2024 Society of Toxicology (SOT) Annual Conference: EHLC Community Presentations

Salt Lake City, Utah

March 10 - 14, 2024

SOT Presentations by EHLC Community Members

This document provides an overview of 2024 SOT presentations from Environmental Health Language Collaborative (EHLC) community members.

Presentation Order	Presentation Title	Presenter, Organization
1	*Improving the findability of toxicology studies for decision making in the era of data sharing*	Michelle Angrish, PhD, U.S. EPA angrish.michelle@epa.gov
2	*How best to combine data from multiple independent studies?*	Jeanette A Stingone, PhD, MPH, Columbia University js5406@cumc.columbia.edu
3	*Digitizing Relationships between Exposures, Biomarkers, and Clinical Outcomes (In the era of AI and exposomics)*	Chirag Patel, PhD, Harvard Medical School chirag_patel@hms.harvard.edu
4	*Challenges and opportunities to improve communication about exposure and risk for collaboration and information exchange*	Elke Jensen, PhD, Dow Chemical Company elke.jensen@dow.com
5*	*Overcoming Barriers to More Scalable Environmental Health Science Research via Harmonized Language**	Andrew Rooney, PhD, NIEHS* andrew.rooney@nih.gov Steve Edwards, PhD, U.S. EPA edwards.stephen@epa.gov

**presentation materials not included*

Presentation 1

Presentation Order	Presentation Title	Presenter, Organization
1	*Improving the findability of toxicology studies for decision making in the era of data sharing*	Michelle Angrish, PhD, U.S. EPA angrish.michelle@epa.gov

Improving the findability of toxicology studies for decision making in the era of data sharing

Michelle Angrish
U.S. EPA

The author declares no conflict of interest.
The views expressed in this presentation are those of the author and do not necessarily reflect the views or policies of the US EPA.

Today's Goals

- Understand the challenges in reusing research.
- Learn how structured data helps to reuse research – and help you!
- Starting practices for making your research findable and therefore, reusable!

- Perspectives from a chemical assessment practitioner with examples:
  - Finding information
  - Bringing structure to unstructured data
  - Standardizing data

Definitions

- Annotation – labeled text with a tag that indicates the type of thing or concept the text represents
- Interoperable – the ability for information to flow to/from tools
- Controlled vocabulary – non-redundant list of preferred terms
- Standardized data extraction format – template for formatting extracted data
- Template – organization framework for extracted data
- Schema – organization framework for templates and metadata

Who are we?

About the Chemical and Pollutant Assessment Division (CPAD)

The Center for Public Health and Environmental Assessment (CPHEA) provides the science needed to understand the complex interrelationship between people and nature in support of assessments and policy to protect human health and ecological integrity. Within CPHEA, sits the Chemical and Pollutant Assessment Division.

Related Information

- About CPHEA
- Organization Chart for CPHEA
- About the Office of Research

On This Page:

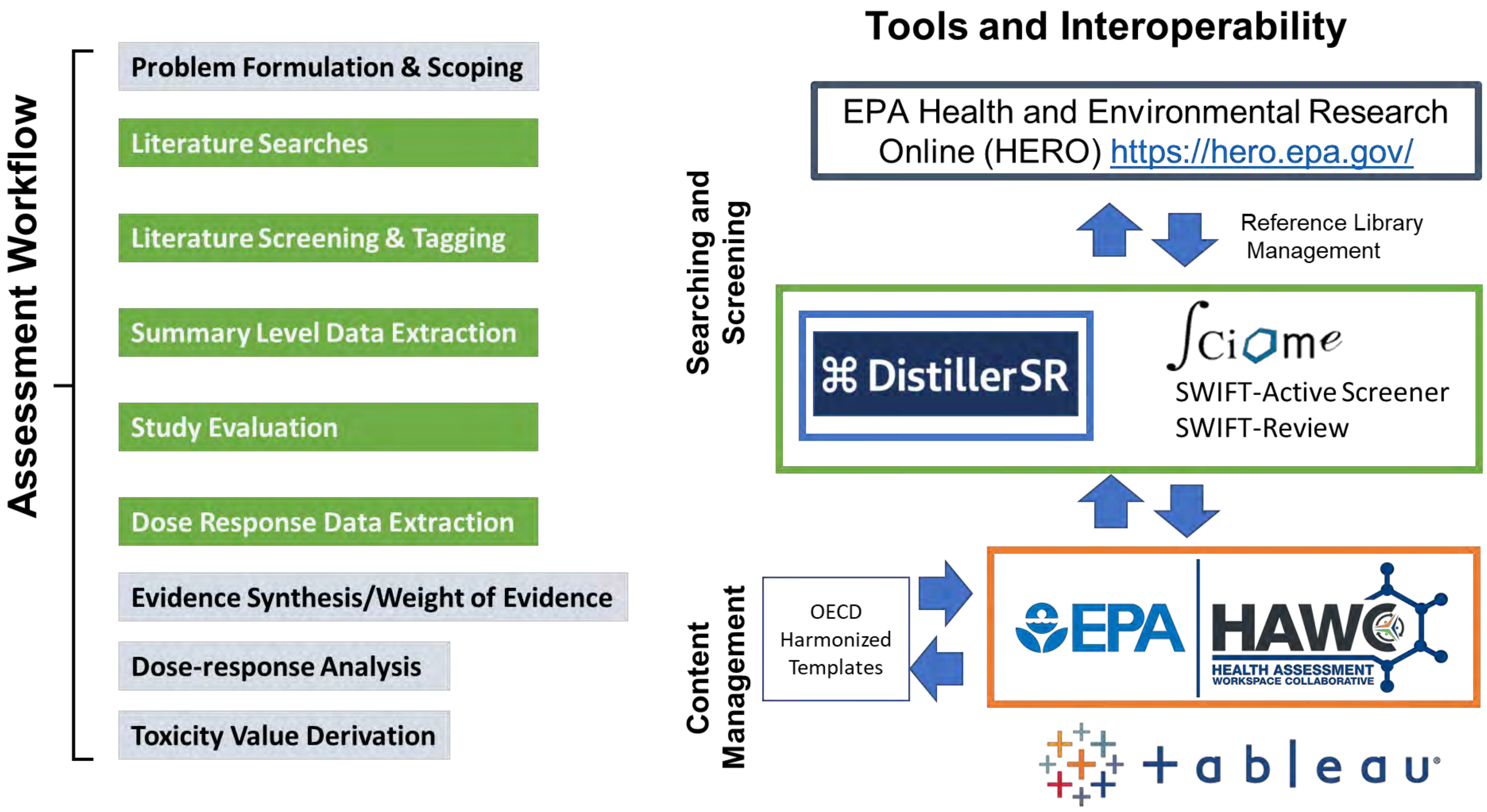
What We Do
Management
Branches/Locations

CPAD scientists develop a range of fit-for-purpose human health risk assessment products based on the evaluation, synthesis, and analysis of the most up-to-date scientific information. Products include the Integrated Risk Information System (IRIS) and Provisionally Peer Reviewed Toxicity Values (PPRTV) assessments. These products are developed through interactions with EPA's program and regional offices, other agencies, the scientific community, industry, policy-makers, and the public. Once finalized, they serve as a major scientific component supporting EPA's regulations, advisories, policies, enforcement, and remedial action decisions. CPAD also conducts cutting-edge research to develop innovative human health risk assessment methods (e.g., systematic review) that facilitate careful evaluation of scientific evidence, as well as tools and models (e.g., benchmark dose modeling software).

EPA's Chemical Pollutant Assessment Division (CPAD)

We are data consumers.

How do we do this?



We use a workflow that includes:

- interoperable tools
- web accessible applications,
- standardized data reporting frameworks
- machine readable data

to find and use the data that generated by data producers.

First we have to find your research and we can only search things that are findable

Data consumers have to know

- what we are looking for and where to find it
- how to search an indexing service
- what services and labels data producers are using

Data producers have to know

- what information data consumers are looking for
- how to label information so that it can be identified

Journal

> Arch Toxicol. 2016 Jan;90(1):217-27. doi: 10.1007/s00204-014-1391-7. Epub 2014 Nov 5.

Title

Interaction of perfluoroalkyl acids with human liver fatty acid-binding protein

Author

Nan Sheng [1], Juan Li [2], Hui Liu [1], Aiqian Zhang [3], Jiayin Dai [4]

Affiliations + expand

PMID: 25370009 DOI: 10.1007/s00204-014-1391-7

Abstract

Abstract

Perfluoroalkyl acids (PFAAs) are highly persistent and bioaccumulative, resulting in their broad distribution in humans and the environment. The liver is an important target for PFAAs, but the mechanisms behind PFAAs interaction with hepatocyte proteins remain poorly understood. We characterized the binding of PFAAs to human liver fatty acid-binding protein (hL-FABP) and identified critical structural features in their interaction. The binding interaction of PFAAs with hL-FABP was determined by fluorescence displacement and isothermal titration calorimetry (ITC) assay. Molecular simulation was conducted to define interactions at the binding sites. ITC measurement revealed that PFOA/PFNA displayed a moderate affinity for hL-FABP at a 1:1 molar ratio, a weak binding affinity for PFHxS and no binding for PFHxA. Moreover, the interaction was mainly mediated by electrostatic attraction and hydrogen bonding. Substitution of Asn111 with Asp caused loss of binding affinity to PFAA, indicating its crucial role for the initial PFAA binding to the outer binding site. Substitution of Arg122 with Gly caused only one molecule of PFAA to bind to hL-FABP. Molecular simulation showed that substitution of Arg122 increased the volume of the outer binding pocket, making it impossible to form intensive hydrophobic stacking and hydrogen bonds with PFOA, and highlighting its crucial role in the binding process. The binding affinity of PFAAs increased significantly with their carbon number. Arg122 and Asn111 played a pivotal role in these interactions. Our findings may help understand the distribution pattern, bioaccumulation, elimination, and toxicity of PFAAs in humans.

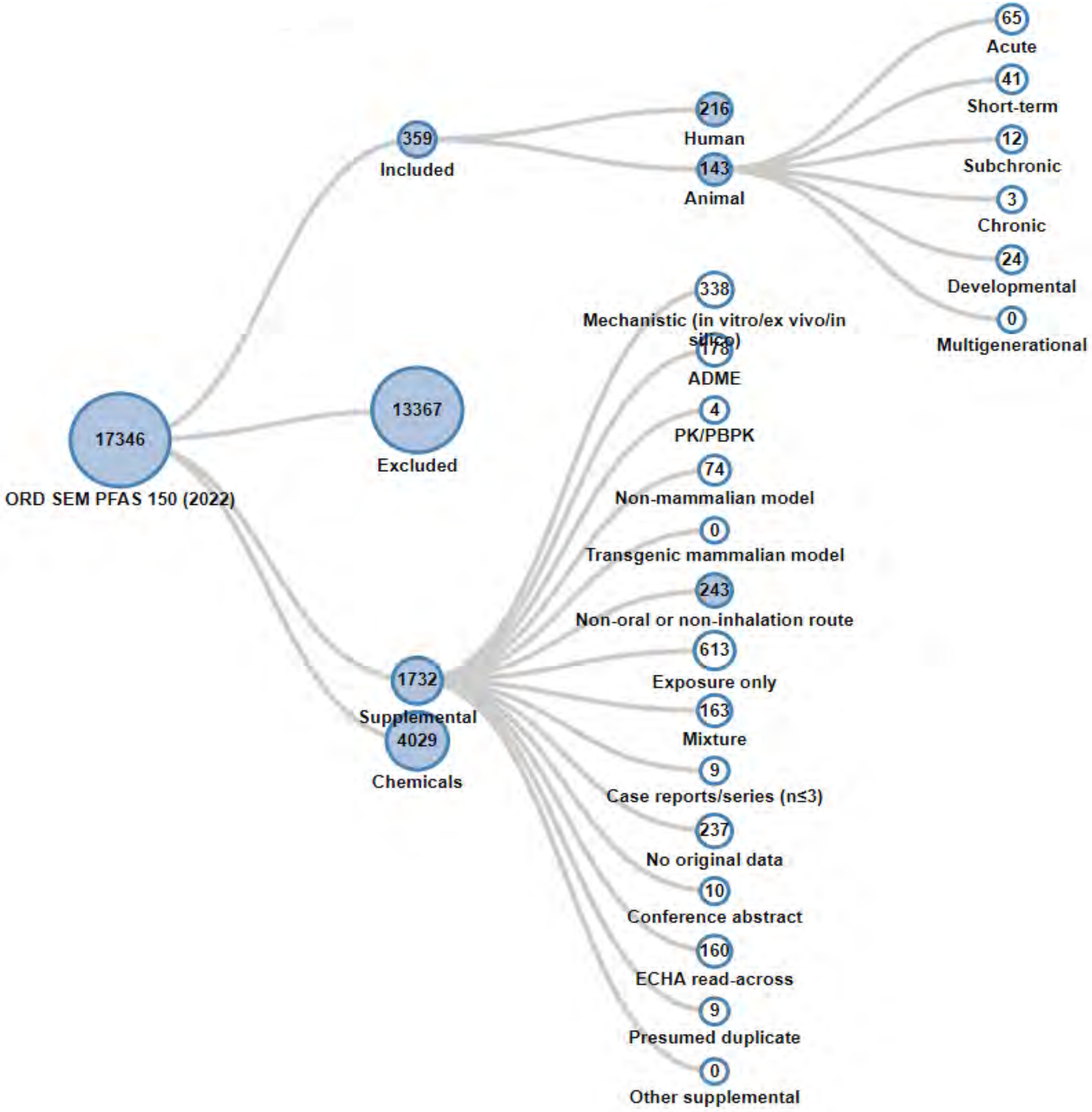
Key words

Keywords: Human liver fatty acid-binding protein; Interaction; Isothermal titration calorimetry; Molecular simulation; Perfluorinated compounds.

We organize your information using tags

- **What are tags and why do we use them?**

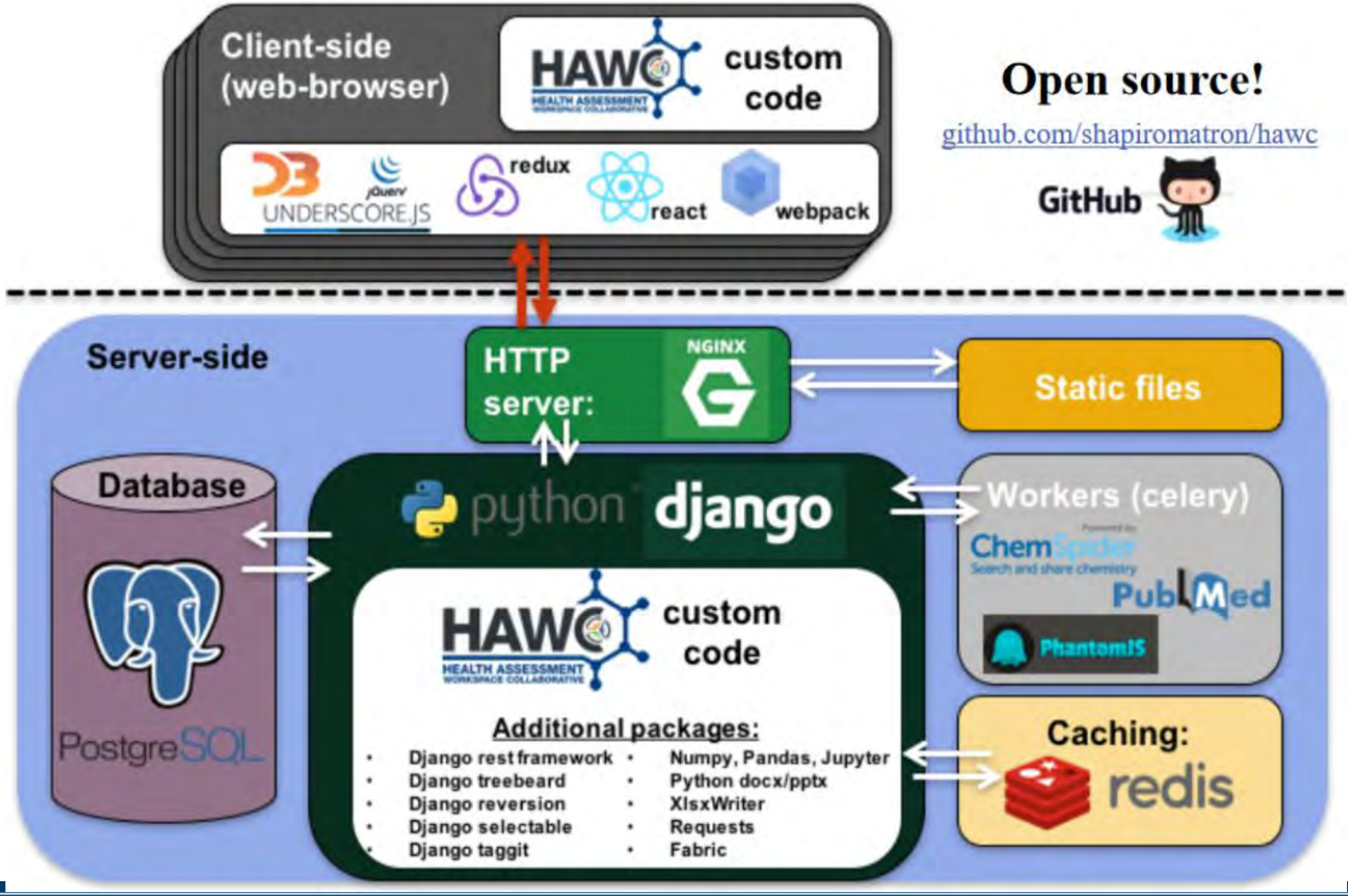
- **Tags** or **labels** are used to **filter** or **flag records** during the review process.
- They are ***kind of like a sticky note*** and help us to ***organize information*** into different bins that can be rapidly recalled.
- Tags are ***standardized*** to picklists and ***controlled vocabularies***.
- Tags are applied manually or automatically by computers based upon classifiers (e.g. search strategies that are specified by key words). If you skimp on key word descriptions, we will not find or might filter out your data!



Quick note: What is HAWC?

The IRIS Program commonly uses the EPA's version of Health Assessment Workspace Collaborative (HAWC) (https://hawcprd.epa.gov/portal/) for _structured data extraction_ and _digitization_ of epidemiological and animal toxicological studies.

- A Python application
  - A web-application data entry in/excel out
  - APIs for automated data in/out
  - Data science stack available for compute
- A relational database
  - Mostly relational data
  - Also binary/nosql data
- An interactive frontend
  - Dynamic visualizations + modern web
- An open-source application
  - We can accept pull-requests from anyone
  - Code freely available on github



Structured Data Extraction Frameworks

Templates for consistent summary of information included in the HAWC database.

Promotes consistency, transparency, and efficiency in that a task is done once and uniformly

Domain/Field Na-me	Picklist or free text	Help text
Experiment	Domain heading	Domain heading
experiment type	Picklist Short-term (1-30 days) Subchronic (30-90 days) Chronic (>90 days) Mechanistic Reproductive Developmental Acute (<24 hr) Other	Select the study type. If multiple study types are covered by the same data entry form, the specific study type should be selected. If none matches, select 'other', highlight and extract the text, and add a comment into the
Test article	Domain heading	Domain heading
test article name	Free text	Select the chemical name (test material) as reported by authors and the appropriate link to chemical information (if available) from the CompTox Chemicals Dashboard. Link to https://comptox.epa.gov/dashboard/
CAS number	Free text	Select the appropriate CAS number.
purity	Free text	Description of the chemical purity (%) including information on contaminants, isomers, etc.
test article source	Free text	Description of the chemical source (i.e. manufacturer or supplier) and lot/batch number of test material
vehicle	Free text	Description of the vehicle (use name as described in methods but also add the common name if the vehicle was described in a non-standard way).

- structured fields for consistent data entry
- Picklists for consistent data entry
- Help text to explain the content that should be entered into a field

https://hawc.epa.gov/study/100517534/

How does this work?

Dosing regime

Route of exposure	Oral gavage
Exposure duration	90 d
Duration observation	91 days
Number of dose-g	
Positive control	
Negative control	
Doses	
Description	

Test article	
test article name	
CAS number	Free text
purity	Free text
test article source	Free text
vehicle	Free text

Female Crl:CD(SD) Rats

Name	Female Crl:CD(SD) Rats
Species	
Strain	
Sex	
Source	
Lifestage exposed	
Lifestage assesse	
Animal Husbandr	
Diet	

Available endpoints

↑ Endpoint	Organ	Obs. Time	Dose [mg/kg-day]			
			0	10	50	200
N	-	-	10	10	10	10
Alanine Aminotransferase (ALT)	Multi-Organ	Day 90	35 ± 6.5	56 ± 41.3 (60%)	45 ± 19.2 (29%)	36 ± 10.2 (3%)[a]
Albumin (A)	Multi-Organ	Day 90	4.7 ± 0.32	5 ± 0.36 (6%)	5 ± 0.62 (6%)	4.7 ± 0.39 (0%)[a]
Albumin/Globulin (A/G) Ratio	Multi-Organ	Day 90	1.79 ± 0.231	1.89 ± 0.189 (6%)	1.88 ± 0.22 (5%)	2.04 ± 0.237 (14%)[a]
Alkaline Phosphatase (ALP)	Multi-Organ	Day 90	55 ± 13	52 ± 12.7 (-5%)	43 ± 10.9 (-22%)	57 ± 11.6 (4%)[a]
Aspartate Aminotransferase (AST)	Multi-Organ	Day 90	78 ± 16.2	108 ± 54.3 (38%)	92 ± 22.2 (18%)	82 ± 15.3 (5%)[a]
Body Weight, Absolute	Whole Body	Day 90	264 ± 27.5	261 ± 30.2 (-1%)	252 ± 22 (-5%)	257 ± 22.6 (-3%)[a]
Brain Weight, Absolute	Brain	Day 90	1.91 ± 0.095	1.93 ± 0.072 (1%)	1.89 ± 0.068 (-1%)	1.9 ± 0.107 (-1%)[a]
Brain Weight, Relative	Brain	Day 90	0.73 ± 0.057	0.747 ± 0.095 (2%)	0.755 ± 0.055 (3%)	0.74 ± 0.053 (1%)[a]
Calcium (CA)	Multi-Organ	Day 90	11 ± 0.44	11.3 ± 0.53 (3%)	11.2 ± 0.43 (2%)	11 ± 0.51 (0%)[a]
Cholesterol (CHOL), Total	Multi-Organ	Day 90	74 ± 20.1	81 ± 23.5 (9%)	83 ± 23.7 (12%)	71 ± 9.5 (-4%)[a]

How can the standards contribute to findable, accessible, interoperable, and reusable data?

- Findable: standardized language provides harmonization in the description of environmental health science findings.
- Accessible: The EHV and data normalized to EHV are made available in EPA HAWC.
- Interoperable: Data curation using standardized terminology makes it easier to build connections, map the normalized terms to other databases.
- Reusable: Data are extracted using structured formats and stored as digital assets.

EPA | HAWC HEALTH ASSESSMENT WORKSPACE COLLABORATIVE

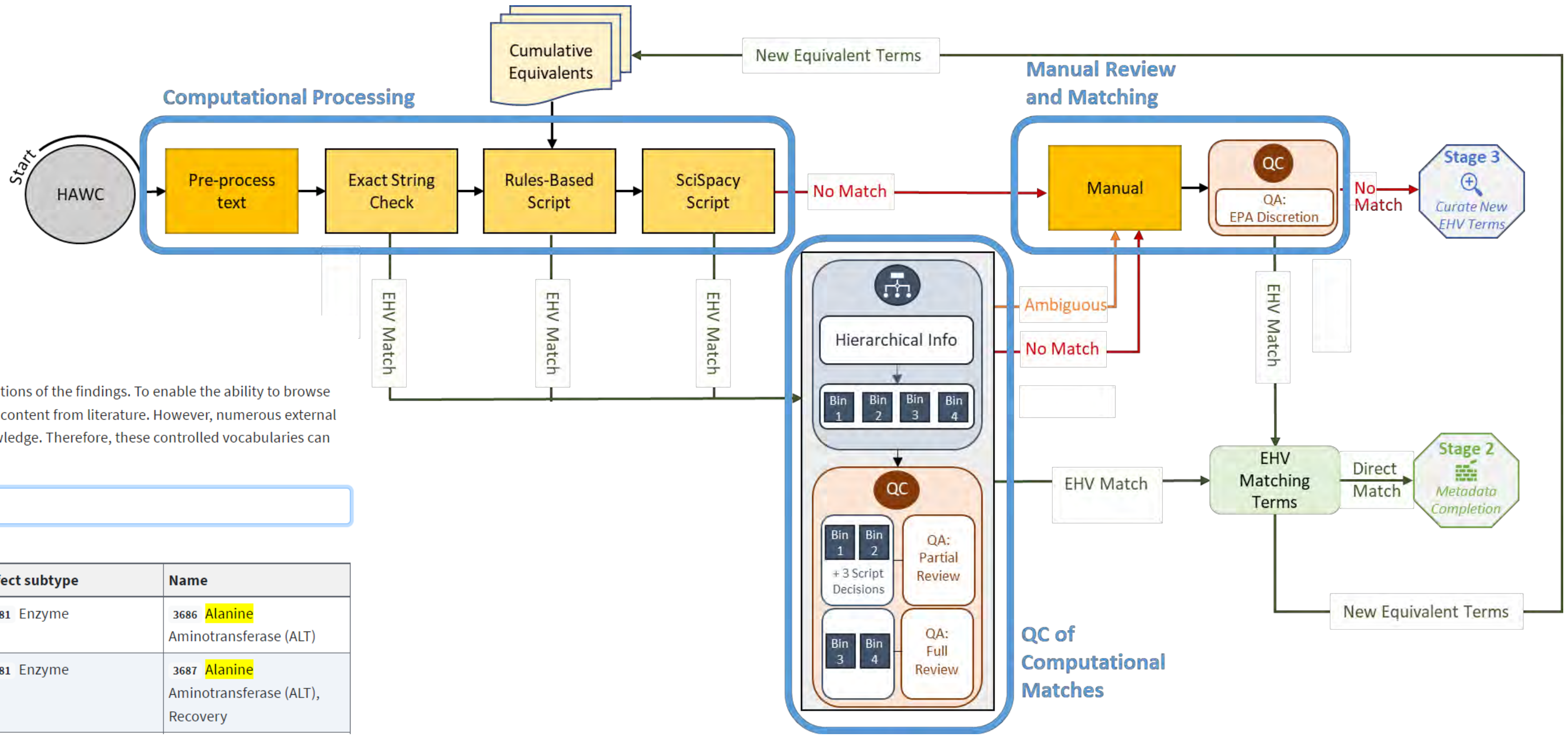
https://hawc.epa.gov/assessment/public/

Data Standardization

Why do we standardize data?

Assessment teams must standardize the language used to report data so that it can be aggregated. This is done digitally with picklists and controlled vocabularies. Standardization such as the Environmental Health Vocabulary (EHV). Standardization makes information more findable and interoperable within and across assessments.

CPAD's workflow for curating new EHV terms in HAWC



Environmental Health Vocabulary (EHV)

Experimental data extracted into HAWC is designed to enable filtering, sorting, and visualizations of the findings. To enable the ability to browse and filter at different levels, a curated controlled vocabulary of terms can be used to extract content from literature. However, numerous external ontologies and thesauri exist in the biological domain that can map health-effects and knowledge. Therefore, these controlled vocabularies can also be mapped to external entities.

alanine

7 items found.

System	Organ	Effect	Effect subtype	Name
4430 Metabolic	4471 Multi-Organ	3843 Clinical Chemistry	3981 Enzyme	3686 Alanine Aminotransferase (ALT)
4430 Metabolic	4471 Multi-Organ	3843 Clinical Chemistry	3981 Enzyme	3687 Alanine Aminotransferase (ALT), Recovery

Examples from the EHV

Environmental Health Vocabulary (EHV)

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- Environmental Health Vocabulary (EHV) https://hawc.epa.gov/vocab/ehv/
- Housed in EPA's Health Assessment Workplace Collaborative (HAWC) https://hawc.epa.gov/assessment/public/

Application of the EHV in an IRIS Assessment

Home / PFHxA (2018) / Chengelis, 2009, 2850404 / 90-Day Oral / Female Crl:CD(SD) Rats / Alanine Aminotransferase (ALT) / Update

Update Alanine Aminotransferase (ALT)

Update an existing endpoint. The Environmental Health Vocabulary (EHV) is enabled for this assessment. Browse to view controlled terms, and whenever possible please use these terms.

Endpoint/Adverse outcome*

3686 **Load ID**

Alanine Aminotransferase (ALT)

Selected term: 3686 | Alanine Aminotransferase (ALT) ×

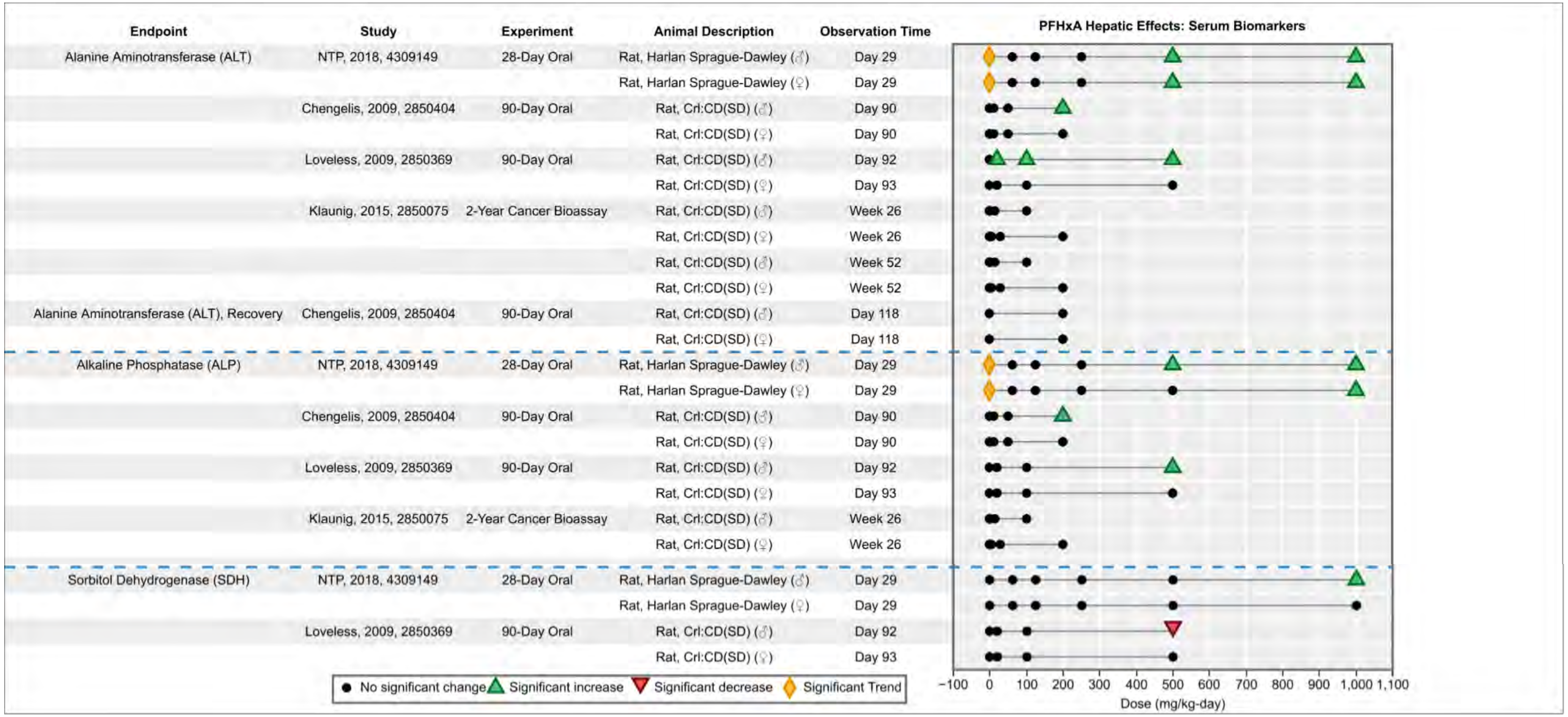
☑ **Use controlled vocabulary**

Short-text used to describe the data in this form. Please use a controlled vocabulary term if possible and if enabled for your assessment. A separate field, "Endpoint Name in Study", captures the name of endpoint as reported. If no preferred term matches the data extracted, type in the desired description. Do not add units — units are summarized in a separate extraction field. If the endpoint is a repeated measure, indicate the time in parentheses, e.g., running wheel activity (6 wk), using the abbreviated format: seconds = sec, minutes = min, hours = h, days = d, weeks = wk, months = mon, years = y.

System	Organ/Tissue/Region	Effect	Effect subtype
Metabolic	Multi-Organ	Clinical Chemistry	Enzyme
Selected term: 4430 | Metabolic ×	**Selected term:** 4471 | Multi-Organ ×	**Selected term:** 3843 | Clinical Chemistry ×	**Selected term:** 3981 | Enzyme ×
☑ **Use controlled vocabulary**	☑ **Use controlled vocabulary**	☑ **Use controlled vocabulary**	☑ **Use controlled vocabulary**

EHV to Facilitate Evidence Assimilation

Ability to aggregate information from various studies reporting the same endpoints



https://hawc.epa.gov/summary/data-pivot/assessment/100500070/pfhxa-animal-toxicology-hepatc-effects-serum-bioma/

EHV Facilitates Data Interaction and Use

- Portal
- › PFHxA (2018)
- » Literature review
- » Management dashboard
- » Study list
- » Study evaluation
- » Endpoint list
- » Summary tables
- » Visualizations
- » Executive summary
- » Downloads
- About HAWC
- HAWC Resources

study design vs. system

System	1-generation reproductive	Acute (<24 hr)	Cancer	Developmental	Reproductive	Short-term (1-30 days)	Subchronic (30-90 days)	Grand Total
Cancer								
Cardiovascular								
Dermal								
Developmental								
Endocrine								
Female Reproductive								
Gastrointestinal								
Hematologic								
Hepatic	12		13			17	28	70
Immune								
Male Reproductive								
Metabolic								
Multi-System								
Muscoskeletal								
Musculoskeletal								
Nervous								
Ocular								
Reproductive								
Respiratory								
Systemic								
Urinary								
Whole Body								
Grand Total	12		13			17	28	70

Study design

Experiment Type

- ☑ 12 1-generation reproductive
- ☑ 13 Cancer
- ☑ 17 Short-term (1-30 days)
- ☑ 28 Subchronic (30-90 days)

System

- ☐ 0 Female Reproductive
- ☐ 0 Gastrointestinal
- ☐ 0 Hematologic
- ☑ 70 Hepatic
- ☐ 0 Immune

Endpoint Name

Concentration

- ☑ 12 Liver Weight, Absolute
- ☑ 2 Liver Weight, Absolute, Recovery
- ☑ 12 Liver Weight, Relative

EHV Facilitates Data Interaction and Use

	1-generation reproductive	Acute (<24 hr)	Cancer	Developmental	Reproductive	Short-term (1-30 days)	Subchronic (30-90 days)	**Grand Total**
Respiratory			4			25	24	**53**
Systemic						5		**5**
Urinary			18			13	28	**59**
Whole Body	44	2	7	2	16	12	6	**89**
Grand Total	**150**	**2**	**196**	**5**	**34**	**323**	**352**	**1062**

Study design

Endpoint Name

- 2 Albumin (A), Recovery
- 8 Albumin/Globulin (A/G) Ratio
- 2 Albumin/Globulin (A/G) Ratio, Recovery
- 10 Alkaline Phosphatase (ALP)
- 2 Alkaline Phosphatase (ALP), Recovery
- 2 Alveolar Macrophages

Study Citation	Experiment Name	Animal Group Name	System	Organ	Effect	Endpoint Name	Doses	Dose Units Name	NOEL	LOEL	BMD	BMDL
Klaunig, 2015, 2850075	2-Year Cancer Bioassay	Male Crl:CD(SD) Rats	Whole Body	Whole Body	Clinical Observation	Survival	0, 2.5, 15, 100	mg/kg-day				
Klaunig, 2015, 2850075	2-Year Cancer Bioassay	Male Crl:CD(SD) Rats	Whole Body	Whole Body	Clinical Observation	Body Weight, Absolute	0, 2.5, 15, 100	mg/kg-day				
Klaunig, 2015, 2850075	2-Year Cancer Bioassay	Male Crl:CD(SD) Rats	Hematologic	Multi-Organ	Hematology	White Blood Cell (WBC)	0, 2.5, 15, 100	mg/kg-day	100			
Klaunig, 2015, 2850075	2-Year Cancer Bioassay	Male Crl:CD(SD) Rats	Hematologic	Multi-Organ	Hematology	White Blood Cell (WBC)	0, 2.5, 15, 100	mg/kg-day	100			

Application of EHV in a Systematic Evidence Map

PFAS-150 Evidence Map Visualizations by literature inventory

ReadMe | Animal Studies | Human Studies

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

EPA

Heat Map

References

	acute							short-term			subchronic		chronic		developmental, F1				Grand Total
	mouse	rat	guinea pig	hamster	rabbit	dog	not reported	mouse	rat	not reported	mouse	rat	mouse	rat	mouse	rat	rabbit	not reported	
Cancer														2					2
Cardiovascular		3				4		1	10		1	6		2		5			30
Dermal		1							2			2				2			7
Developmental															1	21	3	1	24
Reproductive		4						1	12		1	9		2	1	20	3		49
Endocrine									9			7		2		6			24
Exocrine		1																	1
Gastrointestinal		7							6		1	5		1		4			24
Hematologic									11		1	10		2	1	7			31
Hepatic	1	8	1			1		9	17		2	9		2	1	10	1		59
Immune		4						3	10			9		2	1	5			34

https://public.tableau.com/app/profile/literature.inventory/viz/PFAS-150EvidenceMapVisualizations/HumanStudies

Systematic Evidence Map for 150+ Per- and Polyfluoroalkyl Substances (PFAS)

Take Homes

- Be nice to future you!
  - Make your research findable
    - If key information are not in the title, abstract, key words, author lists we probably are not going to find it.
  - Use standards (if they exist) before creating new ones
  - Use a structured process for documenting (extracting) and reporting data
  - Have fun and make data sharing common place and unexceptional!

Useful Resources

- https://force11.org/info/the-fair-data-principles/
- U.S. EPA. ORD Staff Handbook for Developing IRIS Assessments (2022). U.S. EPA Office of Research and Development, Washington, DC, EPA/600/R-22/268, 2022.
- Health Assessment Workspace Collaborative (HAWC) (epa.gov)

Thank you for listening!

- Questions?

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Kaitlyn Hair

David Mellor

Presentation 2

Presentation Order	Presentation Title	Presenter, Organization
2	*How best to combine data from multiple independent studies?*	Jeanette A Stingone, PhD, MPH, Columbia University js5406@cumc.columbia.edu

HOW BEST TO COMBINE DATA FROM MULTIPLE INDEPENDENT STUDIES?

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Conflict of Interest Disclosure Slide

I have no conflicts of interest to disclose.

Acknowledgements

EHLC Data Harmonization Use Case Members

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Oswaldo Lozoya
Andrew Rooney
Kelly Shipkowski
And others….

ICF

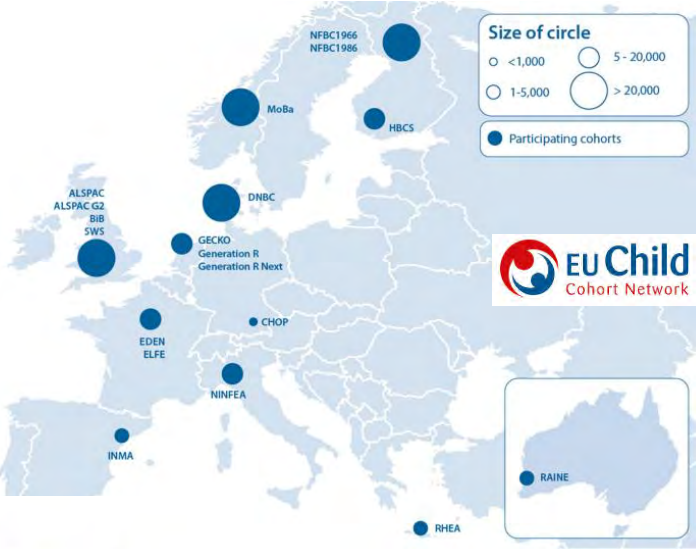
HC Bledsoe
Jennifer Freed
Pearl Kaplan
Jess Wignall

Environmental Health Language Collaborative

Harmonizing Data. Connecting Knowledge. Improving Health.

Growing Interest in Data Harmonization

ECHO
Environmental influences on Child Health Outcomes
A program supported by the NIH



Srp
Superfund
Research Program

But what does language have to do with it???

Background and Purpose of Data Harmonization Use Case within the Environmental Health Language Collaborative (EHLC)

- Increased sharing and interoperability of environmental health data has the potential to foster innovation and enhance data-driven discoveries.

- The **<u>purpose</u>** of our use case is to address the feasibility of and to identify the barriers to using harmonized language for combining data across independent research studies.

- Our **<u>goal</u>** is to develop tools and strategies to facilitate data sharing and harmonization through use of data and metadata standards and annotation of datasets.

Specifics of Our Use-Case: Harmonizing Data Across Two Epidemiologic Research Studies

Two studies from the Human Health Exposure Analysis Resource (HHEAR) Data Repository focused on measures of air pollution exposure and childhood asthma

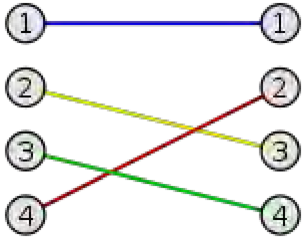
Can we harmonize data across the two studies with the goal of conducting a pooled data analysis? What resources exist? What do we still need?

Retrospective vs Prospective Harmonization

Tools Developed for Retrospective Harmonization

Human-centered protocols/ “brute force”

Software to facilitate mapping between terms



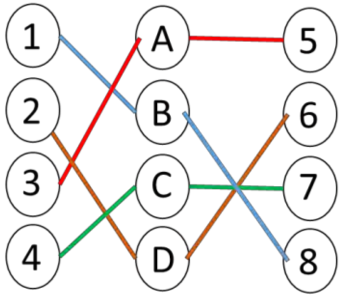
Importance of identifying Commonality across language

Prospective Data Collection/Generation: With what do we align? How do we prepare?

Importance of Community-Agreed Upon Standards

Consideration of Interoperability

Enables Greater Flexibility with Harmonization



Importance of having standard language that can be mapped to diverse sources

What resources exist to identify common language to enable prospective approaches to harmonization?


Sub-domains were grouped by theme
Grouping Domains
See the 'Domains' tab
Listing Semantic Resources
A non-exhaustive list of semantic resources were compiled for each domain
See the 'Brainstorming' tab
Resource list is updated as domains are updated
Subject matter domains were brainstormed
Establishing Domains
See the 'Domains' tab
Developing Criteria
Criteria were developed based on relevant characteristics
Domains are updated as trends in environmental health change
Validating applied criteria
Resources that did not meet criteria are removed
Used existing human research and expert input to identify trends in the field
Trends in Environmental Health
Gathering Resource Details
More information on each resource is being captured
See the 'Semantic resource details + Criteria' tab
Context for the work was established and needs were identified
Scoping the Work
Mapping
Resource details are compiled into a deliverable for use

Domains within Human Epidemiology Studies

Chemicals	Sample Matrices	Lab Instrumentation	Sources of Pollutants	Populations of Interest
Endpoints and Outcomes	Exposure Characterization	Species-Mapping	Confounders and Covariates	Statistical Analysis
	Study Design	Quality Control	Bioprocesses (Pathways)	

Identifying Resources within Domains

CHEMICALS
ChEBI: chemical entities of biological interest
Pubchem
CompTox Chemicals Dashboard
Substance Registry System
ChemSpider

SOURCES OF POLLUTANTS
ENVO: The Environment Ontology
EPA/TSCA has a fair bit here. Follow-up with exposure considerations
ECTO: Environmental Conditions, Treatments and Exposures Ontology

HUMAN ENDPOINTS/OUTCOMES
DOID: Human Disease Ontology
HPO: Human Phenotype Ontology
CMO: Clinical Measurement Ontology
COGAT: Cognitive Atlas Ontology
OECD Harmonized Templates/IUCLID
UMLS
Gap: Positive outcomes, wellness, etc.
Sequence Ontology (SO)
PROMIS®: Patient-Reported Outcomes Measurement Information Systems
PhenX
CompTox Chemicals Dashboard

Back to Use-Case:
Can we harmonize two studies on similar research question together?

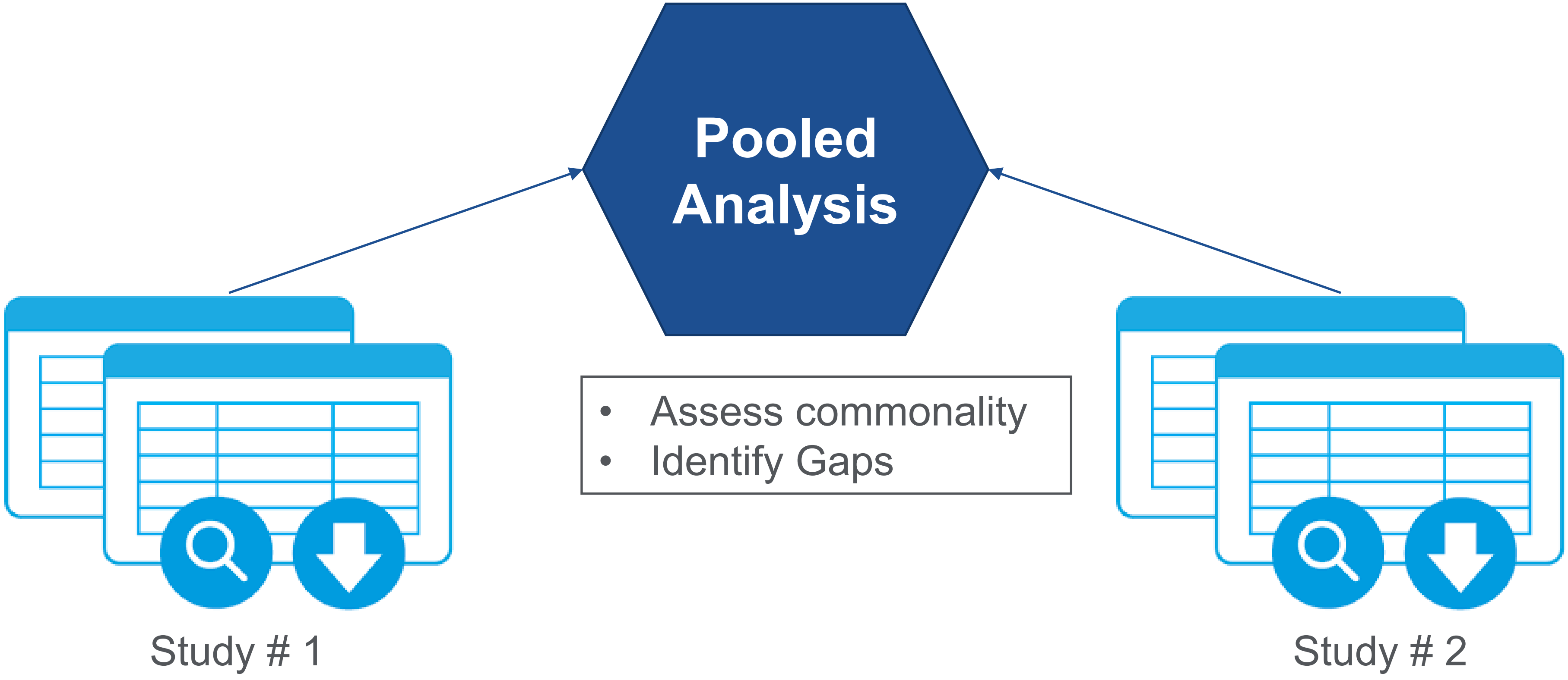


ILLUSTRATION OF Harmonization EXERCISE

DataSet 1

Study 2016_1450
demo_hisp_latino
demo_racialafam
demo_racialwhite
demo_racialasian
demo_racialaioran
demo_racialhawother
demo_racialno
demo_racialno
demo_income_code
actest_asthma_affect_visit1
controller_treatment_b_visit1
controller_treatment_b_visit1
daps_spiro_age_visit1
daps_spiro_gender_visit1

DataSet 2

Study 2016_1407	
ethnicity_form03	
race_form03	black
race_form03	white
race_form03	asian
race_form03	am_indian
race_form03	hawaii
race_form03	unknown
race_form03	refused
household_income	
stop_play_symp_14days	
prescription_control	
prescription_control_now	
age	
gender_form03	
symptoms_14days	
maxsx	
symptoms_14days	
maxsx	
wake_up_14days	
wake_up_14days	
fef_25_75_per_predict	
fev1_per_predict	
fvc_per_predict	
pft_data_accepted	
fvc_best	
fev1_best	
composite_score_form10	
bmi_pct	
bmi	
height_average	
weight_average	
date_form03	
fev1_best/fvc_best	

Tool Main Mapping Page

Mapping Criteria

- Substring match
- Data match
- Heuristic match
- Language model match
- Ontology match

Mapping Options

DAPS_SPIRO_AGE_VISIT1 – AGE AGREEMENT
Variable name substring match score: 100%/14%
Language model similarity: 64%
Heuristic match: age heuristic, time heuristic
Data type match: numeric/numeric
Data distribution match: 95%
Ontology match: Age category

DAPS_SPIRO_AGE_VISIT1 – SYMPTOMS_14days AGREEMENT
Variable name substring match score: 0%/0%
Language model similarity: 31%
Heuristic match: time heuristic
Data type match: numeric/numeric
Data distribution match: 27%
Ontology match: Time category

DAPS_SPIRO_AGE_VISIT1 – HEIGHT_AVERAGE AGREEMENT
Variable name substring match score: 9%/9%
Language model similarity: 13%
Heuristic match: no match
Data type match: numeric/numeric
Data distribution match: 5%
Ontology match: No common category

Criteria Explanation

- Substring Match: score based on the syntactic similarity.
- Heuristic Match: various heuristic matching criteria, such as having dates in the variable values or preset keyword lists (e.g., BMI).
- Ontology Match: if the variables have been mapped to an ontology, number of steps to a common ancestor. May have to incorporate multiple ontologies.
- Data match: whether the data types (ordinal, numeric) are the same, and if yes, whether the distribution of values is comparable.
- Language model match: similarity of embedding scores for the variables and their descriptions.

Slide Courtesy of C. Schmitt

Lessons Learned from Harmonization Exercise around Importance of Common Language

- Language used for variable names and data dictionaries often requires human assessment for mapping

- Combination of lack of standard language AND lack of metadata

- Reminder: Our **goal** is to develop tools and strategies to facilitate data sharing and harmonization through use of data and metadata standards and annotation of datasets.

Recommendations for the Broader Scientific Community

Tool Development

- Reliance on human annotation is not practical for large-scale, timely and consistent harmonization

Community Data Standards

- Gap: Need for common language around context and perspective
  - Models and paradigms used for research; Biases; Evidence-Forms, quality and weight; Evaluation of Evidence

Promotion of Data Harmonization Efforts as part of Standard Scientific Pipelines

- Thinking about FAIR at study design and data collection phases of research

Presentation 3

Presentation Order	Presentation Title	Presenter, Organization
3	*Digitizing Relationships between Exposures, Biomarkers, and Clinical Outcomes (In the era of AI and exposomics)*	Chirag Patel, PhD, Harvard Medical School chirag_patel@hms.harvard.edu

Digitizing Relationships between Exposures, Biomarkers, and Clinical Outcomes (In the era of ***AI*** and ***exposomics***)

Chirag Patel

Society of Toxicology 2024, Salt Lake City

3/12/2024

HARVARD MEDICAL SCHOOL

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Disclosures

- No financial conflicts
- Research funding from National Institutes of Health
  - National Institute on Aging (NIA)
  - National Institute of Environmental Health Sciences (NIEHS)

What are the ***biological processes and biomarkers*** associated with ***exposure and how do they relate to the potential for an adverse outcome***?

Purpose

The purpose of this use case is to explore how harmonized language can help answer the question "What are the biological processes and biomarkers associated with exposure and how do they relate to the potential for an adverse outcome associated with a given exposure?" We are doing this by building upon the other use cases by utilizing their interim results and providing feedback on the general utility of their outputs. Our goal is to connect measured biomarkers to exposure-response relationships by:

- Extending the semantic description of the exposure event to explicitly include measurements as previously done for adverse outcome pathways
- Semantically linking the exposure event to adverse outcomes by connecting the perturbed biological processes with toxicity mechanisms
- Supporting the integration of existing data and resources (e.g., 'omics measurements, adverse outcome pathways)

https://www.niehs.nih.gov/research/programs/ehlc/use-cases/bio

Participants of the working group

Albert Donnay (JHU/Donnay Detoxicology LLC)
Andrew Rooney (NIEHS)
Anna Maria Masci (NIEHS)
Annie Jarabek (US EPA)
Bren Ames (Aye Open Outcomes)
Carmen Marsit (Emory University)
Carol Hamilton (RTI International)
Charles Schmitt (NIEHS)
Chirag Patel (Harvard University)
David Hines (RTI International)
David Reif (NIEHS)
Elaine Faustman (University of Washington)
Ginger Chew (CDC)
Grace Cooney (ICF)
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Rebecca Boyles (RTI)
Rong-Lin Wang (US EPA)
Sam Hall (ICF)
Shannon Bell (RTI)
Stephanie Holmgren (NIEHS)
Steve Edwards (EPA)
Thomas Hartung (Johns Hopkins University)
Vasu Kilaru (US EPA)

EHLC biomarkers working group process

- Led by Chirag Patel, Stephen Edwards; facilitated by Charles Schmitt, Samantha Hall (ICF), Stephanie Holmgren, NIEHS
- Met virtually ~bimonthly-quarterly from 2021-23
- Used the “Integrated Science Assessment” from the EPA as a practical example to map exposures, processes, biomarkers, and disease
- ***PM2.5* and *lung related outcomes*** (asthma, COPD, decreased lung function)

What are the ***biological processes*** *and* ***biomarkers*** associated with ***exposure*** *and how do they relate to the* ***potential*** *for an* ***adverse outcome***?

probabilistic

phenomena

Process

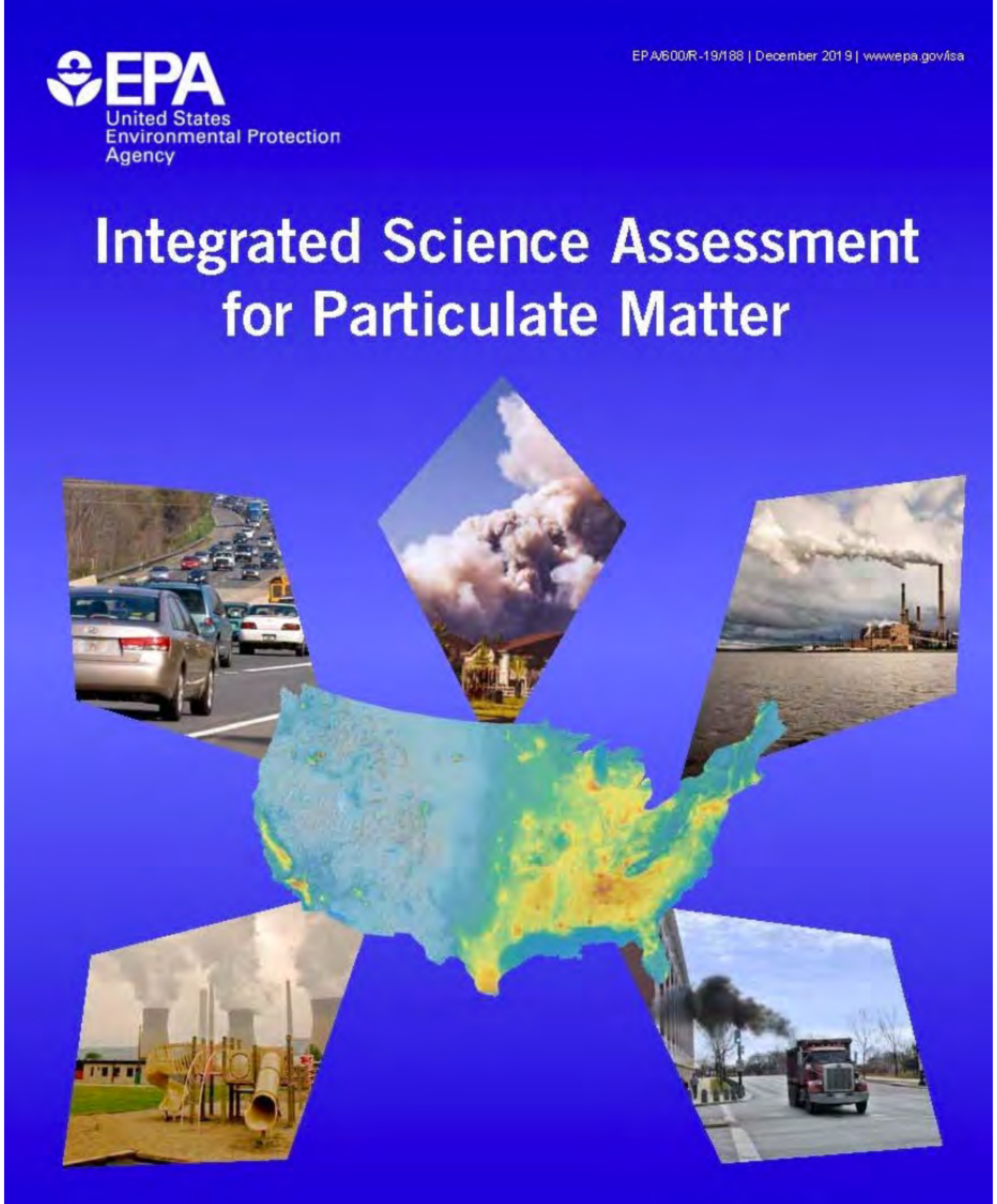
E

Exposure pathway
Source

(Measured by)
Biomarkers [proxy or direct]

D

Disease outcome


EPA/600/R-19/188 | December 2019 | www.epa.gov/isa

EPA
United States
Environmental Protection
Agency

Integrated Science Assessment
for Particulate Matter

EPA.gov
December 2019

Summary of Causality Determinations for Short- and Long-Term Particulate Matter (PM) Exposure and Respiratory Effects

This chapter characterizes the scientific evidence that supports causality determinations for short- and long-term PM exposure and respiratory effects. The types of studies evaluated within this chapter are consistent with the overall scope of the ISA as detailed in the Preface (see Section P.3.1). In assessing the overall evidence, strengths and limitations of individual studies were evaluated based on scientific considerations detailed in the Appendix. The evidence presented throughout this chapter support the following causality determinations. More details on the causal framework used to reach these conclusions are included in the Preamble to the ISA (U.S. EPA, 2015).

Size Fraction	Causality Determinations
Short-Term Exposure	
$PM_{2.5}$	Likely to be causal
$PM_{10-2.5}$	Suggestive of, but not sufficient to infer
UFP	Suggestive of, but not sufficient to infer
Long-Term Exposure	
$PM_{2.5}$	Likely to be causal
$PM_{10-2.5}$	Inadequate
UFP	Inadequate

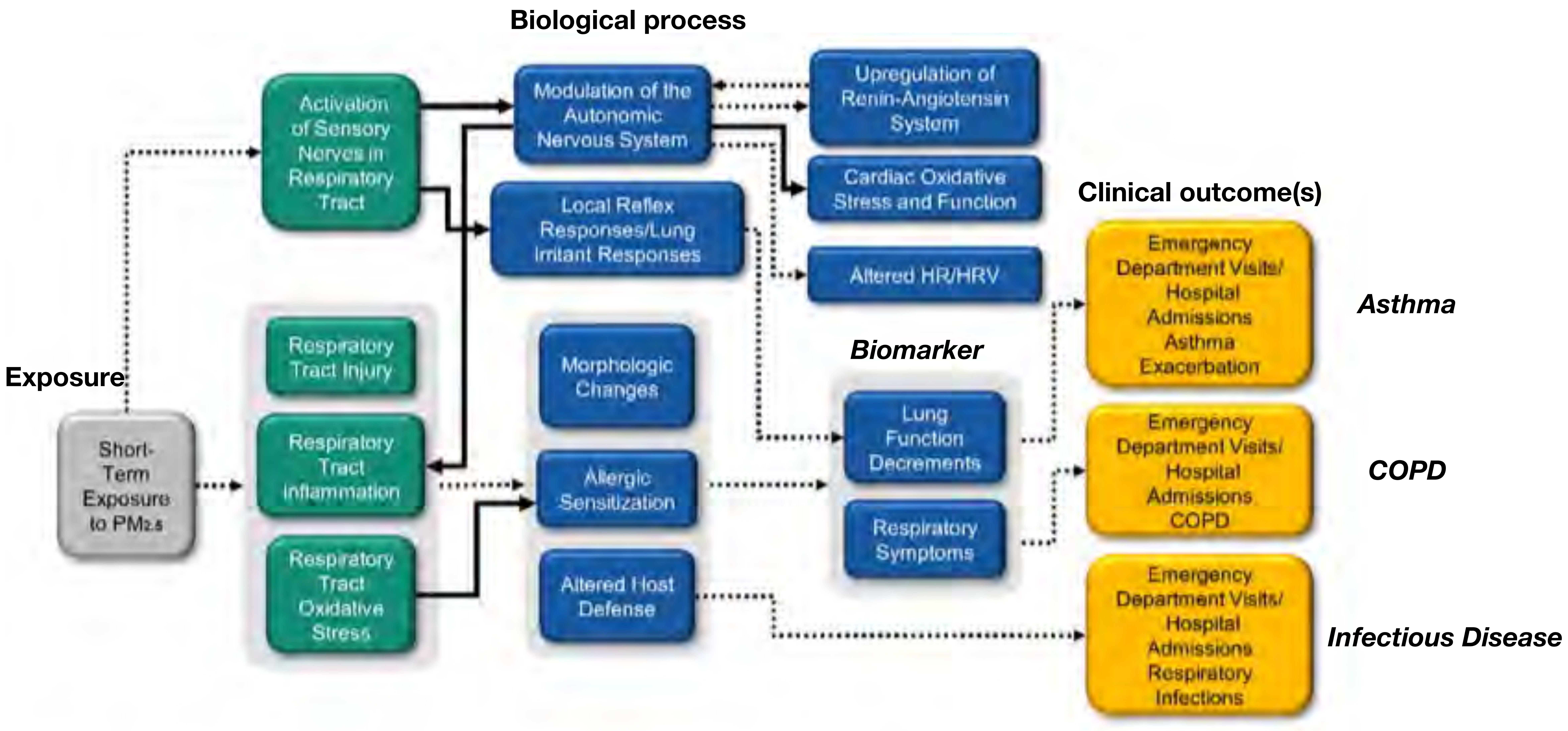
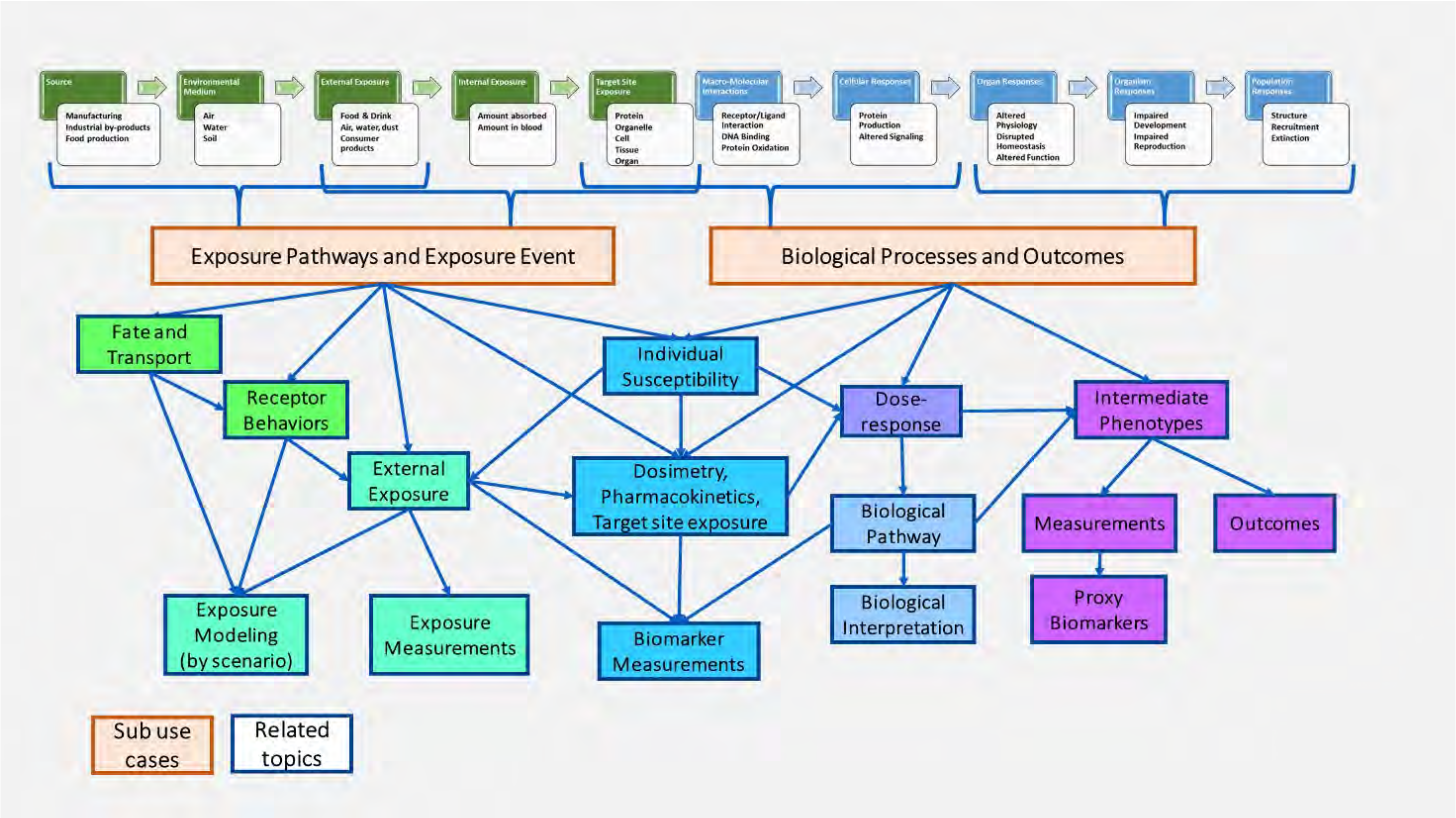


Figure 5-1. Short term effects of exposure to PM2.5 in Lung Disease

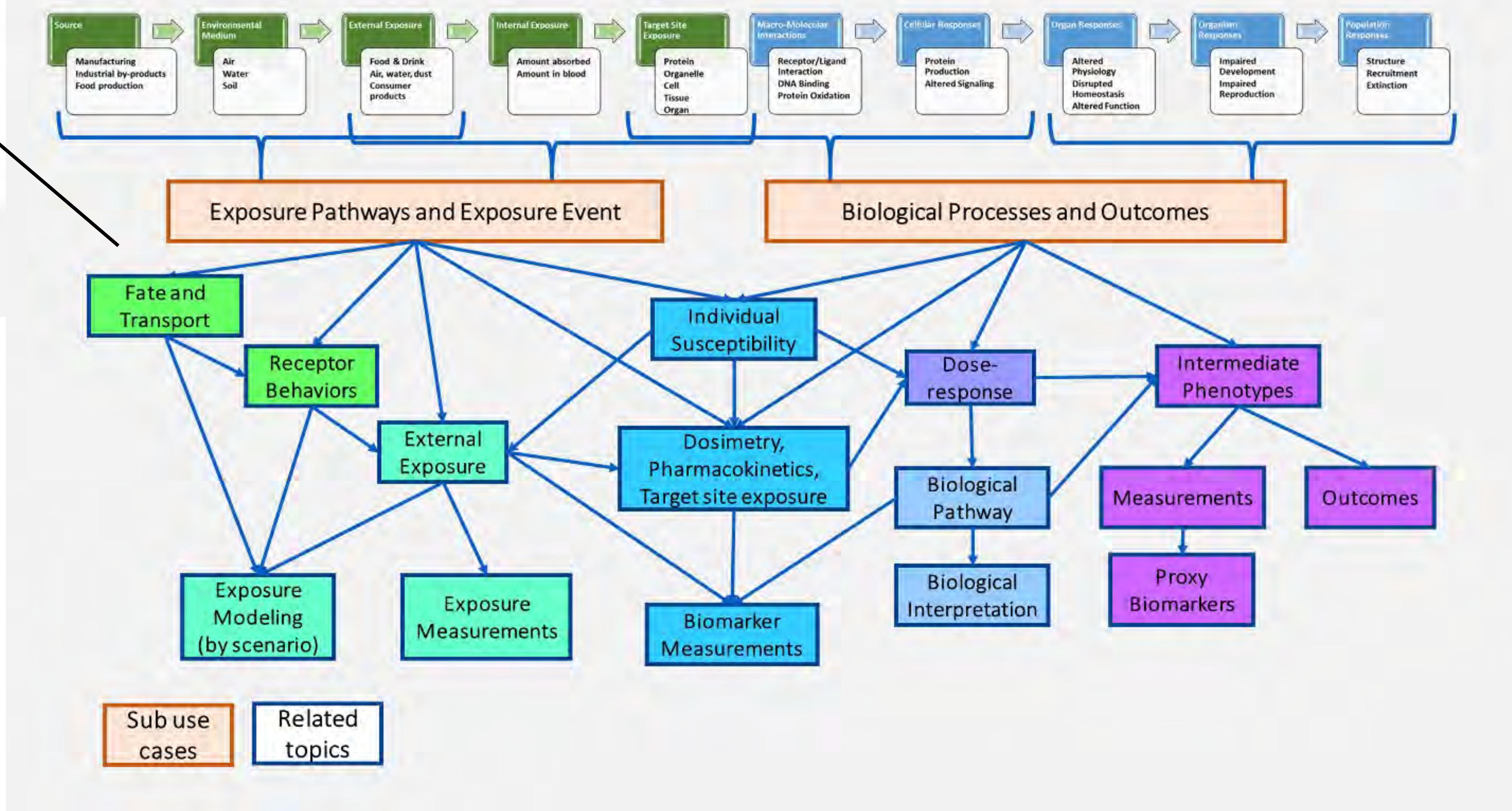


Source
Manufacturing
Industrial by-products
Food production
Environmental Medium
Air
Water
Soil
External Exposure
Food & Drink
Air, water, dust
Consumer products
Internal Exposure
Amount absorbed
Amount in blood
Target Site Exposure
Protein
Organelle
Cell
Tissue
Organ
Macro-Molecular Interactions
Receptor/Ligand Interaction
DNA Binding
Protein Oxidation
Cellular Responses
Protein Production
Altered Signaling
Organ Responses
Altered Physiology
Disrupted Homeostasis
Altered Function
Organism Responses
Impaired Development
Impaired Reproduction
Population Responses
Structure
Recruitment
Extinction
Exposure Pathways and Exposure Event
Biological Processes and Outcomes
Fate and Transport
Receptor Behaviors
External Exposure
Individual Susceptibility
Dosimetry, Pharmacokinetics, Target site exposure
Dose-response
Intermediate Phenotypes
Biological Pathway
Measurements
Outcomes
Exposure Modeling (by scenario)
Exposure Measurements
Biomarker Measurements
Biological Interpretation
Proxy Biomarkers
Sub use cases
Related topics

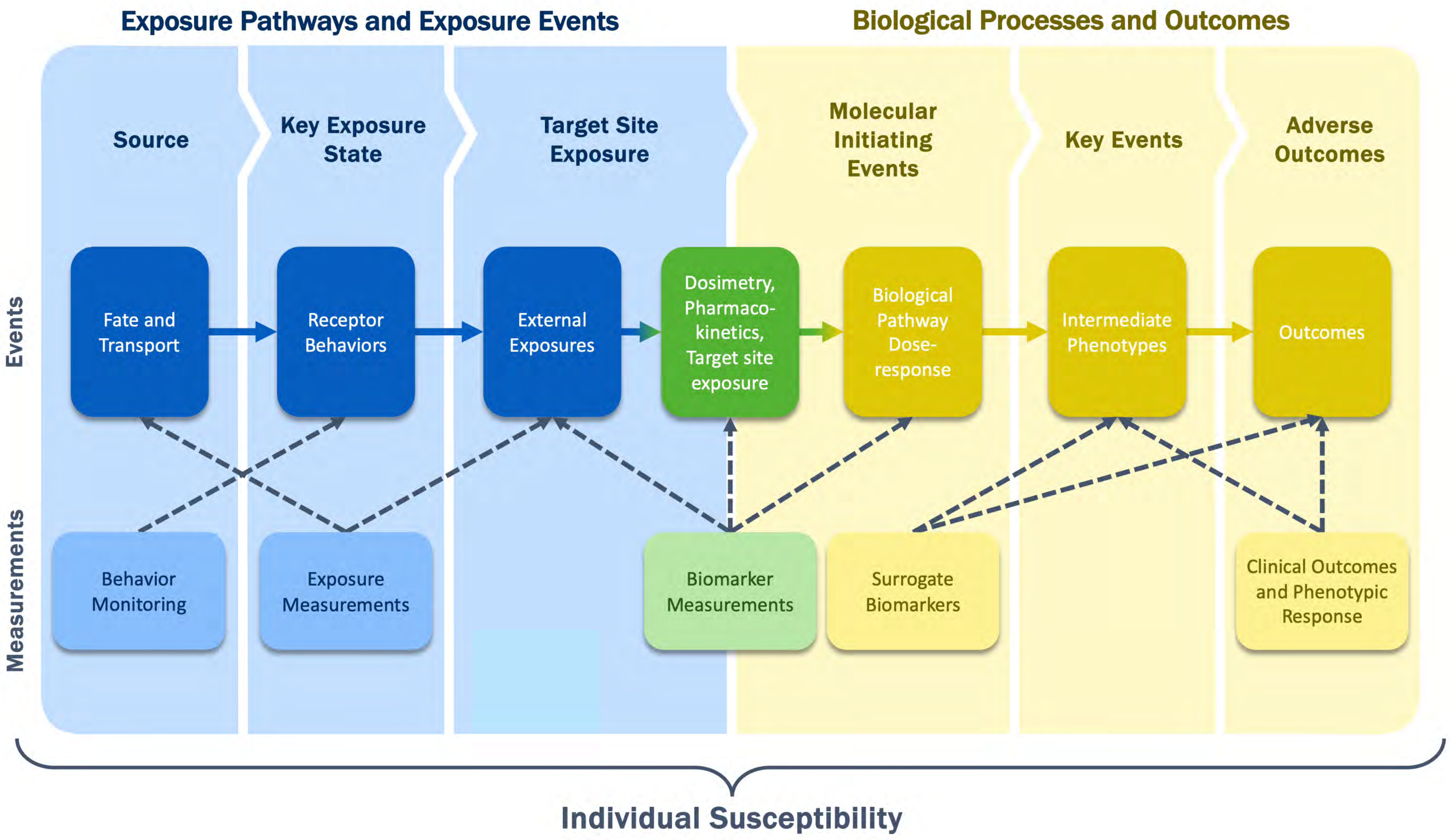
Table 5-14 Study-specific details from animal toxicological studies of short-term $PM_{2.5}$ exposure and respiratory effects in healthy animals.

Study/Study Population	Pollutant	Exposure	Endpoints
Amatullah et al. (2012) Species: mouse Sex: female Strain: BALB/c Age/weight: 6−8 weeks, 18 g	$PM_{2.5}$ CAPs Toronto Particle size: $PM_{0.15-2.5}$ Control: HEPA-filtered air	Route: nose-only inhalation Dose/concentration: $PM_{0.15-2.5}$ 254 μg/m³ Duration: 4 h Time to analysis: at end of exposure Modifier: baseline ECG	Pulmonary function BALF cells
Aztatzi-Aguilar et al. (2015) Species: rat Sex: male Strain: Sprague-Dawley	$PM_{2.5}$ CAPs Mexico City Particle size: $PM_{2.5}$ Control: filtered air	Route: inhalation Dose/concentration: $PM_{2.5}$ 178 μg/m³ Duration: acute 5 h/day, 3 days Subchronic 5 h/day, 4 days/week, 8 weeks Time to analysis: 24 h	Gene expression and protein levels—lung tissue IL-6, components of the RAS and kallikrein-kinin endocrine system-heme oxygenase-1
Budinger et al. (2011) Species: mouse Sex: male Strain: C57BL/6 wild type and IL-6 knockouts Age/weight: 8−12 weeks	$PM_{2.5}$ CAPs Chicago, IL Particle size: $PM_{2.5}$ Control: filtered ambient air	Route: whole-body inhalation Dose/concentration: 88.5 ± 13.4 μg/m³ Duration: 8 h/day for 3 days	BALF and lung tissue-protein level and gene expression of inflammatory mediators Plasma—biomarkers of coagulation
Chiarella et al. (2014) Species: mouse Sex: male Strain: C57BL/6 wild type and Adrβ knockouts Age/weight: 8−12 weeks	$PM_{2.5}$ CAPs Chicago, IL Particle size: $PM_{2.5}$ Control: filtered ambient air	Route: whole-body inhalation Dose/concentration: 109.1 ± 6.1 μg/m³ Duration: 8 h/day for 3 days	BALF and lung tissue—IL-6, norepinephrine Brown adipose tissue—norepinephrine
Clougherty et al. (2010) Species: rat Sex: male Age/weight: 12 weeks	$PM_{2.5}$ CAPs Boston, MA Particle size: PM ≤ 2.5 μm Control: filtered air	Route: whole-body inhalation Dose/concentration: 374 μg/m³ With large variance Duration: 10 days, 5 h/day Time to analysis: respiratory data was collected during exposure at 10 min. intervals using Buxco Coexposure: stress	Pulmonary function • Peak inspiratory flow • Minute volume • Breathing frequency • Inspiratory time • Expiratory time • Expiratory flows • Tidal volume

				nd Exposure Event	Exposure Pathways and Exposure Event		Exposure Pathways and Exposure Event		Exposure Pathways, Exposure Event, Biological Processes and Outcomes		Exposure Pathways, Exposure Event, Biological Processes and Outcomes		Exposure Pathways, Exposure Event, Biological Processes and Outcomes		Biological Processes and Outcomes	
Citation	ISA Figure/Table	Assigned To	Due Date	Exposure Modeling - by Scenario (Ontology/Mappi	External Exposure (Example from Pape	External Exposure (Ontology/Mappi	Exposure Measurements (Example from Pap	Exposure Measurements (Ontology/Mappi	Individual Susceptibility (Example from Pap	Individual Susceptibility (Ontology/Mappi	Dosimetry, Pharmacokinetics, Target site exposure (Example from Pape	Dosimetry, Pharmacokinetics, Target site exposure (Ontology/Mapping)	Biomarker Measurements (Example from Pape	Biomarker Measurements (Ontology/Mappi	Dose-Response (Example from Pap	Dose-Response (Ontology/Mappi
Samat et al., 2012	ISA Figure 5-5	Chirag	5/12/22				10, PM2.5 at school; during 2 48 hour sampling sessions per week. Measurements at school and city wide		age 6-12							
Silverman et al., 2010	ISA Figure 5-2	Chirag	5/13/22		24 hour average PM 2.5 and ozone		EPA Air Quality System monitors; averaged over 24 hours; 20 monitors within 20 miles of NYC		Susceptible groups by age (<6 y, 6-18, 19-49, 50+)						Relative Risk per IQR range	
Zhao et al., 2016	ISA Figure 5-2	Chirag	5/13/22		24 hour average PM 2.5, PMc, SO2, ozone, NO2, Temp		Dongguan Air Monitoring system; averaged over 24 hours								Relative Risk per IQR range	
Stieb et al., 2009	ISA Figure 5-3	Charles Schmitt	6/3/22		Hourly max concentration of CO, NO2, O3, SO2, PM10, PM2.5	Pollutants: chemical IDs, ECTO	National Air Pollution Surveillance system; Environment Canada's weather archive									
Hebbern and Cakmak, 2015	ISA Table 5-1	Charles Schmitt	6/3/22		Hourly max concentration of	Pollutants: chemical IDs, ECTO; Clinical	National Air Pollution Surveillance system; Aerobiology Research Laboratory (Rotational Impact									

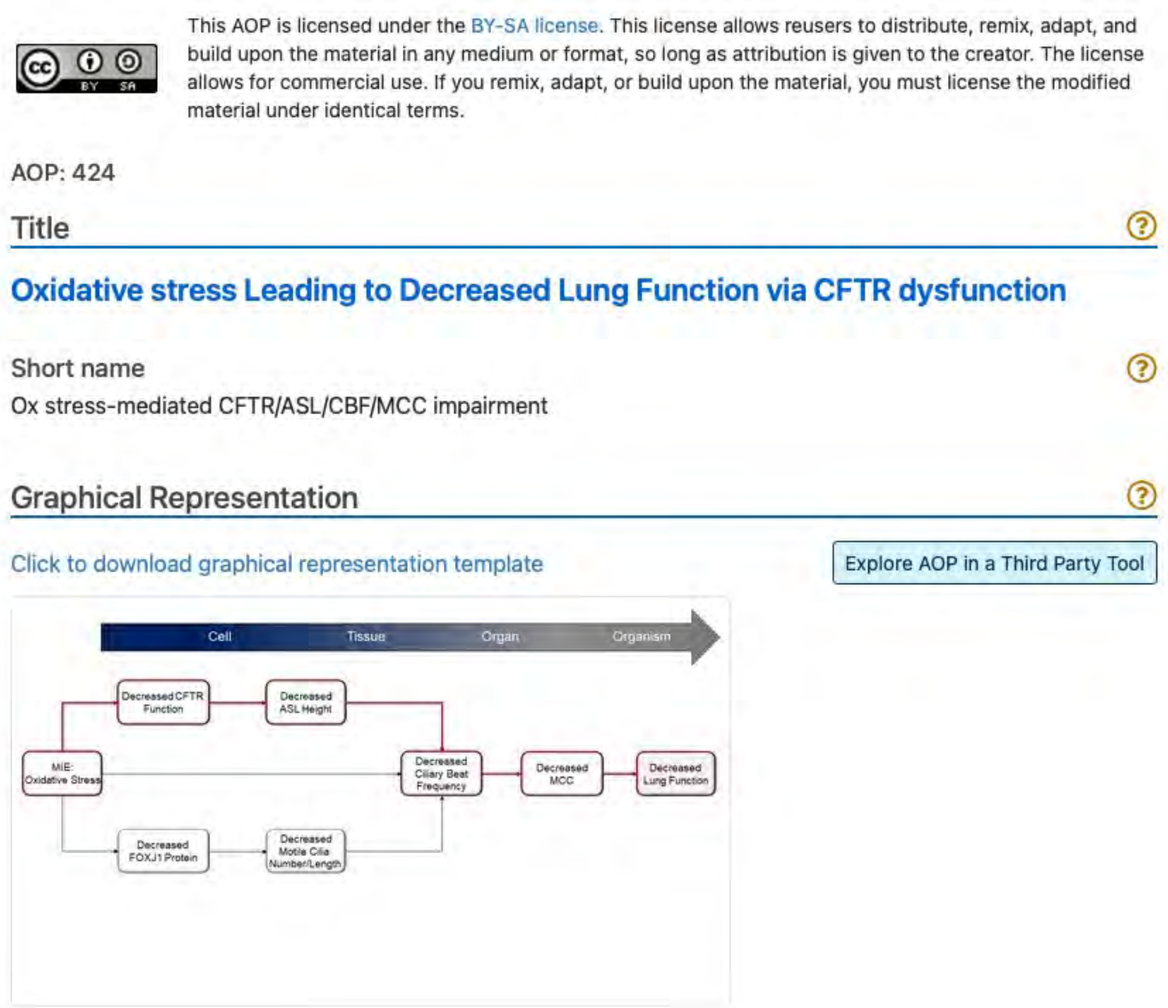


Conceptual diagram: Mapping the trajectory between exposure, pathways, events, and biological outcomes

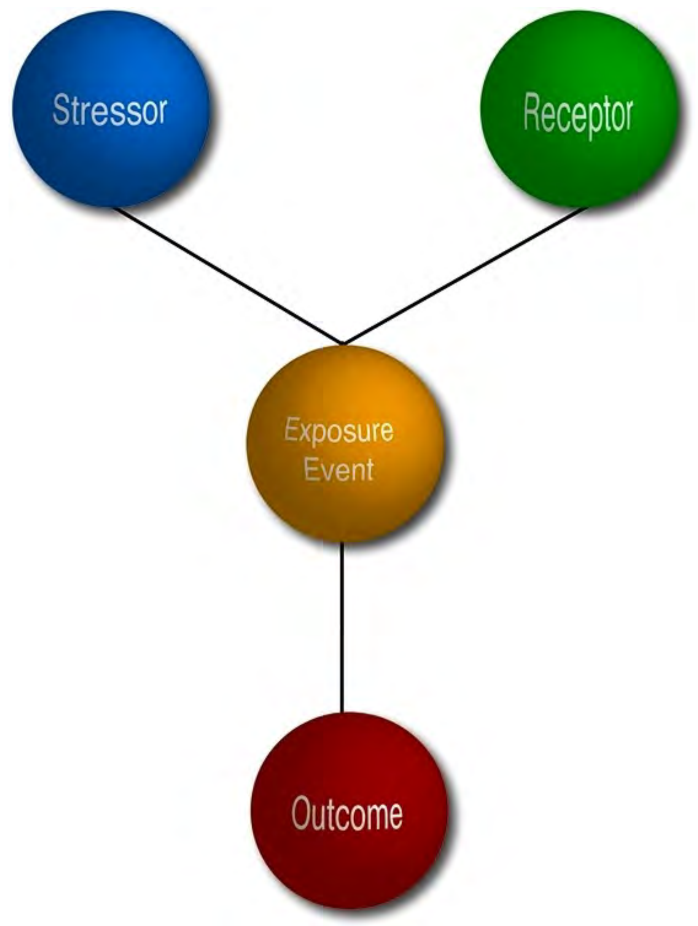


Samantha Hall

Existing knowledge-base-related resources: simple as integrating them together? (A non-exhaustive list)

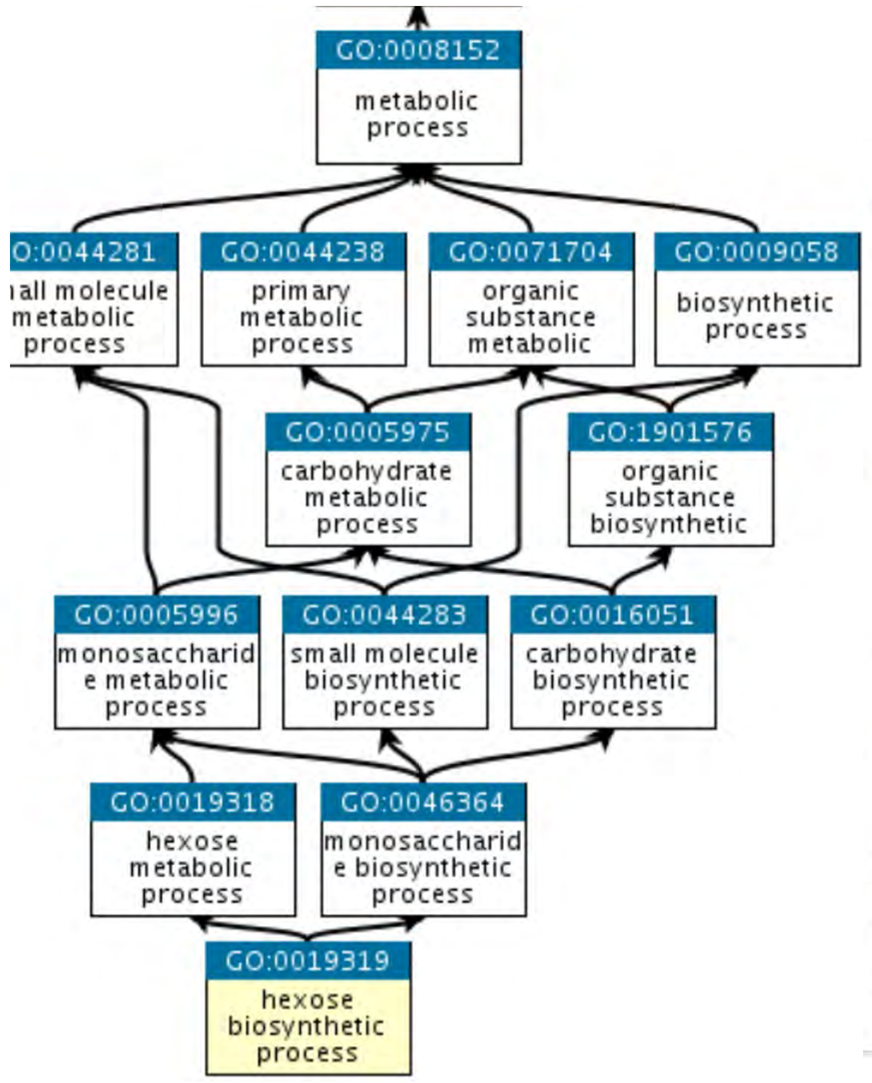


AOP Framework
AOPkb
AOPwiki

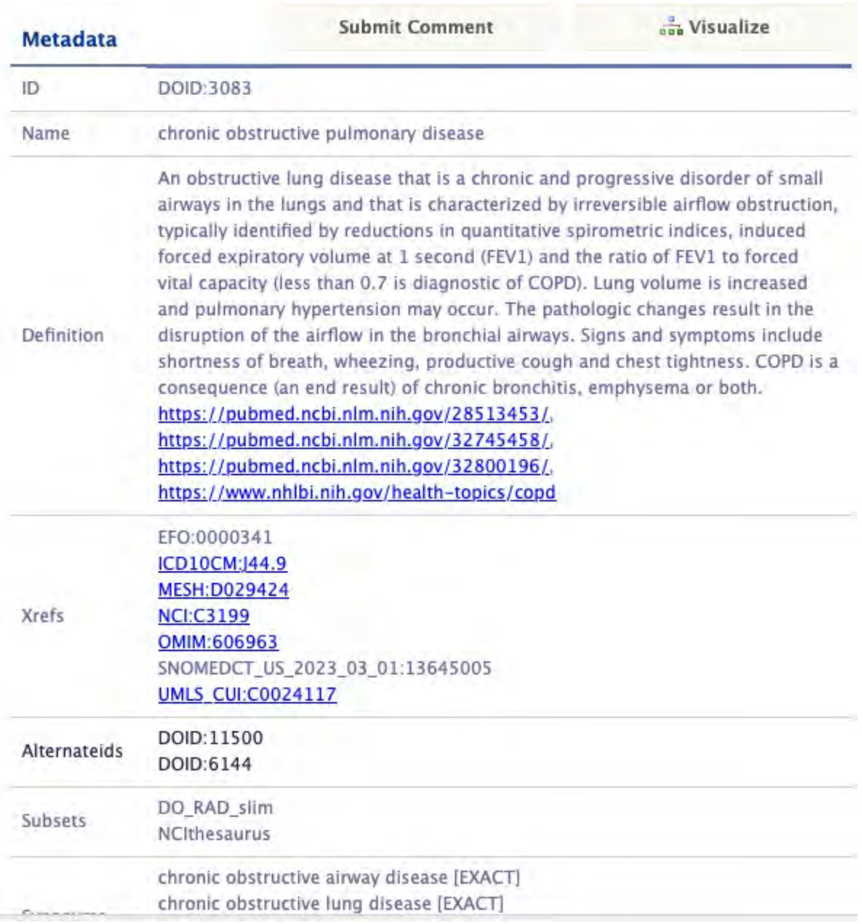


Exposure Ontology (ExO)

Comparative Toxicogenomics Database



Gene Ontology



Disease Ontology

https://aopwiki.org/
https://ctdbase.org/
https://geneontology.org
https://disease-ontology.org/

Table 5-2 Epidemiologic studies of short-term exposure to $PM_{2.5}$ and respiratory symptoms and medication use in children with asthma.

Study	Study Population	Exposure Assessment	Concentration (μg/m³)	$PM_{2.5}$ Copollutant Model Results and Correlations
†Spira-Cohen et al. (2011) Bronx, NY 2002−2005	n = 40, ages 10−12 yr 86% with rescue inhaler use Daily diary for 1 mo No information on participation rate 89% time spent indoors	School outdoor and total personal 24-h avg *r* = 0.17 school and personal children walk to school	Mean School: 14.3 Total personal: 24.1	Correlation (*r*): NA Copollutant models with: NA
†Zora et al. (2013) El Paso, TX March−June 2010	n = 36, ages 6−11 yr 33% ICS use, 47% atopy Weekly measures for 13 weeks 95% follow-up participation	School outdoor 96-h avg Two schools: High and low traffic area *r* = 0.89 between schools, 0.91 between monitors, 0.73−0.86 school and monitor	Mean, max School 1: 13.8, 24.9 School 2: 9.9, 18.5	Correlation (*r*): (School 1, School 2) −0.33, −0.19 NO_2; −0.02, 0.25 benzene; 0.10, 0.33 toluene; 0.47, 0.28 O_3 Copollutant models with: NA
†Rabinovitch et al. (2011); Rabinovitch et al. (2006) Denver, CO 2002−2005	n = 82 (3-yr study), 73 (2-yr study) 65−86% moderate/severe asthma, 82−90% ICS use Daily measures for 4−7 mo No information on participation rate	One monitor 24-h avg, 10-h avg (12−11 a.m.), 1-h max (12−11 a.m.) 4.3 km from school *r* = 0.92 monitor and school	Mean, max for yr 1−3 24-h avg: 6.5−8.2, 20.5−23.7 10-h avg: 7.4−9.1, 22.7−30.2 1-h max: 16.8−22.9, 39−52 (95th)	Correlation (*r*): NA Copollutant models with: NA
†Escamilla-Nuñez et al. (2008) Mexico City, Mexico 2003−2005	n = 147, ages 9−14 yr 43% persistent asthma, 89% atopy Daily diary for mean 22 weeks 94% follow-up participation	One monitor 24-h avg Within 5 km of school or home *r* = 0.77 monitor and school	Mean: 27.8	Correlation (*r*): 0.62 NO_2, 0.54 O_3 Copollutant models with: NA

Study design characteristics captured:

- Study population (inclusion criteria)
- Pollutant
- Exposure and assessment
- Endpoints and outcomes

Some characteristics difficult to extract:

- Risk estimates and standard error
- Outcome definition and phenotyping heterogeneity
- Covariates and modeling approach
- Linkages to external data resources
- "Quality" of a study

Study design plays a large role in making statements about risk: checklists and guidelines for evidence

GRADE Handbook

Introduction to GRADE Handbook

Handbook for grading the quality of evidence and the strength of recommendations using the GRADE approach. Updated October 2013.

Editors: Holger Schünemann (schuneh@mcmaster.ca), Jan Brożek (brozekj@mcmaster.ca), Gordon Guyatt (guyatt@mcmaster.ca), and Andrew Oxman (oxman@online.no)

About the Handbook

The GRADE handbook describes the process of rating the quality of the best available evidence and developing health care recommendations following the approach proposed by the Grading of Recommendations, Assessment, Development and Evaluation (GRADE) Working Group (www.gradeworkinggroup.org). The Working Group is a collaboration of health care methodologists, guideline developers, clinicians, health services researchers, health economists, public health officers and other interested members. Beginning in the year 2000, the working group developed, evaluated and implemented a common, transparent and sensible approach to grading the quality of evidence and strength of recommendations in health care. The group interacts through meetings by producing methodological guidance, developing evidence syntheses and guidelines. Members collaborate on research projects, such as the DECIDE project (www.decide-collaboration.eu) with other members and other scientists or organizations (e.g. www.rarebestpractices.eu). Membership is open and free. See www.gradeworkinggroup.org and Chapter The GRADE working group in this handbook for more information about the Working Group and a list of the organizations that have endorsed and adopted the GRADE approach.

The handbook is intended to be used as a guide by those responsible for using the GRADE approach to produce GRADE's output, which includes evidence summaries and graded recommendations. Target users of the handbook are systematic review and health technology assessment (HTA) authors, guideline panelists and methodologists who provide support for guideline panels. While many of the examples offered in the handbook are clinical examples, we also aimed to include a broader range of examples from public health and health policy. Finally, specific sections refer to interpreting recommendations for users of recommendations.

4.2 GRADE Evidence Profile

See online tutorials at: cebgrade.mcmaster.ca

The **GRADE evidence profile** contains detailed information about the quality of evidence assessment and the summary of findings for each of the included outcomes. It is intended for review authors, those preparing SoF tables and anyone who questions a quality assessment. It helps those preparing SoF tables to ensure that the judgments they make are systematic and transparent and it allows others to inspect those judgments. Guideline panels should use evidence profiles to ensure that they agree about the judgments underlying the quality assessments.

A GRADE evidence profile allows presentation of key information about all relevant outcomes for a given health care question. It presents **information about the body of evidence** (e.g. number of studies), the **judgments about the underlying quality of evidence**, key **statistical results**, and **the quality of evidence rating for each outcome**.

A GRADE evidence profile is particularly useful for presentation of evidence supporting a recommendation in clinical practice guidelines but also as summary of evidence for other purposes where users need or want to understand the judgments about the quality of evidence in more detail.

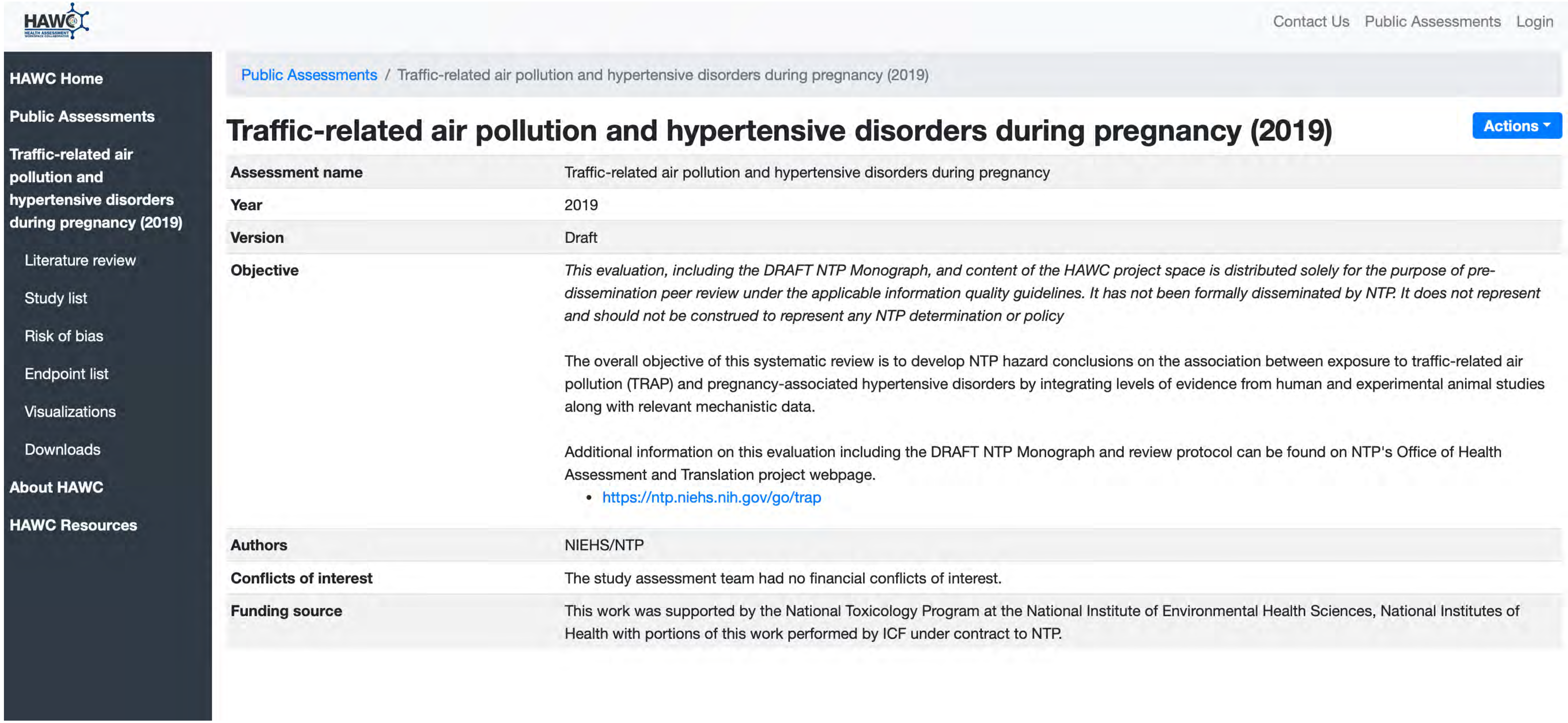
The standard format for the evidence profile includes:

- A list of the **outcomes**
- The **number of studies** and **study design(s)**
- Judgements about each of the **quality of evidence factors** assessed; risk of bias, inconsistency, indirectness, imprecision, other considerations (including publication bias and factors that increase the quality of evidence)
- The **assumed risk**; a measure of the typical burden of the outcomes, i.e. illustrative risk or also called baseline risk, baseline score, or control group risk
- The **corresponding risk;** a measure of the burden of the outcomes after the intervention is applied, i.e. the risk of an outcome in treated/exposed people based on the relative magnitude of an effect and assumed (baseline) risk
- The **relative effect**; for dichotomous outcomes the table will usually provide risk ratio, odds ratio, or hazard ratio
- The **absolute effect**; for dichotomous outcomes the number of fewer or more events in treated/exposed group as compared to the control group
- Rating of the **overall quality of evidence** for each outcome (which may vary by outcome)
- Classification of the **importance** of each outcome
- **Footnotes**, if needed, to provide explanations about information in the table such as elaboration on judgements about the quality of evidence

Example 1: GRADE Evidence Profile

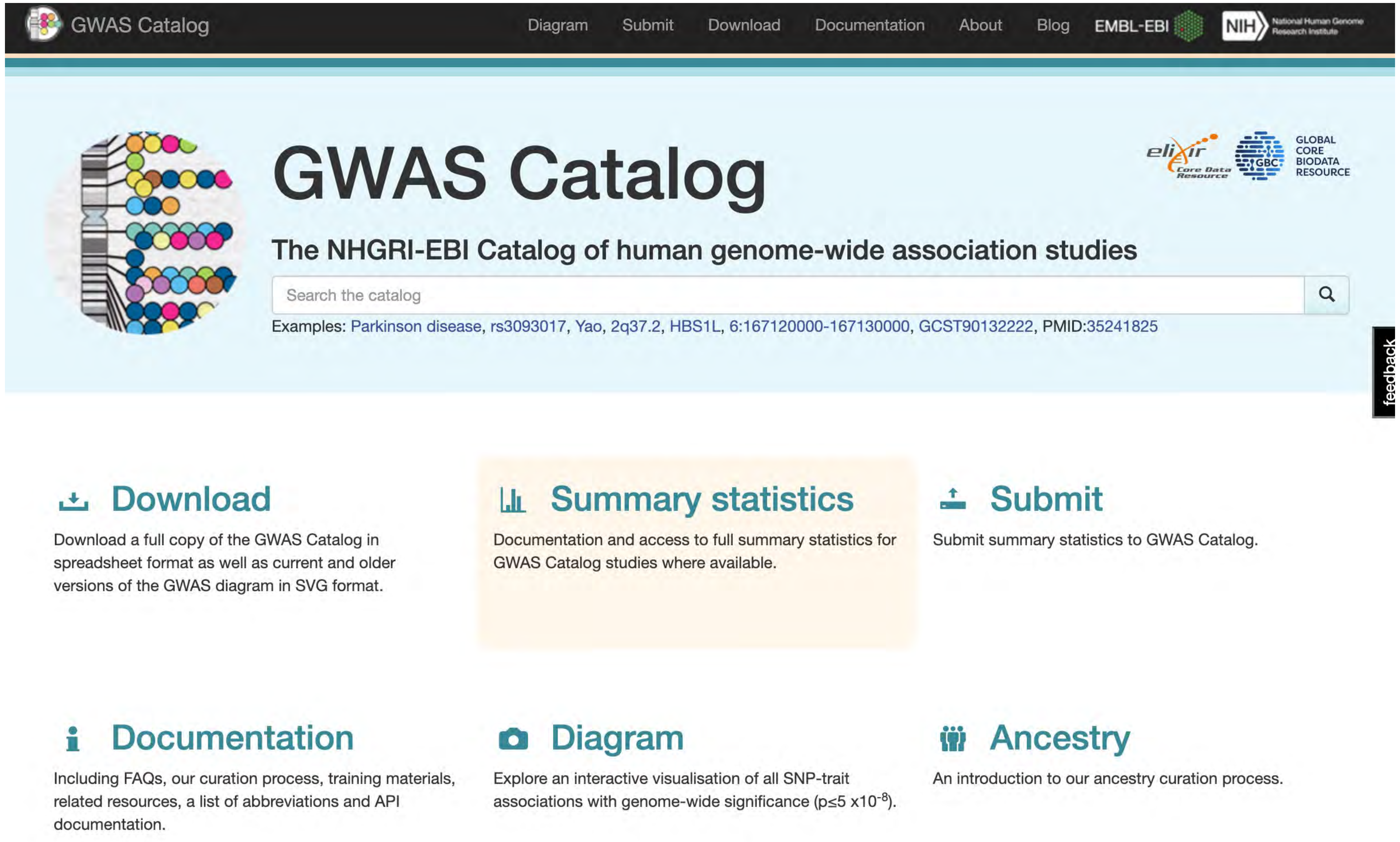
https://gdt.gradepro.org/app/handbook/handbook.html#h.9rdbelsnu4iy

Probabilistic statements (e.g., epidemiological risk) are a challenge to estimate, but required for evidence synthesis



Environmental Health Vocabulary (EHV; available at https://hawc.epa.gov/vocab/ehv/), which is implemented in Health Assessment Workspace Collaborative (HAWC).

Finding inspiration in genome-wide association studies GWAS (G-P): standardized genetic variant, analytic approaches, and study designs



https://www.ebi.ac.uk/gwas/

3,567 publications (as of 9/18/18)
71,673 ***G-P*** associations

3,955 publications (as of 4/21/19)
136,287 ***G-P*** associations

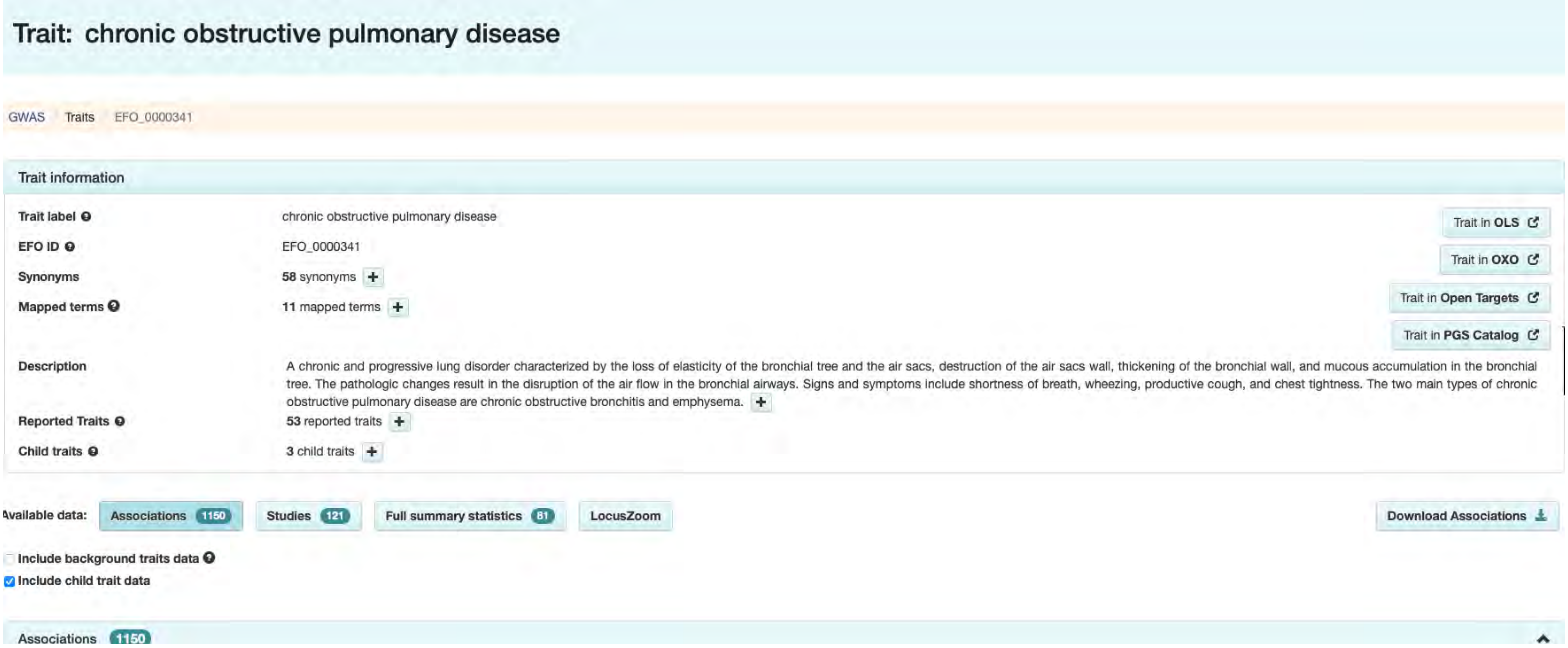
4,493 publications (as of 3/10/20)
179,364 ***G-P*** associations

5,690 publications (as of 5/11/22)
372,752 ***G-P*** associations

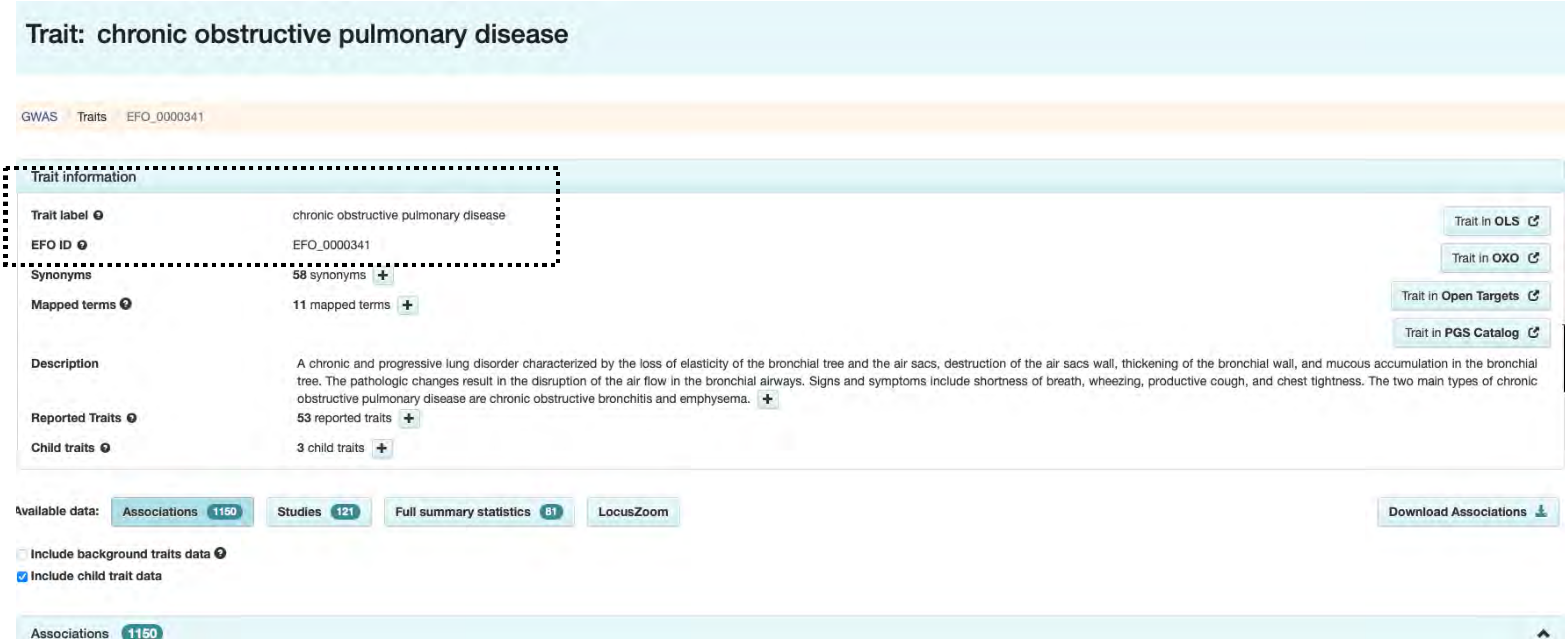
6,245 publications (as of 1/31/23)
471,482 ***G-P*** associations

6,715 publications (as of 1/30/24)
571,148 ***G-P*** associations

GWAS catalog: mapping variants, genes, and disease to enhance identification of gene function and disease etiology



GWAS catalog: mapping variants, genes, and disease to enhance identification of gene function and disease etiology



https://www.ebi.ac.uk/ols4/ontologies/efo?viewMode=tree

GWAS catalog contains underlying risk estimates (e.g., odds ratios) - can we do the same for the "exposome" ?

Associations 1150

Show 5 entries

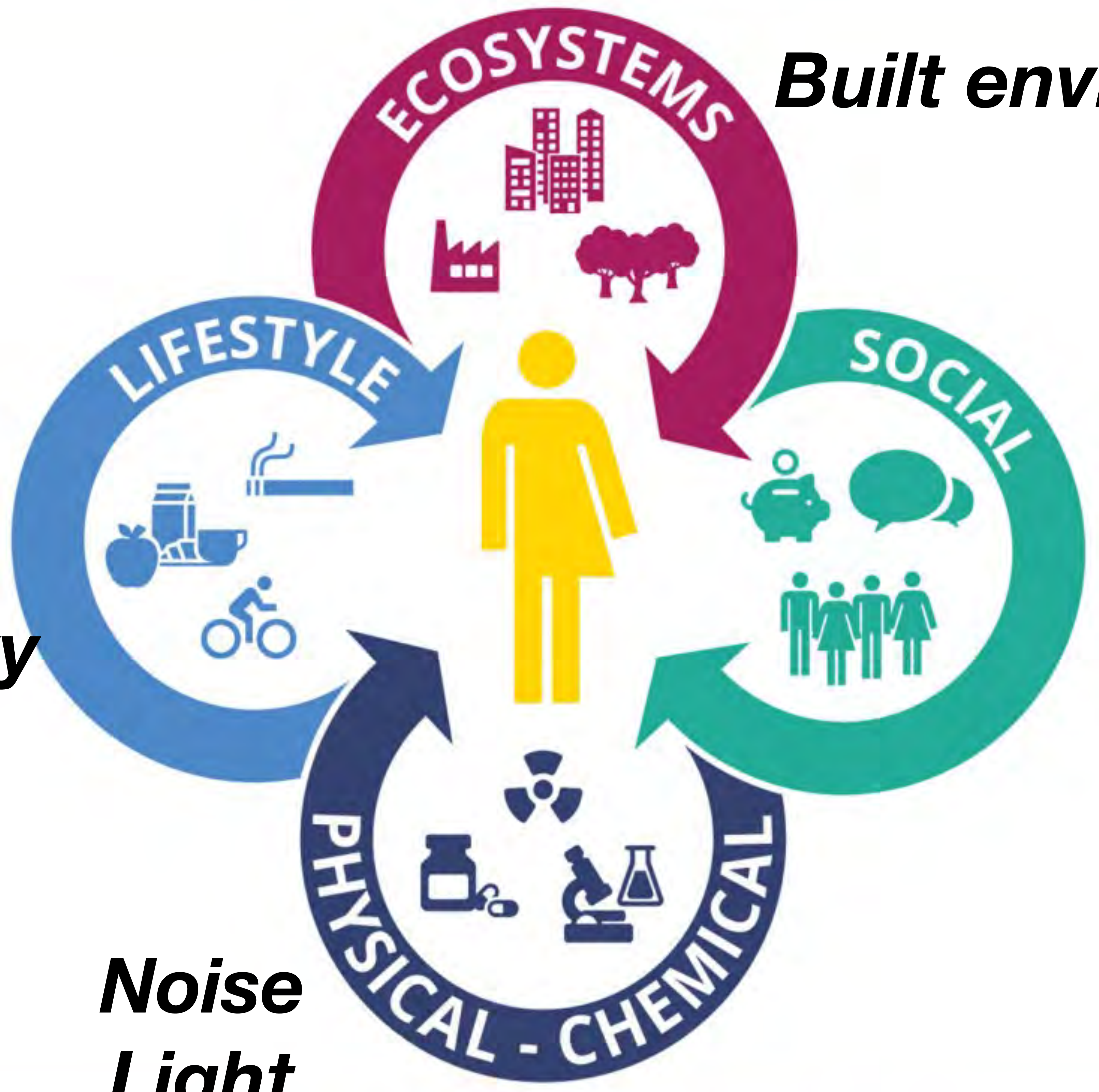
Column visibility | Export | Clear search

Variant and risk allele	P-value	P-value annotation	RAF	OR	Beta	CI	Mapped gene	Reported trait	Trait(s)	Background trait(s)	Study accession	Location
rs2869967-C	6×10^{-10}	(EA)	0.41	1.38	-	[1.25-1.53]	FAM13A	Chronic bronchitis and chronic obstructive pulmonary disease	chronic obstructive pulmonary disease, chronic bronchitis	-	GCST002625	4:88948181
rs34391416-A	5×10^{-8}	(EA)	0.05	1.93	-	[1.53-2.45]	CRACR2B	Chronic bronchitis and chronic obstructive pulmonary disease	chronic obstructive pulmonary disease, chronic bronchitis	-	GCST002625	11:831818
rs139257032-T	3×10^{-7}	(EA)	0.02	3.35	-	[2.12-5.30]	CFAP221	Chronic bronchitis and chronic obstructive pulmonary disease	chronic obstructive pulmonary disease, chronic bronchitis	-	GCST002625	2:119571288
rs12910412-G	5×10^{-7}	(EA)	0.46	1.3	-	[1.17-1.44]	LINC01581, H3P40	Chronic bronchitis and chronic obstructive pulmonary disease	chronic obstructive pulmonary disease, chronic bronchitis	-	GCST002625	15:94163844
rs13141641-T	3×10^{-6}	(EA)	0.58	1.27	-	[NR]	KRT18P51, HHIP-AS1	Chronic bronchitis and chronic obstructive pulmonary disease	chronic obstructive pulmonary disease, chronic bronchitis	-	GCST002625	4:144585304

Showing 1 to 5 of 1,150 entries

« 1 2 3 4 5 … 230 »

The *exposome*: toward a taxonomization of systematic exposures across domains & modalities



Built environment

Behavior;
Smoking
Physical activity

Capital
Education

Noise
Light
Chemicals
Particles (PM)

Vermeulen R, Science 2020
Wild, Int J Epi 2012
Manrai et al., ARPH 2017
Patel and Ioannidis JAMA 2014
Ioannidis et al. STM 2009

Many modalities of the *exposome* to taxonomize

Modality	**Type**	**Examples**
Targeted mass spec	**Tabular; spectra**	**Lead; Cadmium; PFAS**
Geospatial markers	**Area-level; 2D spectra**	**Zipcode-level PM 2.5**
Self-report questionnaire	**Tabular; hierarchical**	**Nutritional recall**
Untargeted mass spec	**Tabular; spectra**	**Mass-charge ratio**
Sensor-based behaviors	**Tabular; spectra**	**Accelerometers**

Patel et al, CEBP 2017
Manrai et al, ARPH 2017
Vermeulen et al, Science 2020

2022 NIEHS Catalytic Workshop Series on the Exposome

Decoding the exposome: data science methodologies and implications in exposome-wide association studies (ExWASs)

Ming Kei Chung [1,2,3], PhD, John S. House [4], PhD, Farida S. Akhtari[4], PhD, Konstantinos C. Makris [5], PhD, Michael A. Langston[6], PhD, Khandaker Talat Islam[7], PhD, Philip Holmes[8], PhD, Marc Chadeau-Hyam [9], PhD, Alex I. Smirnov[10], PhD, Xiuxia Du[11], PhD, Anne E. Thessen [12], PhD, Yuxia Cui[13], PhD, Kai Zhang[14], PhD, Arjun K. Manrai[1], PhD, Alison Motsinger-Reif [4,*], PhD, Chirag J. Patel [1,†,*], PhD and Members of the Exposomics Consortium

[1]Department of Biomedical Informatics, Harvard Medical School, Boston, MA, USA

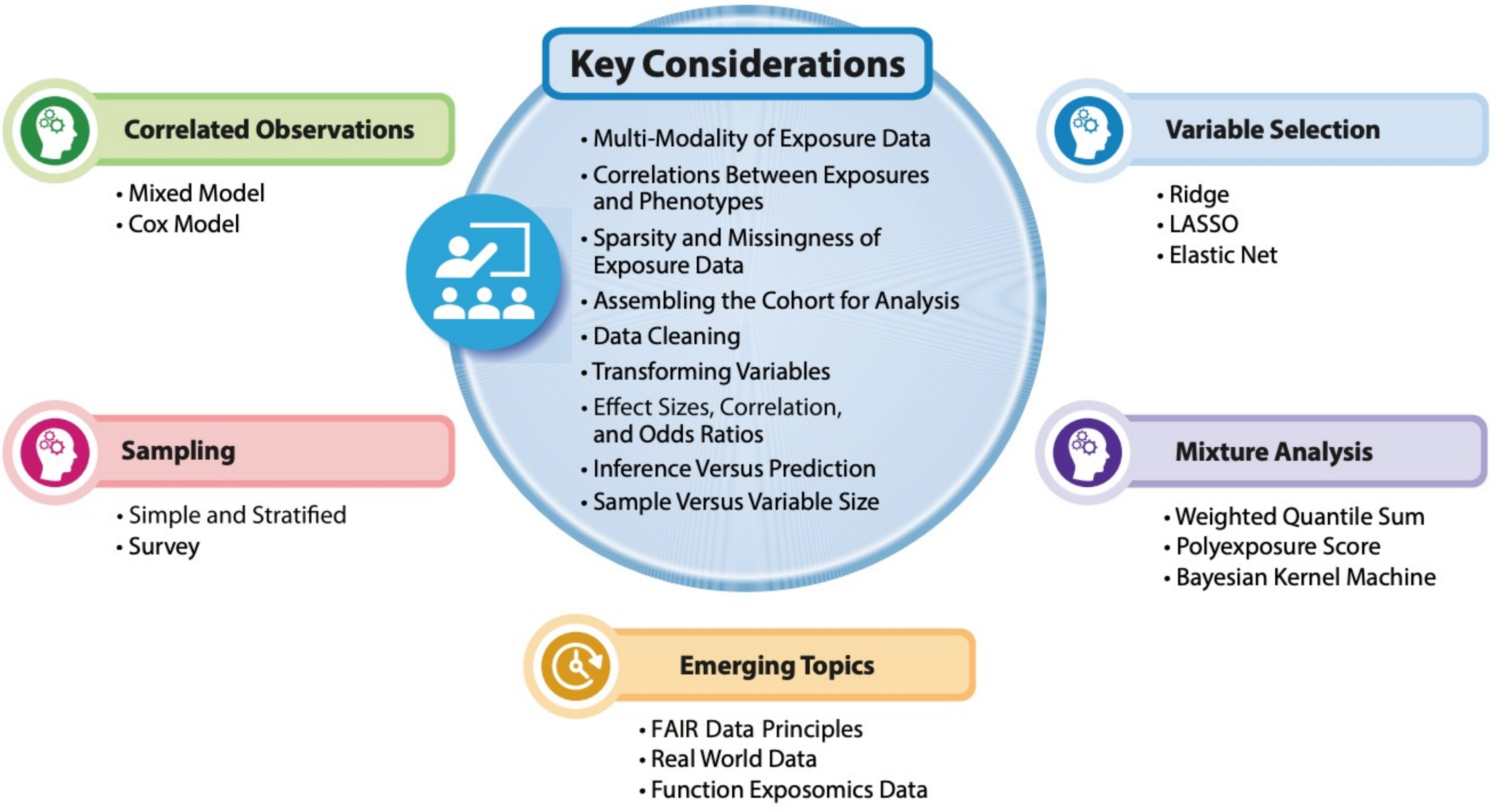


Figure 1. Key considerations for Exposome-Wide Association Studies.

Informatics and Data Analytics to Support Exposome-Based Discovery for Public Health

Arjun K. Manrai,[1] Yuxia Cui,[2] Pierre R. Bushel,[2] Molly Hall,[3] Spyros Karakitsios,[4] Carolyn J. Mattingly,[5] Marylyn Ritchie,[3,6] Charles Schmitt,[7] Denis A. Sarigiannis,[4] Duncan C. Thomas,[8] David Wishart,[9] David M. Balshaw,[2] and Chirag J. Patel[1,10]

Table 1 Data-related recommen

	Recommendation	Examples
1	Catalog contributions of environmental exposures to disease risk (e.g., susceptibility, variance explained) to strengthen the case for exposome research.	Develop requirements for an exposome-disease association catalog.
2	Identify high-throughput (e.g., 'omics, sensor-based) technologies and gaps to allow agnostic assessment of the exposome.	Develop infrastructure to characterize the variability of the exposome in various populations, akin to the NHANES.
3	Incentivize other parties (e.g., 'omics investigators in other disciplines, funding institutions, industrial entities) to integrate the exposome in their programs and develop high-throughput analytics methods to analyze exposome data.	Develop big data analytics and visualization tools to accelerate exposome-related research (e.g., exposome–phenome association studies). Identify how existing 'omics statistical methods can be extended for the exposome research and identify gaps for new method development. Encourage a shift in focus from "one exposure–one phenotype" to multiple exposures, genes, and phenotypes. Develop methods to link the internal and the external exposome. Develop methods to support varieties of study designs (e.g.,

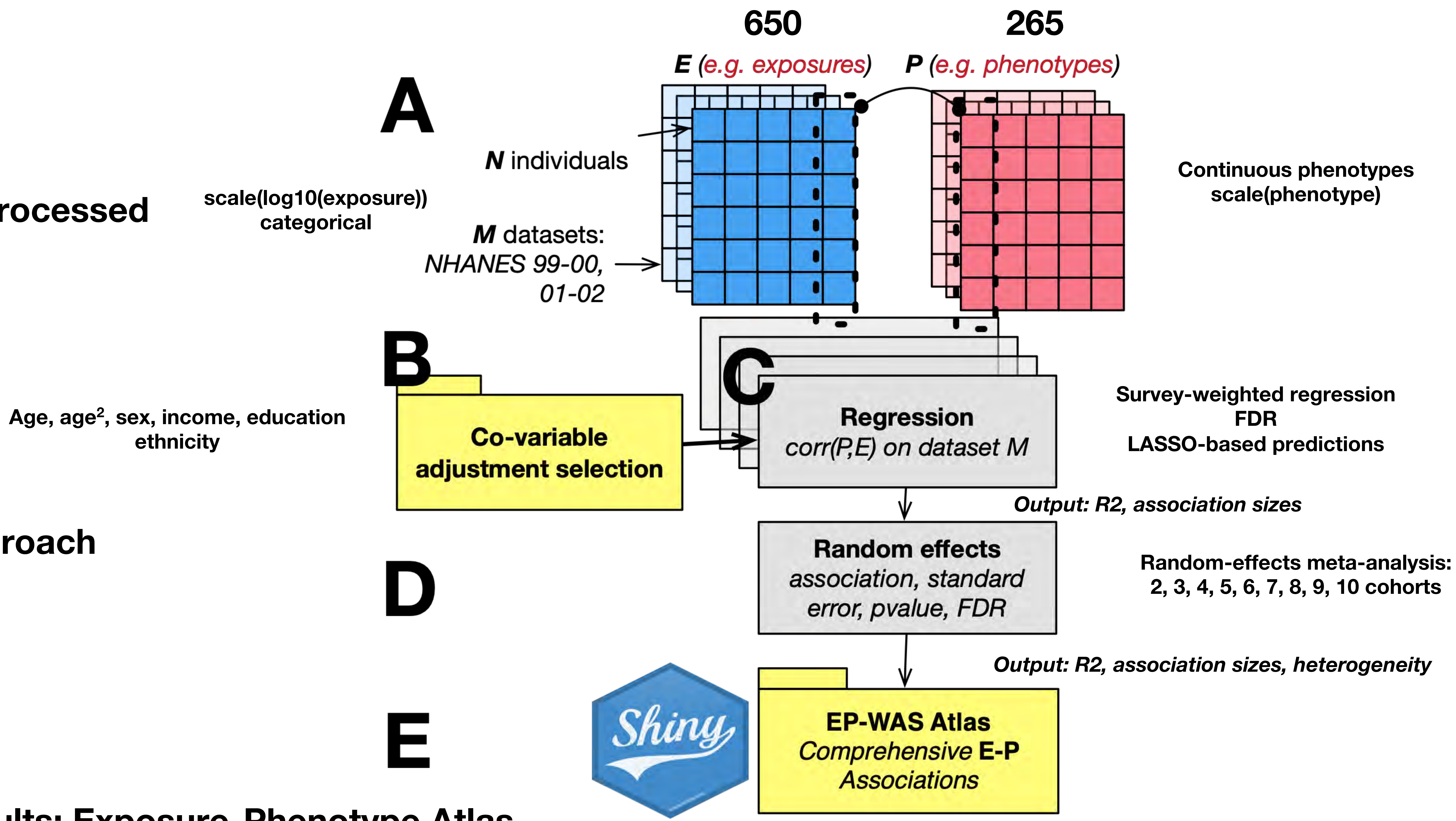
Chung et al, *Exposome* 2024
Manrai et al., *ARPH* 2017

… many analytic approaches to map *E-P* associations

Benchmarking exposome-phenome relationships: *ExWAS* between 650 *E* & 265 *P* in US NHANES
Grand total of ~400k E-P associations

How data are processed

Analytic approach



Reporting of results: Exposure-Phenotype Atlas

Toward an "exposome atlas": cataloging between exposures, processes, and clinical outcomes (e.g., "abstracting" Table 1 & 2 of published studies)

Study Type
Cross sectional
Case-control
Sample size

Exposure Factor
PM 2.5
PFAS

Method of Association
Linear Regression
Logistic Regression

Phenotype
Forced expiratory volume
Body Mass Index
C-Reactive Protein

Inclusion criteria
Demographics
Location of study

Exposure Media
Geocode
Blood biomarker

Association Type
Odds ratio
Hazard Ratio

Clinical Outcome
COPD

Exposure Dose
Per 10ug/m3
Mg/dL

Association Size and Error
1.1 (0.001)
10 (1.5)

Conclusions: digitizing the biological pathways phenomena between exposures and clinical outcomes

- Possible to put together existing resources to map between exposures and clinical outcomes

- However, to enhance triangulation of evidence, risk estimates are required

- A prerequisite for assimilating evidence includes documenting parameters around the study design and the association

- The ***exposome*** provides an opportunity to produce a “catalog” of benchmarks between exposures and biomarkers across experimental study design (e.g., tox and epi)

- Multi-modal AI approaches can introduce new ways of using text to refine knowledge between exposures and disease outcomes but need to be evaluated at scale

Presentation 4

Presentation Order	Presentation Title	Presenter, Organization
4	*Challenges and opportunities to improve communication about exposure and risk for collaboration and information exchange*	Elke Jensen, PhD, Dow Chemical Company elke.jensen@dow.com

SYMPOSIUM: OVERCOMING BARRIERS TO MORE SCALABLE ENVIRONMENTAL HEALTH SCIENCE RESEARCH VIA HARMONIZED LANGUAGE

Challenges and opportunities to improve communication about exposure and risk for collaboration and information exchange

Elke Jensen, PhD, Dow Chemical Company
SOT 2024 Salt Lake City, Utah

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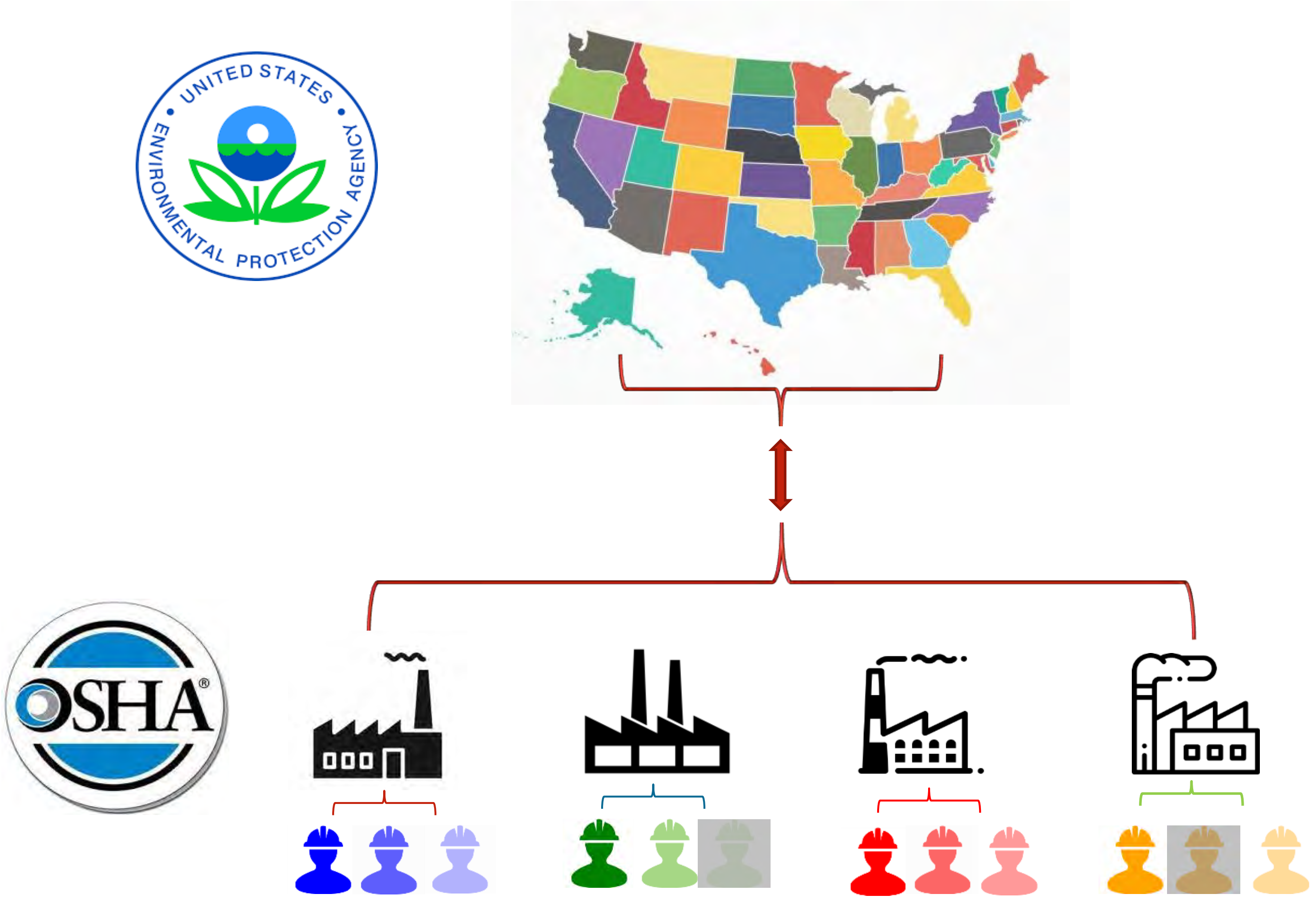
ONE CHALLENGE FOR TSCA RISK EVALUATION

RE must be general and broad and cover all COU.

↕

IH is highly specific and difficult to generalize.



COU = conditions of use
RE = risk evaluation
IH = industrial hygiene

EPA's Data Needs: Elements of Occupational Exposure Assessment

Use Information

- ❑ End-Uses of Chemical Substance
- ❑ Life Cycle of Chemical Substance
  - Industries involving the chemical substance that are parts of the supply chains for the end-uses
  - Recycling operations
  - Disposal operations
- ❑ Production Volume Associated with Each Life Cycle Step

Facility Information

- ❑ Process Description (including concentration)
- ❑ Operations Information
  - Days of operation per year
  - Worker activities
  - Number of sites
- ❑ Industrial Hygiene Information
  - Existing OELs
  - Physical form
  - Potential exposure routes, durations and frequencies
  - Engineering controls
  - Administrative controls
  - PPE
  - Number of potentially exposed workers

Monitoring / Testing Information

- ❑ Inhalation Exposure Mass Concentration
  - Worker and ONU
  - Personal and area concentrations
  - TWA, short-term and peak values
  - Central tendency and high-end values
  - OES-specific or surrogate data
  - Exposure duration & frequency
- ❑ Dermal Applied Dose & Exposure Frequency
- ❑ Dermal Percent Absorption

Modeling Information

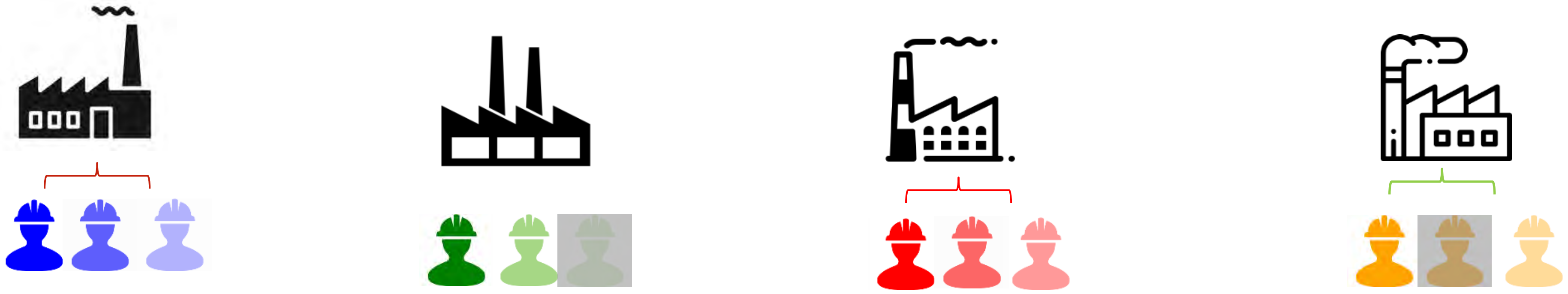
- ❑ Throughput of the Chemical
- ❑ Use Rate of the Chemical
- ❑ Emissions Rate
- ❑ Duration of Operation or Worker Activity
- ❑ Ventilation Rate
  - Exchange rate
  - Workspace volume
- ❑ Dermal Applied Dose and Percent Absorption

WHY LANGUAGE MATTERS…

- ONU – Occupational Non-Users
  - New term introduced under TSCA
  - This term does not exist under OSHA
  - By-standers defined for plant protection (i.e., pesticides) but does not apply in industrial settings (either you're a worker or not)
- Who do we monitor?

HYPOTHETICAL IH META DATA

	Company A	Company B	Company C	Company D
Employee	Engineer	Process engineer	Technician	Process engineer
Activity	Collect 4 oz samples	Sampling, 50 ml	Sampling, 1 L	Sampling, volume not specified
Sampling	Task monitoring	Task monitoring	Full shift monitoring	Full shift monitoring
Exposure modifiers	Not specified	10 minutes	2x per shift	Specified PPE, 5 minutes, 1/week
Engineering controls	Outdoors	Closed loop	Indoors Needle/septum	Outdoors, open jar



HARMONIZATION ↔ COMMUNICATION

- Descriptors need to be well defined, mutually understood
- Meta-data need to be harmonized – especially for combining data sets, understanding aggregate and co-exposures
- Industrial Hygiene Data Standardization (aiha.org)

LEVERAGING EXISTING EXPOSURE/MONITORING DATA

- Merging exposure data from different sources
  - Data collected for different purposes
  - Some existing sources but are organized NOT as centralized database platform rather but a distributed infrastructure (links to external holders of exposure data)
  - IPCheM Portal (europa.eu)
  - ECETOC heatDB
  - …

MOVING FORWARD…

- We need to speak the same language – have the same understanding of scenarios, activities, and other exposure descriptors
  - Permit stakeholders to provide, generate data that is fit-for-purpose
- More dialog between stakeholders
  - Manufacturers
  - Customers
  - Regulatory agencies
- Consistent approach to exposure assessment $\rightarrow$ better risk assessment and risk management

WHAT MIGHT A TSCA PLAYBOOK LOOK LIKE?

Start collecting and generating information ASAP

Communication

- Define conditions of use
- Collect data and information for each COU
  - Products, concentrations, downstream uses / supply chain
  - IH monitoring data
  - Other reporting data: CDR, TRI, etc…
  - Emission controls
- What are best practices? For an enterprise? For an industry?

Communication

Communication

SUMMARY

- To characterize risk properly, must understand exposure
- That means risk managers and risk assessors must understand each other
- *Mutual understanding of the exposure scenario details*
- *Common language and terminology*
- *Harmonized meta data*
- *Broader sharing of data in context*

THANK YOU

- Co-panelists
- SOT
- Dow colleagues
- YOU

Questions related to these presentations?

Reach out to: **EHLC@icf.com**