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Biomarkers: Taking Stock
~ Biomarkers in Risk Assessment ~
Current Use and Future Directions

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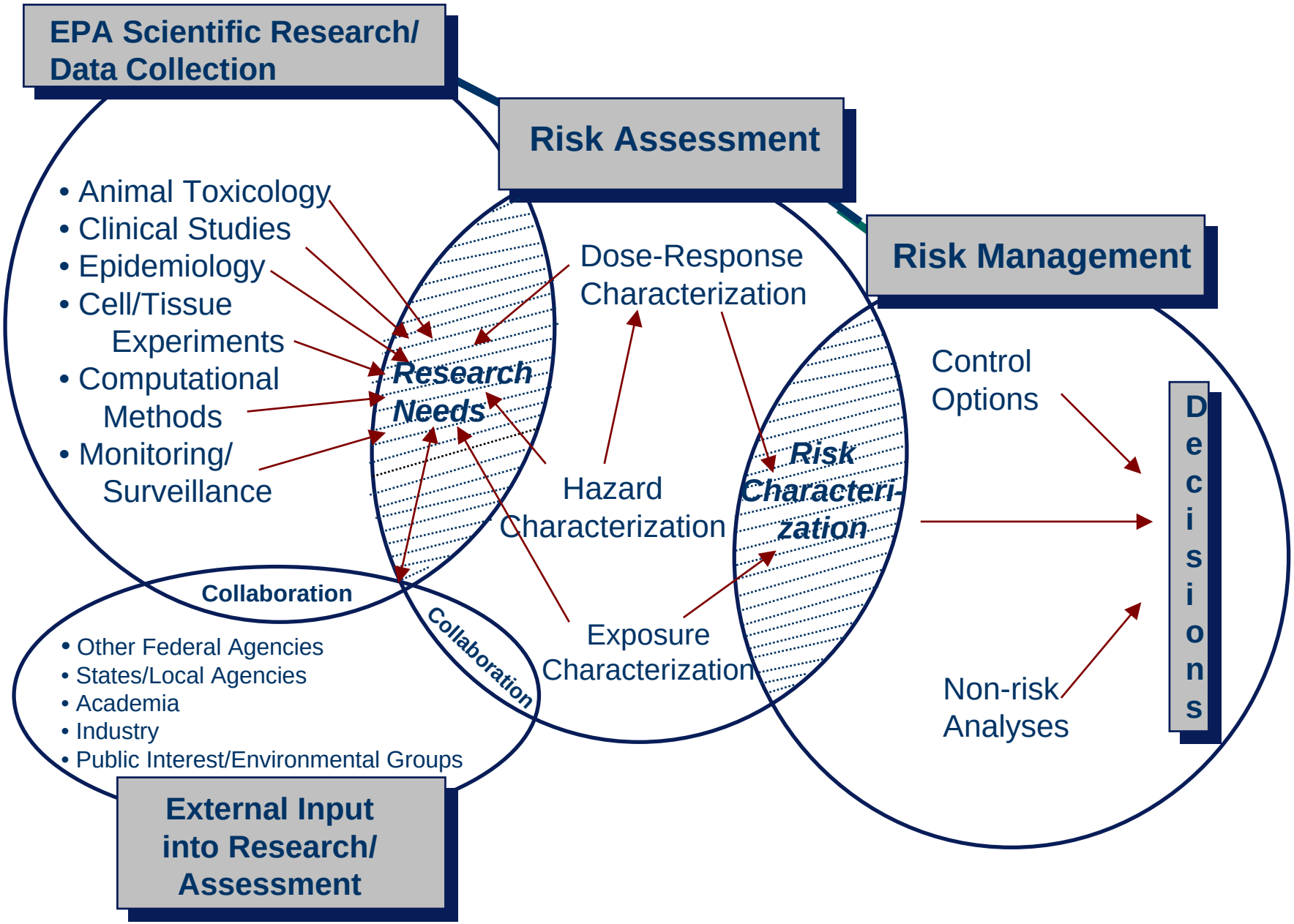
Research ⇄ Assessment ⇄ Management



Recent Emphasis Focuses on the Use of *Mode-of-Action* Data

"The quality of risk analysis will improve as the quality of input improves. As we learn more about biology, chemistry, physics, and demography, we can make progressively better assessments of the risks involved. Risk assessment evolves continually, with reevaluation as new models and data become available."

"Science and Judgment in Risk Assessment" (National Research Council, 1994)

Revision Directions for Risk Assessment Guidelines --

- Emphasize full **characterization**
- Expand role of **mode-of-action** information (and, therefore, ***biomarkers****!*)
- Use **all information** to design dose response approach
- **Two step** dose response assessment

BIOMARKERS --

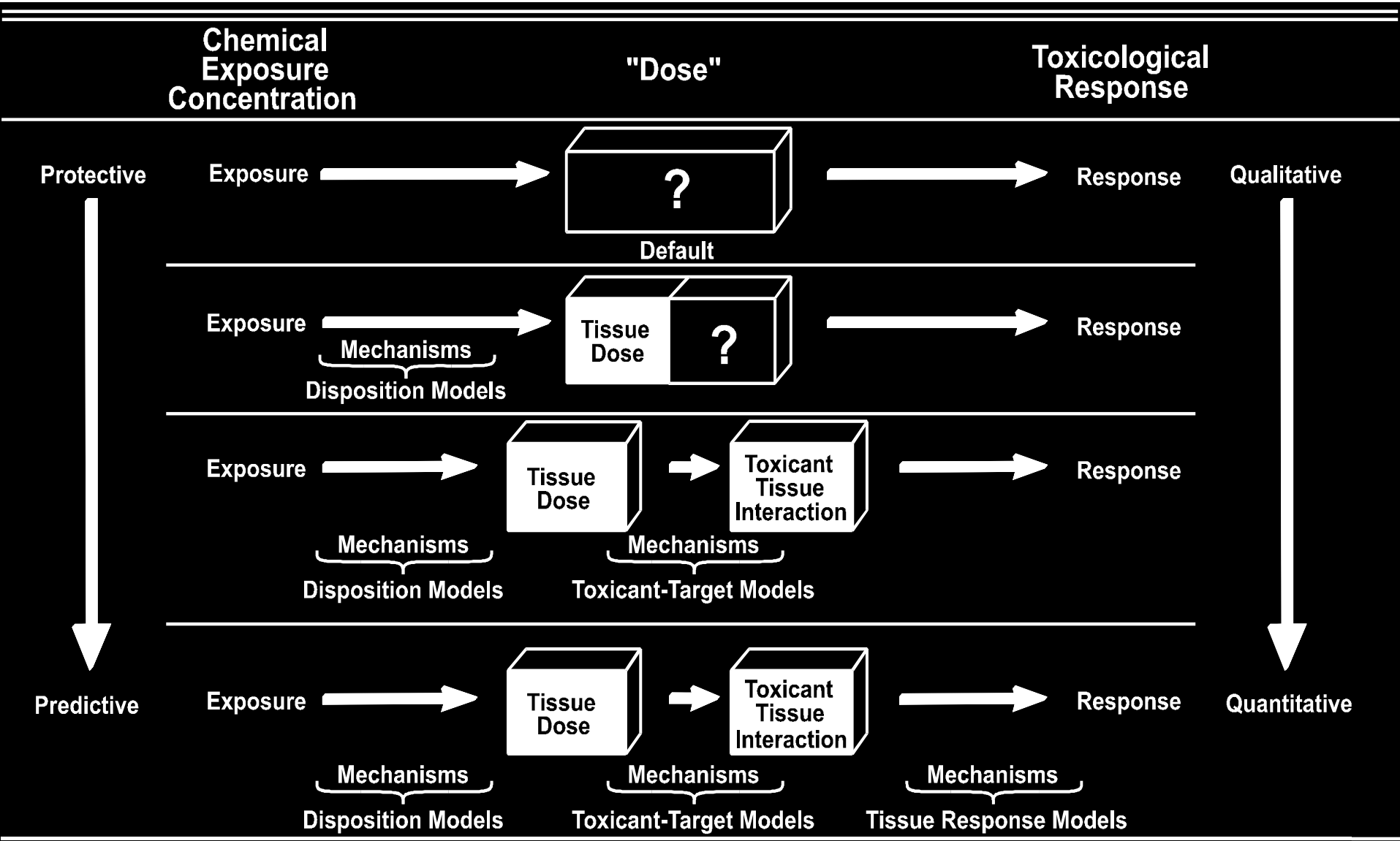
Definition:

Biologic markers are indicators signaling events in biologic systems or samples.

Three types:

- ➔ Exposure
- ➔ Effect
- ➔ Susceptibility

Systematic Characterization of Comprehensive Exposure-Dose-Response Continuum and the Evolution of Protective to Predictive Dose-Response Estimates



Mechanism vs. Mode-of-Action

Mechanism of action:

Detailed molecular description of a key event in the induction of cancer or other health endpoints

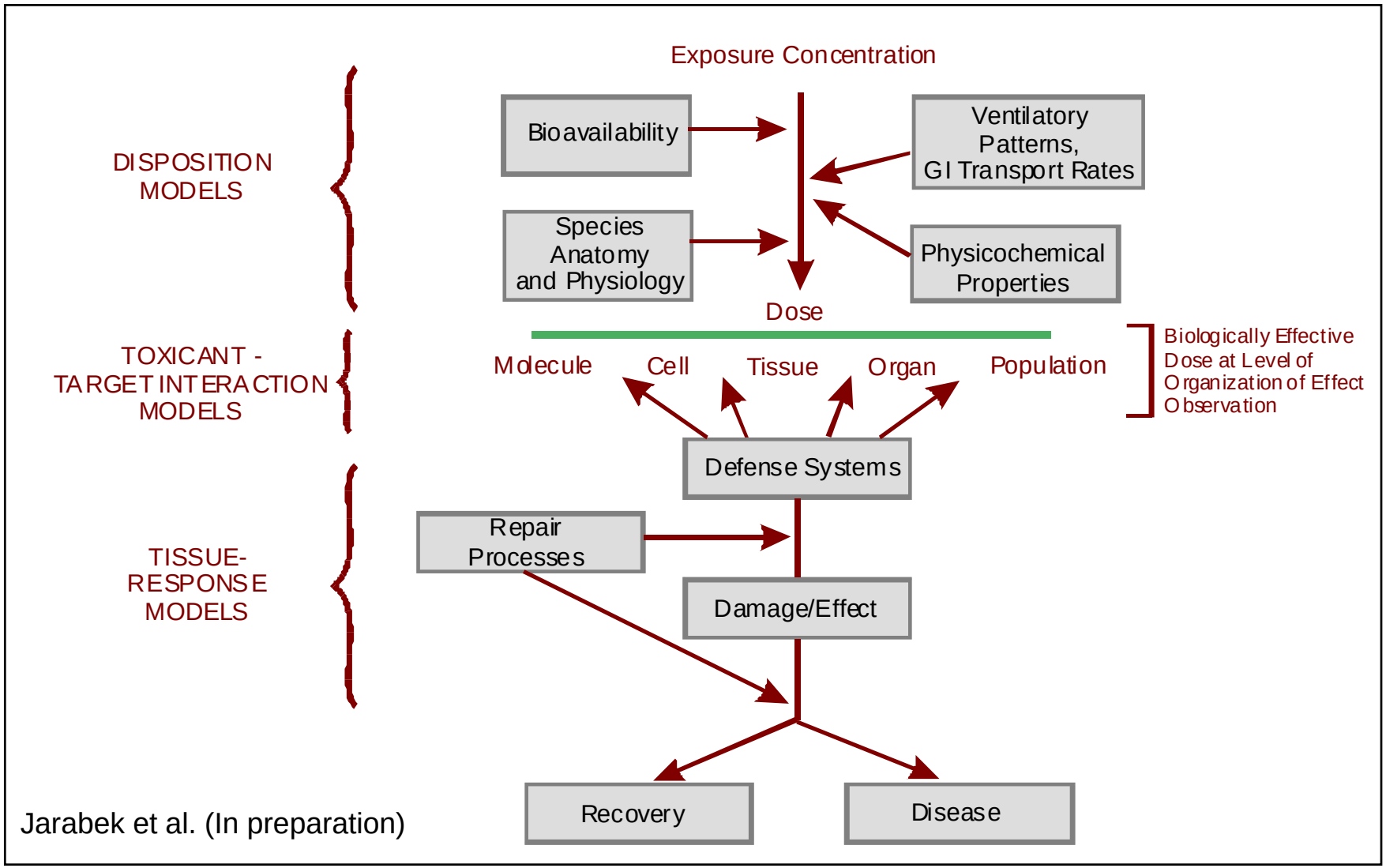
Mode-of-Action:

Key events and processes, starting with the interaction of an agent with a cell, through functional and anatomical changes, resulting in cancer or other health endpoints

Mode-of-Action --

- How does the chemical produce its effect?
- Are there mechanistic data to support this hypothesis?
- Have other mechanistic hypotheses been considered and rejected?

MODE-OF-ACTION:
Species- and Chemical-Specific Influences on Exposure-Dose-Response Relationships



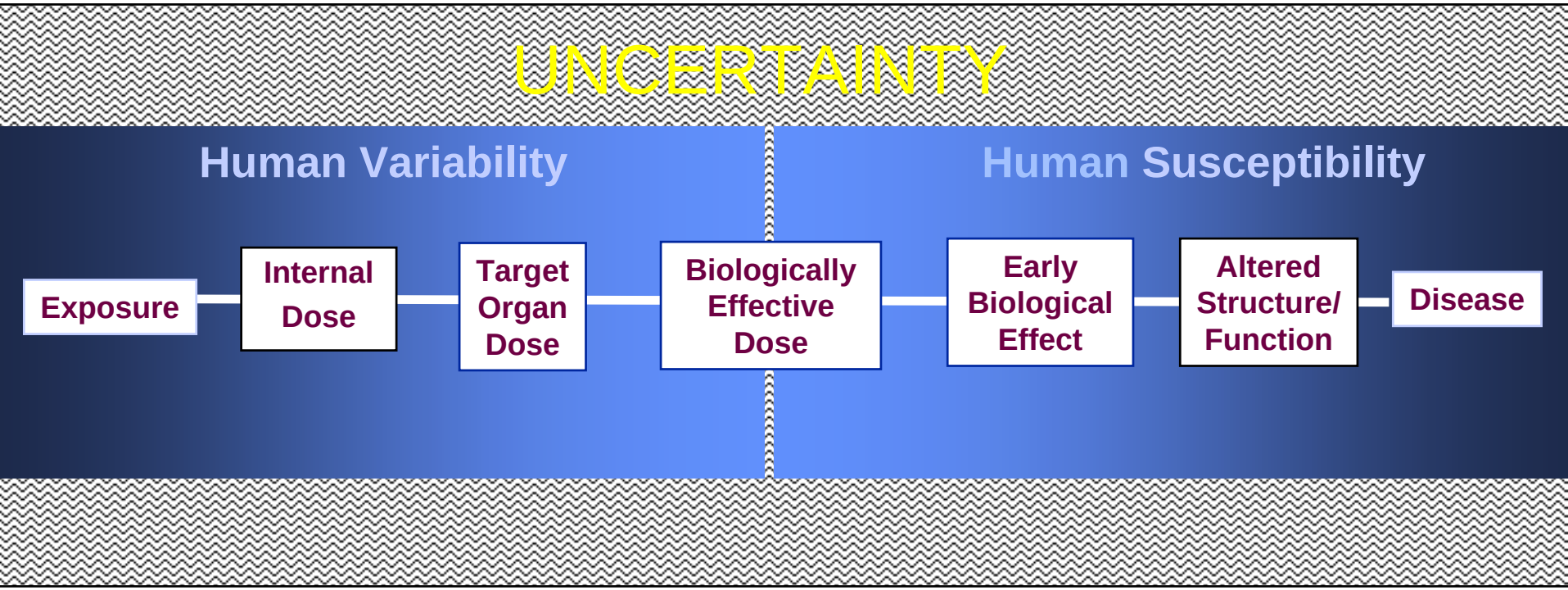
Jarabek et al. (In preparation)

How is mode-of-action information used?

Address Uncertainty in Risk Assessment:

- Comparative Structure Activity Relationships (SAR)
- Relevance of animal data for extrapolation
- Shape of dose-response curve
  - ➔ Range of Observation
  - ➔ Range of Inference
- Susceptibility of individuals/ subpopulations

Uncertainty and the Continuum Between Exposure and Disease



Demonstrating a Mode-of-Action --

To show that a postulated ***mode-of-action*** is operative, it is generally necessary to:

- **outline** the sequence of events leading to effects;
- **identify** key events that can be measured; and
- **weigh** information to determine whether there is a causal relationship between events and cancer formation.

Framework --

- Summary Description of Postulated Mode-of-Action
- Topics:
  1. *"Identify key events" (→ BIOMARKERS**?**)*
  2. *"Strength, consistency, specificity of association"*
  3. *"Dose-response relationship"*
  4. *"Temporal relationship"*
  5. *"Biological plausibility and coherence"*
- Conclusion

Key Event--

DEFINITION:

An empirically observable, precursor step that is a necessary element of the mode-of-action, or is a marker for such an element

Key Event --

Examples:

- Metabolism
- Receptor-ligand changes
- DNA or chromosome effects
- Increased cell growth and organ weight
- Hormone or other physiological perturbations
- Hyperplasia, cellular proliferation

Use of Mode-of-Action Information: *Examples*

- Formaldehyde ⇒ DNA crosslinks
  ⇒ Cell proliferation
- Methylene Chloride ⇒ Pharmacokinetics
  ⇒ Genetic polymorphisms
- d-Limonene ⇒ "-2-u-globulin, etc.
- Chloroform ⇒ Cytotoxicity
- Dioxin ⇒ Receptor-mediated responses

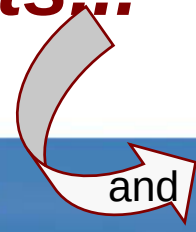
Use of Mode-of-Action Information: *More Examples*

- **BaP** ⇒ **DNA reactive metabolites** ⇒ **Cell proliferation**
- **Amitrole** ⇒ **Increased Thyroid Stimulating Hormone (TSH)** ⇒ **Cell proliferation**
- **Melamine** ⇒ **Increased urinary pH** ⇒ **Irritation**
- ***Perchlorate*** ⇒ ***Altered thyroid homeostasis***
- ***Vinyl Acetate*** ⇒ ***Cytotoxicity*** ⇒ ***Cell proliferation***

Where do we go from here?

- ☑ Development/validation of sensitive tools aimed at understanding mode-of-action
- ☑ Incorporation of "Framework" Concept
- ☑ More Attention to Route-Specific/ Situation-Specific Characterizations
- ☑ Addressing Sensitive Subpopulations

"Biologically-Based Risk Assessments..."



Biologically-Based Risk Assessment

- Refine estimates of dose to relevant targets through use of biomarkers of exposure
- Improve hazard characterization through use of biomarkers of response with mechanistic linkage to endpoints of concern
- Strengthen inferences regarding the shape of dose/response curves outside the range of observation
- Identify targets of opportunity for further study in potentially sensitive human populations