United States Environmental Protection Agency

National Academies Workshop: Strategies and Tools for Conducting Systematic Review of Mechanistic Data to Support Chemical Assessments
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IMPLEMENTING SYSTEMATIC REVIEW METHODS AND APPROACHES IN TSCA RISK EVALUATIONS

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Outline

- Regulatory background
- Components of the TSCA risk evaluation
- TSCA systematic review process
- Data quality evaluation tool
  - Structure and scoring system
  - *In Vitro* Evaluation Criteria
- Summary

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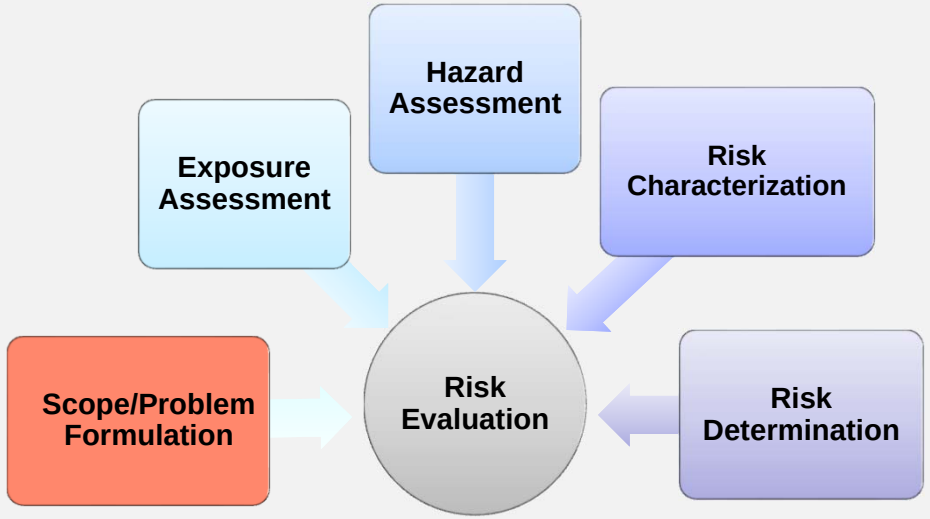
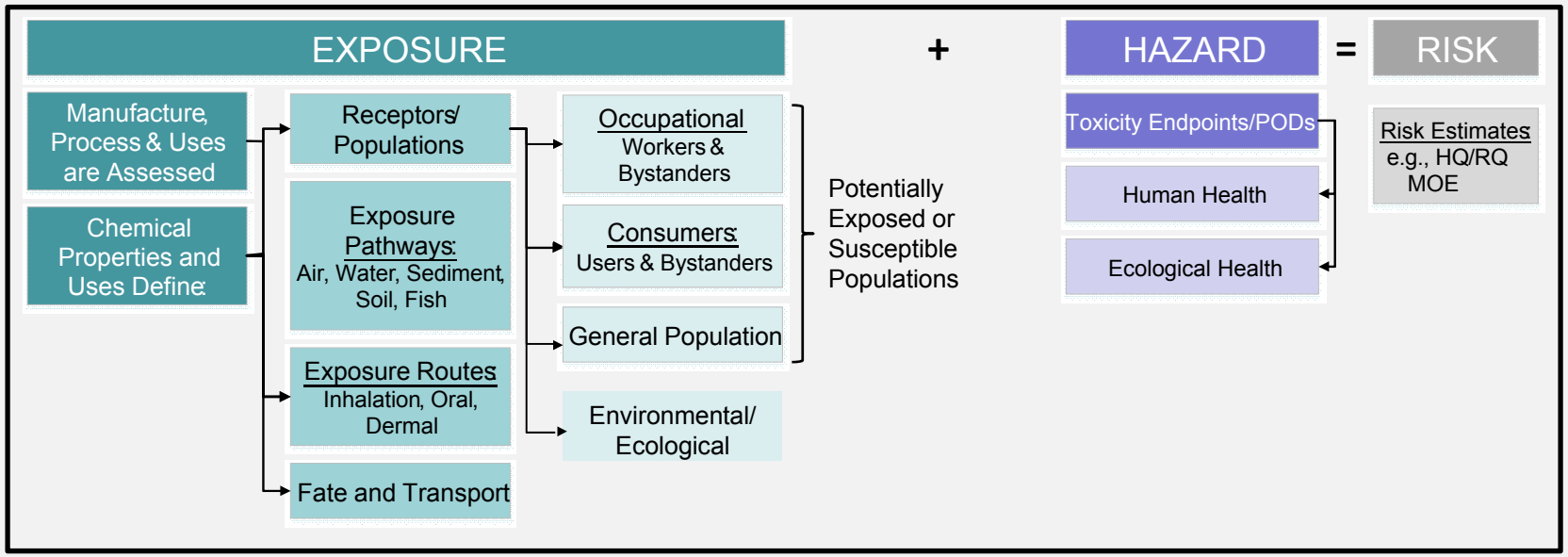
TSCA Background – A Timeline

- **June 22, 2016** - The Frank R. Lautenberg Chemical Safety for the 21st Century Act updated the 1976 Toxic Substances Control Act.
- **December 19, 2016** - EPA issued Federal Register notice on our intent to conduct risk evaluations for the first 10 chemicals under the amended TSCA.
- **June 22, 2017**- EPA released the scoping and supplemental documents for the 1st 10 risk evaluations, finalized new rules, and provided a guidance document for external parties.
- **June 1, 2018-** EPA published problem formulations for the 1st 10 chemicals and systematic review guidance document.
- **December 2019**- EPA will publish final risk evaluations for 1st 10 chemicals by this date.

Components of the TSCA Risk Evaluation





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Fit-for-Purpose TSCA Risk Evaluations

- Assessments have similar structure/format, but level of complexity and data richness may vary
- Assessment of life cycle of the chemical
- TSCA conditions of use define:
  - Exposure Pathways: Air, Water, Sediment, Soil, Diet (fish)
  - Exposure Routes: Inhalation, Oral, Dermal
  - Receptors/Populations
    - Occupational: Workers and Bystanders and Potentially Exposed and Susceptible Populations (PESS)
    - General Population and PESS
    - Consumers: Users and Bystanders and PESS
    - Environmental/Ecological

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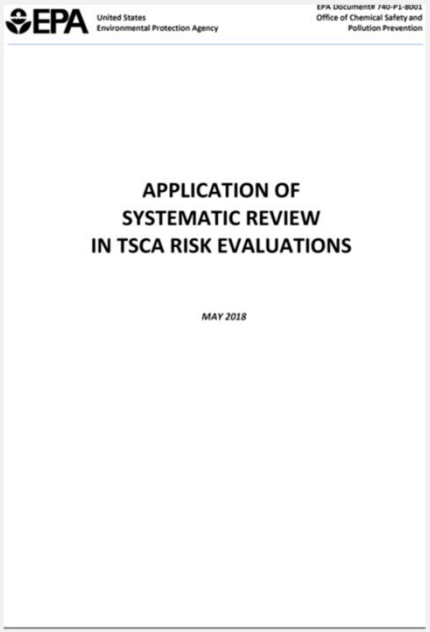
Systematic Review within the TSCA Context

- Aligned with the TSCA science standards (best available science, weight of the evidence)
- The TSCA Risk Evaluation rule[1] did not codify a definition for systematic review, but definition is provided in the preamble.

  "… systematic review is a scientific investigation that focuses on a specific question and uses explicit, pre-specified scientific methods to identify, select, assess, and summarize the findings of similar but separate studies. The goal of systematic review methods is to ensure that the review is ***complete, unbiased, reproducible, and transparent"***[2]

[1] Procedures for Chemical Risk Evaluation Under the Amended Toxic Substances Control Act. EPA-HQ-OPPT-2016-0654.
[2] Institute of Medicine. Finding What works in Health Care: Standards for Systematic Reviews. p.13-34. The National Academies Press. Washington, D.C. 2011

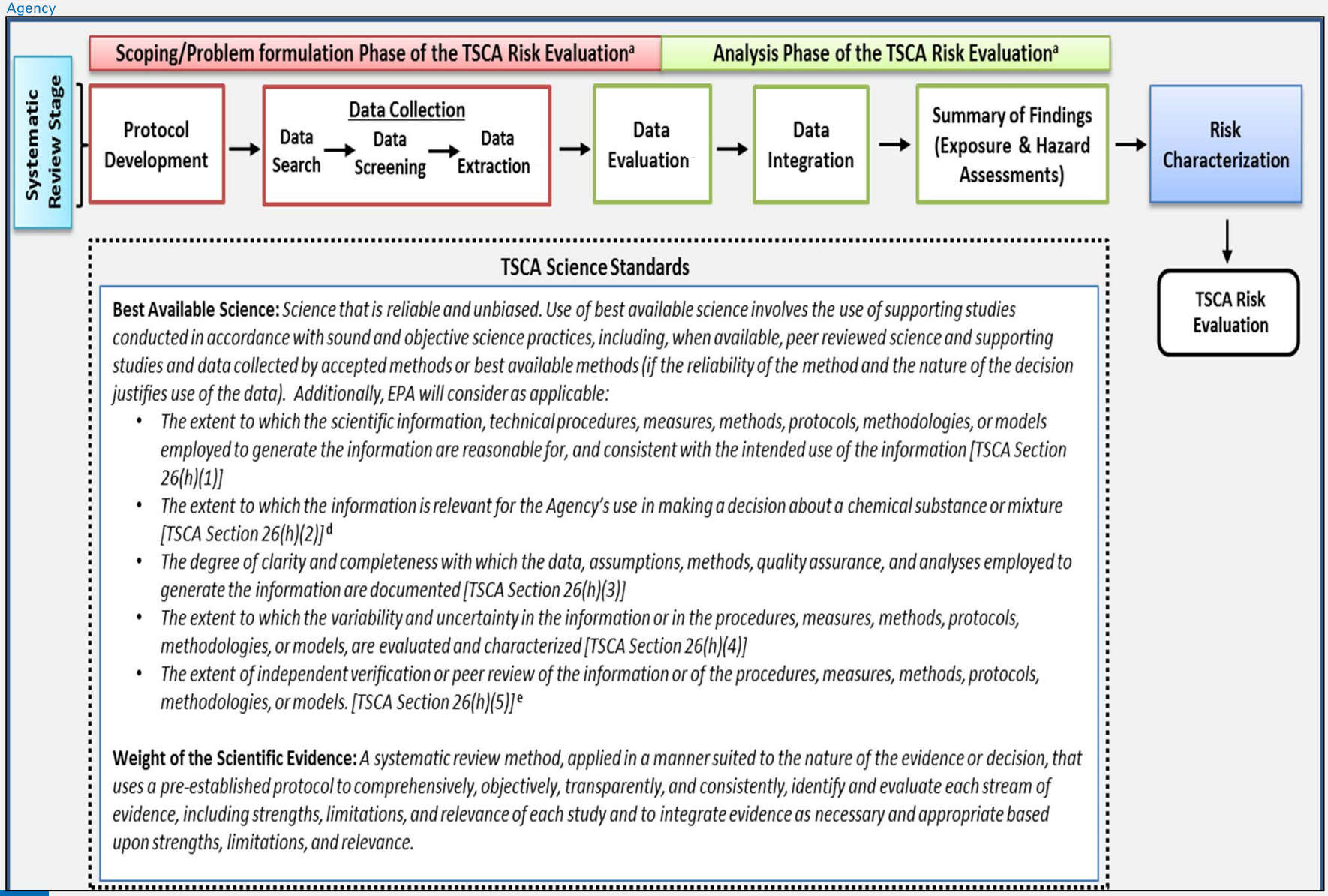
Application of Systematic Review in TSCA Risk Evaluations



- Describes systematic review process of identifying, evaluating and integrating evidence
- Presents pre-established method and criteria to critically assess the quality of data/information supporting risk evaluations
- EPA initiated the systematic review approaches and methods when announcing the first 10 risk evaluations in December 2016
- Supplemental documents for each chemical risk evaluation:
  - Strategy for Conducting Literature Searches: Supplemental file for the TSCA Scope Document
  - Bibliography: Supplemental File for the TSCA Scope Document
  - Problem Formulation document
  - Systematic Review Supplemental File for the draft TSCA Risk Evaluation

Website link to document: https://www.epa.gov/assessing-and-managing-chemicals-under-tsca/application-systematic-review-tsca-risk-evaluations

Application of Systematic Review in TSCA Risk Evaluations



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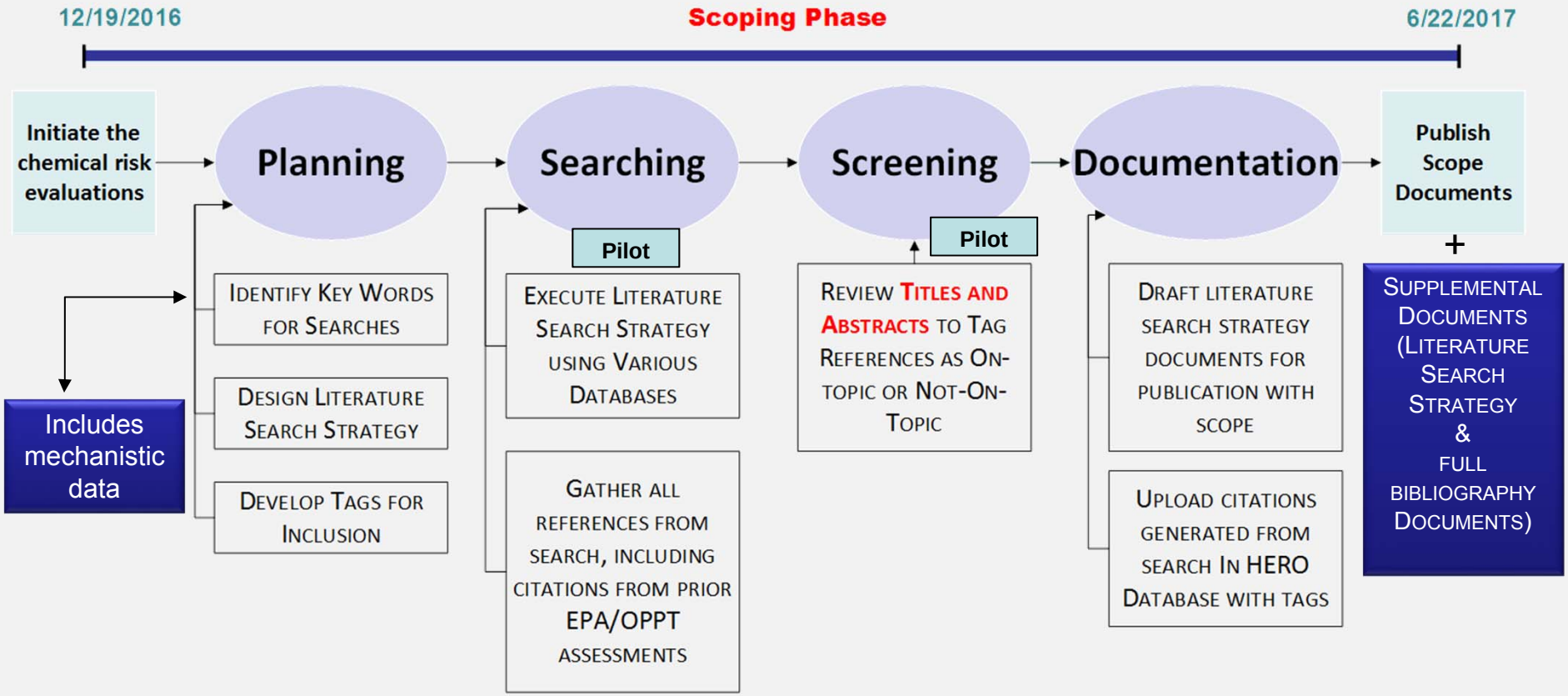
Literature Search and Title/Abstract Screening for the First Ten TSCA Risk Evaluations



Data Collection Phase

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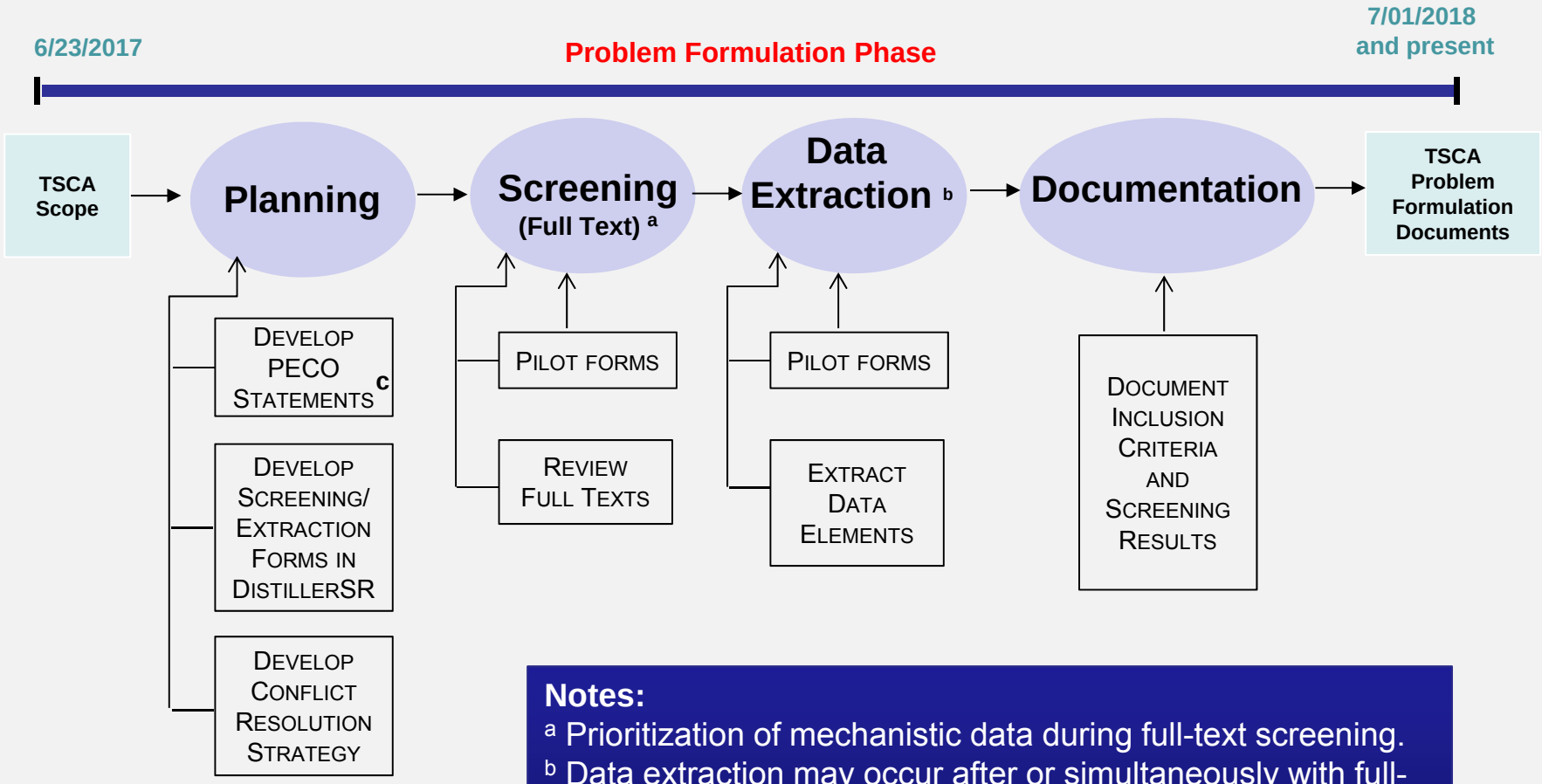
Full Text Screening and Data Extraction for the First Ten TSCA Risk Evaluations



Notes:

[a] Prioritization of mechanistic data during full-text screening.

[b] Data extraction may occur after or simultaneously with full-text screening.

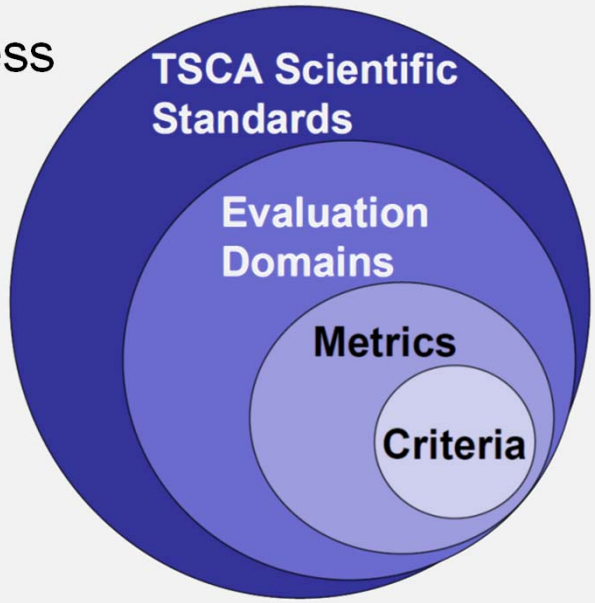
[c] PECO= Population, Exposure, Comparator, Outcome

Evaluation Strategies to Assess Data/Information Quality

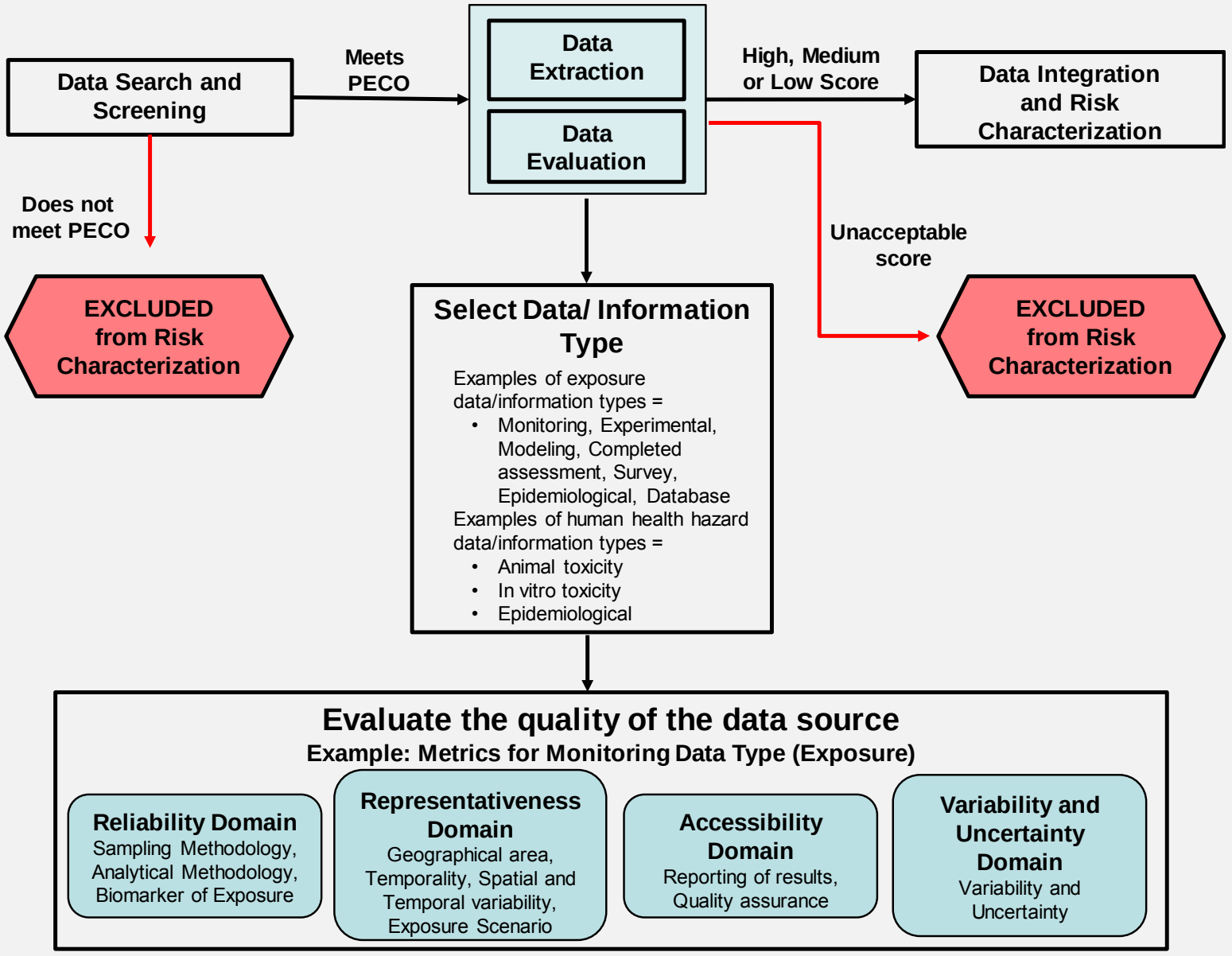
- Structured framework with numerical scoring to categorize quality of data/information sources
- Developed pre-defined criteria for the following data/information streams:
  - Physical/chemical properties
  - Environmental fate
  - Occupational exposure and release data
  - Exposure to general population, consumers and environmental exposures
  - Ecological hazard studies
  - Animal toxicity
  - Epidemiological studies
  - ***In vitro* toxicity**
- Opportunities for optimization or development of new criteria in the future as part of evaluating and integrating new approach methodologies (NAMs) in the TSCA risk evaluation process.

Evaluation Strategies to Assess Data/Information Quality

- General structure
  - *Evaluation domains*: general categories of data/information attributes intended to assess the methodological conduct
  - *Metrics*: sub-categories of attributes
  - *Criteria*: elements or conditions used to assess confidence
- Criteria depend on type of data/information source
- Can be modified to address chemical-specific issues (e.g., asbestos epidemiological criteria)
- Considered various evaluation tools/frameworks during the development process



Data Evaluation Workflow



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Evaluation Strategies to Assess Data/Information Quality

- Tiered approach to check for relevance of data/information starting at screening stage and continuing during evaluation and integration.
- Relevance and reporting quality are integrated in the review process.
  - No distinct reporting criteria/checklist
- Consider any and all available data/information relevant to the risk evaluation (e.g., GLP, guideline and non-guideline studies)
- Consider biases
- Use exclusion criteria (i.e., serious flaws) to eliminate unacceptable studies from further consideration
- Weighting of criteria, when applicable
- Documented in a form template

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Evaluation Method

- Strengths and limitations are considered when assigning a confidence level for each relevant metric.
- Confidence levels and corresponding scores at the metric level:
  - **High:** No notable deficiencies or concerns were identified in the domain metric that are likely to influence results [score of 1].
  - **Medium:** Minor uncertainties or limitations were noted in the domain metric that are unlikely to have a substantial impact on results [score of 2].
  - **Low:** Deficiencies or concerns were noted in the domain metric that are likely to have a substantial impact on results [score of 3].
  - **Unacceptable:** Serious flaws were noted in the domain metric that consequently make the data source unusable. [score of 4 ; not considered in scoring calculation].
  - **Not rated/applicable:** Rating of this metric is not applicable to this data source/data set [no score; not considered in scoring calculation].
- Some metrics have 2 or 3 bins to fit better the nature of the criteria.

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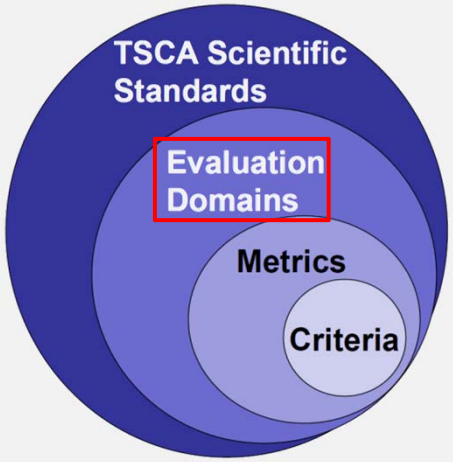
Evaluation Method

- Metrics scores are converted into overall score to categorize the quality level of data/information source.
- Score are used as confidence ranks and not intended to imply precision and/or accuracy of the scoring results.
- Reviewer may adjust overall confidence in case criteria fail to capture professional judgment with proper justification.

Overall Quality Level	Definition	Overall Quality Score
High	No notable deficiencies or concerns are identified and the data therefore could be used in the assessment with a high degree of confidence.	≥ 1 and < 1.7
Medium	Possible deficiencies or concerns are noted and the data therefore could be used in the assessment with a medium degree of confidence.	≥ 1.7 and < 2.3
Low	Deficiencies or concerns are noted and the data therefore could be used in the assessment with a low degree of confidence.	≥ 2.3 and ≤ 3
Unacceptable	Serious flaw(s) are identified and therefore, the data cannot be used for the assessment.	4

Human Health Hazard Information: Main Types of Data Sources and Evaluation Domains

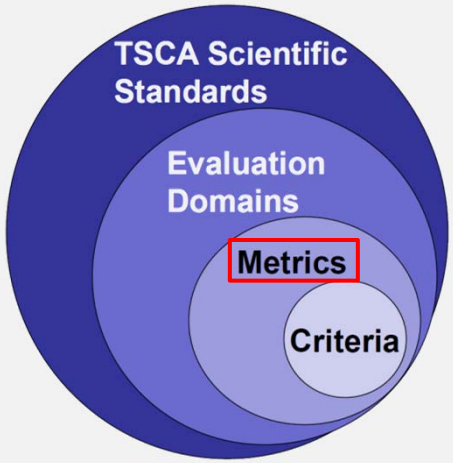
Data Category	Type of Data Sources
Animal Toxicity	Oral, dermal, and inhalation routes: lethality, irritation, sensitization, reproduction, fertility, developmental, neurotoxicity, carcinogenicity, systemic toxicity, metabolism, pharmacokinetics, absorption, immunotoxicity, genotoxicity, mutagenicity, endocrine disruption
In Vitro Toxicity Studies	Irritation, corrosion, sensitization, genotoxicity, dermal absorption, phototoxicity, ligand binding, steroidogenesis, developmental, organ toxicity, mechanisms, high throughput, immunotoxicity



Domains for Animal and *In Vitro* Toxicity Studies
Test Substance
Test Design
Exposure Characterization
Test Organism / Test Model
Outcome Assessment
Confounding / Variable Control
Data Presentation and Analysis

Refer to the Supplemental document supporting the draft TSCA risk evaluation for PV29 to see examples of how the evaluation strategies are being implemented, docket EPA-HQ-OPPT-2018-0604

Human Health Hazard Information: Metrics for the *In Vitro* Evaluation Criteria

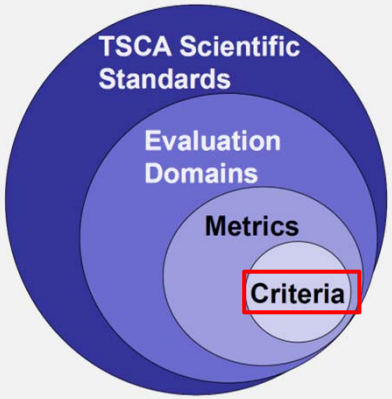


Metrics with Greater Importance (i.e., weighting factor of 2):

1, 4, 5, 10, 11, 14, 16, 18, 20, 23, 25

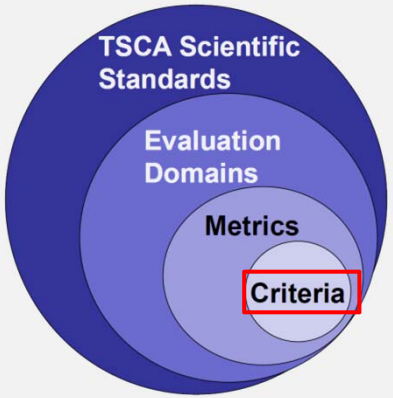
Evaluation Domain	Number of Metrics Overall	Metrics (Metric Number and Description, Type of Bias)
Test Substance	3	• Metric 1: Test Substance Identity • Metric 2: Test Substance Source • Metric 3: Test Substance Purity
Test Design	4	• Metric 4: Negative Controls • Metric 5: Positive Controls • Metric 6: Assay Procedures • Metric 7: Standards for Test
Exposure Characterization	6	• Metric 8: Preparation and Storage of Test Substance • Metric 9: Consistency of Exposure Administration • Metric 10: Reporting of Doses/Concentrations • Metric 11: Exposure Duration • Metric 12: Number of Exposure Groups and Dose Spacing • Metric 13: Metabolic Activation
Test Model	2	• Metric 14: Test Model • Metric 15: Number per Group
Outcome Assessment	4	• Metric 16: Outcome Assessment Methodology • Metric 17: Consistency of Outcome Assessment • Metric 18: Sampling Adequacy • Metric 19: Blinding of Assessors
Confounding/ Variable Control	2	• Metric 20: Confounding Variables in Test Design and Procedures • Metric 21: Outcomes Unrelated to Exposure
Data Presentation and Analysis	4	• Metric 22: Data Analysis • Metric 23: Data Interpretation • Metric 24: Cytotoxicity Data • Metric 25: Reporting of Data

Human Health Hazard: Example of Criteria for Test Substance Identity (*In Vitro* Toxicity)



Domain 1. Test Substance	
Metric 1. Test substance identity Was the test substance identified definitively (i.e., established nomenclature, CASRN, physical nature, physiochemical properties, and/or structure reported, including information on the specific form tested [e.g., salt or base, valence state, isomer, if applicable] for materials that may vary in form)? If test substance was a mixture, were mixture components and ratios characterized?	
High (score = 1)	The test substance was identified definitively (i.e., established nomenclature, CASRN, physical nature, physiochemical properties, and/or structure reported, including information on the specific form tested (e.g., salt or base, valence state, isomer, [if applicable]) for materials that may vary in form. For mixtures, the components and ratios were characterized.
Medium (score = 2)	The test substance and form (if applicable) were identified, and components and ratios of mixtures were characterized, but there were minor uncertainties (e.g., minor characterization details were omitted) that are unlikely to have a substantial impact on results.
Low (score = 3)	The test substance and form (if applicable) were identified, and components and ratios of mixtures were characterized, but there were uncertainties regarding test substance identification or characterization that are likely to have a substantial impact on the results.
Unacceptable (score = 4)	The test substance identity and form (if applicable) could not be determined from the information provided (e.g., nomenclature was unclear and CASRN or structure were not reported) **OR** the components and ratios of mixtures were not characterized.

Human Health Hazard: Example of Criteria for Negative Controls and Reporting of Concentrations (*In Vitro* Toxicity)



Metric 4. Negative controls Was a concurrent negative (untreated, sham-treated, and/or vehicle, as necessary) control group included?		
High (score = 1)	Study authors reported using a concurrent negative control group (untreated, sham-treated, and/or vehicle, as applicable) in which all conditions equal except exposure to test substance.	
Medium (score = 2)	Study authors reported using a concurrent negative control group, but all conditions were not equal to those of treated groups; however, the identified differences are considered to be minor limitations that are unlikely to have substantial impact on results.	
Low (score = 3)	Study authors acknowledged using a concurrent negative control group, but details regarding the negative control group were not reported, and the lack of details is likely to have a substantial impact on the results.	
Unacceptable (score = 4)	A concurrent negative control group was not included or reported **OR** the reported negative control group was not appropriate (e.g., different cell lines used for controls and test substance exposure).	
Not rated/applicable		

Metric 10. Reporting of concentrations Were exposure doses/concentrations or amounts of test substance reported without ambiguity (e.g., point estimate instead of range, analytical instead of nominal)?		
High (score = 1)	The exposure doses/concentrations or amounts of test substance were reported without ambiguity (e.g., point estimate instead of range, analytical instead of nominal).	
Medium (score = 2)	Not applicable for this metric.	
Low (score = 3)	Not applicable for this metric.	
Unacceptable (score = 4)	The exposure doses/concentrations or amounts of test substance were not reported resulting in serious flaws.	

Human Health Hazard: Example of Scoring for In Vitro Toxicity

Domain	Metric	Metric Score	Metric Weighting Factor	Weighted Score
Test substance	1. Test substance identity	1	2	2
	2. Test substance source	2	1	2
	3. Test substance purity	2	1	2
Test design	4. Negative controls	1	2	2
	5. Positive controls	1	2	2
	6. Assay procedures	2	1	2
	7. Standards for test	3	1	3
Exposure characterization	8. Preparation and storage of test substance	2	1	2
	9. Consistency of exposure administration	2	1	2
	10. Reporting of concentrations	1	2	2
	11. Exposure duration	1	2	2
	12. Number of exposure groups and dose spacing	1	1	1
	13. Metabolic activation	3	1	3
Test Model	14. Test model	2	2	4
	15. Number per group	2	1	2
Outcome assessment	16. Outcome assessment methodology	3	2	6
	17. Consistency of outcome assessment	2	1	2
	18. Sampling adequacy	1	2	2
	19. Blinding of assessors	2	1	2
Confounding/variable control	20. Confounding variables in test design and procedures	3	2	6
	21. Outcomes unrelated to exposure	2	1	2
Data presentation and analysis	22. Data analysis	1	1	1
	23. Data interpretation	2	2	4
	24. Cytotoxicity data	2	1	2
	25. Reporting of data	3	2	6
NR= not rated/not applicable		Sum	36	66
		Overall Study Score	**1.8**	**= Medium**

Overall Score = Sum of Weighted Scores/Sum of Metric Weighting Factor

High	Medium	Low
≥1 and <1.7	≥1.7 and <2.3	≥2.3 and ≤3

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Data Integration

- Stage where the analysis, synthesis and integration of information takes place
  - Considers quality, consistency, relevancy, coherence, and biological plausibility
  - Document assumptions and professional judgement
  - Weight of evidence
- Integration strategy may vary by chemical assessment
- Further details on evidence integration will be provided in the draft TSCA risk evaluations.

Challenges/Opportunities for Implementing Systematic Review under Amended TSCA

Challenges

- Statutory deadlines
- Diverse chemical space (data poor vs. data rich)
- Heterogenicity of mechanistic data
- Quality evaluation of various data types
- Generic vs. specific evaluation criteria
- Infrastructure development while doing assessments

Opportunities

- Refinements to the planning phase prior to literature search and screening and moving activities to prioritization phase
- Strengthening quality assessment procedures during piloting
- Incorporation of automated methods to reduce manual sorting and screening and prioritization of references (e.g., e.g., SWIFT, DoCTER)
- Implement/improve tools to support the systematic review process (e.g., HERO database, Distiller SR, Dragon, HAWC)
- Development of new evaluation criteria for data types not currently covered (e.g., new alternative test methods).

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Summary

- Scoping/Problem formulation: Key step to develop fit-for-purpose assessments tailored for TSCA decision making.
- TSCA science standards guide systematic review process for both exposure and hazard information.
- Evaluation tool is available for *in vitro* toxicity studies; PECOs use to prioritize mechanistic evidence during screening.
- New consideration of alternative test methods and strategies, as applicable and available.
- EPA/OPPT anticipates optimization of the evaluation method as risk evaluations are developed for a wide chemical space within the TSCA context.
- Goal is to produce transparent, consistent and scientifically robust risk evaluations.

Acknowledgements

EPA

OPPT's Systematic Review Team

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