

Science Question 1: Methodological Considerations for Evaluating Epidemiologic Studies

Key Points

- 1. Use of specified guidelines for assessing epidemiologic studies, also recommended by NRC, is absent from the preliminary materials document.**
- 2. Four ecological studies in Table 2-9 “Evidence pertaining to cancer following oral exposure to Cr(VI)” are severely limited.**
- 3. Occupational studies of Cr(VI) are of greater quality/utility and should be considered for Table 2-9.**

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Aspects to Consider in Evaluating Epidemiologic Studies (NRC, 2014)

Epidemiologic Studies

- Documentation of study design, methods, population characteristics, and results.
- Definition and selection of the study group and comparison group.
- Ascertainment of exposure to the chemical or mixture.
- Ascertainment of disease or health effect.
- Duration of exposure and follow-up and adequacy for assessing the occurrence of effects.
 - Characterization of exposure during critical periods.
 - Participation rates and potential for selection bias as a result of the achieved participation rates.
 - Measurement error...and other types of information bias.
 - Potential confounding and other sources of bias addressed in the study design or in the analysis of results.

• **Absent from the tables:**

- Characterization of maternal exposures, critical windows of susceptibility
- Studies of qualitative, semi-quantitative exposure assessments- No discussion of potential measurement errors
- No discussion of ecological bias/fallacy

Risk of Bias Assessments of Epidemiologic Studies (NRC, 2014)

Factors to Assess Risk of Bias in Observational Studies	Rationale
Confounding and selection	Difference in the distribution of risk factors between groups
Measurement error	Exposure, outcomes, or confounders are not measured correctly

Adapted from Table 5-1 (NRC, 2014)

- **Preliminary evidence tables present all studies as equal**
- **It is difficult to discuss methodological considerations (Section 1.2.4) including interval validity – Study-specific information is not complete or missing**
- **Guidelines that can be also considered: STROBE, GRADE, Cochrane Collaboration**

Case Study: Table 2-9 “Evidence Pertaining to Cancer Following Oral Exposure to Hexavalent Chromium”

- **Three studies evaluated 5 villages in China (Zhang and Li, 1997, Beaumont et al. 2008; Kerger et al. 2009)**
- **Linos et al. (2011) investigated residents in an industrial region of Greece**

Factors to Assess Risk of Bias	Study Details
Confounding and selection	<p>Ecological in design with no individual data</p> <p>Confounding cannot be assessed. Differential distributions of extraneous factors between comparison groups are expected</p>
Measurement error	<p>Population-level exposures</p> <ul style="list-style-type: none">• Greeks do not typically drink municipal water• Cr(VI) in wells varied within any village of China. Residents also likely drank from municipal water.

Relevance of Occupational Studies of Cr(VI)

- **Discrepancy in study inclusion criteria?**
 - Ecological studies of oral exposures were used to evaluate cancer in Table 2-9
 - Occupational studies of inhalation exposures were used to evaluate gastrointestinal effects in Table 2-1 “Evidence pertaining to gastrointestinal (GI) effects following exposure to Cr(VI)”
- **Relevance of occupational studies for evaluating ingestion exposures**
 - With high exposure concentrations (workers in chromate production industry were exposed in the upper bounds of hundreds $\mu\text{g}/\text{m}^3$ Cr(VI) historically), mucocilliary clearance from the lung can lead to ingestion
 - Oral respiration is possible and hence the potential for ingestion
- **Several meta-analyses of occupational studies have been conducted evaluating GI effects from Cr(VI)**

Example: Occupational cohort studies in Table 2-1 (Birk et al. 2006, Hayes et al. 1979, Luippold et al. 2005)

- **In all 3 studies, standardized mortality ratios (SMRs) have been calculated for oral cavity/pharynx and cancers of the digestive organs**

Factors to Assess Risk of Bias	Study Details
Confounding and selection	Smoking data at the individual level (Birk et al. 2006, Luippold et al. 2005) Information collected on age (all studies) and race (Birk et al. 2006, Luippold et al. 2005)
Measurement error	Vital status and cause of death obtained for each cohort member (all studies) Cr(VI) exposure reconstructed for each cohort based on employment history (Birk et al. 2006)

Conclusions

- **Occupational cohort studies with individual-level data would be of far greater utility than ecological studies**
- **It is challenging to put together a comprehensive database of epidemiologic studies of Cr(VI).**
- **However, for purposes of evidence integration, the process really needs to include consideration/judging the strength of evidence, as recommended by NRC**
- **Good models to consider: The Cochrane Collaboration and their assessments which include a number of topics (e.g., cranberries and UTI, vitamin C and zinc and common cold)**
- **EPA should reissue the evidence tables before proceeding with risk assessment including analyses of risk of bias and generalizability**