Surveying the Epidemiology Evidence: Examples of Triangulation from the IRIS Program

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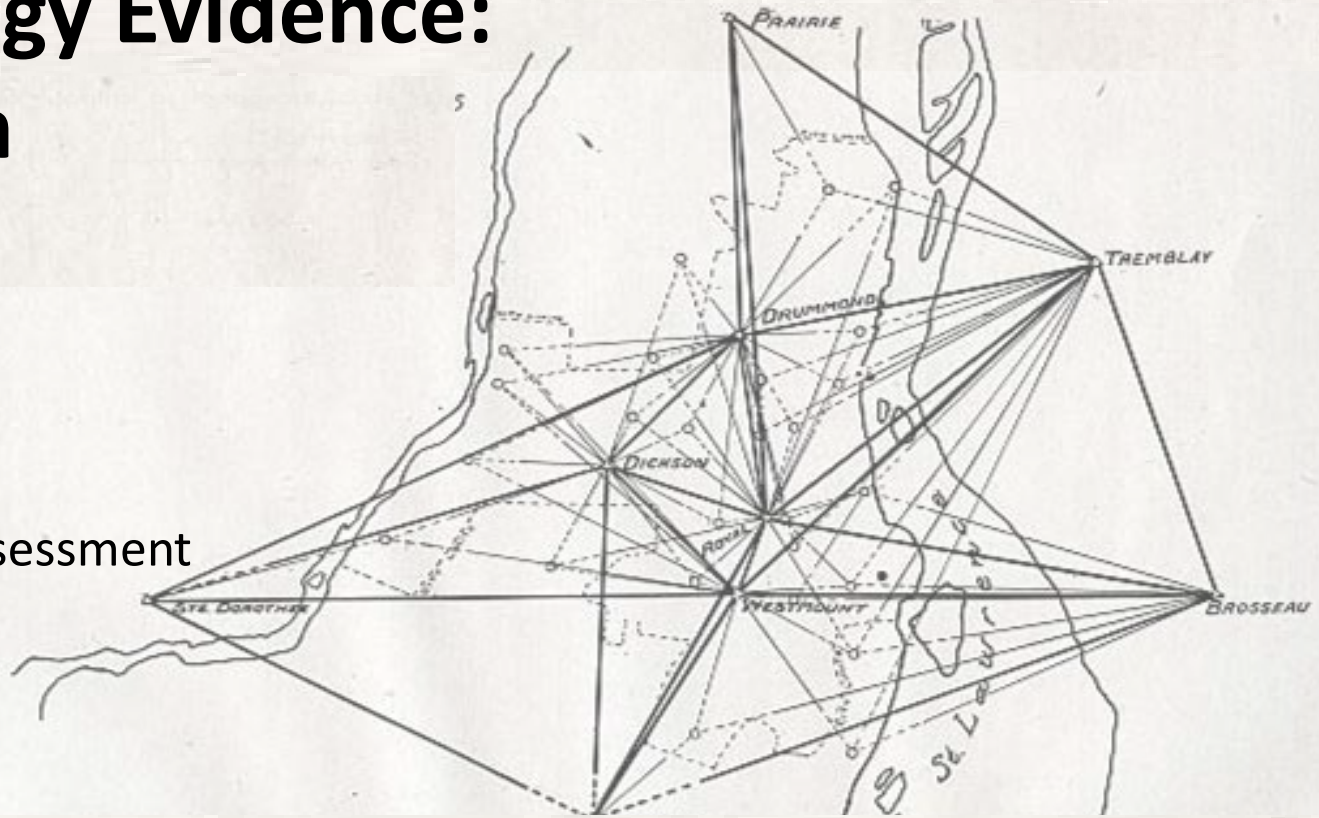


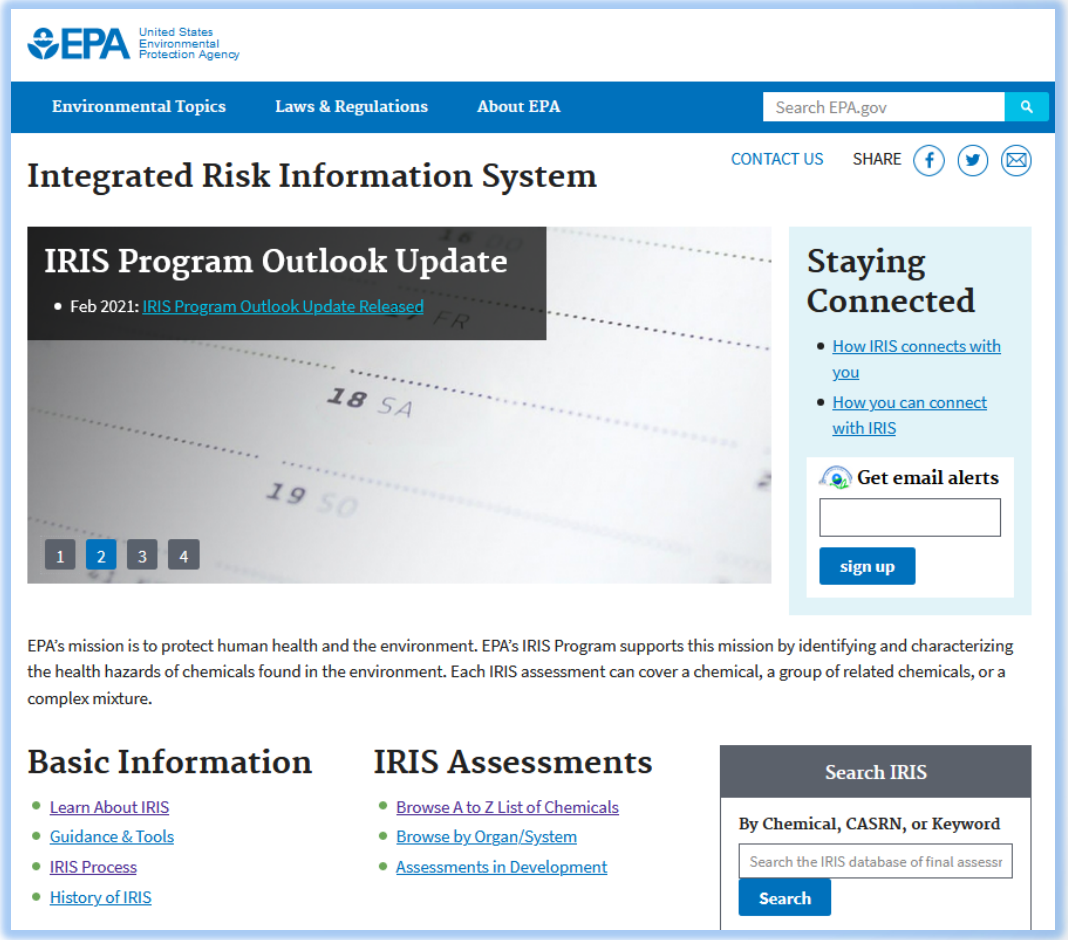
Detail of triangulation points for topographical map of Montreal: https://www.nrcan.gc.ca/maps-tools-publications/maps/100-years-geodetic-surveys-canada/9110

Disclaimer

The views expressed in this presentation are those of the authors and do not necessarily reflect the views or policies of the U.S. Environmental Protection Agency.

EPA's Integrated Risk Information System (IRIS)

- Database of health effects information on hundreds of environmental pollutants
- IRIS assessments contribute to decisions across EPA and other health agencies
- Focus is on toxicity due to lifetime exposure
- Provides toxicity values for cancer and noncancer effects
- Have no direct regulatory impact until combined with extent of exposure, cost of cleanup, available technology, and other regulatory options that are the purview of other EPA programs



EPA's Integrated Risk Information System (IRIS)

IRIS assessments contribute to EPA decisions such as:

- Health-based national standards
- Health-based clean-up levels at local sites
- Health-based advisory levels
- Ranking across chemicals
- Information for the general public
- Cost-benefit analyses

IRIS Supports

- **Clean Air Act (CAA)**

- **Safe Drinking Water Act (SDWA)**
- **Food Quality Protection Act (FQPA)**

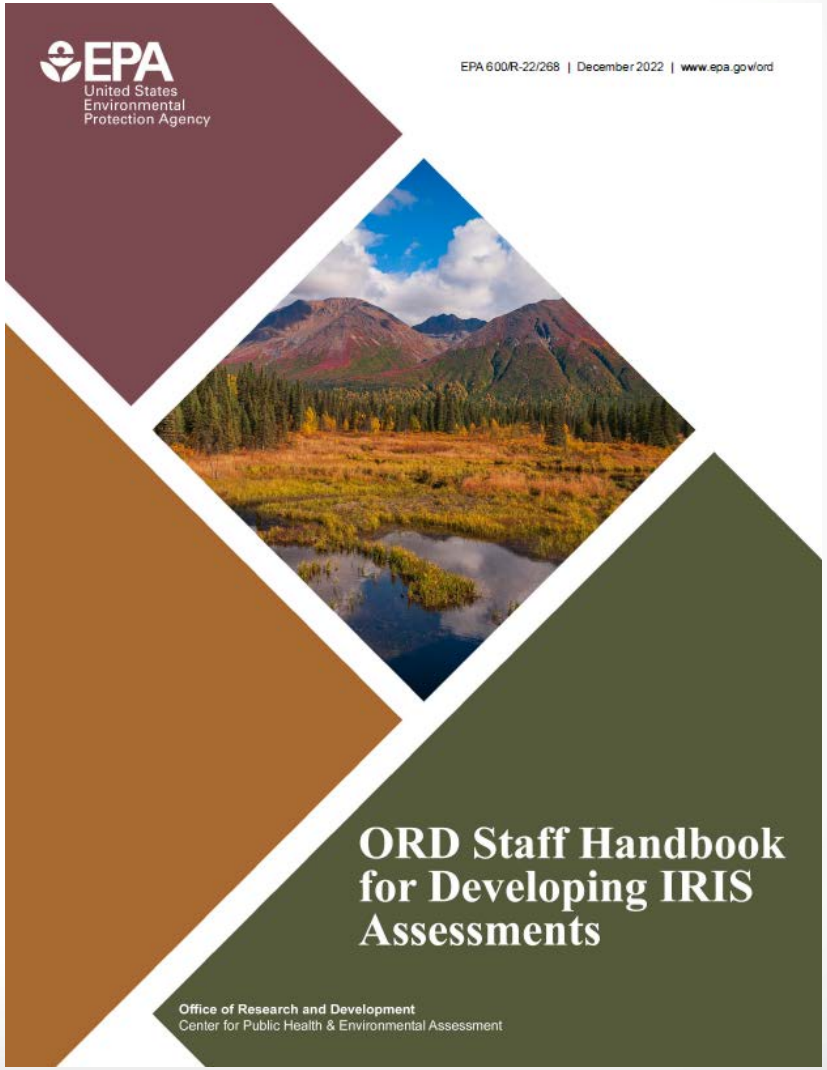
- **Comprehensive Environmental Response, Compensation, and Liability Act (CERCLA)**
- **Toxic Substances Control Act (TSCA)**
- **Resource Conservation and Recovery Act (RCRA)**

Broad Input to

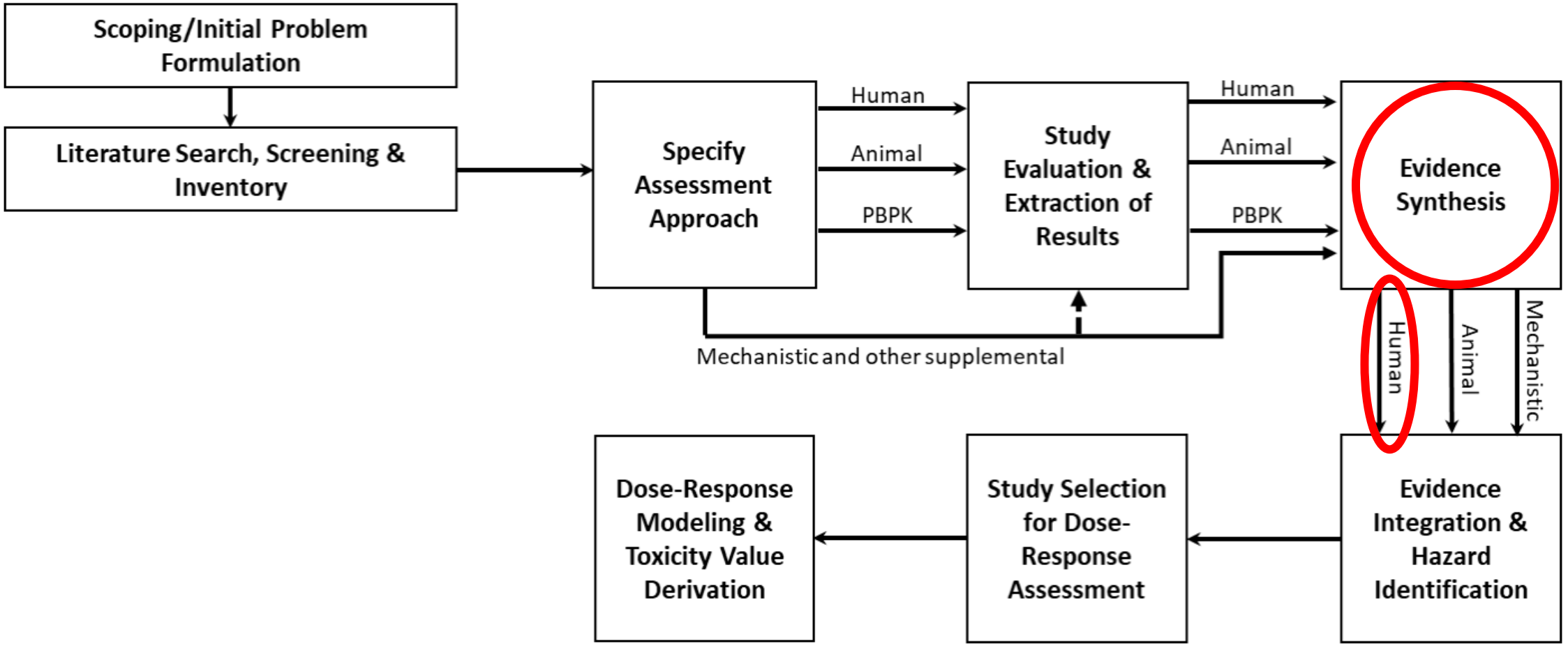
- **Agency Strategic Goals**
- **Regions and States**
- **Children's Health**
- **Environmental Justice**

IRIS Handbook

1. Scoping and Initial Problem Formulation
2. Literature Search, Screening, and Inventory
3. Refine Problem Formulation and Specify Assessment Approach
4. Study Evaluation
5. Extraction and Display of Study Results
6. Evidence Synthesis and Integration
7. Hazard Considerations and Study Selection for Dose-Response
8. Derivation of Toxicity Values



IRIS Assessment Development Process



Triangulation

- The integration of results from different approaches taken to address a research question, where each approach involves different sources of bias, ideally not all in the same direction. *(Lawlor et al., 2016, IJE 45:1866–86; Pearce et al., 2019, Epidemiology 30:311-16)*
- In the context of IRIS: Tool that would potentially enable us to include and use as much information as possible and appropriate.
- For chemical health assessments, triangulation may be applied at multiple levels:
  - **Integration** across evidence streams (e.g., toxicological, epidemiologic, and mechanistic) informing causal determinations.
  - Multiple analyses within a single study
  - **Synthesis** of results within a single stream of evidence (e.g., within the body of epidemiologic studies)

Established approach in U.S. EPA risk assessment

Less formalized in IRIS process

Example 1: Libby Amphibole Asbestos (LAA)

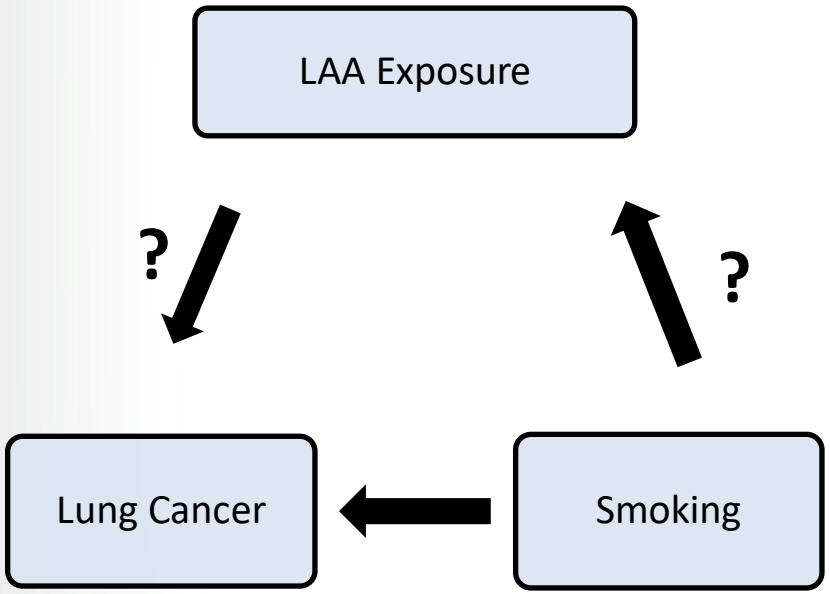
- The IRIS assessment for Libby amphibole asbestos (LAA) derived a toxicity value to quantify risk for lung cancer.
  - For inhalation exposure, this value is the "inhalation unit risk" (IUR)
  - The IUR is the upper-bound excess lifetime cancer risk estimated to result from continuous exposure to an agent at a concentration of 1 µg/m^3 in air
  - Data used to derive the IUR came from an occupational cohort study with incomplete smoking data.
- The potential for uncontrolled confounding by smoking was evaluated using a method (Richardson, 2010) which utilizes a negative control outcome.

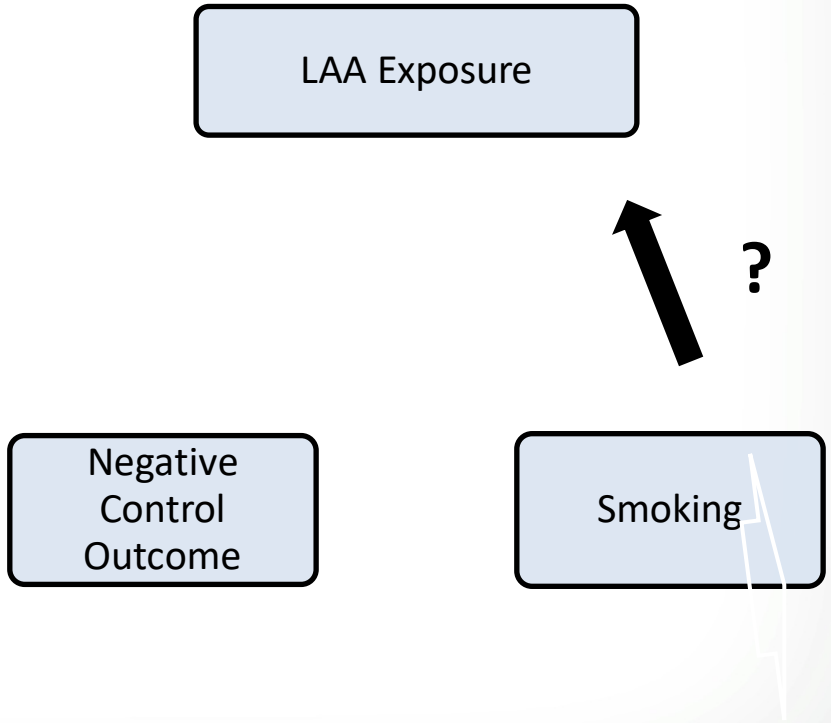
Richardson, D. Epidemiology, 2010. DOI: 10.1097/EDE.0b013e3181c6f7d9

Example 1: Libby Amphibole Asbestos (LAA)

- Why use a negative control? Basically, you examine an association you *expect* to be null.
  - If it IS indeed null, this lends confidence to the results.
  - If it is NOT null, this raises concern for bias in the results.
- Negative control **exposures**
  - Control exposure-outcome association has the same common causes as the **target exposure**-outcome association
  - *Example*: Placebo in a controlled exposure trial
- Negative control **outcomes**
  - Exposure-control outcome association has the same common causes as the exposure-**target outcome** association
  - *Example*: Cancer at a different (unrelated) site than the cancer of interest

Example 1: Libby Amphibole Asbestos (LAA)





If the exposure (LAA) can be used to predict both lung cancer **and** another smoking-related outcome (not related to LAA), confounding may be present.

Example 1: Libby Amphibole Asbestos (LAA)

- If the exposure (LAA) can be used to predict both lung cancer **and** another smoking-related outcome (not related to LAA), confounding may be present.
  - Negative control outcome: chronic obstructive pulmonary disease (COPD) is related to smoking but not believed to be associated with LAA exposure
  - EPA evaluated the relationship between LAA and COPD mortality using an extended Cox proportional hazards model. Depending on the exposure metric, the estimated slope (beta) for COPD was small ($\beta = -0.056$ or -0.135 per fiber/cc-yr) and not statistically significant (*p*-value = 0.102 or 0.116).

- This analysis provides greater confidence that the relationship between LAA and lung cancer is not due to uncontrolled confounding by smoking.

U.S. EPA. IRIS Toxicological Review of Libby Amphibole Asbestos (Final Report). U.S. Environmental Protection Agency, Washington, DC, EPA/635/R-11/002F, 2014.

Example 2: Trichloroethylene (TCE)

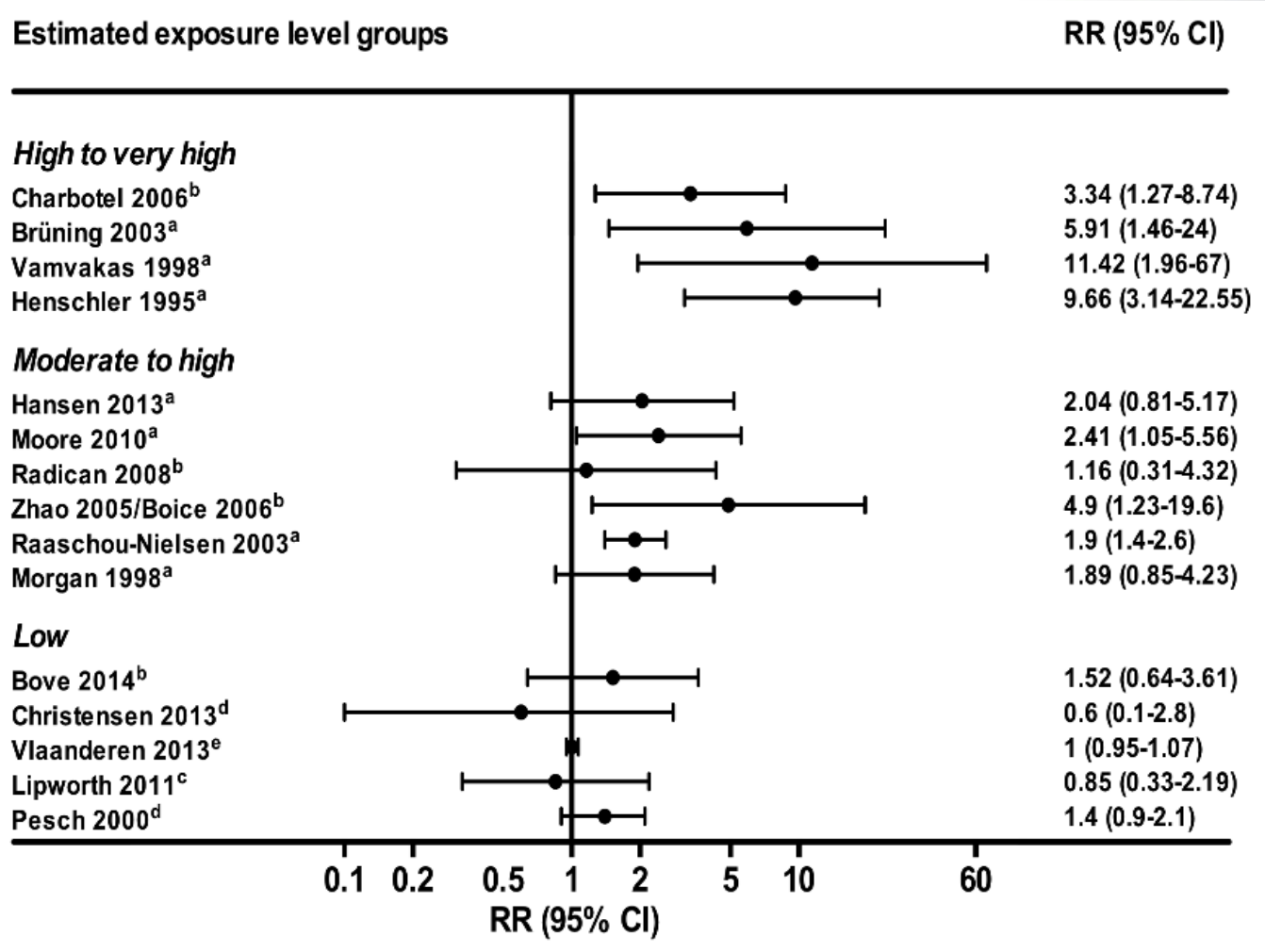
- Associations between TCE and multiple types of cancer were investigated in the National Toxicology Program's 2014 Report on Carcinogens (RoC), and in the 2011 IRIS Toxicological Review
- Evaluating consistency across studies
  - RoC analyses addressed consistency in results among studies; following slides show results grouped by:
    - Exposure range or level
    - Study evaluation confidence and direction of expected bias
- IRIS performed a meta-analysis and evaluated the role of confounders within and across studies

Example 2: TCE and Kidney Cancer (RoC)

Stratification of studies by exposure level

- When grouped by level of exposure, the RR estimates showed the expected pattern (highest RRs for highest exposure group)

NTP (National Toxicology Program). 2014. *Report on Carcinogens, Thirteenth Edition.* http://ntp.niehs.nih.gov/pubhealth/roc/roc13/

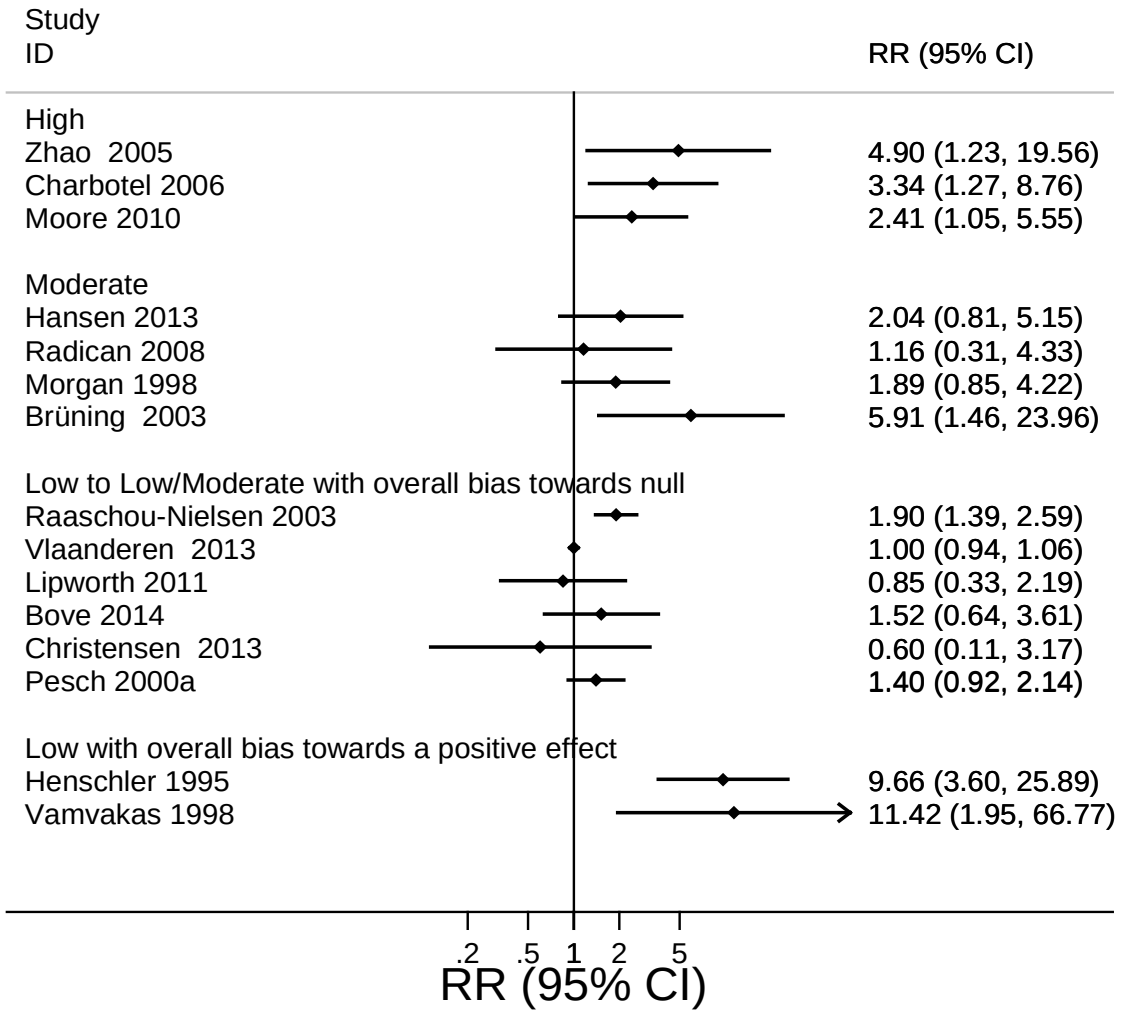


Example 2: TCE and Kidney Cancer (RoC)

Stratification of studies by overall confidence

- The studies with higher overall confidence all had elevated, statistically significant RR estimates
- Moderate confidence studies also had elevated RRs, but these were not always statistically significant, and showed greater spread
- Studies with lower overall confidence showed the expected pattern based on direction of bias (toward or away from the null)

NTP (National Toxicology Program). 2014. *Report on Carcinogens, Thirteenth Edition.* http://ntp.niehs.nih.gov/pubhealth/roc/roc13/



Example 2: TCE and Kidney Cancer (IRIS)

Meta-analysis of highest exposure groups

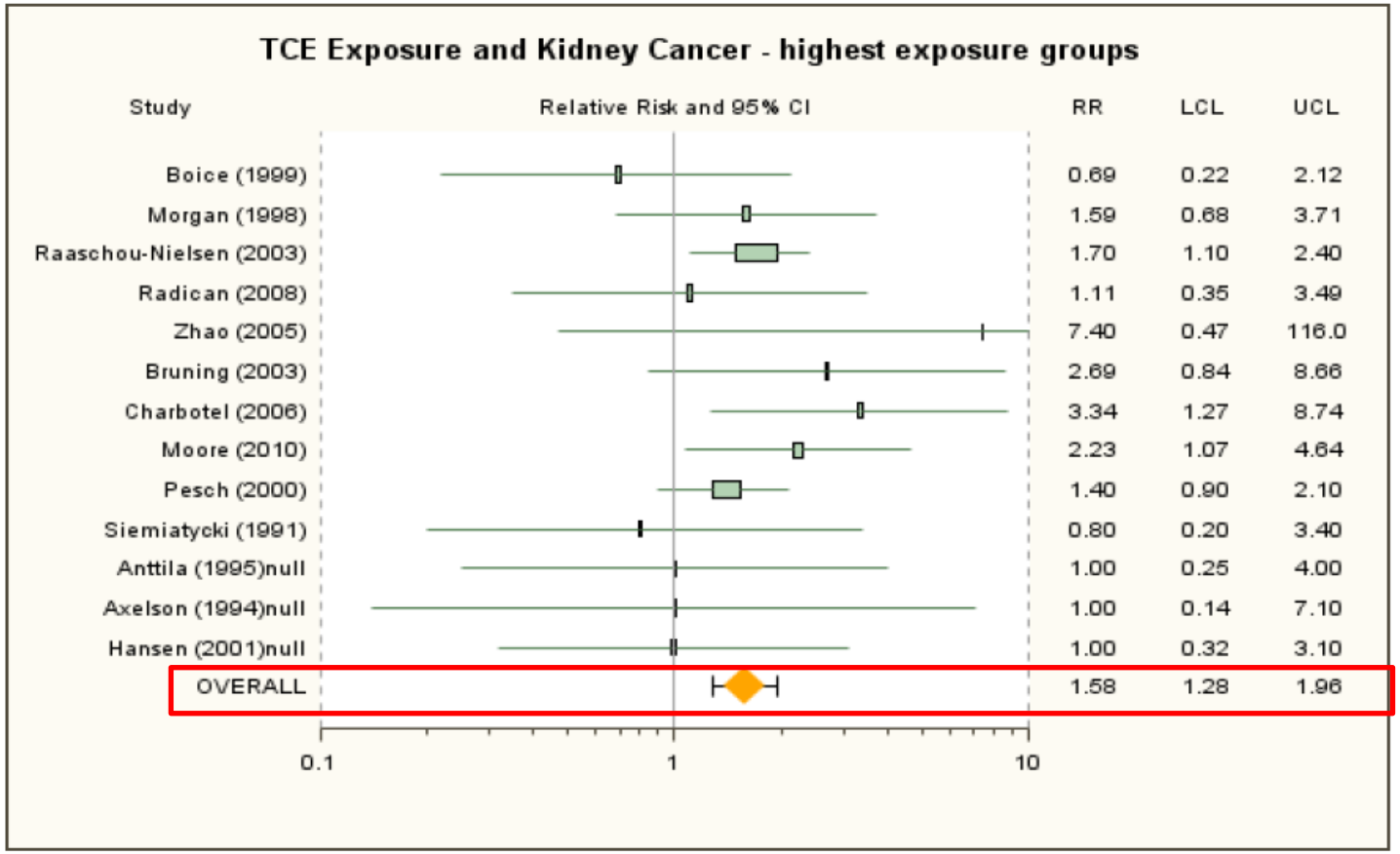


Figure C-7. Meta-analysis of kidney cancer and TCE exposure—highest exposure groups, with assumed null RR estimates for Anttila et al. (1995), Axelson et al. (1994), and Hansen et al. (2001) (see text). Random-effects model; fixed-effect model same. Rectangle sizes reflect relative weights of the individual studies. The summary estimate is in the bottom row, represented by the diamond.

EPA's Toxicological Review of Trichloroethylene (U.S. EPA, 2011).

Example 2: TCE and Kidney Cancer (IRIS)

- The meta-analysis used a priori criteria to select studies with greater overall confidence and yielded a summary RR of 1.58 for the highest exposure groups.
- Can this be explained by confounding from co-exposures? Job titles such as a degreaser often have potential for several exposures, including mineral oils, hydrazine, and other solvents.
  - Mineral oils and other co-exposures were included as covariates in some of the studies.
  - Cutting oil exposure did not appear highly correlated with TCE exposure, and cutting oils and mineral oils have not been associated with kidney cancer in other cohort or case-control studies
  - Conclude that potential co-exposure to other solvents and other chemicals is unlikely to provide an alternative explanation for kidney cancer findings, as the studies included in the meta-analysis varied in the pattern, level, and specific types of co-exposures

Example 2: TCE and Kidney Cancer (IRIS)

- Can this be explained by confounding? Obesity, high body mass index (BMI), and smoking are known risk factors for kidney cancer.
  - Any confounding in cohort studies related to obesity is likely small given the generally healthy nature of an employed population.
  - Five of the nine cohort studies used internal controls, which minimizes potential confounding since exposed and referent subjects are drawn from the same target population.
  - Obesity is less of a concern in occupational cohorts (generally healthy nature of employed population)
  - Most of the case-control studies controlled for BMI (4 out of 6), and for **smoking** (5 out of 6). The one study that adjusted for neither, did report that these factors did not significantly change their results.
  - **Smoking: There was no pattern of increased lung cancer risk in the cohort studies (summary RR from meta-analysis was 0.96 overall and 0.95 for high TCE exposure).**
  - These observations suggest that the association with kidney cancer is not fully explained by uncontrolled confounding

Example 2: TCE and Kidney Cancer (IRIS)

Potential confounding by smoking?

- The meta-analysis summary RR = 1.27 (95% CI: 1.13, 1.43), with no significant heterogeneity.
- Cohort studies had no information on smoking behavior while case-control studies did evaluate confounding by smoking.
  - The summary RR was stronger in the case-control studies that did account for smoking
- The RR for lung cancer was NOT elevated, indicating that the effect of TCE was not being driven by correlation with smoking.

	N	**RRm**	**95% CI**
Kidney Cancer			
All studies	15	1.27	1.13, 1.43
Highest exposure group	10	1.64	1.31, 2.0
Cohort studies	9	1.16	0.96, 1.40
Case-control studies	6	1.48	1.31, 2.04
Lung Cancer (cohort studies)	9	0.96	0.76,1.21
Highest exposure group	6	0.96	0.72, 1.27

Note: Cohort studies included all kidney cancers, while case-control studies included only renal cell carcinoma.

Summary

- Utility of negative control outcomes and/or exposures to identify potential for residual or uncontrolled confounding
- Look at results within and across groups of studies to see if there is an expected pattern of results by study attributes
  - Study confidence
  - Study design
  - Level of exposure
  - Study setting (e.g., occupational versus general population)
- Evaluate potential for confounding across study populations

Conclusion

- Triangulation is the integration of results from different approaches taken to address a research question, where each approach involves different sources of bias, with the goal of including and using as much information as possible and appropriate.
- We presented two examples in the spirit of triangulation from the IRIS program, with the goal of synthesizing results with an evidence stream (epidemiology studies) to arrive at causal conclusions.

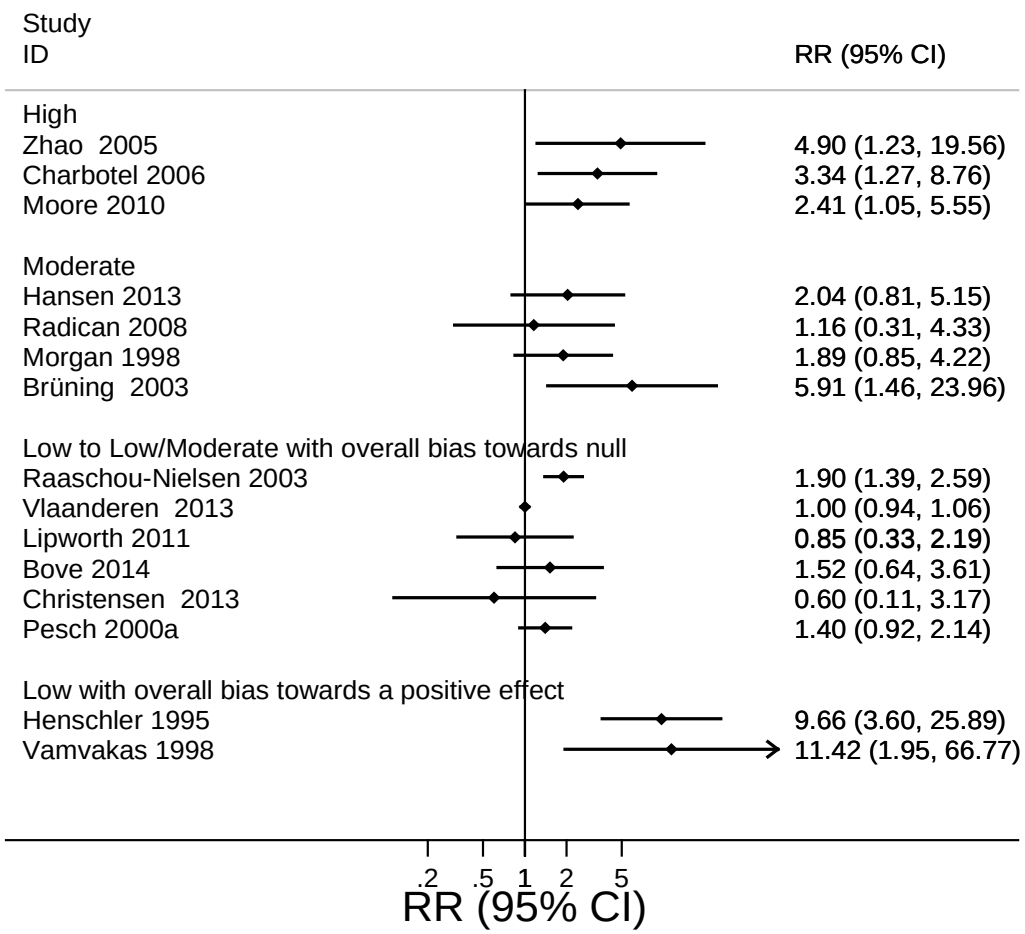
Thank you

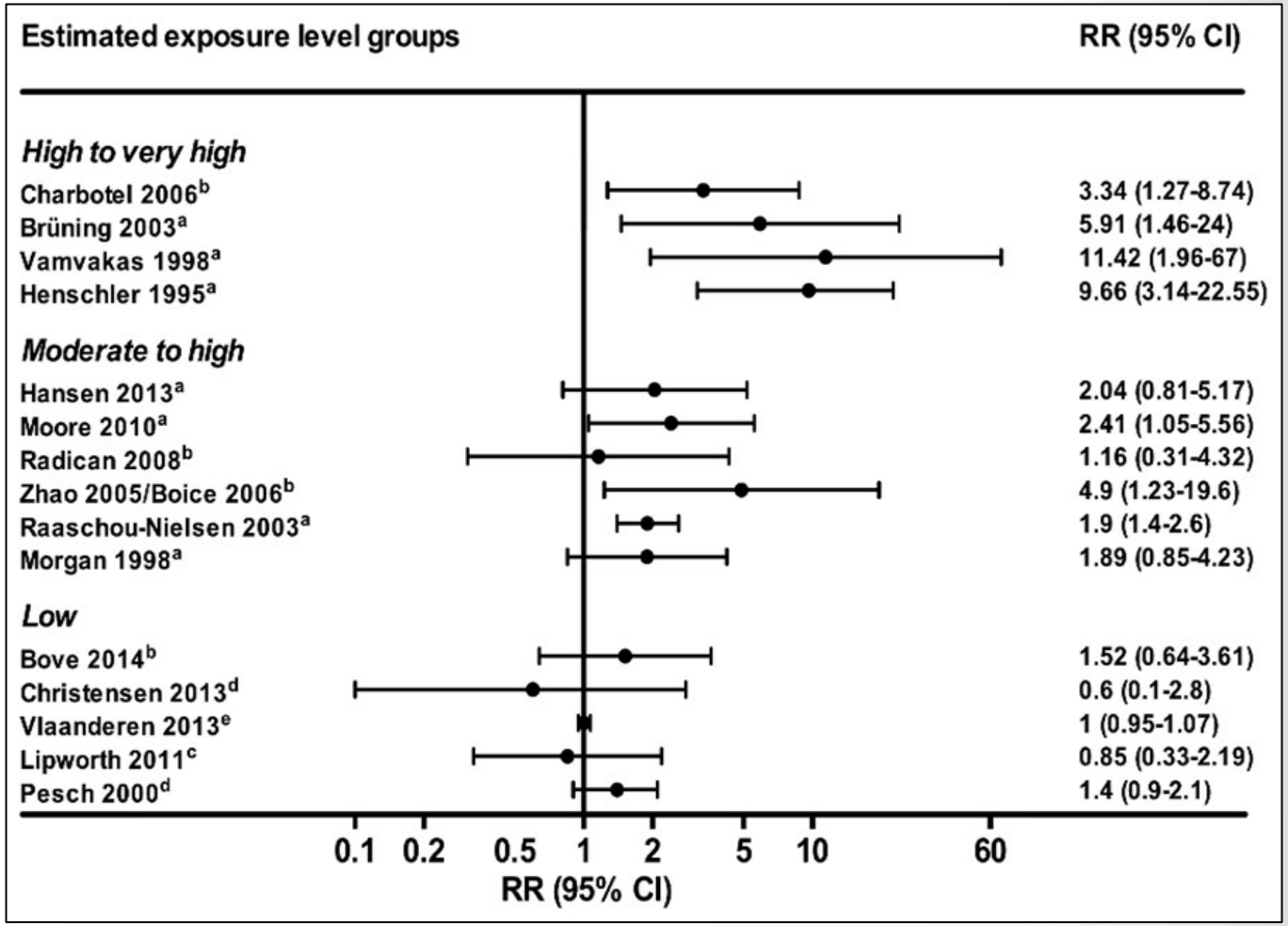
Extra Slides

Evidence synthesis primary considerations

- Risk of bias and sensitivity (across studies)
- Consistency
- Effect magnitude and imprecision
- Dose-response
- Directness of outcome/endpoint measures
- Coherence

Synthesis Example: Epidemiology





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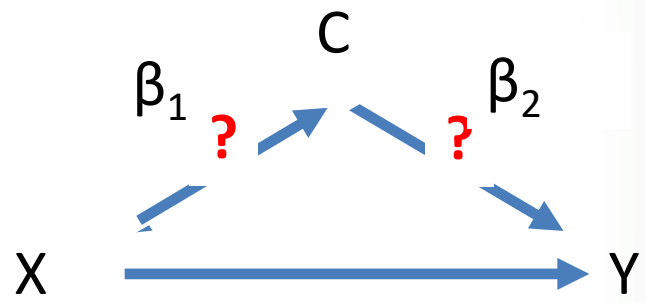
Example 3: Formaldehyde (Draft IRIS assessment)

- External peer review draft reviewed by the NASEM
  - Document available at: https://ordspub.epa.gov/ords/eims/eimscomm.getfile?p_download_id=544587
- Associations between inhalation exposure to formaldehyde and adverse health effects. For this example, focus on:
  - nasopharyngeal cancer (NPC)
  - myeloid leukemia (ML)

Example 3: Formaldehyde (Draft IRIS assessment)

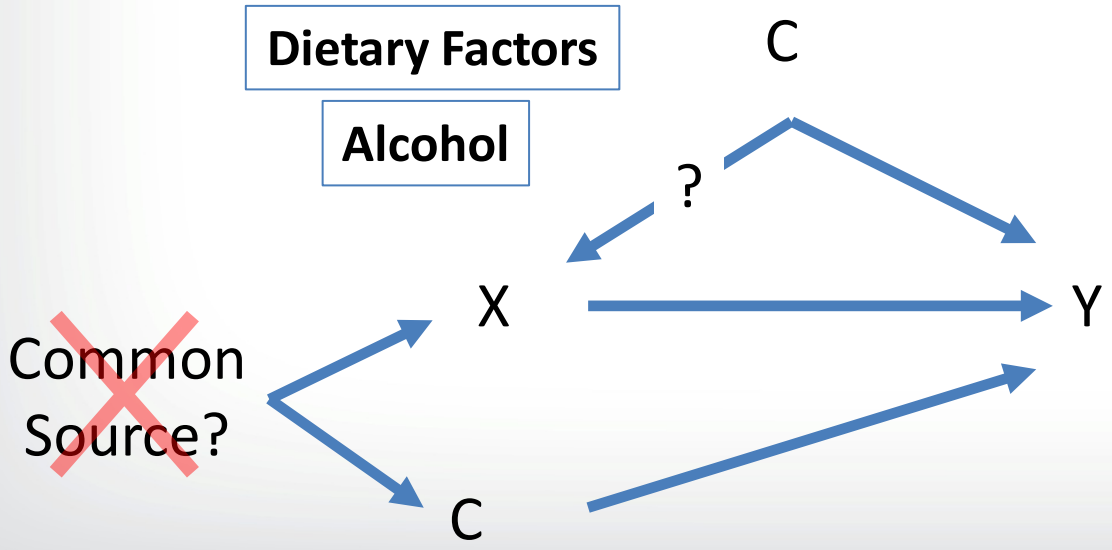
- Can consistent findings across studies be explained by a common confounder?
- Considerations:
  - Risk factor for disease?
  - Associated with formaldehyde exposure?
  - Not in causal pathway (not a mediator)?
  - Strength of potential confounding effects?

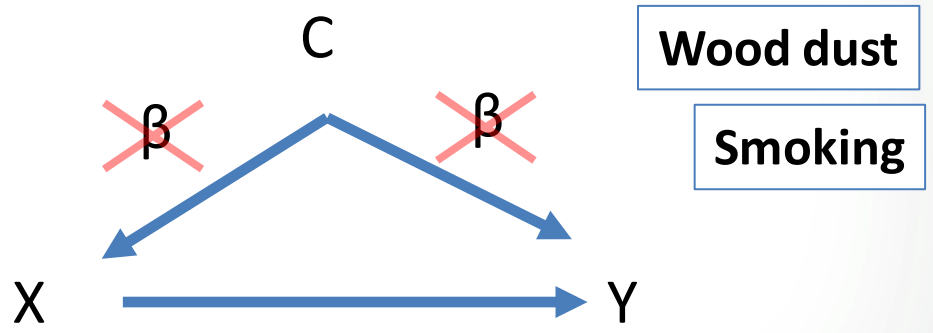


C: potential confounder
X: exposure (formaldehyde)
Y: health outcome
B: magnitude of association

Example 3: Formaldehyde and Nasopharyngeal Cancer (NPC) Confounder Evaluation

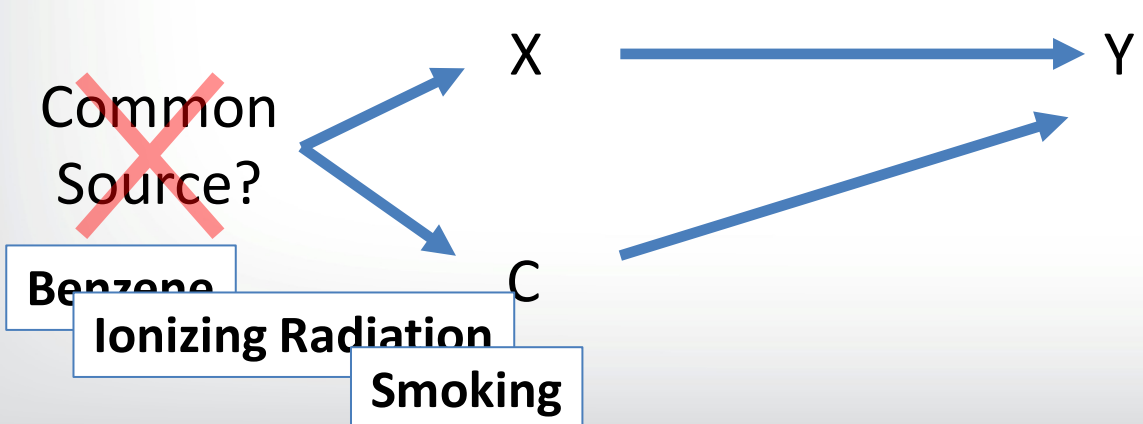
- Known risk factors for NPC: childhood consumption of Chinese salted fish, wood dust, smoking, alcohol consumption, Epstein-Barr virus
- Are the risk factors associated with exposure?
  - Some unlikely to be associated with formaldehyde; therefore not expected to be consistent confounders across all of the studies (dietary exposures, alcohol consumption).
  - Multiple studies controlled for wood dust exposure and for smoking, but neither were found to be a confounder of the association with formaldehyde.

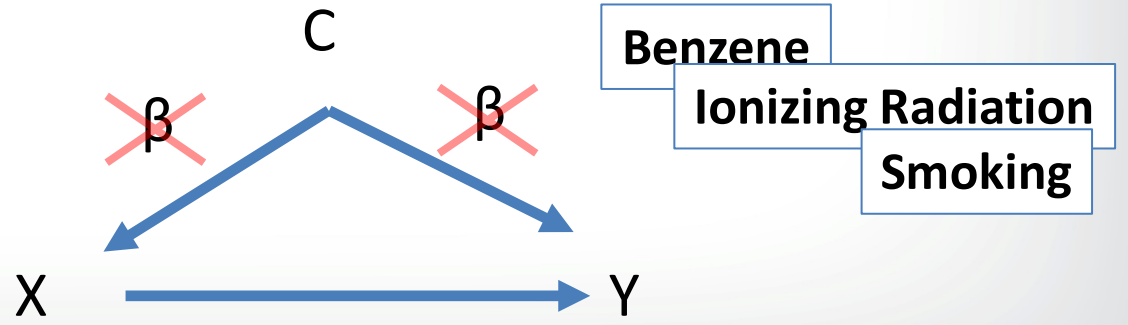




Example 3: Formaldehyde and Myeloid Leukemia (ML) Confounder Evaluation

- Known risk factors for ML: benzene, ionizing radiation, and smoking
- Associated with exposure to formaldehyde?
  - Benzene not used in the embalming process; not a chemical co-exposure in the garment plants. In other studies, benzene was evaluated and not found to be a potential confounder.
  - Ionizing radiation can be a co-exposure for embalmers but limited extent of such radiation exposure unlikely to explain the observed association in this group. Ionizing radiation not known to be a coexposure for industrial or garment workers in the studies considered.
  - Smoking controlled for in some of the studies. In others, smoking was not included in analyses, but no evidence that smoking rates in the industrial or garment worker cohorts were correlated with formaldehyde exposures. Further, the use of internal comparison groups should mitigate any potential confounding effects of smoking because smoking rates within a cohort are likely to be more similar than compared to the general population.





Example 3: Formaldehyde (Draft IRIS assessment)

- Can consistent findings across studies of formaldehyde and NPC and ML be explained by a common confounder?
  - Consistency across multiple studies is demonstrated by a pattern of increased risk in different populations, exposure scenarios, and time periods.
  - Unmeasured confounding or chance unlikely alternative explanations for the observed associations.