THE EPA BI-MONTHLY MEETING
INORGANIC ARSENIC
SCIENCE DISCUSSION

KIMBERLY WISE, PhD
ACC CENTER FOR ADVANCING RISK ASSESSMENT SCIENCE AND POLICY
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SCIENCE ISSUE 2: RISK-OF-BIAS (ROB) APPROACH

American Chemistry Council

Identifying Studies for Use in RoB

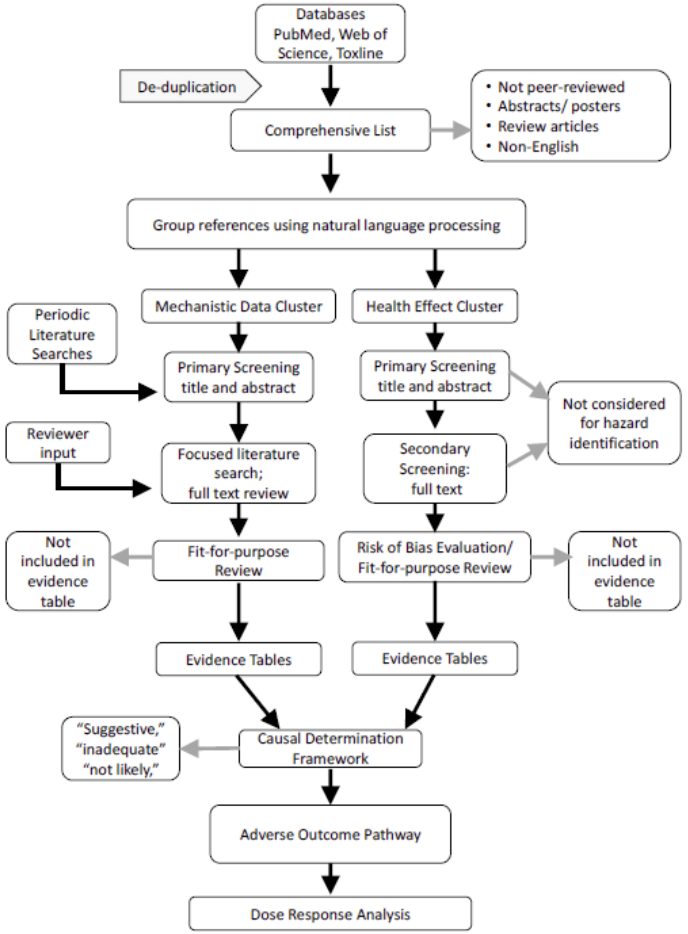

Figure 1-4 Overall Process for Identifying Studies for the Toxicological Review

Excerpt from Figure 1-4, Page 1-47

Recommendations

- Literature search should focus on relevant exposure ranges, as suggested by NRC
  - Table 1-9, should not exclude episodic/acute exposure. This can inform potential toxicity and metabolism.
- Fit for purpose evaluation should be conducted before a RoB/ quality evaluation
  - Should incorporate QA/QC into quality criteria.
- RoB/quality evaluation should be conducted for all data streams, including mechanistic data.
  - Criteria for scoring may need to be adjusted based on design limitations of ecological studies
- Apparent Disconnect between Figure 1-4 and process followed in Section 2
  - literature flow diagram treats mechanistic, MOA, PBPK and other important information as "other studies" that are not evaluated on par with animal and human data.

Determining Data Tiers for RoB (Table 1-8)

OHAT Risk of Bias Questions	Risk of bias ratings							
Were the comparison groups appropriate? (*Confidence in observed association*)	++ or +	Any of the six questions is a - -	Any	Two of the three questions are –	–	Three of the other four questions are –	No more than one of the other five questions is a –	++ or +
Did the study design or analysis account for important confounding and modifying variables? (*Confidence in observed association*)	++ or +	Any of the six questions is a - -	Any	Two of the three questions are –	–	Three of the other four questions are –	No more than one of the other five questions is –	++ or +
Tiering data	Low risk of bias	High Risk of Bias	High Risk of Bias	High Risk of Bias	High Risk of Bias	High Risk of Bias	Low risk of bias	Low risk of bias

Partial excerpt from Table 1-8, Page 1-53

Concerns/Issues

- Scoring is not clear as presented in the table
- Explanation on Page 2-14 is unclear
  - Sometimes 6 questions are referred to; other times three or four questions are referred to.
  - If a study did not measure arsenic, why would it have a low risk of bias?
- How will supporting evidence inform assessments?
  - If this evidence has high RoB and/or low quality scores, why should it be used at all?

RoB Approach for Animal Studies

Table 1-6 Example Risk of Bias Considerations

Category	Risk of Bias Questions*
Selection	1. Was administered dose or exposure level adequately randomized?
	2. Was allocation to study groups adequately concealed?
	3. Were the comparison groups appropriate?
	4. Did the study design or analysis account for important confounding and modifying variables?
	5. Did researchers adjust or control for other exposures that are anticipated to bias results?
Performance	6. Were experimental conditions identical across study groups?
	7. Did researchers adhere to the study protocol?
	8. Were the research personnel and human subjects blinded to the study group during the study?
Attrition	9. Were outcome data complete without attrition or exclusion from analysis?
Detection	10. Were the outcome assessors blinded to study group or exposure level?
	11. Were confounding variables assessed consistently across groups using valid and reliable measures?
	12. Can we be confident in the exposure characterization?
	13. Can we be confident in the outcome assessment?
Selective Reporting Bias	14. Were all measured outcomes reported?
Other	15. Were there no potential threats to internal validity (e.g., statistical methods were appropriate)?

*Note, in consultation with OHAT, questions number 7, 9 and 15 were restated from the 2013 draft (NTP, 2013) so that answering "yes" would consistently indicate lower risk of bias, while answering "no" would indicate higher risk of bias.

Concerns/Issues

- EPA only using Questions 12 and 13 for tiering studies
  - If other questions are not important then how are they used to evaluate/integrate?
  - If exposure is uncertain (- probably high risk of bias) why not exclude? EPA only excludes definitely high risk of bias
  - If there is probably or definitely high risk of bias for outcome assessment, why not exclude/set aside? What will happen with studies that are set aside for additional review or included as supporting evidence?
- Are all included studies treated as equal even though some may have more bias than others?
- Will other important quality elements from Klimisch and ToxRTool be incorporated? http://ihcp.jrc.ec.europa.eu/our_labs/eurl-ecvam/archivepublications/
  - species, sex, strain, exposure route and relevance of each
  - appropriate positive and negative controls

RoB Approach – Animal Studies

Need Clarification

- What is the final RoB rating for each study listed?
- How with they be used for tiering and integration?

Considered Most Important for Tiering

- High Dose Level
- No Blinded Analysis
- Unusual Species

Not Included in Data Tables

6.2 Risk of Bias Overview - Immune System and Lymphatic Effects

Study	Primary (P) or Supporting (S)	Selection			Confounding		Performance			Att.	Detection				SRB	Other
		Randomization	Allocation Concealment	Comparison Group	Confounding (Design)	Unintended Exposure	Experimental Conditions	Protocol Deviations	Blinding (During Study)	Missing Outcome Data	Blinding (Outcome Assessment)	Confounding (Analysis)	Exposure Characterization	Outcome Assessment	Outcome Reporting	Internal Validity
Das et al. (2012b)	P	++	+	n/a	+	+	+	+	+	-	+	+	+	+	+	++
Kozul et al. (2009)	P	-	-	n/a	+	+	++	+	+	-	+	+	-	+	++	++
Nain and Smits (2012)	P	+	+	n/a	+	+	+	+	+	-	++	+	+	++	+	++
Ramsey et al. (2013b)	P	-	-	n/a	+	+	+	+	+	++	++	+	-	+	++	++
Sankar et al. (2013)	P	+	+	n/a	+	+	+	+	+	++	+	+	-	++	+	++
Stepnik et al. (2009)	P	-	-	n/a	+	+	++	+	+	++	+	+	-	+	++	++
Tokar et al. (2010b)	P	+	+	n/a	+	+	+	+	+	++	++	+	-	+	+	++
Waalkes et al. (2003)	P	+	+	n/a	++	+	++	+	+	++	++	+	+	+	+	++
Waalkes et al. (2006a)	P	+	+	n/a	++	+	++	+	+	++	++	+	+	++	+	++
Waalkes et al. (2006b)	P	+	+	n/a	++	+	++	+	+	++	++	+	+	++	+	++