Decision Analytic Approach to Advance AOP Application in Risk Assessment: Characterization Criteria

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Using AOPs for Regulatory Decisions: Confidence and Criteria
Adverse Outcome Pathways: From Research to Regulation
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Overview

- **Background: Motivation and lessons learned**
- **Creating context: Challenges**
- **Decision analytic approach**
- **Characterization criteria**
- **Summary**

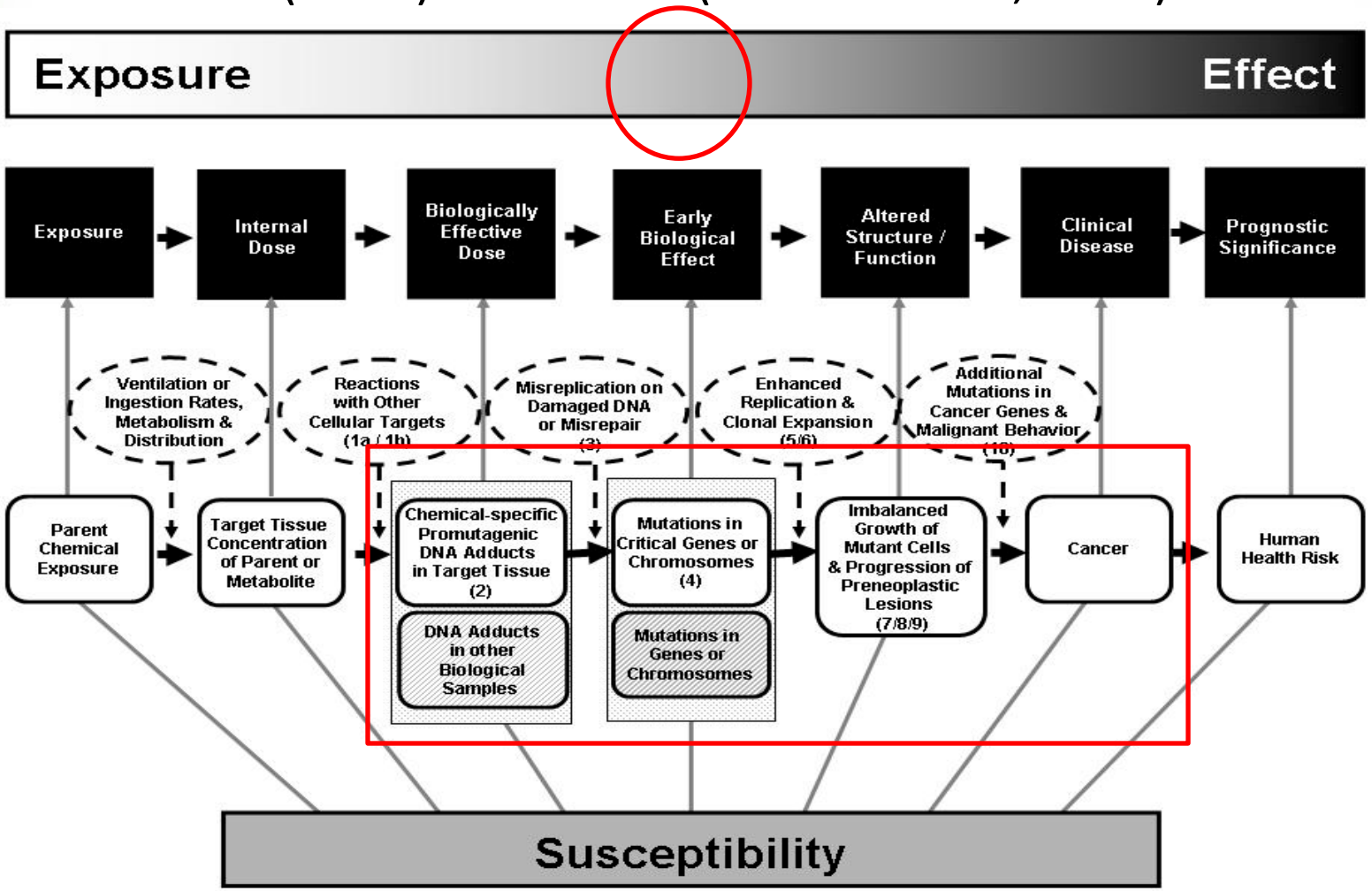
Disclaimer: *These views are those of the author and do not represent US EPA policy.*

Motivation: Multi-scale Modeling

- **Advance biotechnology and systems understanding → Pathway-based assessment to predict adversity**
  - **Protecting the public health and environment requires analysis, translation, and integration of data along source to effect pathways**
  - **Optimization of economic, environmental and societal concerns to support sustainability**
- **Requires transparent and tractable integration of diverse data types across scales**
  - **Spatial**
  - **Temporal**
  - **Biological**

Background: Lessons Learned

Revised NAS Biomarker Scheme: DNA Adducts in DNA-reactive Mode of Action (MOA) for Cancer (Jarabek et al., 2009)



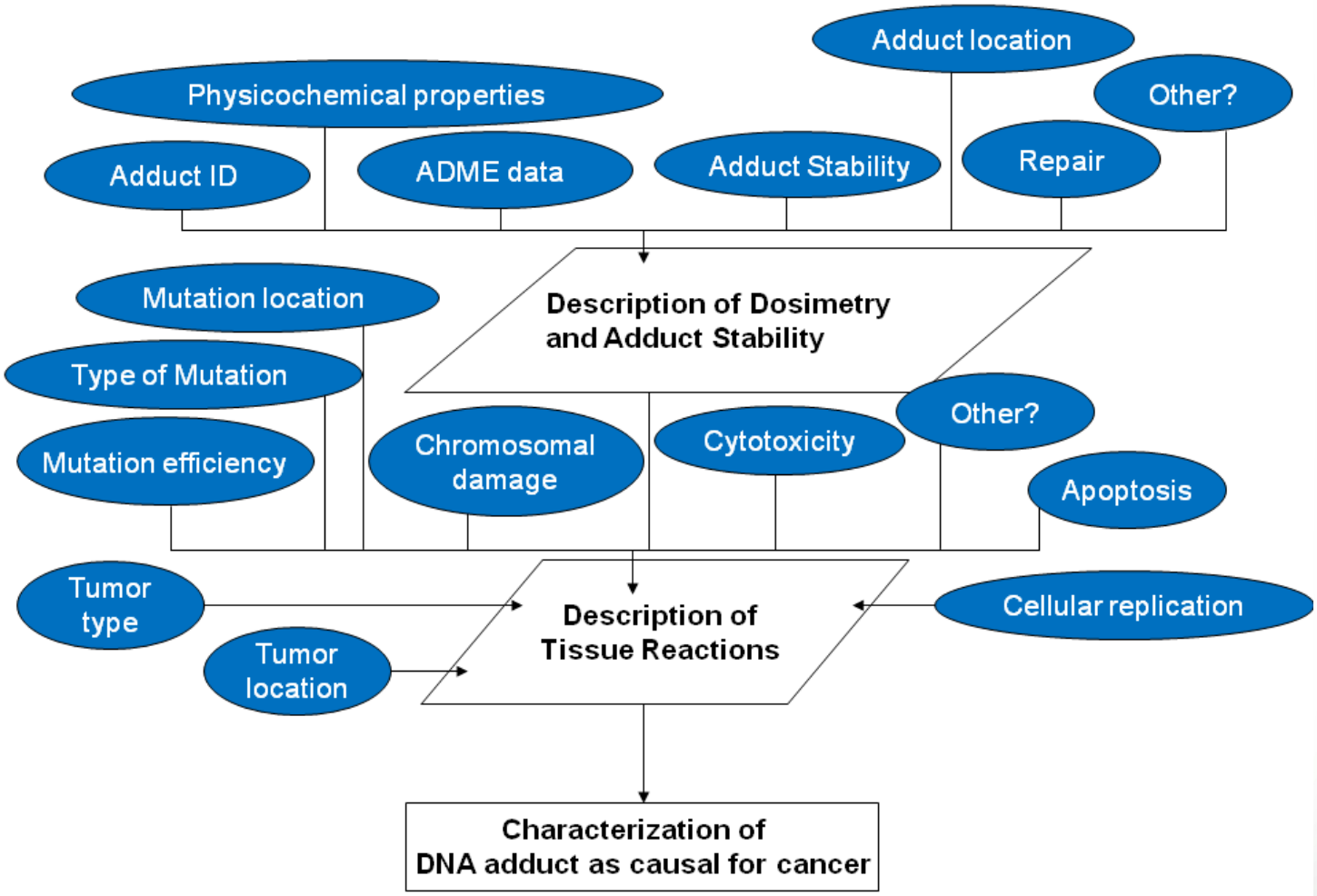
Challenge: Create Context to Transition Risk Assessment

- **Characterize *dose-response* using new endpoints with linkage to traditional outcome measures such as morbidity, mortality, histopathology and tumors**
- **Requires integration of diverse data sets across different domains (e.g., genomic versus population), methods (e.g., measurements / mining / models) and observational contexts**
  - ***in vivo / ex vivo***
  - **Laboratory animal or other test species**
  - **Human and ecological**
- ***Repurposing* of data is typical problem area: Provide explicit evaluation of data quality, utility, and relevance to facilitate formal inferences**
- **Highlight how individual judgments concerning data on parameters for causality of specific steps influence the confidence in ultimate decision; emphasize accuracy and predictive power to establish confidence**

Decision Analytic Approach: Target Context and Causality

- **Key attribute of decision analytic (DA) approach is that it provides formal structure for decision-making: Organize data evaluation to address risk assessment by targeting dose-response relationship**
- **Requires attention to problem formulation**
  - **Target context: Human cancer risk at environmental exposure levels**
  - **Question: *Based on available data, do the key events of the AOP appear to be causal for disease in human target tissue (e.g., liver cancer)?***
- ***DA Step One:* Represent key events or parameters as a process model (i.e., an AOP) of pathogenesis**
  - **Pharmacokinetic (PK) processes (dosimetry)**
  - **Pharmacodynamic (PD) processes (response)**
- ***DA Step Two:* Evaluate extrapolation premises and data quality, reliability and utility to describe those events; summarize judgments**

DA Step One: Populate Process Model



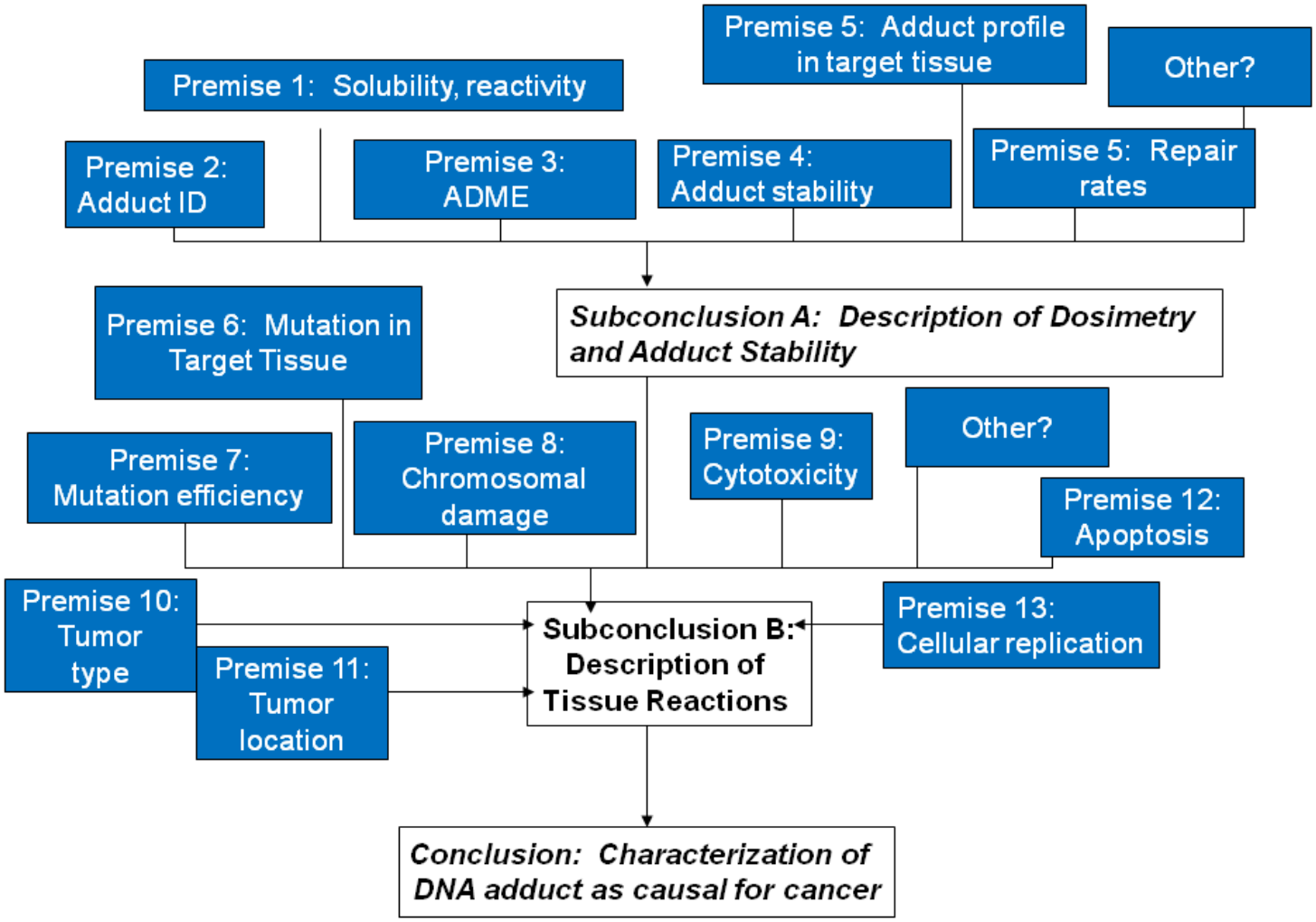
DA Step Two: Evaluate Extrapolation Premises and Data Features

- **A premise is an assumption about the ability of the given data to describe or represent the particular parameter or key event of interest to the process model (or AOP)**
  - **Extrapolation premises are assumptions required to apply data to describe target context**
- **Evaluation entails describing the extrapolation premises and data features (quality, strength of results, utility, relevance) using characterization criteria**
- **Summary judgments on these extrapolation premises and data features define causality of specific key events and ultimately reflect overall confidence in process model (or AOP)**

Characterization Criteria: Evidence Categories

- **Direct empirical (DE):** **Direct observation of phenomenon of interest under conditions of interest**
  - **Typically generated by epidemiological or clinical studies**
  - **Strongest foundation from which to infer human risk**
  - ***Example: Exposure-effect relationship for liver hemangiosarcoma from occupational vinyl chloride exposure***
- **Semi-empirical (SE):** **Phenomenon or situation differs in some systematic way from that of target**
  - **Requires introduction of extrapolation premises; thus, weaker evidence than DE**
  - ***Example: ADME or tumor data in rats***
- **Empirical correlation (EC):** **Based on effect other than effect of interest**
  - **Utility increases if correlation is strong and specific; or bolstered by theory**
  - **Establishing reliability has two (2) components:**
    1) **Evaluation of the foundational quality of the observation, and**
    2) **Quality of the associations**
  - ***Example: Correlation of cytotoxicity and cellular replication with tumors in rat nasal cavity after formaldehyde exposure***
- **Theory-based inference (TBI):** **Observation of effect other than the effect of target interest but there is a theory explaining how it may lead to relevant effect**
  - ***Example: in vitro mutagenicity assays***

DA Step Two: Evaluate Extrapolation Premises and Data Features



Characterization Criteria

- Type of data: Evidence category (DE, SE, EC, TBI)
- Required extrapolation premises (chemical class, species, target tissue, etc.)
- Measurement or modeling method
  - Level of detection, sensitivity, specificity
  - Mining on chemicals in similar class?
  - Empirical or mechanistic model structure?
- Quality (well-documented, peer-reviewed, specific analytical methods, reproducibility, etc.)
- Utility (e.g., established assay)
- Relevance: Exposure range, chemical class, ADME, target tissue, species, cell type, strength (dose-response, sample size or effect size and statistical significance, coherence in observational context, coherence in target context, etc.)

Summary Judgments

- **Evidence category:** **DE > SE > EC > TBI**
- **Data quality:** **Considers characterization criteria (e.g., methodology, reproducibility, specificity, well-documented, peer-reviewed, utility, relevance, etc.)**
- **Strength of study result:** **How compelling is the information; i.e., strength of data to support the proposed parameter or key event in model or AOP. Includes relevant species, dose-response relationship, adequate dose-range, etc.**
- **Observational context support:** **Relative to all the "human", "laboratory animal", or "in vitro / ex vivo" observations in the same context, do these data fit? Do the study results make sense in terms of the available evidence for that context, e.g., is the study consistent with all the laboratory animal data?**
- **Strength of extrapolation premise:** **How well do data or theory support the extrapolation premise; how solid are required assumptions? Is there a systematic departure or difference vis-á-vis target context to consider valuable [i.e., what degree of extrapolation is required to apply to human scenario, e.g., lots of extrapolation (not directly empirical) = low; minimal extrapolation = high]**
- **Relevance to target context:** **Consider data relative to human scenario, e.g., in vitro human data may be more relevant than other in vitro systems; some test systems may demonstrate for specific key events; human data may only be relevant if in range of target scenario**

Example Summary Judgments Table: AFB1

Premise / Data Study citation	Evidence Category (DE; SE; EC; TBI)	Data Quality	Strength of Study Result	Observation Context Support	Strength of Extrapolation Premises	Relevance to Target Context	Obligation to Consider Observation in Final Characterization for Target Context
Human Observational Context							
p53 mutations in human HCC patients Zhang (2006)	SE Mutations in humans	**High** Gene sequence	**Medium** Limited exp data; HBV status not controlled	**High** Mutations in target tissue	**Medium** Only positive HCC evaluated not normal tissue	**High** Mutations in human target tissue	**High**
Laboratory Animal Observational Context							
DNA and protein adducts after oral AFB1 doses in rats (Cupid 2004)	EC Adducts in rat liver	**High** AMS/ ^{14}C	**High** Dose-response in liver and other tissues	**High** Target tissue with dose-response	**High** Target tissue, labeled MS, dose-response	**High** Rat is reasonable surrogate based on PK data	**High**
in vitro / ex vivo Observational Context							
N7-AFB1-G in calf thymus DNA (Essigman 1977)	TBI Adduct in cow thymus DNA (CT-DNA)	**High** Structural identification by MS	**High** Adduct ID in DNA by MS	**Medium** AFB1-adduct formation but not intact target tissue	**Low** Rat liver activation but CT-DNA	**Medium** Calf thymus DNA adduct	**Medium**

Conclusions on Causality and Final Confidence Characterization

- **Consider coherence across all of the data for the PK and PD descriptions to arrive at a conclusion for each component as follows:**
  - ***Within each observation context (low, medium, high):***
    - ***in vivo / ex vivo***
    - **laboratory animal**
    - **human**
  - ***Across all contexts for each* component (low, medium, high):**
    - **Conclusion for Component1: Dosimetry description in target**
    - **Conclusion for Component 2: Description of tissue responses in target context**
- **Conclusion for causality in the target context is based on consideration of the strength of the final characterization of both dosimetry and response components:**
  - ***Causality = Conclusion 1 + Conclusion 2 (low, medium, high)***
- **Final confidence reflects causality conclusion (low, medium, high)**

Summary

- Decision analytic approach offers necessary data organization and formal structure to support decision-making
  - Transparent
  - Explicit rationale regarding use of data for dose-response analysis
  - Evaluation of data quality, utility and reliability for intended characterization (target context)
  - Integration of diverse data sets
  - Considers coherence weighted across all data
- Qualitative expression of confidence (low, medium, high) readily amenable to more quantitative, probabilistic approaches (e.g., multi-criteria decision analysis, MCDA)

Acknowledgment & References

- Dr. Douglas Crawford-Brown, Department of Environmental Science and Engineering, UNC Chapel Hill and University of Cambridge Centre for Climate Change Mitigation Research

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Cultural and Operational Needs

- Access to discover, collect, and integrate data in a coordinated fashion
  - Encourage data repositories with maintenance and management
  - Enhance open access and change publication practice
- Mitigating uninformed use of models
  - Making application limitations known
  - Documentation of parameter values
- Facilitating collaboration *and* accommodating confidentiality
- Repurposing of data for new analysis requires context for data (meta data) including annotation and curation history; also requires dedicated data managment
- Peer review: Transparency of assumptions and uncertainty propagation
- Visualization
- Simplicity of interfaces