EPRI Comments on Systematic Review Protocol for the Hexavalent Chromium (CrVI) IRIS Assessment

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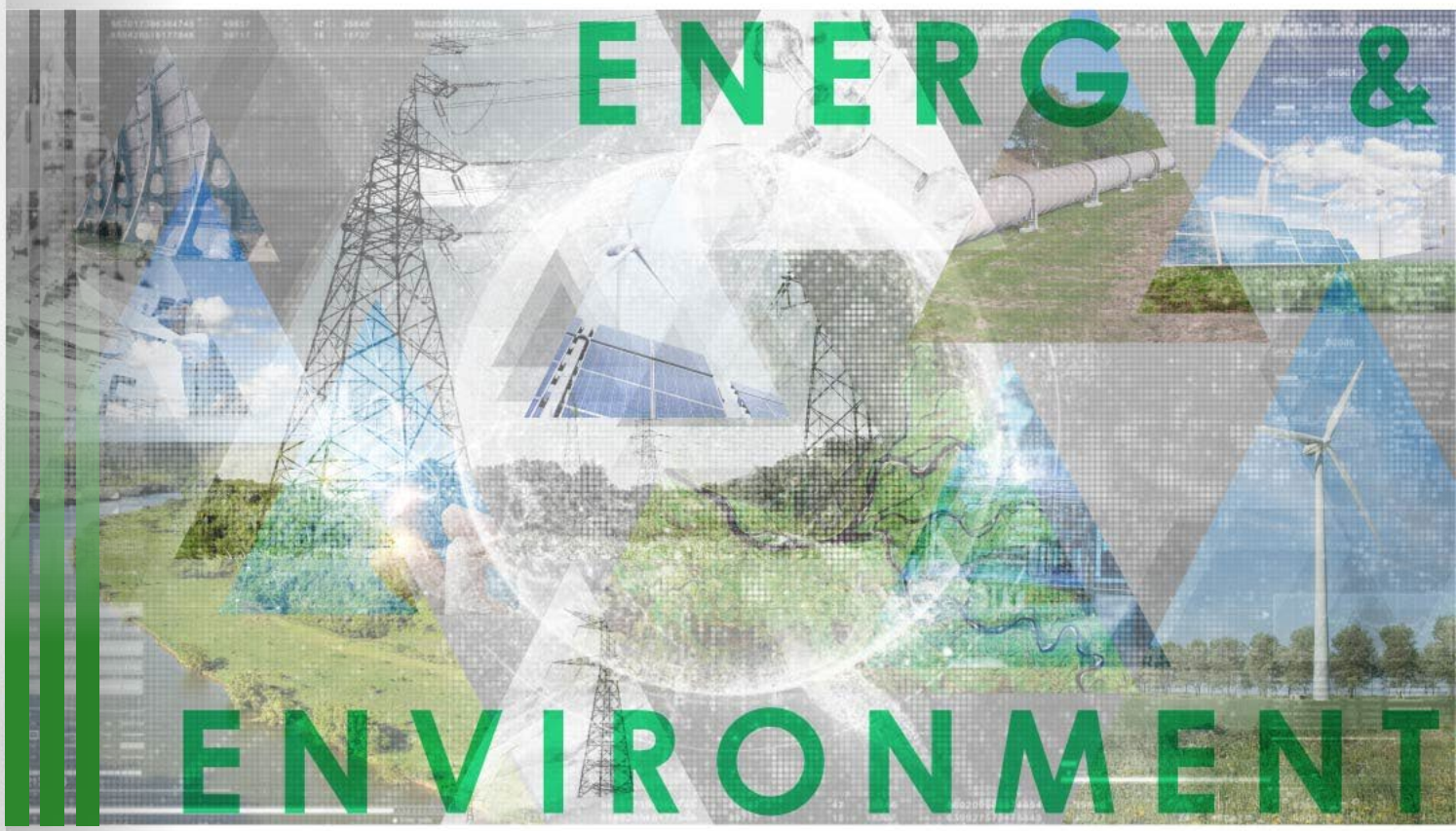

Overview of Comments

- EPRI will be submitting more extensive comments to the docket on April 28th
  - 12 specific comments
- Focus in today's teleconference on Topic 1: Systematic Review Methods as Described in the Protocol
  - 5 comments included today
  - Focused primarily on epidemiologic and mechanistic data related to CrVI-induced lung carcinogenesis
  - Also pertinent issues related to gray literature and screening process

Comment 1: Mechanistic Data

- Mechanistic data are a critical element of the IRIS assessment
  - Provide important contextual information and data for determining carcinogenic MOA
- Protocol is vague on how these data will be incorporated into the systematic review
  - Are formal assessments of this evidence stream being conducted, i.e., internal validity, study quality?
  - How will the data be used to inform MOA decisions and provide judgments about dose-response modeling?

Recommendation: Provide more clarity on the identification, selection, and review of mechanistic data, including process for risk of bias and study quality evaluation.

Comment 2: Handling of Gray and Unpublished Studies

- Protocol indicates that "if the data substantially affect assessment decisions or conclusions (i.e., potential to impact the PECO statement, hazard conclusion, and dose-response analysis), EPA can obtain external peer review if the owners of the data are willing to have the study details and results made publicly accessible."
- Protocol further states that "unpublished data from personal author communication can supplement a peer-reviewed study if the information is made publicly available."
- This may be a transparent and flexible method to review and include pertinent data, but there are concerns about the execution of the process.
  - Given that the literature search has already been conducted, it is reasonable to assume that unpublished data have also been identified, and the peer-review process has been undertaken; HERO should clearly indicate those studies.
  - EPRI is currently funding studies investigating CrVI lung reduction kinetics, which could potentially be classified under this category if the studies cannot be published before the deadline specified in the IRIS Stopping Rule. How will EPA determine *which* unpublished data merit further evaluation for potential inclusion?
  - If unpublished data are included, a procedure is needed for evaluating those data in a manner similar to peer-reviewed papers with respect to risk of bias and other elements of validity.

Recommendation: Identify unpublished studies in HERO, and provide clarification about the process for selecting and evaluating such studies.

Comment 3: Screening Process

- Without specifications of inclusion criteria, the screening process is difficult to follow
  - In the HERO database, 58 studies specified as "included" under the epidemiology category; inclusion criteria not clear
  - Compared studies in recent EPRI-supported systematic review and meta-analysis of CrVI and stomach cancer (Suh et al., 2019, *Crit Rev Toxicol*) to studies in HERO
  - 13 studies in Suh et al. (2019) published well before the last literature search update (May 2018) were not marked as included in HERO, e.g., studies of ferrochromium, cement production, chromium pigment production, and chrome-plating workers
- Information provided in the protocol is not sufficient to reproduce the categorizations in HERO
  - Example: Proctor et al. (2003, 2004) provide critical exposure information on Painesville chromate production worker cohort ["included" Proctor et al. (2016) study]. Both studies are in the HERO database, but not associated with the "included" tag.
  - Example: Thompson et al. (2015, 2017) evaluated mutagenic potential of CrVI in the oral mucosa and duodenum of Big Blue® rats. These are in the HERO database, but neither is associated with the "included" tag.
- The protocol indicates that the "exposure characteristics" category for the potentially relevant supplemental materials consists of "exposure studies that include data unrelated to toxicological endpoints, but which provide information on exposure sources or measurement properties of the environmental agent (e.g., demonstrating a biomarker of exposure)."
  - 185 studies are tagged in HERO as exposure studies with potentially relevant supplemental information, but it is unclear how these will be used to obtain important contextual information about CrVI exposure and to supplement the systematic review.

Recommendation: Provide clarity on how the studies were placed in the various categories listed in the HERO database as well as in the description of the exposure characteristic category under the potentially relevant supplemental material.

Comment 4: Epidemiological Study Exposure Domain Appraisal

- The prompting questions, follow-up questions, and considerations that apply to most exposure and outcomes in Table 9 do not adequately reflect the particular challenges associated with evaluating exposure to CrVI in epidemiology studies.
- Questions regarding the exposure assessment should include the following considerations with regard to CrVI:
  - **Were individual-level measures of exposure collected?** Significant misclassification of exposure occurs in ecological studies.
  - **Are the analytical results specific to CrVI?** In the past IRIS assessment, epidemiologic data with exposure information limited to total chromium were used to assess the potency of CrVI.
  - **Is the chemical form of CrVI described?** Industries produce exposure to different forms of CrVI, variability in chemical form influences the carcinogenic potential. For example, there is no clear association between increased risk of lung cancer and exposure to CrVI among stainless-steel welders, even though exposure concentrations and cumulative dose would suggest that increased risk should be measurable (also supported by animal studies). Exposures to sparingly soluble forms of CrVI (e.g., those generated in pigment and chemical production industries), provide the strongest association of increased lung cancer risk and thus also offer the most robust dose-response information; animal studies support this observation.
  - **Are the analytical methods for measuring exposure validated or subject to bias?** CrVI can reduce to CrIII in some collection media; potential to underestimate exposure by using methods that do not maintain Cr in hexavalent state prior to analysis.
  - **Is there any evaluation of exposure-rate effects?** Although lung cancer risk assessment has traditionally relied on cumulative exposure as a metric, evidence of a dose-rate effect has been reported in both animal and occupational epidemiology data.

Recommendation: Expand and tailor the questions and considerations regarding study quality evaluation of epidemiological study exposure assessment.

Comment 5: Epidemiological Study Confounding Domain Appraisal

- Similarly, the prompting questions, follow-up questions, and considerations that apply to most exposure and outcomes in Table 9 do not adequately reflect the specific challenges associated with evaluating confounding in CrVI epidemiology studies.
- Confounding in occupational cohorts with CrVI exposure can occur by exposures to other carcinogens in the workplace, in other places of employment (which may be particularly problematic for short-term workers), and from non-occupational exposures, most notably smoking, and also asbestos.
- Questions regarding confounding evaluation should include the following CrVI-specific considerations:
  - Assessment and quantitative evaluation of smoking as a confounding variable
  - Consideration of asbestos exposure as a confounding variable
  - Consideration of co-exposures to other carcinogens (e.g., welding fumes, asbestos, arsenic and radiation)

Recommendation: Expand and tailor the confounding domain to be specific to CrVI-exposed cohorts and populations, with consideration of co-exposures and duration of exposure.

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