The OHAT approach:

Assessing risk-of-bias in individual epidemiological studies to support evidence integration, public health decision making

Kyla Taylor, PhD
Andrew Rooney, PhD

Health Assessment and Translation Group (formerly OHAT)
Integrative Health Assessments Branch
Division of Translational Toxicology, NIEHS

Disclaimer

- The views and opinions presented here do not necessarily represent the views of NIEHS, NIH, or the US federal government

Today's talk

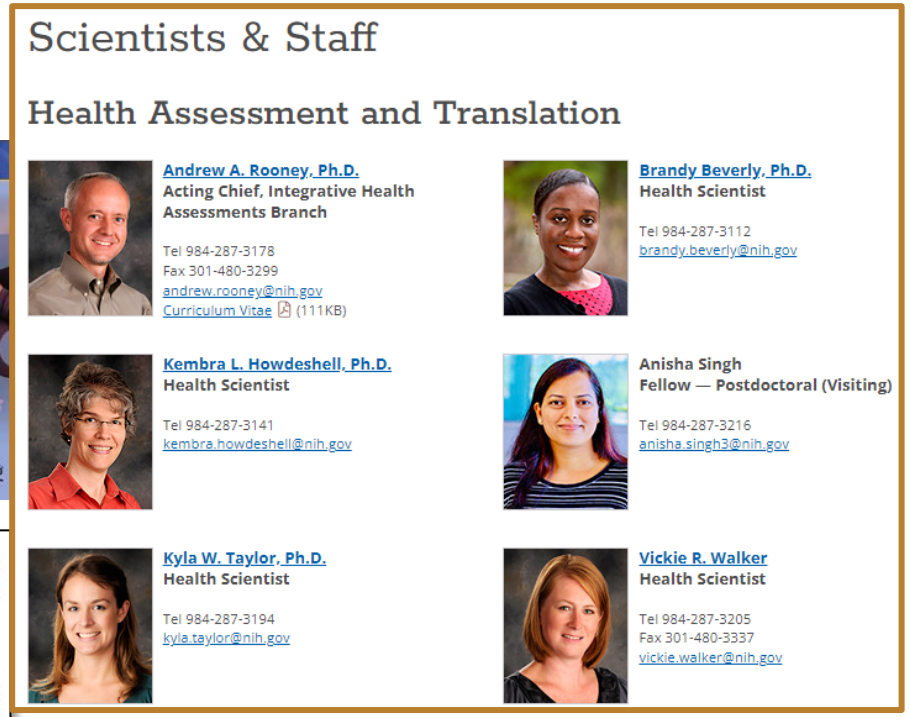
- Introduction to Health Assessment and Translation group (formerly OHAT)
- Background on risk-of-bias
- OHAT risk-of-bias tool
  - Domains for observational studies in humans
  - How to make a risk-of-bias judgement
- Risk-of-bias for an individual study and across studies
- Evidence integration

National Institute of Environmental Health Sciences
Division of Translational Toxicology

Health Assessment and Translation Group (formerly OHAT)

Integrative Health Assessments Branch, Division of Translational Toxicology, NIEHS

- Serves as environmental health resource to the public, government and regulatory agencies
- Develops and applies innovative approaches to produce fit-for-purpose literature assessments to support public health decision making
- Conduct literature-based evaluations
  - NTP Monographs and NTP Research Reports
  - Hazard assessments
  - Systematic reviews and meta-analyses
  - Systematic evidence maps

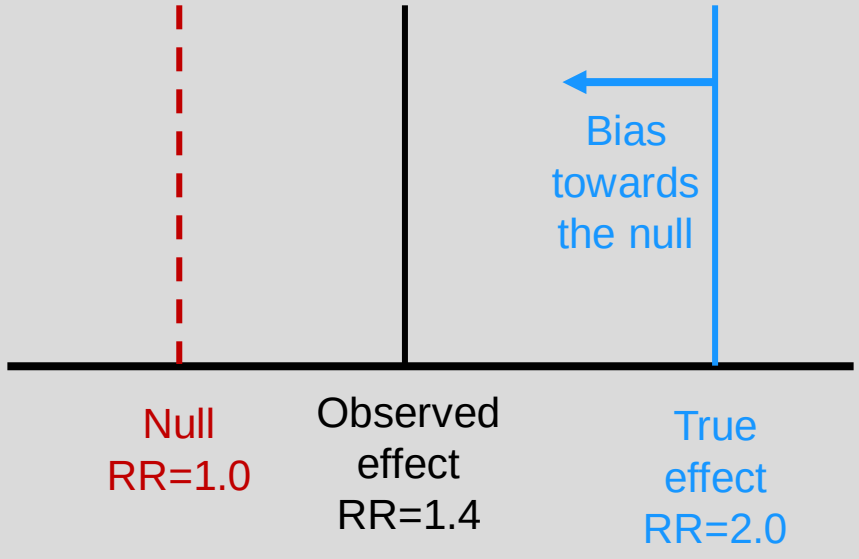


https://www.niehs.nih.gov/research/atniehs/labs/iha/ohat/index.cfm

What is risk-of-bias?

- Bias is a systematic error, or deviation from the truth, in results or inferences
- Can lead to underestimation or overestimation of true effect
  - Bias *towards* or *away from the null*
- Actual bias cannot be measured
- However, potential for bias can be systematically and transparently judged by experienced reviewer

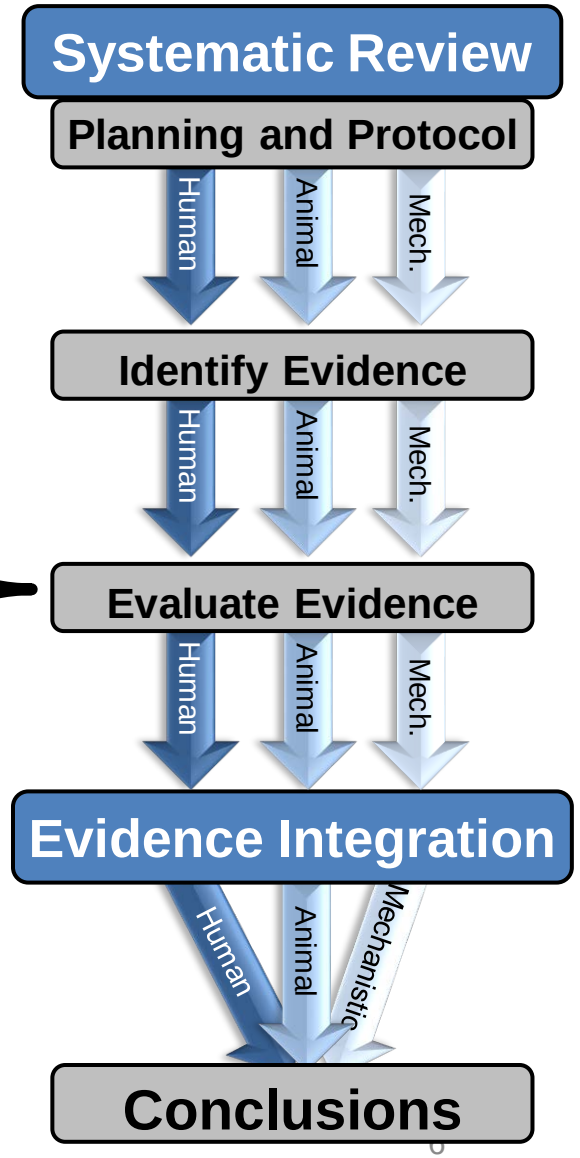
Direction of bias



Why assess risk-of-bias in systematic review?

- Critical, transparent, and consistent evaluation of the body of evidence is required for a systematic review
- Identifying and characterizing risk-of-bias in an individual study informs assessment of confidence in a body of evidence

Risk-of-bias in individual study



OHAT risk-of-bias tool

OHAT approach

- Parallel approach to assessing risk-of-bias in human and non-human studies
- Study design determines applicability of questions
- Domain based assessment
- Facilitates consideration of risk-of-bias across evidence streams with common terms and categories

RoB Domains	Risk-of-bias prompting questions	Animal	Human	
			RCT	Obs.*
Selection	1. Was administered dose or exposure level adequately randomized?	■	■	
	2. Was allocation to study groups adequately concealed?	■	■	
	3. Did selection of study participants result in appropriate comparison groups?			■
Confounding	4. Did the study design or analysis account for important confounding and modifying variables?			■
Performance	5. Were experimental conditions identical across study groups?	■		
	6. Were the research personnel and human subjects blinded to the study group during the study?	■	■	
Attrition/ exclusion	7. Were outcome data complete with respect to attrition or exclusion from analysis?	■	■	■
Detection	8. Can we be confident in the exposure characterization?	■	■	■
	9. Can we be confident in the outcome assessment?	■	■	■
Selective reporting	10. Were all measured outcomes reported?	■	■	■
Other sources of bias	11. Were any other potential threats to internal validity	■	■	■

*For observational studies, applies to different study designs (e.g., cohort, cross-sectional, case-control)

OHAT risk-of-bias tool

OHAT approach

- Seven risk-of-bias questions that are relevant to human observational studies

RoB Domains	Risk-of-bias prompting questions	Animal	Human	
			RCT	Obs.*
	1. Was administered dose or exposure level adequately randomized?			
	2. Was allocation to study groups adequately concealed?			
Selection	3. Did selection of study participants result in appropriate comparison groups?			
Confounding	4. Did the study design or analysis account for important confounding and modifying variables?			
Performance	5. Were experimental conditions identical across study groups?			
	6. Were the research personnel and human subjects blinded to the study group during the study?			
Attrition/ exclusion	7. Were outcome data complete with respect to attrition or exclusion from analysis?			
Detection	8. Can we be confident in the exposure characterization?			
	9. Can we be confident in the outcome assessment?			
Selective reporting	10. Were all measured outcomes reported?			
Other sources of bias	11. Were any other potential threats to internal validity			

*For observational studies, applies to different study designs (e.g., cohort, cross-sectional, case-control)

OHAT risk-of-bias tool

Risk-of-bias judgements for each domain

Definitely Low
Direct evidence of low risk-of-bias practices
Probably Low
Indirect evidence of low risk-of-bias practices
Probably High/NR
Indirect evidence of high risk-of-bias practices
Definitely High
Direct evidence of high risk-of-bias practices

NR= Not reported

- Specific guidance for assessing risk-of-bias will change across evaluations
  - Especially for exposure assessment, outcome assessment, selection, and confounding
- Project-specific protocol customizes guidance
  - Developed with input from subject matter experts/technical advisors
  - Peer review of protocol/risk-of-bias assessment
- Direction and magnitude of bias considered

Note: Not Reported (NR) is assumed to be equivalent to probably high risk of bias

NTP Evaluation of Traffic-Related Air Pollution and Selected Health Outcomes

PROTOCOL FOR A SYSTEMATIC REVIEW OF TRAFFIC-RELATED AIR POLLUTION AND SELECTED HEALTH OUTCOMES

Project Co-Leaders: Brandiese E.J. Beverly, PhD and Kembra Howdeshell, PhD, Office of Health Assessment and Translation (OHAT), DNTP

Summary: NTP is conducting a systematic review to evaluate the evidence for an association between traffic-related air pollution and hypertensive disorders of pregnancy. The protocol is detailed in this document.

Date Original Protocol Published: June 2016

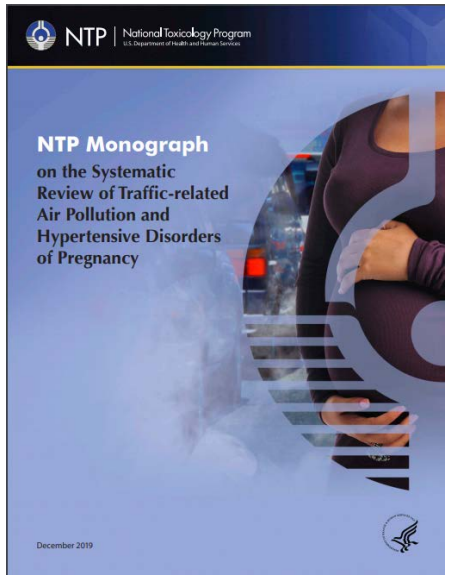
Date Revised Protocol Published: December 12, 2019; reflecting revisions made through August 7, 2019

Documentation of Revisions to the Protocol: The principal revisions are detailed in the Protocol History and Revisions Table on Page 32 including the reasons for each revision. In addition, updated language or new text starts with the word "Revision:". Strikethrough text indicates original text that has been modified, and new text is marked in bold text.

Project-specific risk-of-bias criteria

***RoB Question:** Can we be confident in the exposure characterization?*

- For each question we use project specific RoB criteria to determine if an individual study "fits" into one of the four rating options
- For example, a "definitely low" rating requires "direct evidence"



Cohort - Definitely Low Risk-of-bias (++)
Direct evidence that more than one traffic-related air pollutant was reported **AND** exposure was consistently assessed using well-established methods that directly measure exposure, **OR** exposure was assessed using less-established methods that directly measure exposure and are validated against well-established methods, **AND** exposure was assessed in a relevant time-window and reasonably well aligned with the outcome, **AND** there is sufficient range or variation in exposure measurements across groups to potentially identify associations with health outcomes, **AND** there is evidence that most of the exposure data measurements are above the limit of quantitation for the assay, and measured with good accuracy and precision such that different exposure groups can be distinguished. **Note:** Data on cross-validation R2 and/or sensitivity/subgroup analyses (e.g., selecting only subjects residing within a specified short distance from a road site monitor) may indicate a study has lower risk of bias, but the absence of such analyses will not penalize a study.

Project-specific risk-of-bias criteria

Question: Can we be confident in the exposure characterization?

Cohort - Definitely Low Risk-of-bias (++)

Direct evidence that more than one traffic-related air pollutant was reported

AND exposure was consistently assessed using well-established methods that directly measure exposure,

OR exposure was assessed using less-established methods that directly measure exposure and are validated against well-established methods,

AND exposure was assessed in a relevant time-window and reasonably well aligned with the outcome,

AND there is sufficient range or variation in exposure measurements across groups to potentially identify associations with health outcomes,

AND there is evidence that most of the exposure data measurements are above the limit of quantitation for the assay, and measured with good accuracy and precision such that different exposure groups can be distinguished.

Note: Data on cross-validation R2 and/or sensitivity/subgroup analyses (e.g., selecting only subjects residing within a specified short distance from a road site monitor) may indicate a study has lower risk of bias, but the absence of such analyses will not penalize a study.

Cohort – Probably Low Risk-of-bias (+)

Indirect evidence that the exposure was consistently assessed using well-established methods that directly measure exposure,

OR exposure was assessed using less-established methods that directly measure exposure,

AND exposure was assessed in a relevant time-window and reasonably well aligned with the outcome,

AND there is sufficient range or variation in exposure measurements across groups to potentially identify associations with health outcomes, •

AND there is evidence that most of the exposure data measurements are above the limit of quantitation for the assay and measured with good accuracy and precision such that different exposure groups can be distinguished.

Probably High Risk of Bias (-) or (NR)

Indirect evidence that the exposure was assessed using poorly validated methods that directly measure exposure

AND indirect evidence that exposure assessment does not adequately reflect relevant exposure levels (e.g., poor density of data, poor data quality, many missing values, substantial data misalignment),

OR there is evidence that the exposure was assessed using indirect measures that have not been validated or empirically shown to be consistent with methods that directly measure exposure (e.g., questionnaire, self-report without validation),

OR there is insufficient information provided about the exposure assessment, including validity and reliability, but no evidence for concern about the method used (record “NR” as basis for answer).

Definitely High Risk of Bias (--)

Direct evidence that the exposure was assessed using methods with poor validity,

AND direct evidence that exposure assessment does not adequately reflect relevant exposure levels (e.g., poor density of data, poor data quality, many missing values, substantial data misalignment),

OR evidence of substantial exposure misclassification.

Web-based study assessment in HAWC

Individual reviewer

Selective Reporting

Were all measured outcomes reported?

Show details

Reviewer 1

Copy

Probably low risk of bias

All outcomes outlined in the abstract, introduction, and methods are reported, but most data was provided only qualitatively.

+ Create new override

Judgment

Probably low risk of bias

Bias direction

not entered/unknown

Normal

All outcomes outlined in the abstract, introduction, and methods are reported, but most data was provided only qualitatively.

HAWC
HEALTH ASSESSMENT WORKSPACE COLLABORATIVE

Web-based study assessment in HAWC

Attrition

Were outcome data complete with respect to attrition or exclusion from analysis?

Show details

Reviewer 1	Reviewer 2
++ Copy	+ Copy
Definitely low risk of bias	*Probably low risk of bias*
Authors explain attrition, deemed not to affect outcomes (++): "For the current study, we finally excluded five children who had lived in these areas for less than 1 year and four children who did not consent to take IQ test, resulting in 331 subjects eligible for our study."	331 of the 340 identified subjects were enrolled in the study. Five were excluded for not living in the region for an appropriate duration and one for lack of consent, however the authors do not discuss the exclusion of the other 3 individuals.

Final assessment

Judgment

Definitely low risk of bias

++

Bias direction

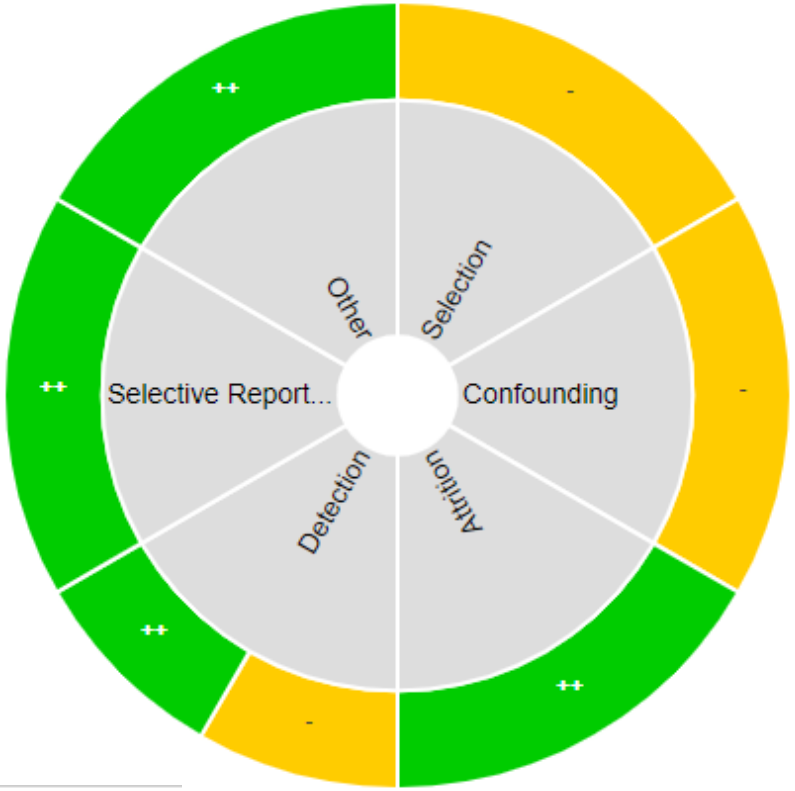
not entered/unknown

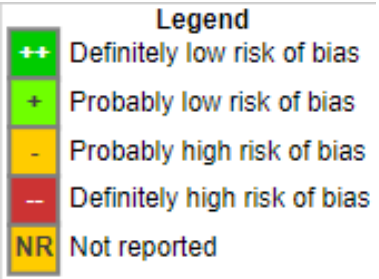
Normal

Data were relatively complete (i.e., <5% loss). Of the 340 subjects selected for inclusion, 5 were excluded because they lived in the area for less than a year with an additional 4 not consenting to participate.

Overall risk-of-bias in an individual study

RoB for an individual study

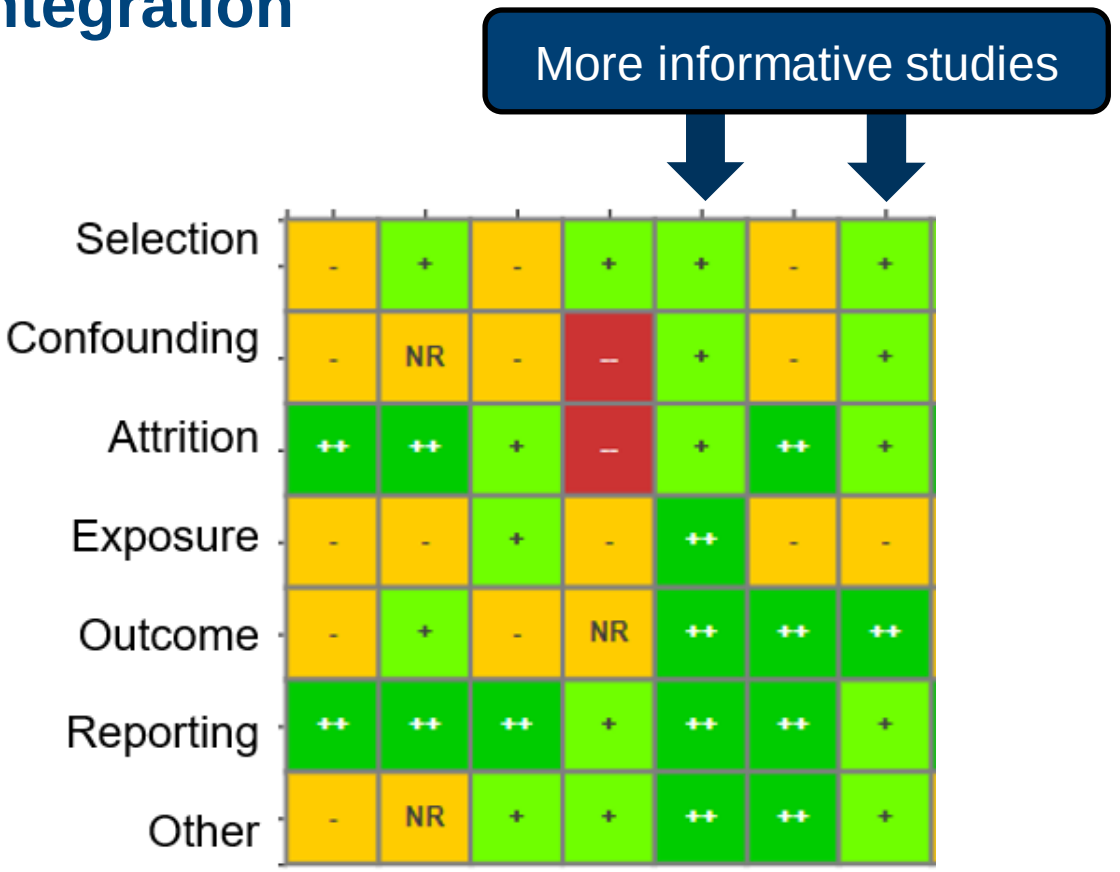




- Tiered approach for determining study quality of an individual study
- Not all domains contribute equally to overall risk-of-bias for a study
- Key domains typically include
  - confounding bias
  - exposure characterization
  - outcome assessment

How RoB is incorporated into evidence integration

- Lower RoB studies are more informative for developing conclusions
- However, studies are not excluded from an evaluation if they are higher RoB
  - Typically summarized
  - They may provide important information
  - Can be used in sensitivity analyses



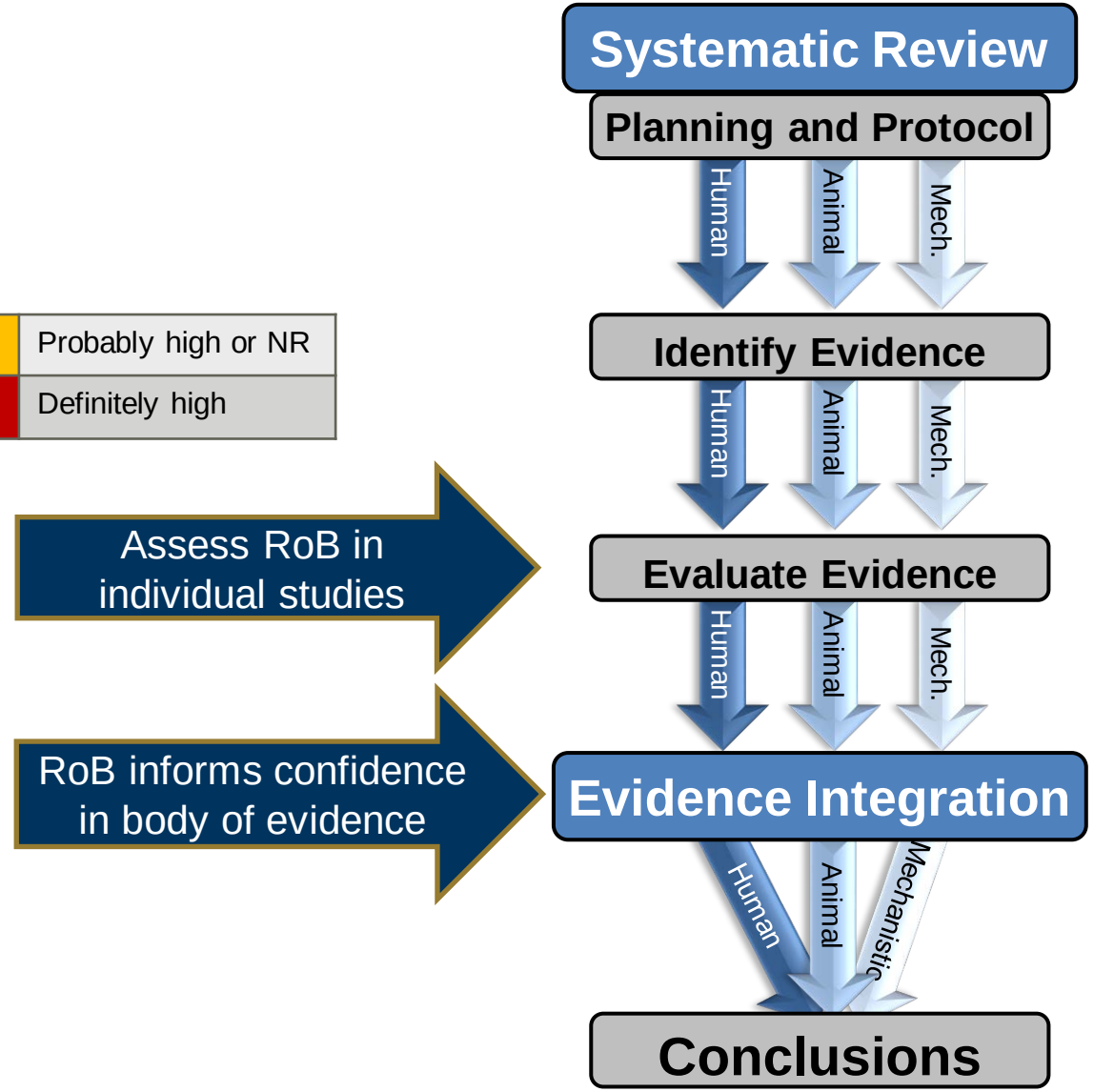
To summarize….

OHAT risk-of-bias tool

- Six risk-of-bias domains (7 RoB questions) for observational studies
- Four response options:

+ +	Definitely low	-	Probably high or NR
+	Probably low	- -	Definitely high

- Assess risk-of-bias individual studies
- Risk-of-bias across studies used to support evidence integration
  - Low RoB studies are most informative to conclusions
  - RoB across studies contribute to confidence in body of evidence



Thank you!

Acknowledgements

Andrew Rooney, PhD

Brandy Beverly, PhD

Kembra Howdeshell, PhD

Vickie Walker

Anisha Singh, PhD

Fellow

Ruth Lunn, DrPH

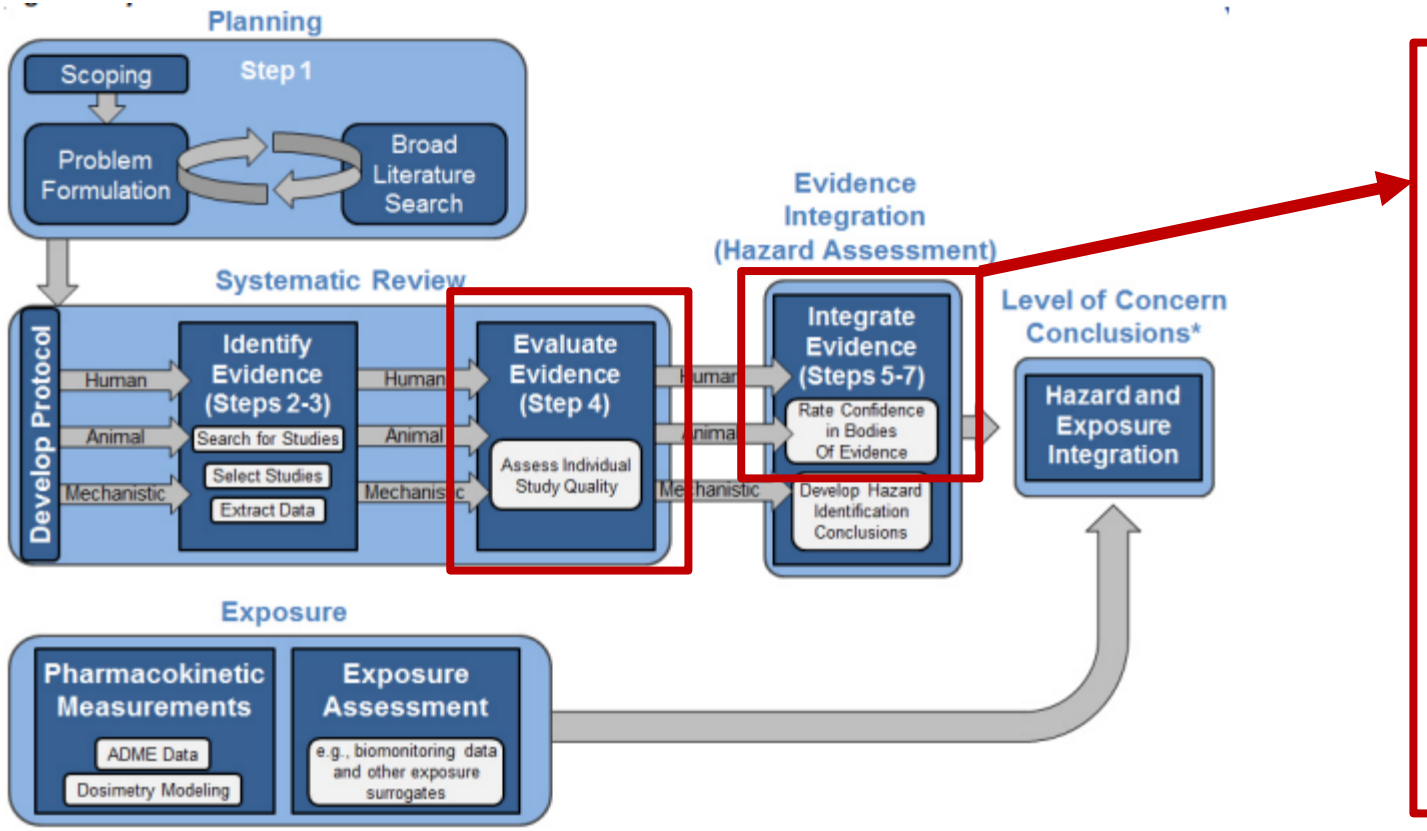
Suril Mehta, DrPH

Amy Wang, PhD

National Institute of Environmental Health Sciences

Division of Translational Toxicology

Risk-of-bias in the context of OHAT hazard identification or level of concern conclusion



ADME = absorption, distribution, metabolism, excretion

*NTP is currently updating the NTP approach for reaching level of concern conclusions (expected 2016/2017)