ToxStrategies

IRIS Public Science Meeting – Systematic Review Protocol for Hexavalent Chromium IRIS Assessment

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Comments on behalf of the American Chemistry Council

Commend the use of systematic review – it *can* improve the risk assessment process:

- Focused Review Specific to Chemical Knowledge Base
- Transparent Identification of Evidence by Outcome
- Clear Process for Hazard Classification Based on Totality of Evidence
- Transparency and Objectivity in Selection of Candidate Studies Based on Study Validity
- Consideration of Quantitative Techniques to Combine Studies (vs. Single Candidate Study Approach)
- Facilitates Quantitative Uncertainty Analysis

Challenges in providing public comment on the protocol

Draft protocol issued prior to release of the IRIS Handbook

- Unclear if methods described in the protocol are consistent with that of the IRIS handbook
- *Request immediate release of the Handbook discussed at previous NAS meetings*

Protocol is retrospective

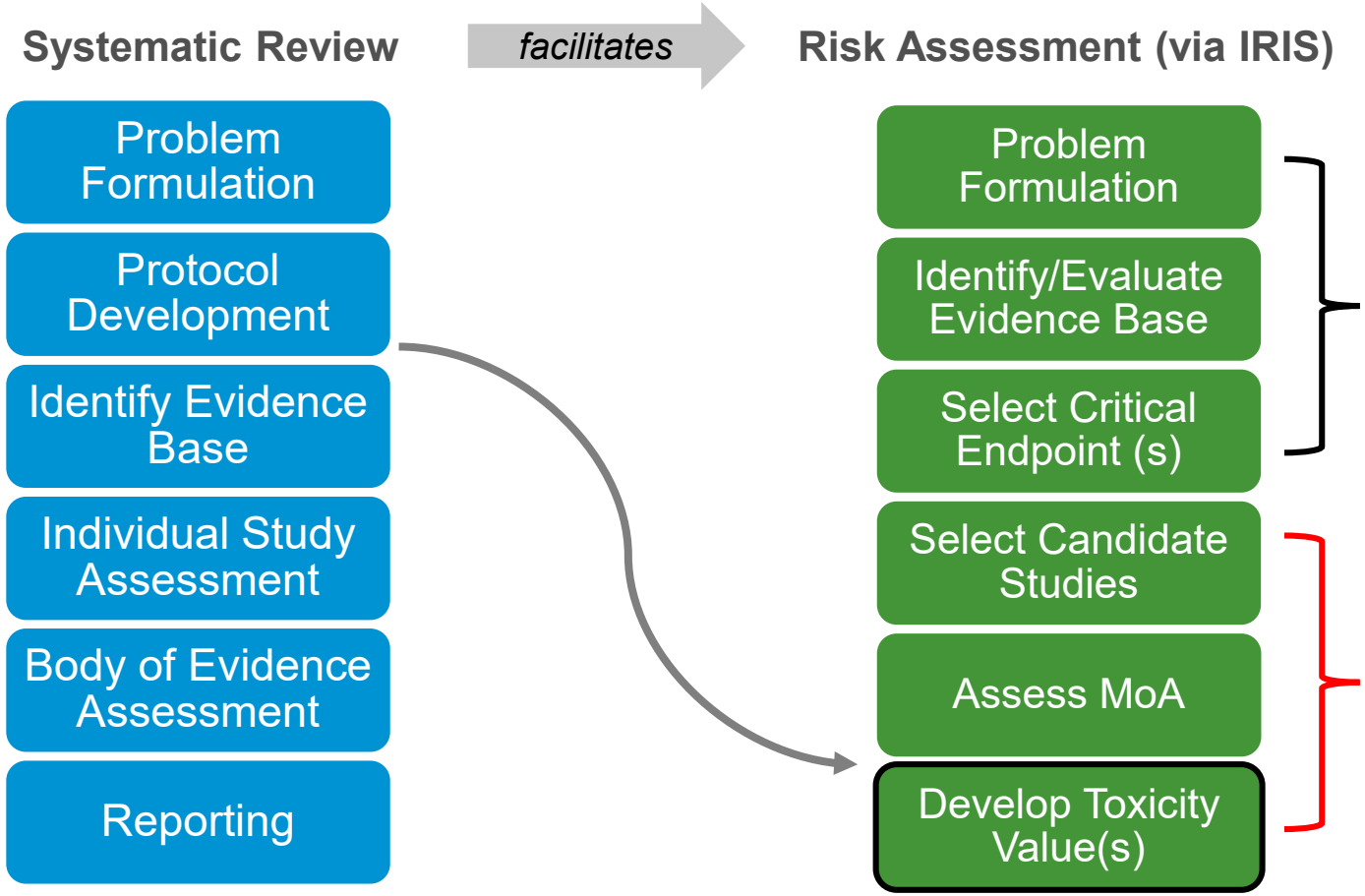
- Fundamentally inconsistent with systematic review guidance (which requires *a priori* release of the protocol)

Several steps of the review have already been completed yet only partial results from the completed steps appear to have been provided

- Appears to combine multiple literature search efforts and multiple platforms (DRAGON, HAWC, HERO, DistillerSR); unclear if all screening completed was systematic

Difficult to understand how comments will or even could be addressed

Protocol could better facilitate the development of toxicity values via the risk assessment process specific to Cr(VI)



- Acknowledges the Cr(VI) landscape*
- Focuses the review on selected endpoints
- Describes approach to identify and appraise studies* and characterize hazard

- Lacks detail for risk assessment aspects beyond hazard characterization
- *Evaluation of MoA recognized as a key issue for Cr(VI) related to the extrapolation approach, yet largely unaddressed in the protocol in this capacity

Output = toxicity values
(not hazard characterizations)

Unclear if the protocol (and PECO) match the specific aims

Specific Aim (Section 3.2)	Rationale for Refinement or Clarification
"The systematic review will focus on identifying data from inhalation exposures that are useful for deriving quantitative estimates for lung cancer and nasal effects rather than revisiting the qualitative identification of hazard for these outcomes"	The majority of the protocol appears to be focused on hazard identification (e.g., Section 7. Organizing the Hazard Review; Section 9. Synthesis within Lines of Evidence; Section 10. Integration Across Lines of Evidence [for Hazard ID]) Several subsequent specific aims relate to hazard characterization (e.g., "to conclude whether a substance is hazardous to humans") Unclear how studies that are useful for deriving quantitative estimates are differentiated from others
"Characterize uncertainties and identify key data gaps…"	Protocol does not contain a section for uncertainty analysis (qualitative or quantitative); this is a specific recommendation made by the NAS (2014) to the IRIS program
"Evaluate mechanistic events associated with exposure to Cr(VI)…" "The primary focus will be on the analysis of mechanistic evidence for cancer and noncancer effects of the GI tract following oral exposures to Cr(VI)" "Because the hazard identification of lung cancer and nasal effects will not be revisited, the mechanistic analyses for these health effects will focus on evidence that may affect the dose-response assessment."	PECO does not address mechanistic evidence (the Outcomes only include cancer outcomes and selected noncancer outcomes) Mechanistic data are not "included"; no clear criteria for determining which data were tagged as "potentially relevant" and/or prioritized/deprioritized No critical appraisal for mechanistic data planned (or possible for selected studies only) Unclear if the aim of investigating the mechanistic events is to assess MoA (i.e., how are the mechanistic data being defined and/or used – surrogate for MoA or otherwise? Mode vs. mechanism of action?

Clarifications on literature search(es) and platforms

Does Figure 1 contain all evidence being considered?

- **Gray literature? (other than EPA Chemistry Dashboard?)**
- **Non-peer reviewed data (that was included)?**
- **"Backward" searching?**

How does what is in HERO compare to that from Figure 1 and HAWC?

- **Some HERO tags match Figure 1; others do not**
- **Several HERO tags not in Figure 1 (e.g., "not in literature search", "2019 lit search GI occupational")**
- **HERO tags appear to have changed during protocol review period**

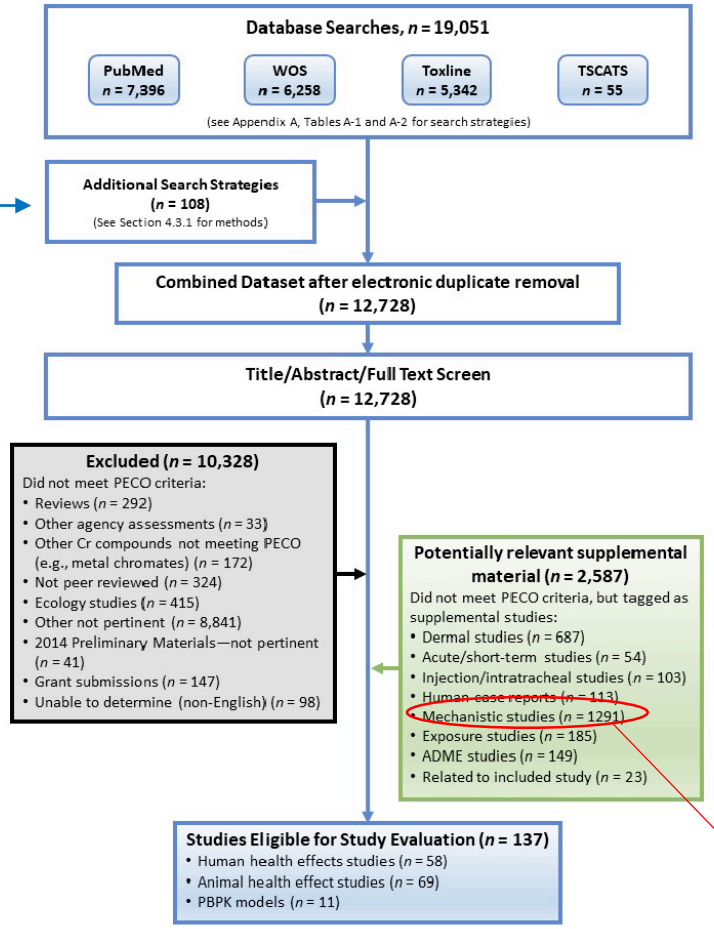


Figure 1. Literature search flow diagram for Cr(VI).

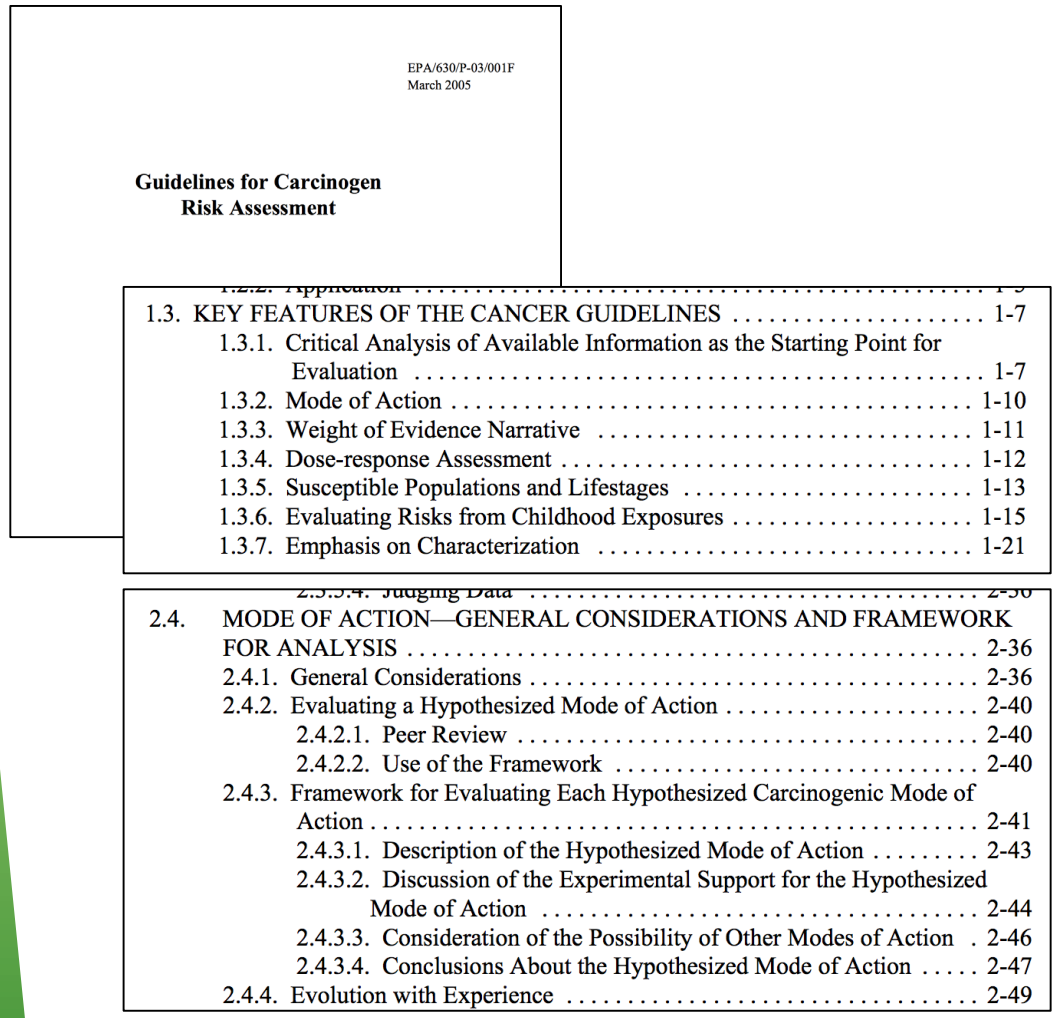
***Result** = difficult to comment on potentially missing studies with changing results, various platforms (and versions of software?)*

Potentially relevant – not "included" – difficult to understand selection of mechanistic studies:

- TiAb screen (no clear inclusion criteria; single screener; excluded if not relevant in 2014)?
- Re-review of excluded (subset only; driven by machine learning; 2 reviewers)?
- Deprioritization/Prioritization (and KCC tagging)?
- "May be processed" through an additional round (p.21)?
- ***Clarification on inclusion and evaluation of mechanistic evidence is needed***

HAWC reports 1267 mechanistic studies on 4/22 but 1245 on 4/23

Suggest modifying overall approach to better reflect the Guidelines for Carcinogen Risk Assessment (and MoA specifically)



EPA/630/P-03/001F
March 2005

Guidelines for Carcinogen Risk Assessment

Protocol does not contain a section for evaluation of MoA (notably lacks the evidence to decision methods that will be employed for MoA)

- Rather, protocol includes reference to categorization of mechanistic data via the key characteristics of carcinogens (limited to organization of data); later in protocol, MoA is discussed primarily in context of evidence synthesis and hazard ID (and not dose-response extrapolation)

Unclear why hypothesized MoAs for Cr(VI) are not also discussed (particularly considering they were utilized in two of the most recent authoritative assessments cited in the protocol)

- Presents potential uncertainty in identification of “potentially relevant” mechanistic data

Additional clarifications suggested based on compliance with systematic review methodologies

Provide a timeline for completion

- Consistent with that required of PROSPERO

Provide clarification of the status of each step as part of the protocol

- Consistent with that required of PROSPERO

Provide clarification re: posting of protocol on Zenodo

- Suggested in protocol but does not appear to be in the Zenodo repository

Update the study quality criteria to reflect topic-specific refinements

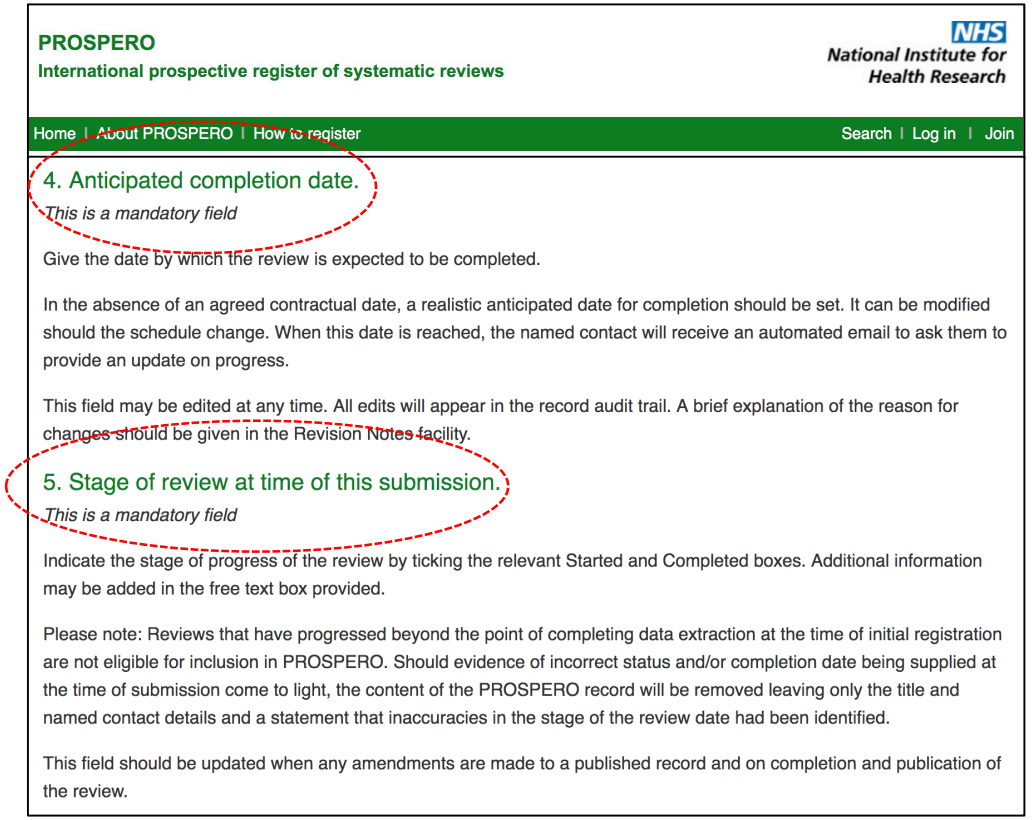
- Suggested by authoritative bodies; feasible considering that literature search has been completed

Include process for addressing the methodological quality and relevance of mechanistic data

- Note importance of construct validity in assessing such

Enhance the section of the protocol that addresses development of toxicity values, particularly related to combined-data approaches (e.g., meta-regression)

Add section related to uncertainty analysis



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4. Anticipated completion date.

This is a mandatory field

Give the date by which the review is expected to be completed.

In the absence of an agreed contractual date, a realistic anticipated date for completion should be set. It can be modified should the schedule change. When this date is reached, the named contact will receive an automated email to ask them to provide an update on progress.

This field may be edited at any time. All edits will appear in the record audit trail. A brief explanation of the reason for changes should be given in the Revision Notes facility.

5. Stage of review at time of this submission.

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Indicate the stage of progress of the review by ticking the relevant Started and Completed boxes. Additional information may be added in the free text box provided.

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