

Case Study 2: Integrating Evidence Across Multiple Exposures

Brandy Beverly, PhD
National Toxicology Program
US National Institute of Environmental Health Sciences

June 3-4, 2019

**NAS Workshop: Evidence Integration in Chemical Assessment:
Challenges Faced in Developing and Communicating Human Health Effect Conclusions**





NTP Office of Health Assessment and Translation

- OHAT serves as an environmental health resource for public and regulatory agencies
- Conduct literature-based evaluations to assess the evidence that environmental substances cause adverse health effects
 - Systematic review (SR)
 - Evidence mapping
- Promote SR methods development and uptake in environmental health
 - Encourage harmonization
 - Engage collaboration for ongoing challenges

NTP Monographs



NTP Reports



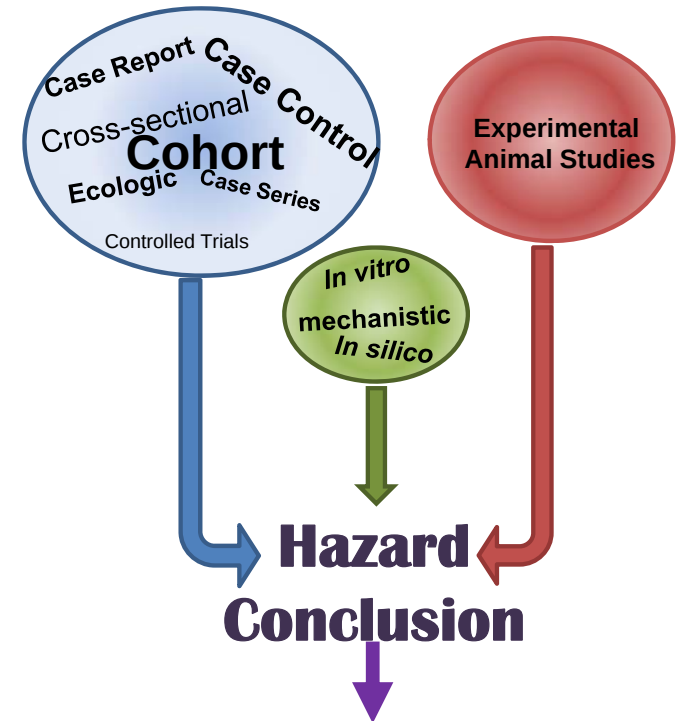
Workshops





Systematic Review and Environmental Health

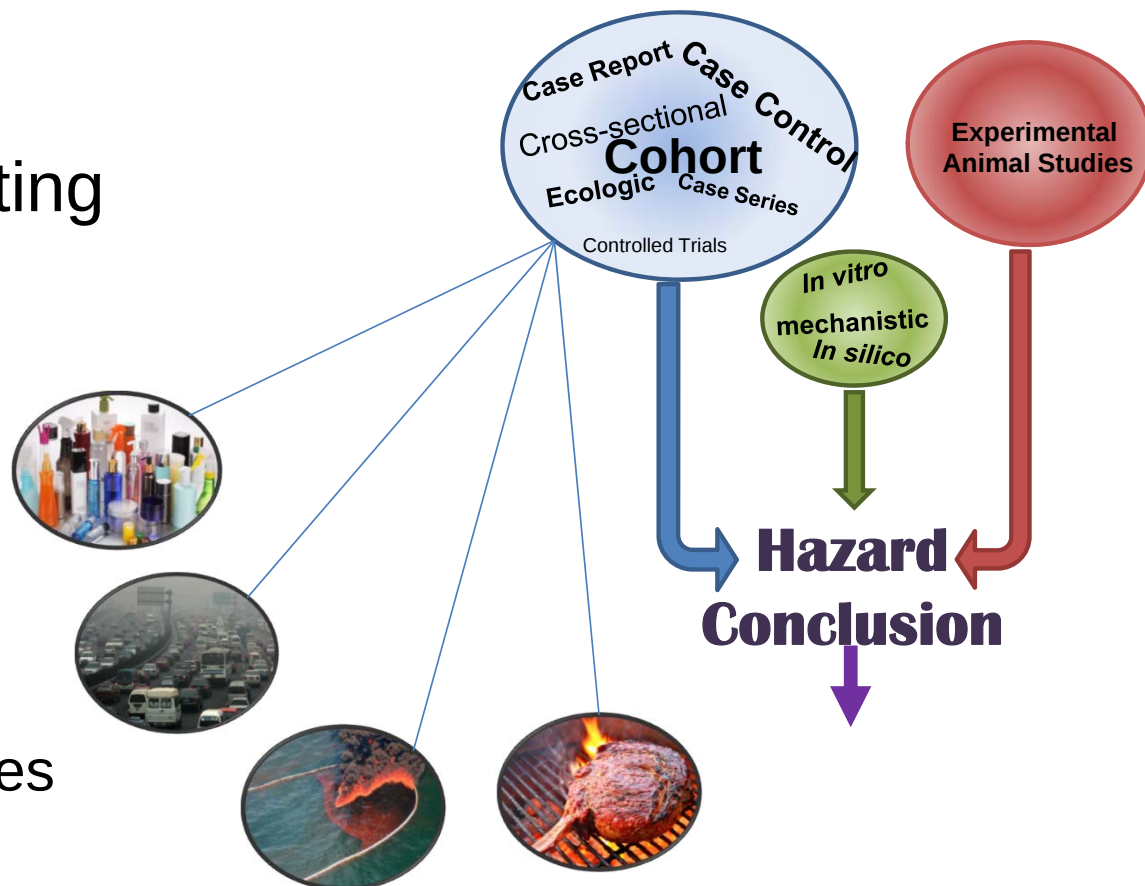
- Large, complex, and diverse data
- Human evidence consisting largely of observational studies
- “Real world” exposures
 - Known/uncharacterized contaminants
 - Multiple chemicals/mixtures
 - Cumulative effects





Systematic Review and Environmental Health

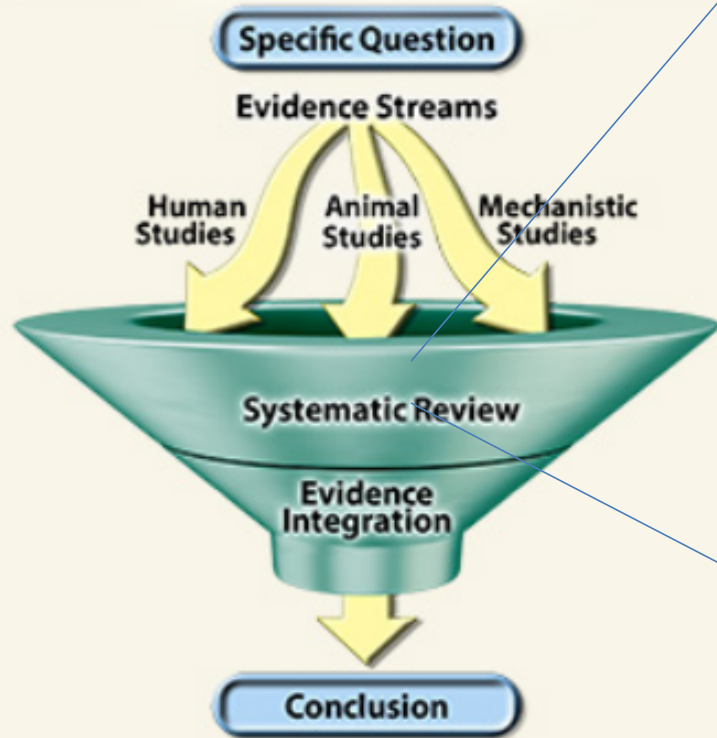
- Large, complex, and diverse data
- Human evidence consisting largely of observational studies
- “Real world” exposures
 - Known/uncharacterized contaminants
 - Multiple chemicals/mixtures
 - Cumulative effects





OHAT Approach for Conducting Systematic Review

OHAT Approach



Systematic Review

Planning and Protocol



Identify Evidence



Evaluate Evidence



Evidence Integration



- Specific research question (e.g., single exposure single effect)

- Problem Formulation
- Protocol development
- Search, select
- Extract
- Individual study quality
- Confidence in body of evidence



Health Effects of Air Pollution is a Complex Question

- Nomination to NTP: Evaluate emerging children's health issues associated with air pollution
- Which exposure(s)?
 - Focus on exposure with sufficient data but where new review could be impactful
 - Heavy metals, traffic, ambient air
 - Traffic-Related Air Pollution (TRAP)
 - Noted challenge and advantage of complex exposure





Traffic-Related Air Pollution

- TRAP: Air pollution exposures derived from primary emissions from motor vehicles due to fossil fuel combustion
- Sources of TRAP: Passenger cars, diesel trucks and buses, and “non-road” equipment
- Pollutants include carbon dioxide, carbon monoxide, particulate matter, oxides of nitrogen and sulfur, etc.





Health Effects of Air Pollution is a Complex Question

- Emerging children's health issues associated with air pollution
- Which outcome(s)?
 - Association between maternal hypertension during pregnancy and adverse outcomes in the infant
 - Preterm delivery
 - Low birthweight
 - Small for gestational age
 - Prematurity-related neonatal diseases
 - Hypertensive disorders of pregnancy
 - Evidence suggesting TRAP is significantly associated with hypertensive disorders of pregnancy





NTP conducted a systematic review evaluating potential associations between exposure to traffic-related air pollution (TRAP) and hypertensive disorders of pregnancy

- Gestational Hypertension
- Preeclampsia/Eclampsia, HELLP
- Chronic hypertension with superimposed preeclampsia
- Changes in blood pressure during pregnancy



Addressing complex questions with SR

- Systematic review approaches are highly effective at transparently evaluating evidence on groups of studies addressing the **same or similar endpoints**
- Broad topics like “Is PM_{2.5} associated with cardiovascular toxicity?” can be **addressed with series of specific questions**

– All cardiovascular endpoints



Hypertension



Blood Pressure



Atherosclerosis



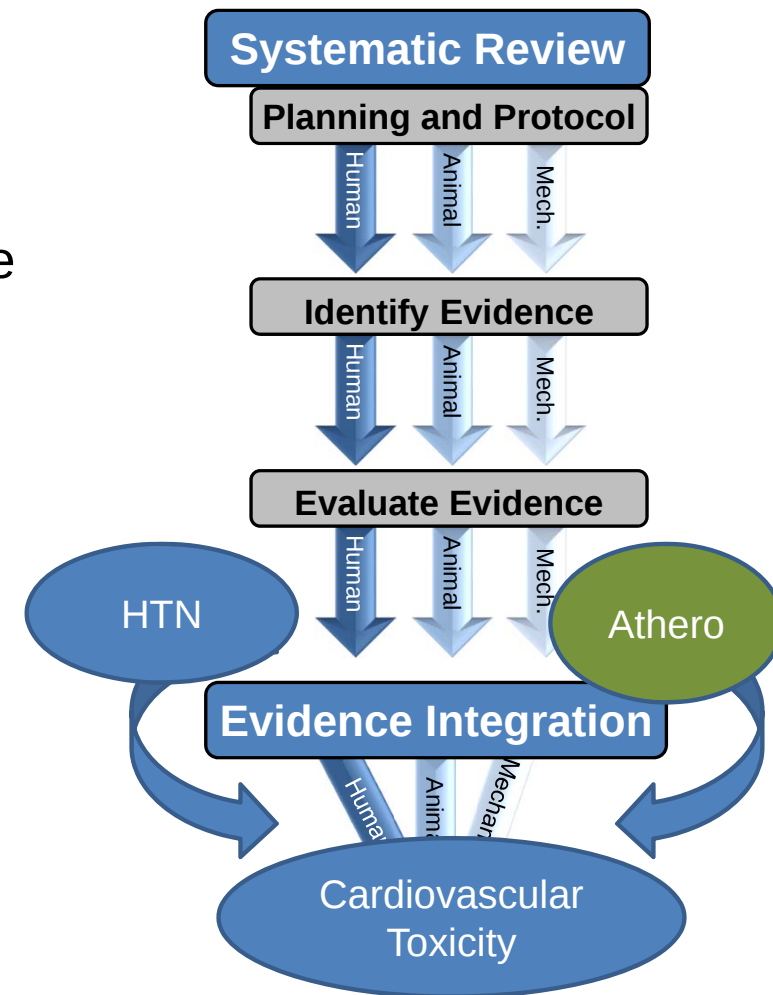
Plaque formation





Stepwise Evaluation of Multiple Outcomes

- Develop separate bodies of evidence
 - Hypertension
 - Atherosclerosis
 - Confidence in body of evidence for each outcome
- Synthesize across bodies of evidence
 - Re-evaluate confidence collectively and develop conclusions

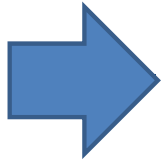




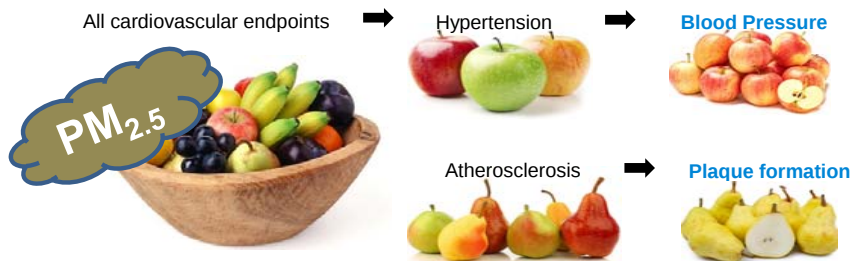
Multiple Exposure-Outcome Pairs

- Is TRAP associated with cardiovascular toxicity?

- Single or multiple health outcomes



Multiple exposures



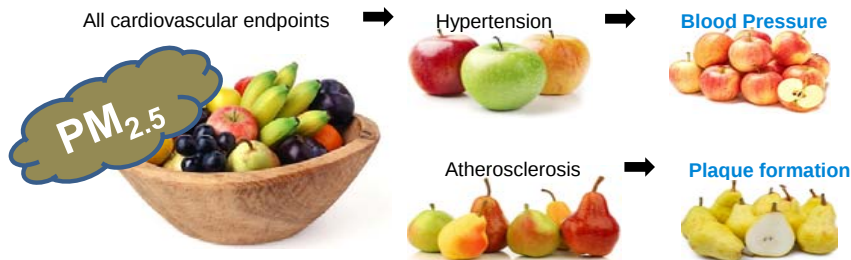
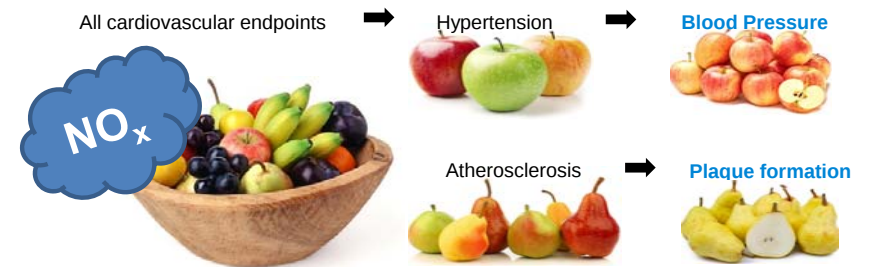
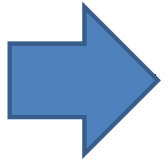


Multiple Exposure-Outcome Pairs

- Is TRAP associated with cardiovascular toxicity?

- Single or multiple health outcomes

Multiple exposures



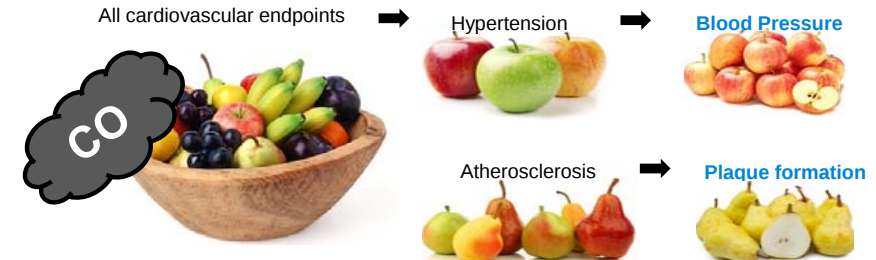
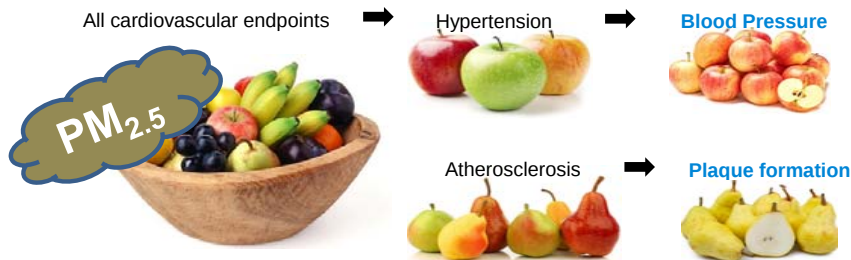
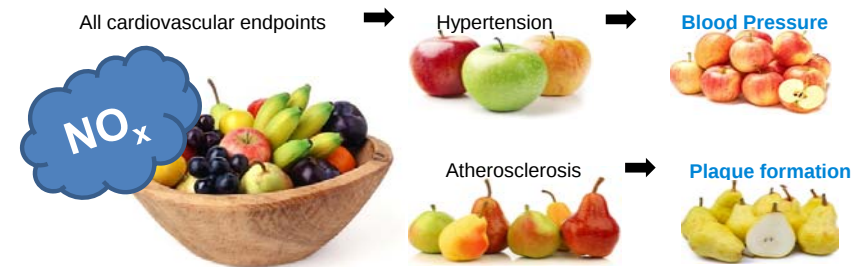
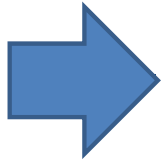


Multiple Exposure-Outcome Pairs

- Is TRAP associated with cardiovascular toxicity?

- Single or multiple health outcomes

Multiple exposures



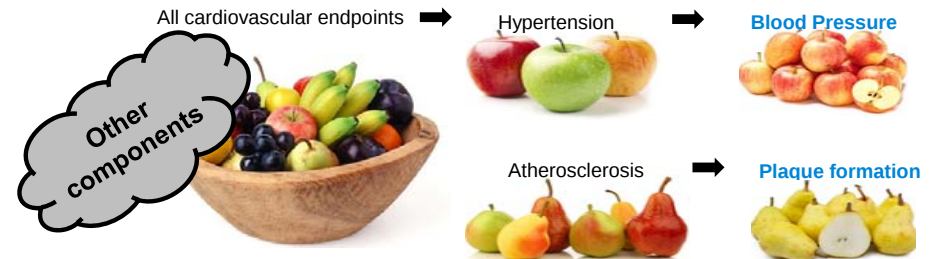
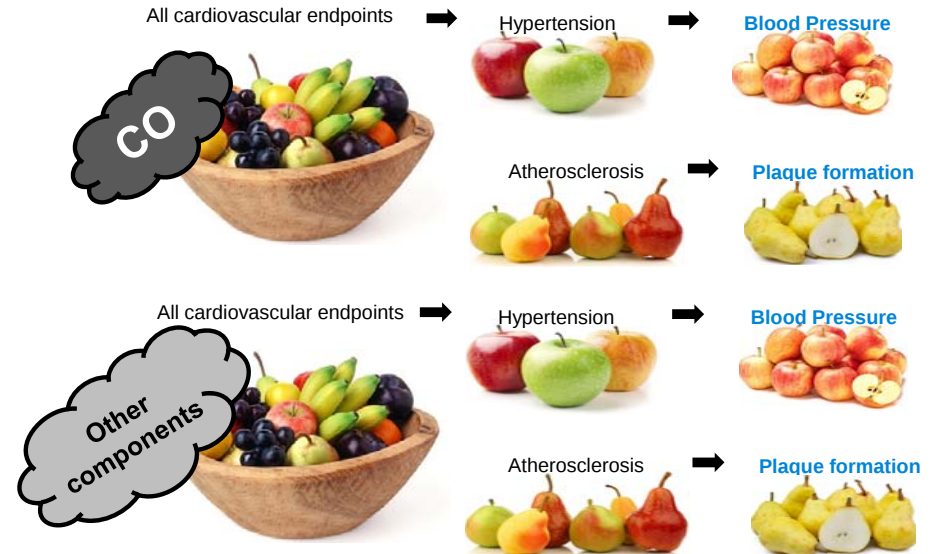
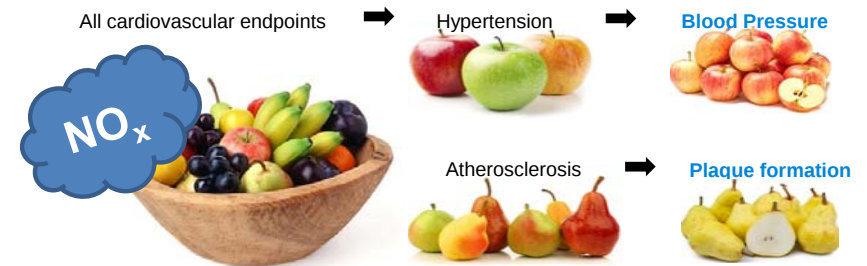
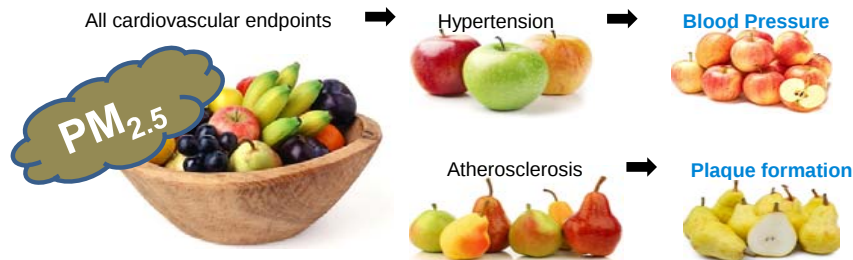
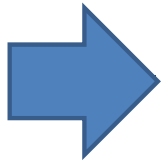


Multiple Exposure-Outcome Pairs

- Is TRAP associated with cardiovascular toxicity?

- Single or multiple health outcomes

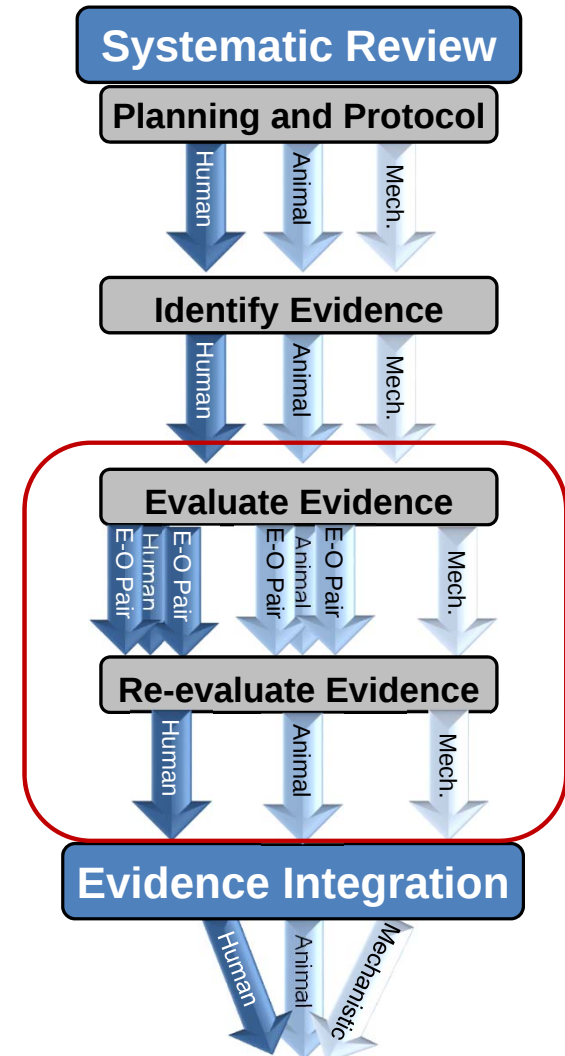
Multiple exposures





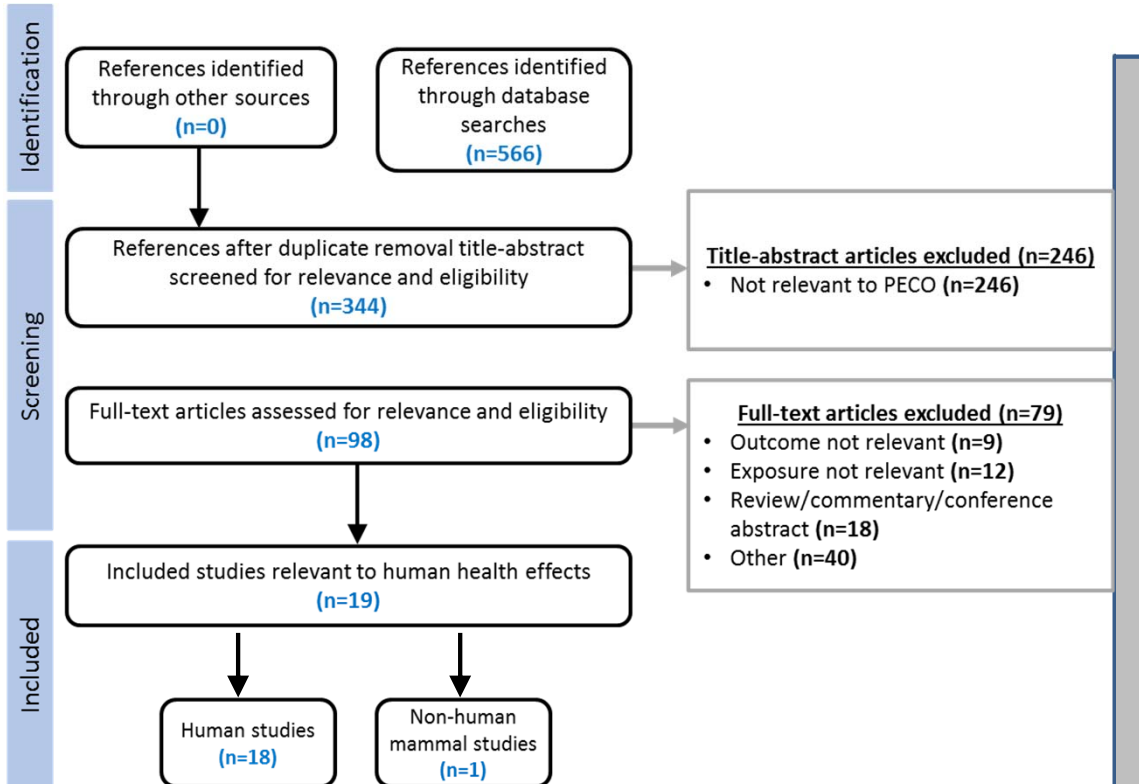
Stepwise Evaluation of Exposure-Outcome Pairs

- Develop separate bodies of evidence
 - Exposure-outcome pairs (PM_{2.5}, other TRAP surrogates, direct traffic measures)
 - Assess individual study quality/risk of bias
 - Evaluate confidence in exposure-outcome pair bodies of evidence
- Synthesize across bodies of evidence
 - Re-evaluate confidence collectively and develop conclusions
 - Datasets
 - Overlapping or separate studies and populations?
 - Data or studies that control/adjust for other exposures?
 - Consider data on mechanism(s)
 - Overlapping/ independent?



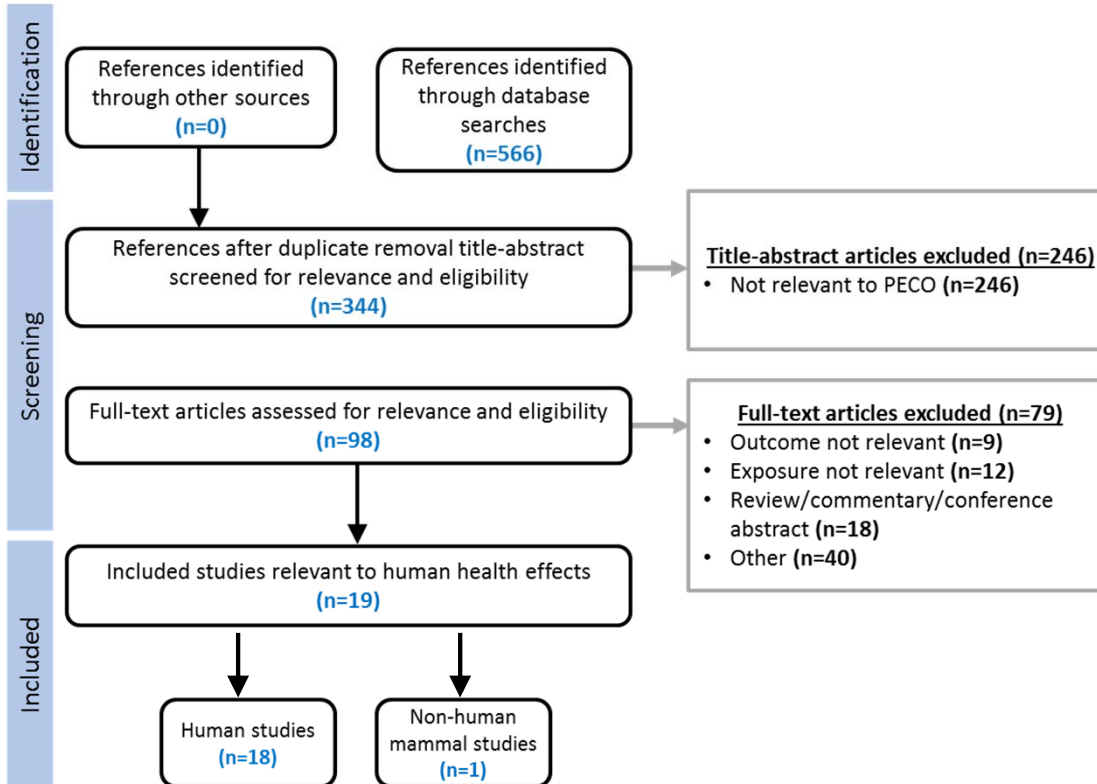


Develop Exposure – Outcome Pairs for TRAP





Develop Exposure – Outcome Pairs for TRAP

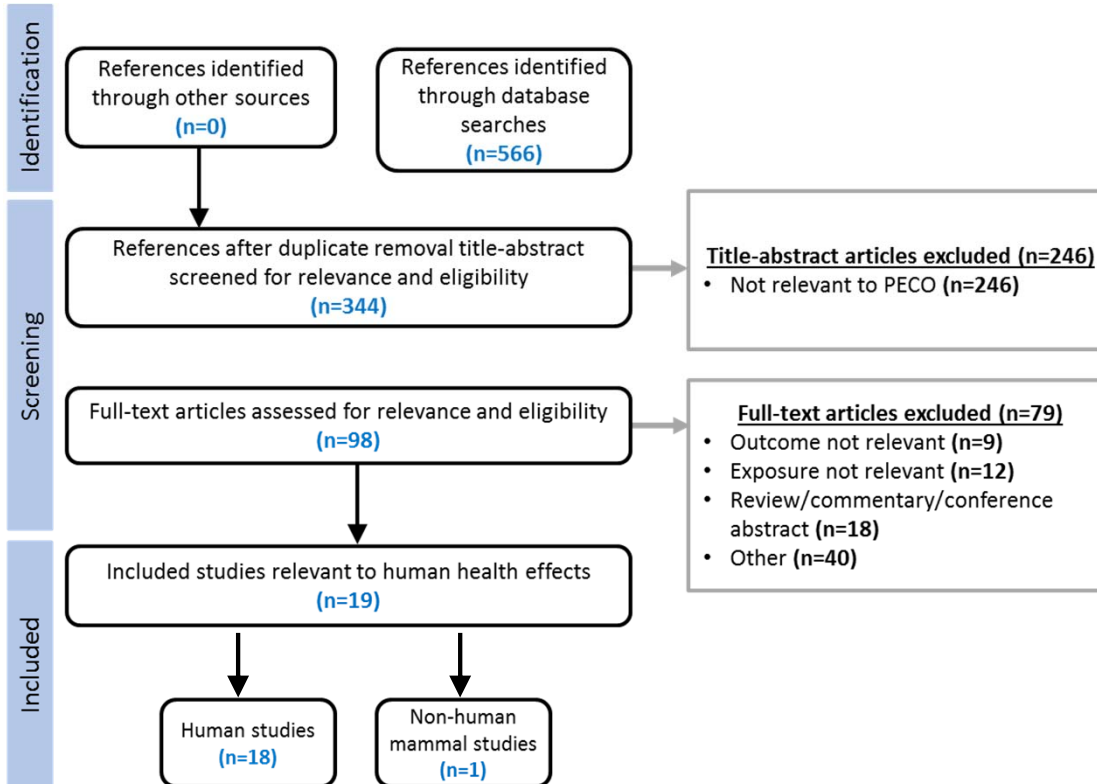


Exposure – Outcome Pairs

- PM_{2.5} +
- NO₂ +
- NO_x +
- CO +
- EC +
- BC +
- Traffic Density +
- Proximity to Road +



Develop Exposure – Outcome Pairs for TRAP



Exposure – Outcome Pairs

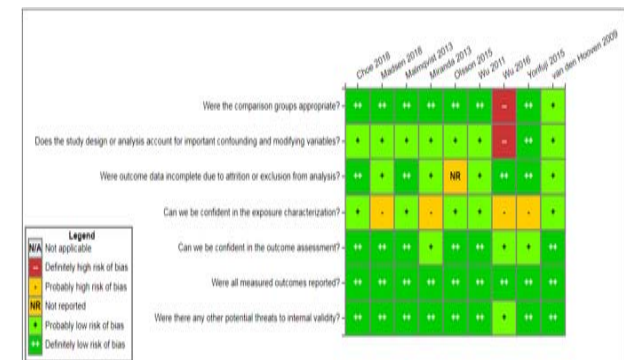
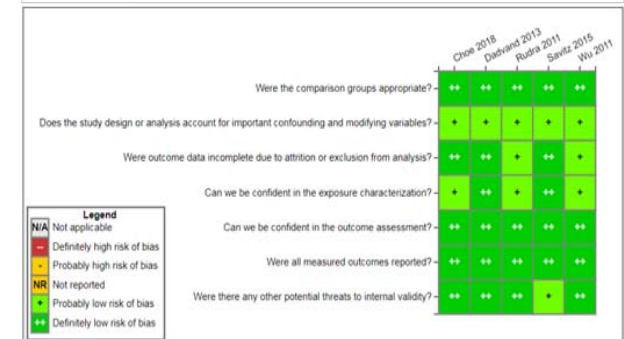
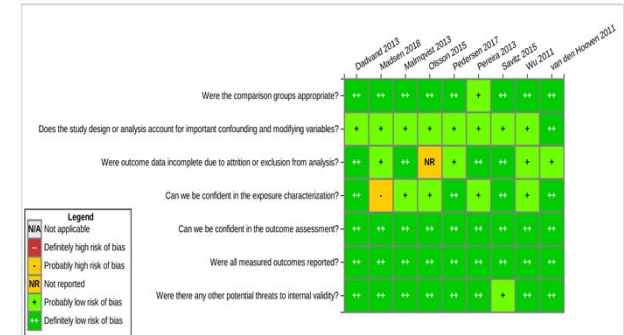
- PM_{2.5} +
- NO₂ +
- NO_x +
- CO +
- EC +
- BC +
- Traffic Density +
- Proximity to Road +
- Preeclampsia
- Gestational Hypertension
- Hypertensive Disorders of Pregnancy
- Blood pressure changes during pregnancy



Risk of Bias Considerations

Exposure – Outcome Pairs

1. RoB considerations are health outcome-specific
 - Differences across how health effects were evaluated
2. Exposure-specific ROB considerations
 - Difference across exposures

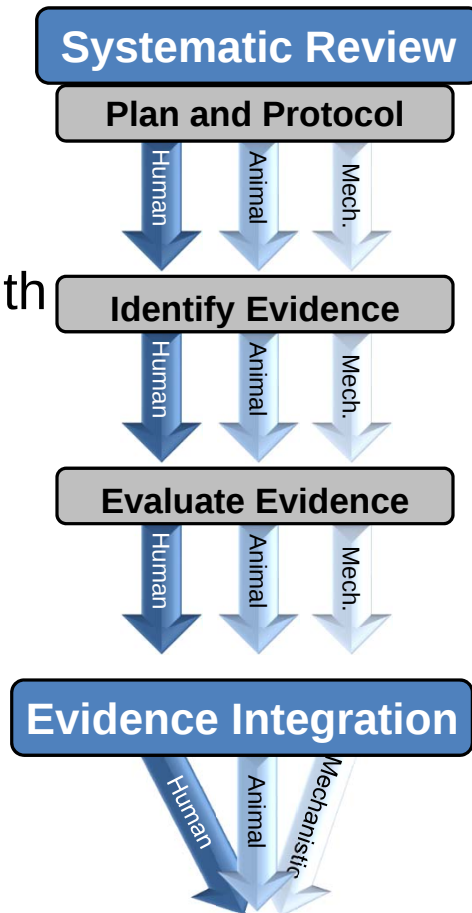
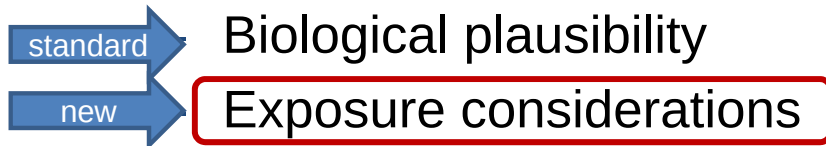




Mechanistic Data

Mechanistic Data Considered in Multiple steps of the Review

- Problem Formulation
 - Outline proposed use of mechanistic data
- Identify
 - Focused on data with relevance to human and animal health data
- Evaluate
 - Consider Quality and Applicability (e.g., dose relevance)
- Evidence Integration





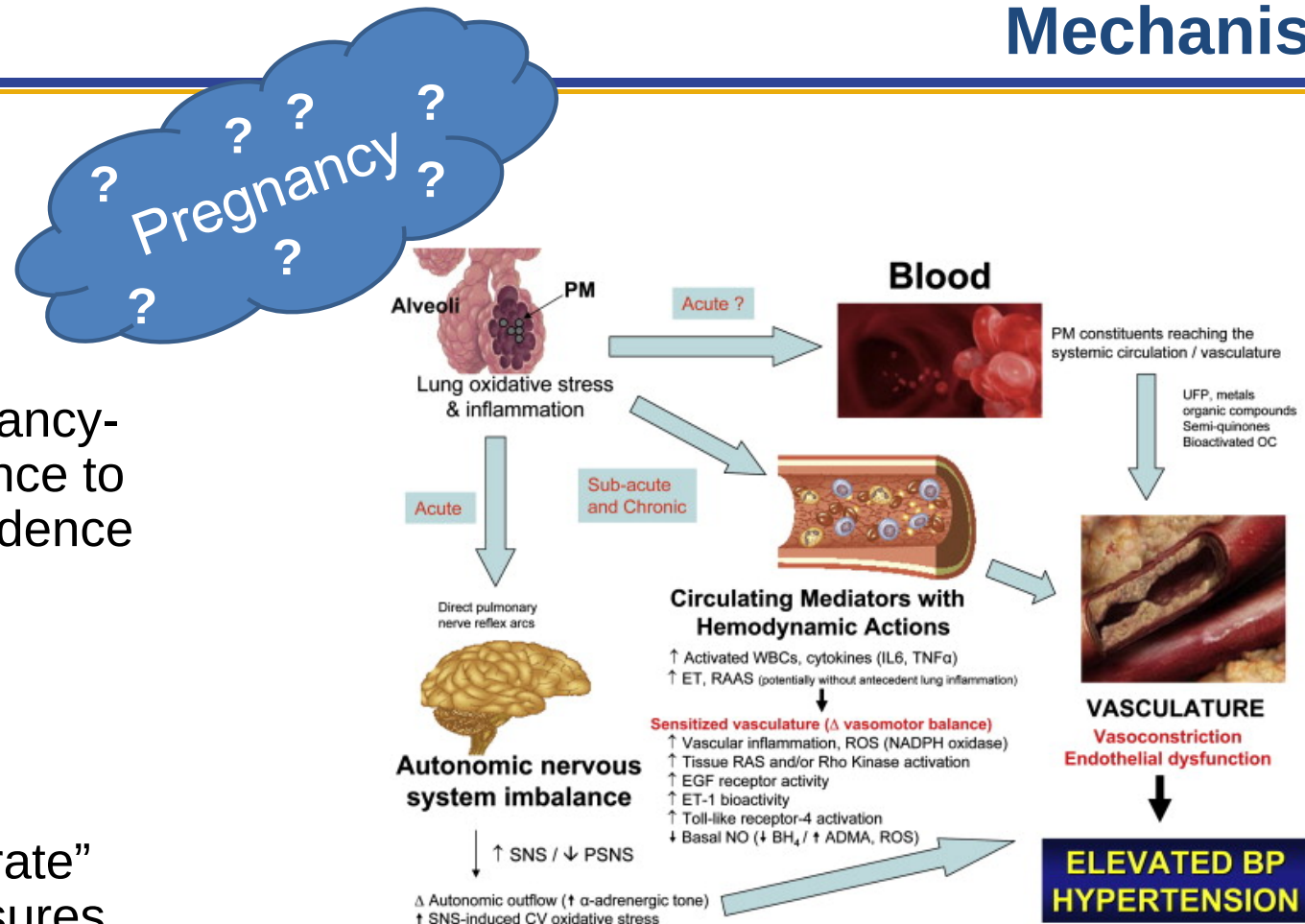
Mechanisms

- Biological Plausibility

- Is there pregnancy-specific evidence to increase confidence in BOE?

- Exposure considerations

- Are the “separate” multiple exposures really separate?

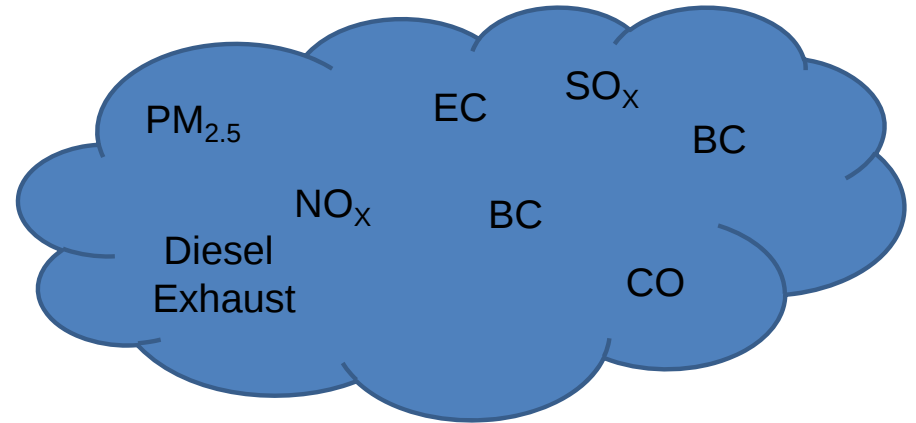
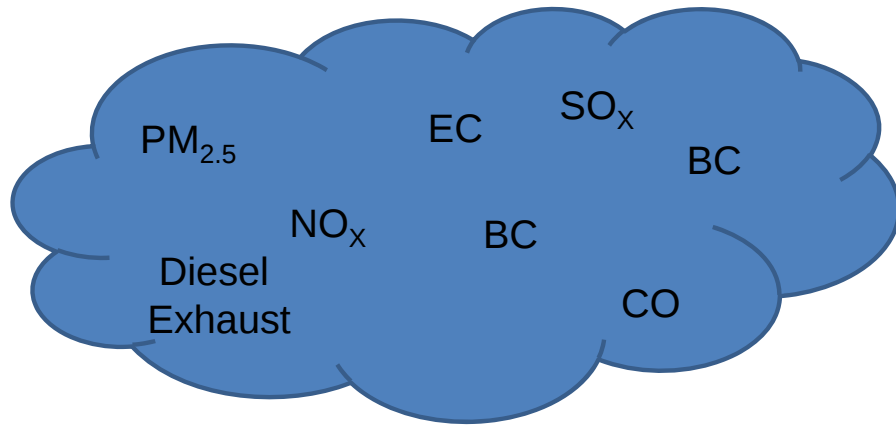


Brook and Rajagopalan, 2009



Understanding the Exposure

The role of the part in the whole....

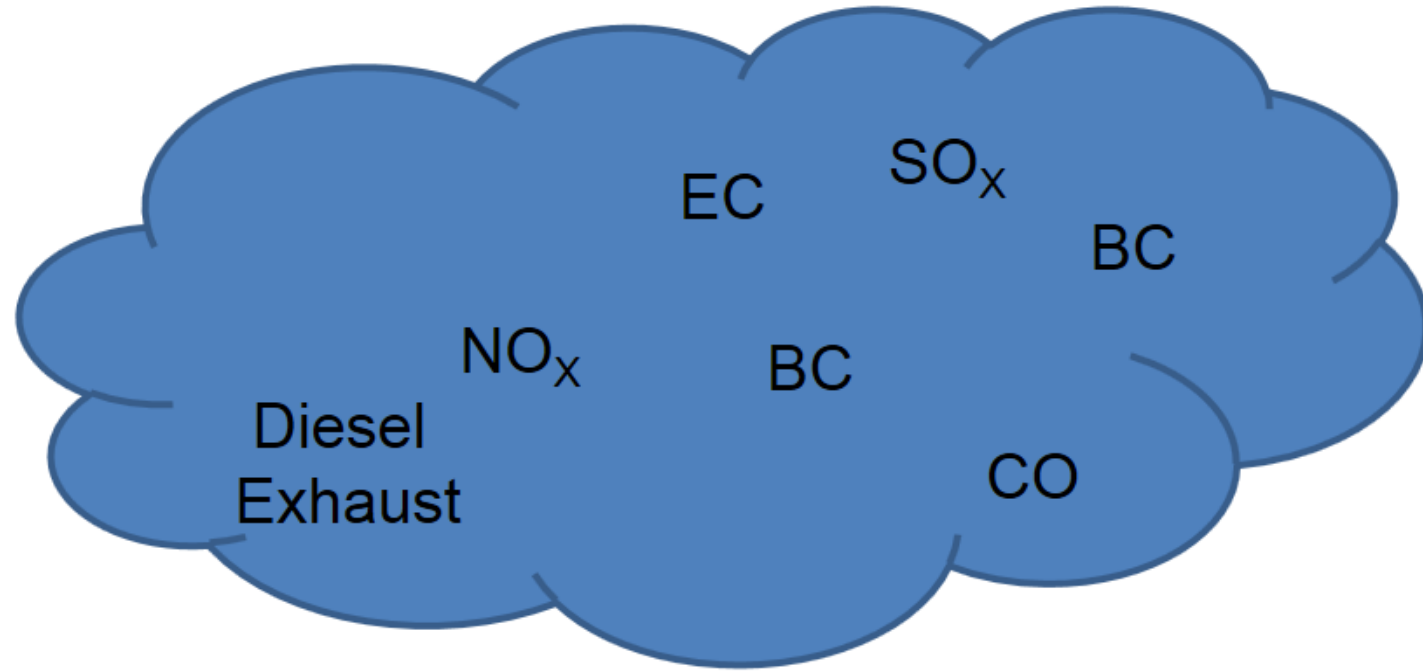


Can we reach conclusions on the individual components and/or broad exposure?

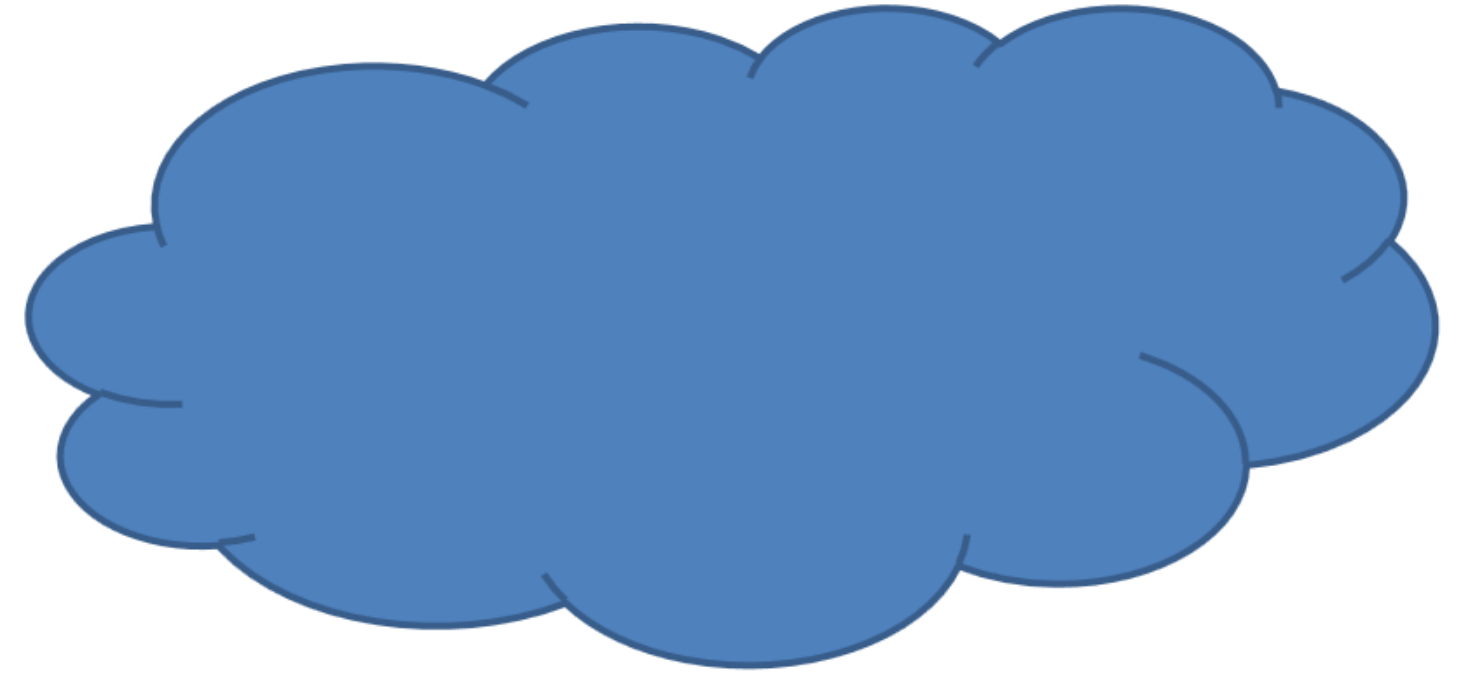


Understanding the Exposure

The role of the part in the whole....



PM_{2.5}



PM_{2.5}

NO_x

EC

SO_x

BC

CO

BC

Diesel Exhaust

Can we reach conclusions on the individual components and/or broad exposure?



Summary/Conclusions

- TRAP was evaluated using a stepwise approach (E-O pairs)
- Flexibility to refine methods to address EH challenges (e.g., real world exposures)
- Leveraging new tools/techniques in tox testing to tackle these challenges
- Utility
 - Use of data-rich source substance
 - Develop conclusions on data-poor substance



<https://ntp.niehs.nih.gov/go/trap>



Thank you Questions?

