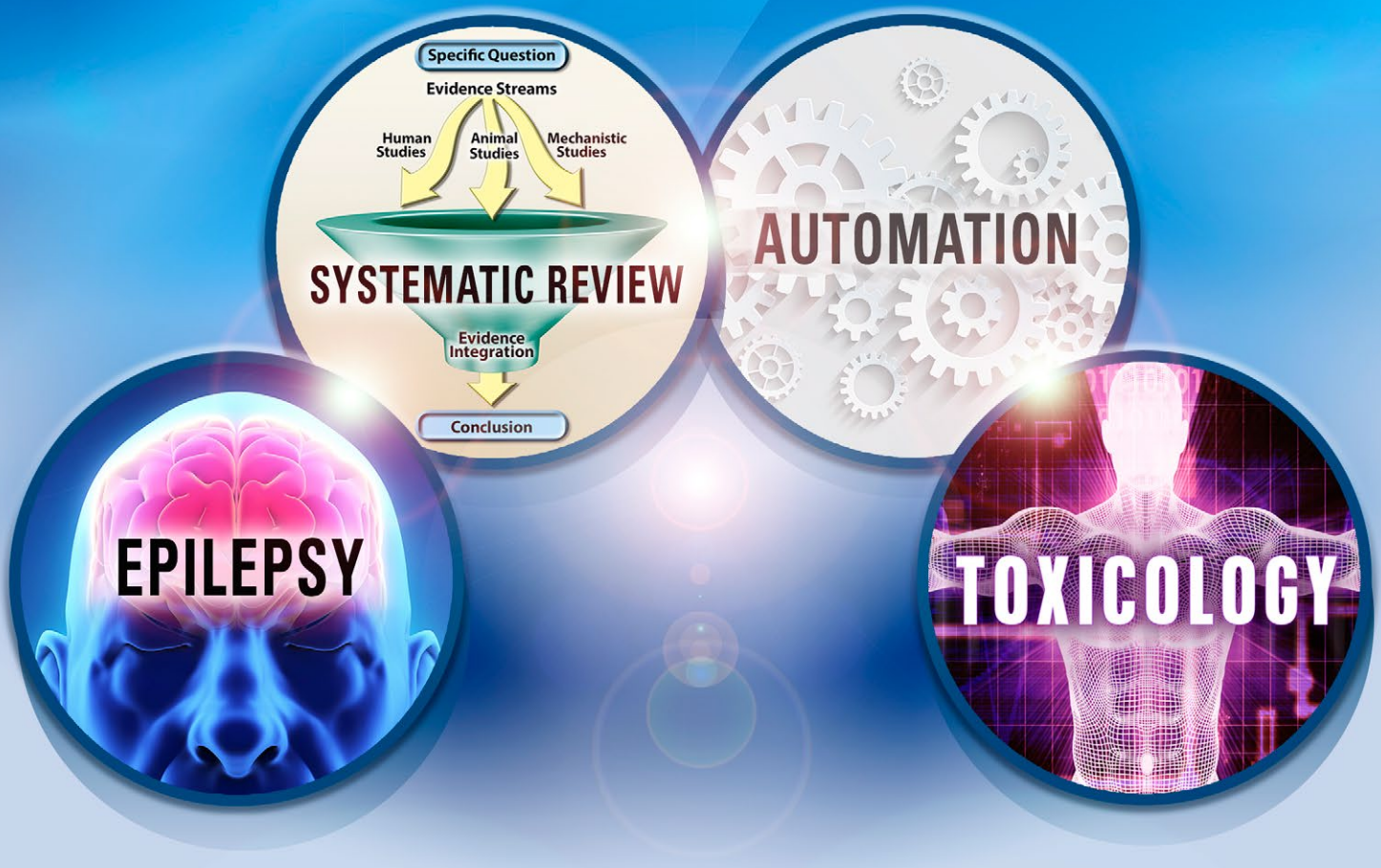
National Toxicology Program
U.S. Department of Health and Human Services



4th International Symposium on

Systematic Review and Meta-Analysis of Laboratory Animal Studies

August 24-25, 2017

NIEHS Building 101, Rodbell Auditorium

111 TW Alexander Drive, Research Triangle Park, N.C.

Revised August 22, 2017 to include participant list and additional poster abstract.

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Welcome

Dr. Andrew Rooney

Acting Director
Office of Health Assessment and Translation (OHAT)
National Institute of Environmental Health Sciences (NIEHS)
National Toxicology Program (NTP)

On behalf of the organizing committee for the 4th International Symposium on Systematic Review and Meta-Analysis of Laboratory Animal Studies, I would like to welcome you to our symposium in Research Triangle Park, North Carolina, USA.

The role of systematic review and meta-analysis in preclinical science is evolving rapidly and these changes are reflected in our program of Keynote and Platform presentations. We hope that newcomers and experts alike will enjoy the strategic overviews of why these research tools are important and the explicit examples of how they are evolving to answer a diverse range of research questions.

We hope you will enjoy these presentations and use them as the focal point for thought provoking and stimulating discussions, exchanging ideas and forging new collaborations.

Best Regards,

Andrew Rooney, Ph.D.

Organizing Committee

Andrew Rooney, Ph.D. and Vickie Walker
National Toxicology Program at the National Institute of Environmental Health Sciences

NTP is an interagency program focused on evaluating substances in our environmental to identify potential hazards through research, testing, and analysis activities. Information generated by NTP is communicated to health research and regulatory agencies, medical and scientific communities, and the public to inform decisions that protect human health.

Emily Sena, Ph.D. and Gillian Currie, Ph.D.
Collaborative Approach to Meta-Analysis and Review of Animal Data from Experimental Studies (CAMARADES)

The CAMARADES collaboration provides a supporting framework for groups involved in the systematic review and meta-analysis of data from experimental animal studies. CAMARADES aims to provide a central focus for data sharing; to act as a resource for those wishing to carry out such reviews; to provide a web based stratified meta-analysis bioinformatics engine; and to act as a repository for completed reviews.

Xabier Arzuaga, Ph.D.
U.S. Environmental Protection Agency, National Center for Environmental Assessment, Integrated Risk Information System

EPA's mission is to protect human health and the environment. EPA's IRIS Program supports this mission by identifying and characterizing the health hazards of chemicals found in the environment.

David Howells, Ph.D.
University of Tasmania School of Medicine, Australia

The University of Tasmania's Faculty of Health is globally recognized for the quality of health professional education and transformative health and medical research. In 1965, the School of Medicine was created in response to the needs of the community. There was a workforce shortage of doctors in Tasmania, so the School of Medicine was established to specialize in medical education.

Juleen Lam, Ph.D.

University of California, San Francisco

UCSF is a collection of dedicated scientists, clinicians, students and staff who share a common drive to make the world a better place by advancing health and the human condition. Care and compassion are as critical as science and discovery in fulfilling our mission to drive change, and make a difference for individual patients and whole populations.

Rob de Vries, Ph.D.

Systematic Review Centre for Laboratory Animal Experimentation, Department for Health Evidence, Radboud University Medical Center, The Netherlands

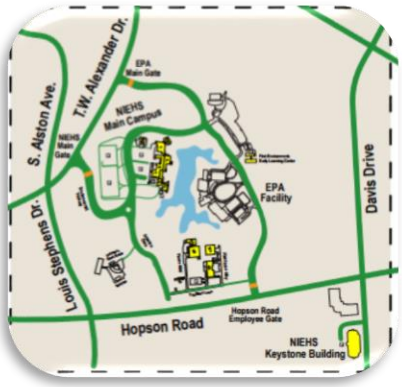
SYRCLE's aim is to promote the concept of systematic reviews of animal studies (SRs) in research. SRs contribute to more evidence-based choice of animal models, the implementation of the 3Rs and better patient safety.

Meeting Support

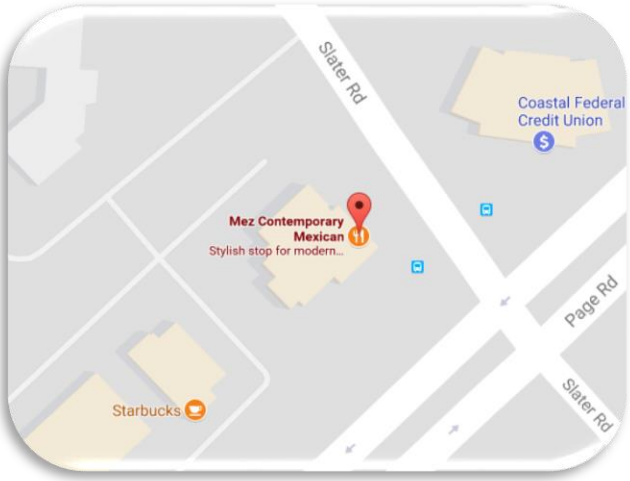
Canden Byrd, Laura Thomas, and Susan Blaine

Venues

National Institute of Environmental Health Sciences
111 T.W. Alexander Drive, Research Triangle Park, NC 27709
United States of America
NIEHS Building 101, Rodbell Auditorium
Telephone: (919) 541-3345



Mez Contemporary Mexican
Dinner: Thursday, August 24 at 7:00 PM EDT
5410 Page Road, Durham, NC 27703
United States of America
Telephone: (919) 941-1630



Agenda

Thursday, August 24

Time	Presentation
8:30 AM	**Welcome and Opening Remarks** John Bucher | *NIEHS, NTP*
8:40 AM	**Uptake of Systematic Review and Meta-Analysis in Toxicology and Public Health** Andrew Rooney | *NIEHS, NTP*
Session 1: Systematic Reviews or Meta-Analyses in Toxicology and Public Health Chair: Juleen Lam	
9:00 AM **Keynote**	**Navigating the Science – Opportunities to Improve Health Through Advances in Systematic Reviews** Tracey Woodruff | *University of California, San Francisco*
9:45	**Implementing the Systematic Review Approach in Non-Clinical Fields: The Importance of Education** Rob De Vries | *SYRCLE*
10:00	**Systematic Evidence Map of Transgenerational Inheritance of Health Effects** Vickie Walker | *NIEHS, NTP*
10:15	**Aerobic but Not Resistance Exercise Can Induce Inflammatory Pathways via Toll-like 2 and 4: A Systematic Review** Paula Andréa Malveira Cavalcante | *Federal University of São Paulo (UNIFESP), Brazil*
10:30 – 10:45 AM	**Break**
10:45	**Systematic Reviews and Meta-Analysis for Environmental Health: Proof-of-Concept Case Study Examples** Juleen Lam | *University of California, San Francisco*
11:00	**Ensuring Only High-quality Systematic Reviews Get Published: New Obligations and Strategies for Environmental Health Journals** Paul Whaley | *Lancaster University*
11:15	**Association Between Exposure to p,p'-DDT and its Metabolite p,p'-DDE With Obesity: Integrated Systematic Review and Meta-Analysis** Michele La Merrill | *University of California, Davis*
11:30	**Office of the Report on Carcinogens Systematic Review of Cancer Studies in Experimental Animals** Gloria Jahnke | *NIEHS, NTP*
11:45	**Performing Scoping Studies With SWIFT-Review and SWIFT-Active Screener** Brian Howard | *Sciome*
12:00 – 1:15 PM	**Lunch**

Session 2: Automation of Systematic Reviews

Chair: Andrew Rooney

Time	Presentation
1:15 PM **Keynote**	**Semi-Automating Evidence Synthesis via Machine Learning and Natural Language Processing** Byron Wallace | *Northeastern University*
2:00	**Systematic Review Facility (SyRF) – A Toolbox for Systematic Review and Meta-Analysis** Gillian Currie | *CAMARADES*
2:15	**Machine Learning Approaches to Assist the Screening Stage of Pre-Clinical Systematic Reviews** Alexandra Bannach-Brown | *University of Edinburgh, Aarhus University*
2:30	**SWIFT-Active Screener: Reducing Literature Screening Effort Through Machine Learning for Systematic Reviews** Ruchir Shah | *Sciome*
2:45	**The Vision of SLIM – A Systematic Living Information Machine** Jing Liao | *University of Edinburgh*
3:00 – 3:15 PM	**Break**
3:15	**Text Mining as a Tool to Aid the Assessment of Reporting of Risk of Bias and Other Methodological Quality Criteria** Zsanett Bahor | *University of Edinburgh*
3:30	**Applying the Key Characteristics Paradigm in Cancer Hazard Identification** Kate Guyton | *IARC Monographs*
3:45	**Lessons From the Conduct of Two Systematic Reviews in Risk Assessment: Focus on Collaborative Software Tools** Katya Tsaoiun | *Evidence-based Toxicology Collaboration, Johns Hopkins Bloomberg School of Public Health*
4:00	**Evaluation of Mechanistic Data Based on Key Characteristics of Carcinogens: Application of a Text Mining Tool and a Quantitative Evaluation Framework** Daniele Wikoff | *ToxStrategies*
4:15 PM	**General Discussion**
4:45 PM	**Poster Session/Social**
5:45 PM	**Adjourn**
7:00 PM	**Dinner**

Friday, August 25

Time	Presentation
8:30 AM	**Welcome Back and Opening Remarks** Andrew Rooney | *NIEHS, NTP*
Session 3: Systematic Review/Meta-Analysis Methods Development Chair: David Howells	
8:35 AM **Keynote**	**Do's and Don'ts in Meta-Analysis of Animal Study Data** Kim Wever | *SYRCLE*
9:20	**Impact of Choice of Effect Size and Meta-Analysis Method on Identifying Differences Between Groups of Animal Studies** Malcolm Macleod | *University of Edinburgh*
9:35	**Lessons Learned From a Systematic Review of Prenatal Exposure to Bisphenol A and Hyperactivity** Carol Kwiatkowski | *The Endocrine Disruption Exchange (TEDX)*
9:50	**Preferred Reporting Items in Systematic Reviews and Meta-Analysis – In Vivo Animal Research Extension (PRISMA–IVA)** Marc Avey | *ICF*
10:05	**An Application of the Aggregate Exposure Pathway (AEP) and Adverse Outcome Pathway (AOP) Frameworks to Mechanistically Integrate Data Sources Across Multiple Species Into Cumulative Risk Assessment (CRA)** David Hines | *U.S. Environmental Protection Agency*
10:20 – 10:35 AM	**Break**
10:35	**Network Meta-Analysis for Preclinical Studies** Emily Sena | *University of Edinburgh*
10:50	**Application of SR to Fit-For-Purpose Evaluation of Tox21 Assays** Robert Wright | *Johns Hopkins University*
11:05	**Protocol Registration for Systematic Reviews of Animal Studies Relevant for Human Health in PROSPERO** Marc Avey | *ICF*
11:20	**Identification of Key Characteristics of Male Reproductive Toxicants as an Approach for Screening and Sorting Mechanistic Evidence** Xabier Arzuaga | *U.S. Environmental Protection Agency*
11:35	**Meta-Analysis of Animal Studies in Environmental Health: Challenges, Opportunities, and Lessons Learned From Evaluating Evidence From Endocrine Active Chemicals** Weihsueh Chiu | *Texas A&M University*

Session 4: New/Late Breaking Systematic Reviews or Meta-Analyses Chair: Rob De Vries	
Time	**Presentation**
11:50	**MVA85A TB Vaccine: Synthesis of Animal Studies Raised Fundamental Questions** Paul Garner | *Centre for Evidence Synthesis in Global Health, Liverpool School of Tropical Medicine*
12:05	**A Perfect Storm of Bias – The Use and Misuse of Observational Scoring in Animal Studies Exemplified by the Rat Grimace Scale** Otto Kalliokoski | *University of Copenhagen*
12:20	**How Authors of Biomedical Research Describe the Design Aspects of the Study and Implications for Variance Estimation and Automation of Reviews** Annette O'Connor | *Iowa State University*
12:35 – 1:45 PM	**Lunch**
Session 5: Systematic Reviews or Meta-Analyses in Epilepsy and Other Human Diseases Chair: Emily Sena	
1:45 PM **Keynote**	**Identification and Characterization of Outcome Measures Reported in Animal Models of Chronic Epilepsy** Michele Simonato | *University of Ferrara*
2:30	**Why Be Systematic – Preclinical Stroke as an Exemplar** David Howells | *University of Tasmania, Australia*
2:45	**Systematic Evidence Mapping of Chemical Exposures and Parkinson's Disease to Support Future Research** Ana Antonic | *University of Melbourne, Melbourne School of Engineering*
3:00	**Language Inclusion and Search Approaches in "Systematic" Reviews of Animal Toxicity and Communicable Disease Studies** Kristine Alpi | *North Carolina State University*
3:15 PM	**General Discussion**
3:45 PM	**Closing Remarks**
4:00 PM	**Adjourn**

Poster Session

Thursday, August 24 at 4:45 PM EDT

Sponsor:

Evidence-Based Toxicology Collaboration (EBTC)
EBTC is a collaboration of science, regulatory and industry leaders, united in their vision to improve the public health outcomes and reduce human impact on the environment by bringing evidence-based approaches to safety sciences.

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1. **Neepa Choksi |** *ILS, Inc., Research Triangle Park, NC, USA*
   Curation and Analysis of a Rodent Uterotrophic Database: Insights on Data Quality and Reproducibility

2. **Allen Davis |** *NCEA, ORD, US EPA, Research Triangle Park, NC, USA*
   Quantitative Meta-analytic Approaches for the Systematic Synthesis of Data and Hazard Identification: A Case-Study of Decreased Pain Sensitivity Due to Trimethylbenzene Exposure

3. **Emmi Felker-Quinn |** *NCEA, ORD, US EPA, Research Triangle Park, NC, USA*
   Systematic Review and Assessment of Links Between Sulfur Deposition, Sulfur Cycling, and Mercury Cycling in North American Ecosystems

4. **Beruk Kiros |** *DNTP, NIEHS, NIH, Research Triangle Park, NC, USA*
   Use of Text-Mining and Machine Learning Approaches to Conduct a Rapid Literature Survey on Environmental Chemicals and the Thyroid

5. **Carol Kwiatkowski |** *The Endocrine Disruption Exchange (TEDX)*
   To Scope or Not to Scope: The Role of Scoping Reviews in Environmental Health

6. **Juleen Lam |** *University of California, San Francisco*
   Estimating and Valuing Health Impacts of Formaldehyde Exposure to Improve Decision-Making

7. **Elizabeth Maull** | *NICEATM, DNTP, NIEHS, NIH, Research Triangle Park, NC*
   Development of a Curated Database of In Vivo Developmental Toxicity Data

8. **Zsuzsanna Nemeth** | *Leonard M. Miller School of Medicine, University of Miami*
   A Systematic Review of the Role of Cannabis in the Etiology of Acute Pancreatitis

9. **Annette O'Connor** | *Iowa State University, Ames, IA, USA*
   A Tool for Tagging/Highlighting/Extracting Text From PDF's: AFLEX Tagging Tool

10. **Kieron Rooney** | *Faculty of Health Sciences and Charles Perkins Centre, University of Sydney, Australia*
    An Institutional Approach to Enhancing Best Practice in Animal Research

11. **Emily Sena** | *The University of Edinburgh, Edinburgh, United Kingdom*
    The Impact of Systematic Review of Animal Studies on Research Culture

12. Andy Shapiro | *DNTP, NIEHS, NIH, Research Triangle Park, NC, USA*
HAWCPROJECT.ORG: A Content Management System for Human Health Assessments

13. Andy Shapiro | *DNTP, NIEHS, NIH, Research Triangle Park, NC, USA*
Table Builder: A Content Management System for Carcinogenicity Health Assessments for the IARC Monographs and the NTP Report on Carcinogens

14. Joanne Spahn | *U.S. Department of Agriculture, Washington, D.C., USA*
Application of Text-Mining and Machine Learning Technology in Nutrition Systematic Review Screening: A Pilot Study

15. Joanne Spahn | *U.S. Department of Agriculture, Washington, D.C., USA*
Identifying Needles in a Haystack: Use of Text-Mining and Machine Learning Technology to Improve Efficiency in Conducting Nutrition-Related Systematic Reviews

16. Rob de Vries | *SYRCLE, Radboud University Medical Center, Nijmegen, The Netherlands*
From Animal Model to Translational Strategy: A Systematic Literature Review of Animal Models for Cystic Fibrosis

17. Rob de Vries | *SYRCLE, Radboud University Medical Center, Nijmegen, The Netherlands*
From Animal Model to Translational Strategy: A Systematic Review of Experimental Design in the Preclinical and Clinical Studies of Methotrexate for Rheumatoid Arthritis (RA)

18. Kim Wever | *SYRCLE, Radboud University Medical Center, Nijmegen, The Netherlands*
A Systematic Review and Meta-Analysis of the Protective Effects of Metformin in Experimental Myocardial Infarction

19. Kim Wever | *SYRCLE, Radboud University Medical Center, Nijmegen, The Netherlands*
Standardized Mean Differences Cause Funnel Plot Distortion in Publication Bias Assessments

20. Daniele Wikoff | *ToxStrategies, Asheville, NC, USA*
Development of a Quantitative Weighting Framework to Systematically Evaluate the Validity of Relative Potency Estimates From a Heterogeneous Evidence Base for Dioxin-Like Compounds

21. Erin E. Yost | *NCEA, US EPA, Research Triangle Park, NC, USA*
Focusing and Refining the Evaluation of Reproductive Endpoints in a Systematic Review of PCBs

Keynote Presentations

Systematic Reviews or Meta-Analyses in Toxicology and Public Health

Navigating the Science – Opportunities to Improve Health Through Advances in Systematic Reviews

Tracey Woodruff | *University of California, San Francisco*

Automation of Systematic Reviews

Semi-Automating Evidence Synthesis via Machine Learning and Natural Language Processing

Byron Wallace | *Northeastern University*

Systematic Review/Meta-Analysis Methods Development

Do's and Don'ts in Meta-Analysis of Animal Study Data

Kim Wever | *SYRCLE, Department for Health Evidence, Radboud University Medical Center, The Netherlands*

Systematic Reviews or Meta-Analyses in Epilepsy and Other Human Diseases

Identification and Characterization of Outcome Measures Reported in Animal Models of Chronic Epilepsy

Michele Simonato | *University of Ferrara*

Oral Presentations

Implementing the Systematic Review Approach in Non-Clinical Fields. The Importance of Education.

Rob B.M. de Vries[1]

1. SYstematic Review Centre for Laboratory animal Experimentation (SYRCLE), Department for Health Evidence, Radboud University Medical Center, Nijmegen, The Netherlands

Over the last decade and a half, several initiatives have been taken to translate the systematic review methodology from clinical medicine to new fields, notably to preclinical animal research and toxicology. Such translation is hampered by a host of issues, for example, by poor reporting standards and/or low methodological quality in the new field and by high heterogeneity among the evidence to be combined. A hurdle to which less attention seems to have been paid is unfamiliarity with the methodology. The lack of awareness in the new field may lead to misconceptions about the concept of systematic review and its advantages and thereby cause resistance to the methodology. Moreover, the conduct of high quality systematic reviews requires (the involvement of experts with) methodological knowledge and skills, which by definition are scarce in a new field of application.

A crucial tool to tackle the issue of unfamiliarity is education. In this presentation, the focus will be on the educational programme developed by SYRCLE. The different elements of this programme will be presented, from the introductory e-learning module via hands-on trainings to intensive coaching of researchers conducting their own systematic reviews. Special attention will be paid to the training programme that SYRCLE has developed for the staff and experts of the European Food Safety Authority (EFSA). Moreover, the evaluations of the different forms of education and the qualitative feedback received will be discussed. Based on the lessons we learned, we will make recommendations on how to implement (this form of) education on a larger scale.

Systematic Evidence Map of Transgenerational Inheritance of Health Effects

Vickie R. Walker[1], Abee L. Boyles[1], Katherine E. Pelch[1], Stephanie D. Holmgren[2], Andrew J. Shapiro[3], Chad R. Blystone[4], Michael J. Devito[5], Retha R. Newbold[6], Robyn Blain[7], Pamela Hartman[7], Kristina A. Thayer[8] and Andrew A. Rooney[1]

1. Office of Health Assessment and Translation (OHAT), Division of National Toxicology Program (NTP), National Institute of Environmental Sciences (NIEHS), National Institutes of Health (NIH), Research Triangle Park, NC, USA
2. Office of Scientific Information Management, NIEHS, NIH, Research Triangle Park, NC, USA
3. Program Operations Branch, DNTP, NIEHS, NIH, Research Triangle Park, NC, USA
4. Toxicology Branch, DNTP, NIEHS, NIH, Research Triangle Park, NC, USA
5. NTP Laboratory, DNTP, NIEHS, NIH, Research Triangle Park, NC, USA
6. Researcher Emeritus, DNTP, NIEHS, NIH, Research Triangle Park, NC, USA
7. ICF, Research Triangle Park, NC, USA
8. U.S. Environmental Protection Agency (EPA), National Center for Environmental Assessment (NCEA), Research Triangle Park, NC, USA

BACKGROUND: An increasing number of reports suggest early life exposures result in adverse effects in offspring who were never directly exposed; this phenomenon is termed “transgenerational inheritance.” Given concern for public health implications for potential effects of exposures transmitted to subsequent generations, it is critical to determine how widespread and robust this phenomenon is and to identify the range of exposures and possible outcomes.

OBJECTIVES: This report examines the evidence for transgenerational inheritance associated with exposure to a wide range of stressors in humans and animals to identify areas of consistency, uncertainty, data gaps, and to evaluate general risk of bias issues for the transgenerational study design.

METHODS: A protocol was developed to collect and categorize the literature into a systematic evidence map for transgenerational inheritance by health effects, exposures, and evidence streams following the OHAT approach for conducting literature-based health assessments.

RESULTS: A PubMed search yielded 63,758 unique records from which 281 relevant studies were identified and categorized into a systematic evidence map by evidence streams (49 human and 232 animal), broad health effect categories, and exposures. Data extracted from the individual studies are available in HAWC. There are relatively few bodies of evidence where multiple studies evaluated the same exposure and the same or similar outcomes. Studies evaluated for risk of bias generally had multiple issues in design or conduct.

CONCLUSIONS: The evidence mapping illustrated that risk of bias, few studies, and heterogeneity in exposures and endpoints examined present serious limitations to available bodies of evidence for assessing transgenerational effects. Targeted research is suggested to address inconsistencies and risk of bias issues identified, and thereby establish more robust bodies of evidence to critically assess transgenerational effects - particularly by adding data on exposure-outcome pairs where there is some evidence (i.e., reproductive, metabolic, and neurological effects).

Aerobic but Not Resistance Exercise Can Induce Inflammatory Pathways via Toll-like 2 and 4: A Systematic Review

Paula Andréa Malveira Cavalcante[1,3,4], Marcos Fernandes Gregnani[2,3,4], Jessica Salles Henrique[5,6], Fábio H. Ornellas[1,3,4], Ronaldo Carvalho Araújo[1,2,3,4]

1. Medicine (Nephrology) Program, Federal University of São Paulo (UNIFESP), São Paulo, SP, Brazil
2. Molecular Biology Program, Federal University of São Paulo (UNIFESP), São Paulo, SP, Brazil
3. Laboratory of Exercise Genetics and Metabolism, Federal University of São Paulo (UNIFESP), São Paulo, SP, Brazil
4. Department of Biophysics, Federal University of São Paulo (UNIFESP), São Paulo, SP, Brazil
5. Neurology/Neuroscience Program, Federal University of São Paulo (UNIFESP), São Paulo, SP, Brazil
6. Exercise Neurophysiology Laboratory, Federal University of São Paulo (UNIFESP), São Paulo, SP, Brazil

Over the last decade and a half, several initiatives have been taken to translate the systematic review methodology from clinical medicine to new fields, notably to preclinical animal research and toxicology. Such translation is hampered by a host of issues, for example, by poor reporting standards and/or low methodological quality in the new field and by high heterogeneity among the evidence to be combined. A hurdle to which less attention seems to have been paid is unfamiliarity with the methodology. The lack of awareness in the new field may lead to misconceptions about the concept of systematic review and its advantages and thereby cause resistance to the methodology. Moreover, the conduct of high quality systematic reviews requires (the involvement of experts with) methodological knowledge and skills, which by definition are scarce in a new field of application.

A crucial tool to tackle the issue of unfamiliarity is education. In this presentation, the focus will be on the educational programme developed by SYRCLE. The different elements of this programme will be presented, from the introductory e-learning module via hands-on trainings to intensive coaching of researchers conducting their own systematic reviews. Special attention will be paid to the training programme that SYRCLE has developed for the staff and experts of the European Food Safety Authority (EFSA). Moreover, the evaluations of the different forms of education and the qualitative feedback received will be discussed. Based on the lessons we learned, we will make recommendations on how to implement (this form of) education on a larger scale.

Systematic Reviews and Meta-Analysis for Environmental Health: Proof-of-Concept Case Study Examples

Juleen Lam[1], Erica Koustas[2], Patrice Sutton[1], Tracey Woodruff[1]

1. University of California, San Francisco, CA, USA
2. Scientific consultant to University of California, San Francisco, CA, USA

The Navigation Guide is a systematic review methodology developed to synthesize available scientific evidence to address environmental health-related questions. This approach is based on Cochrane/GRADE methods and includes the same elements (development of a protocol, evaluating risk of bias, evaluating and integrating evidence, etc.) but accounts for differences inherent to environmental health assessments, i.e., the reliance on human observational studies in the absence of randomized controlled trials (RCTs) and the fact that population exposure to exogenous environmental chemicals often precedes any evidence of their safety. To date, we have completed six proof-of-concept case studies demonstrating the application of systematic review methods to address a broad range of environmental health-related questions. One recent case study involved exposures to polybrominated diphenyl ethers (PBDEs) flame retardant chemicals and associations with measures of intelligence (such as Intelligence Quotient, IQ) and Attention Deficit/Hyperactivity Disorder (ADHD). We included fifteen studies and rated individual studies with low to probably-low risk of bias and the overall body of evidence as “moderate” quality with “sufficient” evidence for an association between IQ and PBDEs. Our meta-analysis of four studies estimated a 10-fold increase in PBDE exposure associated with a decrement of 3.70 IQ points (95% CI: 0.83, 6.56). We concluded the body of evidence was of “moderate” quality for ADHD with “limited” evidence for an association with PBDEs, based on the heterogeneity of association estimates reported by a small number of studies. We concluded there was “sufficient” evidence supporting an association between developmental PBDE exposure and reduced IQ. Systematic reviews and meta-analyses can be a valuable contribution for maximizing transparency in performing assessments, facilitating clear presentations for the basis for scientific judgments, and summarizing the available data in a robust and reproducible manner.

Ensuring Only High-Quality Systematic Reviews Get Published: New Obligations and Strategies for Environmental Health Journals

Paul Whaley[1]

1. Lancaster Environment Centre, Lancaster University and Environment International, Elsevier

Systematic reviews are becoming increasingly prevalent in the environmental health literature, driven by recognition of their value as a “gold standard” method for reliably synthesising evidence relevant for public health and environmental policy-making. However, early evidence suggests that environmental health journals are publishing too many low-quality systematic reviews. This brings the risk that flawed reviews will be mistaken for gold-standard research, potentially resulting in environmental health challenges being misidentified, subsequent policy being based on incorrect interpretations of the available evidence, and ultimately the value of systematic review in decision-making being undermined. In this context, the new obligations being placed on scientific journals by the research and policy communities’ growing interest in systematic review methods are discussed. Experience is shared of efforts at the journal Environment International to raise the standard of published systematic reviews, including appointment of the first Associate Editor for Systematic Reviews at an environmental health journal, the use of Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) reports in the submission process, improved communication with submitting authors, and changes to the peer-review process. The results of two international projects to develop quality assurance and control interventions for systematic reviews are also presented, one a code of practice for environmental health systematic reviews directed at researchers and the other a toolkit to enhance the peer-review of systematic reviews, along with a theory of change as to how these are anticipated to be effective for raising the standard of published manuscripts.

Association Between Exposure to p,p'-DDT and its Metabolite p,p'-DDE With Obesity: Integrated Systematic Review and Meta-Analysis

Michele A. La Merrill[1], German Cano-Sancho[2], Andrew G. Salmon[3]

1. University of California, Davis, CA, USA
2. Oniris, Nantes, France
3. Office of Environmental Health Hazard Assessment, California Environmental Protection Agency, Oakland, CA, USA

Background: The prevalence of obesity is increasing in all countries, becoming a substantial public health concern worldwide. Increasing evidence has associated obesity with persistent pollutants such as the pesticide DDT and its metabolite p,p'-DDE.

Objectives: To systematically review the literature on the association between exposure to the pesticide DDT and its metabolites, and obesity to develop hazard identification conclusions.

Methods: We applied a systematic review-based strategy to identify and integrate evidence from epidemiological, in vivo and in vitro studies. The evidence from prospective epidemiological studies was quantitatively synthesized by meta-analysis. We rated the body of evidence and integrated the streams of evidence to systematically develop hazard identification conclusions.

Results: We identified seven epidemiological studies reporting prospective associations between exposure to p,p'-DDE and adiposity assessed by body mass index (BMI) z-score. The results from the meta-analysis revealed positive associations between exposure to p,p'-DDE and BMI z-score (β=0.13 BMI z-score (95% CI 0.01; 0.25) per log increase of p,p'-DDE). Two studies constituted the primary in vivo evidence. Both studies reported positive associations between exposure to p,p'-DDT and increased adiposity in rodents. We identified 19 in vivo studies and seven in vitro studies which supported the biological plausibility of the obesogenic effects of p,p'-DDT and p,p'-DDE.

Conclusions: We concluded that the p,p'-DDT and p,p'-DDE are "presumed" to be obesogenic for humans, based on a moderate level of primary human evidence, a moderate level of primary in vivo evidence, and a moderate level of supporting evidence from in vivo and in vitro studies.

Office of the Report on Carcinogens Systematic Review of Cancer Studies in Experimental Animals

Gloria D. Jahnke[1]

1. Office of the Report on Carcinogens (ORoC), NTP, NIEHS, NIH, Research Triangle Park, NC, USA

The NTP Office of the Report on Carcinogens (ORoC) evaluates substances that pose a hazard to people residing in the US for possible listing in the Report on Carcinogens (RoC), a congressionally-mandated, science-based biennial report. The cancer hazard evaluation is captured in a monograph which informs a substance profile in the RoC. The approach to conducting cancer hazard evaluations for human and animal cancer studies incorporates principles of systematic review, with the goal of increasing transparency (to the public and others) on how conclusions are reached and strengthening consistency across evaluations of different substances. The ORoC process for systematic review of cancer studies is detailed in the RoC Handbook for Preparing RoC Monographs; the approach for animal cancer studies is outlined below.

- Identification of Relevant Literature
- Protocol Development
- Systematic Extraction of Data
- Study quality and utility assessment by two independent reviewers using structured questions that address the following study elements: Study design, Exposure conditions, Outcome assessment and measurement, Confounding, Analysis and reporting, Study judgment – Principal strengths and limitations and overall utility of the study are addressed.
- Animal Cancer Hazard Evaluation
- Scientific evidence is synthesized across studies, with greater weight given to studies of greater utility and higher study quality.
- A level of evidence conclusion (sufficient/not sufficient) is determined based on RoC listing criteria for animal studies.

To date, we have applied this method to five RoC monographs that have undergone peer review. The findings of the human and animal cancer evaluations and supporting mechanistic data, other relevant information, and federal regulations are reported as a profile in the RoC. The NTP, with assistance from other federal health and regulatory agencies and nongovernmental institutions, prepares the Report on Carcinogens for the Secretary, DHHS.

Performing Scoping Studies With SWIFT-Review and SWIFT-Active Screener

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Identifying addressable questions for systematic reviews can be a challenge, especially in environmental health where evidence from human, animal, and in vitro studies is often integrated in assessments. Text-mining and machine learning tools hold promise to help with problem formulation. Here we discuss two software applications designed specifically for the purpose of (partially) automating the problem formulation and scoping processes of systematic review. The two applications, SWIFT-Review and SWIFT-Active Screener, work together to allow users to more efficiently explore large volumes of literature, incorporating visual tools that enable users to quickly identify topics that have been extensively studied as well as emerging areas of research. Machine learning features such as topic modeling and active learning are integrated as well, allowing users to automatically cluster and prioritize the available literature for screening. In this presentation, we will highlight a popular scoping workflow conducted using these tools, showcasing several recent projects conducted at NIEHS and EPA. In addition, we will discuss numerous upcoming enhancements to these tools designed to further enhance scoping performed at EPA, including integration with the HERO database.

Systematic Review Facility (SyRF) – A Toolbox for Systematic Review and Meta-Analysis

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Systematic review & meta-analysis are powerful approaches to summarising research, but conducting a systematic review is time and resource-intensive and the rate of publication of new material means that they rapidly become outdated. Systematic Review Facility (SyRF) hosts an online platform to perform all stages of a systematic review and meta-analyses. The platform is flexible for individual projects and can be used to: screen large reference sets between multiple researchers; extract, store and analyse data; design annotation and data extraction fields; assign multiple researchers to different roles within a project and apply to access data from completed reviews to perform secondary analyses. Additionally, SyRF provides online educational resources and assistance through our online helpdesk.

The tools available include; the ability to perform a “living” systematic search, where the search is performed every 24 hours to help provide a continually updated summary of what is known; machine learning to aid screening where investigators only have to screen a fraction of the search results; automatic annotation where regular expression (Regex)-based approach is used to assess for the reporting of risk of bias items, more specifically the reporting of random allocation to group, blinded assessment of outcome and sample size calculation.

Tools under development include those to perform: machine assisted data extraction, duplicate removal, search filters for animal studies and PDF retrieval. To work towards the vision of providing a continually updated summary of what is known we also plan to provide an automatic link to publisher’s website.

The present SyRF toolbox has dramatically reduced the time frame for performing a systematic review and meta-analysis, enables collaboration between research centres and, reduces human errors and subjectivity when assessing for risk of bias within studies. The present SyRF toolbox and the tools under development will facilitate living systematic reviews.

Machine Learning Approaches to Assist the Screening Stage of Pre-Clinical Systematic Reviews

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Objectives: The screening phase of a systematic review (SR) is time-consuming. The number of papers being published in biomedical sciences is growing, which in turn extends the time required to screen articles for inclusion in a SR. The longer this process takes, the more out of date the results are when published. Machine learning (ML) approaches aim to reduce the amount of time required to perform this stage by analysing papers and ranking documents by relevancy, based on a sample of documents screened for inclusion by two independent human screeners.

Methods: Here we invite 5 ML groups to implement classifiers to assist the screening stage in 2 preclinical systematic reviews. The neuropathic pain dataset is an update to an existing SR where the training set of dual human screened data is more than 33,000 studies. The depression dataset is a recent SR, where the optimal amount of training data required to achieve a high performing algorithm is determined. Performance was assessed using sensitivity and specificity.

Results: In the neuropathic pain dataset, the best performing ML approach achieved sensitivity of 0.978 and specificity of 0.708. In the depression dataset, the best performing ML approach achieved sensitivity of 0.987 and specificity of 0.860. The performance of the ML algorithms were improved with the implementation of error analysis in the depression dataset, where the ML algorithm identifies potential human errors in the test set.

Conclusion: Here, we show that ML tools have a high level of performance. They can reduce the time required to conduct the screening stage of a SR. ML tools are now integrated into existing computer-based systematic review tools (such as SyRF.org.uk) for ease of use and allowing for more widespread use of ML approaches in SR.

SWIFT-Active Screener: Reducing Literature Screening Effort Through Machine Learning for Systematic Reviews

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Evidence-based toxicology is an emerging discipline in which researchers within government, industry and non-profit research organizations are increasingly employing systematic review in order to rigorously investigate, analyze and integrate the evidence from peer-reviewed publications. A critical and time-consuming step in this process is screening the available literature to select relevant articles for further review. To address this problem, we have developed SWIFT-Active Screener, a web-application which uses novel statistical and computational methods to prioritize articles for inclusion while offering guidance on when additional screening will no longer yield additional relevant articles. We tested Active Screener on 20 diverse systematic review studies in which human reviewers have previously screened, in total, more than 115,000 titles and abstracts. When compared to a traditional screening procedure, this method resulted in a 54% reduction in screening burden, on average, while still achieving at least 95% recall; when tested on a subset of the 13 studies that contain >1,000 articles, the reduction in screening burden improved to 71%. While these results are very promising, machine-learning prioritization approaches such as this can only be deployed confidently if users are ensured that critical articles are not missed. Accordingly, Active Screener employs a novel algorithm to estimate recall while users work, thus providing a statistical basis for decisions about when to stop screening. We tested this algorithm using the 20 historical datasets and demonstrate that in all cases the method could accurately predict when simulated screeners had achieved or slightly exceeded 95% recall. In Active Screener, these unique methodological advancements are implemented as a user-friendly web application that allows users to manage their review, track its progress and provide conflict resolution. In this presentation, we will provide an overview of the software and methods and showcase several screening projects recently conducted at NIEHS, EBTC, TEDX and USDA.

The Vision of SLIM – A Systematic Living Information Machine

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Systematic review (SR) and meta-analysis (MA) are useful tools to summarize data from primary research to inform future studies. Increasing numbers of new primary studies are being conducted and reported, however SRs can take years to complete and results are often out-of-date when published. The Systematic Living Information Machine (SLIM) aims to change the game.

We have developed an online platform to support SR and MA, Systematic Review and Meta-analysis Facility (SyRF). SLIM provides automation tools to accelerate reviews completed through SyRF, including classifiers to automate the screening process, text mining to help annotate full-text publications with risk of bias items, and a comprehensive MA application. We have established workflows for easily integrating new automation tools and MA packages from diverse sources as they are developed.

As we advance the capabilities of SLIM and SyRF, researchers will be able to create "living" SR & MA projects. These projects will be capable of automatically updating searches, selecting appropriate studies for inclusion in the review and extracting relevant information for meta-analysis. Researchers will be able to select the data of interest and an analysis plan to create a time-stamped snapshot of current results for publication. Meanwhile, the SLIM-enabled living project will continue to update, incorporate relevant data and provide live results, enabling researchers to monitor the progress in their fields.

SLIM will become a living data hub, harvesting data through automatically updated projects. It will provide a portal for researchers to combine specific data across projects to answer broader, more complex scientific questions.

Text Mining as a Tool to Aid the Assessment of Reporting of Risk of Bias and Other Methodological Quality Criteria

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Systematic reviews are useful tools when summarising research evidence, but they are limited by the time taken to perform them, meaning results are often outdated by the time of publishing. Because of the increasing rate at which new primary evidence is published we need more efficient tools to summarise these data.

Aims: The reporting of measures taken to reduce risks of bias is an important feature assessed in systematic reviews. We aimed to see whether text mining approaches could reliably identify reporting of risks of bias, and thus shorten the time to perform this part of the review process.

Methods: Using 5261 studies identified through a systematic search of animal models of psychosis, we developed regular expressions to mine full-text articles and “call” papers as reporting each of randomisation, blinding and sample size calculation (SSC). We tested the tool against previous risk of bias ascertainment by a human reviewer, using success thresholds for sensitivity and specificity of 80%.

Results: Tested in the original dataset, we achieved a sensitivity of 80% and specificity of 91% for randomisation, sensitivity of 83% and specificity of 95% for blinding, and sensitivity of 100% and specificity of 96% for SSC. When tested in dataset of other in vivo models, we achieved a sensitivity of 100% and specificity of 62% for randomisation, sensitivity of 88% and specificity of 98% for blinding, and sensitivity of 88% and specificity of 97% for sample size calculation.

Conclusion: Data mining has the potential to accelerate the assessment of risk of bias within systematic reviews of in vivo studies, but additional datasets are needed to help refine regular expressions and make the tool applicable across different fields of pre-clinical research.

Applying the Key Characteristics Paradigm in Cancer Hazard Identification

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An international Working Group of experts convened by the International Agency for Research on Cancer (IARC) identified 10 key characteristics, one or more of which are commonly exhibited by established human carcinogens (Smith et al., 2016; PMID: 26600562). The ten characteristics are distinct from the hallmarks of cancer, reflecting the ability of a carcinogen to 1) act as an electrophile either directly or after metabolic activation; 2) be genotoxic; 3) alter DNA repair or cause genomic instability; 4) induce epigenetic alterations; 5) induce oxidative stress; 6) induce chronic inflammation; 7) be immunosuppressive; 8) modulate receptor-mediated effects; 9) cause immortalization; and 10) alter cell proliferation, cell death, or nutrient supply. In the cancer hazard identification process, these characteristics provide the basis for an objective approach to identifying and evaluating evidence from pertinent mechanistic studies. The 10 key characteristics are used to systematically search the literature for evidence on relevant endpoints, and support objective evaluation of the overall strength of mechanistic information. Additionally, mapping of high-throughput assays to the 10 key characteristics can facilitate systematic evaluation as an additional mechanistic data stream. Recent IARC Monograph evaluations demonstrate the applicability of the approach for mechanistically diverse agents. For some compounds, there was strong evidence for only one (2,4-D) or no (parathion, trichlorophenol) key characteristics. Interestingly, strong evidence for two key characteristics (is genotoxic, induces oxidative stress) was found for glyphosate, diazinon and malathion, with malathion additionally showing three others (induces chronic inflammation, modulates receptor-mediated effects, alters cell proliferation). On the other hand, strong evidence for a different set of key characteristics (modulates receptor-mediated effects, is immunosuppressive, and induces oxidative stress) was found for DDT, tetrabromobisphenol A, and tetrachloroazobenzene. These developments lay groundwork for future evaluations where such data may fill important gaps in evidence of carcinogenicity.

Lessons From the Conduct of Two Systematic Reviews in Risk Assessment: Focus on Collaborative Software Tools

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In this presentation we will present the processes and lessons learned for two case studies: a systematic review (SR) of the Zebrafish Embryotoxicity Test as a predictor of developmental toxicity, and a review of the predictability of the publicly available Tox21/ToxCast data for hepatotoxicity as determined in experimental animals and humans. We will show how the knowledge from the first SR influenced the approach to the second project and how it has affected time lines. The presentation will focus on capacity building, engaging multidisciplinary geographically distributed teams, highlighting the use of collaborative tools with text-mining capabilities that help facilitate and improve the quality of the systematic review process. Two commercial programs were used in these projects, and advantages and drawbacks of both will be presented. Directions for future development of such collaborative tools assisting in SRs will be outlined from the practitioner's perspective.

Evaluation of Mechanistic Data Based on Key Characteristics of Carcinogens: Application of a Text Mining Tool and a Quantitative Evaluation Framework

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The evaluation of the mechanistic data stream in a systematic review is an element unique to the field of toxicology. Methods established in evidence-based medicine are not sufficient to integrate such a data stream, due to the heterogeneity of study types, volume of data, and context of the data relative to the research question. Recently Smith et al., (2016) proposed an approach to organize mechanistic data relevant to potentially carcinogenic agents via ten key characteristics of carcinogens (KCC); however, this approach does not provide solutions for accommodating large volumes of heterogeneous data, nor does the approach incorporate data quality, directionality, and concordance with adverse outcomes. Herein, we describe tools and approaches developed and implemented to go beyond organization of the KCC, that is, to systematically evaluate data using the KCC approach. As a first step, we assessed the utility of a text-mining and machine learning tool (SWIFT) in the identification and characterization of KCC data by 1) validating a process using five systematic review datasets, and 2) applying the approach as a problem formulation method via characterization of literature for 20 substances of varying carcinogenic potential. Following identification and characterization, data can be evaluated using a framework that incorporates data quality, directionality, and concordance with adverse outcomes. The framework has three components (reliability - quality, strength - relevance, and activity – active/inactive) that are evaluated using an algorithm which provides a score for each KCC, and subsequent categorization as weak, moderate, or strong. The algorithm allows for flexibility in component weighting, and the scoring approach allows for the incorporation of many study types, including laboratory animal data and high throughput screening data. Resulting data are then considered relative to evidence stream (e.g., human vs. laboratory animal) and tumor responses. Application of text mining and the quantitative framework to multiple mechanistic datasets for chemicals that are associated with different types of cancers, and in different models, demonstrates (a) the importance of problem formulation and the utility of a text mining tool in aiding such, (b) it is essential to follow categorization of data by KCC with further evaluation according to study quality and relevance, and (c) that evaluation of complex and diverse data (i.e., endpoints measured at the tissue, cellular, and molecular level) relative to tumors observed in multiple evidence streams is critical. These tools aid in providing a transparent and reproducible process for the assessment of mechanistic data in systematic reviews.

Impact of Choice of Effect Size and Meta-Analysis Method on Identifying Differences Between Groups of Animal Studies

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Background: In contrast to meta-analyses of clinical studies, reviews of animal data involve large numbers of individually small studies with heterogeneous effects. Because the observed standard deviation may deviate more from the population standard deviation when sample size is small, there may be a particular problem when standardised mean difference (SMD) effect sizes are used. We sought to investigate the impact of this phenomenon.

Methods: We simulated meta-analyses of animal stroke. We extracted the distribution of 57 model parameters (including group sizes) from meta-regression of data from 3116 animal experiments. For each variable we recorded the beta coefficient and prevalence. We then used R to simulate individual studies, adding an additional variable of interest (VoI) in a proportion of studies. We varied the overall effect and the effect of the VoI. We calculated normalized mean difference (NMD) and SMD effect sizes for each of 100 simulated studies, and combined these in a meta-analysis. We used random effects meta-analysis to measure the global effect, and partitioning of heterogeneity (PH) or univariate meta-regression (UM) to measure the impact of the VoI. Each meta-analysis was simulated 1000 times, and we calculated the proportion of meta-analyses (MA) reaching statistical significance.

Results: Statistical power was always higher using NMD. With a VoI present (proportion: 32 of 100 simulated studies), where the VoI effect was zero, PH reported significance in 76% of MA; for UM this was 5%. Where VoI had a 10% effect, UM reported significance in 30% of MA. Where VoI had a 20% effect, UM reported significance in 86% of MA. Where VoI had 40% effect, UM reported significance in 100% of MA.

Conclusions: Univariate meta-regression of NMD effect size estimates are preferable to SMD effect size estimates (where power is reduced) and partitioning of heterogeneity (where the false positive rate is high).

Lessons Learned From a Systematic Review of Prenatal Exposure to Bisphenol A and Hyperactivity

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Sharing experiences in the application of systematic review methods to environmental health questions is an important step in the evolution of this new methodology. This systematic review of prenatal exposure to bisphenol A (BPA) and hyperactivity serves as a case study to share lessons learned. BPA is a widespread environmental chemical that has been shown to disrupt neurological development in rodents and humans. Using the US National Toxicology Program's Office of Health Assessment and Translation (OHAT) framework, we performed a systematic review and meta-analysis to determine the relationship between early life exposure to BPA and hyperactivity, a key diagnostic criterion of attention deficit hyperactivity disorder. Screening identified 29 rodent and 3 human studies. Each study was evaluated using the OHAT risk of bias tool. A random effects meta-analysis (MA) was conducted on rodents exposed to 15-25 µg/kg/day BPA. OHAT methods were used to assess confidence in the bodies of evidence and integrate across evidence streams to arrive at a conclusion about hazard to humans. During the process of conducting and submitting the review for publication, many lessons were learned that are relevant to the broader field of systematic review in toxicology and environmental health. These will be presented, including topics such as choosing appropriate variables for MA, using MA results to assess confidence in the body of evidence, defining plausible dose-response curves, and assessing the relevance of animal data to humans. Other topics to be discussed include getting appropriate peer-reviewers, and the challenges of publishing a systematic review in environmental health. The purpose of the presentation is to raise issues that will spark discussion to help move the field forward.

Preferred Reporting Items in Systematic Reviews and Meta-Analysis – In Vivo Animal Research Extension (PRISMA–IVA)

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In order to address incomplete reporting of clinical systematic reviews, the Preferred Reporting Items in Systematic Reviews and Meta-Analysis (PRISMA) statement was developed, endorsed and implemented by leading journals. This led to substantive improvements in reporting of clinical systematic reviews. Previous assessments of systematic reviews of animal data have indicated similar deficiencies in reporting exist. Given these problems, as well as unique issues surrounding animal data and the increasing number of systematic reviews using this data being published, we propose that an extension to PRISMA is needed to address in vivo animal research.

Objective: To develop a guideline to improve the reporting elements of systematic reviews of in vivo animal research (PRISMA-IVA).

The protocol for PRISMA-IVA was developed according to published guidelines from the EQUATOR network. (1) Environmental Scan: We identified existing guidance on reporting preclinical and clinical systematic reviews and synthesized these into >200 unique reporting items (e.g. title clearly indicates the report uses animal data). A systematic search has been performed to identify all preclinical systematic reviews published in 2015-2016 and an assessment of current reporting practices is being performed. (2) Consensus Building Process: Empiric evidence collected in Phase 1 will inform a three-round modified Delphi process. A panel of experts (~40 representing several stakeholder groups) will be asked to electronically rank the importance of proposed reporting items. Items with high level of agreement will be used by a core group of individuals to help formulate a final checklist. (3) Dissemination: A final version of the PRISMA-IVA guideline and accompanying elaboration and explanation document will be submitted for publication consideration. A strong implementation plan will also be developed. We anticipate that PRISMA-IVA will improve the completeness and transparency of reporting of preclinical systematic review, facilitate reproducibility, increasing their usefulness for stakeholders.

An Application of the Aggregate Exposure Pathway (AEP) and Adverse Outcome Pathway (AOP) Frameworks to Mechanistically Integrate Data Sources Across Multiple Species Into Cumulative Risk Assessment (CRA)

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Toxicologists use dose-response data from both in vivo and in vitro experiments to evaluate the effects of chemical contaminants on organisms. Cumulative risk assessments (CRAs) consider the effects of multiple stressors on multiple endpoints, and utilize environmental exposure and toxicological data to estimate the likelihood of adverse outcomes (AOs) that can span human and non-human species. Meta-analyses can provide the data integration necessary for CRAs, but mechanism-based approaches to cross-species data integration are lacking due to differences among organisms that include exposure scenarios, physiological traits, experimental design and measurement techniques, endpoint characterization, and terminology. This work develops methods for the integration of data into CRAs from various studies that investigate toxicological effects in different species. We use the Aggregate Exposure Pathway (AEP) and Adverse Outcome Pathway (AOP) frameworks to organize data and provide a common platform to evaluate risk. We present a case study focused on perchlorate to demonstrate how this technique can facilitate integration of data sources from multiple taxa into CRAs through a meta-analysis spanning eight vertebrate and four invertebrate species. The AEP illustrated exposure differences among species, while we observed a dose-response concordance across species in the AOP. Results suggested that endpoints in frogs and rats (Xenopus laevis and Rattus sp., respectively) may be more sensitive to perchlorate exposure than AOs in other organisms, but also highlighted knowledge gaps for groups such as fish (Danio rerio and Gambusia holbrooki). This mechanistic framework 1) organizes data, 2) highlights data gaps, and 3) facilitates analyses and visualizations of risk. Connecting data with key events in AOPs across species illustrates the need for a common ontology to facilitate systematic review of data sources. The views expressed in this abstract are those of the authors and do not necessarily reflect the views or policies of the U.S. Environmental Protection Agency.

Network Meta-Analysis for Preclinical Studies

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Meta-analysis findings are routinely used in clinical research to support evidence-based healthcare decisions but similar uses remain underdeveloped and underutilised in preclinical research. A major limitation of current approaches is the use of pairwise comparisons (i.e. treatment versus control, or control versus exposure). This does not allow for the comparative effectiveness of different interventions to be determined. Network meta-analysis allows for the comparison of multiple interventions at the same time to determine relative effects. This approach may have specific preclinical applications, for example, deciding which of many putative interventions to take forward to clinical trial. Although used in clinical research, network meta-analysis is yet to be applied to preclinical research.

We have piloted this approach to investigate the effect of anaesthetic neuroprotection in ischaemic stroke outcome in rodents. We performed a random effects network meta-analysis using the netmeta package in R. We compared 16 anaesthetic agents, developing a closed-network with both direct and indirect evidence. The highest ranking anaesthetic was sevoflurane (37.9% improvement in neurological outcome 95% CI 29.1%-46.6%). Going forward, we plan to determine how to approach the substantial heterogeneity and potential risks of bias observed in preclinical datasets which may cause violations in network meta-analysis assumptions such as transitivity and consistency; and to develop a framework and guidance to use these tools in a preclinical setting.

Network meta-analysis will allow for evidence-based ranking of the effects of interventions. It borrows strength from indirect comparisons to gain certainty about all treatment comparisons and allows us to estimate comparative effects that have not been investigated in head-to-head experiments. There are likely challenges specific to preclinical data that remain to be investigated and this methodological development is ongoing.

Application of SR to Fit-For-Purpose Evaluation of Tox21 Assays

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There is a great interest and regulatory drive to limit the dependency on in vivo data in the hazard assessment of chemicals. How to make practical use of high-throughput datasets like the Tox21/ToxCast data in the hazard assessment of chemicals in the context of Mode-of-Action, Adverse Outcome Pathways and Systems Pharmacology concepts is beginning to be explored by many groups. We will present an integrated strategy that incorporates the principles of evidence-based methodology and describe the approach taken by the multi-stakeholder EBTC Tox21 work group. The work group is pioneering using a systematic literature review of the effects of the approved drugs on the liver of experimental animals (mice, rats, Beagle dogs and non-human primates), the data from Tox21 and ToxCast databases containing in vitro assays results, and liver effects in patients as observed in Adverse Events (AE) databases and similar resources will be presented in order to assess if the observations in the Tox21 dataset are predictive of adverse events as observed in the liver in experimental animals and/or patients. The challenges and proposed solutions associated with extraction, visualization, integration and interpretation of the data of the three diverse evidence streams in a non-biased, evidence-based approach will be described. Productive use of new technologies such as text mining and machine learning in conducting the SRs, data extraction and visualization will be highlighted.

Protocol Registration for Systematic Reviews of Animal Studies Relevant for Human Health in PROSPERO

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The prospective registration of a review protocol is important in the conduct of systematic reviews, since it allows research users to establish that the findings presented were not driven by the data collected. PROSPERO, a well-established international, prospective register of systematic review protocols in human health, will be developed to accommodate the registration of systematic reviews of animal studies relevant for human health, e.g. preclinical and toxicological animal studies. Here, we describe how the ontology for these review protocols was developed, and the advantages of registration in this 'sibling' register linked to PROSPERO.

In 2015 we conducted a survey among experts in the field of preclinical systematic reviews to scope support for protocol registration of preclinical reviews in a 'sibling' PROSPERO. All 43 respondents supported this initiative, and 81% indicated that they would make use of preclinical review protocol registration in PROSPERO. Our survey also recorded the experts' opinions on how to integrate the fields in PROSPERO's existing registration form, with SYRCLE's published review protocol format for animal studies (e.g. which fields should be mandatory versus optional for registration).

The resulting registration form consists of 40 fields, 26 of which are mandatory for registration. Following our planned launch July 2017, searching PROSPERO will yield results from the human, as well as the 'sibling' animal review register, making it easier to identify relevant reviews from both evidence streams. Prospective registration reduces the risk of unnecessary duplication of reviews and minimizes the potential for publication bias, selective outcome reporting, and bias in the review process, by ensuring that there is a record of all planned review methodology against which the completed review can be checked.

Through this development we aim to further improve the quality of systematic reviews across fields, and promote the evaluation of all evidence that impacts human health.

Identification of Key Characteristics of Male Reproductive Toxicants as an Approach for Screening and Sorting Mechanistic Evidence

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The application of systematic review practices in human health assessment includes integration of multi-disciplinary evidence from epidemiological, experimental, and mechanistic studies. Although mode of action analysis relies on the evaluation of mechanistic and toxicological outcomes, the process of organizing and analyzing studies and results can be challenging due to the diversity of research models, methods and endpoints, and the variety of known pathways for chemical-induced toxicity. The recently proposed Ten Key Characteristics of Carcinogens provide a useful approach for screening and sorting chemical-specific mechanistic data on carcinogenesis. Our objective was to identify a set of key characteristics that could be used for screening mechanistic evidence on chemical-induced adverse effects in the male reproductive system. Seven key characteristics were identified and include alterations in: 1) reproductive hormone levels/production, 2) hormone receptors, 3) germ/somatic cell functions, 4) cell signaling pathways, 5) epigenetic modifications, 6) DNA damage, and 7) reactive oxygen species production. These key characteristics are based on a survey and analysis of established mechanisms for recognized male reproductive toxicants. As a proof of principle, this set of key characteristics was used to organize mechanistic and experimental evidence on a PCB mixture (Aroclor 1254)-induced adverse outcomes in the male reproductive system. A database was developed to capture experimental design details and mechanistic outcomes identified in Aroclor 1254 studies. The resulting database can be used to organize and analyze the available mechanistic evidence. The proposed key characteristics of male reproductive toxicants provide a method that can facilitate the systematic screening and sorting of mechanistic evidence considered for mode of action analysis. Disclaimer: The views expressed are those of the authors and do not necessarily represent the views or policies of the US EPA.

Meta-Analysis of Animal Studies in Environmental Health: Challenges, Opportunities, and Lessons Learned From Evaluating Evidence From Endocrine Active Chemicals

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There is a long history of performing meta-analysis for human epidemiology and clinical trial data, and its benefits for experimental animal studies have recently been recognized. Most of the work on meta-analysis in this area has focused on “pre-clinical” data – i.e., studies of therapeutic interventions meant to inform design or interpretation of clinical trials. However, some unique challenges are posed by experimental animal studies that study exposures to environmental chemicals. Studies of environmental chemical exposures are often more heterogeneous than pre-clinical studies of therapeutics in terms of their experimental design. Additionally, unlike pre-clinical data, such studies often involve multiple treatments at different dose levels. Furthermore, the purpose of evaluating this evidence is both qualitative -- to identify potential human health hazards – as well as quantitative – to characterize the dose-response relationship. A committee of the National Academies of Sciences, Engineering, and Medicine has recently grappled with these issues as part of its task to conduct systematic reviews of human and animal toxicology data for selected endocrine active chemicals. As part of these reviews, we demonstrated some possible approaches to apply meta-analysis and meta-regression to experimental animal data on environmental chemicals, both to inform confidence in the body of evidence for causality as well as to characterize dose-response relationships across studies. Such approaches offer opportunities to improve future risk assessments of environmental chemicals, and addressing some remaining methodological and other challenges could facilitate their wider application.

MVA85A TB Vaccine: Synthesis of Animal Studies Raised Fundamental Questions

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In 2015 we published a systematic review summarising the effects of a new TB vaccine on mortality, measures of pathology and lung bacterial load in animals. Evidence from the outcomes reported in the review suggested evidence of efficacy in individual animals showed no clear benefit, and that one trial in macaques had more deaths in the new vaccine group, yet was published after a trial in South Africa had started recruiting children in an effectiveness trial.

The publication generated much indignation and debate, some public but mostly internal. The review was followed up by an investigative reporter, resulting in a BBC Radio 4 40-minute programme in May 2017 and reports in the British Medical Journal. One of the enduring questions was whether the macaque trial was originally purposed as an efficacy study, or as a trial testing the animal model for TB, and comments from TB specialists that this review may harm TB research investment, and drive “negative trials underground”.

The presentation will provide some details of the experience of publishing this independent review as a researcher, the uncertainties that the review threw up, and the clear need for proper prospective protocol driven animal research with protocols that are registered in the public domain.

A Perfect Storm of Bias – The Use and Misuse of Observational Scoring in Animal Studies Exemplified by the Rat Grimace Scale

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Observational scoring in laboratory-animal-based research is marred by frequent use of (too) small groups and extensive suppression of negative results. The non-intrusive nature of visual scoring means it can be tacked onto nearly any study protocol and the low investment, both in time and material, means that results can casually be discarded should they not conform to expectations. This breeds a culture of “long-shot” experimental designs that begets impossible-to-replicate findings.

An illustrative example can be constructed from the rat grimace scale (RGS): a method for detecting and scoring pain in laboratory rats. With a near-complete lack of published studies where the RGS could not confirm the authors’ hypotheses, and a median group size of eight animals, we can assume widespread suppression of negative findings. We would expect – based on Monte Carlo simulations using the original validation data – a considerable number of false negative results (17% of studies), even under ideal conditions. Add to this the true negatives and less-than-ideal experimental designs.

We expect to find publication bias within nearly any field of study; a perfect track record, or a near-unanimous one, presents a special case, however. Using Bayesian inference we can demonstrate that if we allow for even a remote chance of the RGS not being indicative of pain in rats at all, but being just a reflectance of the experimenter’s preconceived notions, the method itself falls under suspicion given its too-perfect record.

The RGS is far from the only observational method which suffers from a near-complete suppression of negative results. It is however my hope that by calling these methods into question on their being too good to be true, we can incentivize the publication of negative results. These will in turn assist in separating useful observational methods from ones with all the predictive power of astrology.

How Authors of Biomedical Research Describe the Design Aspects of the Study and Implications for Variance Estimation and Automation of Reviews

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In meta-analyses, estimates of effect size and variance are used to make inference about treatment effects. If the variance is underestimated, this leads to incorrectly narrow confidence intervals and Type 1 errors in hypothesis testing. This error will transfer to meta-analyses in systematic reviews if not recognized and corrected by reviewers. Variance is often incorrectly estimated when non-independent observations occur due to design elements such as split-plot design, pseudo-replication, or repeated measures. In some disciplines these are common features of preclinical experiments. The impact of poor reporting of design elements related to bias on the conduct of systematic reviews is well known. However the use and reporting of design elements that impact the variance estimation has not been evaluated. With the aim of determining the potential impact on data used in meta-analyses of preclinical systematic reviews, 100 stroke studies randomly selected from references provided by The CAMARADES group and 100 studies randomly selected from reviews available at the NTP OHAT, were evaluated for elements that could impact variance estimation. Data extraction is complete for the stroke studies and in progress for the toxicology studies dataset. 92 stroke studies allocated at individual level. 40 stroke studies featured a repeated measures element; only 12 studies explicitly indicated repeated measures in the statistical analysis. 44 stroke studies described data collection approaches that suggested, pseudo-replication, none used the term "pseudo-replication". No stroke studies used a split plot design. Results for the NTP dataset are pending. Investigators often employ design features that impact variance estimation but recognition of the features requires expertise is study design. Reporting of these features often does not rely upon key-words, therefore recognition by automated methods of text recognition will be difficult. This means reviewers must assess the potential for the variance estimate to be underestimated and the associated type-1 error.

Why Be Systematic – Preclinical Stroke as an Exemplar

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CAMARADES was born of a combination of frustration at the loss of a candidate drug's neuroprotective effects as experimental rigor increased during wide ranging stroke modelling and the chance co-localisation of David Howells and Malcolm McLeod at the then National Stroke Research Institute in Melbourne. Vigorous discussion of the problem led to the decision to adapt systematic review and meta-analysis, which was in regular clinical use in Dr McLeod's home institution, to both determine whether the problems were endemic in the field and to determine whether they could be used to identify drug candidates with true therapeutic potential. Analysis of numerous candidate drugs indicated that translational failure was widespread and that the best available candidates were not always taken forward to clinical trial. Failure to report measures to prevent experimental bias were widespread and publication bias was also common. The impact of both on reported effect sizes were substantial and, in the case of the NXY-059 data set, the former probably contributed expensive clinical trial failure. Analysis of data for tissue plasminogen activator illustrated that stroke models faithfully reproduced the critical time-dependence of human stroke but overall there was a mismatch between timing of experiments in animals and humans and that preclinical scientists usually failed to study drug effects in the face of co-morbidities common in the clinic. Importantly, there was a strong interaction between these comorbidities and individual candidate drugs with the anaesthetic agents required from surgically intensive stroke modelling. Systematic review and meta-analysis data were also used to redesign bench experiments. For the combination of magnesium, melatonin and minocycline trialled in hypertensive rats, the new appropriately powered, randomised and blinded results suggested that for many drugs, true efficacy might be substantially lower than indicated by the published literature. However, for therapeutic hypothermia, a robust and reproducible effect was detected. Large scale multinational collaborations have been built to provide a framework for testing future candidate drugs with the same rigor expected in clinical trials (Multi-PART) and to use machine-learning (SLIM) to accelerate the process of systematic review and analysis.

Systematic Evidence Mapping of Chemical Exposures and Parkinson's Disease to Support Future Research

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Parkinson's disease (PD) is a devastating neurological disorder affecting over 1.5 million people in the USA. With over 85% of cases being idiopathic and sporadic, there is a strong suggestion that exposure to certain environmental chemicals may play a role in disease etiology. This project collects and categorizes the literature into a systematic evidence map of chemical exposure on PD by evidence streams and exposure, to determine the extent of information available for potential follow-up systematic reviews (SRs) and to help identify chemicals for further targeted testing project. A PubMed search was used to identify relevant literature for PD endpoints and results were then imported into SWIFT-Review. Within SWIFT-Review, records were first categorized by article type followed by evidence stream and exposure. The resulting records were then cross-referenced using four databases that describe chemical uses: CPCat, National Library of Medicine, ChemoText and Expocast. ToxCast/Tox21 high-throughput screening (HTS) data were also used to identify chemicals with in vitro activity related to PD-related biological pathways. The search yielded a total of 91,598 records, of which 44,340 relevant studies were identified and categorized into a systematic evidence map by specific exposures and exposure categories. For example, pharmaceuticals and endogenous compounds had the most records including dopamine (13,763) and carbidopa (1,412); while rotenone (952), catechol (763) and manganese (624) were the most reported environmental chemicals. Evidence mapping identified several candidates for potential SRs, in particular catechol, which is used as a pesticide and as a precursor in perfumes and pharmaceuticals. The majority of chemicals with high activity in PD-related Tox21 assays did not appear to be well studied and would be potential candidates for future targeted testing. The presentation will illustrate how systematic evidence mapping can help identify data gaps and targeted questions that could be addressed in SRs or with additional research.

Language Inclusion and Search Approaches in “Systematic” Reviews of Animal Toxicity and Communicable Disease Studies

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Including non-English articles in systematic reviews (SR) is emphasized in guidelines. This study evaluated whether funding, international collaboration, or adherence to quality standards is associated with increased use of non-English articles in SRs or meta-analyses (MA) of animal studies. We searched PubMed for SRs or MAs of toxicity (N=111) or communicable disease (N=69) studies in animals from 2006-May 31, 2017. Inclusion criteria and data extraction forms were developed based on a pilot evaluation of a random sample of 10% of the studies. Variable reporting of SR elements necessitated inclusion of studies when the study authors called their search “systematic” and provided search strategy and inclusion criteria. Two independent reviewers evaluated each study for inclusion with discrepancies resolved by consensus. 35 toxicity studies and 32 communicable disease studies met study inclusion criteria and underwent data extraction (by TV) and checked by another (KA), as well as compared with PubMed indexing related to publication type, country of author affiliations, and funding source. Of the 35 included toxicity SRs, only 18 (51%) mentioned language in their search strategies or inclusion/exclusion criteria, 44% were limited to English (n= 8) while 56% included at least one non-English language (6 unrestricted, 4 selected [e.g., French, Spanish, Portuguese, German]). Language discussion in CD SRs was more frequent (n=22, 69%) although not statistically significantly different (p=0.15) with 41% limited to English (n=9), 8 unrestricted and 5 selected. Funding source was not associated with an increased use of non-English literature. In spite of guidelines and freely available translation tools, both funded and unfunded SR authors are often silent on or cite lack of funding for translations as a reason for not including non-English or non-native language literature.

Poster Presentations

Curation and Analysis of a Rodent Uterotrophic Database: Insights on Data Quality and Reproducibility

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***Neepa Choksi[2]** will present this poster.

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High-quality *in vivo* estrogenic response data is critical for the validation of high-throughput *in vitro* screening (HTS) assays and can also be used to better inform targeted testing with *in vivo* screening assays. A comprehensive database of such data was compiled from over 1000 articles from the scientific literature describing uterotrophic assay experiments performed using over 1500 separate protocols. The database includes data on over 40 descriptors for over 900 chemicals, including species, strain, route of administration, dosing length, number of doses used, maximum test dose, and test outcome. Each protocol was evaluated for conformity to six predefined criteria based on EPA/OECD guidelines for the uterotrophic assay. Each article was reviewed by two independent reviewers, after which a consensus score was assigned. Comparison of the database to published lists of ToxCast™ chemicals identified 607 articles of relevance, covering 215 ToxCast chemicals. Of those 607 articles, 112 conformed to the six predefined criteria, allowing *in vivo* comparisons for 132 chemicals to be made to the ToxCast data. Database analyses will include an evaluation of uterotrophic assay variability, comparison of ToxCast data to *in vivo* data, and comparison of uterotrophic data to published *in vitro* performance standards substances for the validation of *in vitro* estrogen receptor (ER) transactivation assays from ICCVAM. These analyses will provide insights into the variability of uterotrophic data and allow for the evaluation of the utility of *in vitro* assay data, including those from HTS, for predicting *in vivo* responses. *This project was funded in whole or in part with Federal funds from the NIEHS, NIH under Contract No.HHSN27320140003C.*

Quantitative Meta-analytic Approaches for the Systematic Synthesis of Data and Hazard Identification: A Case-study of Decreased Pain Sensitivity Due to Trimethylbenzene Exposure

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Traditionally, human health risk assessments have relied on qualitative approaches for hazard identification, often using the Hill criteria and weight of evidence determinations to integrate data from multiple studies. Recently, the National Research Council has recommended the development of quantitative approaches for evidence integration, including the application of meta-analyses. The following hazard identification case study applies qualitative as well as meta-analytic approaches to trimethylbenzene (TMB) isomers exposure and the potential neurotoxic effects on pain sensitivity. In the meta-analytic approach, a pooled effect size is calculated, after consideration of multiple confounding factors, in order to determine whether the entire database under consideration indicates that TMBs are likely to be a neurotoxic hazard. The pain sensitivity studies included in the present analyses initially seem discordant in their results: effects on pain sensitivity are seen immediately after termination of exposure, appear to resolve 24 hours after exposure, and then reappear 50 days later following foot-shock. Qualitative consideration of toxicological and toxicokinetic characteristics of the TMB isomers suggests that the observed differences between studies are due to testing time and can be explained through a complete consideration of the underlying biology of the effect and the nervous system as a whole. Meta-analyses and –regressions support this conclusion: when all studies are included and possible confounders (isomer, testing time, laboratory, etc.) are accounted for, the pooled effect sizes are ≥ 0, thus indicating that TMBs are a possible neurotoxic hazard to human health. This case study demonstrates how traditional, qualitative hazard identification methods can be combined with quantitative methods to provide a more robust consideration of all relevant information for the purpose of hazard identification.

Disclaimer: The views expressed in this abstract are those of the authors and do not necessarily represent the views or policies of the U.S. Environmental Protection Agency.

From Animal Model to Translational Strategy: A Systematic Literature Review of Animal Models for Cystic Fibrosis

Cathalijn Leenaars[1,2], **Rob de Vries[1],** F.R. Stafleu[2], C. Punt[3], W. Beumer[3], F.L.B. Meijboom[2], M. Ritskes-Holtinga[1]

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3. Procure

For Cystic Fibrosis (CF), a multitude of animal models is available. A complete and structured overview of all available animal models, which can help researchers to choose an appropriate model for their specific research question, is so far lacking. Our SR is meant to answer the question "What are the currently available animal models for CF?" and will also shed light on the sub-question "What has been measured as a surrogate for CF?"

We developed a search string for PubMed and Embase based on terms used for cystic fibrosis and standard animal filters. We defined "animal model for CF" as animals in which a spontaneous or induced pathological process can be investigated, in which the process, according to the authors, is intended to represent CF in humans in one or more respects. We excluded studies not addressing CF; studies not in animals (e.g. studies in cells or unicellular organisms and studies describing ex-vivo measurements of tissue dissected from healthy animals), abstracts (without a full description of materials and methods) and reviews not containing new data. Studies in which a pharmacological agent is administered to healthy animals to study ADME (Absorption, Distribution, Metabolism, Excretion) or safety have also been excluded.

Literature searches were performed on28-Dec-2015; from PubMed 7976 references were retrieved, from Embase 9403. After duplicate removal, 12310 references were imported into EROS (Early Review Management System) for screening of the title and abstract. 9700 references were excluded based on screening of the titles and abstracts. 1153 were excluded based on screening of the full text. The included 844 references have preliminary been distributed over the following groups of models: Genetic (662 publications), Infection (84 publications), Pharmacological (54 publications), Administration of patient materials (other than pathogens; 18 publications), Xenografts (17 publications), Diet (5 publications) and Other (4 publications).

Data-extraction is currently in progress. In the final review, the retrieved models will be tabulated. Models will be clustered by induction method, species and strain.

This project is funded by the Netherlands Organisation for Scientific Research (NWO_313-99-310).

From Animal Model to Translational Strategy: A Systematic Review of Experimental Design in the Preclinical and Clinical Studies of Methotrexate for Rheumatoid Arthritis (RA)

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Systematic review (SRs) of animal studies may shed light on the comparability of experimental designs for preclinical and clinical studies. We are performing an SR studying experimental designs for methotrexate (MTX) efficacy studies in Rheumatoid Arthritis (RA). Research Questions are: 1.) Are the experimental designs of the pre-clinical animal studies comparable with those of the clinical trials? 2.) Are the improvements (in swelling, pain, fatigue, bone- and cartilage damage) found in RA animal models comparable with the improvements found in patients? A search for all relevant references has been performed in PubMed and Embase, using a search strategy to identify animal and human experimental studies on RA with MTX. We excluded studies of other disorders and other drugs, observational studies, safety and ADME (Absorbtion, Distribution, Metabolism, Excretion) studies, in vitro and in silico studies, abstracts providing little experimental detail and reviews without primary data. Our search resulted, after duplicate removal, in 8217 references of which the titles and abstracts were screened for inclusion. 6698 references were excluded at this stage, and the full text of the remaining 1429 was screened. After exclusion of 734 papers based on the full text, data are currently being extracted from the remaining 695 papers. Approximately 25% of the included papers is on animal studies, the remainder is on human studies.

We will compare the design of the animal and human studies and perform assessments of the risk of bias in both. We will perform meta-analyses to investigate the effects of study design on outcome effect size.

This project is funded by the Netherlands Organisation for Scientific Research (NWO_313-99-310).

A Systematic Review and Meta-Analysis of the Protective Effects of Metformin in Experimental Myocardial Infarction

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Compared to alternative antihyperglycemic drugs, metformin reduces cardiovascular mortality and morbidity in patients with diabetes mellitus, despite similar glycemic control. Metformin has therefore been proposed to have direct cardiovascular protective properties, a hypothesis which has been confirmed in a wealth of animal models of myocardial infarction. Unfortunately, translation of these promising preclinical findings to the clinical situation has been disappointing. We therefore conducted a systematic review, quality assessment and meta-analysis of animal studies on the effect of metformin in experimental myocardial infarction, in order to critically assess the quality and outcome of these studies.

From the results of a comprehensive search in PubMed and EMBASE, 27 studies met our predefined inclusion criteria, 11 of which reported on ex vivo experiments and 18 on in vivo experiments.

Our primary endpoint infarct size as percentage of area at risk was significantly reduced by metformin in vivo (mean difference -18.70 [95%CI -25.39, -12.02]) and ex vivo (mean difference -14.73 [95% CI -20.53, -8.93]). A subgroup analysis revealed that this effect was only present in studies with temporary (rather than permanent) coronary occlusion. Out of our four secondary outcomes, beneficial effects of metformin on the left ventricular ejection fraction, left ventricular end-systolic diameter, and mortality, but not cardiac hypertrophy, were observed. Reporting of measures to reduce bias was extremely poor (randomization 63%, blinding 33%), rendering all studies at unclear risk of selection, performance and/or detection bias. None of the studies provided a justification of the chosen sample size using a power calculation.

We conclude that metformin limits infarct-size after temporary coronary occlusion, but our certainty in the evidence is limited by the questionable internal study validity. We recommend an adequately powered, high-quality confirmatory animal study to precede a randomized controlled trial of acute administration of metformin in patients undergoing reperfusion for acute myocardial infarction.

Standardized Mean Differences Cause Funnel Plot Distortion in Publication Bias Assessments

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As meta-analyses are increasingly used for the synthesis of biomedical research evidence, there is a growing need for methodological research into optimal analysis methodology. Meta-analyses often include an assessment of publication bias based on asymmetry testing of funnel plots in which the effect size is plotted against the standard error (SE). Here, we use empirical datasets and illustrative simulations to show that funnel plots using the standardized mean difference (SMD) plotted against the SE are susceptible to distortion and misinterpretation. We also investigate the potential of using a sample size-based precision estimate, or using the Normalized Mean Difference (NMD), as alternative approaches in both simulated and empirical data. For two published preclinical meta-analyses, converting the raw mean difference to a SMD resulted in significant overestimation of funnel plot asymmetry by both Egger's regression and trim and fill analysis. In simulated unbiased meta-analyses, publication bias as assessed by Egger's regression and trim and fill analysis was systematically overestimated in SMD-SE funnel plots. Distortion was more severe when an intervention effect was present, and when the primary studies had a small sample size. In biased simulations, there was clear distortion of SMD-SE funnel plots, but not of funnel plots in which the SMD was plotted against a precision estimate based on the study sample size ($1/\sqrt{n}$), or funnel plots of the NMD plotted against the SE. We conclude that, although commonly reported, funnel plots using the SMD in combination with the SE are unsuitable for publication bias assessments and can lead to false-positive results, especially when sample sizes are small (e.g. in preclinical studies). We propose using the NMD (when possible), or the SMD plotted against a precision estimate based on the sample size, as more reliable alternatives.

Systematic Review and Assessment of Links Between Sulfur Deposition, Sulfur Cycling, and Mercury Cycling in North American Ecosystems

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The review of the current secondary National Ambient Air Quality Standards (NAAQS) for oxides of nitrogen and sulfur and particulate matter includes, but is not limited to, the ecological effects of sulfur (S) deposition. The Integrated Science Assessment (ISA) provides the scientific foundation for review of the secondary NAAQS for oxides of sulfur and other closely related criteria pollutants. One of the subjects in the ISA is the link between atmospheric S deposition and mercury methylation within aquatic and wetland ecosystems. Mercury methylation in the environment results in human exposure to methylmercury through consumption of fish. Relevant scientific literature was identified using automated screening techniques of machine learning and citation mapping based on the references included in the previous ISA addressing ecological effects of oxides of sulfur (published in 2008). These approaches identified approximately 6500 papers published between 2008 and 2015 related to the non-acidifying effects of S deposition, and keyword searches and title screening within this set of publications identified 203 publications for detailed review. Recent research has expanded the geographic scope of inference of links between S cycling and methylmercury from the Northeastern peat bogs and lakes described in the 2008 ISA to now include streams, rivers, and freshwater marshes across the continental United States. Advances in microbial ecology have enhanced mechanistic explanations of mercury methylation. Observational studies, experimental S additions, and long-term field collections provide evidence of quantitative relationships between S and methylmercury production or concentration. The views expressed in this abstract are those of the authors and do not necessarily represent the views or policies of the US EPA.

Use of Text-Mining and Machine Learning Approaches to Conduct a Rapid Literature Survey on Environmental Chemicals and the Thyroid

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The thyroid system is vital for normal development and function in vertebrates and can be perturbed by exposure to certain environmental chemicals. Understanding the available research literature is challenging because of the enormity of the evidence base. Text-mining and machine learning approaches, including SWIFT-Review and SWIFT-Active Screener software applications, hold promise to help address this problem. The first objective of our study was to survey the thyroid literature using SWIFT-Review, focusing on publication types, chemicals, evidence streams (i.e., human, animal, *in vitro*), and types of thyroid-related endpoints. The second objective was to evaluate the machine-learning capabilities of both (SWIFT-Review and SWIFT-Active Screener) applications to priority rank relevant studies. PubMed search strategy was used to retrieve thyroid relevant literature through November 2016 resulting 235,960 records. Within SWIFT-Review, these records were first categorized by publication type (research versus non-research) and then by chemicals using filters for the >8,000 chemicals included in the Tox21 chemical library and ~1,400 chemicals implicated as possible endocrine disruptors (EDCs). The resulting records were then cross-referenced to specific thyroid-related outcomes and evidence streams. Out of the total number of records, 202,998 were identified as research records. Of these, 113,337 unique records were tagged for both EDC and Tox21 chemicals. In the thyroid literature, endogenous compounds including thyroid hormones and iodine were the most frequently tagged. The most frequently tagged environmental chemicals include perchlorate and PCBs. Using as few as 10 training records, SWIFT-Review obtained 95% recall of the relevant studies within the top 50% of priority ranked 534 PCB studies. SWIFT-Active Screener achieved 99.3% actual recall of relevant studies after screening 30% of 4,269 records related to thyroid hormone receptor and cancer. Text-mining and machine learning programs can be valuable tools for surveying large literature databases and for priority ranking relevant studies.

To Scope or Not to Scope: The Role of Scoping Reviews in Environmental Health

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Many of the challenges of conducting systematic reviews in environmental health and toxicology can be addressed by the use of systematic scoping techniques. Scoping provides data to plan the protocol and frame the research question. It identifies specific endpoints and exposures that have sufficient evidence for systematic review. Scoping is also useful for identifying research gaps that can be addressed in the design of future studies.

TEDX recently published two scoping reviews that demonstrate the role of the scoping process. They include many features of systematic review, such as a planned protocol with a PECO statement, a comprehensive literature search, unbiased screening for study inclusion, and systematic categorization and summarization of relevant studies. Data extraction included the number and age of subjects, the models used (e.g. human, rodent, fish), exposure routes and duration, doses/concentrations measured, and outcomes assessed. Scoping reviews do not assess individual studies for quality or risks of bias, determine health effects, evaluate confidence in the body of evidence, or integrate evidence streams.

In this poster presentation, the features of scoping reviews and results of our two reviews will be displayed. Our review of polycyclic aromatic hydrocarbons and female reproduction identified two endpoints for systematic review: fertility, and pregnancy/fetal viability. These areas have sufficient research for systematic review, as well as mechanistic data that address the biological plausibility of potential effects. Our review of melamine revealed neurological impacts, reproductive function, and anthropometric outcomes as possible candidates for systematic review, based on evidence streams and replication of endpoints.

Scoping reviews provide immense value to the field by summarizing the body of evidence and paving the way for well-informed and efficient systematic reviews, as well as by identifying specific areas for future study.

Estimating and Valuing Health Impacts of Formaldehyde Exposure to Improve Decision-Making

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Introduction: Asthma is pertinent to government and industry decision-making about formaldehyde in building products; exposure is prevalent and the direct and indirect health costs of asthma may be significant. The evidence linking exposure to formaldehyde and asthma has not yet been evaluated in a systematic and transparent manner, an essential step to understanding the strength of the relationship and quantifying the health benefits of decision-making.

Methods: We applied the Navigation Guide systematic review methodology to evaluate the question: “Is exposure to formaldehyde associated with diagnosis, signs, symptoms, exacerbation, or other measures of asthma in humans?” and incorporated established economic valuations related to asthma to quantify the costs related to formaldehyde exposure in the U.S. population.

Results: We assembled a multi-disciplinary review team; developed the protocol; searched the literature; and identified relevant human studies using pre-specified inclusion/exclusion criteria. Included studies have direct measures of formaldehyde; measure exposure via use of building materials that include formaldehyde; or are occupational exposures. Key confounders include socioeconomic status and exposure to active or passive cigarette smoke; as well as age for studies including children <6 years old. To date, we have identified 1,544 relevant records, 8 of which met our inclusion criteria. We will: complete the literature search; assess the internal validity of individual studies; rate the quality and strength of the entire body of available evidence; derive effect estimates from a subset of studies using meta-analysis; and apply the effect estimates in combination with established economic valuations to estimate the quantified costs of asthma effects from formaldehyde exposure. This presentation will describe the complete results and conclusions, including recommendations for improved methods for decision-making about environmental chemicals.

Development of a Curated Database of In Vivo Developmental Toxicity Data

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Results of tests to evaluate chemicals for potential adverse effects on fetal development inform product development decisions, as well as inform the public and other stakeholders. Regulatory agencies also use results to support acceptance and product labeling. Currently accepted in vivo testing protocols used to generate these data are time- and resource-intensive and require the use of animals. Advances in science and technology offer the promise of alternative approaches in in vitro models that use human cells and tissues that may increase assessment throughput. As high-quality in vivo reference data are critical to establishing the biological relevance, usefulness, and limitations of any alternative approach, we have conducted a systematic search for high-quality mammalian developmental toxicity studies. We focused on identifying agents that are associated with a range of developmental toxicity effects, ranging from subtle effects on fetal weight, increased incidence of variations, to terata and post-implantation loss. Agents were selected based on the availability of “high quality” studies (i.e. appropriately designed and powered with relevant endpoints, as well as covering likely different modes of action). These studies underwent further evaluation and assessment to identify and extract data. The resulting dataset, consisting mostly of data from National Toxicology Program prenatal developmental toxicity studies, consisted of results from tests of over 70 agents. These data, which include detailed maternal (e.g., maternal weight gain) and fetal outcomes, are currently being entered into a searchable electronic database. This comprehensive database will be made available to the public to serve as a resource for evaluating the performance of alternative methods that measure key events in pathways associated with developmental toxicity. *This project was funded in whole or in part with Federal funds from the NIEHS, NIH under Contract No. HHSN273201500010C*.

A Systematic Review of the Role of Cannabis in the Etiology of Acute Pancreatitis

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Introduction: Acute Pancreatitis (AP) is a common disorder with an overall mortality rate of 20%. Cannabis, the most commonly used illicit drug among young people in the world, was first reported as a possible cause of AP in 2004. This systematic review examines the etiology of cannabis-induced AP, whose occurrence is on the rise worldwide.

Methods: A systematic review of PubMed/Medline, Embase, Scopus, and the Cochrane Library databases was undertaken by a medical librarian. Without language or year limitations, search terms included “Cannabis” and “Acute Pancreatitis” with all variations. AP was determined by symptoms meeting 2 of 3 Revised Atlanta Classification criteria (Pain consistent with AP; amylase or lipase > 3x upper limit of normal; imaging consistent with AP). Cannabis-induced AP was defined by a preceding use of cannabis in the absence of common causes of AP when reported. Two authors independently reviewed each study for relevance and inclusion.

Results: After a screen of 239 titles, 16 met inclusion criteria (1 prospective series, 1 case series, 12 case reports, 2 abstracts of case reports) dating between 2004 and2016. A total of 26 cases of cannabis-induced AP were included, 23/26 (88.5%) men, 24/26 under age 35. AP was correlated with increased cannabis use in 18 patients. Recurrent AP related temporally to cannabis use was reported in 15. Thirteen patients reported no further AP episodes after cannabis cessation.

Conclusion: Cannabis is a probable cause of AP and recurrent AP, though its mechanism remains unclear. It occurs primarily in younger male patients under age 35. As cannabis availability rises, this trend is likely to increase globally, making cannabis-induced pancreatitis a public health concern. Cannabis should be included as a probable cause of toxin-induced AP. Toxicology screens should be considered in all patients with idiopathic AP.

Keywords: Cannabis; Marijuana; Acute Pancreatitis; Toxin; Idiopathic.

A Tool for Tagging/Highlighting/Extracting Text From PDF's: AFLEX Tagging Tool

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In systematic reviews, it is becoming increasingly common to tag/highlight/extract the text that supports a data item in a review. However, the tools commonly used for systematic reviews are not designed to seamlessly conduct this task. Therefore, there is a need for tools designed for systematic reviews to tag and extract text for data items, which is customizable for review needs and are compatible with other tools.

The AFLEX team at Iowa State University have developed the "AFLEX tagging tool". The focus has been on developing a tool that is customizable and exports data for subsequent text analysis. We also recognized the need to tag/highlight/extract disjointed text for the same data item. For example, important characteristics for the data item "study population" may be described using several sentences separated by information about housing. For extracting the text, it is preferable to extract only the disjointed text about the study population. Similarly, there is often a need to tag/highlight/extract text across pdf paragraphs or pages. The tool meets all these needs and is designed according to the user-centered design principles. Reviewers are able to upload the desired .pdf documents and select parts of it that they want to tag. The list of items that can be highlighted in the text, tagged and extracted is modifiable by the end-user. Once the pdf is uploaded, the reviewers can select the corresponding tags and the system will store all this information along with additional reviewer comments (see picture below). Once extracted the data can be shared with an R shiny app that enables conflict resolution based on the text extracted. The data are stored in an integrated database. Tes data can be exported as .csv, .xml, and .JSON and be used by other pieces of software and tools such as machine learning algorithms.

An Institutional Approach to Enhancing Best Practice in Animal Research

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Inadequate reporting is a limitation to best practice methodology in research involving animals. Significant focus has been placed on improving study description with tools such as the ARRIVE guidelines. These reporting guidelines can improve the methodology of studies by requiring them to meet certain standards. More recently, attention has shifted to full and accurate reporting of research results. The increased adoption of open access publishing and development of policies from national funding agencies begin to address this issue. For example, as of January 2013 any publications arising from Australian Research Council support must be deposited into an open access institutional repository.

However, what of research involving the use of animals that is not published? Many academics know of at least one experiment for which the data sits, unpublished in the bottom drawer of their filing cabinet or computer backup. Be it the research student project that didn't quite work, or did but for which results didn't indicate any effect of the experimental variable.

The current convention places responsibility for dissemination on investigators and their apparent choice to publish. The challenge we seek to address then is how institutions may support best practice methodology and reporting in animal research. This group was established in May of 2017 and is a collaboration between the University of Sydney Research Portfolio, The University Library and Researchers within the University of Sydney. The overarching focus for this group is to enhance the conduct and reporting of animal research at the University of Sydney through development of an open access repository for unpublished data from all studies approved by Animal Ethics. We aim for the repository to include structured descriptions of study methodology, as well as all results. Our strategy for academic engagement is currently in development and will be presented at the conference for discussion.

The Impact of Systematic Review of Animal Studies on Research Culture

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Objective: The Lancet Waste Series suggests that studies should be designed with reference to systematic reviews of existing evidence and that new research should be interpreted in the context of such reviews. Assessment of animal studies through systematic review is not yet an intrinsic part of the research cycle. We hypothesise that these analyses have the potential to improve the design, conduct and reporting of animal studies but in vivo researchers need to see their conduct as positive and useful. We assessed the response to and impact of independent systematic review using examples from two different research domains.

Methods: We present evidence resulting from systematic reviews of studies investigating the anti-inflammatory agent, interleukin-1 receptor antagonist (IL-1 RA), for the treatment of ischaemic stroke, and the MVA85A vaccine for tuberculosis challenge in animals.

Results: Where systematic review is accepted and valued by researchers, we saw an improvement in the quality and range of evidence produced to support the use of IL-1 RA for the treatment of stroke. In an updated systematic review published in 2016, we observed larger sample sizes and the median quality score increased from 6/15 (IQR 5-7) to 11.5 (9.8-12) compared to the original review, published in 2009. Systematic review has had a positive impact on stroke research culture and resulted in more complete reporting and more robust findings that are more likely to be reproducible. In contrast, we observed a visceral objection to independent systematic assessment of the evidence supporting the MVA85A vaccine for tuberculosis challenge.

Conclusion: Independent assessment of animal research is an important component of the research cycle that can have a profound impact on how studies are carried out. These contrasting examples highlight how systematic review can positively influence research culture but also how those conducting independent systematic reviews have a duty to ensure that the potential users of the research understand their aims and the potential impact of using this research.

HAWCPROJECT.ORG: A Content Management System for Human Health Assessments

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Decision-makers and researchers frequently conduct literature-based assessments of the potential for chemicals or other exposures to pose a threat to human health. Such assessments typically consist of a critical review of a literature corpus to identify adverse health effects, to extract data for exposure-response relationship modeling, and/or to elucidate toxicity mechanisms. The systematic review methodology increases the transparency and objectivity in an evaluation by using a pre-defined, multistep process to identify, critically assess, and synthesize evidence. In addition to extraction of data, systematic review may also include an assessment of potential bias in a body of literature. A clear and detailed presentation of problem formulation, analysis and outputs, as well as properly documented search strategies and intermediate decisions, are critical to ensure transparency of the process. We address these challenges by creating a modular, web-based content-management system to synthesize multiple data sources into overall human health assessments of chemicals. This free, open-source web-application, HAWC (Health Assessment Workspace Collaborative, https://hawcproject.org/), integrates and documents the overall workflow from literature search, literature screening, risk of bias assessment, data extraction, dose-response analysis using EPA benchmark dose modeling software (BMDS), and data synthesis by enabling creation of customizable visualizations of evidence and risk of bias. Each HAWC assessment can be composed of some of all of these steps, based on the goals of the assessment, and at the discretion of assessment owners. User access is assessment-specific; project-managers can create public or private assessments, and can share with their team during development and ultimately release publicly as supplemental information to final reports (e.g., the US National Toxicology Program (NTP) monograph of immunotoxicity associated with PFOA/PFOS exposure, or the National Academy of Science's report on low-dose toxicity from endocrine active chemicals). All data and figures are exportable in user-friendly formats. To date, over 400 assessments have been created by users, and has been adopted for use by the NTP, the US EPA, TCEQ, and the WHO IARC monographs program. Crucial benefits of such a system include improved integrity of the data and analysis results, greater transparency, standardization and consistency in data collection and presentation.

Table Builder: A Content Management System for Carcinogenicity Health Assessments for the IARC Monographs and the NTP Report on Carcinogens

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The International Agency for Research on Cancer (IARC) Monographs program and the NTP Report on Carcinogens (RoC) are each tasked with evaluating evidence for determination if agents, substances, or mixtures may pose a cancer hazard to humans. To do so requires an extensive literature search and systematic review of the evidence. Evidence synthesis requires data extraction and interpretation of data in multiple domains, including 1) exposure data, 2) epidemiology evidence, 3) animal evidence in test model systems, and 4) mechanistic evidence on key characteristics of carcinogenicity, such as genotoxicity. Standardized tables are commonly reported to synthesize evidence, and are included in final reports for summarizing strength of certainty of these findings. A web-based content management system was designed for capturing these data. The software allows collaborators to extract reported evidence, list potential covariates and confounders, and indicate study strengths and limitations. The data-extraction fields are standardized for each evidence stream; this allows for collaborators to enter data in parallel, but in a consistent format. The software is reactive; whenever a user changes any data in the system, it is updated for all other users of the system in real-time (helpful during IARC monograph meetings). Statistical analysis can be performed in the software (such as Cochrane Armitage trend test or pairwise tests for animal bioassay data). Data visualizations can be created (such as forest-plot viewing) and filtering of data by cancer target, which can be informative for report writers during the data analysis and data interpretation portions of report writing, especially when the number of extracted-elements are large. Further, data can be managed in the software system, and QA/QC of data-entry is integrated into the software. Finally, reports can be created for download in Excel or in Microsoft Word. The table builder software was designed using the Meteor Javascript web framework and uses a Mongo database, and is open-source and publicly available at https://github.com/shapiromatron/tblBuilder. To date, the table builder software has been used for 11 IARC and 4 RoC Monographs (including both finalized monographs and those currently under development).

Application of Text-Mining and Machine Learning Technology in Nutrition Systematic Review Screening: A Pilot Study

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Background: Text-mining and machine learning (TM/ML) technology may improve the efficiency of the systematic review process. TM/ML facilitates prioritization of relevant studies so the next stage of the review can proceed while less relevant articles are screened. USDA's Nutrition Evidence Library (NEL) pilot-tested the performance of TM/ML enabled software (SWIFT Active Screener) for screening nutrition-related research.

Methods: Literature search results from four reviews were imported into SWIFT Active Screener, and were dual-screened at the title/abstract level using predetermined inclusion/exclusion criteria. Two reviews used seed articles to prime the TM/ML algorithm. Percent citations screened to identify 95% of included studies and recall at 10%, 30%, and 50% of title/abstract screening were assessed. Area under the curve (AUC) was determined by graphing the rates of correctly labeled included citations against falsely labeled included citations. Workload saved over sampling (WSS) was assessed to estimate the percent reduction in potential effort achieved by TM/ML prioritization relative to screening citations in random order. Observations were made on strengths and challenges of integrating this TM/ML enabled software within the systematic review process.

Results: Percent of records screened to identify 95% of relevant articles ranged from 28.8 to 63.6%. At the 30% screened point in each project, approximately 89 to 100% of included articles were identified. AUC ranged from 0.877 to 0.922, where 1.0 is a perfect score and 0.50 is equivalent to random ordering. The percent reduction in potential effort achieved at the 95% recall level ranged from 31.4 to 66.2%.

Conclusion: TM/ML has the potential to improve literature screening efficiency, and improve systematic review workflow, but modifications in standard review processes and software usability are needed to maximize benefits.

Identifying Needles in a Haystack: Use of Text-Mining and Machine Learning Technology to Improve Efficiency in Conducting Nutrition-Related Systematic Reviews

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Background: Text-mining machine learning (TM/ML) technology can improve the efficiency of literature screening by provisionally identifying relevant articles up front. However, there is a dearth of nutrition studies that have formally evaluated the utility of TM/ML technologies in enhancing efficiency. The objective of this study was to assess the performance of TM/ML technology in two scoping reviews of public health nutrition evidence, in comparison with conventional manual screening.

Methods: TM/ML performance was measured prospectively by conducting a scoping review followed by a manual screening process. For the scoping review, PICO tables were developed, broad inclusion criteria were drafted and a preliminary literature search was conducted. TM/ML technology, using SWIFT-Review, was used to screen studies at the title/abstract level. For the conventional screening project, SWIFT Active Screener was used. The articles were dual-screened at the full-text level using a well-defined inclusion/exclusion criterion. Sensitivity and positive predictive value was calculated independently for both questions.

Results: For the systematic review question on dietary patterns (DP) and hypertensive disorders of pregnancy, TM/ML technology identified all 7 articles that were eventually identified using the manual process. The sensitivity of the TM/ML was 100% and the positive predictive value (PPV) was 87.5%. For the second systematic review on DP and gestational diabetes mellitus, TM/ML technology identified 9 of the 11 articles that were subsequently identified through manual screening. For this systematic review, the sensitivity was 81.8%, whereas the PPV was 39.1%.

Conclusion: The ability of TM/ML to locate most of the articles upfront during the scoping process suggests that this technology has the potential to expedite study screening/selection and reduce manual screening workload in nutrition-related systematic reviews.

Development of a Quantitative Weighting Framework to Systematically Evaluate the Validity of Relative Potency Estimates From a Heterogeneous Evidence Base for Dioxin-Like Compounds

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Risk assessments for dioxin-like compounds (DLCs) are typically conducted using a toxic equivalency factor (TEF) approach using TEF values. These values are point estimates based on a qualitative assessment of a heterogeneous dataset of relative estimates of potency (REPs) that can span several orders of magnitude. Many entities have acknowledged the importance of characterizing the variability and uncertainty in the TEFs, much of which is inherent to the range of quality and relevance of the underlying evidence base. As such, the objective of this research was to develop an objective, consensus-based, quantitative weighting framework that systematically accounted for both internal and external validity. Six main study characteristics were identified as most important: (1) study type (e.g., in vivo, human/non-human), (2) study model (e.g., organismal, unicellular), (3) pharmacokinetics (accounts for kinetic differences between TCDD and other congeners), (4) REP derivation method (e.g., statistically-based modeling, ratios), (5) REP derivation quality (study design components, such as age and number of animals, number of dose levels, etc.) and (6) endpoint (e.g., toxic, biochemical). The output of the framework being an integrated evidence base that reflects the characteristics believed to be most important for evaluating REP quality and relevance for human health risk assessment, including a numerical weight for each REP. The framework provides flexibility both in how the REP weights are determined (e.g., linear vs. log scales) as well as how it is applied to the database. In an example application, we applied different scale types for each characteristic (based on expert judgment), then utilized a multinomial logistic classifier machine learning model to develop numerical weights for each REP value. The weights can then be used to develop weighted distributions of REPs. Thus, the framework provides a topic-specific model to systematically integrate data quality and relevance into a quantitative characterization of an outcome (relative potency), resulting in a robust, objective, and transparent means to quantitatively characterize the variability and uncertainty inherent in health risk estimates.

Focusing and Refining the Evaluation of Reproductive Endpoints in a Systematic Review of PCBs

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Systematic review of animal toxicology literature will often reveal a wide range of health outcomes associated with exposure to a given chemical. This is particularly true for chemicals that have an exceptionally large number of studies available, such as polychlorinated biphenyls (PCBs). Risk assessors charged with evaluating these data-rich chemicals generally do not have the time and resources available to evaluate every potential health effect. Therefore, in such cases, it may be helpful to focus the systematic review on the outcomes identified as most relevant for protecting public health. Here, using a literature inventory which captures experimental design and health outcome details from studies that evaluated reproductive effects in PCB-exposed laboratory animals, we describe considerations that may be useful for refining a large and complex database. The goal is to identify the most relevant adverse health effects to move forward for further evaluation. Major considerations for identifying the most relevant health effects include the biological significance of the outcomes identified in the database, the number and types of studies evaluating each outcome, and the sensitivity of each outcome to the chemical exposure. Once the most relevant adverse health effects are identified, studies reporting these outcomes can continue through study quality evaluation and further review. The views expressed in this abstract are those of the authors and do not necessarily reflect the views or policies of the U.S. Environmental Protection Agency.

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Alphabetical list of pre-registered attendees (webcast registrants not included)

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