

Advancing Systematic Review Methods and Tools

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Board of Scientific Counselors (BOSC) Subcommittee Chemical Safety for Sustainability (CSS) and Health and Environmental Risk Assessment (HERA) National Research Programs Virtual Meeting on February 2-5, 2021

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Office of Research and Development Center for Public Health and Environmental Assessment

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Assessment Methods in the IRIS Program

- Described in the ORD Staff Handbook for Developing IRIS Assessments ("IRIS Handbook"), released November 2020 for public comment (ends March 1, 2021)
- Includes systematic review and doseresponse methods
- Handbook will undergo peer-review by National Academy of Sciences (NAS) in Spring 2021 & expect report Summer 2021
- Core methods previously reviewed by NAS in 2018 and published in journal articles (Appendix B, Part 3)



NAS (2018): Progress Toward Transforming the Integrated Risk Information System (IRIS) Program: A 2018 Evaluation https://www.nap.edu/catalog/25086/progress-toward-transforming-the-integrated-risk-information-system-iris-program



Systematic Review Method Development

Systematic Review Activity	Status
Finding and screening studies for relevance	√ Methods stable and templates available. Specialized software used to manage process, including use of artificial intelligence (AI) which reduces level of effort and cost by 40-60%. Level of software intra-operability is functional.
Data extraction of study design and results from full- text	 √ Stabilized on entities we extract for epidemiological and animal studies. √ Use of structured web-based forms for epidemiological and animal studies. In progress Extraction stabilizing on entities for <i>in vitro</i> and PBPK models.
Semi-automating process of data extraction *Collaborative multi- year effort across ORD, OCSPP	In progress (animal toxicology): Will begin to incorporate for fields where models perform well (e.g., species, strain, sex) and develop additional training sets to improve model performance for other entities (endpoints assessed, results). Will be approached using a "human-in-the loop" approach. "Automated/Machine Learning Approaches" (Michele Taylor presentation) Next up (epidemiological and exposure studies): Develop training sets for model development (2021-2022). Downstream: Develop training sets for full-text extraction of in vitro, ADME/toxicokinetic, PK/PBPK evidence.
Intra-operability across software platforms	Downstream: Ensure ability of HAWC to import extraction conducted elsewhere. Pertinent to "Semantic Ontology Mapping" (Michelle Angrish presentation)



Systematic Review Method Development

Systematic Review Activity	Status
Organizing and evaluating mechanistic evidence	In progress: "Organizing and Evaluating Mechanistic Evidence" (Catherine Gibbons presentation)
Study Evaluation	 √ Methods stable for epidemiology and animal toxicology, with dissemination in many published articles. √ 2021 Dosimetry and Mechanism-Based Models Umbrella Quality Assurance Project Plan (QAPP) for PBPK models In progress (in vitro studies): "Organizing and Evaluating Mechanistic Evidence" (Catherine Gibbons presentation)
Evidence Synthesis/Integration	 ✓ Structured frameworks for synthesis and integration of epidemiology, animal toxicology, and mechanistic evidence presented in IRIS Handbook. Will refine as needed based on external peer review. Developing examples and monitoring implementation to provide more information to staff on how to operationalize consistent application and decision documentation. In progress: Enhancements in HAWC to use forms for documenting evidence synthesis and integration decisions in evidence profile tables (web-based and interactive).



- IRIS Handbook and assessment-material templates (assessment plan, protocol, draft assessment)
- Draft template for "fit for purpose" systematic evidence map (SEM) publication
 - SEM is a pre-decisional analysis, publishable in journals ("PFAS Systematic Evidence Maps" Laura Carlson presentation)
- Publicly accessible Health Assessment Workspace Collaborative (HAWC) project to share targeted resources, many of which are evergreen

AW		Contact About Public Assessments Your HAWC -
«	Home / IRIS PPRTV SEM Template Figures	s and Resources (2021)
Selected assessment	IRIS PPRTV SEM	Template Figures and Resources (2021)
IRIS PPRTV SEM		Actions -
Resources (2021)	Assessment name	IRIS PPRTV SEM Template Figures and Resources
Available modules	Year	2021
Literature review	Version	template repository
Management dashboard		
Study list		
Study evaluation		
Endpoint list		
Visualizations		
Executive summary		

- Commonly used data visualization templates
- Example answers for common study evaluation scenarios for animal toxicity studies
- Latest controlled vocabulary for data extraction
- Tips for using software
- Training slides on searching grey literature



- Presentations in this session will mention a variety of specialized software used within HERA to manage the systematic review process
- Rapidly evolving field and requires extensive community engagement with developers and users to stay current
- Considerations for which software applications to use:
 - Performance, cost, ability of software developer to provide technical support to a large group, ability to make interoperable with HERO and other systematic review software, adaptability for environmental human health assessments
- Resourcing: HEEAD-HERO and CPAD staff, CCTE partnerships (e.g., ECOTOX, Chemicals Dashboard), OCSPP, and extramural contracts



Engagement

- Across EPA with other groups that conduct systematic reviews, e.g., CPHEA-HEEAD, OW, OPPT
- EPA Systematic Review Communities of Practice
- Working closely with CCTE (i.e., data curation workflows used for ECOTOX and Chemicals Dashboard, use of Chemicals Dashboard for chemical information presented in assessments)
- National and international collaborations (e.g., NTP, EFSA, International Collaboration for the Automation of Systematic Reviews, GRADE Working Group)
 - Includes discussions of approaches to maximize information retrieval and sharing of extracted data "Semantic Ontology Mapping" (Michelle Angrish presentation)

Engagement, continued

NAS workshops

- Upcoming workshops on (1) triangulation in evidence integration, and (2) artificial intelligence/open data practices. COVID has impacted scheduling.
- Evidence Integration in Chemical Assessments Workshop (Jun 2019)
- Strategies and Tools for Conducting Systematic Reviews of Mechanistic Data to Support Chemical Assessments (December 2018)
- Training
 - Training is typically hands on and includes within EPA, international and state engagements
 - -Academic partnerships, e.g., ~25 student interns over past 2 years



Gauging Success

- Delivery of assessment products to partners and stakeholders
- Assess quality via feedback during review of IRIS Handbook and assessment products
- Semi-automation "Automated/Machine Learning Approaches" (Michele Taylor presentation)
 - Track time saved to complete task (and money saved)
 - Retain "human-in-the-loop" to assess performance of new machine-learning capabilities
- Publications
- Intra-operability (longer-term)
 - Ability to access extracted data from Chemicals Dashboard in ToxVal and utilize in readacross analyses
 - Moving data into HAWC, ability to conduct statistical analyses on stored data
- Monitor ability to meet Agency needs on high priority, emerging topics, or rapid risk assessment request, e.g., ("PFAS Systematic Evidence Maps" Laura Carlson presentation)
- Monitor uptake of methods by other groups (within and outside of EPA)





HERA SESSION 2: Advancing Systematic Review Methods								
2:50 – 3:05	Advancing SR Methods and Tools Intro with Charge Question	Kris Thayer, CPHEA						
3:05 – 3:25	Organizing and Evaluating Mechanistic Evidence	Catherine Gibbons, CPHEA						
3:25 – 3:45	Automated Data Extraction	Michele Taylor, CPHEA						
3:45 - 4:05	Semantic Ontology Mapping	Michelle Angrish, CPHEA						
4:05 – 4:25	Application of Systematic Evidence Map Methods to Characterize Available Evidence for PFAS	Laura Carlson, CPHEA						
4:25 – 5:00	BOSC Subcommittee discussion and Qs/As	Katrina Waters, Chair						
5:00	ADJOURN							



Incorporating the principles of systematic review into the HERA portfolio of assessment products has been a goal of the HERA program for the last several years. In order to achieve this goal, the **HERA** program intends to advance the field of systematic review more broadly. Based on the progress to date and currently planned products, what suggestion(s) or recommendation(s) does the Subcommittee offer on HERA's research to advance methods for systematic review? [Research Area 3, Output 3.4]



Organizing and Evaluating Mechanistic Evidence: IRIS Systematic Review Methodology

U.S. EPA Office of Research and Development Board of Scientific Counselors Subcommittee Chemical Safety for Sustainability and Health and Environmental Risk Assessment National Research Programs

> Catherine Gibbons Center for Public Health & Environmental Assessment Chemical & Pollutant Assessment Division February 4, 2021

> The views expressed in this presentation are solely those of the author(s) and do not necessarily reflect the views and policies of the U.S. Environmental Protection Agency (EPA)

Approach for systematically reviewing mechanistic studies

- Goals:
 - Transparent, operationalized method of systematically identifying mechanistic data
 - Fit-for-purpose methodology for evaluating mechanistic evidence—tailoring effort to assessment needs
- **Problem:** Difficult to know *a priori* how to tailor the effort
- Solution: Develop workflow for prioritization of studies to allow stepwise customization and refinement for responding to key questions and issues signaled by human and animal evidence
 - Release of interim products for public comment (IRIS Assessment Plan; Protocol) give opportunities for stakeholder engagement in this stepwise process

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What is mechanistic evidence?

- Data from observational and experimental studies that inform biological or chemical events associated with toxic effects but are not generally considered to be adverse outcomes on their own
 - *In vivo* (cellular, biochemical, molecular)
 - In vitro or ex vivo (human or animal tissues or cells)
 - Non-animal or non-mammalian alternative animal models
 - Big data ('omics or high-throughput assays) and in silico analyses
 - ADME, TK, physico-chemical properties

Importance in human health assessments

- Identify precursor events for apical toxicity endpoints
- Inform susceptibility (species, strain, or sex differences; at-risk populations or lifestages)
- Inform human relevance of animal data (note: the level of analysis will vary depending on the impact of the animal evidence)
- Provide biological plausibility (i.e., to human or animal health effect data when evidence is weak or critical uncertainties are identified)
- Establish mechanistic relationships (or lack thereof) across sets of potentially related endpoints/outcomes to inform the consideration of coherence during evidence integration
- Aid extrapolation (high-to-low dose; short-to-long duration; route-toroute)
- Improve dose-response modeling and characterization of uncertainties

Mechanistic study identification

- Initial broad chemical-specific literature search designed to identify primary studies (i.e., original data sources of health effects)
 - PECO provides screening criteria for human epidemiological and animal toxicology studies that provide apical health effect evidence
 - These studies are evaluated for reporting quality, risk of bias and sensitivity and often undergo full data extraction of study design and results
- "Potentially relevant supplemental information," including mechanistic, is more difficult to define for efficient screening
 - Toxicological significance is not always clear at outset
 - Importantly, being tagged as supplemental information does not indicate exclusion from consideration

Sepa Mechanistic study inventories

- Organizational categories based on characteristics of the available evidence that are grouped based on biological understanding and anticipated assessment uncertainties, e.g., key characteristics, key events, health effects
- Multi-purpose:
 - Produce high-level database snapshot for IRIS Assessment Plan/Protocol, aka Evidence Mapping
 - Facilitate efficient reviews and analyses by subject-matter experts
 - Create inventory for extracting study information and increasing transparency of decision-making

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Organizational Frameworks for Mechanistic Data

Development and support by HERA scientists

- Developmental neurotoxicity (Carlson et al., 2020)
- EBTC-GRADE Workshop Report on evidencebased methods to construct mechanistic frameworks (ALTEX, accepted manuscript)
- Key Characteristics, with UC Berkeley and CalEPA: Organizational concept based on shared characteristics of chemicals that lead to toxic effects
 - Carcinogens (Smith et al., 2016; 2020)
 - Male reproductive toxicants (Arzuaga et al., 2019)
 - Female reproductive toxicants (Luderer et al., 2019)
 - Endocrine disrupting chemicals (La Merrill et al., 2020)
 - Under development: hepatotoxicants, neurotoxicants, cardiovascular toxicants

Potential frameworks to support evaluation of mechanistic data for developmental neurotoxicity outcomes: A symposium report

Laura M. Carlson ^a \approx \boxtimes , Frances A. Champagne ^b, Deborah A. Cory-Slechta ^c, Laura Dishaw ^a, Elaine Faustman ^d, William Mundy ^{e, 1}, Deborah Segal ^f, Christina Sobin ^g, Carol Starkey ^{h, 2}, Michele Taylor ^a, Susan L. Makris ^f, Andrew Kraft ^{f, a}



https://keycharacteristics.org/



Neurotoxicology and Teratology Volume 78, March–April 2020, 106865

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Study list

Downloads

Home / 1-Naphthol (2019) / Literature review / References

Not relevant to PECO (11) Unable to obtain full-text (5) -Supplemental material (497) Cell signaling/function (23) Receptor binding/activity (11) Genotoxicity (30)

References tagged:

Supplemental material > Mechanistic > Genotoxicity

Ames BN, Kammen HO, Yamasaki E 1975

Hair dyes are mutagenic: Identification of a variety of mutagenic ingredients

Proceedings of the National Academy of Sciences 72:2423-2427.

HAWC

We have previously described a sensitive bacterial test for dectecting carcinogens as mutagens. We have previously described a sensitive bacterial test for detecting carcinogens as mutagens. We show here that 89% (150/169) of commercial oxidative-type (hydrogen peroxide) hair dye formulations are mutagenic in this test. Of the 18 components of these hair dyes, nine show various degrees of mutagenicity:2,4diaminoanisole, 4-nitro-o-phenylenediamine, 2-nitro-p-phenylenediamine, 2,5-diaminoanisole, 2-amino-5-nitrophenol, mphenylenediamine, o-phenylenediamine, 2-amino-4-nitrophenol, and 2.5-diaminotoluene. Three hair dve components (pphenylenediamine, 2.5-diaminotuluene, and 2.5-diaminoanisole) become strongly mutagenic after oxidation by H2O2; the mutagenic product of p-phenylenediamine is identified as the known trimer, Bandrowski's base. 2.4-Diaminotoluene, a hair dye component until recently, is also shown to be mutagenic: this compound has been shown to be a carcinogen in rats and is used in large amounts in the polyurethane foam industry. About 20,000,000 people (mostly women) dye their hair in the U.S. and the hazard could be considerable if these chemicals are actually mutagenic and carcinogenic in humans.

Supplemental material > Mechanistic > Genotoxicity

HAWC searches/imports: 1 naphthol supplemental mechanistic HERO Import for tagging

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Distiller

- Forms for initial screening as well as study detail extraction for building inventories
 Currently piloting in vitro and genetic toxicology testing-specific extraction forms
- In Vitro Literature Inventory Genetox Literature Inventory Form FORM STATUS Please select the appropriate option below to indicate the status of the form. FORM STATUS Select an Answer \sim Select an Answer \sim REFERENCE Please select the appropriate option below to indicate the status of the form. Enter an abbreviated citation for this reference: e.g., Smith, 1978, Smith and Jones, 1978 or Smith et al., 1978 (for more than 3 authors). REFERENCE General Data Extraction Instructions Enter an abbreviated citation for this reference: e.g., Smith, 1978, Smith and Jones, 1978 or Smith et al., 1978 (for more than 3 authors). Add one row per result being extracted, including positive and negative controls. You can enter results in the table or click "Add" to open a form for entry. Select a row and click "Clone" to copy informa Specific Question Instructions STUDY TYPE If endpoint is gene mutation, specify locus in text box Animal (in vivo) · Test Conditions: Describe, if needed, any important study details for interpreting the result, such as information on dose groups, duration of exposures, etc. Dose/Concentration: Enter Lowest Effective Dose (LED) or Highest Ineffective Dose (HID) in mg Cr(VI). Human (in vivo) Results: Select "+/-" if results appear equivocal. If dose was also toxic, select result with (T). Cytotoxicity: Describe method used to determine cytotoxicity in the study. If no measure of cytotoxicity was reported, select "not tested." □ In vitro Indicate whether the study reports human (in vivo), animal (in vivo), and/or in vitro genetox data. EXPOSURE INFORMATION Edit Add New Row SUPPLEMENTAL DATA MOA/Mechanistic 11 Chemical Form 1 Dose Level Genetox Exposure Name Chemical Synonym Used by Author ADME/Toxicokinetics No data available in table Showing 0 to 0 of 0 entries Indicate if there are additional supplemental data reported in this study. SPECIES AND CELL INFORMATION **EXCLUSION FACTORS** ON₀ New Row () Yes Primary or Immortalized Species/Cell Name Clear Response No data available in table Are there any clear exclusion factors (predefined by assessment team)? Showing 0 to 0 of 0 entries DATA EXTRACTION GENETOX DATA EXTRACTION ON₀ Add Edit Delete () Yes Exposure Form Species/Cell Form Genotoxicity Evaluated Assay/Endpoints Cytotoxicity Detection Health Effect Clear Response Findings Name Assay/Endpoint Details Method Name 10 Should detailed quantitative data be extracted from this study? No data available in table

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Narrow the focus for mechanistic syntheses

- Focused approach primarily driven by whether uncertainties exist in the human and animal evidence base
- Areas of focus for mechanistic analyses determined by:
 - Key science issues identified during problem formulation
 - Health effects indicated by human and animal evidence
 - The level of potential influence for making hazard ID and doseresponse decisions
 - Known MOAs and pathways of toxicity
- Flexible approach
 - Syntheses can range from a high-level summary to a detailed MOA analysis with mechanistic study evaluations
 - Determined by availability of adequate chemical-specific data



Examples of Focused Key Science Issues for Evaluation

Hexavalent chromium systematic review protocol

- Mutagenic MOA evaluation after oral or inhalation exposure
- Differences in detoxification of Cr(VI) to Cr(III) via oral exposures across species

Methylmercury assessment plan

Accuracy of different biomarkers of human exposure (e.g., hair; cord or maternal blood)

PFAS systematic review protocol

- Toxicokinetic differences across species and sexes
- Human relevance of hepatic effects (e.g., PPARα receptor activation)



Rationale for prioritizing mechanistic outcomes for more in-depth analysis

- All studies informing mechanistic analyses of focused key science issues are considered
- A subset of these may be "prioritized" for further evaluation of a mechanistic event or for study-level evaluations (reporting quality, risk of bias, sensitivity)
 - If the assessment requires a more intensive evaluation to support human and/or animal evidence conclusions (or even a single key event) or
 - If event/MOA/AOP is controversial and/or has conflicting evidence
- Prioritization factors based on overall informativeness to the mechanistic pathway/MOA, for example:
 - Influence on biological plausibility of causal association
 - Exposure design and relevancy to susceptible risk group
 - Sensitivity and specificity of selected model test system
 - Informativeness to key event in a proposed MOA and/or AOP
 - Assays providing evidence for causal linkages between key events

Rationale for prioritizing mechanistic outcomes for more in-depth analysis

- Factors influencing prioritization strategy are clearly described
 - Example: Prioritization decisions for the focused evaluation of a key mechanistic event can be summarized in a table:

	THORICZEG	Deprioritized
Population	Humans	Non-mammalian species
	Experimental animals	Non-human cells in vitro
	 In vitro studies in human primary or immortalized cells derived from liver 	
Exposure	 Humans: Quantified (e.g., levels; duration) oral or inhalation exposure to chemical X 	Injection, dermal exposuresNo specific exposure to chemical
	Animals:	X (e.g., mixtures)
	 Quantified oral (drinking water, gavage, diet), inhalation 	
	 Repeat-dose studies ≥28 days 	
	In vitro: all	
Comparison	 Human and animal studies: Inclusion of a comparison group (e.g., pre- or post-exposure; no exposure; lower exposure level) 	No comparator
	 In vitro studies: untreated controls 	
Outcome	 Examining mechanistic endpoints relevant to interpretations of hepatic health effects in humans 	 Endpoints not relevant to noncancer hepatic toxicity, including genotoxicity tests

Prioritized

Deprioritized

Prioritization of mechanistic studies relevant to hepatic toxicity



Example: Targeted PECO for mutagenic MOA analysis

 Depending on the question and evidence available, some assessments may develop a targeted mechanistic PECO that clearly defines studies prioritized for study-level evaluation of specific mechanistic outcomes that will be highly impactful to assessment decisions

<u>P</u> opulations	Studies in humans and mammals in vivo (including transgenic rodent models); primary human cells in vitro.
<u>E</u> xposures	Exposure to chemical X by inhalation or oral (drinking water, diet, or gavage) routes.
<u>C</u> omparators	Occupational studies: A comparison or referent population exposed to lower levels (or no exposure/exposure below detection limits) of chemical X, or exposure to chemical X for shorter periods of time,
	Animal studies: a concurrent control group exposed to vehicle-only treatment or an untreated control,
<u>O</u> utcomes	Gene mutation (prior to tumorigenesis), micronuclei, and chromosomal aberrations.

Mechanistic PECO for studies measuring gene and chromosomal mutations useful for analyzing a mutagenic MOA using a database rich in genotoxicity studies

Pilot in vitro study evaluation domains

Animal study evaluation domains	Pilot in vitro study evaluation domains							
Reporting quality								
Risk of Bias								
Allocation	N/A							
Observational bias/blinding	Observational bias/blinding							
Confounding/variable control	Variable control							
N/A	Specificity							
Selective reporting	Selective reporting							
Attrition	N/A							
Sensi	tivity							
Chemical characterization and administration	Chemical characterization and administration							
Exposure timing, frequency, and duration	Exposure timing, frequency, and duration							
Endpoint sensitivity and specificity	Endpoint sensitivity							
Results presentation	Results presentation and analysis							



Status and next steps for in vitro study evaluation

- Internal pilot testing to refine domains and descriptions
- In vitro evaluation domains are now in HAWC (first use with chloroform studies)
 - Determine whether in vitro domains need modification before application to other major study types, e.g., ex vivo and 3D tissue model systems, 'omics methods, and other NAMs, as needed
- Developing outcome-specific criteria will be critical
 - Key for enabling evaluation assistance from non-experts
 - Key for adapting existing domain-based study evaluation criteria from human and animal studies to mechanistic outcomes
 - Shareable
- Continuing external engagement (within and outside of EPA)
 - Discussions and collaborations with other groups developing in vitro criteria (e.g., OCSPP; NTP's Report on Carcinogens)
 - EBTC-GRADE Workshop on the development of mechanistic frameworks (June 2019)
 - NASEM Workshops on the systematic review of mechanistic data (2018, 2013) 17

Thank you



IRIS Program Planning

Kris Thayer James Avery Vicki Soto Dahnish Shams

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Automating Data Extraction

Michele M. Taylor US EPA/ORD/CPHEA/CPAD

> HERA BOSC February 4, 2021

The views and opinions expressed here do not reflect official US Environmental Protection Agency policy.



Automating Data Extraction

GOALS

To develop a systematic method that allows for semi-automated extraction of data to increase efficiency and more easily integrate with other data management platforms

WHY?

To increase efficiency and interoperability for more streamlined, usable data.

PROGRESS

- Algorithms have been developed that extract common entities (chemical, dose, species) from animal toxicology studies
- PDFs can now be converted to machine-readable text so that algorithms can mine/extract data

PATH FORWARD

Support automated data extraction for various disciplines including:

- Epidemiology
- Ecotoxicology
- Environmental Fate/Exposure

Interoperable Software Tools



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Children's Health | Prenatal exposure to pollutants and birth outcomes

Materials and Methods

Study subjects. Study subjects are Dominican and African-American women residing in Washington Heights, Central Harlem, and the South Bronx, New York, who delivered at New York Presbyterian Medical Center (NYPMC), Harlem Hospital (HH), or their satellite clinics (Perera et al. 2002; Whyatt et al. 2002); Table 1 presents demographic and exposure characteristics of the population. Ethnicity was self-identified. Women were eligible if they were nonsmokers; were 18-35 years of age; were registered at the obstetrics and gynecology clinics at NYPMC and HH by the 20th week of pregnancy; were free of diabetes, hypertension, or known HIV; and had resided in the area for at least 1 year. The mean gestational age at enrollment was 39.5 weeks. Two hundred ninetyeight women were considered to be fully enrolled in the study; that is, they had been monitored prenatally during the third trimester using a personal air monitor and had delivered, and a maternal and/or umbilical cord blood sample had been collected.

The 214 subjects included in the present analysis are those with adduct measurements in umbilical cord blood samples (in some cases the amount of blood collected was inadequate for the assay), and complete questionnaire and medical record data were used as covariates in the multiregression models. Fully enrolled subjects missing any of these data points (n = 84)were excluded from the analysis. Only nonsmokers were included. Nonsmokers were initially defined as having answered "no" to the question "presently, does a household member

and education was also collected. The questionnaire was based on that used in a prior study of women and newborns and adapted for the New York City population (Perera et al. 1998).

Biologic sample collection and analysis. Maternal blood (30-35 mL) was collected within 1 day postpartum, and umbilical cord blood (30-60 mL) was collected at delivery. Samples were transported to the laboratory immediately. The buffy coat, packed red blood cells, and plasma samples were separated and stored at -70°C. A portion of each sample was shipped to the Centers for Disease Control and Prevention (CDC) for analysis of cotinine (2 mL) and pesticides (10 mL). Plasma cotinine was analyzed by the CDC using high-performance liquid chromatography atmospheric-pressure ionization tandem mass spectrometry as described previously (Bernert et al. 1997, 2000). The limit of detection for cotinine was 0.05 ng/mL.

DNA adducts. BaP-DNA adducts in extracted WBC DNA from maternal and cord blood were analyzed by the HPLC/fluorescence method of Alexandrov et al. (1992), which uses an HPLC method to detect BaP tetromers. This assay is a sensitive and specific method for measuring BaP-DNA adducts in WBCs from individuals exposed to BaP (Bartsch 1996). The method has a coefficient of variation of 12%. Samples from motherchild pairs were run in the same batch.

Information abstracted by the research workers from mothers' and infants' medical records after delivery included date of delivery; gestational age at birth (based on the last menstrual period); infant sex, birth weight, length, head circumference, infant malformations, and Apgar scores; maternal height, prepregnancy weight, and total weight gain; complications of pregnancy and delivery; and medications used during pregnancy.

Measures relevant to birth outcomes.

Statistical analysis. As described above, to exclude active smokers we removed subjects with cotinine levels > 15 ng/mL. Additional analyses were also done after further removing the nine subjects who reported smoking any amount during pregnancy, and the results were materially unchanged. Adducts were used both as a continuous variable and as a dichotomous one. We defined high adducts as > 0.36 adducts/10⁻⁸ nucleotides (the median of the detectable adduct values or the upper 20% percentile). As in prior studies, in the analysis of the relationship between adducts and birth outcomes, cord blood adducts were used as the independent variable (Perera et al. 2000). The maternal and cord plasma concentrations of cotinine were significantly correlated (Spearman's rank, r = 0.887; p < 0.001). Therefore, in the 30 cases where the umbilical cord cotinine levels were not available, the mothers' values were used. High/low cotinine was dichotomized using

Table 1. Demographic and exposure characteristics of the population.^a

All	African American	Dominican
$(n = 214)^2$	(n = 84)	(n = 130)
EPA

Data Downloadable in Several Formats for Increased Interoperability

Text PDF

Toxicology and Applied Pharmacology 208 (2005) 127 - 136 www.elsevier.com/locate/ytaap

Impact of maternal dietary exposure to endocrine-acting chemicals on

progesterone receptor expression in microdissected hypothalamic

medial preoptic areas of rat offspring

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Received 18 December 2004; accepted 2 February 2005 Available online 17 March 2005



Text PDF

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GAPDH or HPRT, and a similar tendency was also noted for PR expression, normalized for the input amount of total RNA. With ERα, SRC-2, GnRH, and CALB, no obvious change in expression was apparent.

- +

Automatic Zoom \$

Gene expression changes due to MXC

Based on the sexually dimorphism or alteration in the gene expression by EE, ER α , ER β , PR, and SRC-1 were selected for gene expression analysis in the MPOA of animals exposed to other EACs.

In males, MXC at 1200 ppm decreased the PR level when normalized for GAPDH expression, and a tendency for decrease was also noted from 24 ppm with this normalization (Fig. 3). A similar tendency for decrease in PR expression (non-significant) was also observed with the other normalization procedures. No apparent expression change in ER α , ER β , or SRC-1 was observed after MXCexposure.

In females, MXC at 1200 ppm increased the PR expression on normalization for the HPRT value and a similar tendency was also noted with normalization for GAPDH (Fig. 4). With $ER\beta$ and SRC-1, a dose-unrelated decrease in expression was observed at 240 ppm, on







56 D

Fig. 4. Gene expression data for the MPOA at PND 10 of female pups exposed maternally to MXC. Data are ratios to control values, expressed as mean \pm SD, and normalized for the input amount of total RNA, or GAPDH or HPRT expression. *Significantly different from the controls (*P < 0.05 by Dunnett's test).

normalization for the input amount of total RNA, and a decreasing tendency at this dose was also noted with normalization for GAPDH expression. ER α did not show any apparent expression change with MXC treatment in females.

Gene expression changes with DINP or GEN

In males, neither DINP nor GEN changed the expression levels of ER α , ER β , PR, or SRC-1 (Fig. 5). In females, expression levels of PR with DINP at 20,000 ppm were decreased when normalized for GAPDH expression and a similar tendency for decrease (non-significant) was also observed on normalization for the HPRT value, no such change/tendency being detected when correction was for the input amount of total RNA (Fig. 6). GEN at 1000 ppm did not cause any apparent expression change in the genes



Import Extracted Data into Data Extraction Software

- Export the machine-extracted data into other software applications where extraction is currently done (now 100% manual), aka "pre-populated" forms
- Our standard process includes a primary extractor and another person to QC.Thus, humans can fill in the blanks and QC the machine-extracted data.
- This creates a workflow where we can onboard and evaluate machine-extracted data as the models are developed

Reference Label(s):									
Add Labels here									
M7 is suidaly assessed recenter that regulater	Cultural Former, and as to This Form. Next Reference	•	or Skin	to block					
nunity by engaging its counter-re-ceptor SIRPα on	Submit Form and go to This Form • Next Reference		or skip	to Next			8		
agocytes and its secreted ligand	PLEASE REVIEW THE FORM FOR COMPLETENESS BEFORE SUBMITTING!!!								
	Reference (short format), e.g., Smith (1978), Smith and Jones (1978) or Smith	et al. (1	978) (fo	or 3 or n	nore a	uthor	s).		
	Evidence Type	Animi	Nas						
	*human for epidemiological data: animal for studies conducted in animals	A11114	and M						



NIST-TAC Challenge Reboot

DRAFT Annotation Guidelines

ANNOTATION INSTRUCTIONS

Each document has 24 types of entities (defined in Table 1) to annotate (see figure 1). Annotation of a document includes assigning entity types to mentions and assigning mentions to groups (defined in Table 2).

Endpoint protein concentration

Figure 1: a sample annotation in

which 'protein concentration' is a mention of entity type

'Endpoint'.

Steps to annotating a PDF document include:

Preparing Article for Annotation:

- Copy the text from the articles' PDF file into a text file using the article id as the name of the text file (e.g., pubmed id).
- 2. Clean the text file by ...TBD
- 3. Ensure the Abstract, Methods, and Results section of the file are clear. If not, add a label to the document indicating the section type.
- 4. Import the text file into your assigned annotation folder (e.g., sysreview/vwalker for Vickie Walker).

Conducting Annotation:

- 1. Annotate all mentions with their respective entity types, see Section Annotating Mentions
- 2. Annotate groups, in the following order, See Section Annotating Groupings
 - 2.1. TreatmentGroups
 - 2.2. DoseGroups
 - 2.3. DoseDurationGroups

2.4. EndpointGroups

2.5. AnimalGroups

ANNOTATING MENTIONS

Table 1. Entity Types

Category	Annotation Tag	Description
ARTICLE	Funding	Text indicating source of funding
	COI	Text indicating conflict of interest; declarations or
		none to report
EXPOSURE	TestArticle	Test article or exposure evaluated
	Vehicle	The solution the test article is in
	TestArticlePurity	Purity of test article
	TestArticleVerification	Text indicating that the test article was confirmed
ANIMAL GROUP	GroupName	If reported, an indicator of a treatment group or
		positive/negative control group (ie DES-10 or
		control or treated).
	GroupSize	The number of animals in a group
	Species	The species names
	Strain	The strain names
	Sex	Gender of the animal group(s)
DOSE GROUP	Dose	Dose
	DoseUnits	Units of dose
	DoseDuration	Duration of treatment (dose)
	DoseDurationUnits	Units of dose duration
	DoseRoute	Route of administration
	AgeAtDose	Age when dose is given
	AgeUnits	Units used for animal ages
	AgeAtFirstDose	Age at which first dose is given
	AgeAtLastDose	Age at which last dose is given
ENDPOINT	Endpoint	Endpoint evaluated
	EndpointUnitOfMeasure	Units of measured endpoint
	EndpointMethod	Text describing the method used to assess the
		outcome
	AgeAtEndpoint	Age at assessment

General Guidelines for Annotating Mentions:

10

Training Sets for Algorithm Building

Quick Match	match whole word 🗹 ignore punctuation 🗹	ignore case	urrences	788325	Entities	Grou	ıps	Relations
is known about the comb	ned toxicity of DBP and BaP.	In the current study, m	ale		expo	osure (0)		
Sprague Dawley rats were	subchronically exposed to single	doses of DBP			+ chemical	→ dos	se	
(250mg/kg), single doses	chemical of BaP (5mg/kg) and com	bined doses of DBP and	<mark>chemical</mark> BaP.		Name of new Start Entity:	w relation	n type End Entit	y:
Significant adverse effect	s were observed on the reproduct	ve system, including			chemical	•	dose	
decreased sperm count, i	ncreased production of abnormal	sperm, changes in serum			Creat	e New R	elation Ty	/pe
testosterone levels and in	egular arrangements of the semir	niferous epithelium.						
Biochemical analyses sho	wed that the activities of superoxi	de dismutase and	Ma	nual Annotation Leveraging	<mark>g Ontologie</mark>	s		
glutathione peroxidase d	ecreased after exposure to these E	Ds. Therefore, our						
	chemical					-		
data suggest that exposu	e to DBP and BaP, in eithe	r separate or combined			Collapse	411	Exp	and All
doses, can affect the repr	oductive system of male rats adve	rsely via oxidative				Toggle	Spans	
stress-related mechanism	s. No significant additive effect wa	as observed after			S	ave and	Proceed	
These	e results indicate that exposure to	mixtures of EDs have			Va	lidate An	notation	5

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Automating Data Extraction

NEXT STEPS:

- Develop and disseminate guidance on data extraction which ties into ontology (Michelle Angrish will discuss next)
- Collaborate Across Disciplines (Exposure/Ecotox/Epi) to Develop Fit for Purpose Algorithms
- Develop Training Sets (Manually Annotating)
- Put Quality Controls Checks in Place



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- Elisa Aiassa

Ben Ling

•

 This work will be expanded into other disciplines (ECOTOX) and includes extensive collaboration across CSS and HERA as well as other agencies/offices conducting assessments



Semantic Ontology Mapping

Michelle Angrish US EPA/ORD/CPHEA/CPAD

> HERA BOSC February 4, 2021

The views and opinions expressed here do not reflect official US Environmental Protection Agency policy.



Approach for Semantic Ontology Mapping

• Problem:

- Information retrieval and knowledge organization is a semantic and conceptual challenge because the formal record of scientific research is almost exclusively a written study report
 Solution:
 - Apply ontologies to increase the efficiency of information retrieval and prioritization
 - Expand controlled vocabulary to normalize information extracted using systematic review methodology
 - Standardized data extraction formats for enhanced interoperability between systematic review tools and databases
 - Develop knowledge organization systems to enhance data curation and evidence integration frameworks



Information Retrieval Challenge

- SR methods provide a mechanism for ensuring a chemical assessment fully and transparently uses all relevant evidence.
- The extent that this evidence can be retrieved is heavily constrained by current approaches to storing and cataloguing scientific knowledge.



The formal record of scientific research is almost always a written study report



- Reports stored in siloed databases that:
- •Cover different portion of total literature
- •Have unique data schemas and search interfaces



Searches return a large proportion of false positives that must be manually evaluated.

- Information retrieval is a lengthy process that may still exclude relevant records
 - The content of a document is represented by a number of key words, plus the words in the titles and abstracts.
 - Only information known by researchers and coded as conceptually related in a database is retrieved.



Semantic Factor

Semantic Factor

- Semantic because meaning is a function of the relationship between words and the context in which they were presented so even if a person uses a word incorrectly the correct meaning is still interpreted.
- If an information retrieval strategy does not include all the words and their related concepts (in a database specific manner) then relevant documents will be overlooked.

Table 1. Demonstration of how variation in language used by study authors in title, abstract, and author keywords fields affects search results in PubMed. Database syntax is used to ensure the phrase entered is the exact one being searched for. Date of searches: 15 July 2020.

PubMed Query	Results
"PAHs" [Title/Abstract] OR "PAHs" [Other Term]	15,912
"PAH" [Title/Abstract] OR "PAH" [Other Term]	22,605
"polycyclic aromatic hydrocarbon" [Title/Abstract] OR	4,545
"polycyclic aromatic hydrocarbon" [Other Term]	
"aromatic polycyclic hydrocarbons" [Title/Abstract] OR	59
"aromatic polycyclic hydrocarbons" [Other Term]	
"polycyclic aromatic hydrocarbons" [Title/Abstract] OR	19,311
"polycyclic aromatic hydrocarbons" [Other Term]	

Whaley et. al., EHP, 2020



Conceptual Factor

Conceptual Factor

- For any topic or domain of interest there is an expansive network of related concepts and sub-concepts that may also be relevant to a SR or SEM.
- Having a complete map of the relationships among these concepts is necessary if the full body of assessment relevant literature is to be retrieved.





The Solution: Knowledge Organization Systems

- Knowledge organization system (KOS) for environmental health science information.
- Controlled Vocabulary (CV) list of words and phrases (concepts) used to tag content in a database to make that content retrievable via navigation or search (Pomerantz, 2015)
- Ontologies representation of the properties of relations between concepts
- Useful for:
 - Information retrieval
 - Normalizing extracted data from written text
 - Developing standardized data extraction formats
 - Facilitating software application interoperability
 - Data integration

Efficiency in the Chemical Assessment Workflow





Ontologies for Information Retrieval*

Search Tree Recent Searches

Query Expansion

- Litsearches may only capture 50-80% of relevant studies
- Ontology tools can expand the search concepts

sodium-iodide symporter MeSH Supplementary Concept Data 2020

Go sodium-iodide symporter Details Concepts Release: 2019AA V Searching Search Type: Word **MeSH Supplementary** sodium-iodide symporter Searching Source: All Sources C070626 Unique ID PubMed.gov for **RDF Unique Identifier** http://id.nlm.nih.gov/mesh/C070626 AIR PubMed.gov for ALT Entry Term(s) NIS protein "sodium-iodide AOD NIS protein, human "sodium-iodide NIS protein, mouse AOT symporter" based on Na(+),I(-)-cotransporter symporter" using Nis protein, rat Search Results (11) SLC5A5 protein, human 11 MeSH concepts C0142963 sodium-iodide symporter SIc5a5 protein, mouse UMLS C1153375 sodium:iodide symporter activity Slc5a5 protein, rat returns ~1475 articles C1420204 SLC5A5 gene sodium iodide symporter C1504824 SLC5A5 protein, human sodium-iodide cotransporter C1705808 SLC5A5 wt Allele solute carrier family 5 (sodium iodide symporter), member 5 protein, human C4727133 SLC5A5 Positive solute carrier family 5 (sodium iodide symporter), member 5 protein, mouse C1882146 Oncolytic Measles Virus Encoding Thyroida solute carrier family 5 (sodium iodide symporter), member 5 protein, rat C4331494 VSV-hIFNbeta-NIS _____ thyroid iodide transporter b.

*Work done in collaboration with Endocrine Disruptor Screening program in EPA/OCSPP



Ontologies for Information Retrieval and Prioritization*

Query Expansion*

– Can return very large number of studies (1000K to >>22K studies for the NIS example)

• Topic Modeling and Clustering via semantic concepts

elect Parameters — Paste Parameters 	ues in each group for all specified groups. For example, specifying endpoint: Sodium-Iodide Sympi 1 Sodium-Iodide Symporter AND either Mammal OR Human.
iource ✔ Baker ✔ Kiros	Article Type Non-Research 🧭 Research 🗭 Systematic Review
vidence Stream (January 2020)	Key MIE or Target Mechanism
Animal ③ Human ③ In Vitro ③ ♀. Choose one or more options	Sadium-ladide Symporter (NIS) 🔘 🔍 Choose one or more options
ividence Stream (Animal/In Vitro)	
Q, Choose one or more options	
Tag Heatmap	
Advanced Options	
Tag Heatmap	

*Work done in collaboration with Endocrine Disruptor Screening program in EPA/OCSPP



- Graphical view of cluster concepts
- Papers clustered via semantic concepts and annotated with MeSH Terms or named entities
- •Built & filtered from cluster concepts
- Interactive component allows user to select concepts to further filter the clusters



Controlled Vocabularies for Templates

Outline for the NIEHS & EPA Retrospective and Prospective Coordination on Annotation Guidelines for Toxicology

FORM	INSTRUCTIONS
Animal Species Name	Create a name for to uniquely describe this animal group (used to identify
Species Select an Answer	Select the species from the dropdown menu. If a non-mammalian species
Strain	Enter the strain used. Use "not reported" if appropriate.
Sex Select an Answer	Enter the sex evaluated for this subform. If the sexes will be extracted sep males and females are presented the option "both" is used and sex-specifi the studies most informative for hazard would be fully extracted in HAW0

Animal Literature Inventory							
1 FORM STATUS							
Please select the appropriate option below to indicate the status of the form.							
Select an Answer 🗸 🗸							
 REFERENCE Enter an abbreviated citation for this reference: e.g., Smith, 1978, Smith and Jones, 1978 or S 	Smith et a	al., 1978 (for more than 3 a	uthors).				
3. ANIMAL SPECIES							
Enter details on the animal species, strain and sex below. If multiple species and/or sexes are	evaluate	d seperately, create new lir	nes as needed.				
Add Edit Delete Clone New Row							Search:
Animal Species Name		11	Species		^{↓↑} Strain	11	Sex
			No data available in table				
Showing 0 to 0 of 0 entries							
4. ANIMAL EXPOSURE		Cancer					_
Enter details on the study design and chemical exposure below. If multiple study designs wer	e · ci	Cancer					
Add Edit Delete Clone New Row	in Sr	Cardiovascular		ture and Manag	gement.		rch:
Animal Exposure Name	-	Dermal					ation
Showing 0 to 0 of 0 entries		Developmental			~	or Skip to Next 💼	
5. HEALTH OUTCOMES Enter details on the medite outcomes and used below. If multiple health outcomes upon and		Endocrine					
Add Edit D 3 Clone New Row	F	Exocrine			INSTRUCTIONS		rch:
		Controintenting					
Health Outcome the	н	Gastrointestinai			Create a name for to ur	niquely describe this health	effect
Showing 0 to 0 of 0 entries		Hematologic					
6. ANIMAL DATA EXTRACTION		Hepatic					
Combine data from the subforms above and extract the NOEL/LOAEL. Use as many lines as		Immunic					
Add Edit Delete Clone New Row	H		-		Select a health outcom	e category evaluated from Cancer.	the drorch:
		Select an Answer	~			cancer.	
	Eva	aluated Endpoints			List ALL endpoints asse	essed for health outcome s	ystem a
					Example for reproduct	ive health outcomes: prepi	utial sen
					weight, seminal vesicle	s weight	iciai sep
				//	Example for neurologic	al health outcomes: autisn	nspectr
					Calibrated Severity Sco	ие	

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Controlled Vocabularies for Data Interoperability

Environmental Health Vocabulary (EHV) - a recommended terminology for outcomes/endpoints - October 2020

Updated on October 5, 2020, this version contains the list of Preferred Terms for the key fields Endpoint, Edit Delete System, Organ, Effect and Effect Subtype in HAWC. Start with the ReadMe tab for additional instructions.

	Endpoint/Adverse outcom	le*				940	Load ID	Demonstrating using
	Selected term: 940 Total B	ilirubin (TBIL	U ×				۵	vocabulary digitized
	Use controlled vocabula	ary	Organ/Tissue/Region	Effe	ect	Effect subtype		by mapping to Unified Medical
	Hepatic		Liver	He	epatobiliary Component	Clinical Chemistry		Language Syntax
	Selected term: 888 Hepati	c × ary	Selected term: 889 Liver ×	Sel 934	ected term: Hepatobiliary Component × Use controlled vocabulary	Selected term: 935 Clinical Chemistry	bulary	(UMLS) • Critical for interfacing with
					Total Biliru Total Bilirubin			other databases and tools!
Here we w	ant to define	Endpoi	nt/Adverse outcome*		Total Bilirubin (TBILI))	Or w	e can select to use
custom tex	t, but it auto	Total B	ilirubin (TBILI) custom text		Total Bilirubin (TBILI)) (48d)	the E	EHV.
populates	with existing	🗌 Use	controlled vocabulary		Total Bilirubin (TBILI)), Blood		
text	-				Total Bilirubin (TBILI)), Recovery		
					Total Bilirubin (TBILI)), Recovery, Serum		

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Expert Curation of Controlled Vocabularies

	Environmental Hea recommended terr outcomes/endpoin	alth Vocabulary (EHV) - a Updated on Oct ninology for <u>System, Organ, E</u> ts - October 2020	ober 5, 2020, this version contains the list of Pref ffect and Effect Subtype in HAWC. Start with the R	erred Terms for the key fields <u>Endpoint</u> , Edit Delete eadMe tab for additional instructions.
Synaptics results Synaptics Syn	Synaptica [®] KMS 9.0.5 Hierarchy Search Results Effect + Effect Subtype + Endpoint + Cardiovascular 3122 + Cardiovascular 3122 + Cardiovascular 3122 + Dermal 3144 + Developmental 1303 + Endocrine 583 + Gastrointestinal 1193 + Hematologic 1001 + Hepatic 888 + Liver 889 + Abnormal Appearance 924 + Cholesterol 945 + Enlarged Organ 954 + Enlarged Organ 954 + Enzyme Activity 969 + Hemostasis 914 + Hepatobiliary Component 934 + Hepatobiliary Function 942 + Histopathology 957 + Hormone 960 + Inflammation 963 + Lipid Metabolism 890 + Clinical Chemistry 891 +	Add Terms Clinical Chemistry 891 (Effect Subtype) Clinical Chemistry 891 Save Refresh Copy Categories History Subsume Deactivate Delete Restore *Term Name: Clinical Chemistry * *ID: 891 * Definition:	Synaptica Synaptica KOS for expert curation of EHV Nad exploration of relationships	It Visualize Type: Radial Map ~ Language: English ~ thways Node Style: Boxes Dots wery Low Density Lipopr Phospholipid 904 y Lipopr y Lipopr DGAT-1 Activity 805 very Low Density Lipopr Clinical Chemistry 891 Triglycerides (TRIG) 808 Triglycerides (TRIG) 808 Phospholipid 904 y Lipopr Very Low Density Lipopr DGAT-1 Activity 805 Triglycerides (TRIG) 808 Phospholipid 904 y Lipopr Very Low Density Lipopr Distrigue Production DGAT-1 Activity 805 Triglycerides (TRIG) 808 Very Low Density Lipopr Drat-2 Activity 806 Triglycerides (TRIG) 808 Hepatic Lipa Very Low Density Lipopr

Controlled Vocabularies for Data Management

						no apparent treatment-related effect treatment-related increase treatment related decrease
Endpoint	Study	Animal Description	Route	Exposure Duration		 treatment-related decrease
Alanine Aminotransferase (ALT), Blood	Haskell Laboratory 1995	Rat, Crl:Cd Br (♀)	inhalation - vapor	2 yr (6 hr/d, 5 d/wk)	+++-	•
		Rat, Crl:Cd Br (占)	inhalation - vapor	2 yr (6 hr/d, 5 d/wk)	•	_
Albumin (A), Blood	Haskell Laboratory 1995	Rat, Crl:Cd Br (♀)	inhalation - vapor	2 yr (6 hr/d, 5 d/wk)	+++-	•
		Rat, Crl:Cd Br (占)	inhalation - vapor	2 yr (6 hr/d, 5 d/wk)	+	•
Alkaline Phosphatase (ALP), Blood	Haskell Laboratory 1995	Rat, Crl:Cd Br (♀)	inhalation - vapor	2 yr (6 hr/d, 5 d/wk)	+	•
	Malley et al. 1996	Rat, Crl:Cd Br (♀)	inhalation - vapor	90 d (6 hr/d, 5 d/wk)	•••	• 🔺
	Haskell Laboratory 1995	Rat, Crl:Cd Br (순)	inhalation - vapor	2 yr (6 hr/d, 5 d/wk)	+	•
Aspartate Aminotransferase (AST), Blood	Haskell Laboratory 1995	Rat, Crl:Cd Br (Q)	inhalation - vapor	2 yr (6 hr/d, 5 d/wk)	•••••	•
		Rat, Crl:Cd Br (占)	inhalation - vapor	2 yr (8 hr/d, 5 d/wk)	+•	_
Cholesterol (CHOL), Total, Blood	Haskell Laboratory 1995	Rat, Crl:Cd Br (Q)	inhalation - vapor	2 yr (8 hr/d, 5 d/wk)	+	•
		Rat, Crl:Cd Br (ਟ)	inhalation - vapor	2 yr (6 hr/d, 5 d/wk)	+	•
Focal Liver Necrosis	Malley et al. 1998	Rat, Crl:Cd Br (占)	inhalation - vapor	2 yr (8 hr/d, 5 d/wk)	+	A
Liver Histopathology	Malley et al. 1998	Rat, Crl:Cd Br (Q)	inhalation - vapor	2 yr (6 hr/d, 5 d/wk)	+	•
Liver Weight, Absolute	BioDynamics 1991	P0 Rabbit, New Zealand (♀)	inhalation - vapor	GD 6-18 (6 hr/d)	• • • • • • • • • • • • • • • • • • •	• •
	Malley et al. 1996	Mouse, Crl:CD-1(ICR)BR (Q)	inhalation - vapor	90 d (8 hr/d, 5 d/wk)		• •
		Mouse, Crl:CD-1(ICR)BR (ਟ)	inhalation - vapor	90 d (6 hr/d, 5 d/wk)	• • • • • • • • • • • • • • • • • • •	• •
		Rat, Crl:Cd Br (Q)	inhalation - vapor	90 d (8 hr/d, 5 d/wk)	· · · · · · · · · · · · · · · · · · ·	• •
	Malley et al. 1998	Rat, Crl:Cd Br (Q)	inhalation - vapor	2 yr (6 hr/d, 5 d/wk)	+• 🔺	A
	Malley et al. 1996	Rat, Crl:Cd Br (占)	inhalation - vapor	90 d (6 hr/d, 5 d/wk)	· • • • • • • • • • • • • • • • • • • •	• •
	Malley et al. 1998	Rat, Crl:Cd Br (占)	inhalation - vapor	2 yr (6 hr/d, 5 d/wk)	•	
Liver Weight, Relative	BioDynamics 1991	P0 Rabbit, New Zealand (♀)	inhalation - vapor	GD 6-18 (6 hr/d)		• • •
	Malley et al. 1996	Mouse, Crl:CD-1(ICR)BR (Q)	inhalation - vapor	90 d (6 hr/d, 5 d/wk)	• • • • • • • • • • • • • • • • • • •	• •
		Mouse, Crl:CD-1(ICR)BR (ਟ)	inhalation - vapor	90 d (6 hr/d, 5 d/wk)		• •
		Rat, Crl:Cd Br (Q)	inhalation - vapor	90 d (6 hr/d, 5 d/wk)	· · · · · · · · · · · · · · · · · · ·	
		Rat, Crl:Cd Br (순)	inhalation - vapor	90 d (6 hr/d, 5 d/wk)		• •
Total Bilirubin (TBILI), Blood	Haskell Laboratory 1995	Rat, Crl:Cd Br (Q)	inhalation - vapor	2 yr (6 hr/d, 5 d/wk)	+	
		Rat, Crl:Cd Br (년)	inhalation - vapor	2 yr (8 hr/d, 5 d/wk)	+	
Triglycerides (TRIG), Blood	Haskell Laboratory 1995	Rat, Crl:Cd Br (♀)	inhalation - vapor	2 yr (6 hr/d, 5 d/wk)	••••	400,000, 450,000, 000,000, 000,000

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Demonstrating use of the Environmental Health Vocabulary (EHV) in the EPA Health Assessment Workplace Collaborative (HAWC) for data management and integration.

- e.g., data grouped by endpoint
- HAWC facilitates transparency and data accessibility

Controlled Vocabularies for Data Interoperability

Explore by

endpoint name

	(2020) / Endpoints / D	loassay enupoint neathap	Summary											
Visual Data C	Customize											Dashboar	d selection: system vs. test subject	× :
					system vs. test subje	ct							Study Citation	00
		Mouse		Ra	bbit			Rat					I BioDynamics 1991	۲
[Combined	Female	Male	Combined	Female	Combined		Female		Male	Grand	Total		
Cardiovascular													2 Covance 2000	٠
Dermal													2 Dupont, 1991, 5380491	۲
Developmental													Z ECHA, 1995, 6299219	۲
Endocrine													2 ECHA, 2001, 6299228	۲
Gastrointestinal													2 ECHA, 2007, 5701160	۲
Hematologic													2 ECHA 2007 6299223	۲
Hematopoletic		4	E		1	2		10		45				
Immune		4	2		1	2		10		15	4	D	2 ECHA, 2011, 5701148	۰.
⊂ Multi-System													Experiment Type	0 6
Multi-system														
Musculoskeletal													S Developmental	
Nervous													6 Reproductive	
Ocular													18 Short-term (1-30 days)	
Repiratory													16 Subchronic (30-90 days)	
Reproductive														
Respiratory													Generation	 Ø
Urinary													I First-generation (F1)	
Whole Body													24 N/A (not apportional study)	
[System]													34 N/A (not generational-study)	
Grand Total		4	5		1	2		18		15	4	5	10 Parent-generation (P0)	
					Species & Sex							ର୍ 🛓	Endpoint Name	0 0
Study Citation			Experiment Name			Animal Group Name		System	Organ	Effect	Endpoint Name	<u> </u>		
													 0 Liver Histopathology, Recover 	y î
Ladics et al. 2008			gavage rats 8:2 Fluoro	telomer alcohol		Male Sprague-Dawley Ra	ıt	Hepatic	Liver	Organ	Liver Weight,		O Liver Weight, Absolute	
										Weight	Relative		C. A. Lincollisisht Absolute Deep	_
													7 15 Liver Weight Polative	
Ladics et al. 2008			gavage rats 8:2 Fluoro	telomer alcohol		Female Sprague-Dawley	Rat	Hepatic	Liver	Organ	Liver Weight,		45 Liver Weight, Relative	
										Weight	Relative		C V Elver Weight, Relative to Brain	
													 0 Liver Weight, Relative to Brain 	۱,
Saillenfait et al. 199	97		Developmental Oral R	at		P0 Female Sprague Dawl	ley Rat	Hepatic	Liver	Organ	Liver Weight,		Recovery	
										Weight	Relative		 0 Liver Weight, Relative, Recov 	ery
							_							
Saillenfait et al. 199	97		Developmental Oral R	at		F1 Male/Female Sprague	Dawley	Hepatic	Liver	Organ	Liver Weight,			
						rtat				vveight	Relative			

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Semantic Ontology Mapping for Automated Workflows

Information Retrieval and Prioritization



Ontologies for query expansion, study retrieval, and clustering using semantic concepts

Study Screening and Tagging

HDistillerSR

SEPA United States Environmental Protection

Health & Environmental Research Online (HERO)

Data Extraction

Publication Information

Refid 469756

Title

Abstract

Alterations of Cytokines and MAPK Signaling Pathways are Related to the Immunotoxic Effect of Perfluorononanoic Acid

The developmental toxicity of perfluorohexane sulfonate (PFHxS) is largely unknown despite widespread environmental contamination and presence in human

IK. To thoroughly investigate PFHxS toxicity in developing rats and to mimic a realistic human exposure situation, we examined a low dose close to huma relevant PFHxS exposure, and combined the dose-response studies of PFHxS with a fixed dose of twelve environmentally relevant endocrine disrupting chemicals (EDmix). Two reproductive toxicity studies in time-mated Wistar rats exposed throughout a were performed. Study 1 included control, two dose of PFHxS and two doses of PFHxS+EDmix (n = 5-7). Study 2 included control, 0.05, 5 or 25 mg/kg body weight/day PFHxS, EDmix-only, 0.05, 5 or 25 mg PFHxS/kg plus EDmix (n = 13-20).PFHxS caused no overt toxicity in dams and offspring but decreased ma combination with the EDmix. A marked effect on T4 levels was seen in both dams and offspring, with significant r enic effects in male offspring, manifested as slight o PFHxS can induce developmental toxicity and in addition results of the co-exposure studies indicate EDmix potentiate the effect of each other on various endpoints, despite their different modes of action. Hence, risk assessment mixture toxicity and background exposures are not taken into account.

Annotation tools for data extraction from study pdfs

Term Mapping and Curation



Semantic concept matching for data normalization

Standard Data Extraction Formats

FORM STATUS Frace-scient the assessments antipulation to	infinite the status of the trem					
Select an Annuer V						
REFERENCE						
Enter an abbreviated citation for this reference	er e.g., Smith, 1978, Smith and Jones, 1978 or 5	Selth et al., 1978 (for more than 3 author	*5).			
ANMALSPECIES						
Enter details on the animal species, strain and	ses below. If multiple species and/or severs are	evaluated separately, create new lines a	is needed.			
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ANNAL DYDORE Dere deals in the tably dags and deals in Marine 10, Denie Care Werk Animal Dynamer Niewe Dering to a the table and the original Dere deals in the original anime evolution Animal Dyname Kares	i oosave belou. Finaltijde stude doegen eer 	e exiluted, create non-lines as needed II Budy Conign No Noted, create non-lines as needed II (Nearth Contains 6 System No	ii Broke data available in table	II One Levels	Describits	Sandy ^[1] Dee Duration Sandy
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Structured formats for data interoperability

Data Integration, Display, and Download d u **HEALTH ASSES** Aetabolic Endpoint Details C Joptices Contraction of the second seco



Semantic Ontology Mapping Moving Forward

- Expand ontology query expansion and topic clustering tool capability
- Standardize data extraction formats and normalize content within those fields across EPA
- Expand EHV to other domains
 - -exposure
 - mechanistic
 - methods
 - others
- Map EHV to other ontologies
 - Using KOS for
 - advanced queries
 - better understanding of the data
 - integration with other databases (i.e. EPA Comptox Chemicals Dashboard)

Internal EPA Collaborators to Achieve this Vision





External Collaborations and Partnerships





Application of Systematic Evidence Map Methods to Characterize Available Evidence for PFAS

Laura Carlson US EPA/ORD/CPHEA/HEEAD

HERA BOSC

February 4, 2021

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³Center for Computational Toxicology and Exposure (CCTE)

⁴ICF,VA, USA



Systematic Evidence Maps (SEM)

- Pre-decisional analysis that uses systematic review methods to compile and summarize evidence but does not reach assessment hazard or toxicity value conclusions
 - Front end compilation of evidence
 - Publishable in journals
- Used for:
 - Prioritization
 - Problem formulation and scoping
 - Identifying data gaps
 - Need for assessment update?
- EPA IRIS Program began creating SEMs in 2019, now becoming a routine analysis for HERA products such as IRIS, PPRTV, and other fit for purpose assessment products



Systematic Evidence Maps (SEM)

- Rapid preparation weeks to a few months in most cases with experienced teams and use of specialized software
- Tailored to meet decision making needs
 - Include summarization of study designs and results, can also include study evaluation, identification of studies to possibly consider for dose response analysis
- Use of standardized template format reduces time to prepare and review
- Highly visual with interactive displays
- Structured data entry that is made available to the public
 - Enhances transparency and re-use across assessment groups, including by other Federal and State programs
- Results can be disseminated in reports, interactive data interfaces, and EPA Comp Tox Chemicals Dashboard (<u>https://comptox.epa.gov/dashboard</u>)



Per- and Polyfluoroalkyl Substances (PFAS) I 50 SEM

- One component of the EPA PFAS Action Plan involves the use of new approach methods to help fill information gaps. This ongoing work involves tiered toxicity testing of a structurally diverse landscape of PFAS using a suite of in vitro toxicity and toxicokinetic assays
- One goal is to use existing in vivo toxicity data to infer (read-across) missing information for a similar PFAS target (similarity starting point is "structural similarity")
- PFAS "150" SEM conducted to help identify in vivo data





- PFAS 150 Systematic Evidence Map (SEM)
 - Started September 2019; Public report in FY2021
- Experience with 150 PFAS was encouraging, so we are expanding the work to include:
 - Characterization of an additional 430 PFAS (2021)
 - Expanded list of ~9,000 PFAS substances and structures (2022)
- Not included are PFAS under assessment by EPA
 - PFBS, GenX chemicals, PFOS, PFOA, PFBA, PFHxA, PFHxS, PFNA, PFDA



Methods

- Use information from the EPA CompTox Chemicals Dashboard to create higher throughput methods to search for hundreds of chemicals at a time (new semi-automated processes)
- Search journal databases (PubMed, WoS, Toxline (pre-2019)) and grey literature from Chemicals Dashboard ToxVal database and manual searches of ECHA for additional studies
- Create interactive literature inventories to show landscape of studies
- Conduct full data extraction and study evaluation on animal toxicology studies of repeat dose, developmental or reproductive design
- Publish report and make animal toxicity information accessible via EPA PFAS Dashboard
- A related analysis is focusing on the epidemiological data (journal article)



Use of Machine-Learning to Screen at Title and Abstract Level

- Used SWIFT Active (about 5-10 seconds per title/abstract)
- Machine-learning can decrease the screening burden by 40-60%

3572056: Nrf2 Signaling Elicits a Neuroprotective Role Against PFOS-mediated Oxidative Damage and Apoptosis Sun, P., Nie, X., Chen, X.; Neurochemical Research; Pg2446-2459; 2018

Perfluorooctanesulfonate (PFOS) may cause neurotoxicity through the initiation of oxidative stress. In the current study, we investigated the role of anti-oxidant nuclear factor erythroid 2-related factor 2 (Nrf2) pathway in PFOS-induced neurotoxicity. We found that human neuroblastoma SH-SY5Y cells exhibited significant apoptotic cell death following PFOS exposure, and this process was accompanied with apparent accumulation of reactive oxidative species (ROS). In addition, we revealed that PFOS exposure caused marked activation of Nrf2 pathway and the expression of Nrf2 transcription target heme oxygenase-1. We further found that pre-treatment with ROS scavenger N-acetyl-L-cysteine (NAC) dramatically ameliorated PFOS-induced ROS production and Nrf2 signaling. In keeping with these findings, western blot and Cell Counter Kit-8 analyses revealed that pre-incubation with NAC suppressed PFOS-induced expression of pro-apoptotic proteins and impairment of neuronal viability. Moreover, antagonizing Nrf2 pathway with Nrf2 inhibitor brusatol resulted in increased ROS production and enhanced PFOS-induced expression of apoptosis related proteins. Finally, we showed that PFOS exposure altered mitochondrial transmembrane potential and disrupted normal mitochondrial morphology in SH-SY5Y cells. Whereas treatment with NAC ameliorated PFOS-induced mitochondrial disorders, co-incubation with brusatol augmented PFOS-induced mitochondrial deficits, consequently contributing to neuronal apoptosis. These results manifest that Nrf2 pathway a protective role in PFOS-induced neurotoxicity, providing new insights into the prevention and treatment of PFOS-related toxicities.

Include/Exclude Question	
Include this reference?* Ves, include the reference (it's PECO or supplemental material) No, exclude the reference	Instructions + ×
Main	Human: Any population festage (occupational or general population, including children and other
Supplemental Material Tags	Animal: Nonhuman mammalian animal species (whole organism) of any lifestage (including preconception, in utero, lactation, peripubertal, and adult stages). Screener note: Mechanistic information including in-vitro assays will be tagged as supplemental
what type of supplemental content in vitro/ex vivo/in silico studies	material E
Non-oral or non-inhalation route of administration ADME and toxicokinetic Exposure characteristics (no health outcome assessment) Mixture studies (only use for experimental studies)	Relevant forms: All PFAS chemicals. Many common names and synonyms should appear as keyword green highlighting, but also include no abstract studies where the title mentions PFAS (or other words such as perfluorinated) but does not mention specific chemicals.
/e and Next	Human: Any exposule to PFAS via the oral and inhalation routes. Studies will also be included if biomarkers of PFAS exposure are evaluated (e.g. measured PFAS in tissues or bodily fluids) but the exposure route is unclear or reflects multiple routes. Other exposure routes, including dermal will be tracked during title and abstract screening and tagged as "potentially relevant supplemental

information."

Animal: Any exposure to PFAS (including mixtures containing PFAS) via the oral and inhalation routes. Studies involving exposures to mixtures will be included only if they include an arm with exposure to a PFAS alone. Other exposure routes, including dermal or injection, will be tracked during title and abstract screening and tagged as "potentially relevant supplemental information."



*⇔***EPA**

PFAS I 50 SEM Screening Results

EPA

PFAS I 50 SEM Literature Inventory: Animal Studies

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ReadMe Animal Studies Human Studies Toxicological Studies Examining Exposure to PFAS by Study Design and Health System Heat Map References **a** ^ subchronic 3M (1999) acute short-term chronic Ø Anand et al. (2012) not not rat mouse doa guinea pig hamster rabbit rat mouse rat mouse rat mouse reported reported Apollo Scientific Ltd. (2019) (ECHA Summ. 0 2 Cancer \wedge Bodin et al. (2016) 0 3 4 10 2 2 Cardiovascular 6 0 Bomhard and Loser (1983) 1 2 2 Dermal 0 Case et al. (2001) Developmental 0 Covance Laboratoroes (2000) 11 2 Endocrine 7 Ø DuPont (1990a) \sim 1 Exocrine 7 5 1 **Chemicals Evaluated - by Name** Gastrointestinal 7 Hematologic 12 10 2 2 1-Butanesulfonic acid. 1.1.2.2.3.3.. 1 \wedge 16 9 Hepatic 8 1 1 6 2 2 1H,1H,2H-Perfluorocyclopentane 6 4 12 З 9 1 2 Immune 1H.1H.5H-Perfluoropentanol 1 Lymphatic 1 2-Chloro-1.1.1.2-tetrafluoroethane Metabolic 3 3 1 1 3-Methoxyperfluoro(2-methylpent. 3 Musculoskeletal/Connect. 7 3 V 5 3.3.4.4.5.5.6.6.6-Nonafluorohexene 10 Nervous 6 2 7 2 2 Not reported (but NOAEL. 3 3 Chemicals Evaluated - by CASRN 4 Ocular 3 9 2 12 76-05-1 Renal \wedge 307-35-7 1 < > 2 335-27-3 Notes: Column totals, row totals, and Grand Totals indicate total numbers of distinct references. Some ECHA studies sources may be counted as multiple references in these counts, based on how data 335-99-9 2 were reported in the dossier. Care was taken during categorization and extraction to ensure that endpoints were not repeated from overlapping ECHA summaries. 338-83-0 1 \sim Study Details Chemicals Evaluated - by DTXSID DTXSID0036926 2 ^ Health System Study Design Route Sex Short Citation Species Cancer Haskell Laboratories (1995) chronic inhalation rat both download underlying data Malley et al. (1998) Cardiovascular DuPont (1992b) acute inhalation rat male DuPont (1992d) DTXSID1074915 dog male Unnamed Report (1992b) (ECHA Summary) DTXSID2044397 DuPont (1994) DTXSID3038939 not reported

~35 PFAS

~130 studies

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PFAS 150 SEM Literature Inventory: Interactive Features

ReadMe Animal Studies Human Studies

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

Heat Map

	acute			short-term		subchronic		chronic	developmental, F1		Grand
	rat	dog	guinea pig	rat	mouse	rat	mouse	rat	rat	rabbit	Total
Cancer								2			2
Cardiovascular		1		3		1	1	2			7
Developmental									2	2	3
Endocrine								2			5
Gastrointestinal								1			3
Hematologic				3		1	1	2			6
Hepatic			1	3		1	1	2		1	8
Immune						1		2			6
Nervous						1	1	2			6
Ocular					-	1	1	2			3
Renal				3		1	1	2			6
Reproductive						1	1	2			8
Respiratory						1	1	2			6
Systemic/Whole Body	1		1	3	2	1	1	2			10
Grand Total	1	1	1	3	2	1	1	2	2	2	13

References		
DuPont (1992a)	Ø	^
DuPont (1992d)	0	
DuPont (1992f)	0	
DuPont (1992g)	0	
Haskell Laboratories (1995)	0	
Hoet et al. (2001)	0	
Malley et al. (1996)	0	
Malley et al. (1998)	Ø	~

Chemicals Evaluated - by Name

1-Butanesulfonic acid, 1,1,2,2,3,3,		\land			
1H,1H,2H-Perfluorocyclopentane					
1H,1H,5H-Perfluoropentanol					
2-Chloro-1,1,1,2-tetrafluoroethane	13				
3-Methoxyperfluoro(2-methylpent					
3,3,4,4,5,5,6,6,6-Nonafluorohexene		\sim			
Chemicals Evaluated - by CASRN					

2837-89-0	13
Grand Total	13

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

Study Details	5						Chemicals Evaluated -	by DTXSID
Health System	Study Design	Route	Species	Sex	Short Citation		DTXSID7029245	13
Cancer	chronic	inhalation	rat	both	Haskell Laboratories (1995)	^	Grand Total	13
					Malley et al. (1998)			
Cardiovascular	acute	inhalation	dog	male	DuPont (1992d)			
	short-term	inhalation	rat	both	DuPont (1991c)			
				male	DuPont (1990b)			
					DuPont (1992a)	¥		
- → + a b l e a	1 U						$\leftarrow \rightarrow$	$\leftarrow \ll \square$

Explore by PFAS
SEPA

PFAS 150 SEM Literature Inventory: Interactive Features

ReadMe Animal Studies Human Studies

Explore by health category

Toxicological Studie	s Examini	ing Expo	osure to	PFAS by	Study D	esign an	d Healt	h System										
Heat Map																References		
			short-term	1	subc	hronic	chr	onic		developm	ental, F1		multigen	Grand		Case et al. (2001)	Ø	^
	not reported	rat	mouse	not reported	rat	mouse	rat	mouse	rat	mouse	rabbit	not reported	mouse	Total		DuPont (1991a) DuPont (1991b)	0	
Cancer														2	^	Mallev et al. (1996)	ā	
Cardiovascular									4					29		Mylchreest et al. (2005)	õ	
Dermal														7		O'Connor et al. (2014)	õ	
Developmental									19		3	1	1	22		Saillenfait et al. (1997)	ā	
Endocrine														25		Takahashi et al. (2014)	ā	\checkmark
Exocrine														1			-	
Gastrointestinal														23		Chemicals Evaluated - by Name		
Hematologic														32				
Hepatic														54		1H,1H,2H-Perfluorocyclopentane	1	^
Immune						1			4					35		2-Chloro-1,1,1,2-tetrafluoroethane	3	
Lymphatic														1		3,3,4,4,5,5,6,6,6-Nonafluorohexene	1	
Metabolic						1								12		6:2 Fluorotelomer alcohol	3	
Musculoskeletal/Connect														12		6:2 Fluorotelomer methacrylate	1	
Nervous														34		6:2 Fluorotelomer sulfonic acid	2	×
Not reported (but NOAEL														6		Chemicals Evaluated - by CASRN		
Ocular														21				
Renal														43	$\mathbf{\vee}$	76-05-1	3	\sim
	<													>		647-42-7	3	
Notes: Column totals, row tota	als, and Grand	1 Totals ind	icate total n	umbers of di	istinct refe	ences Some	ECHA stur	lies sources r	nav be cour	nted as multi	ole referen	ces in these	counts base	d on how da	ata	678-39-7	1	
were reported in the dossier. (Care was take	n durino ca	tegorization	n and extract	tion to ensu	re that endp	oints were	not repeated	from over	lapping ECHA	summarie	s.	counts, Dase	0.011100/02	aca.	1493-13-6	1	
												-				1623-05-8	2	~

Health System	Study Design	Route	Species	Sex	Short Citation		DTXSID0061826	
Developmental	developmental, F1	inhalation	rat	both	DuPont (1991b)	^	DTXSID1074915	
					Malley et al. (1996)		DTXSID2044397	
					Unnamed Report (1981b) (ECHA Summary)		DTXSID3047558	
					Unnamed Report (2017f) (ECHA Summary)		DTXSID5044572	
					Unnamed Report (2017g) (ECHA Summary)		DTXSID6027426	
			rabbit	both	DuPont (1991a)	~	DTXSID6047575	

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PFAS 150 SEM Literature Inventory: Interactive Features

	Toxicological Stud	ies Exam	nning ext	osure to	PFAS Dy	Study L	Jesign an	id Healt	n System								
	Heat Map																References
				short-terr	n	subo	chronic	chi	ronic		developn	nental, F1		multigen	Grand		Bodin et al. (2016)
		not reporte	ed rat	mouse	not reported	rat	mouse	rat	mouse	rat	mouse	rabbit	not reported	mouse	Total		Covance Laboratoroes (2000) Grossman et al. (1992)
	Cancer							2							2	^	Haskell Laboratories (1995)
	Cardiovascular					6	2	2		4					29		Ladics et al. (2008)
	Dermal					2									7		Malley et al. (1996)
	Developmental														22		Malley et al. (1998)
	Endocrine					7		2							25		Serex et al. (2014)
	Exocrine														1		
	Gastrointestinal					5		1							23		Chemicals Evaluated - by Nam
udv	Hematologic					10	2	2							32		
uuy	Hepatic					9	2	2							54		2-Chloro-1,1,1,2-tetrafluoroethane
	Immune					9	1	2		4					35		3,3,4,4,5,5,6,6,6-Nonafluorohexene
	Lymphatic														1		6:2 Fluorotelomer alcohol
	Metabolic					3	1		1						12		6:2 Fluorotelomer sulfonic acid
	Musculoskeletal/Conne	rt				3									12		8:2 Fluorotelomer alcohol
	Nervous					7	2	2							34		N-Ethylperfluorooctanesulfonamide
	Not reported (but NOA	iL													6		Chemicals Evaluated - by CASE
	Ocular		4			9	1	2							21		chemical Dividuced by chemi
	Renal					9	2	2							43	\sim	76-05-1
		<													>	•	382-28-5
	Notes: Column totals, row	otals and Gr	and Totals in	dicate total	numbers of d	istinct refe	erences Some	e ECHA stur	lies sources r	nav be cou	nted as mult	inle referen	res in thes	counts base	d on how d	lata	647-42-7
	were reported in the dossi	er. Care was t	aken during (ategorizatio	n and extract	tion to ensi	ure that end	points were	not repeated	i from ove	rlapping ECH	A summarie	5.				678-39-7
	·		-	-													2058-94-8
	Study Details																Chemicals Evaluated - by DTXS
	Health System St	udy Design	Route	Species	Sex	Sh	nort Citation	1									DTXSID1032646
	Cancer ch	ronic	inhalation	rat	both	Ha	askell Labora	atories (19	995)					^			DTXSID1074915
						M	alley et al. (2	1998)									DTXSID5044572
	Cardiovascular su	bchronic	inhalation	rat	both	M	alley et al. (2	1996)									DTXSID6047575
				mouse	both	M	alley et al. (2	1996)									DTXSID6067331
						-											

Explore design

ŝ

Set EPA

PFAS 150 SEM Literature Inventory: Epidemiology Studies

ReadMe Animal Studies Human Studies

∰ + a b | e a u

Epidemiological Studies Examining Exposure to PFAS by Study Design and Health System Heat Map References cohort 3M Company (2000) 00000000 case-control \wedge Aimuzi et al. (2019) denera pregnant general pregnant ger children infants children children infants occupational population Bao et al. (2017) women population women popu Berg et al. (2015) Cancer Cardiovascular 1 Berg et al. (2016) Developmental 4 Bjerregaard-Olesen et al. (2019) 1 2 2 Blake et al. (2018) Endocrine \checkmark DI I (2010) 9 1 Hematologic Hepatic 1 1 **Chemicals Evaluated - by Name** 2 Immune 2 4 2 Nafion 1 Metabolic 2 2 ~ 9 4 Perfluoroheptanesulfonate Nervous 1 Perfluoroheptanesulfonic acid 4 Other 1 22 1 Perfluoroheptanoic acid Renal 1 15 3 Perfluorooctanesulfonamide Reproductive 1 1 Perfluorooctanesulfonyl fluoride 2 Respiratory 1 1 1 ~ Systemic/Whole Body 1 **Chemicals Evaluated - by CASRN** Grand Total 2 9 2 1 14 8 10 2 6 9 < 307-35-7 2 ~ 22 375-85-9 Notes: Column totals, row totals, and Grand Totals indicate total numbers of distinct references 375-92-8 4 12 376-06-7 Study Details 422-64-0 3 15 754-91-6 2010 04 0

Lingth Custom	Shudu Danian	Desulation	Exposure	Matuix	C	Shout Citation	
Realth System	Study Design	Population	weasurement	Watrix	Sex	Short Citation	
Cancer	case-control	general population	biomonitoring	blood	female	Bonefeld-Jørgensen et al. (2014)	^
						Ghisari et al. (2017)	
						Hurley et al. (2018)	
						Wielsøe et al. (2018)	
					male	Hardell et al. (2014)	
	cohort	occupational	occupational	Null	both	3M Company (2000)	
						Olsen et al. (2004)	
	cross-sectional	general population	biomonitoring	blood	male	Christensen et al. (2016a)	\sim

• ~10 PFAS

~95 studies

 $\leftarrow \rightarrow \leftarrow \ll \Box$

22 15

12

2

15

Chemicals Evaluated - by DTXSID

DTXSID1037303

DTXSID3038939 DTXSID3059921

DTXSID5027140

DTXSID6062599 DTXSID8047553

Example HAWC Data Extraction

Figure 33. 2-Chloro-1,1,1,2-tetrafluoroethane and Hepatic Effects

SEPA

						no apparent treatment-related effect treatment-related increase treatment-related decrease
Endpoint	Study	Animal Description	Route	Exposure Duration		
Alanine Aminotransferase (ALT)	Haskell Laboratory 1995	Rat, Crl:Cd Br (♀)	inhalation - vapor	2 yr (6 hr/d, 5 d/wk)	••••••	•
		Rat, Crl:Cd Br (ି)	inhalation - vapor	2 yr (6 hr/d, 5 d/wk)		
Albumin (A)	Haskell Laboratory 1995	Rat, Crl:Cd Br (♀)	inhalation - vapor	2 yr (6 hr/d, 5 d/wk)	•••••	•
		Rat, Crl:Cd Br (ି)	inhalation - vapor	2 yr (6 hr/d, 5 d/wk)	+++	•
Alkaline Phosphatase (ALP)	Haskell Laboratory 1995	Rat, Crl:Cd Br (♀)	inhalation - vapor	2 yr (6 hr/d, 5 d/wk)	+ ⊷→	•
	Malley et al. 1996	Rat, Crl:Cd Br (♀)	inhalation - vapor	90 d (6 hr/d, 5 d/wk)	⊷ ⊷	•
	Haskell Laboratory 1995	Rat, Crl:Cd Br (ି)	inhalation - vapor	2 yr (6 hr/d, 5 d/wk)	+++	•
Aspartate Aminotransferase (AST)	Haskell Laboratory 1995	Rat, Crl:Cd Br (♀)	inhalation - vapor	2 yr (6 hr/d, 5 d/wk)	+++	•
		Rat, Crl:Cd Br (්)	inhalation - vapor	2 yr (6 hr/d, 5 d/wk)	++	
Focal Liver Necrosis	Malley et al. 1998	Rat, Crl:Cd Br (්)	inhalation - vapor	2 yr (6 hr/d, 5 d/wk)	•••••	_
Liver Histopathology	Malley et al. 1998	Rat, Crl:Cd Br (♀)	inhalation - vapor	2 yr (6 hr/d, 5 d/wk)	→ • • • • •	•
Liver Weight, Absolute	BioDynamics 1991	P0 Rabbit, New Zealand (♀)	inhalation - vapor	GD 6-18 (6 hr/d)	↓ → →	• •
	Malley et al. 1996	Mouse, Crl:CD-1(ICR)BR (♀)	inhalation - vapor	90 d (6 hr/d, 5 d/wk)	→	• •
		Mouse, Crl:CD-1(ICR)BR (්)	inhalation - vapor	90 d (6 hr/d, 5 d/wk)	↓ →	• •
		Rat, Crl:Cd Br (♀)	inhalation - vapor	90 d (6 hr/d, 5 d/wk)	→	• •
	Malley et al. 1998	Rat, Crl:Cd Br (♀)	inhalation - vapor	2 yr (6 hr/d, 5 d/wk)	+•	
	Malley et al. 1996	Rat, Crl:Cd Br (ି)	inhalation - vapor	90 d (6 hr/d, 5 d/wk)		• •
	Malley et al. 1998	Rat, Crl:Cd Br (්)	inhalation - vapor	2 yr (6 hr/d, 5 d/wk)	•	•
Liver Weight, Relative	BioDynamics 1991	P0 Rabbit, New Zealand (♀)	inhalation - vapor	GD 6-18 (6 hr/d)	→	• •
	Malley et al. 1996	Mouse, Crl:CD-1(ICR)BR (♀)	inhalation - vapor	90 d (6 hr/d, 5 d/wk)	l +→	• •
		Mouse, Crl:CD-1(ICR)BR (්)	inhalation - vapor	90 d (6 hr/d, 5 d/wk)	• • • • • • • • • • • • • • • • • • •	• •
		Rat, Crl:Cd Br (♀)	inhalation - vapor	90 d (6 hr/d, 5 d/wk)	→	• •
		Rat, Crl:Cd Br (්)	inhalation - vapor	90 d (6 hr/d, 5 d/wk)	• • • • • • • • • • • • • • • • • • •	• •
Total Bilirubin (TBILI)	Haskell Laboratory 1995	Rat, Crl:Cd Br (♀)	inhalation - vapor	2 yr (6 hr/d, 5 d/wk)	+++	•
		Rat, Crl:Cd Br (♂)	inhalation - vapor	2 yr (6 hr/d, 5 d/wk)	•••••	•
					0 50,00	0 100,000 150,000 200,000 250,000 30 Dose (mg/m3)



Example HAWC Data Extraction

Figure 33. 2-Chloro-1,1,1,2-tetrafluoroethane and Hepatic Effects

Endpoint	Study	Animal Description	Route	Exposure Duration	
Alanine Aminotransferase (ALT)	Haskell Laboratory 1995	Rat, Crl:Cd Br (♀)	inhalation - vapor	2 yr (6 hr/d, 5 d/wk)	
		Rat, Crl:Cd Br (්)	inhalation - vapor	2 yr (6 hr/d, 5 d/wk)	
Albumin (A)	Haskell Laboratory 1995	Rat, Crl:Cd Br (♀)	inhalation - vapor	2 yr (6 hr/d, 5 d/wk)	
		Rat, Crl:Cd Br (♂)	inhalation - vapor	2 yr (6 hr/d, 5 d/wk)	
Alkaline Phosphatase (ALP)	Haskell Laboratory 1995	Rat, Crl:Cd Br (♀)	inhalation - vapor	2 yr (6 hr/d, 5 d/wk)	
	Malley et al. 1996	Rat, Crl:Cd Br (♀)	inhalation - vapor	90 d (6 hr/d, 5 d/wk)	
	Haskell Laboratory 1995	Rat, CrI:Cd Br (ి)	inhalation - vapor	2 yr (6 hr/d, 5 d/wk)	
Aspartate Aminotransferase (AST)	Haskell Laboratory 1995	Rat, Crl:Cd Br (♀)	inhalation - vapor	2 yr (6 hr/d, 5 d/wk)	
		Rat, Crl:Cd Br (ථ)	inhalation - vapor	2 yr (6 hr/d, 5 d/wk)	
Focal Liver Necrosis	Malley et al. 1998	Rat, Crl:Cd Br (♂)	inhalation - vapor	2 yr (6 hr/d, 5 d/wk)	
Liver Histopathology	Malley et al. 1998	Rat, Crl:Cd Br (♀)	inhalation - vapor	2 yr (6 hr/d, 5 d/wk)	
Liver Weight, Absolute	BioDynamics 1991	P0 Rabbit, New Zealand (♀)	inhalation - vapor	GD 6-18 (6 hr/d)	
	Malley et al. 1996	Mouse, Crl:CD-1(ICR)BR (♀)	inhalation - vapor	90 d (6 hr/d, 5 d/wk)	
		Mouse, Crl:CD-1(ICR)BR (්)	inhalation - vapor	90 d (6 hr/d, 5 d/wk)	
		Rat, Crl:Cd Br (♀)	inhalation - vapor	90 d (6 hr/d, 5 d/wk)	
	Malley et al. 1998	Rat, Crl:Cd Br (♀)	inhalation - vapor	2 yr (6 hr/d, 5 d/wk)	
	Malley et al. 1996	Rat, Crl:Cd Br (ீ)	inhalation - vapor	90 d (6 hr/d, 5 d/wk)	
	Malley et al. 1998	Rat, Crl:Cd Br ()	inhalation - vapor	2 yr (6 hr/d, 5 d/wk)	
Liver Weight, Relative	BioDynamics 1991	P0 Rabbit, New Zealand (♀)	inhalation - vapor	GD 6-18 (6 hr/d)	
	Malley et al. 1996	Mouse, Crl:CD-1(ICR)BR (Q)	inhalation - vapor	90 d (6 hr/d, 5 d/wk)	
		Mouse, Crl:CD-1(ICR)BR (3)	inhalation - vapor	90 d (6 hr/d, 5 d/wk)	
		Rat, Crl:Cd Br (♀)	inhalation - vapor	90 d (6 hr/d, 5 d/wk)	
		Rat, Crl:Cd Br (ீ)	inhalation - vapor	90 d (6 hr/d, 5 d/wk)	
Total Bilirubin (TBILI)	Haskell Laboratory 1995	Rat, Crl:Cd Br (♀)	inhalation - vapor	2 yr (6 hr/d, 5 d/wk)	
		Rat, Crl:Cd Br (ீ)	inhalation - vapor	2 yr (6 hr/d, 5 d/wk)	
					r

treatment-related decrea	lated effect se ise			
Malley et al. 199	8 / 2-Year Inhalation S	study in Rats / Fem	ale Crl:CD BR Rat / Live	r Weight, Absolute
Trend result		not reported		
Results notes		"There were no c one-year interim significant organ in test rats. "	ompound-related effects on me sacrifice or at the 24-month ter weight changes were observed	ean absolute or mean relative organ weight in ma minal sacrifice for any exposure concentration (T), but these are most likely attributable to higher i
Dose 1	Number of Animals	s Response (g)	Standard Deviation	Liver Weight, Absolute
0	87	9.758	1.17	12.0
2,000 ^a	87	10.35	1.46	11.5 -
10,000 ^{b,c}	87	10.56	1.55	11.0 - *
50,000 ^b	87	10.82	1.47	9 10.5 - I •
NOAEL (No observed	adverse effect level)			5 10.0 - T

Methodology "Three hundred study, animals w

"Three hundred eighty four male and 384 female weanling CrI:CD BR rats were received from Charles River Laboratories, Inc., Portage, Michigan. Prior to being used in the study, animals were evaluated by clinical observations and body weight determinations during a 3-week quarantine period. Rats were housed three per cage, genders separate, in stainless steel, wire-mesh cages suspended above cage boards. Rats were housed in four laminar flow animal rooms with males and females housed together by exposure level. Within each room, male and female rats were housed on separate cage racks. A system of rotation was employed to relocate cage racks within the animal room each week and to reposition the cages on the rack every two weeks. Animal rooms were targeted at a temperature of 23+/- 2°C and a relative humidity of 55 +/-15%. Animal rooms were artificially illuminated (fluorescent light) on a 12-hour light/dark cycle. Throughout the test period, except during exposure, each cage of females and each cage of males were supplied with a feeder filled daily with approximately 50 or 70g of irradiated Purina Rodent Chow #5056 (chunk), respectively. In case of premature death or scheduled sacrifice, the amount of chow was adjusted according to the number of animals remaining in a cage. Rats were allowed firee access to the food and to tap water except during

Close

Facilitate Dose-Response Analysis with BMDS Online

Malley et al. 1998 / 2-Year Inhalation Study in Rats / Female Crl:CD BR Rat / Liver Weight, Absolute

Trend result	not reported
Results notes	"There were no compound-related effects on mean absolute or mean relative organ weight in males or females at the one-year interim sacrifice or at the 24-month terminal sacrifice for an significant organ weight changes were observed, but these are most in test rats."

Home / PFAS 150 (2020) / Malley et al. 1998 / 2-Year Inhalation Study in Rats / Female Crt:CD BR Rat / Liver Weight, Absolute

_

Liver Weight, Absolute

Dose (ppm) >	Number of Animals	Response (g)	Standard Deviation
0	87	9.758	1.17
2,000 ^a	87	10.35	1.46
10,000 ^{b,c}	87	10.56	1.55
50,000 ^b	87	10.82	1.47
^a NOAEL (No observed adv	verse effect level)		

^b Significantly different from control (p < 0.05)

^c LOAEL (Lowest observed adverse effect level)

€PA



Methodology

"Three hundred eighty four male and 384 female weanling CrI:CD BR rats were received from Charles River Laboratories, study, animals were evaluated by clinical observations and body weight determinations during a 3-week quarantine period in stainless steel, wire-mesh cages suspended above cage boards. Rats were housed in four laminar flow animal rooms wi level. Within each room, male and female rats were housed on separate cage racks. A system of rotation was employed to week and to reposition the cages on the rack every two weeks. Animal rooms were targeted at a temperature of 23+/- 2°C were artificially illuminated (fluorescent light) on a 12-hour light/dark cycle. Throughout the test period, except during expo were supplied with a feeder filled daily with approximately 50 or 70g of irradiated Purina Rodent Chow #5056 (chunk), resp sacrifice, the amount of chow was adjusted according to the number of animals remaining in a cage. Rats were allowed free the second sec

Endpoint Deta	alls
Endpoint name	Liver Weight, Absolute
System	Hepatic
Organ	Liver
Effect	Organ Weight
Effect subtype	Absolute
Diagnostic description	Female absolute liver weight
Observation time	24 mo
Data reported?	✓
Data extracted?	✓
Values estimated?	-
Location in literature	Table 2
Expected response adversity direction	increase from reference/control group
NOAEL	2,000 ppm
LOAEL	10,000 ppm
Monotonicity	
Statistical test description	Dunnett's test
Trend result	not reported
Results notes	"There were no compound-related effects on mean absolute or mean relative organ weight in males or females at the one-year interim sacrifice or at the 24 month terminal sacrifice for any exposure concentration (Table II). Some



Contact About Public Assessments Your H

Methodology

"Three hundred eighty four male and 384 female weanling Cri:CD BR rats were received from Charles River Laboratories. Inc. Portage Michigan Prior to being

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Download Data Sets

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SELECTED ASSESSMENT

PFAS 150 (2020)

AVAILABLE MODULES

Literature review

Management dashboard

Study list

Study evaluation

Endpoint list

Visualizations

Executive summary

DOWNLOADS

Download datasets

PFAS 150 (2020) downloads

All data from HAWC are exportable into Excel. Developer exports in JSON format are also available (please contact us for more information).

• Literature-review



Microsoft Excel spreadsheet

• Study evaluation report

Download

(no individual reviews)

Download complete

(includes individual reviews - team-members and higher only)

Microsoft Excel spreadsheet

• Animal bioassay data



rt Endpoint summary

Microsoft Excel spreadsheet



Preliminary Results: PFAS 430

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

Heat Map															
			acute				short-term		subchro	chronic	developmental, F1		multige	not repo	Grand
	rat	mouse	pig	dog	not reported	rat	mouse	not reported	rat	rat	rat	not reported	not reported	not reported	Total
Cardiovascular	5		1	6		22	1		4	2	6				46
Dermal	6	1				7			1						15
Developmental											19				19
Reproductive	5								6	2	19		1		52
Endocrine	2					18			5		7				31
Gastrointestinal	5	2				12			4		3				25
Hematologic						20			8		3				30
Hepatic	5					30	1		6	1	5				46
Immune	6	1					1		5		4				38
Lymphatic						9			2		1				12
Metabolic						7			3	1					10
Musculoskeletal/Connect						9			4		1				13
Nervous	17			2	1	18		1	11		8				54
Ocular	6	1				8			6			-			21
Renal	5					25			8	2	7				44
Respiratory	17	3	1			17			3		8				49
Sensory	1	1					-			1					2
Systemic/Whole Body	42	4	1	4	7	37	1		9	2	16				116
Not reported (but NOAEI	10	2			2	12		2	2		0	1			40

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

Study Details					
Health System	Study Design	Route	Species	Sex	Short Citation
Cardiovascular	acute	inhalation	rat	both	Eastman Kodak (1992)
					Unnamed Report, 2019 (ECHA Summary)b
				male	E.I. duPont de Nemours and Co. (1992)
			pig	not reported	Steffey et al. (1998)
			dog	male	Dodd and Vinegar (1998)

References	
Blake et al. (1970)	Ø
Brock et al. (1995)	0
Chambers et al. (1950)	0
Chen et al. (2018)b	0
Ding et al. (2009)	0
Dodd and Vinegar (1998)	0
Dupont (1992)a	0
Dupont (1992)b	Ø
Chemicals Evaluated - by Nar	me
1-(Perfluorohexyl)ethane	3
1-(Perfluorohexyl)octane	1
1,6-Diiodoperfluorohexane	6
1,6-Divinylperfluorohexane	2
1H-Perfluorohexane	6
1H,1H,5H-Perfluoropentyl methacr	4
Chemicals Evaluated - by CAS	SRN
307-55-1	10
335-36-4	1
355-02-2	3
355-20-4	2
355-37-3	6
355-93-1	4
Chemicals Evaluated - by DT	SID
DTXSID1022134	11
DTXSID1061073	2
DTXSID1073365	З
DTXSID3032620	2
DTXSID4059966	6
DTXSID4066389	2

PFAS 430 & Xagency Literature Searches (November 2019) ToxNet, PubMed, 11/21/2019 WoS, 11/21/2019 11/21/2019 (n = 9,386) (n = 3,995) (n = 931) Following duplicate removal, SWIFT Review used to analyze 11.614 records from database searches Identification of potentially relevant records based on application of SWIFT-Review evidence stream tags, n = 6.785 TIAB Screen in SWIFT Active (n = 6,785) Excluded (n = 6.014) 518 records manually screened and excluded 392 records predicted as not relevant in 159 records considered relevant or SWIFT Active (and not manually screened) supplemental material based on SWIFT Active Records identified from other sources (n = 1,204) ATSDR AEGL ToxVal ECHA (n = 7) (n = 370) (n = 460) (n = 32) Reference list from TedEx Tableau CEBS included studies (n = 1) (n = 34) (n = 300) Excluded, did not meet all PECO (n = 619) Title & Abstract Screen in DistillerSR (n = 1,781) Tagged as supplemental material (n = 545) Sum of TIAB excluded or supplemental (n = 1,164) Full-Text Screen in DistillerSR (n = 617) Excluded (n = 167) Not PECO relevant (n = 147) Unable to obtain full text (n = 6) Included after Full-Text Screening (n = 185) No data provided (n = 14) Animal (n = 137); Human (n = 48); PBPK model (n=0) Tagged as supplemental material (n = 264) Sum of full-text excluded or supplemental (n = 432) Human and Animal studies Summarized in the Literature Inventory (n= 185) Animal (n = 137); Human (n = 48) Tagged as Supplemental Material TIAB + Full text + Inventory (n = 922) Mechanistic (including in vitro/ex vivo/in silico studies)(n = 163) Non-mammalian model systems (n = 12) Non-oral or non-inhalation route of administration (n = 179) Transgenic mammalian model systems (n = 1) ADME and toxicokinetic (n = 85) · Exposure characteristics (no health outcome assessment) (n = 344) Mixture studies (n = 25) Foreign language (n = 1) Records or other assessments with no original data (n = 52)

Case reports (n = 3)
Conference abstract (n = 1)
ECHA read-across (n = 53)
Animal disease model (n=3)



Preliminary Results: PFAS 430

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

Heat Map															
	acute				short-term subchro.		subchro	chronic	developm	developmental, F1		not repo	Grand		
	rat	mouse	pig	dog	not reported	rat	mouse	not reported	rat	rat	rat	not reported	not reported	not reported	Total
Cardiovascular	5		1	6		22	1		4	2	6				46
Dermal	6	1				7			1						15
Developmental											19				19
Reproductive	5								6	2	19		1		52
Endocrine	2					18			5		7				31
Gastrointestinal	5	2				12			4		3				25
Hematologic						20			8		3				30
Hepatic	5					30	1		6	1	5				46
Immune	6	1					1		5		4				38
Lymphatic						9			2		1				12
Metabolic						7			3	1					10
Musculoskeletal/Connect						9			4		1				13
Nervous	17			2	1	18		1	11		8				54
Ocular	6	1				8			6			-			21
Renal	5					25			8	2	7				44
Respiratory	17	3	1			17			3		8				49
Sensory	1	1					-			1					2
Systemic/Whole Body	42	4	1	4	7	37	1		9	2	16				116
Not reported (but NOAEI	10	2			2	12		2	2		0	1			40

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

Study Details					
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Cardiovascular	acute	inhalation	rat	both	Eastman Kodak (1992)
					Unnamed Report, 2019 (ECHA Summary)b
				male	E.I. duPont de Nemours and Co. (1992)
			pig	not reported	Steffey et al. (1998)
			dog	male	Dodd and Vinegar (1998)

References	
Blake et al. (1970)	Ø
Brock et al. (1995)	0
Chambers et al. (1950)	0
Chen et al. (2018)b	0
Ding et al. (2009)	0
Dodd and Vinegar (1998)	0
Dupont (1992)a	0
Dupont (1992)b	Ø
Chemicals Evaluated - by Na	me
1-(Perfluorohexyl)ethane	3
1-(Perfluorohexyl)octane	1
1,6-Diiodoperfluorohexane	6
1,6-Divinylperfluorohexane	2
1H-Perfluorohexane	6
1H,1H,5H-Perfluoropentyl methacr	4
Chemicals Evaluated - by CAS	SRN
307-55-1	10
335-36-4	1
355-02-2	3
355-20-4	2
355-37-3	6
355-93-1	4
Chemicals Evaluated - by DT	SID
DTXSID1022134	11
DTXSID1061073	2
DTXSID1073365	З
DTXSID3032620	2
DTXSID4059966	6
DTXSID4066389	2

PFAS 430 & Xagency Literature Searches (November 2019) ToxNet, PubMed, 11/21/2019 WoS, 11/21/2019 11/21/2019 (n = 9,386) (n = 3,995) (n = 931) Following duplicate removal, SWIFT Review used to analyze 11.614 records from database searches Identification of potentially relevant records based on application of SWIFT-Review evidence stream tags, n = 6.785 TIAB Screen in SWIFT Active (n = 6,785) Excluded (n = 6.014) 518 records manually screened and excluded 392 records predicted as not relevant in 159 records considered relevant or SWIFT Active (and not manually screened) supplemental material based on SWIFT Active Records identified from other sources (n = 1,204) ATSDR AEGL ToxVal ECHA (n = 7) (n = 370) (n = 460) (n = 32) Reference list from TedEx Tableau CEBS included studies (n = 1) (n = 34) (n = 300) Excluded, did not meet all PECO (n = 619) Title & Abstract Screen in DistillerSR (n = 1,781) Tagged as supplemental material (n = 545) Sum of TIAB excluded or supplemental (n = 1,164) Full-Text Screen in DistillerSR (n = 617) Excluded (n = 167) Not PECO relevant (n = 147) Unable to obtain full text (n = 6) Included after Full-Text Screening (n = 185) No data provided (n = 14) Animal (n = 137); Human (n = 48); PBPK model (n=0) Tagged as supplemental material (n = 264) Sum of full-text excluded or supplemental (n = 432) Human and Animal studies Summarized in the Literature Inventory (n= 185) Animal (n = 137); Human (n = 48) Tagged as Supplemental Material TIAB + Full text + Inventory (n = 922) Mechanistic (including in vitro/ex vivo/in silico studies)(n = 163) Non-mammalian model systems (n = 12) Non-oral or non-inhalation route of administration (n = 179) Transgenic mammalian model systems (n = 1) ADME and toxicokinetic (n = 85) · Exposure characteristics (no health outcome assessment) (n = 344) Mixture studies (n = 25) Foreign language (n = 1) Records or other assessments with no original data (n = 52)

Case reports (n = 3)
Conference abstract (n = 1)
ECHA read-across (n = 53)
Animal disease model (n=3)



Linking SEMs to the EPA CompTox Chemicals Dashboard



Chemicals Dashboard – Links Tab





External Links

	Orection Home Advanced Search Batch Search List	ts Predictions Downloads		Copy Share Submit Comment	C Search all data
DETAILS	Perfluoroc 754-91-6 D Searched by DSSTox Su	octanesulfonam DTXSID3038939 Ibstance Id.	Publications	Analytical	Prediction
	General	loxicology	Tublications	Analytical	riediction
EXECUTIVE SUMMARY	EPA Substance Registry Service	ACToR	G Google Books	RSC Analytical Abstracts	2D NMR HSQC/HMBC Prediction
PROPERTIES	PubChem	애 DrugPortal	G Google Scholar	🗟 Tox21 Analytical Data	Carbon-13 NMR Prediction
	Chemspider	СТР	G Google Patents	MONA: MassBank North America	Proton NMR Prediction
ENV. FATE/TRANSPORT	(E) CPCat	ChemPortal	PPRTVWEB	mzCloud	LSERD
HAZARD	DrugBank	ToxCast Dashboard 2	PubMed	NIST IR Spectrum	
	Wikipedia	ATSDR Toxic Substances Portal	IRIS Assessments	NIST MS Spectrum	
ADME	MSDS Lookup	Clor PDF Report	EPA HERO	MassBank	
EXPOSURE		CREST One of the test of test	NIOSH Skin Notation Profiles	NEMI: National Environmental Methods Index	
	CC Rescent Chemicals	Superfund Chemical Data matrix	RSC Publications	NIST Antoine Constants	
BIOACTIVITY	ChemHat: Hazards and Alternatives Toolbox			IR Spectra on PubChem	
SIMILAR COMPOUNDS	Wolfram Alpha	W NIOSH IDI H Values	Springer Materials	NIST Kovats Index values	
CENIDA (RETA)	ECHA Infocard		Eederal Register	Protein DataBank	
GEINRA (BEIA)	ChemAgora	Chemical Checker	Regulations.gov		
RELATED SUBSTANCES	ChEBI		Bielefeld Academic Search Engine		
SAMONAMS	NIST NIST Chemistry Webbook	HAWC Public Assessments	CORE Literature Search		
511(61(11))5		Tableau Evidence Map			
LITERATURE	WEBWISER				
LINKS	PubChem Safety Sheet				
	MIOSH Chemical Safety Cards				



Questions?

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