

SPAN Leadership Committee / Training Core Leaders WebEx

Tuesday, October 29, 2019 • 2:00 - 3:00 p.m. EDT

Attendees

Xabier Arzuaga (U.S. EPA)
Brandy Beverly (National Toxicology Program)
Candice Brinkmeyer-Langford (Texas A&M University)
Cynthia Browning (Brown University)
Andrew Buermeyer (Oregon State University SRP)
Danielle Carlin (NIEHS)
Subham Dasgupta (OSU)
Jazmin Diaz (PROTECT-RCM)
Caredwen Foley (BU School of Public Health)
Angela Gutierrez (University of Kentucky)
David Hein (University of Louisville)
Heather Henry (National Institute of Environmental Health Sciences)
Amber Kramer (Oregon State University)
Priyanka Kushwaha (University of Arizona - Tucson, AZ)
Adeline Lopez (MDB)
Gabriele Ludewig (University of Iowa)
Marina Malovichko (University of Louisville)
Craig Marcus (Oregon State University)
Pamela Mellon (UCSD)
Jennifer Moore (University of Kentucky)
Denise Moreno (University of Arizona)
David Purdy (The University of Iowa)
Stacy Schkoda (North Carolina State University)
Tom Sheahan (Northeastern University - PROTECT)
Vidushi Shukla (Brown University)
Lura Slowinski (Northeastern University)
Aidan Stone (Brown University)
Brittany Trottier (National Institute of Environmental Health Sciences)
Jean van Seventer (Boston University School of Public Health)
Banrida Wahlang (University of Louisville)
Zhengui Xia (Univ of Washington)
Luoping Zhang (University of California, Berkeley)

Agenda Items

- **Systematic Review – Dr. Brandy Beverly**
 - National Toxicology Program (NTP) was established in 1978; extends and expands the scientific basis for public health decision making on the potential toxicity for environmental agents.
 - NTP does testing and research on nominations that come in from other agencies and the public.
 - Dr. Beverly works on the analysis side of the process at OHAT.

- Office of Health Assessment and Translation (OHAT) is an environmental health resource for public and regulatory agencies.
- What is systematic review and why are we using it?
 - Literature-based evaluation to assess evidence that environmental substances cause adverse health effects.
 - Use it to make hazard identification conclusions (i.e. whether a particular substance is thought to be a hazard to human health).
 - Multistep process to identify, select, and critically assess and synthesize data from published studies to answer a specific research question.
 - There has been a lot of encouragement for various government agencies to use systematic review methodologies to reach decisions because it:
 - Provides explicit systematic methods,
 - Minimizes bias,
 - Results in more reliable findings, and
 - Provides transparency into how conclusions are reached which is very important for informing decision-making.
- OHAT was an early adopter of systematic review and evidence integration for use in environmental health research. They are heavily involved in promoting systematic review methods development and uptake within environmental health.
- Clinical medicine provided the origins for systematic review, but it has since been adapted for environmental health.
- The OHAT handbook for conducting systematic review and evidence integration is used by several groups and agencies both domestically and abroad.
- The handbook can be broadly categorized into two sections – the systematic review process where evidence is identified and synthesized and then the evidence integration where information is taken from different types of evidence and put together to reach a conclusion
- These steps can be further broken down into four large categories:
 - Problem Formulation and Protocol Development – identifying the research question and outlining how the systematic review will be conducted,
 - Identifying Evidence,
 - Evaluating Evidence, and
 - Integrating Evidence.
- Major steps of the systematic review process:
 - **Problem formulation** is the most critical step!
 - Refining the question
 - It's not a broad question but rather understanding what information is needed to make a decision or inform the work being done.
 - Tailor the evaluation to address that specific question.
 - Considers the purpose, scope (what information are you going to need and how specific do you need to be), depth of analysis (what pieces of information do you need), approach, available resources (time, people, tools, etc.), feasibility (what can you do with the resources that you have), etc.
 - This step allows for asking deliberate questions about how the review will be conducted a priori.
 - There are two key elements to problem formulation: scoping and framing.

- Scoping: the background information you need in order to figure out what the issue is.
 - Framing: how to take all that information and define both a research question and the literature search strategy needed to gather the necessary studies to address that question.
- Developing a PECO statement (population of interest, exposure, comparators, outcome of interest) informs the literature search strategy.
- OHAT evaluated emerging children’s health issues associated with ambient air pollution. They enlisted stakeholders and subject matter experts to help with problem formulation. Identified emerging air pollution related health issue affecting both mother and child: hypertensive disorders of pregnancy. Studies found traffic related air pollution (TRAP) is potentially associated with hypertensive disorders during pregnancy. They selected this very focused question that they could try to answer with a systematic review. Their PECO question was: does exposure to higher levels of TRAP induce hypertension during pregnancy in pregnant women compared to those exposed to lower levels?
 - Population of Interest: Pregnant women
 - Exposure: TRAP
 - Comparators: Pregnant women exposed to lower levels of TRAP
 - Outcome of Interest: Hypertension during pregnancy
- **Protocol development** outlines how the systematic review will be conducted
 - Typically includes:
 - Background of the problem
 - Rationale being used to conduct review
 - Literature search strategy that will be used
 - Inclusion/exclusion criteria based on PECO statement
 - Methods that will be used to conduct the review
 - The developed protocols are typically published before the review is conducted.
- **Identification of evidence**
 - First develop a literature search strategy
 - Informed by PECO statement.
 - Usually involves looking at more than one database.
 - Very important to enlist help of technical experts with experience in information technology/library sciences to create a literature search strategy that will yield the most relevant results for the particular research question.
 - Selection of Studies: After relevant articles are identified, they must be screened to determine whether they will be included in the systematic review.
 - There are two levels of screening (level 1 and 2) for inclusion
 - Level 1 (title and abstract): does this study fit the PECO statement?
 - Level 2 (full text): does this study fit the specifics of the inclusion/exclusion criteria?

- Two independent screeners resolve any conflicts through either discussion or by bringing in a third person
- There are tools available to increase transparency in how decisions are made for inclusion/exclusion and also reduce the screening burden by utilizing machine learning capabilities (ex. Distiller and Swift ActiveScreener).
- **Evaluation of evidence**
 - Assess study quality and risk of bias.
 - Risk of bias/internal validity asks the question “Are there aspects of the study design or reporting that would introduce bias to the results?”
 - How can bias affect results?
 - Famous study published in 1963 with rats in a T maze where the dark side of the T was associated with a reward.
 - Students were told there were “maze bright” rats bred together to find the reward faster and more times per day and “maze dull” rats bred together who found the reward slower and fewer times per day.
 - Students took the rats from the two groups and had them do the T Maze again and reported results confirming the “maze bright” rats were finding the reward faster/more times than the “maze dull” rats.
 - However, there was actually no difference between the rat groups.
 - Study shows that because the students were expecting a certain behavior from those animals, they reported results that confirmed their inherent bias.
 - OHAT has a Risk of Bias Tool to address selection, performance, detection, and attrition bias.
 - Selection: a systematic difference in comparator groups.
 - Performance: the researchers change their behavior because they know there are different groups.
 - Detection: people assessing the outcome are aware of the different groups.
 - Attrition: unequal loss of information across groups.
 - Tool asks questions related to these types of bias and helps determine whether there are areas of bias that should be considered during evaluation of groups of studies.
- **Evidence integration** is when everything is brought together to reach conclusions.
 - Process for reaching conclusions on the confidence across a body of studies within an evidence stream and then integrating those conclusions across the evidence streams with consideration of other relevant data.
 - Evidence streams are groups of human/animal/mechanistic studies that are relevant to addressing the research question.
 - Environmental health data relevant to address the question can be from large, diverse, and complex datasets and the conclusions need to consider all data.
 - Evidence integration not just a prescriptive step in putting it all together, but has to be fit for purpose.

- How you integrate evidence depends on the question being asked, the information needed to make decisions, and the ultimate goal of the assessment.
- Most of the frameworks for evidence integration in environmental health are based on the GRADE framework (GRADE = Grading or Recommendations Assessment, Development and Evaluation). GRADE is used in clinical medicine to assess the certainty of the evidence and strength of the recommendations.
- There are many forms of evidence integration in three broad categories from guided expert judgement to structured qualitative to quantitative. These are not mutually exclusive. OHAT falls under Structured Qualitative approach, but opportunities exist to incorporate quantitative and qualitative approaches in order to reach decisions.
- Systematic review approaches are effective at transparently evaluating evidence on groups of studies addressing the same or similar endpoints.
 - Broad topics can be addressed with a series of specific questions.
 - Can group your studies together based on different endpoints and then evaluate those endpoints.
- Confidence ratings are a measure of how confident you are that the findings from a group of studies reflect the true relationship between exposure and outcome.
 - OHAT confidence ratings developed within a GRADE framework as a two-step process:
 - First step is to set your initial confidence based on study design features. Four features considered as types of studies included in the assessment are evaluated: that there's a controlled exposure, that the exposure occurs prior to the outcome, that there's individual outcome data, and that there's a comparison group used.
 - Depending on the types of studies they can have any number of these features.
 - Number of features translates to level of initial confidence (4 features = high, 3 features = moderate, etc.)
 - Second step is to consider factors that increase or decrease your confidence.
 - Example: if there's evidence of a large magnitude of effect or evidence of a dose response that increases confidence that the associations reflected in the results represent the true relationship between the exposure and the outcome.
 - Example: if there's unexplained inconsistency or if there's elements of bias that are part of the study design or reporting that introduce bias into the results that decreases confidence in the bodies of evidence.

- Use the confidence rating to translate to levels of evidence. Takes into consideration the confidence rating and the direction of the effect.
 - Can do this for both human and animal studies and then put it all together to reach a hazard conclusion.
- Hazard conclusions are conducted in two steps:
 - First step is looking at where your human and animal evidence meet. Hazard conclusions are on a four-point scale: known, presumed, suspected, and not classifiable.
 - Second step is to consider the impact of any relevant mechanistic data and the biological plausibility of the effect. Can increase or decrease hazard conclusion if there's strong enough evidence to do so from the supporting information.
- Note: mechanistic data application falls towards the end of the framework while trying to understand biological plausibility, but mechanistic data needs to be considered in multiple steps of the review.
 - In problem formulation you would outline your proposed use of mechanistic data.
 - When identifying relevant evidence and developing a search strategy will need to focus any mechanistic data used to that which is relevant to human and animal health data.
 - During evaluation have to consider a level of study quality and applicability since mechanistic studies are distant to the health effect; must be anchored to the human or animal data and there has to be an assessment of the quality.
 - In evidence integration mechanistic data tends to be used to inform biological plausibility, but there are other aspects in which it can be used including when talking about complex exposures.
- Conclusions for the combined TRAP exposure were used to reach the overall hazard conclusions.
- Takeaways:
 - Systematic review is a predefined, multistep process to evaluate evidence.
 - Requires you to develop your question ahead of time.
 - Provides a transparent mechanism for documenting decision-making.
 - Is fit for purpose (what you're planning on doing depends on what you need to address your question).
 - Requires planning and good problem formulation to be successful.
- **Question from Danielle:** How could a trainee go about something like this without the resources of a large organization like OHAT?
- **Response:** The take home message is to use explicit transparent criteria for evaluating evidence, it doesn't have to be a full systematic review, but using systematic approaches can be really helpful. Another option is to use very targeted questions with small datasets. You could also do systematic evidence mapping or scoping efforts, using systematic review elements but without going all the way to the end product of a systematic review.
- **Comment** from UC Berkeley: Trainee Helen Guo was awarded a Society of Toxicology Undergraduate Research Grant to perform a systematic review of benzene and non-Hodgkin lymphoma with Dr. Luoping Zhang.
- **Question from Luoping Zhang:** What is the best software?

- **Response:** OHAT uses HAWC, but there are lots of options out there.
- **Dr. Xavier Arzuaga (EPA IRIS Program) – discussion of EPA opportunities for trainees**
 - Volunteer service program at EPA Center for Public Health and Environmental Assessment
 - Goal is to give trainees educational opportunities in the development of human health and ecological risk assessment.
 - Students learn about systematic review, study evaluation, literature searches etc., as well as computational tools being used by EPA for evidence analysis.
 - Trainees mentored by EPA staff scientists.
 - Products generated are EPA publications (i.e. systematic review protocols, journal articles, evidence maps).
 - Students who are interested in participating should contact Amanda Persad (persad.amanda@epa.gov) and Dahnish Shams (shams.dahnish@epa.gov). They will need to send their CV, proof of enrollment, and the completed volunteer service agreement.
- **2019 SRP Annual Meeting Trainee Session Update** (see <https://srp2019.org/agenda/>)
- **Reminder to use the SRP Data Collection Tool (DCT) to submit Trainee Highlights!**
 - Awards, publications, honors
 - Photos of activities
 - SRP uses these entries to learn about what trainees are doing and to select trainees to highlight in the E-Posted! We also consider submitted photos for the E-Posted Photo of the Month!
 - Helps you with the Annual Update Process!
- **Reminder to update CareerTrac**
 - Streamlined Excel form to add information for new trainees. It can be emailed to the trainee directly or downloaded and emailed
 - Data collection form
- **KC Donnelly Externship**
 - Time to start thinking about opportunities!
 - Letters of intent are due by **December 22**.
 - Applications will be accepted between **January 1** and **January 31** of each year.
 - Brittany Trottier is the contact for the KC Donnelly Externship (brittany.trottier@nih.gov)
 - <https://www.niehs.nih.gov/research/supported/centers/srp/training/donnely/index.cfm>
- **Wetterhahn Award**
 - Wetterhahn Award applications for 2019 were due August 1, 2019.
 - This year's winner will be announced at the SRP Annual Meeting in November.
 - <https://www.niehs.nih.gov/research/supported/centers/srp/training/wetterhahn/index.cfm>
- **Training Core Activities and Round-robin/sharing** of highlights from all of you (i.e., the Superfund Centers and R01 grantees)

Reminder: If you'd like your activities included, please send them to Danielle Carlin (danielle.carlin@nih.gov) and Addie Lopez (adeline.lopez@nih.gov) at least 2 weeks before the next scheduled SPAN WebEx.

- **Reminder to send updates to SPAN Leadership Committee**
 - These will be taken September/January of each year (please limit to 1 – 2 graduate students/Post-Docs per Center to keep up with the listserv)
 - Please email your nominations to danielle.carlin@nih.gov and indicate the current status of the new member (e.g., graduate student or Post-Doc)
 - Membership on the SPAN Leadership Committee is a two-year term.

Additional Information

- **SRP Website – for SPAN/Training**
 - <http://www.niehs.nih.gov/research/supported/srp/training/index.cfm>
 - Notes from all previous SPAN Teleconferences/WebEx Discussions are posted here.
 - Training Core Leaders, please send Adeline Lopez (adeline.lopez@nih.gov) any news items of interest to trainees (e.g., trainee success stories, pictures, job announcements).
 - SRP e-posted: Trainee Highlights
- **SRP/NIEHS on LinkedIn:** <https://www.linkedin.com/groups/8565066>