NTP
National Toxicology Program

Webinar on the OHAT Approach for Systematic Review

Office of Health Assessment and Translation
National Institute of Environmental Health Sciences

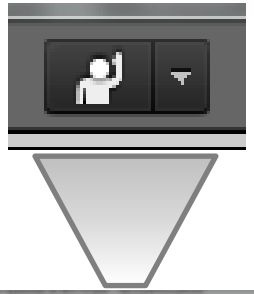
September 26, 2013

Format and Logistics

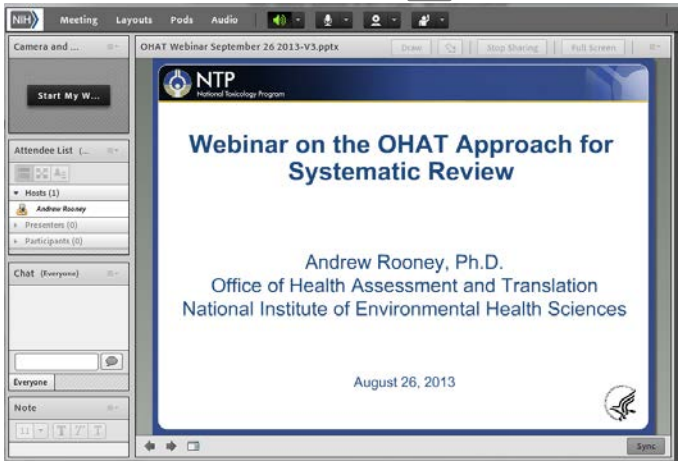
- Brief OHAT staff presentation on a topic or theme

- Question and answer session on that topic
  - Use “Raise Hand” function if you would like to ask a question
  - Participants will be called upon in the order questions are received and phone line will be unmuted
  - Participants can ask their question directly

“Raise Hand” icon is on the menu bar at the top of screen



- Topics and timing
  - 4 topics as listed in the agenda
  - Remaining time (~60 minutes) for additional discussion



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Andrew Rooney, Ph.D.
Office of Health Assessment and Translation
National Institute of Environmental Health Sciences

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Goals

1) to gain additional clarity on issues raised in public comments and

2) to discuss NTP's progress at working through the case studies to test the systematic review framework

Topics or Themes

- Evaluating study quality and utility
- Confidence ratings in a body of evidence, where do you start?
- Evidence integration
- Update on case studies and next steps
- Additional discussion or questions from participants

OHAT Approach to Evaluating Study Quality and Utility

Definitions: Study Quality and Utility

- **Reporting quality**
  How well was the study reported?

- **Internal validity or risk of bias**
  How credible are the findings based on design and conduct of the study?

- **Directness and applicability**
  How well does the study address the topic under review?

Steps in Draft OHAT Approach Where Study Quality and Utility are Considered

Step 1: Prepare topic

Step 2: Search for and select studies

Step 3: Extract data from studies

Step 4: Assess individual study quality

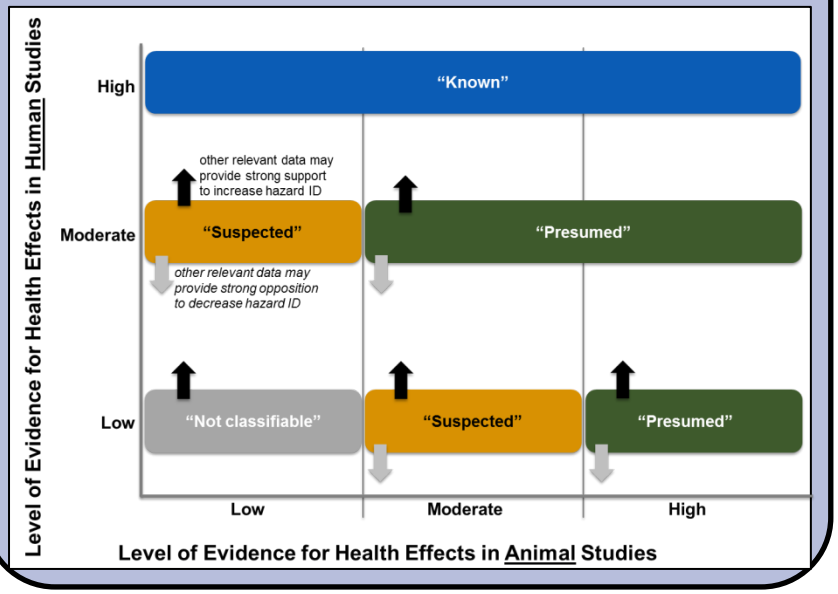
Step 5: Rate confidence in body of evidence

Initial Confidence by Key Features of Study Design	Factors Decreasing Confidence	Factors Increasing Confidence	Confidence in the Body of Evidence
High (++++) 4 Features	Risk of Bias Unexplained Inconsistency Indirectness Imprecision Publication Bias	Large Magnitude of Effect Dose Response All Plausible Confounding • Studies report an effect and residual confounding is toward null • Studies report no effect and residual confounding is away from null Consistency • Across animal models or species • Across dissimilar populations • Across study design types Other e.g., particularly rare outcomes	High (++++)
Moderate (+++) 3 Features			Moderate (+++)
Low (++) 2 Features			Low (++)
Very Low (+) ≤1 Features			Very Low (+)

Features
- Controlled exposure
- Exposure prior to outcome
- Individual outcome data
- Comparison group used

Step 6: Translate confidence ratings into level of evidence for health effect

Step 7: Integrate evidence to develop hazard identification conclusions



Study Quality and Utility are Assessed in Several Different Steps

- Eligibility criteria (STEPS 1 and 2)
  - Critical aspects of study design or limitations in applicability
- Internal validity or risk of bias (STEP 4)
  - Study design and conduct
  - Reporting quality: Non-reporting has negative impact on risk of bias and attempts will be made to follow up with study authors
  - Confounding
- Directness and applicability (STEP 5)
  - Route, timing and duration of exposure
  - Upstream indicators
  - Relevance of animal model for human health
- **Questions?**

Confidence Ratings in a Body of Evidence,

Where do You Start?

Definitions: Body of Evidence and Initial Confidence

- A confidence rating for a body of evidence is developed by considering its strengths and weaknesses
- **What comprises a "body of evidence"?**
  - Studies with data on the same or related outcomes as defined in the protocol
- **What do we mean by "initial confidence"?**
  - The starting point for a study or group of studies prior to examining strengths and weaknesses

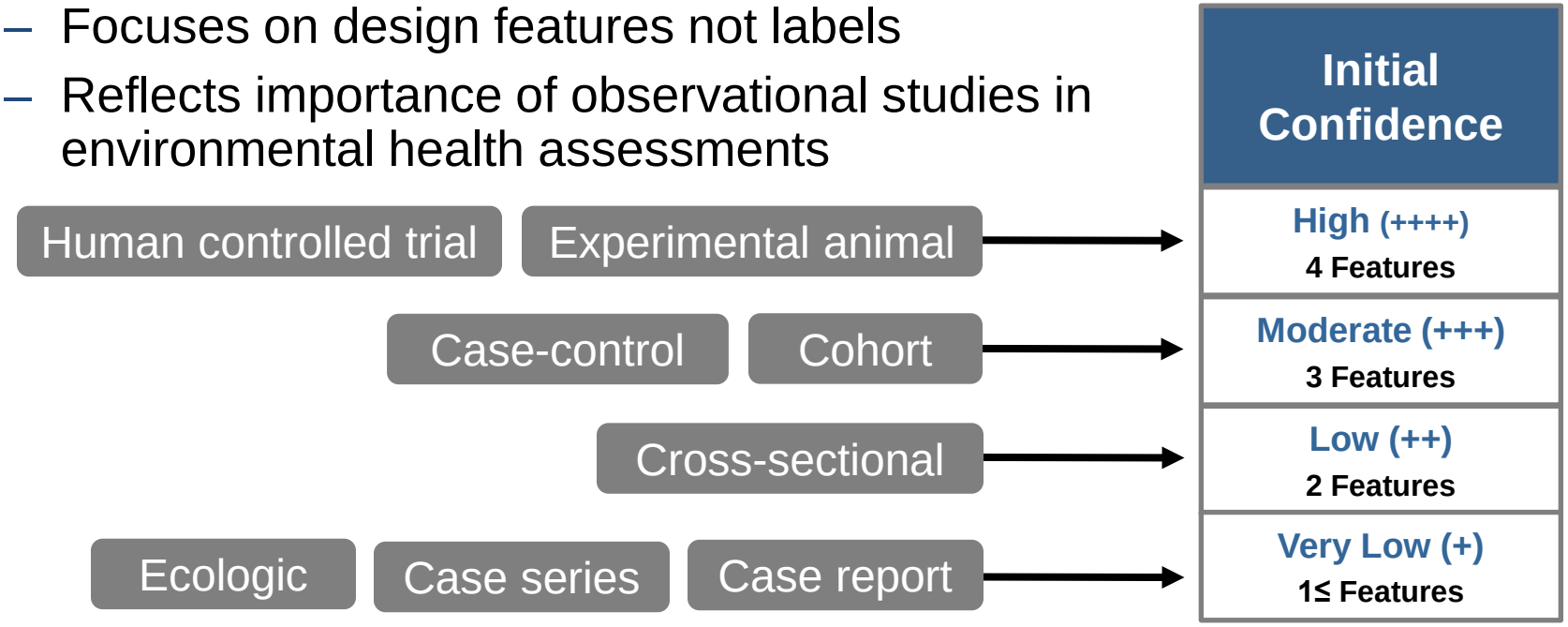
Method for Rating Confidence in a Body of Evidence

Initial Confidence by Key Features of Study Design	Factors Decreasing Confidence	Factors Increasing Confidence	Confidence in the Body of Evidence
High (++++) **4 Features**	❖ **Risk of Bias** ❖ **Unexplained Inconsistency** ❖ **Indirectness** ❖ **Imprecision** ❖ **Publication Bias**	❖ **Large Magnitude of Effect** ❖ **Dose Response** ❖ **All Plausible Confounding** • Studies report an effect and residual confounding is toward null • Studies report no effect and residual confounding is away from null ❖ **Consistency** • Across animal models or species • Across dissimilar populations • Across study design types ❖ **Other** e.g., particularly rare outcomes	High (++++)
Moderate (+++) **3 Features**			Moderate (+++)
Low (++) **2 Features**			Low (++)
Very Low (+) **≤1 Features**			Very Low (+)

Features
- Controlled exposure
- Exposure prior to outcome
- Individual outcome data
- Comparison group used

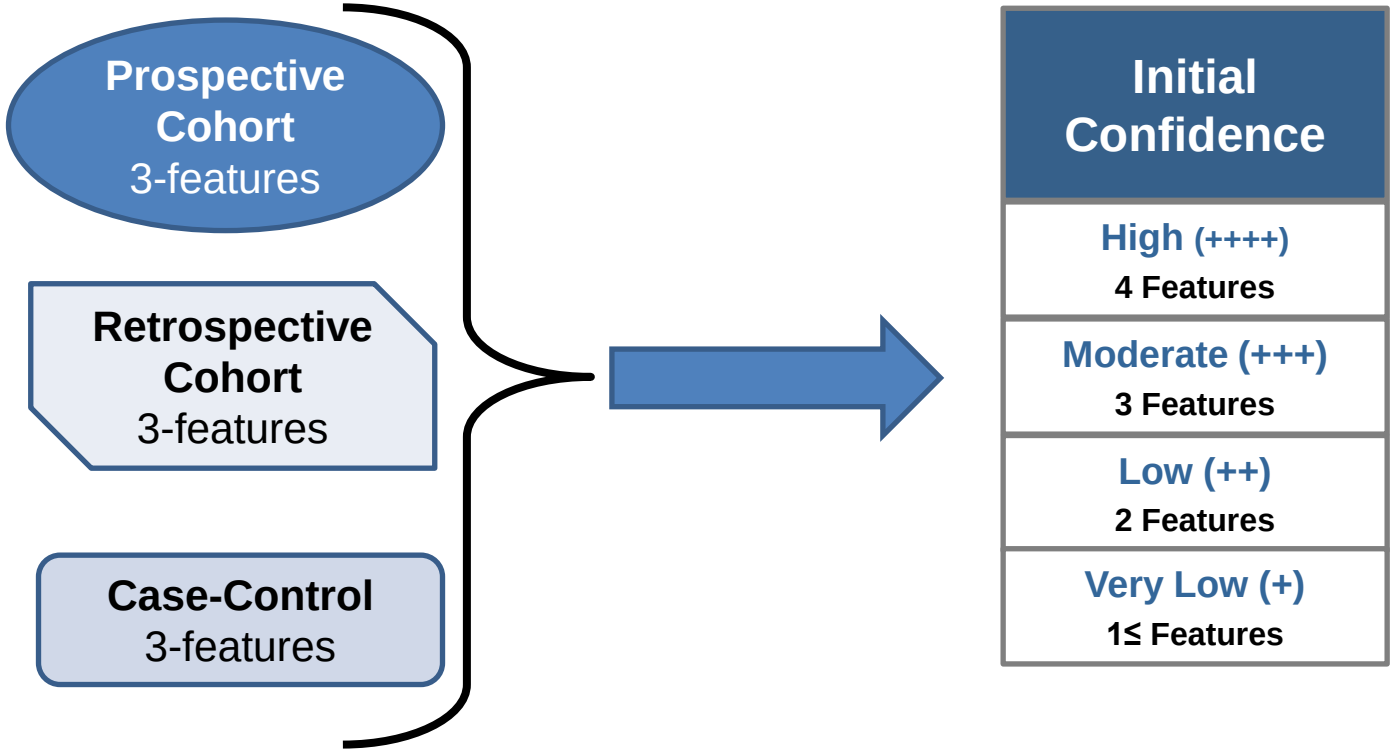
Initial Confidence in Body of Evidence

- Initial Confidence Based on Key Study Design Features
  - Controlled exposure
  - Exposure prior to outcome
  - Individual outcome data
  - Comparison group used
- This Method Stratifies Initial Confidence:
  - Focuses on design features not labels
  - Reflects importance of observational studies in environmental health assessments



Initial Confidence by Study Design Features

- Starting point for evaluating confidence in a collection of studies in same initial confidence category
- Evaluate as a group for the same outcome
- **Questions?**



Evidence Integration

Further Consideration of Hazard Identification

- **Previous Hazard ID Categories**
  - **Known** to be a hazard to humans
  - **Presumed** to be a hazard to humans
  - **Suspected** to be a hazard to humans
  - **Not classifiable or not identified** to be a hazard to humans

- **Updated**
  - "**Not classifiable**" separated from "**Not identified**"

Evidence Integration in Step 7 of draft OHAT Approach

Step 1: Prepare topic

Step 2: Search for and select studies

Step 3: Extract data from studies

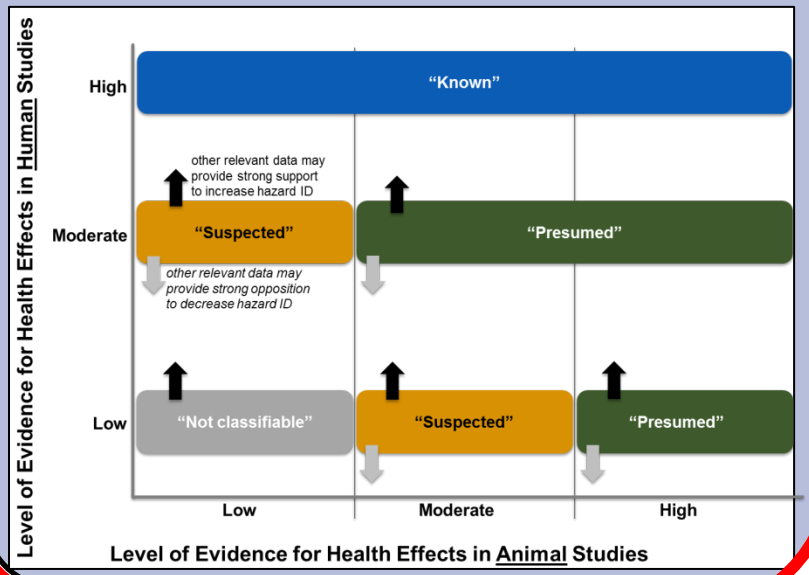
Step 4: Assess individual study quality

Step 5: Rate confidence in body of evidence

Initial Confidence by Key Features of Study Design	Factors Decreasing Confidence	Factors Increasing Confidence	Confidence in the Body of Evidence
High (++++) 4 Features Moderate (+++) 3 Features Low (++) 2 Features Very Low (+) ≤1 Features **Features** • Controlled exposure • Exposure prior to outcome • Individual outcome data • Comparison group used	❖ Risk of Bias ❖ Unexplained Inconsistency ❖ Indirectness ❖ Imprecision ❖ Publication Bias	❖ Large Magnitude of Effect ❖ Dose Response ❖ All Plausible Confounding • Studies report an effect and residual confounding is toward null • Studies report no effect and residual confounding is away from null ❖ Consistency • Across animal models or species • Across dissimilar populations • Across study design types ❖ Other e.g., particularly rare outcomes	High (++++) Moderate (+++) Low (++) Very Low (+)

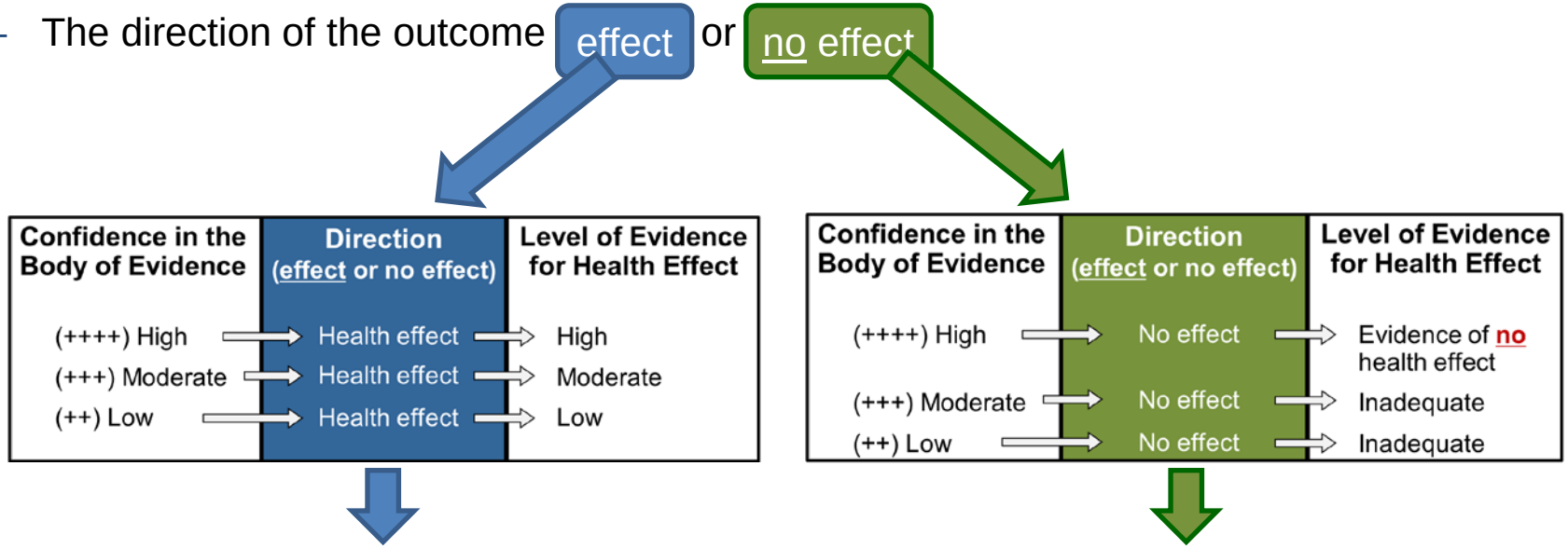
Step 6: Translate confidence ratings into level of evidence for health effect

Step 7: Integrate evidence to develop hazard identification conclusions



Hazard Identification in Draft OHAT Approach

- STEP 6: Level of evidence for health effect (on an outcome basis) reflects
  - Confidence in association between exposure to the substance and outcome
  - The direction of the outcome effect or no effect



- STEP 7: Integrate evidence by combining evidence streams to develop hazard ID
  - **Known** to be a hazard to humans
  - **Presumed** to be a hazard to humans
  - **Suspected** to be a hazard to humans
  - **Not classifiable** to be a hazard to humans

Evidence of no health effect supports Hazard ID conclusion of

- **Not identified** to be a hazard to humans

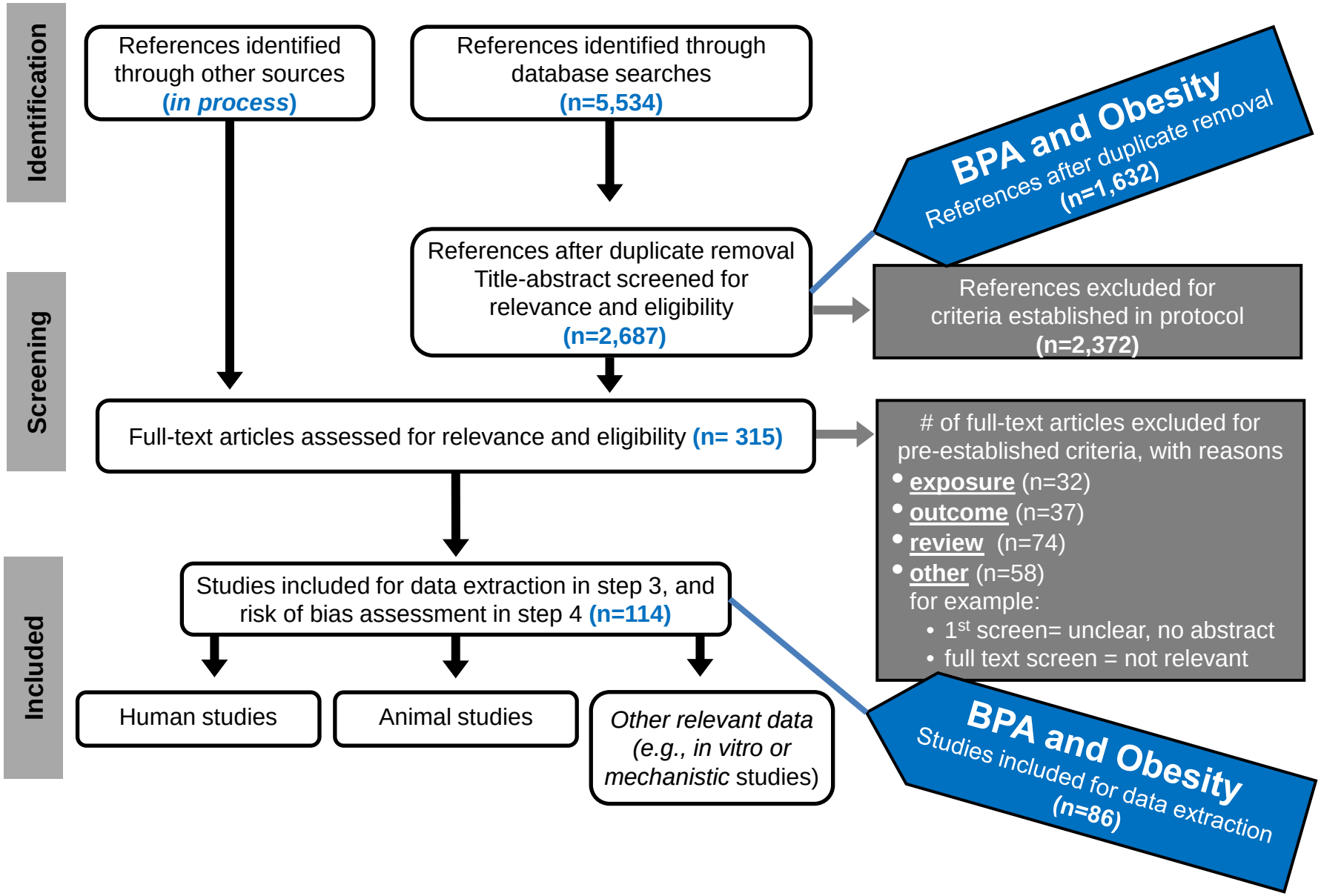
- **Questions?**

Update on the Case Studies

Progress on Case Studies

- Case studies to evaluate OHAT Approach or “Framework”
  - PFOA / PFOS exposure and immunotoxicity
  - BPA exposure and obesity
- Developing template protocol as case studies progress
- Screening studies nearing completion

Case-study Progress : PFOA/PFOS and Immunotoxicity



Plans for Case Studies

- Plan to post screening results in October 2013
- Data extraction started
  - Refinement of DRAGON software ongoing
  - Expect completion in December 2013
- Then “lessons learned” webinar
  - Expect to hold webinar in late Spring 2014
  - Goal is to discuss the OHAT Approach or Framework
- **Questions?**

Acknowledgements

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Additional Discussion

or

Questions?