Evidence Integration of Environmental and Human Health Hazard Data Under the Toxic Substances Control Act (TSCA)

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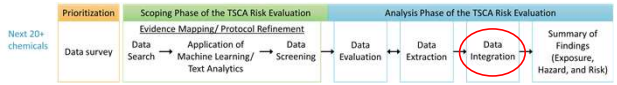
Systematic Review Process

Systematic Review is a comprehensive, unbiased, transparent and reproducible way to identify relevant literature on a topic.

The Toxic Substances Control Act (TSCA) requires EPA to use information in a way that is consistent with the best available science and to base decisions on the weight of the scientific evidence (U.S. EPA, 2018).

Data integration is the step in the systematic review process where EPA analyzes, synthesizes, and integrates hazard information to establish hazard thresholds used for risk characterization. It involves weighing scientific evidence for quality and relevance, thus meeting the TSCA science standards (U.S. EPA, 2018).

Key Stages of the Systematic Review Process in TSCA Risk Evaluations



Key Terms in Data Integration

Data Quality	Quantitative score calculated following evaluation of discipline-specific and data type-specific data evaluation domains and metrics according to predefined scoring criteria and accounting for metric weighting factors.
Weight of the Scientific Evidence	Weight of scientific evidence means a systematic review method, applied in a manner suited to the nature of the evidence or decision, that uses a preestablished protocol to comprehensively, objectively, transparently, and consistently, identify and evaluate each stream of evidence, including strengths, limitations, and relevance of each study and to integrate evidence as necessary and appropriate based upon strengths, limitations, and relevance. (40 CFR Part 702)
Strength of the Evidence Score for Hazard	Qualitative judgment describing the strengths, limitations, and relevance of the body of information related to hazard or exposure.
Confidence Level for Risk Estimation	Qualitative judgment describing the certainty of the risk estimate considering the strength the evidence scores for hazard and exposure and the limitations, and relevance.

Methods

EPA weighs the scientific evidence and considers quality and relevance when integrating data for both human health and environmental hazard.

Human Health Hazard Data Integration

- EPA considers quality, consistency, relevancy, coherence, and biological plausibility when integrating evidence across human, animal, and if needed, mechanistic information (U.S. EPA, 2018).
- Most risk evaluations describe the endpoint-specific considerations used to integrate data but did not use a formal method.
- In contrast, when integrating information on cardiac defects of TCE, EPA used an approach that considers strength of the evidence (e.g., magnitude, dose-response, etc.) in addition to reliability (quality) and relevance (U.S. EPA, 2016).
- Pieces of evidence scored on a semiqualitative score:
  - ***Strength*** – Low, medium, high: +, ++, +++ or -, --, ---
  - ***Reliability*** – Unusable, low, medium, high: 0, +, ++, or +++
  - ***Relevance*** – None, low, medium, high: 0, +, ++, or +++
- Summary scores considered consistency of strength across studies and amplitude of overall study grades:
  - None (neutral/ambiguous): negative (weakens), positive (supports), +, -, 0
  - Most influenced by studies with the strongest, clearest effects and/or the most consistent results

Method (continued)

Environmental Hazard Data Integration

- For environmental hazard data integration, EPA considers quality and relevance, including biological, physical/chemical, and environmental relevance (U.S. EPA, 1998).
- Ideally, EPA would have multiple sources of high-quality, quantitative and relevant data for each exposure pathway being assessed for a chemical, however this is generally unlikely.
- If there is sufficient data availability, a stressor-response analysis may be conducted to compare the chemical dose or concentration to multiple responses (e.g., % mortality, growth, reproduction), or to multiple species' responses (i.e., a species sensitivity distribution [SSD]). If enough data is available, EPA prefers using a probabilistic approach to integrate data (e.g., SSD), as compared to a deterministic approach.

Figure 1. Summary of Hierarchy Guiding Integration of Environmental Hazard Data (From Highest to Lowest Preference)

1. Relevant and high-quality quantitative lab or field data
2. Relevant but medium quality quantitative lab or field data
3. Relevant but low-quality quantitative lab or field data
4. Qualitative information that is relevant (e.g., descriptive field/mesocosm studies.)

   or, Quantitative data that is not relevant (e.g., the test uses an analogue or mixture and not the substance of concern),

   or, Analogue and Structure Activity Relationship (SAR)/Quantitative Structure Activity Relationship (QSAR) information.

- However, if only limited and/or low-quality quantitative data are available, EPA will weigh the scientific evidence and integrate the data appropriately (e.g., derive a geometric mean, use the most sensitive endpoint with sufficient data quality and relevance, use the highest quality data available), while also discussing any uncertainties or data gaps associated with the environmental hazard analysis.

Human Health Hazard Example

Cardiac Defects: TCE

- **Epidemiology studies (+)**
  - Suggestive evidence of an effect of TCE on cardiac defects in humans (*summary score: +*)
- **Animal toxicity studies (0)**
  - Oral: Ambiguous to weakly positive (0/+) for TCE; positive (+) for TCA and DCA metabolites
  - Inhalation: Negative (-)
  - Overall: mixed, ambiguous (*summary score: 0*)
- **Mechanistic studies (++)**
  - Strong and consistent supporting information for effects of TCE and metabolites on cardiac development and precursor effects (*summary score: ++*).
- **Overall Summary Score (+)**
  - The database overall was determined to be both reliable and relevant after integration of the three evidence areas (epidemiology, animal, mechanistic).
  - Positive overall evidence that TCE may produce cardiac defects in humans.

Figure 2. Results of Integration Within and Across Lines of Evidence

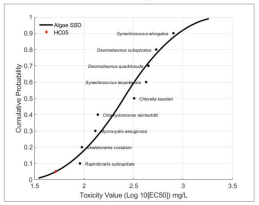
Evidence Area	Summary Score
Epidemiology studies	+
In vivo animal toxicity studies	0
Mechanistic studies	++
Overall	+

Environmental Hazard Data Example

Aquatic Species Hazard: TCE

- For the TCE risk evaluation EPA had enough data available to integrated environmental hazard data using species sensitivity distributions (SSDs), a probabilistic approach for integrating data.
- First, using the results of the systematic literature search, acute toxicity data for algae, aquatic invertebrates, fish, and amphibians were curated to prioritize study quality and to assure comparability between toxicity values (e.g., comparing EC_{50}s to EC_{50}s).
- Next, EPA created two SSDs, one using only algae hazard data and the other using acute hazard data for all other aquatic species.

Figure 3. Species Sensitivity Distribution (SSD) for Algae Species Using EC_{50}s

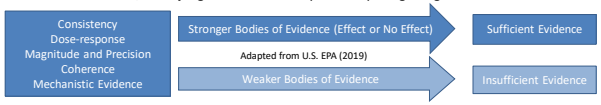


- EPA used each SSD to calculate a hazardous concentration for a percentage of species (HCp), which can be used in a risk evaluation to calculate a concentration of concern (COC) (e.g., a hazard value divided by an assessment factor).
- EPA calculated HC_{05}s (hazardous concentrations for 5% of species) using each SSD, which served as a helpful line of evidence in addition to the deterministic approaches EPA has for integrating data to calculate COCs.
- The SSDs also provided visual representations of species' sensitivities, allowing EPA to quickly determine whether certain groups of species would be are sensitive than others.

Next Steps

Human Health — **Example:** MeCl Immunotoxicity Appendix M

- Harmonize methods under TSCA with EPA's Office of Research and Development (U.S. EPA, 2019).
  - For chemical-specific relevant health effects, such as neurotoxicity, EPA will synthesize separate lines of evidence (i.e., phenotypic human and animal data, mechanistic information if needed).
  - Focus on aspects that best inform causal interpretations (adapted from Bradford Hill criteria).
  - For each health effect, make judgments in summary tables by integrating across all lines of evidence.



- As ORD methods evolve, EPA will update its data integration processes under TSCA.

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