AOPs 101: The How and Why of Development and Use

HUMAN TOXICOLOGY PROJECT CONSORTIUM

ASCCT

SEMINAR OVERVIEW

- What are AOPs? *Kristie Sullivan, PCRM*

- Why are AOPs important, and how can they be useful? *Catherine Willett, HTPC*

- AOPs: Getting Started *Terry Schultz, University of Tennessee-Knoxville*

- Case study demonstrations

SEMINAR OVERVIEW

- **Constructing AOPs for Developmental Toxicities *Nicole Kleinstreuer, ILS, inc./NICEATM***

- Development of an AOP for skin sensitization and practical applications
Grace Patlewicz, DuPont

- Development and use of hepatic AOPs in the SEURAT project cluster
Mathieu Vinken, Free University Brussels
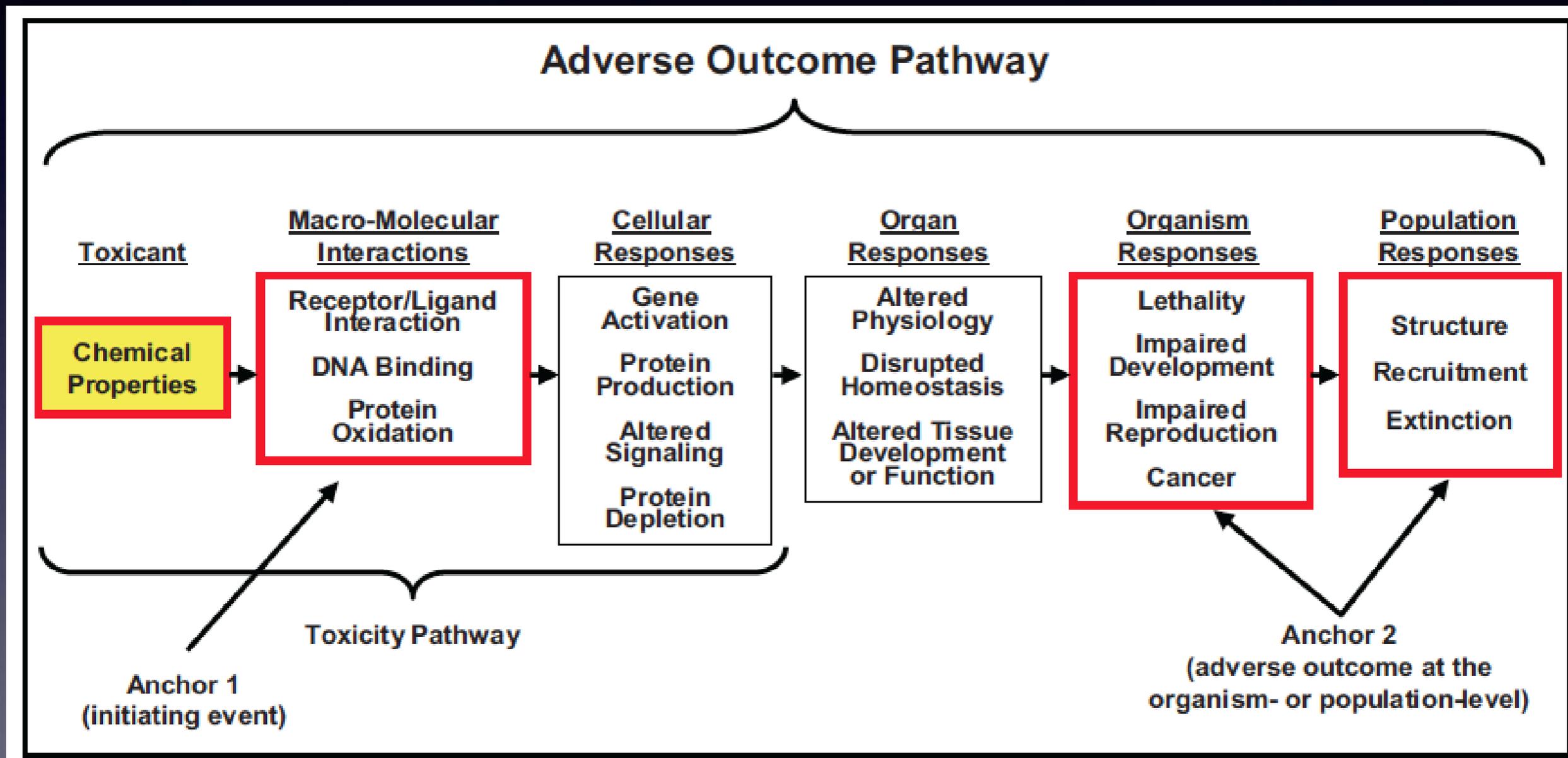
- Additional questions and discussion

A Conceptual Framework
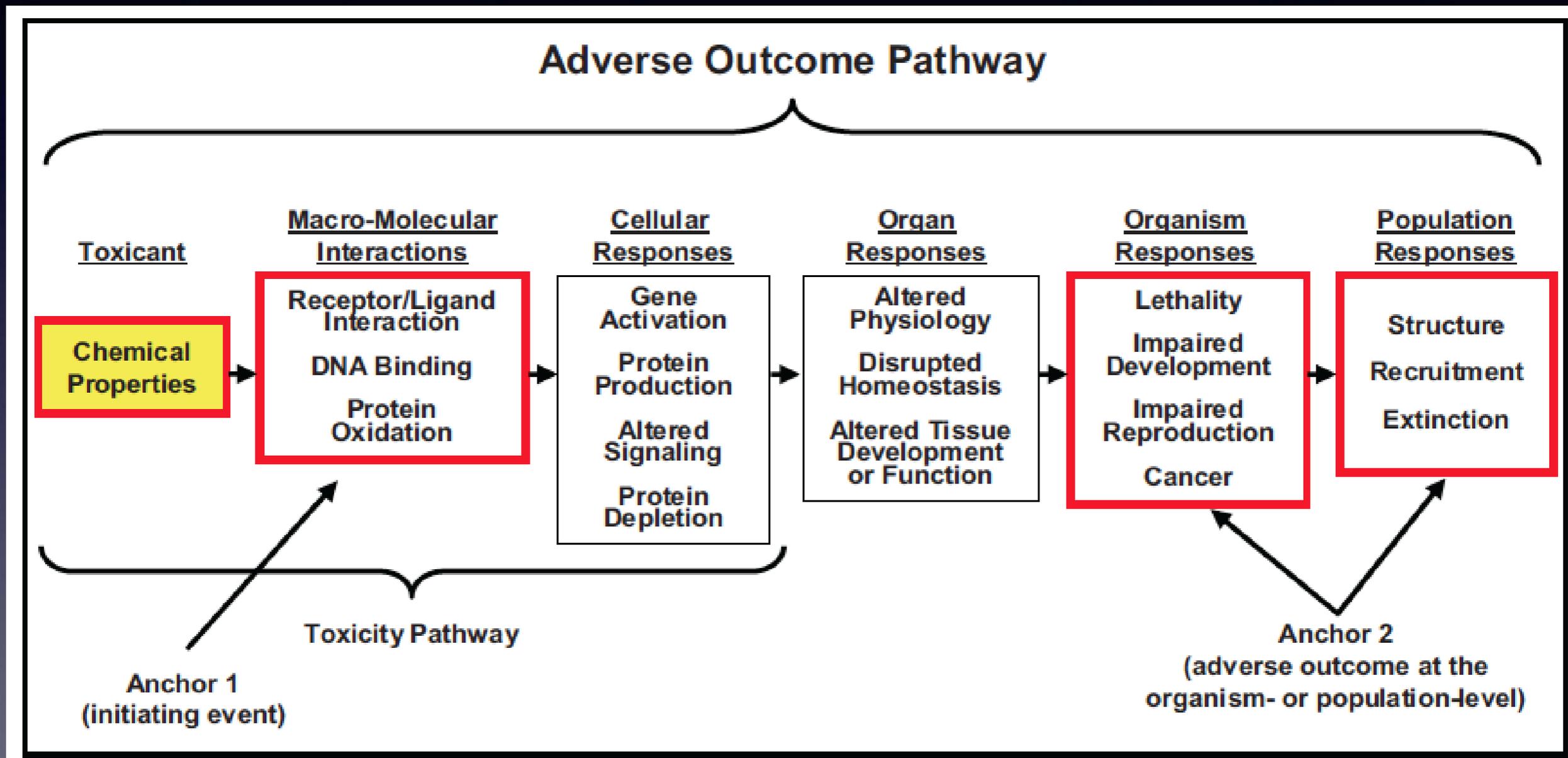

Ankley et al. 2010, Environ Tox Chem 29(3): 730-741

Ankley et al. Defintion

"An AOP is a conceptual construct that portrays existing knowledge concerning the linkage between a direct molecular initiating event (e.g., a molecular interaction between a xenobiotic and a specific biomolecule) and an adverse outcome at a biological level of organization relevant to risk assessment."
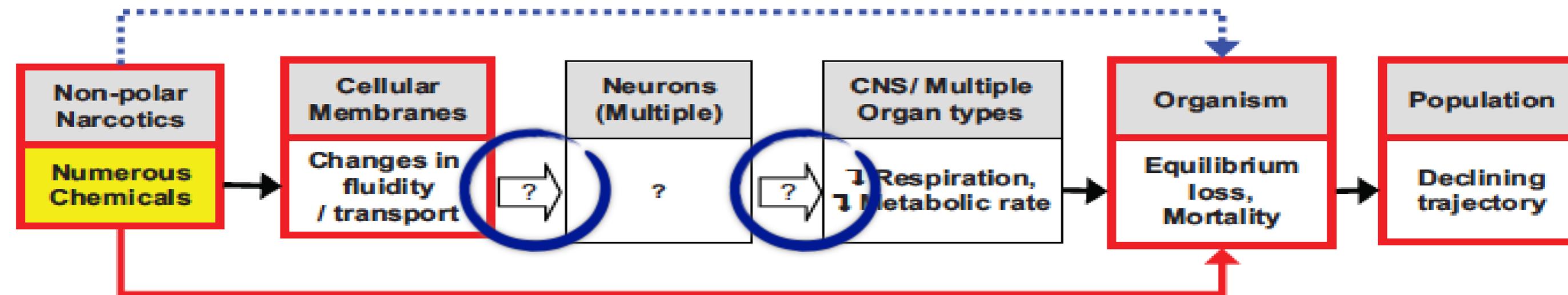
Historical Consideration

- In defining "AOP", Ankley et al. sought to incorporate the concepts of

  - toxicity pathway

  - mechanism of action

  - mode of action

- but to also provide more consistent terminology and a framework more relevant for risk assessment

- and to provide a structure for toxicological information across different levels of biological organization
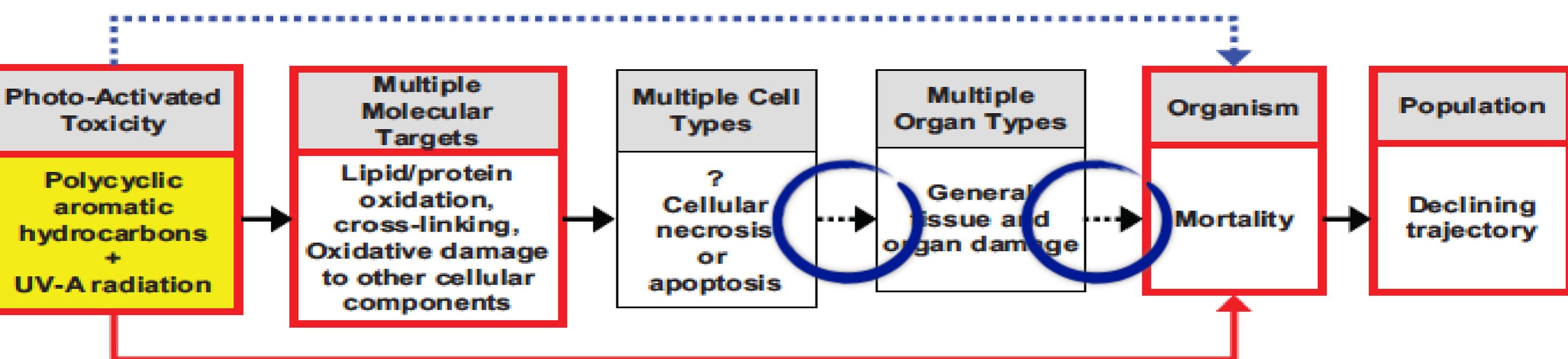
A Conceptual Framework

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AOP: *Narcosis – Baseline Toxicity*

Non-polar Narcotics	Cellular Membranes	Neurons (Multiple)	CNS/ Multiple Organ types	Organism	Population
Numerous Chemicals	Changes in fluidity / transport	?	↑ Respiration, ↑ Metabolic rate	Equilibrium loss, Mortality	Declining trajectory

AOP: *Photo-Activated Toxicity – Systemic Toxicity*

Photo-Activated Toxicity	Multiple Molecular Targets	Multiple Cell Types	Multiple Organ Types	Organism	Population
Polycyclic aromatic hydrocarbons + UV-A radiation	Lipid/protein oxidation, cross-linking, Oxidative damage to other cellular components	? Cellular necrosis or apoptosis	General tissue and organ damage	Mortality	Declining trajectory

KEY

→ Established mechanistic linkage with quantitative or semi-quantitative data

┅► Plausible linkage with limited data

→ (red) Empirical linkage based on quantitative exposure-response data

┅┅► (blue) Predictive model linkages based on chemical structure/property and quantitative exposure-response data

⇒? Hypothetical linkage

☐ Potential biomarker associated with exposure/response information