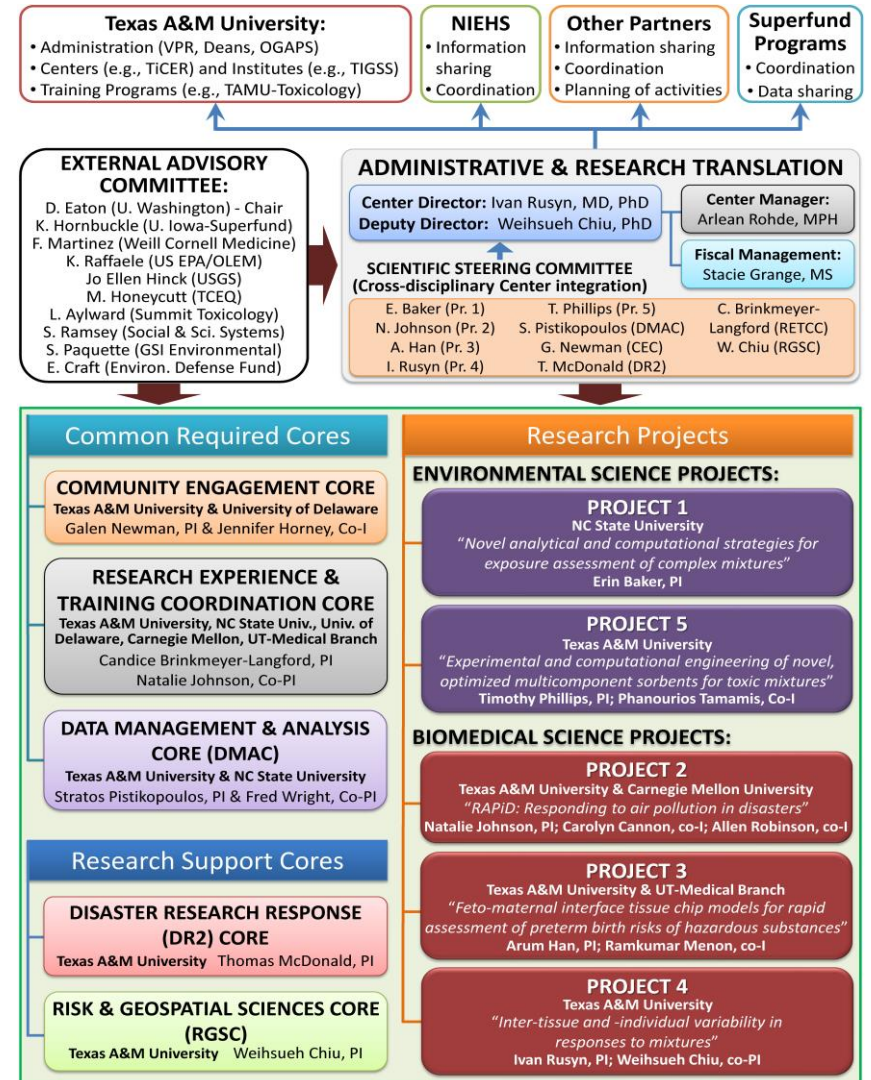
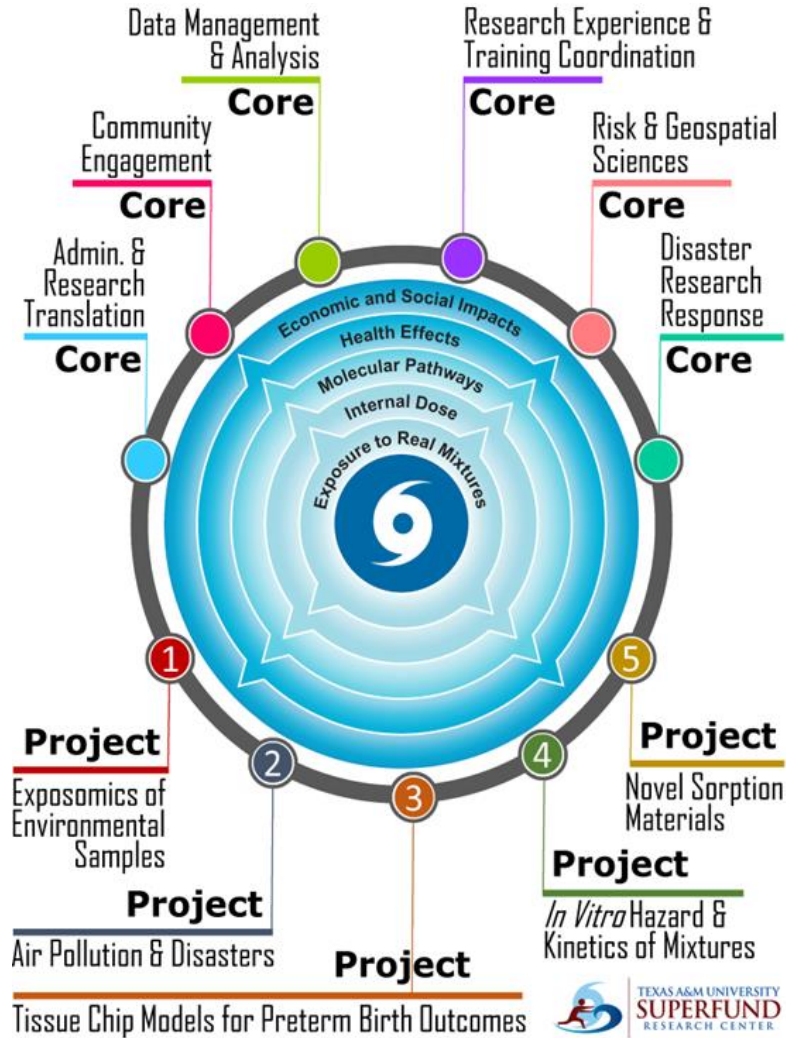
Case Studies in “Cells to Solutions”: Next Generation Risk Assessment in the Context of Environmental Disasters

Weihseh A. Chiu, PhD
Deputy Director and Risk & Geospatial Science Core Director
Texas A&M Superfund Research Center

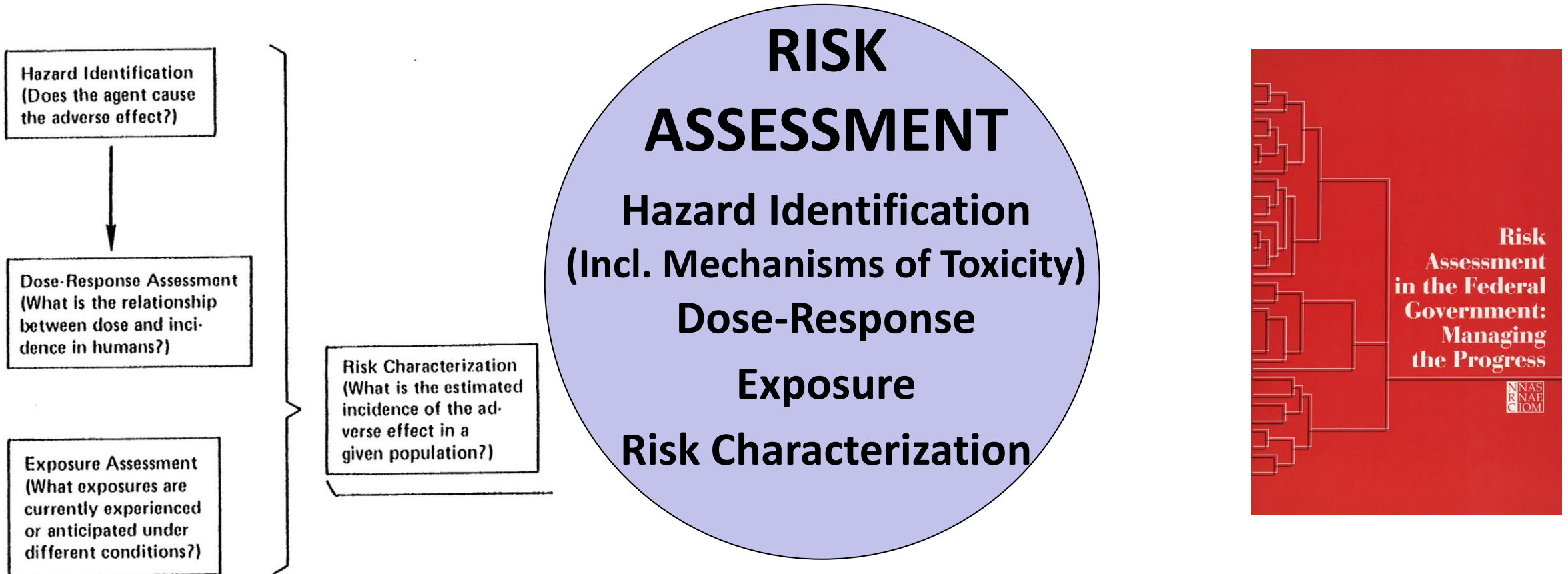




Thanks to all Texas A&M Superfund Research Center PIs, Trainees, Staff, Advisors, and Partners

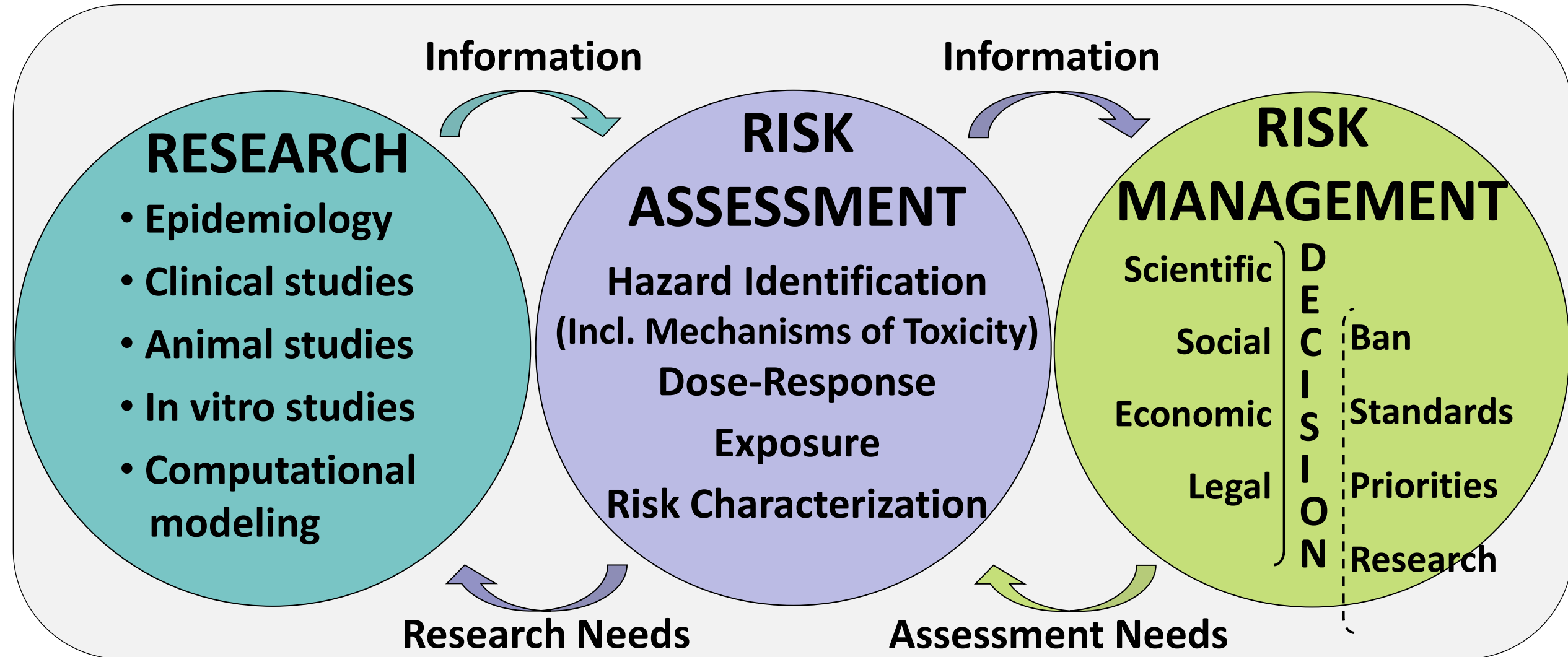


Risk Assessment Context



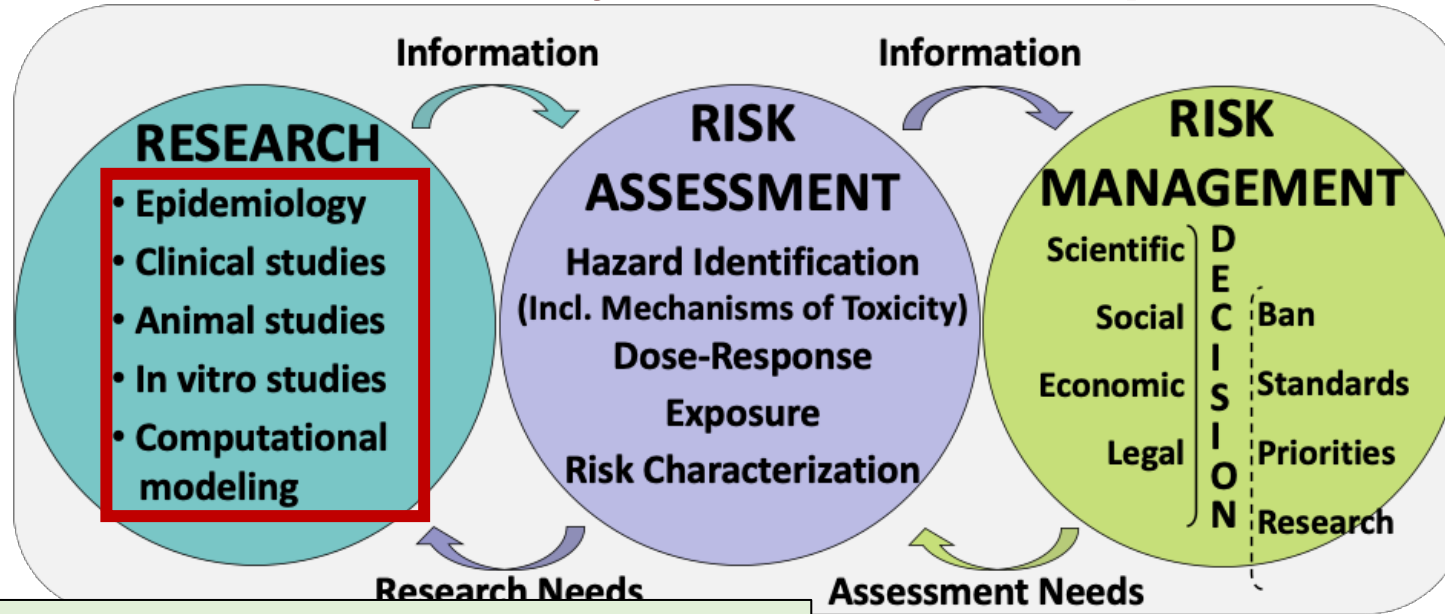
National Research Council. 1983. Risk Assessment in the Federal Government: Managing the Process. Washington, DC: The National Academies Press. DOI: <https://doi.org/10.17226/366>

Risk Assessment Context





The Long Road from Research to Action: Trichloroethylene as an Example


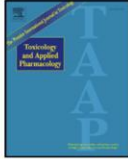


2009: Research on population pharmacokinetics

Contents lists available at ScienceDirect

Toxicology and Applied Pharmacology

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

Characterizing uncertainty and population variability in the toxicokinetics of trichloroethylene and metabolites in mice, rats, and humans using an updated database, physiologically based pharmacokinetic (PBPK) model, and Bayesian approach

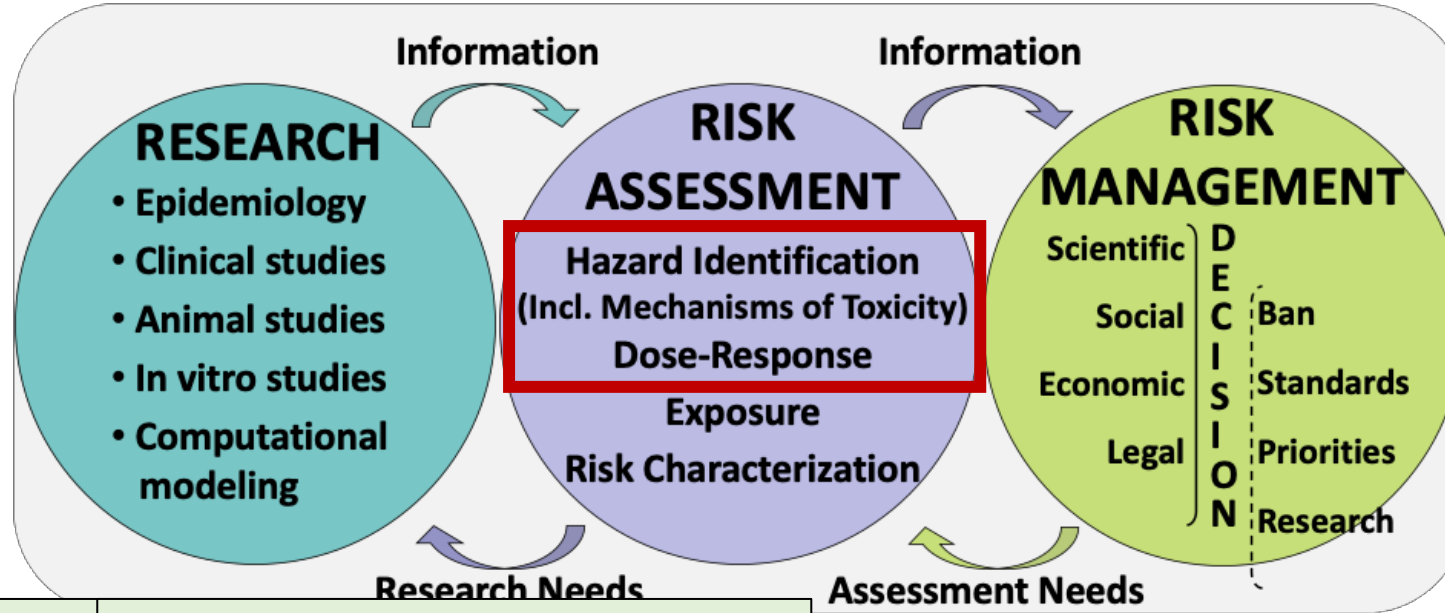
Weihshueh A. Chiu ^{a,*}, Miles S. Okino ^{b,1}, Marina V. Evans ^{a,2,3}

^a National Center for Environmental Assessment, US Environmental Protection Agency, Washington DC, 20460 USA

^b National Exposure Research Laboratory, US Environmental Protection Agency, Las Vegas, NV 89193, USA



The Long Road from Research to Action: Trichloroethylene as an Example



2009: Research on pharmacokinetics | **2011: EPA IRIS Toxicological Review with Toxicity Values**



Characterizing uncertainty and trichloroethylene and metabolite updated database, physiological Bayesian approach

Weihshueh A. Chiu ^{a,*}, Miles S. Okino ^{b,1}

^a National Center for Environmental Assessment, US Environmental Protection Agency
^b National Exposure Research Laboratory, US Environmental Protection Agency

Integrated Risk Information System (IRIS) Chemical Assessment Summary | U.S. Environmental Protection Agency National Center for Environmental Assessment

Trichloroethylene; CASRN 79-01-6

Human health assessment information on a chemical substance is included in the IRIS database only after a comprehensive review of toxicity data, as outlined in the [IRIS assessment development process](#). Sections I (Health Hazard Assessments for Noncarcinogenic Effects) and II (Carcinogenicity Assessment for Lifetime Exposure) present the conclusions that were reached during the assessment development process. Supporting information and explanations of the methods used to derive the values given in IRIS are provided in the [guidance documents located on the IRIS website](#).

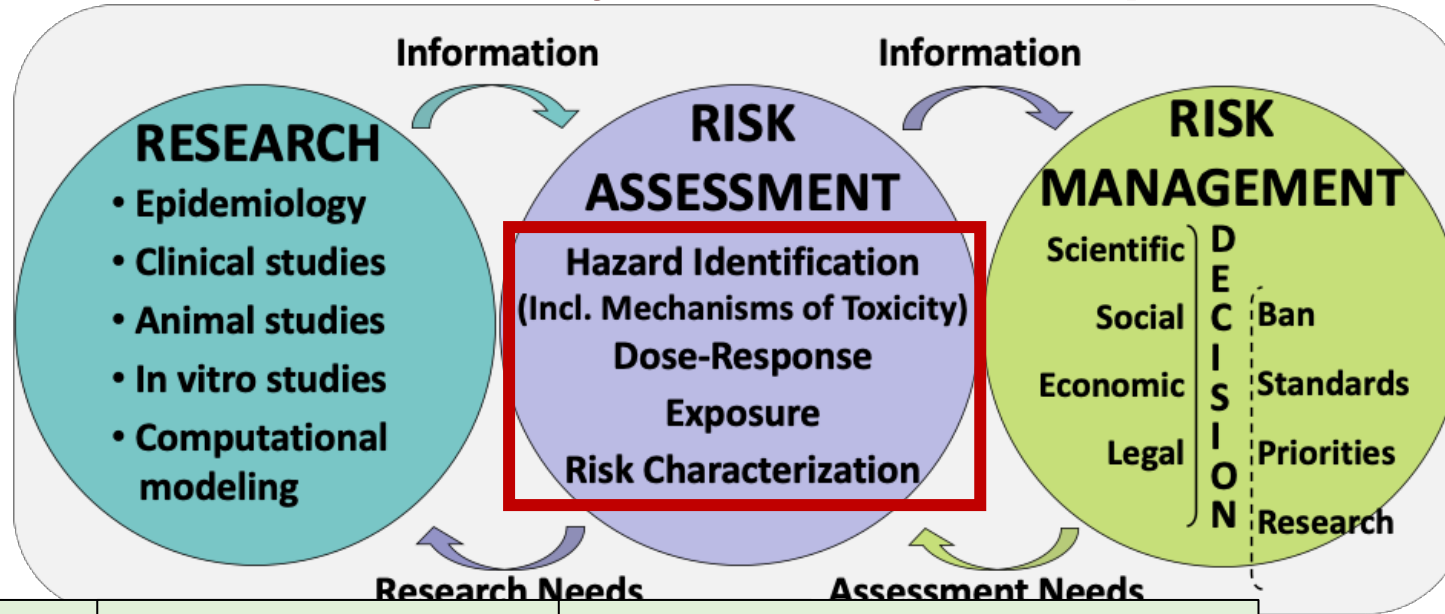
STATUS OF DATA FOR TRICHLOROETHYLENE

File First On-Line 03/31/1987


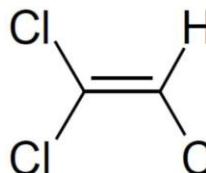
Category (section)	Assessment Available?	Last Revised
Oral RfD (I.A.)	yes	09/28/2011



The Long Road from Research to Action: Trichloroethylene as an Example

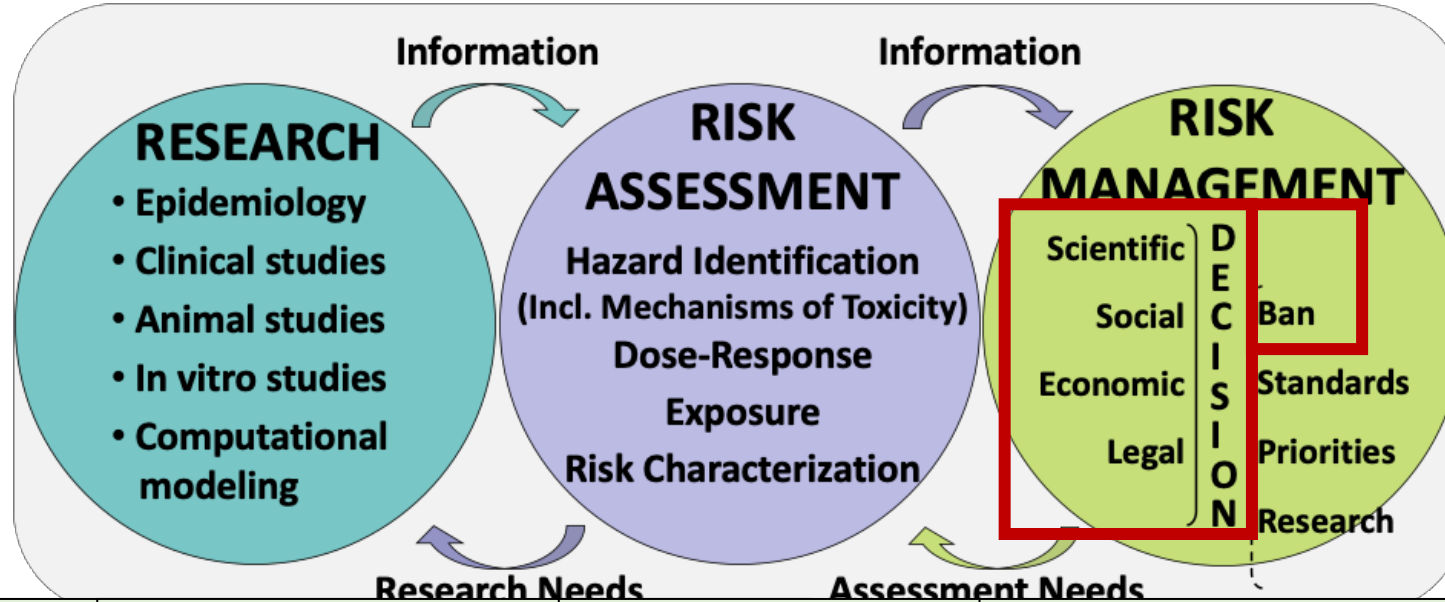


2009: Research on pharmacokinetics	2011: EPA IRIS Toxicity Review with Toxicity	2020: EPA Risk Evaluation
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 <p>Characterizing uncertainty and trichloroethylene and metabolites in an updated database, physiological and Bayesian approach</p> <p>Weihshueh A. Chiu ^{a,*}, Miles S. Okino ^{b,1},</p> <p>^a National Center for Environmental Assessment, US Environmental Protection Agency ^b National Exposure Research Laboratory, US Environmental Protection Agency</p>	<p>Integrated Risk Information System (IRIS) Chemical Assessment Summary</p> <p>Trichloroethylene; CASRN 79-01-6</p> <p>Human health assessment information on a chemical substance is only available after a comprehensive review of toxicity data, as outlined in the IRIS development process. Sections I (Health Hazard Assessments for Acute and Intermediate Term Exposure) and II (Carcinogenicity Assessment for Lifetime Exposure) present the results of the assessment development process. Supporting information and methods used to derive the values given in IRIS are provided in the IRIS website.</p> <p>STATUS OF DATA FOR TRICHLOROETHYLENE</p> <p>File First On-Line 03/31/1987</p> <table border="1"> <thead> <tr> <th>Category (section)</th> <th>Assessment Available</th> </tr> </thead> <tbody> <tr> <td>Oral RfD (I.A.)</td> <td>yes</td> </tr> </tbody> </table>	Category (section)	Assessment Available	Oral RfD (I.A.)	yes	<p>EPA Document #740R18008 November 2020 Office of Chemical Safety and Pollution Prevention</p> <p>EPA United States Environmental Protection Agency</p> <p>Risk Evaluation for Trichloroethylene</p> <p>CASRN: 79-01-6</p> 
Category (section)	Assessment Available					
Oral RfD (I.A.)	yes					



The Long Road from Research to Action: Trichloroethylene as an Example



2009: Research on pharmacokinetics	2011: EPA IRIS Toxicity Review with Toxicity	2020: EPA Risk Evaluation	2023: EPA Proposed Rule Banning TCE
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^a National Center for Environmental Assessment, US Environmental Protection Agency
^b National Exposure Research Laboratory, US Environmental Protection Agency

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Trichloroethylene; CASRN 79-01-6

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STATUS OF DATA FOR TRICHLOROETHYLENE

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EPA United States Environmental Protection Agency

Risk Evaluation Trichloroethylene

CASRN: 79-01-6

ClC(Cl)=CCl

EPA United States Environmental Protection Agency

Environmental Topics | Laws & Regulations | Report a Violation | About EPA

News Releases: [Headquarters](#) | [Chemical Safety and Pollution Prevention \(OCSPP\)](#)

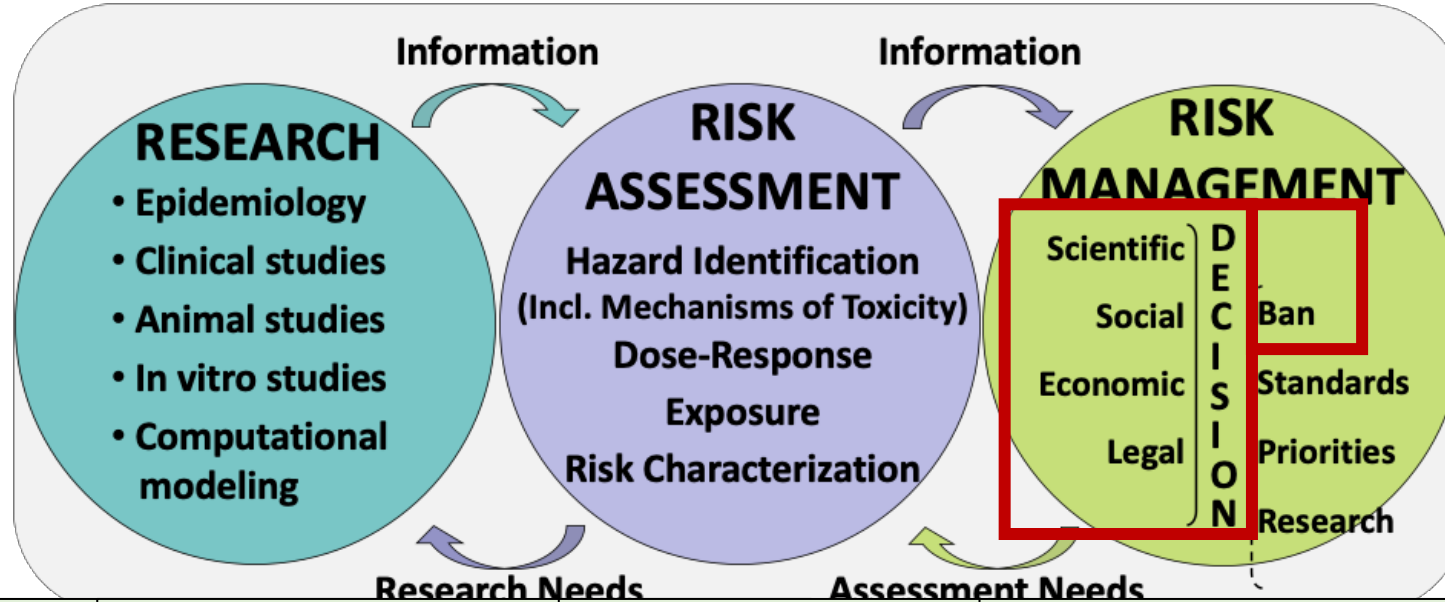
Biden-Harris Administration Proposes Ban on Trichloroethylene to Protect Public from Toxic Chemical Known to Cause Serious Health Risks

Proposal aligns with President Biden's Cancer Moonshot by reducing toxic exposures known to cause cancer

October 23, 2023



The Long Road from Research to Action: Trichloroethylene as an Example



2009: Research on pharmacokinetics	2011: EPA IRIS Toxicity Review with Toxicity	2020: EPA Risk Evaluation	2023: EPA Proposed Rule Banning TCE	2024: EPA Final Rule Banning TCE
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ELSEVIER Toxicology journal homepage

Characterizing uncertainty and trichloroethylene and metabolites in an updated database, physiological Bayesian approach

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Trichloroethylene; CASRN 79-01-6

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Risk Evaluation Trichloroethylene

CASRN: 79-01-6

ClC(Cl)=CCl

EPA United States Environmental Protection Agency

Environmental Topics ▾ Laws & Regulations ▾

News Releases: [Headquarters](#) | [Chemical Safety and Pollution Prevention](#)

Biden-Harris Administration Announces Final Rule Banning Trichloroethylene to Protect Public Health

Proposal aligns with President Biden's Cancer Prevention Plan to reduce exposure to known and suspected carcinogens.

October 23, 2023

Federal Register / Vol. 89, No. 242 / Tuesday, December 17, 2024 / Rules and Regulations

ENVIRONMENTAL PROTECTION AGENCY
40 CFR Part 751 [EPA-HQ-OPPT-2020-0642; FRL-8317-02-OCSP] RIN 2070-AK83 Trichloroethylene (TCE); Regulation Under the Toxic Substances Control Act (TSCA)
AGENCY: Environmental Protection Agency (EPA).

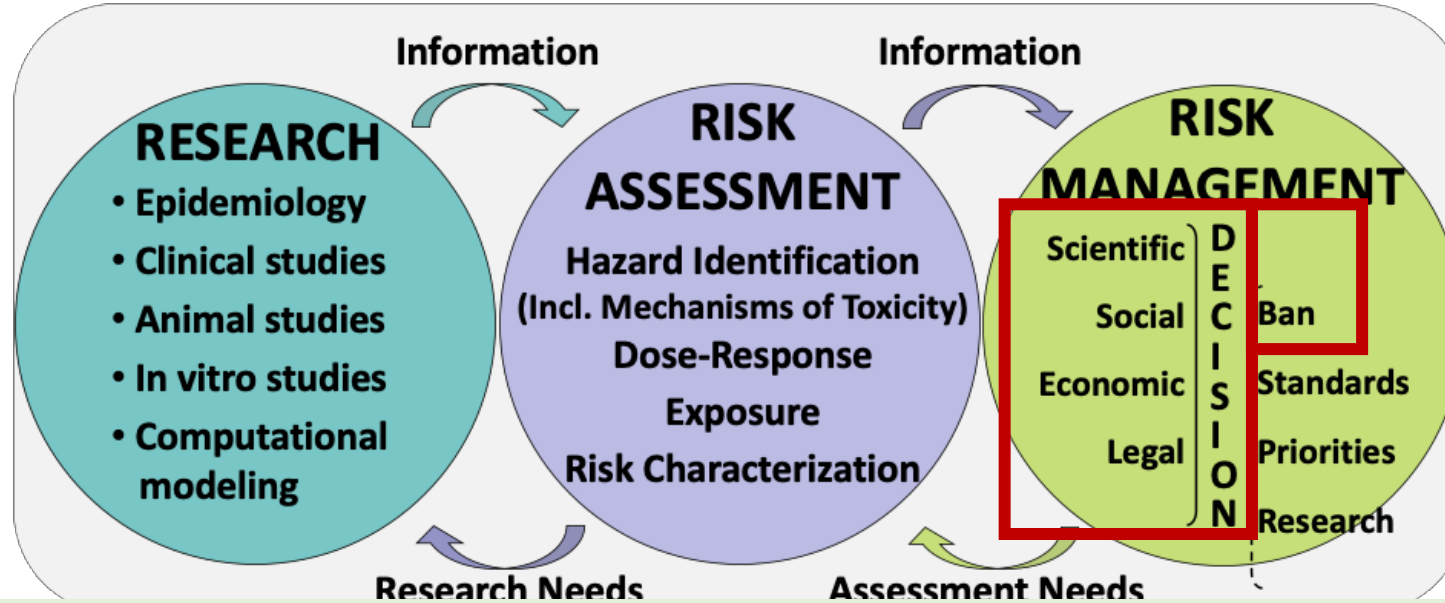
ACTION: Final rule.

SUMMARY: The Environmental Protection Agency (EPA or Agency) is finalizing a rule to address the unreasonable risk of injury to health presented by trichloroethylene (TCE) under its conditions of use. TSCA requires that EPA address by rule any unreasonable risk of injury to health or the environment identified in a TSCA risk evaluation and apply requirements to the extent necessary so that the chemical no longer presents unreasonable risk. EPA's final rule will, among other things, prevent serious illness associated with uncontrolled exposures to the chemical by preventing consumer access to the chemical, restricting the industrial and commercial use of the chemical while also allowing for a reasonable transition period with interim worker protections in place where an industrial and commercial use of the chemical is being prohibited, and provide time-limited exemptions for critical or essential uses of TCE for which no technically and economically feasible safer alternatives are available.

DATES: This final rule is effective on January 16, 2025.



The Long Road from Research to Action: Trichloroethylene as an Example



2009: Research on pharmacokinetics
2011: EPA IRIS Toxicity Review
2020: EPA Risk Evaluation
2023: EPA Proposed Rule Banning TCE
2024: EPA Final Rule Banning TCE

EPA's Strategic Phaseout of TCE and Related Chemicals

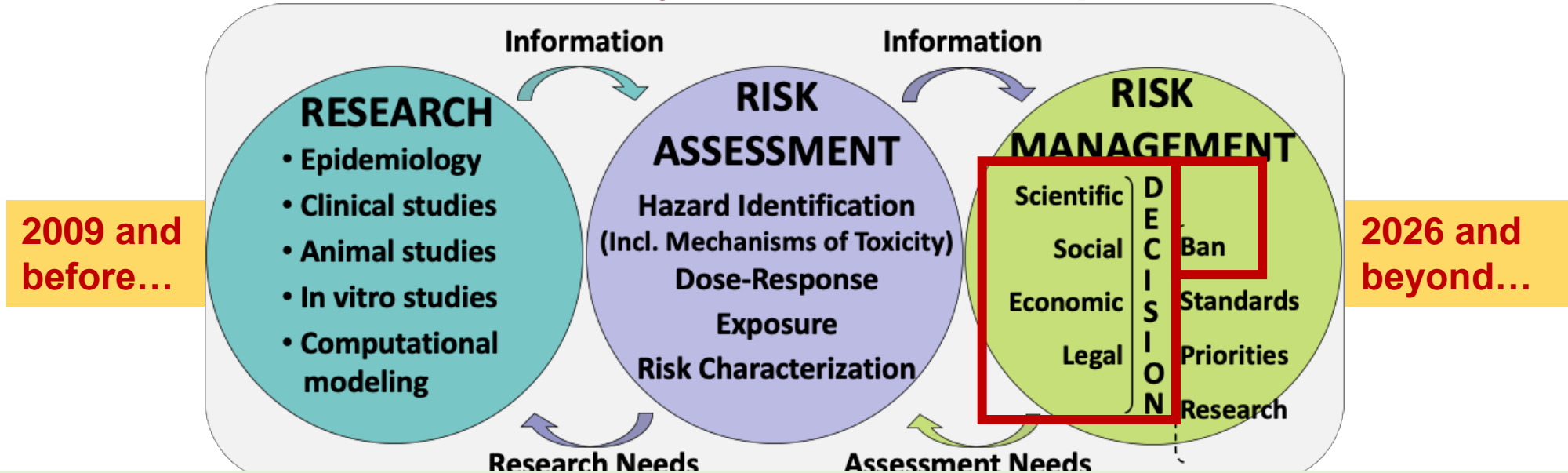


TSCA section 6(g) exemptions

Use during 50-year phaseout requires strict worker protections so inhalation exposures to TCE stay below 0.2 ppm.



The Long Road from Research to Action: Trichloroethylene as an Example



2009: Research on pharmacokinetics **2011: EPA IRIS Toxicity Review** **2020: EPA Risk Evaluation** **2023: EPA Proposed Rule Banning TCE** **2024: EPA Final Rule Banning TCE**

- **December 17, 2024** – Final rule published
- **January 10, 2025** – First legal challenges by companies to stay or reconsider the rule
- **January 13, 2025** – Fifth Circuit Court of Appeals granted a motion to temporarily stay the rule's effective date
- **January 16, 2025** – Third Circuit left the temporary administrative stay of the effective date in place pending further order of the court
- **January 28, 2025** – EPA temporarily delayed the effective date of the rule until March 21, 2025.
- **March 21, 2025** – EPA signed a notice further postponing the effective date of the requirements imposed on each of the TSCA section 6(g) exemptions in the final TCE rule for 90 days until June 20, 2025.

- **March 28, 2025** – Court lifted the administrative stay for all portions of the rule except for the provisions for the TSCA section 6(g) exemptions.
- **May 27, 2025**, EPA moved to hold the case in abeyance because it intends to reconsider the final rule
- **June 17, 2025** – EPA further postponed the effective date of the **TSCA section 6(g) exemptions** until August 19, 2025,
- **August 18, 2025** – EPA further postponed the effective date of the **TSCA section 6(g) exemption** requirements until November 17, 2025.
- **November 14, 2025** – EPA further postponed the effective date of the **TSCA section 6(g) exemption** requirements until **February 17, 2026.**

TSCA section 6(g) exemptions

Use during 50-year phaseout requires strict worker protections so inhalation exposures to TCE stay below 0.2 ppm.

Risk Assessment Context



Houston, we've had a problem here.

— *Jim Lovell* —

AZ QUOTES

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BETTER. STRONGER



FASTER

RESEARCH

- Epidemiology
- Clinical studies
- Animal studies
- In vitro studies
- Computational modeling

RISK MANAGEMENT

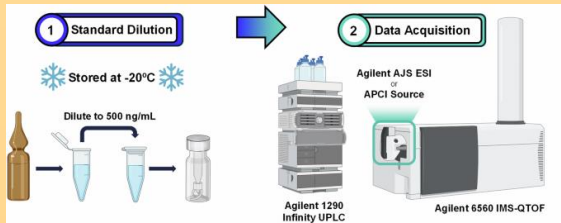
Public	D E	Ban
Local		
Public	C S	Standards
Local		
	I O N	Priorities
		Research



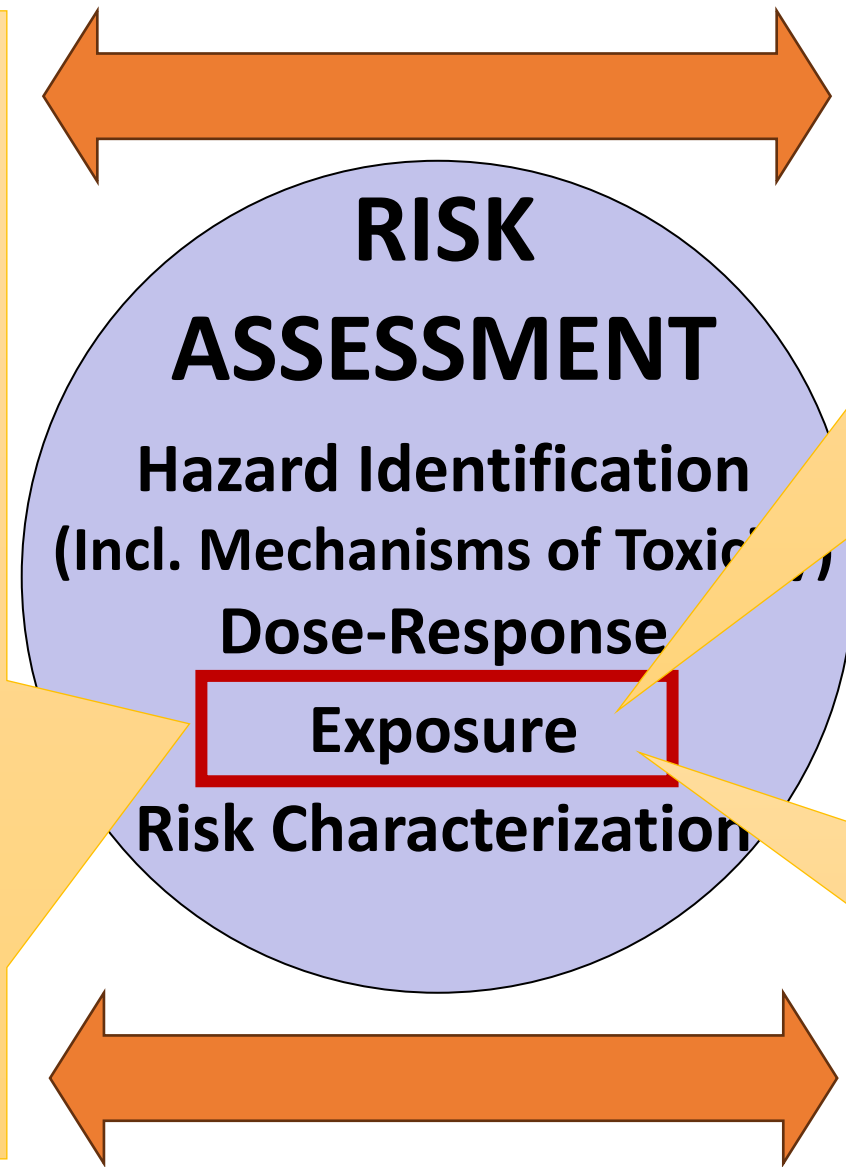
Toolbox for Next Generation Risk Assessment: Exposure

Non-Targeted Analytical Methods

- **IMS-MS:** Ion Mobility Spectrometry-Mass Spectrometry



- **PTR-MS:** Proton-Transfer-Reaction Mass Spectrometry on mobile platform



Geospatial Analysis and Visualization

- Geographic Information System (GIS)-based Spatial-Temporal Analysis
- Public-facing GIS Dashboards for visualization and communication

Engagement and Research Translation

- Partnering with government agencies, non-profits, and communities

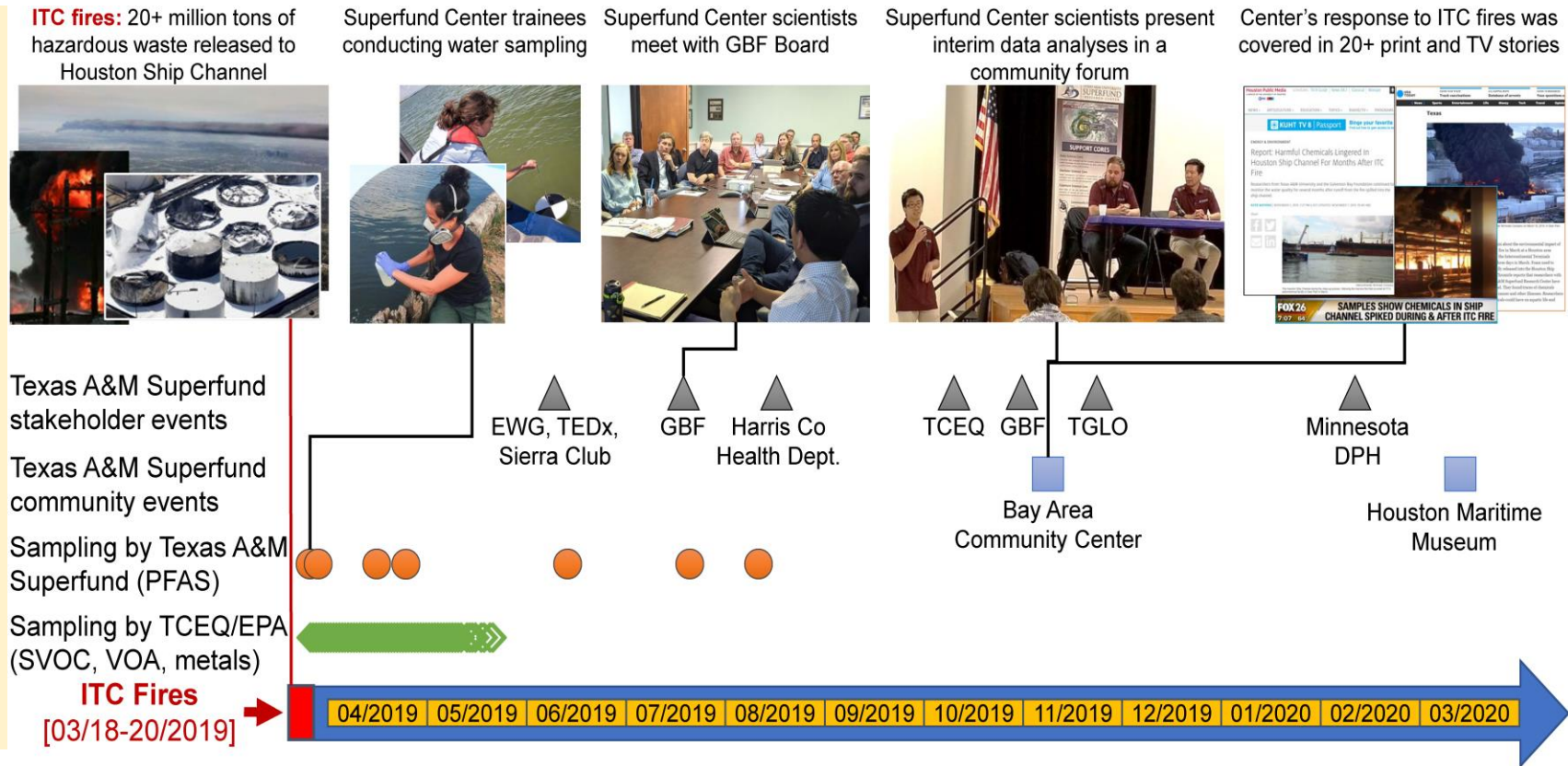
An example of the DR2 by Texas A&M University Superfund Center – 2019-2020 (Research Translation and Community Engagement)

Key Technical Approaches:

- Data mining
- Geospatial analytics and visualization
- Non-targeted analysis using Ion Mobility Spectrometry-Mass Spectrometry (IMS-MS)

Key Non-Technical Approaches:

- Research translation with risk assessment focus
- Engagement with government agencies, non-profits, and communities



Submitted: Mar 2020; Accepted: Jun 2020

Submitted: Jan 2021; Accepted: May 2021

Submitted: Jun 2021; Accepted: Aug 2021

Environmental Pollution
Volume 265, Part B, October 2020, 115009

Temporal and spatial analysis of per and polyfluoroalkyl substances in surface waters of Houston ship channel following a large-scale industrial fire incident ☆

nature > journal of exposure science & environmental epidemiology > articles > article

Article | Published: 02 June 2021

Spatial and temporal distribution of surface water contaminants in the Houston Ship Channel after the Intercontinental Terminal Company Fire



Journal of Environmental Sciences
Volume 115, May 2022, Pages 350-362

Analysis of per- and polyfluoroalkyl substances in Houston Ship Channel and Galveston Bay following a large-scale industrial fire using ion-mobility-spectrometry-mass spectrometry

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ITC fires: 20+ million tons of hazardous waste released to Houston Ship Channel



Superfund Center trainees conducting water sampling



Superfund Center scientists meet with GBF Board



Superfund Center scientists present interim data analyses in a community forum



Center's response to ITC fires was covered in 20+ print and TV stories



Cycle 1 of the Center (2017-2022):

“Rapid” Exposure Assessment =
12-24 months

(SVOC, VOA, metals)

ITC Fires

[03/18-20/2019]



Submitted: Mar 2020; Accepted: Jun 2020

Submitted: Jan 2021; Accepted: May 2021

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An example of the DR2 by Texas A&M University Superfund Center – 2023 (the “One Center” approach)

February 3, 2023



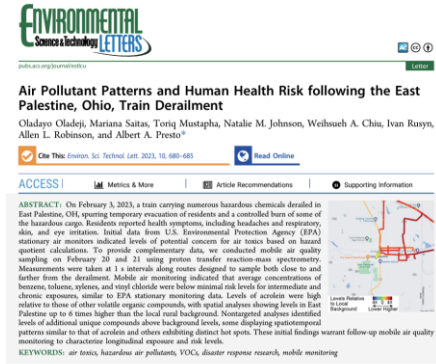
February 21, 2023



March 16, 2023



July 12, 2023



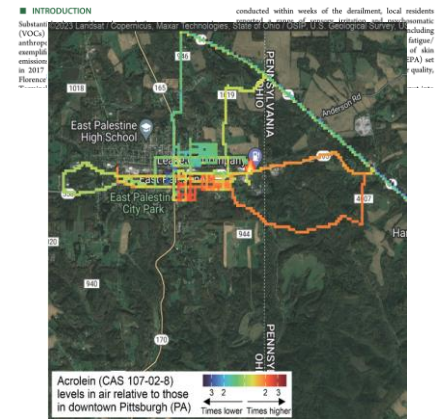
November 6-7, 2023



February 24, 2023



4,000 views



January 2024
R21 funded



TEXAS A&M UNIVERSITY
SUPERFUND
RESEARCH CENTER

An example of the DR2 by Texas A&M University Superfund Center – 2023 (the “One Center” approach)

February 3, 2023

February 21, 2023

March 16, 2023

July 12, 2023

November 6-7, 2023

Cycle 2 of the Center (2022-2027):
“Rapid” Exposure Assessment =
6-9 months

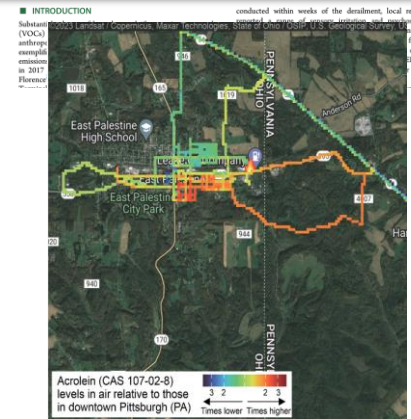


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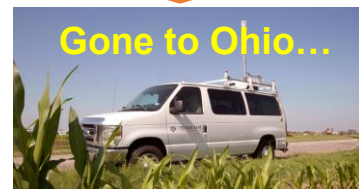
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January 2024
R21 funded



TEXAS A&M UNIVERSITY
SUPERFUND
RESEARCH CENTER

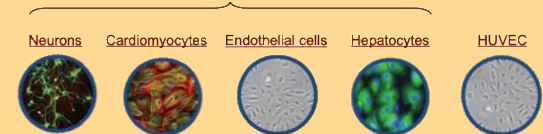


Toolbox for Next Generation Risk Assessment: Hazard Identification & Dose-Response

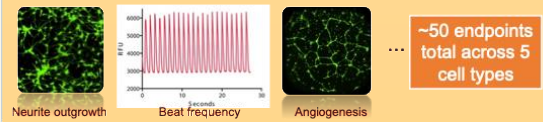
New Approach Methodologies in Toxicology

• *In Vitro*

Human induced pluripotent stem cell (iPSC)-derived cells

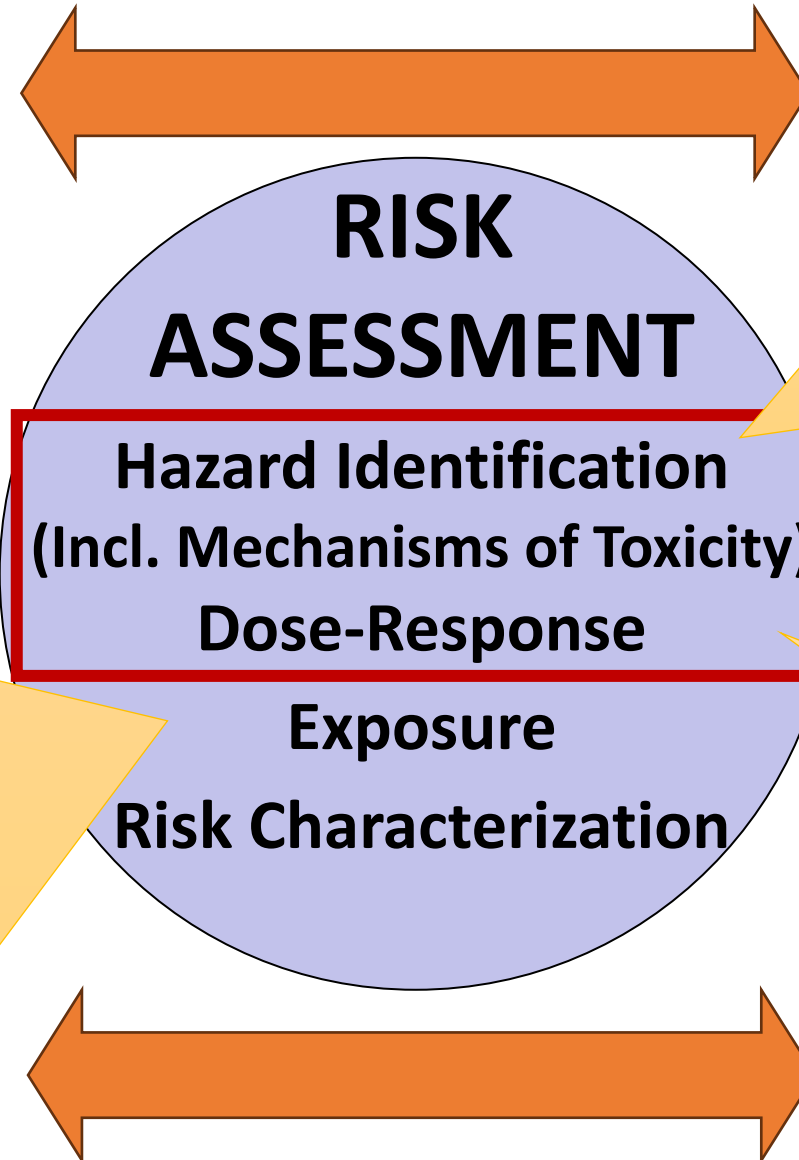


- Cytotoxicity
- Neur. growth
- Beating
- Angiogenesis
- Mitochondria
- Angiogenesis



• *In Silico*

Two-Stage Machine Learning for Human Health Points of Departure



Data Analysis and Visualization

- Data mining and AI/Machine Learning
- Geographic Information System (GIS)-based Spatial Analysis and Visualization

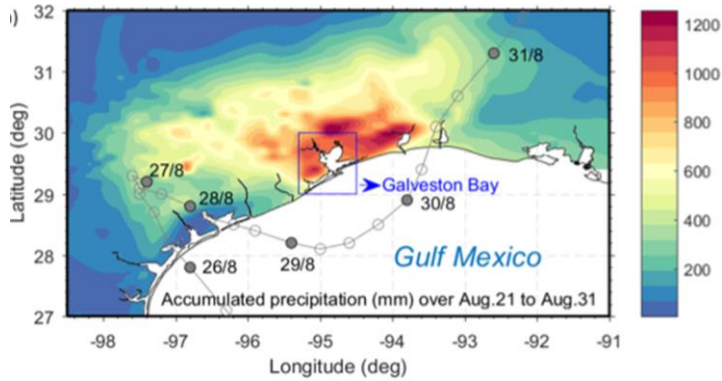
Engagement and Research Translation

- Partnering with government agencies, non-profits, and communities



Hurricane Harvey Case Study: Rapid Hazard ID

Hurricane Harvey: A massive rain event



...leading to major
contaminant re-distribution

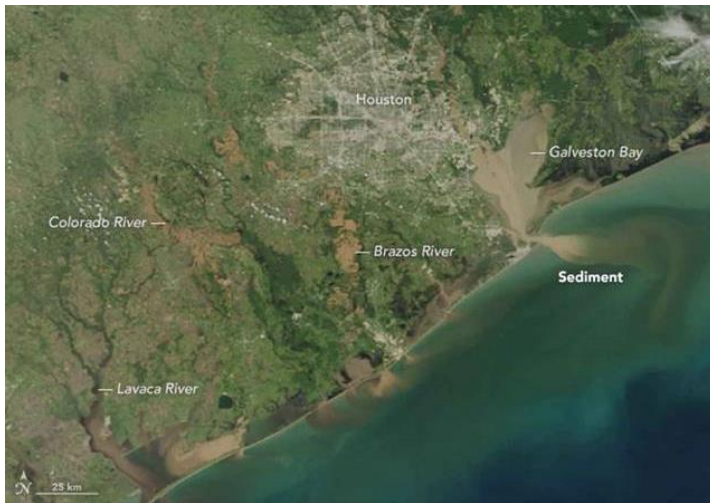
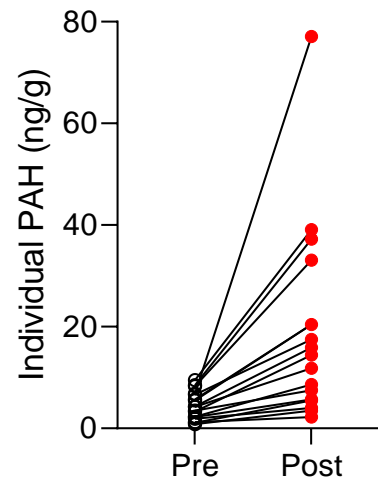
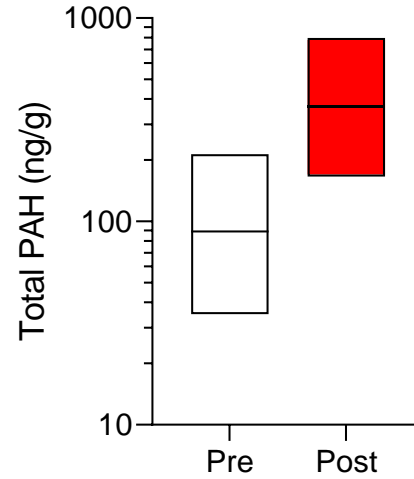


Image credits: Tim Dellapena and Anthony Knap (Texas A&M)

PAH concentrations in sediments (Houston Ship Channel/ Galveston Bay)



Camargo *et al* Mar Pollut Bull 2020 Nov 27; 111872

Potential PAH contamination in the residential areas

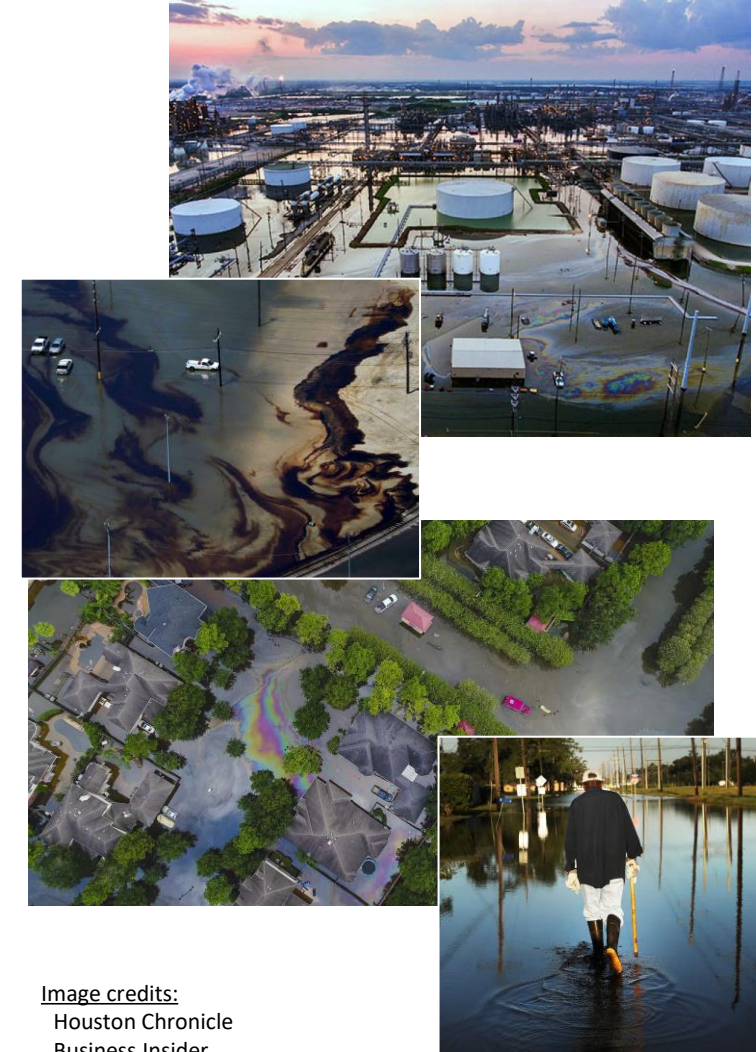


Image credits:
Houston Chronicle
Business Insider
The New York Times



Hurricane Harvey Case Study: Rapid Hazard ID

Risk Characterization of Environmental Samples Using *In Vitro* Bioactivity and Polycyclic Aromatic Hydrocarbon Concentrations Data

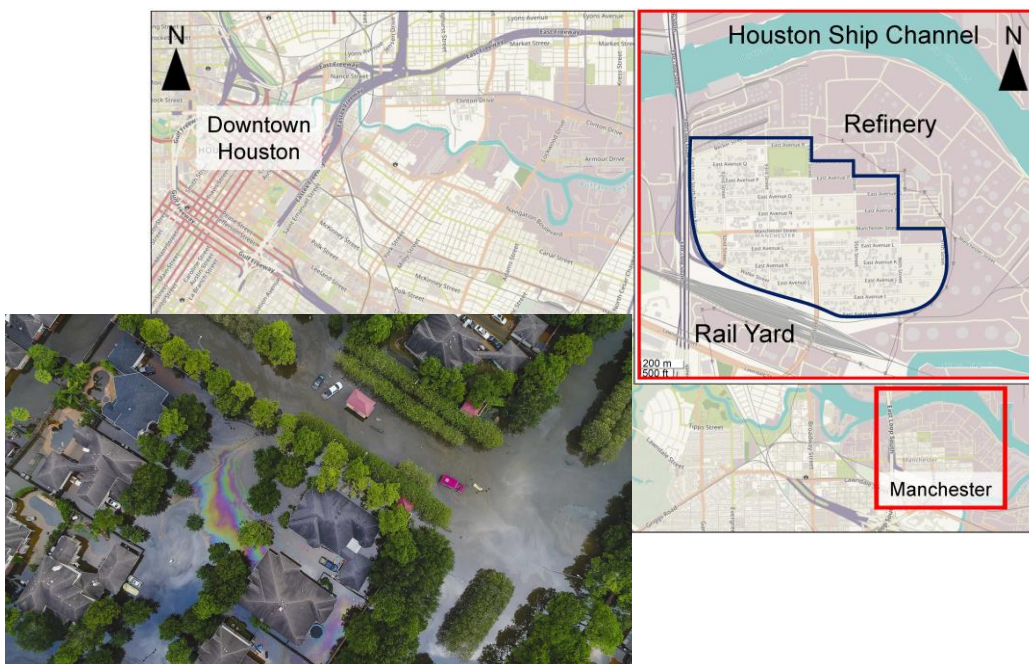
Zunwei Chen, Dillon Lloyd, Yi-Hui Zhou, Weihsueh A Chiu, Fred A Wright, Ivan Rusyn ✉

Toxicological Sciences, Volume 179, Issue 1, January 2021, Pages 108–120,

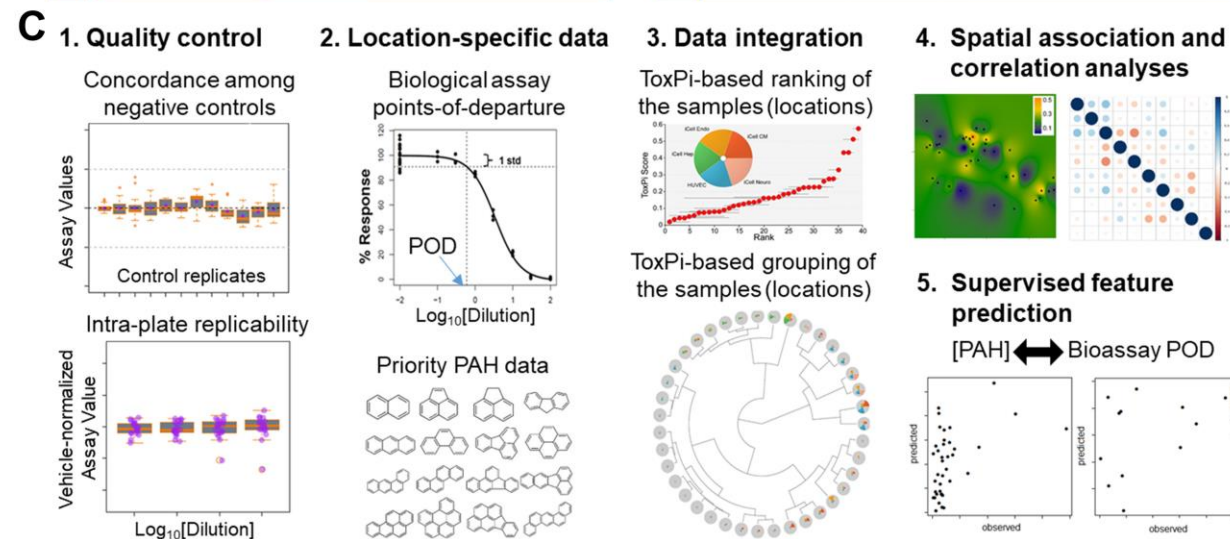
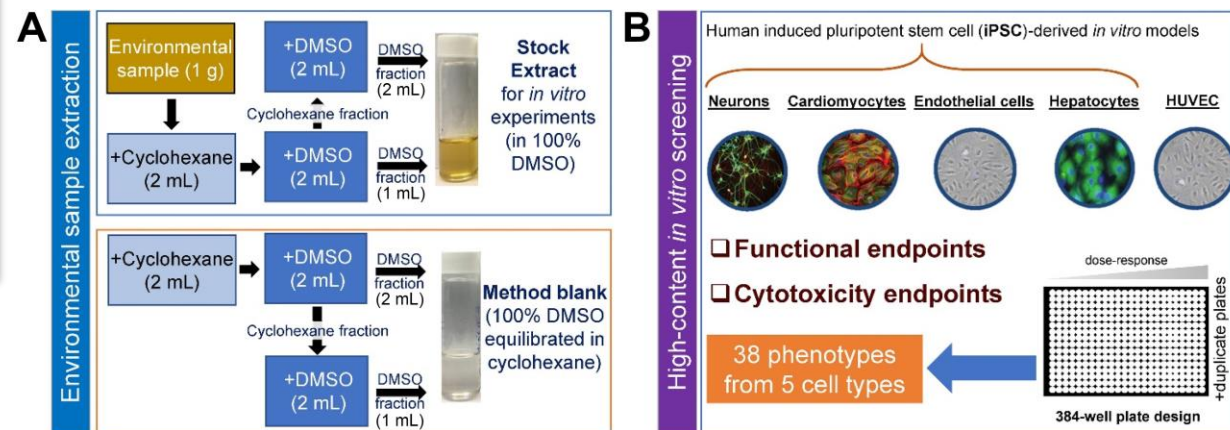
<https://doi.org/10.1093/toxsci/kfaa166>

Published: 09 November 2020

Study area: “Real” mixtures



Study design: Chemical-biological data





Risk Characterization of Environmental Samples Using *In Vitro* Bioactivity and Polycyclic Aromatic Hydrocarbon Concentrations Data

Zunwei Chen, Dillon Lloyd, Yi-Hui Zhou, Weihsueh A Chiu, Fred A Wright, Ivan Rusyn ✉

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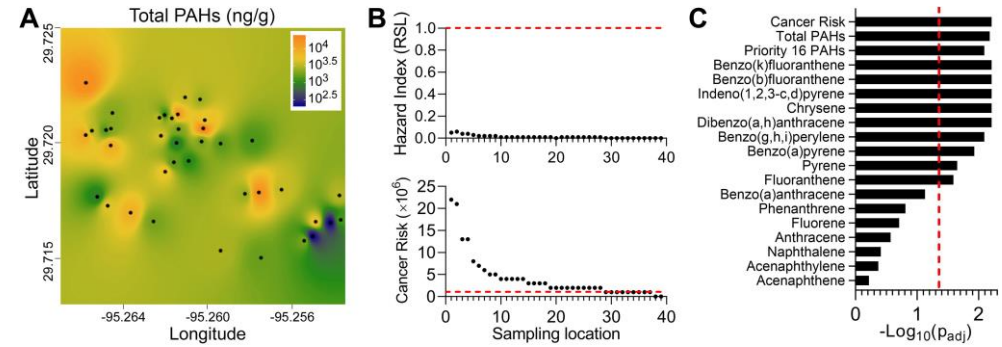
<https://doi.org/10.1093/toxsci/kfaa166>

Published: 09 November 2020

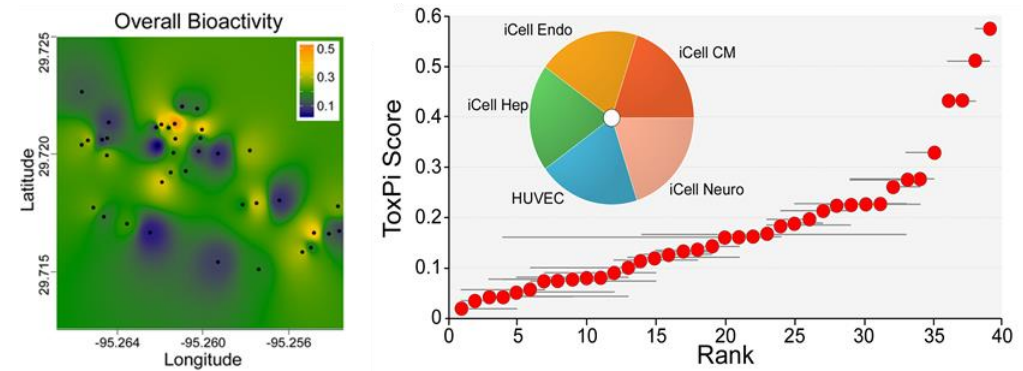
Conclusions:

- Significant evidence of spatial correlation of a subset of PAH contaminants and of cell-based phenotypes
- We show that the cell-based bioactivity data can be used to predict environmental concentrations for several PAH contaminants, as well as overall PAH summaries and cancer risk
- Demonstrated that cell-based profiling can be used for rapid hazard screening of environmental samples by anchoring the bioassays to concentrations of PAH
- NAMs can be used for identification of the areas of concern and direct quantitative risk characterization

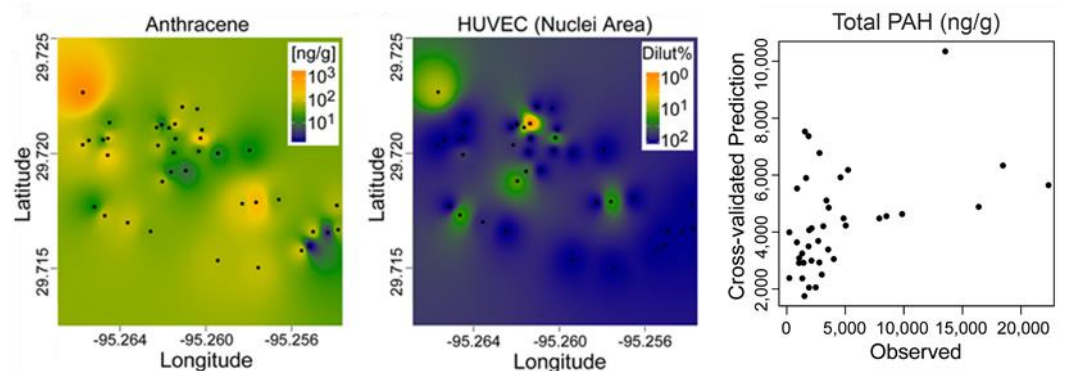
Spatial patterns in PAH contamination and cancer risk



Spatial patterns in bioactivity (*in vitro* studies)



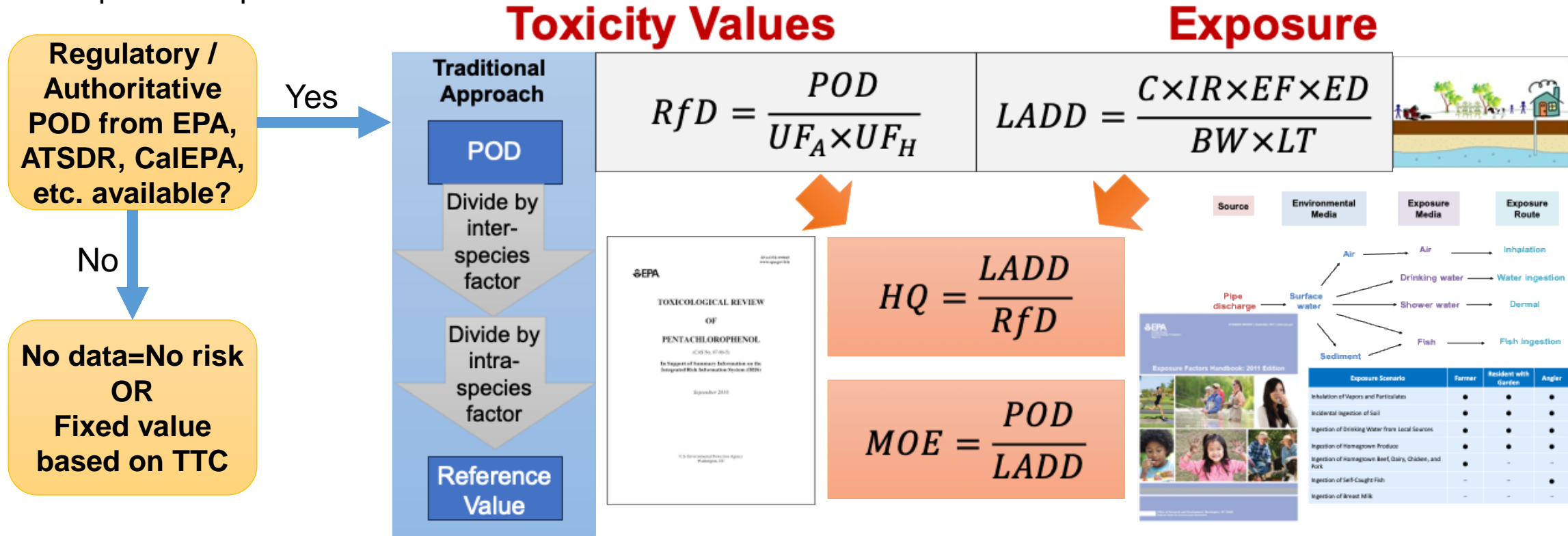
Correlations between PAH and bioactivity





A Tiered Hierarchy of Points of Departure

- **Dose-Response Assessment** requires **Points of Departure (PODs)** for deriving Toxicity Values to compare to Exposure estimates



- **Regulatory/authoritative PODs** cover a very limited set of chemicals.
- **Counterfactual:** If we were to have new regulatory/authoritative assessments based on animal studies in the absence of any human data, we would make decisions based on them!
- **Proposed Approach:** Use *in silico* methods derive surrogate or predicted PODs calibrated to existing regulatory/authoritative PODs.



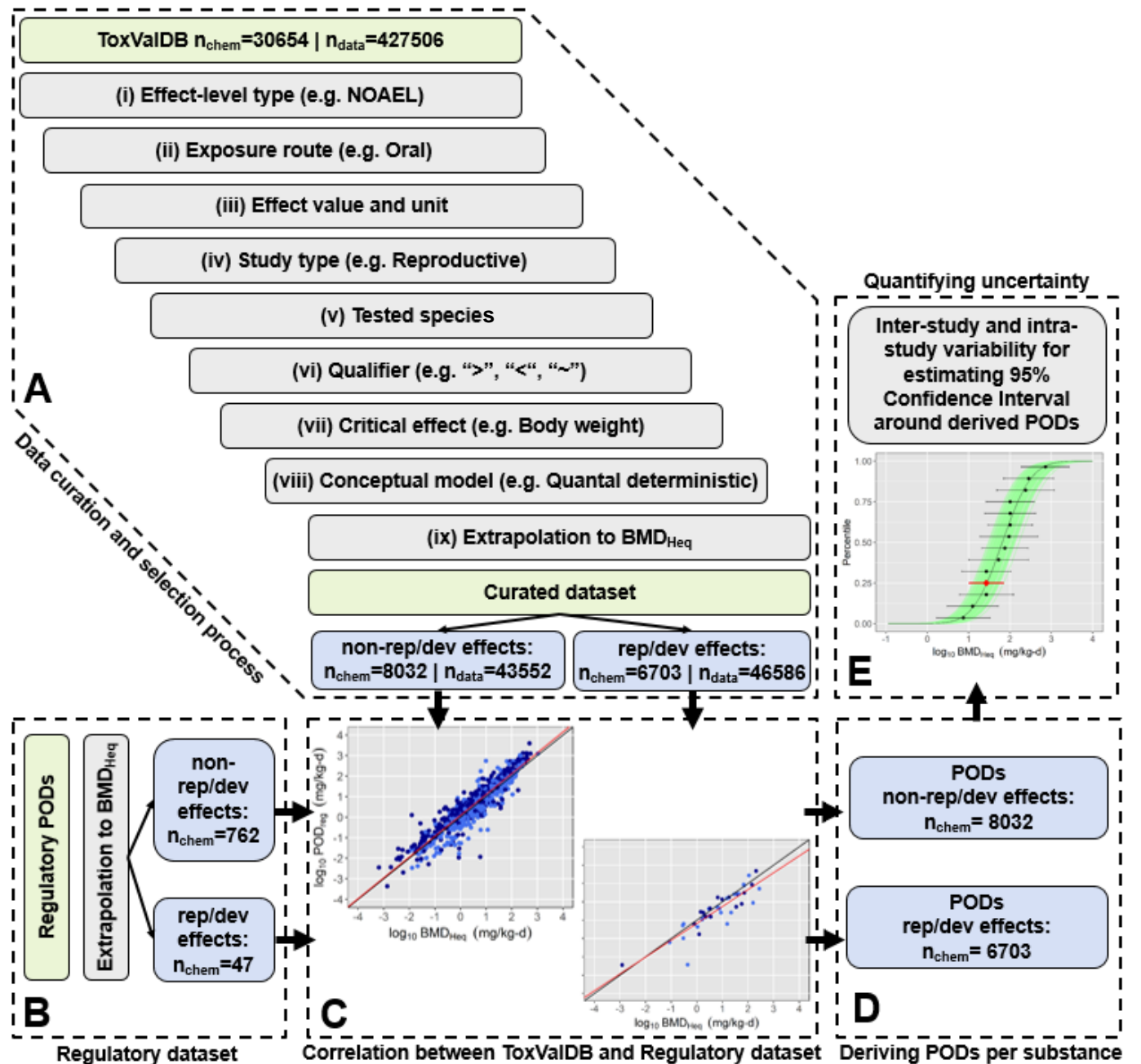
Surrogate POD based on analysis of ToxValDB

Approach: Expand coverage of chemicals with (non-cancer) toxicity values by

- Created a consistent and curated data set of *in vivo* chronic dose-response toxicity data from EPA ToxValDB
- Developed a statistical approach for calibrating toxicity data against regulatory values
- Quantified uncertainty from inter- and intra-study variability

Results: Surrogate PODs can be derived using the 25th %ile from ToxValDB

- Oral PODs expanded by $n > 10,000$ Aurisano et al. [2023](#)
- Inhalation PODs expanded by $n > 2,000$ Aurisano et al. [2024](#)





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ToxValDB $n_{\text{chem}}=30654$ | $n_{\text{data}}=427506$

(i) Effect-level type (e.g. NOAEL)

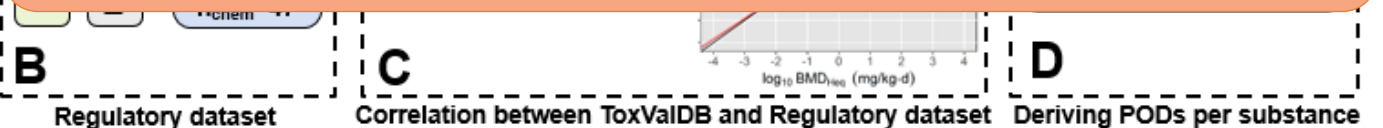
Implemented by EPA for Oral PODs:

- Database-calibrated assessment process (DCAP)
- Peer review by their Board of Scientific Counselors in January 2025 (<https://www.epa.gov/bosc/database-calibrated-assessment-product-dcap-panel>)
- Applied to 1001 chemicals that currently lack human health assessments (Harrill et al. 2026 <https://doi.org/10.1080/10937404.2025.2552108>) .

Limitations

- Tens of thousands of chemicals have no or inadequate data in ToxValDB.
- *In vivo* testing data on these chemicals unlikely to expand substantially in the near future.

AI/Machine Learning to the Rescue?





QSAR-Based PODs based on Chemical Descriptors

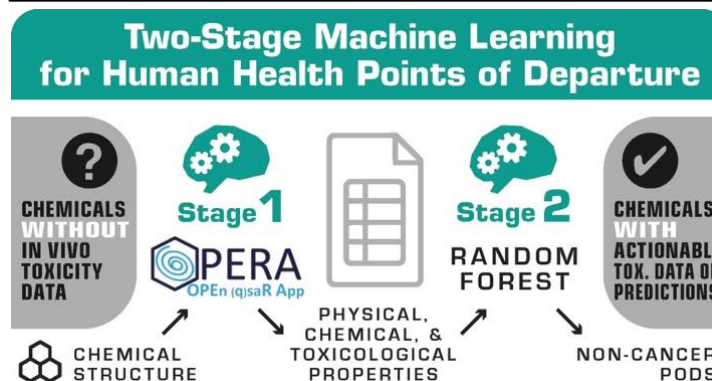
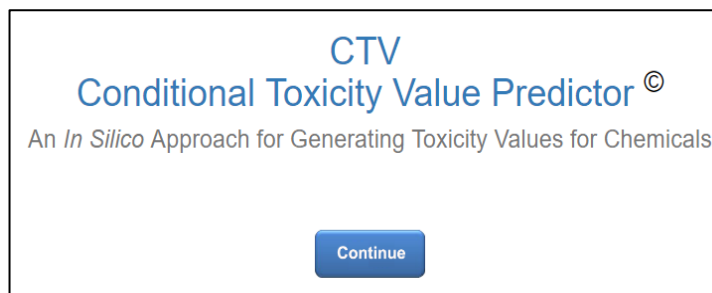
Conditional Toxicity Value (CTV) Predictor (2018)

- QSAR built on regulatory toxicity values
- Predicts oral and inhalation (experimental) NOAELs

Two-Stage Machine Learning Model (2024)

- QSAR for PODs building on surrogate oral PODs from Aurisano et al. (2023)
- Model for inhalation PODs in development

Both approaches perform better than ToxCast/in vitro NAMs for predicting regulatory PODs



<https://wchiu.shinyapps.io/Two-Stage-ML-Results-Browser/>

Approach	RMSE	MedA E	R ²
CTV	N.R.	0.70	0.45
Two-Stage ML (general non-cancer)	0.69	0.40	0.48
Two-Stage ML (repro/dev)	0.58	0.31	0.49
ToxCast+httk (general non-cancer)	1.87	1.22	<0
ToxCast+httk (repro/dev)	1.52	0.84	<0

RMSE: Root-mean-squared-error (log10 units)

MedAE: Median absolute error (log10 units)

R²: Coefficient of determination (<0 means worse than naive constant model)



QSAR-Based PODs based on Chemical Descriptors

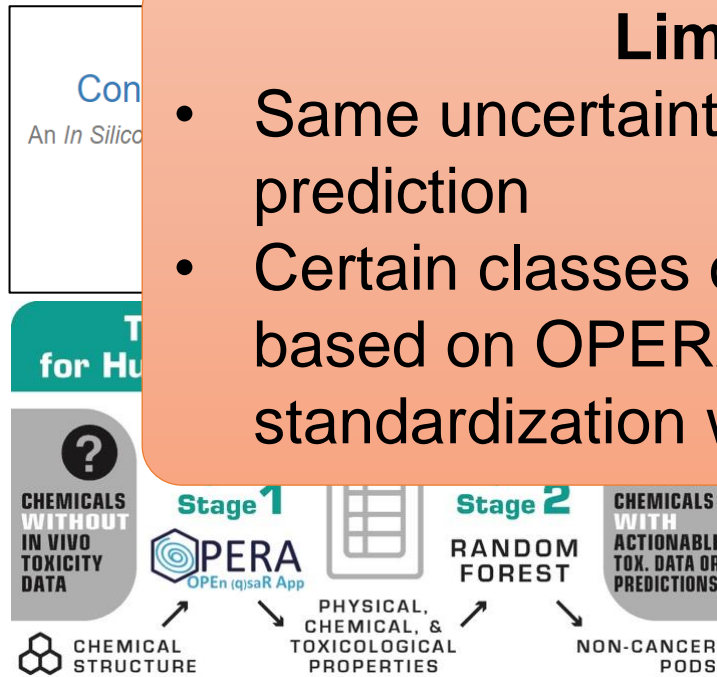
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Limitations

- Same uncertainty estimate for every prediction
- Certain classes of chemicals excluded based on OPERA QSAR standardization workflow

			R ²	
			0.45	
			0.48	
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	cancer)	1.87	1.22	<0
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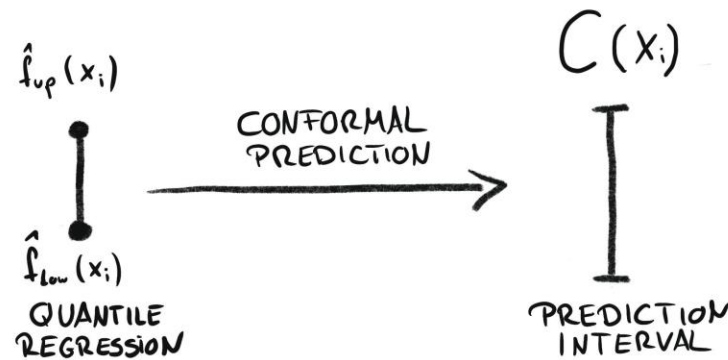
QSAR-Based PODs based on Chemical Descriptors

Use of “Uncertainty-Aware” AI/ML methods

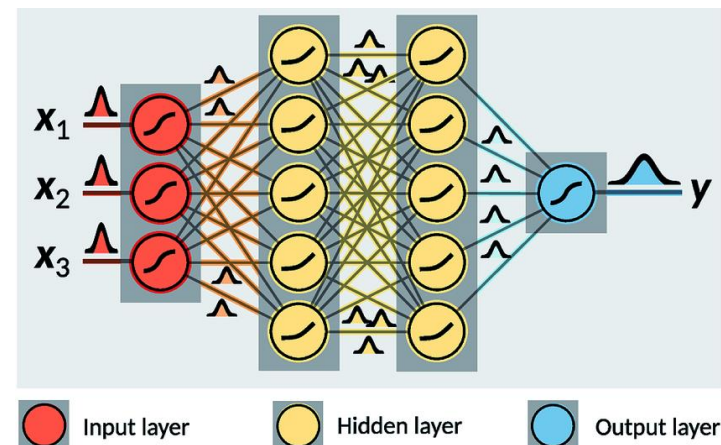
- Addresses aleatoric *and* epistemic uncertainty for each prediction
- Applied to >130K marketed chemicals
- Web-app for additional chemicals (enter SMILES)

<https://dtu-quantitative-sustainability-assessment.shinyapps.io/poduam/>

• Conformal prediction (CP)



• Bayesian neural network (BNN)

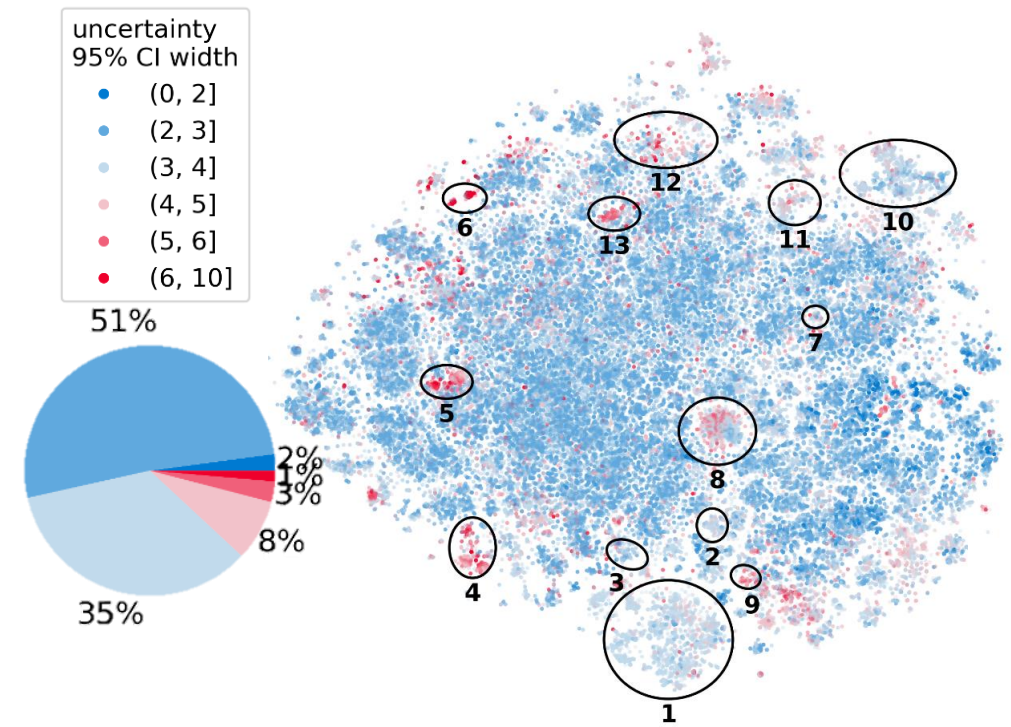
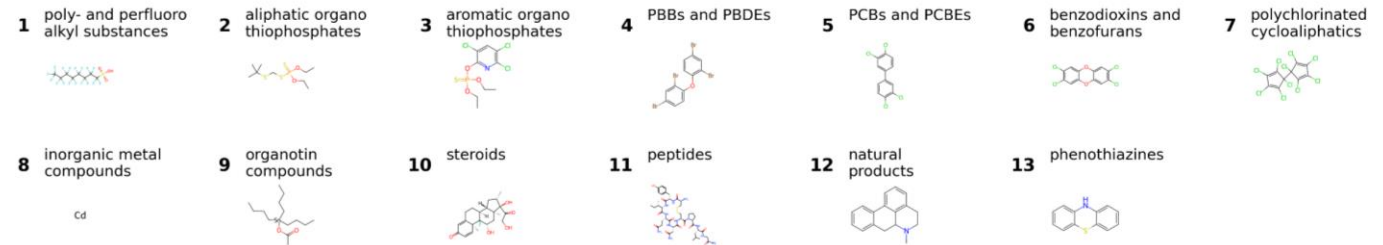




QSAR-Based PODs based on Chemical Descriptors

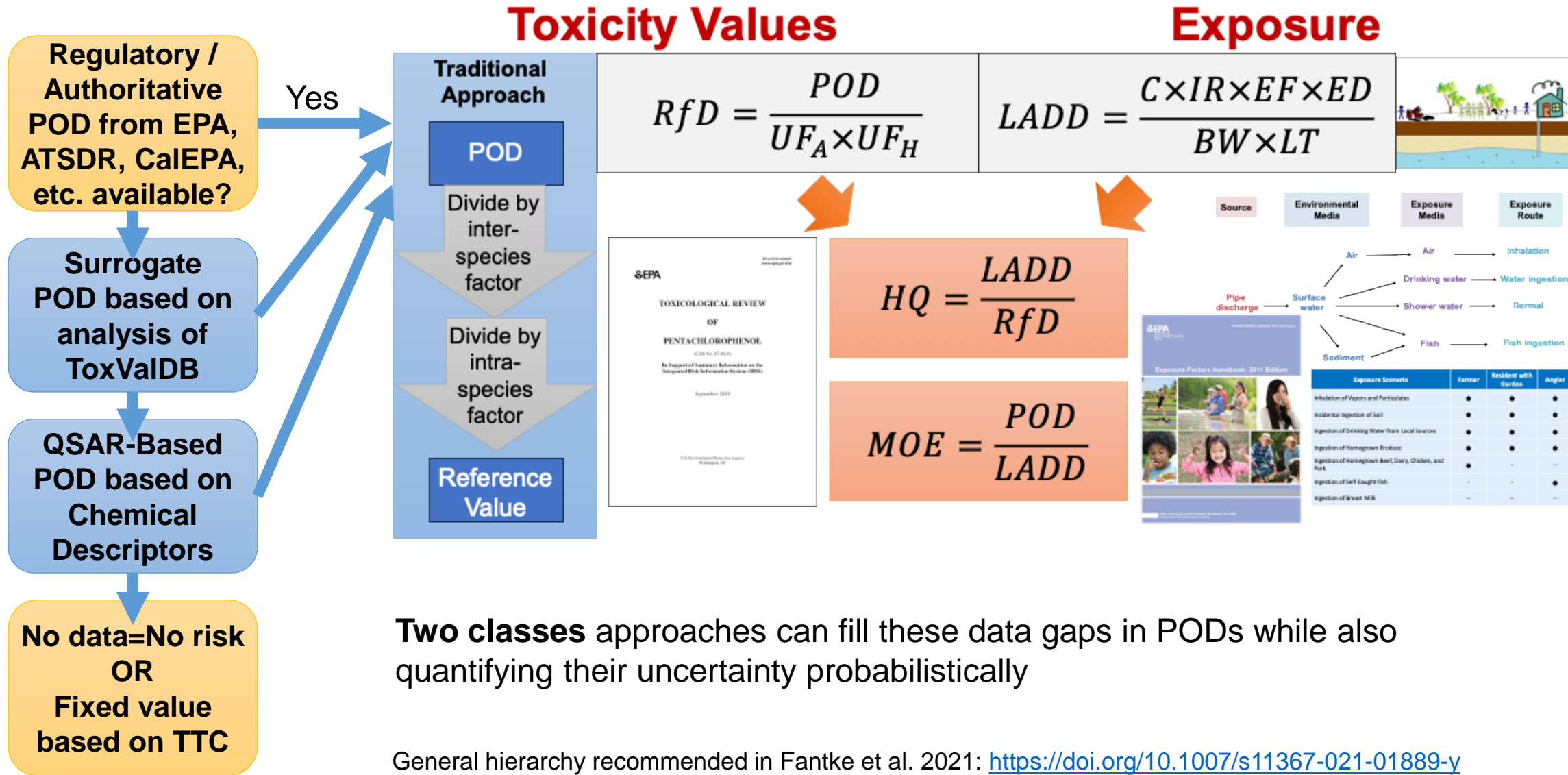
Use of “Uncertainty-Aware” AI/ML methods

- **Uncertainty hotspots**
 - polychlorinated and polybrominated compounds
 - metals and organometallics
 - alkaloids and phenothiazines
 - Peptides
- **Drivers of uncertainty**
 - low representation in the training data
 - low applicability of molecular descriptor developed for small organic molecules
 - (highly toxic) outliers





A Tiered Hierarchy of Points of Departure



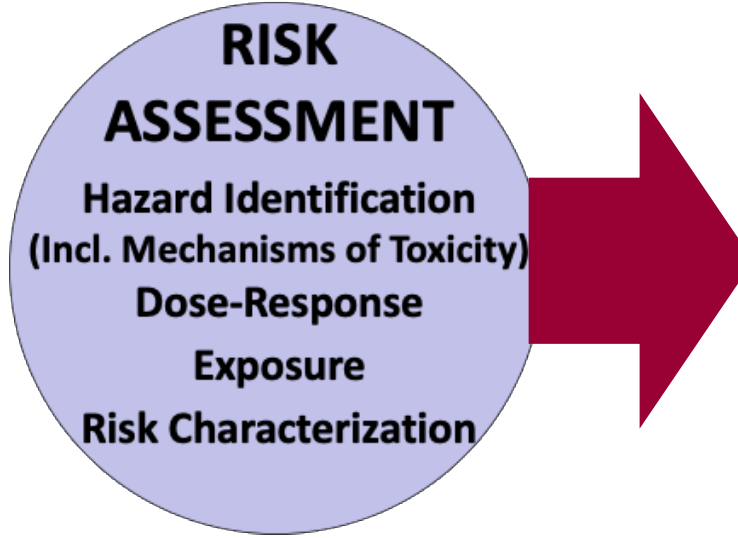
Two classes approaches can fill these data gaps in PODs while also quantifying their uncertainty probabilistically



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Texas A&M Superfund Research Center: Developing *Better, Stronger, Faster* Risk Assessment Approaches through the Lens of Disasters

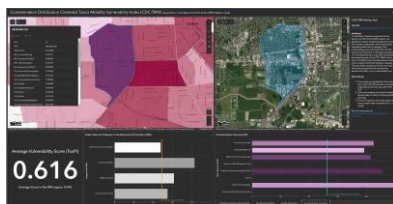
Non-Targeted Approaches for Better Exposure Assessment



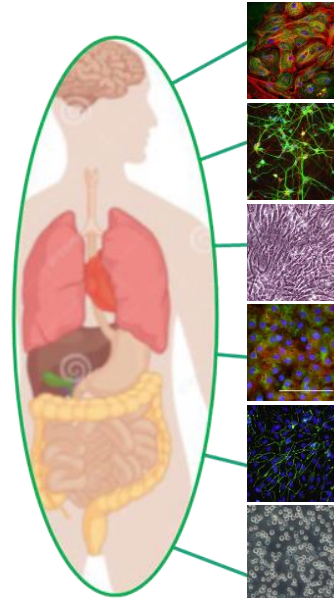
Broad Engagement for Better Translation and Implementation



Geospatial Tools for Stronger Communication



In Vitro Approaches for Faster Hazard Identification



Regulatory /
Authoritative
POD from EPA,
ATSDR, CalEPA,
etc. available?

Surrogate
POD based on
analysis of
ToxValDB

QSAR-Based
POD based on
Chemical
Descriptors

No data=No risk
OR
Fixed value
based on TTC

In Silico Approaches for Faster Dose- Response Assessment