

Translating Science to Support Decisions Overview

Assessing Health Effects Evidence

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Division of the National Toxicology Program

National Institute of Environmental Health Sciences

NTP Board of Scientific Counselors Meeting

December 12, 2018





Translating Science to Support Decisions

Regulatory
Toxicology

Science



Regulation/Policy

- **Literature analysis**

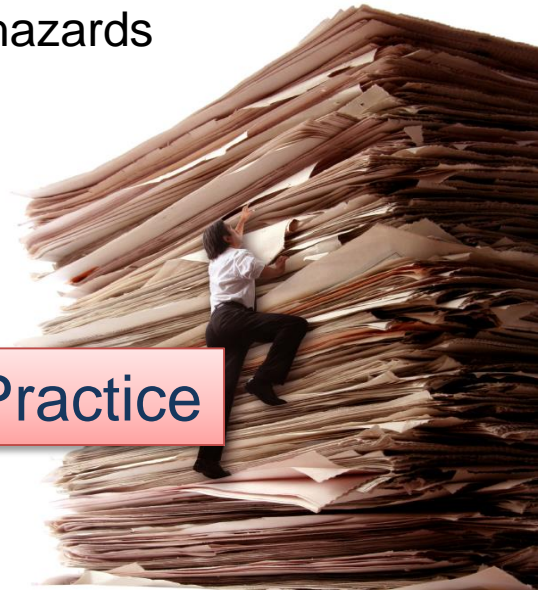
- Well established procedures to identify human health hazards
- Developing new approaches to better inform evidence-based research decisions

Modern
Toxicology

Innovation



Practice





Translating Science to Support Decisions

Regulatory
Toxicology

Science



Regulation/Policy

- **Literature analysis**

- Well established procedures to identify human health hazards
- Developing new approaches to better inform evidence-based research decisions

- **Challenges**

- Maintain transparent, critical evaluation of the evidence
- Find and translate “evidence” despite volume of research
 - 3 science articles published per minute
 - 2 million+ research publications per year





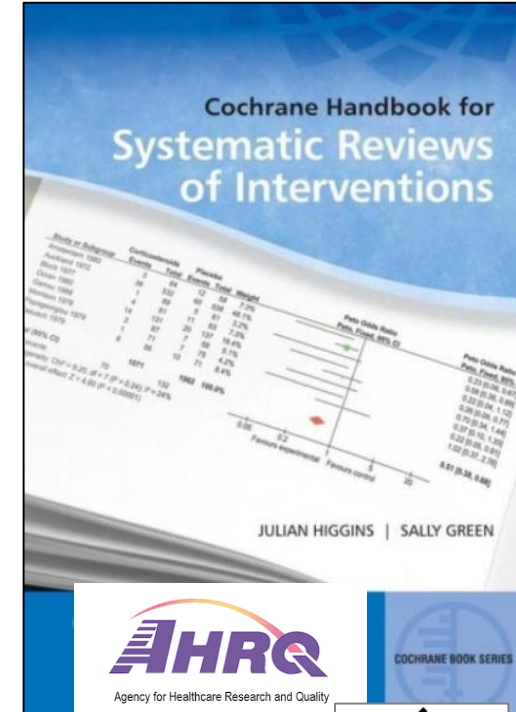
Critical Evaluation with Increased Transparency and Objectivity

- **Systematic Review**

- Predefined, multistep process to identify, select, critically assess, and synthesize evidence to answer a specific research question

- **Established for Clinical Questions**

- Cochrane Collaboration, Agency for Healthcare Research and Quality (AHRQ) Evidence-based practice centers, etc.
- Address healthcare interventions



Agency for Healthcare Research and Quality





Systematic Reviews in Environmental Health

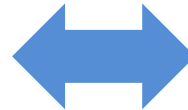
- NTP Leadership in Development and Conduct of Systematic Review Approaches
 - Office of the Report of Carcinogens
 - Office of Health Assessment and Translation
- What's Different?
 - Needs to address the breadth of relevant data
 - Includes approach to reach hazard identification conclusions
 - Requires procedure to integrate evidence streams



Human Data



Experimental Animal Data



Mechanistic Data



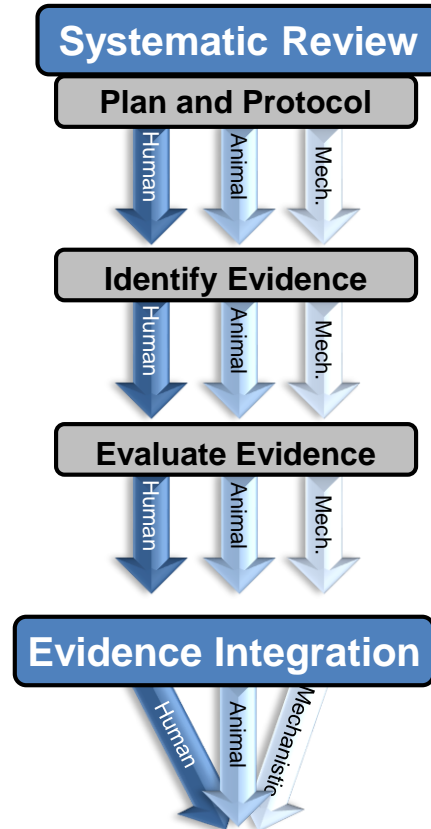
Systematic Review and Evidence Integration

Systematic Review

- **Plan:** Problem formulation develops specific research question
Protocol outlines process
- **Identify Evidence:** Conduct comprehensive literature search
Select relevant studies and extract data
- **Evaluate Evidence:** Assess individual study quality/risk of bias
Complete data analysis or meta-analysis

Evidence Integration

Develop hazard conclusions by conclusions by integrating evidence from human and experimental animal studies with consideration of the degree of support from mechanistic data

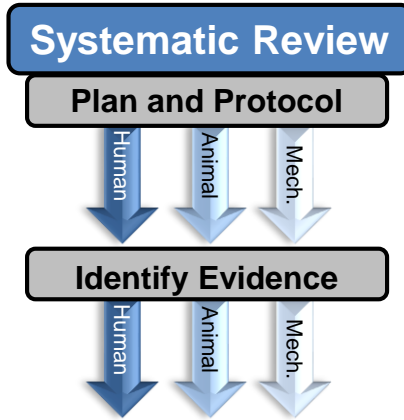




Systematic Review and Evidence Integration

Tools of the Trade

- Identify the Evidence
 - Search
 - **Strategy:** Informationist + Subject experts
 - **Searching multiple databases:** PubMed, Embase, etc.





Systematic Review and Evidence Integration

Tools of the Trade

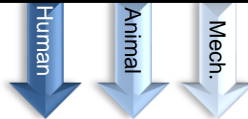
- Identify the Evidence
 - Screen
 - **Software platforms**
 - Active learning algorithms
 - **Manual screening**
 - 2 independent reviewers

 SWIFT-ACTIVESCREENER

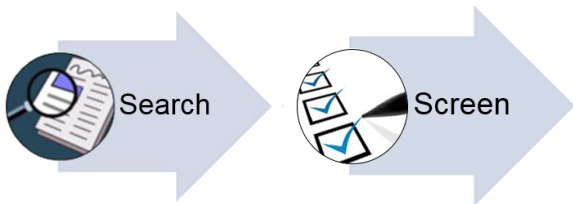
 DistillerSR

Systematic Review

Plan and Protocol



Identify Evidence



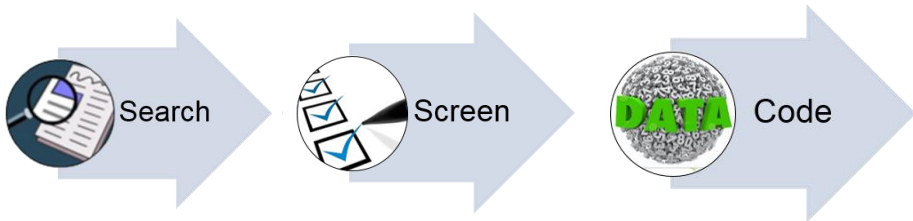


Systematic Review and Evidence Integration

Tools of the Trade

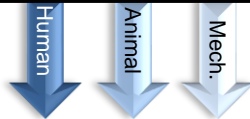
- Identify the Evidence
 - Data Extraction
 - **Software platforms**
 - Capture / extract / “code”
 - Study design
 - Results

⌘ DistillerSR



Systematic Review

Plan and Protocol



Identify Evidence

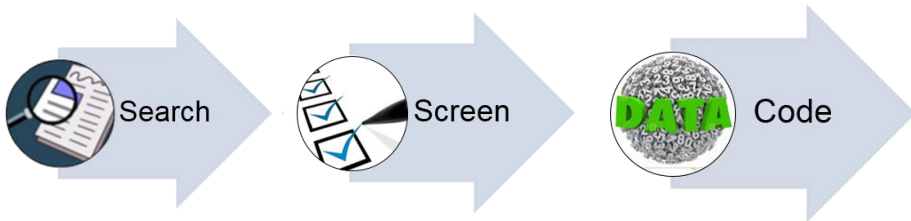




Systematic Review and Evidence Integration

Tools of the Trade

- Identify the Evidence
 - Data Extraction
 - **Software platforms**
 - Capture / extract / “code”
 - Study design
 - Results



Bibliographic Details

Home / PFOA/PFOS Exposure and Immunotoxicity (2015) / DeWitt 2009 /

DeWitt 2009 Actions

Study type Animal Bioassay

Full citation DeWitt JC, Copeland CB, and Luebke RW. 2009. Suppression of humoral immunity by perfluorooctanoic acid is independent of elevated serum corticosterone concentration in mice. *Toxicol Sci* 109(1): 106-112.

Abstract The T-cell-dependent antibody response is suppressed in mice exposed to 3.75, 7.5, 15, and 30 mg PFOA (perfluorooctanoic acid)/kg body weight (bw). Reduced bw accompanied immunosuppression at 15 and 30 mg/kg. We investigated the hypothesis that the observed immunosuppression is secondary to elevated serum corticosterone levels by assessing immune function in adrenalectomized (adx) or sham-operated C57BL/6N female mice exposed to 0, 7.5, or 15 mg PFOA/kg bw in drinking water for 10 days. Bw, primary antibody responses to a T-dependent antigen, clinical serum chemistries related to liver health, and serum corticosterone levels were evaluated. Exposure to 15 mg/kg decreased bw by approximately 10% after 8 days of dosing and until 2 days postdosing in both adx and sham animals; bw of adx animals were still reduced 5 days postdosing. IgM antibody titers were statistically reduced by 15% in sham animals and 18% in adx animals exposed to 15 mg/kg and by 11.8% in adx animals exposed to 7.5 mg/kg. Corticosterone concentrations were elevated by 157% in dosed sham animals relative to control animals and were reduced by 27% in dosed adx animals relative to control animals (neither changes were statistically significant). Clinical serum chemistries related to liver health were not statistically altered by either dose or adrenalectomy. The failure of adrenalectomy to protect mice from the immunosuppressive effects of PFOA indicates that suppression of antibody synthesis is not the result of liver toxicity or stress-related corticosterone production.

Reference hyperlink • [PubMed](#)

COI reported Not reported

Funding source University of North Carolina, U.S. EPA Cooperative Training Agreement (CT829472)

Study identifier (DeWitt, 2009 #342)

Author contact? ☒

Author contact details Authors provided additional details in response to email in April – May 2015 for risk of bias clarification.

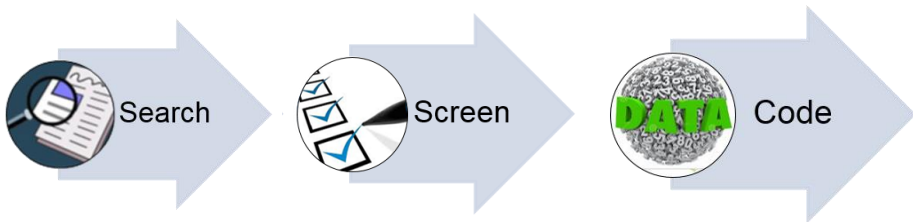
Summary and/or extraction comments Data available: body weight; alkaline phosphatase (ALP); alanine aminotransferase (ALT); aspartate aminotransferase (AST); sorbitol dehydrogenase (SDH); blood gamma-glutamyl transpeptidase (GGT); blood glucose; cholest



Systematic Review and Evidence Integration

Tools of the Trade

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Experimental Methods

Available animal bioassay experiments

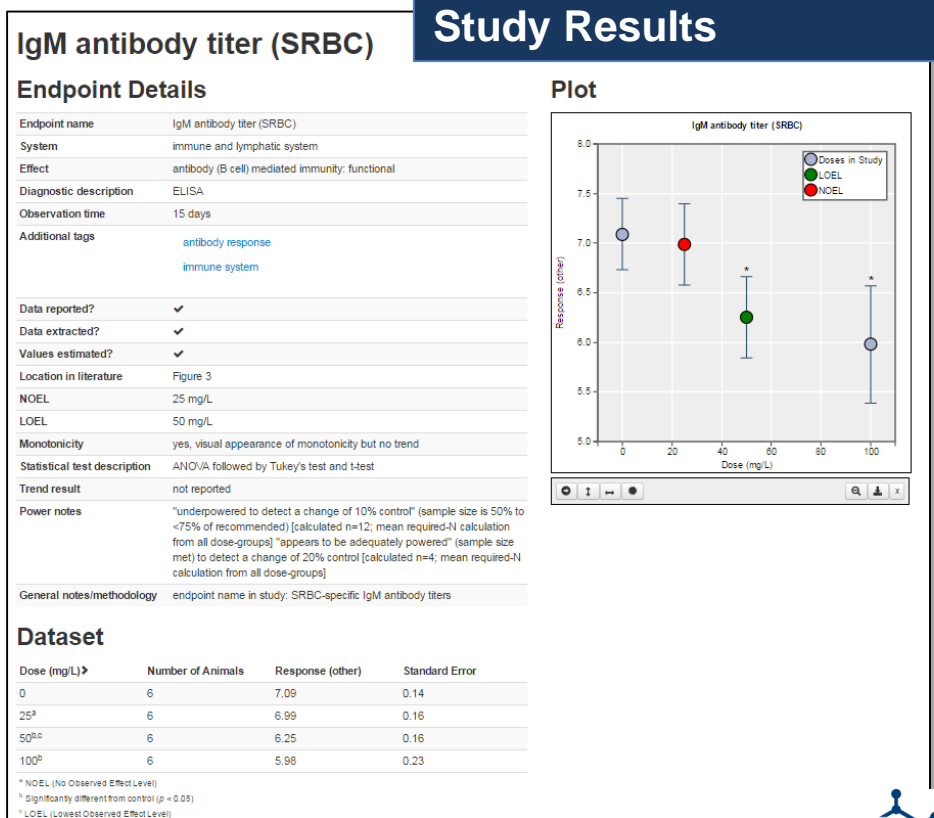
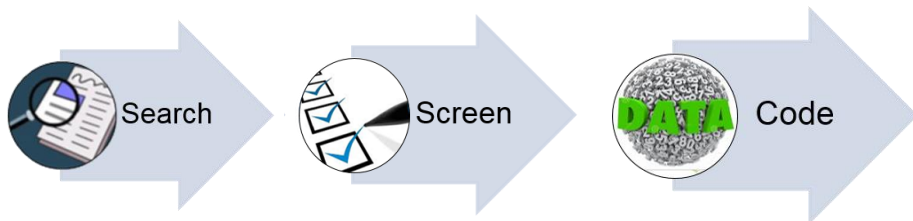
Name	Type	Description
Sham-operated	Short-term (1-30 days)	C57BL/6N female mice (6–7 weeks of age) were purchased from Charles River Laboratories (Raleigh, NC). Half of the mice were adx, and half received sham adrenalectomy operations (sham); surgeries were performed at Charles River Laboratories prior to arrival at the U.S. EPA. Once at the U.S. EPA's animal facilities (accredited by the Association for Assessment and Accreditation of Laboratory Animal Care), animals were housed in groups of six in polycarbonate cages with hardwood chip bedding (Beta chip; Northeast Products, Warrensburg, NY). They were provided a 12-h light:dark cycle (light, 0600–1800 h; dark, 1800–0600 h), maintained at $22.3 \pm 1.1^\circ\text{C}$ and $50 \pm 10\%$ humidity, and given ad libitum access to both food (5P00 Prolab RMH 3000; PMI Nutrition International, Richmond, IN) and water. Animals were acclimated for 1 day before dosing began. All procedures employed in this study were approved in advance by the Institutional Animal Care and Use Committee of the National Health and Environmental Effects Research Laboratory, U.S. EPA.
Adrenalectomized	Short-term (1-30 days)	C57BL/6N female mice (6–7 weeks of age) were purchased from Charles River Laboratories (Raleigh, NC). Half of the mice were adx, and half received sham adrenalectomy operations (sham); surgeries were performed at Charles River Laboratories prior to arrival at the U.S. EPA. Once at the U.S. EPA's animal facilities (accredited by the Association for Assessment and Accreditation of Laboratory Animal Care), animals were housed in groups of six in polycarbonate cages with hardwood chip bedding (Beta chip; Northeast Products, Warrensburg, NY). They were provided a 12-h light:dark cycle (light, 0600–1800 h; dark, 1800–0600 h), maintained at $22.3 \pm 1.1^\circ\text{C}$ and $50 \pm 10\%$ humidity, and given ad libitum access to both food (5P00 Prolab RMH 3000; PMI Nutrition International, Richmond, IN) and water. Animals were acclimated for 1 day before dosing began. All procedures employed in this study were approved in advance by the Institutional Animal Care and Use Committee of the National Health and Environmental Effects Research Laboratory, U.S. EPA.



Systematic Review and Evidence Integration

Tools of the Trade

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Systematic Review and Evidence Integration

Tools of the Trade

- Evaluate the Evidence
 - Assess Individual Study Quality

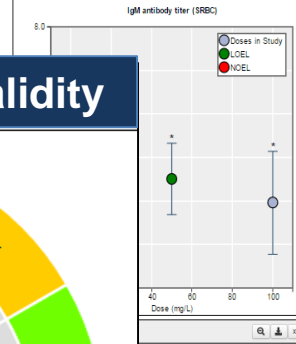
Study Quality

IgM antibody titer (SRBC)

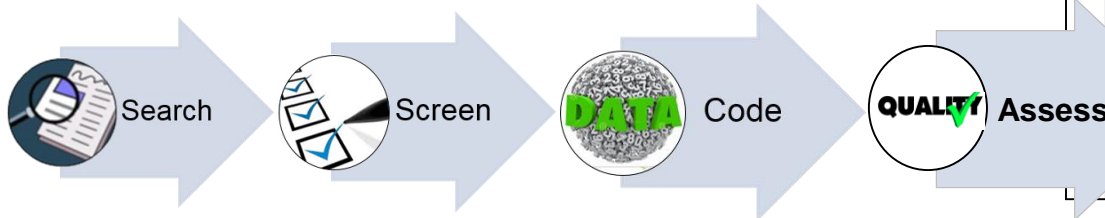
Endpoint Details

Endpoint name	IgM antibody titer (SRBC)
System	immune and lymphatic system
Effect	antibody (B cell) mediated immunity: functional

Plot



Risk of Bias / Internal Validity





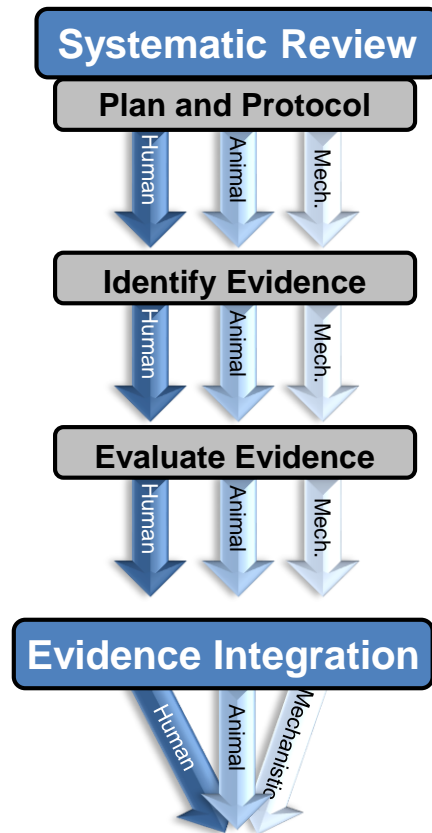
Systematic Review and Evidence Integration

Tools of the Trade

- Tools support transparent process
- Tools provide access to the evidence to support decision making



- Found
- Filtered
- Assessed
- Categorized
- Translated
- Synthesized





Systematic Reviews of Health Effects Evidence

Translating Evidence into Conclusions that Support Policy

Regulatory
Toxicology

Science

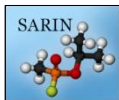


Regulation/Policy



Occupational Exposure to Cancer Chemotherapy Agents

- **Conclusions on:** Adverse outcomes (genetic toxicity and spontaneous abortions)



Sarin

- **DRAFT Conclusions on:** Long-term neurological effects following acute exposure



Traffic-related Air Pollution

- **DRAFT Conclusions on:** Gestational hypertension



Fluoride

- **Developing Conclusions on:** Potential developmental neurotoxicity

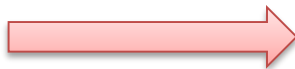


Support of National Academy of Sciences (NAS) Activities

Translating Evidence into Conclusions that Support Policy

Regulatory
Toxicology

Science



Regulation/Policy

2019: Evidence Integration in Chemical Assessments: Challenges Faced in Developing and Communicating Human Health Effect Conclusions **Andrew Rooney**

2018: Strategies And Tools For Conducting Systematic Reviews of Mechanistic Data to Support Chemical Assessments **Andrew Rooney, Amy Wang**

2017: Gulf War and Health, Volume 11: Generational Health Effects of Serving in the Gulf War (2017) **Vickie Walker**

2017: NTP systematic review of "Mountaintop Removal Mining: Impacts on Health in the Surrounding Community" **Abee Boyles (DERT, formerly NTP)**

2015-2017: Application of Systematic Review Methods in an Overall Strategy for Evaluating Low-Dose Toxicity from Endocrine Active Chemicals" **Andrew Rooney**



Focused Questions

- Systematic review approaches are very effective at transparently evaluating evidence on groups of studies addressing the same or similar endpoints
- **Example Objective:** To develop NTP hazard identification conclusions on the association between exposure to PFOA and immunotoxicity
 - All measures of immunotoxicity ➡ Immunosuppression ➡ antibody response





Focused Questions for a Systematic Review

- Systematic review approaches are very effective at transparently evaluating evidence on groups of studies addressing the same or similar endpoints
- **Example Objective:** To develop NTP hazard identification conclusions on the association between exposure to PFOA and immunotoxicity
 - All measures of immunotoxicity ➡ Immunosuppression ➡ antibody response



Experimental Animal Data

- antibodies to T-cell antigens
- anti-SRBC IgM
- anti-SRBC IgG

Human Data

- antibodies to vaccines
- anti-tetanus IgM
- anti-rubella IgM

In vitro and Mechanistic Data

- *in vitro* IgM
- mechanisms of antibody production/response



Systematic Review is Not Always the Answer

- What are they best at?
 - Reaching conclusions
 - Addressing narrowly focused questions
- Challenges
 - Resource intensive
 - Process takes time
 - Addressing broad questions
 - Multiple exposures
 - Multiple health outcomes





Systematic Review Is Not Always the Answer

- Active debate and methods development in the field
 - Society of Toxicology Workshop – March 14, 2019
 - Potential Alternatives to Systematic Reviews (Chair: **Brandy Beverly**)
 - Systematic Mapping as a Tool for Regulatory Risk Assessment (T. Harrison)
 - Rigor and Resources for Systematic Reviews in Toxicology (D. Wikoff)
 - Illustrating Fit for Purpose in Systematic Evidence Maps (**Vickie Walker**)
 - Using Scoping Reviews to Guide Systematic Reviews and Future Research (Carol Kwiatkowski)





Translating Science to Support Decisions

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Regulation/Policy

Systematic Review

- **Literature analysis**

- Well established procedures to identify human health hazards
- Developing new approaches to better inform evidence-based **research** decisions

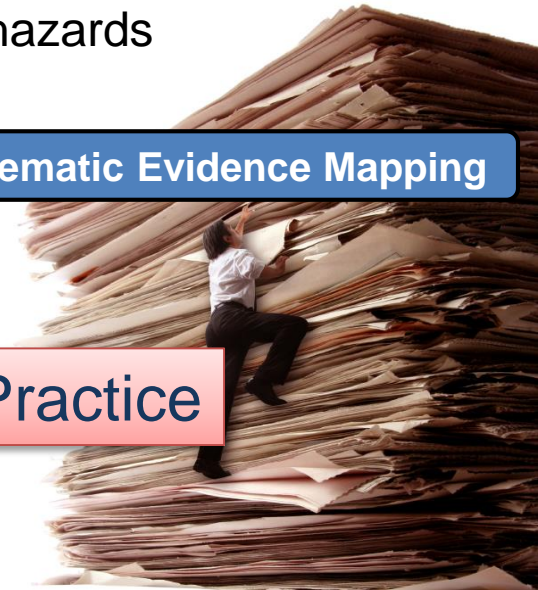
Systematic Evidence Mapping

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Innovation



Practice





Fit for Purpose Evaluation Format

- **Systematic Review**

- Predefined, multistep process to identify, select, critically assess, and synthesize evidence to answer a specific research question

- **Goals:**



Answering a specific research question



Support decision making



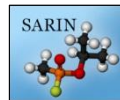
Hazard conclusions

- **Conclusions to Inform Policy Decisions**



Occupational Exposure to Cancer Chemotherapy Agents

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Sarin

- **DRAFT Conclusions on:** Long-term neurological effects following acute exposure



Traffic-related Air Pollution

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Fluoride

- **Developing Conclusions on:** Potential developmental neurotoxicity



Fit for Purpose Evaluation Format

- **Systematic Review**

- Predefined, multistep process to identify, select, critically assess, and synthesize evidence to answer a specific research question

- **Goals:**

- ➡ Answering a specific research question
- ➡ Support decision making
 - ➡ Hazard, evidence conclusions

- **Scoping Review and Evidence Mapping**

- Summary and categorization of literature prepared to rapidly map the key concepts, types of evidence, and gaps in research by systematically searching, selecting and presenting the evidence

- **Goals:**

- ➡ Characterize state of knowledge on a topic or question
- ➡ Support decision making
 - ➡ Interactive, reader-driven
 - ➡ Identify data “pockets” and gaps

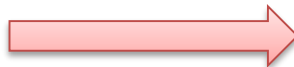


Systematic Reviews of Health Effects Evidence

Developing New Approaches to Better Inform Evidence-based Research Decisions

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Toxicology

Innovation



Practice

Evidence
Mapping

Exposure	Congenital Malformations		Endocrine System		Growth		Nervous System		Prematurity-Related Neonatal Outcomes	Reproductive System		Other Outcomes		Grand Total
	Animal	Human	Animal	Human	Animal	Human	Animal	Human		Animal	Human	Animal	Human	
17OHPC	5	13	2		5	30	2	5	21	4		2	1	44
allylestrenol		2	2				3			2		1		10
chlormadinone acetate			1											1
cyproterone acetate	9		3		5		8			6		1		17
desogestrel						1								1
dienogest	1				1									1
drospirenone				1			2					2		4
dydrogesterone		4	1			4	1					2		9
ethynodiol diacetate		2												2
gestodene							1					1		1
levonorgestrel	1	3	3		2	3	2	1		1		1		9
lynestrenol	1	1			1									2
MDAP			1	1										1
megestrol acetate	1													1
MPA	7	4	5		6	5	4	7		4	2	3	1	26
norethindrone	3	2	3		3	1	2			6		1		10
norethindrone acetate	1				1		1			2		1		3
norethynodiol					1									1

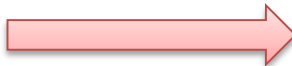


Systematic Reviews of Health Effects Evidence

Developing New Approaches to Better Inform Evidence-based Research Decisions

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Toxicology

Innovation



Practice



Evidence Mapping to Inform **PROBLEM FORMULATION**

- Environmental Exposures and Inflammation-based Atherosclerosis



Evidence Mapping to inform **HEALTH EFFECT SCOPING**

- Prenatal Exposure to Progestogens



Evidence Mapping to support **STATE OF THE SCIENCE**

- Transgenerational Inheritance

Walker et al. 2018 An evidence map and state-of-the-science evaluation. *Environment International* 115: 48-69.



DNTP Translational Toxicology Pipeline Plan

Fit for Purpose Literature Evaluations

Evidence Mapping

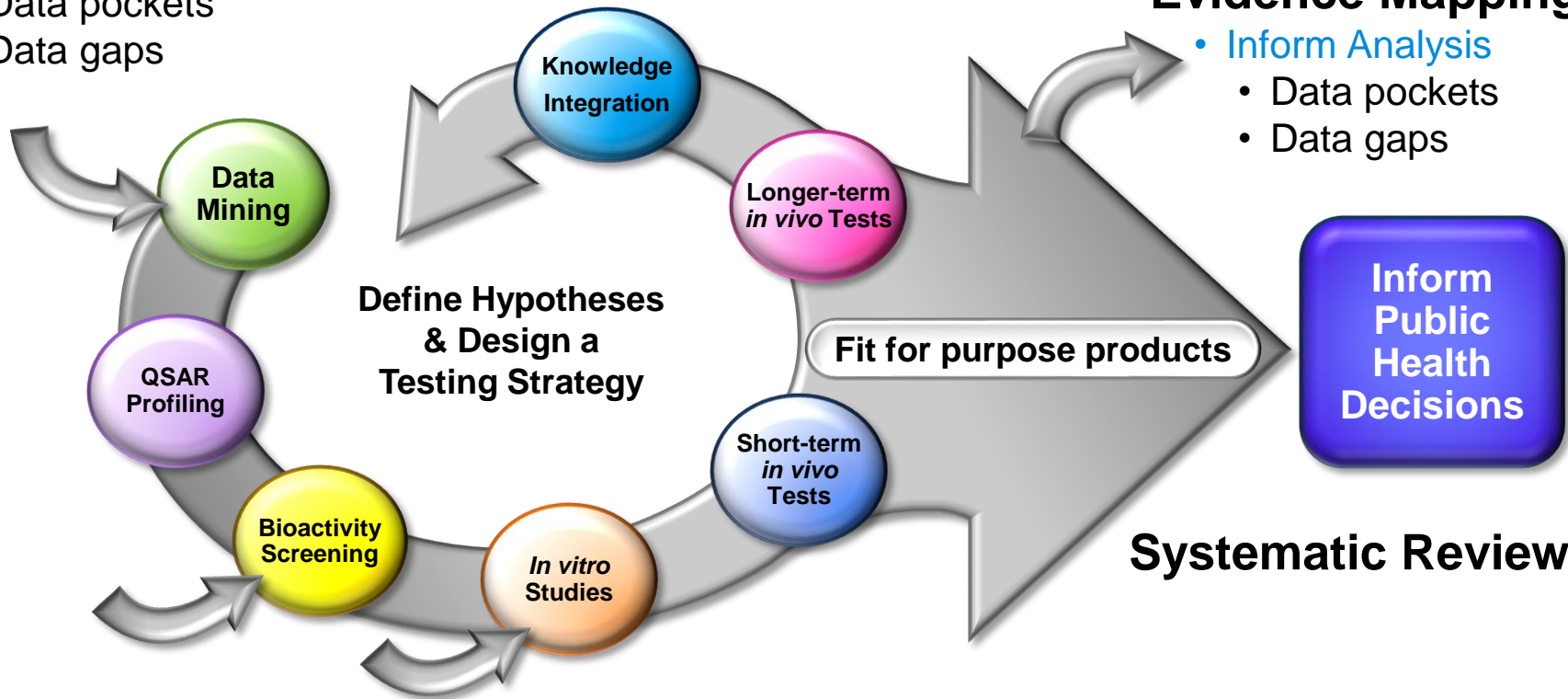
- Inform Research

- Data pockets
- Data gaps

Evidence Mapping

- Inform Analysis

- Data pockets
- Data gaps





New Approaches to Inform Evidence-Based Research Decisions

- Literature Scoping and Evidence Mapping Approaches

— Vickie Walker

- Integrating Literature Analysis into the NTP Research Pipeline

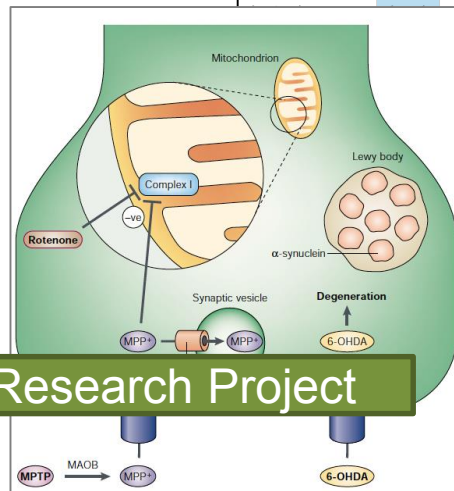
- Windy Boyd

Evidence Mapping

Mapping

	Genital Malformations		Endocrine System		Growth		Nervous System		Prematurity-Related Neonatal Outcomes	Reproductive System		Other Outcomes		Grand Total
Exposure	Animal	Human	Animal	Human	Animal	Human	Animal	Human	Human	Animal	Human	Animal	Human	
17OHPc	5	13	2		5	30	2	3	21	4		2	1	44
allylestrenol		2	2											10
chlormadinone acetate			1											1
cyproterone acetate	9		3		5		8			6		1		17
desogestrel						1								1
dienogest	1				1									1
drospirenone			1				2					2		4
dydrogesterone		4	1			4	1					2		9
ethynodiol diacetate		2												2
gestodene							1					1		2
levonorgestrel	1	3	3			2	3	2	1	1		1		9
					1									2
				1										1
														1
							6	5	4	7				26
						3	1	2				3	1	10
						1		1				1		3
						1				2				1

mitochondrion



Parkinson's Disease Research Project



Thank you

Questions?