The Importance of Mode of Action in "Fit for Purpose" Assessment

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Outline

- Considering the NAS Report (as ***background***)
  - Science & Decisions: Advancing Risk Assessment
- ***Coordinating & Extending*** Specific Recommendations
  - Potential Contribution of Other (International) Initiatives
- Dose Response tailored to Need
  - Appropriate consideration of Mode Of Action (MOA) in this context
  - Tiered, “Purpose Oriented” Assessment
    - examples
  - Implications for recommendation re “deviation from default”

NAS Committee:Advancing Risk Assessment - Background

- ***"Chemical Risk assessment at a crossroads"***
- Facing substantial challenges, e.g.,
  - long delays in completing complex risk assessments, some of which take decades
  - lack of data
  - the need to address the many unevaluated chemicals in the marketplace
- Recommendations for practical improvements to the U.S. Environmental Protection Agency (EPA)
  - Shorter (2-5 y) and
  - longer (10-20 y) term

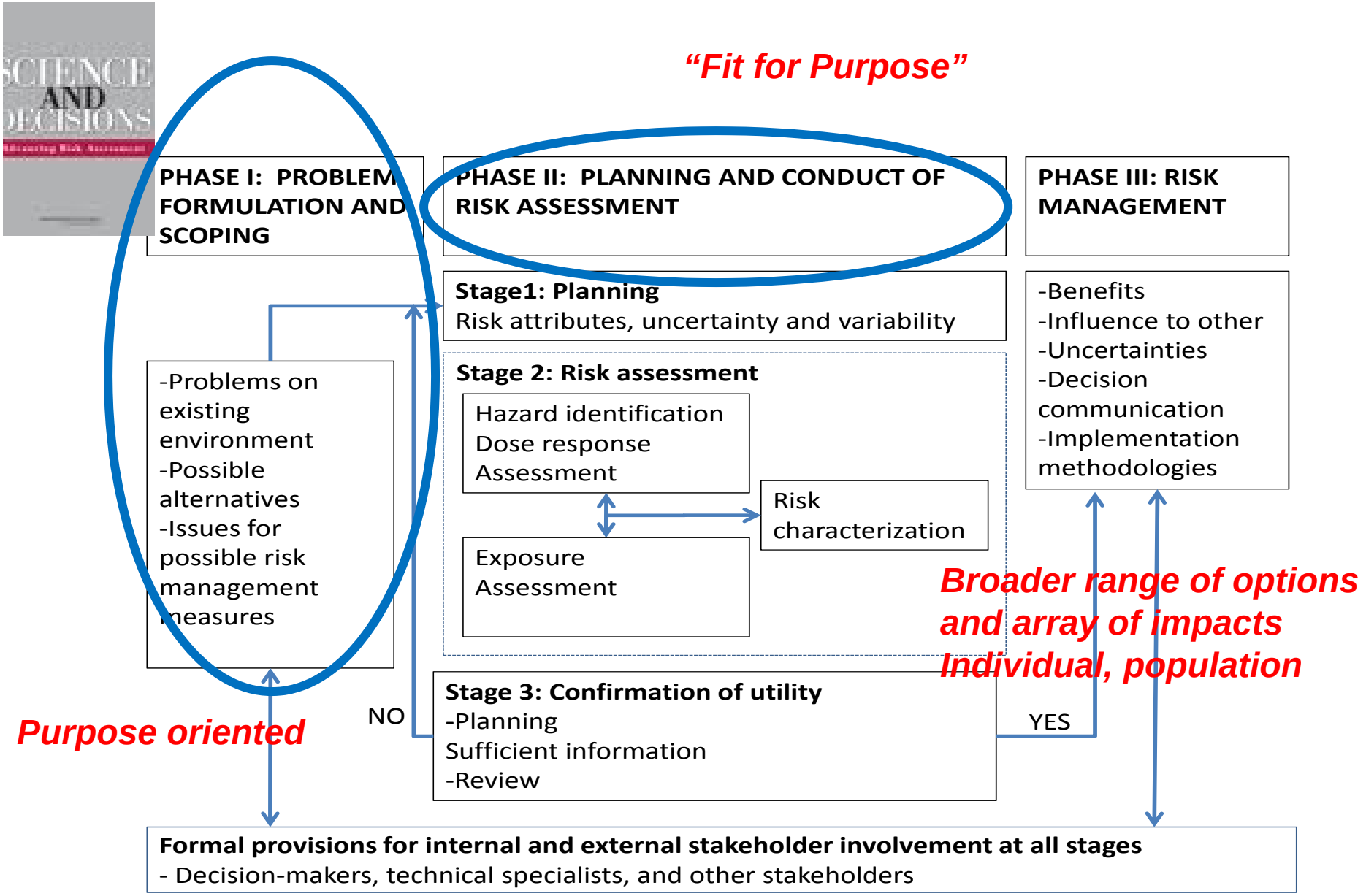


Figure S-1 A framework for risk based decision making that maximizes the utility of risk assessment

Unified Approach to Default Dose Response Assessment

- "A consistent approach to risk assessment for cancer and non-cancer effects is scientifically feasible and needs to be implemented"
- "Because the RfD and RfC do not quantify risks for different magnitudes of exposure…their use in risk-risk and risk-benefit comparisons and risk management decision-making is limited"
  - This seemed to prevail over discussions related to mode of action

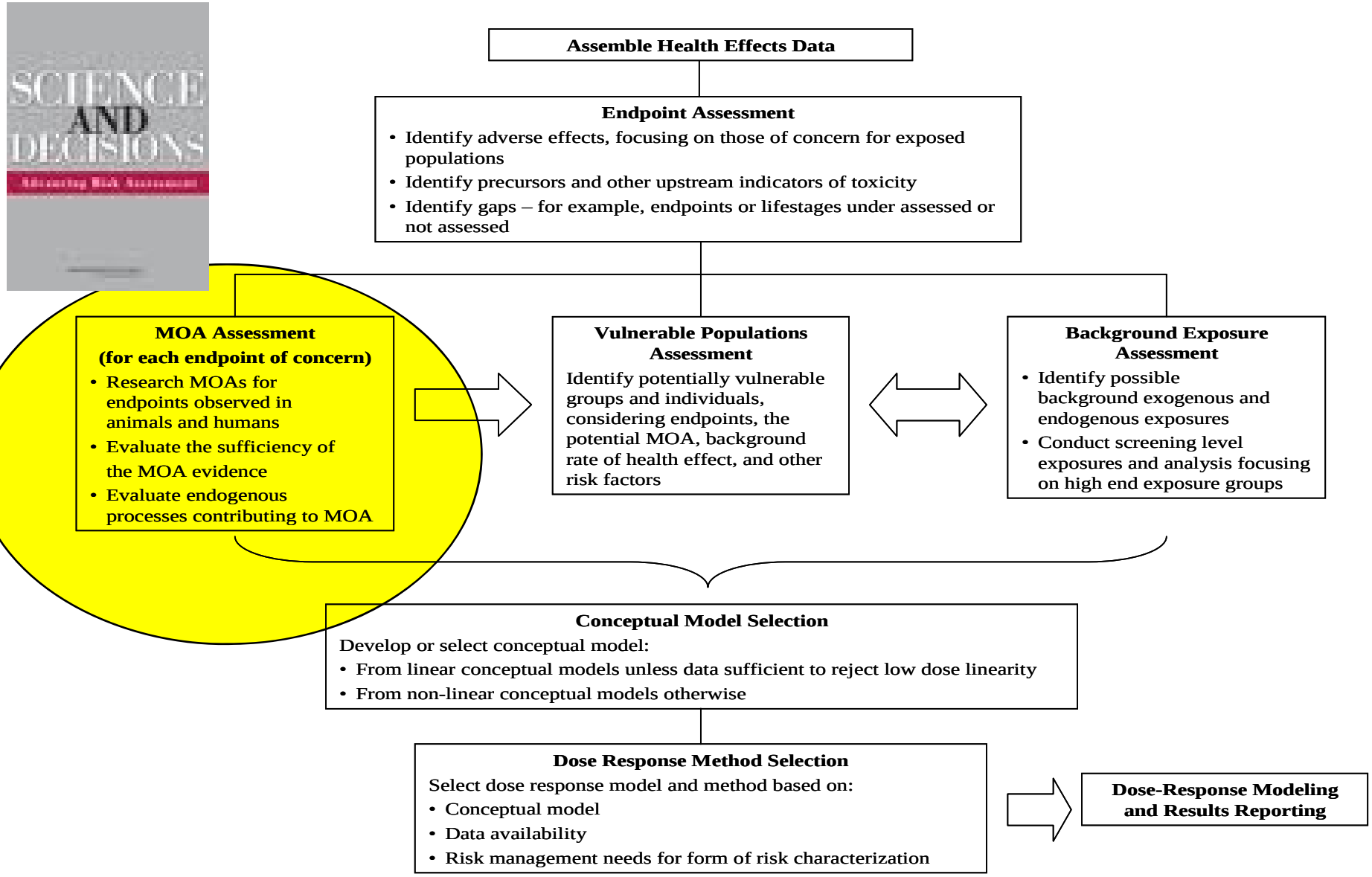
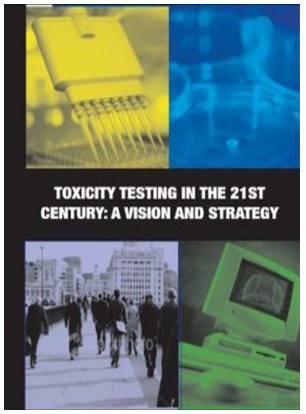


Figure 5.8 New unified process for selecting approach and methods for dose-response assessment for cancer and noncancer .

Reconciling Recommendations on Efficiency, Problem Formulation & Dose-Response

- Mode of action is the critical basis to enable us to be predictive
- The need for more efficient assessment as a basis to address the many unevaluated chemicals in the marketplace identified by the Committee as one of the more significant challenges requires:
  - Moving to more predictive, mode of action based approaches
- Requires transitioning to a change in paradigm to focus early on information relevant to MOA

U.S. NRC Toxicity Testing in the 21st Century



Dose Response Assessment

Chemical Characterization

Mode of Action

Compounds

Metabolite(s)

Assess Biological Perturbation

Affected Pathway

Measures of dose in vitro

Dose Response Analysis for Perturbations of Toxicity Pathways

Population Based Studies

Calibrating in vitro and human Dosimetry

Exposure Guideline

Human Exposure Data

Hazard Characterization

Exposure Assessment

Risk Characterization

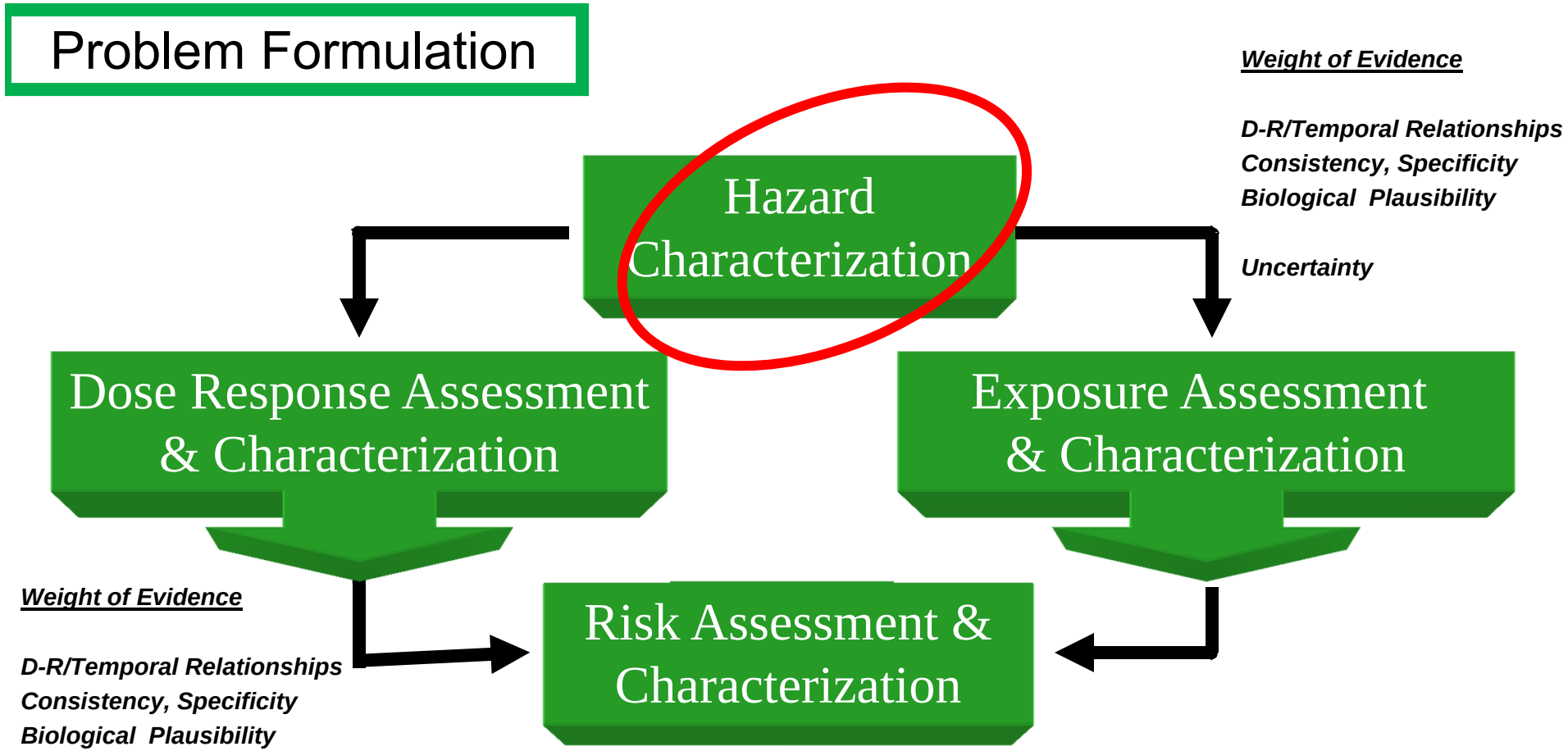
The Need to Evolve Risk Assessment

- Better predictability
  - Broader application to larger numbers of chemicals
- Higher relevance
  - Moving from default to more biologically based to more accurately estimate risk
    - Relevant pathways
    - Relevant doses
    - Relevant species
- Requires early assimilation in a mode of action context
- More weight of evidence for dose-response
- Regulatory risk assessment needs to provide the impetus and market for more progressive testing strategies

Moving from "Default" in Risk Assessment

- The vast majority of assessments are currently based on default assumptions
  - i.e., with no understanding of how the chemical induces effects
- Often, mechanistic data do not contribute directly to dose-response analysis & risk characterization
  - Limits our capability to be predictive
- We also don't use much of the data on dose-response
  - Focus on the lowest effect level in the longest term study
- A function of:
  - Focus on ***identification*** rather than ***characterization*** of hazard

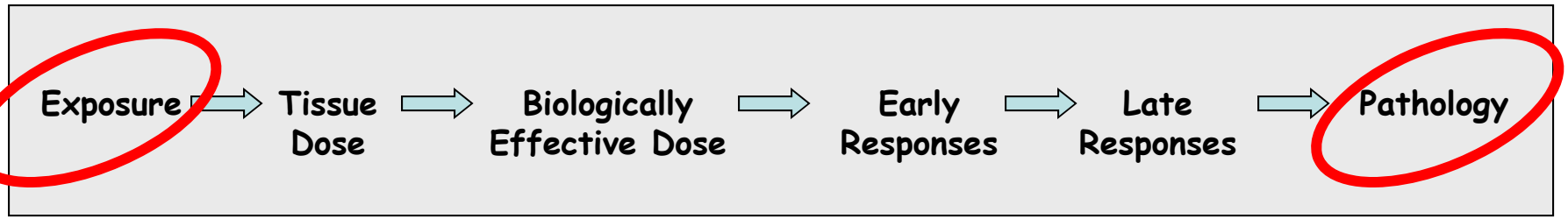
The Need to Move On
Revised NAS 4-Step Paradigm



Hazard Characterization (early focus not only on effect but how the effect is induced - mode of action)

Exposure-Response Continuum

Mode of Action involves identification of several key events between exposure and effect



Physiologically Based Pharmacokinetic Models

Tissue Dose Metric

Mode of Action

Toxicokinetics

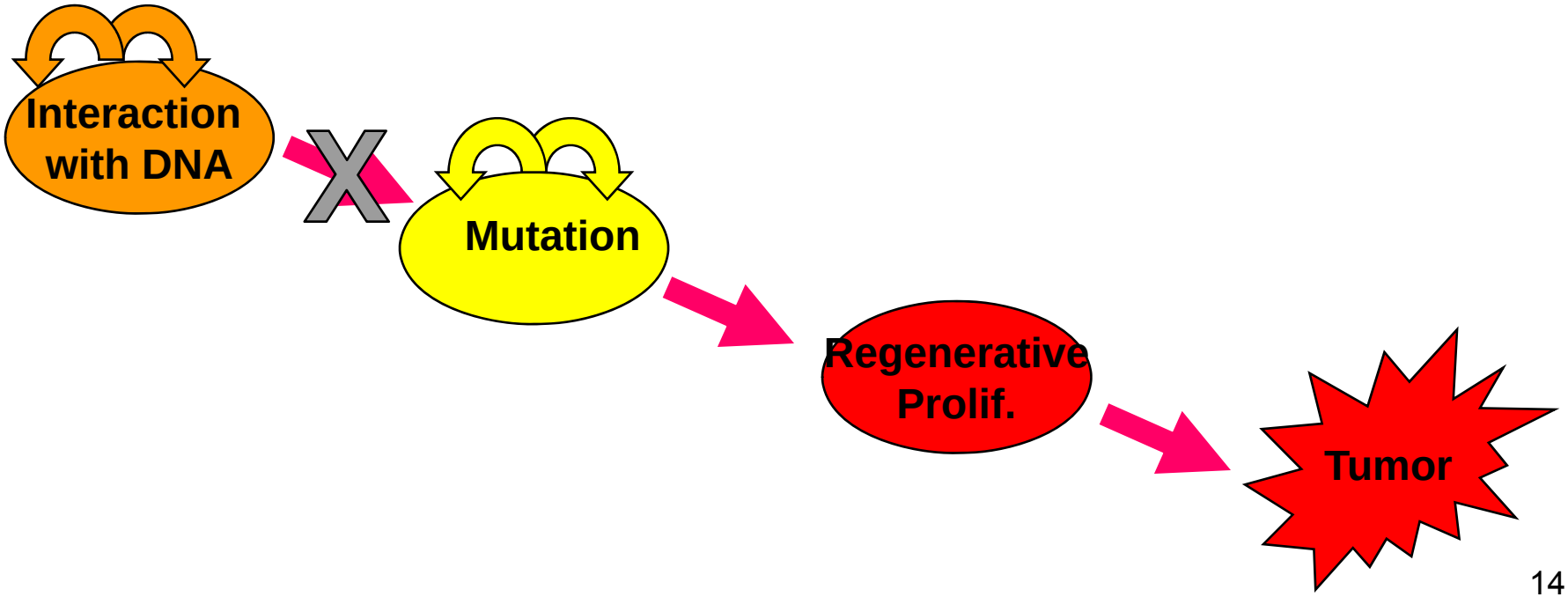
Toxicodynamics

Transitioning the Risk Assessment Community

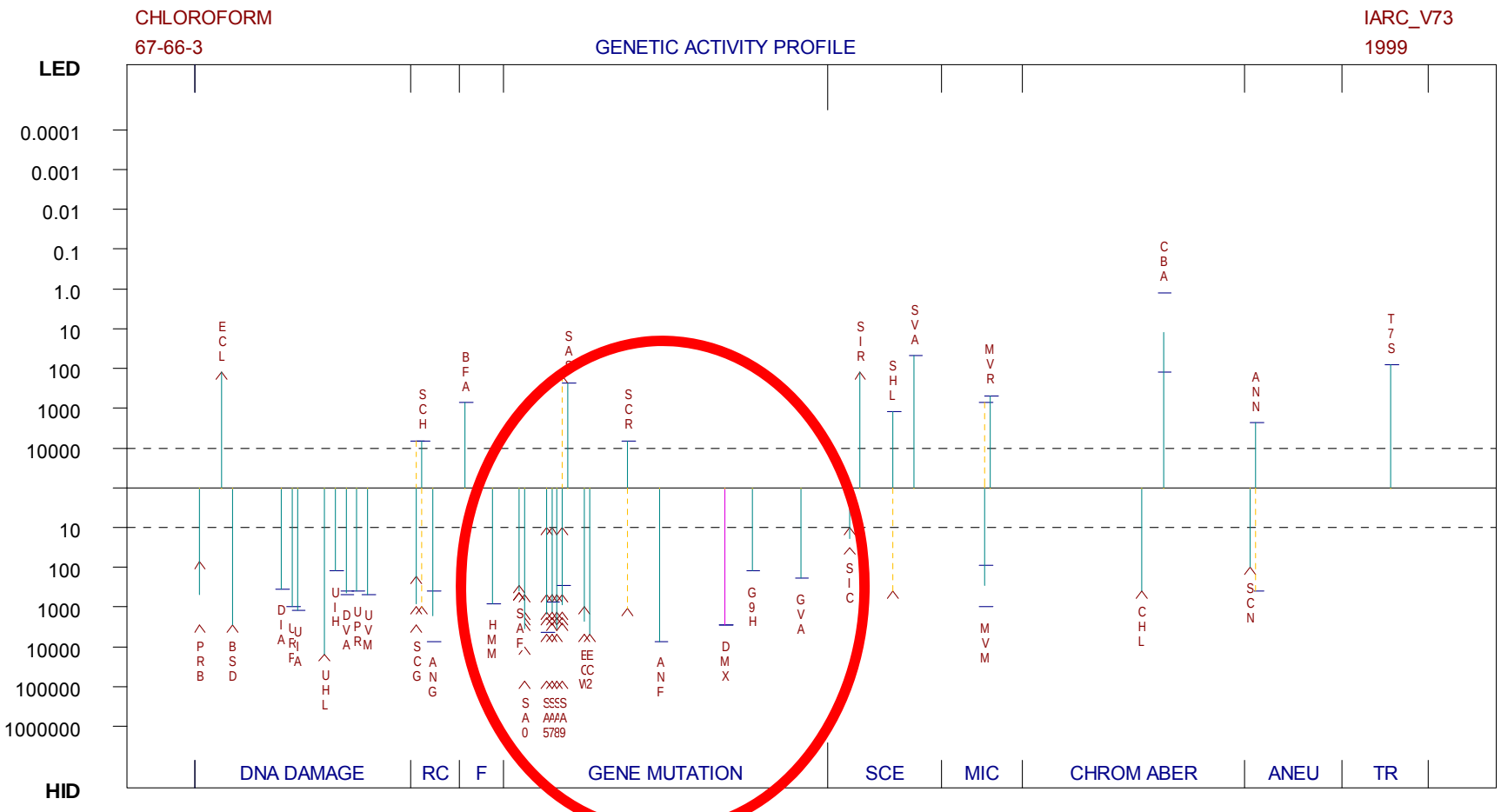
- Importance of early assimilation of data to consider patterns (including dose-response) in context of mode of action
  - mechanistic underpinning is critical
  - e.g., integration of data on genotoxicity and cancer to consider likelihood of a Mutagenic Mode of Action
- Potential contribution of predictive (Q)SAR tools/genomic data
  - Need for mechanistic underpinning
- Need to look across chemicals
  - Combined exposures

What is a Mutagenic Mode of Action for Tumours?

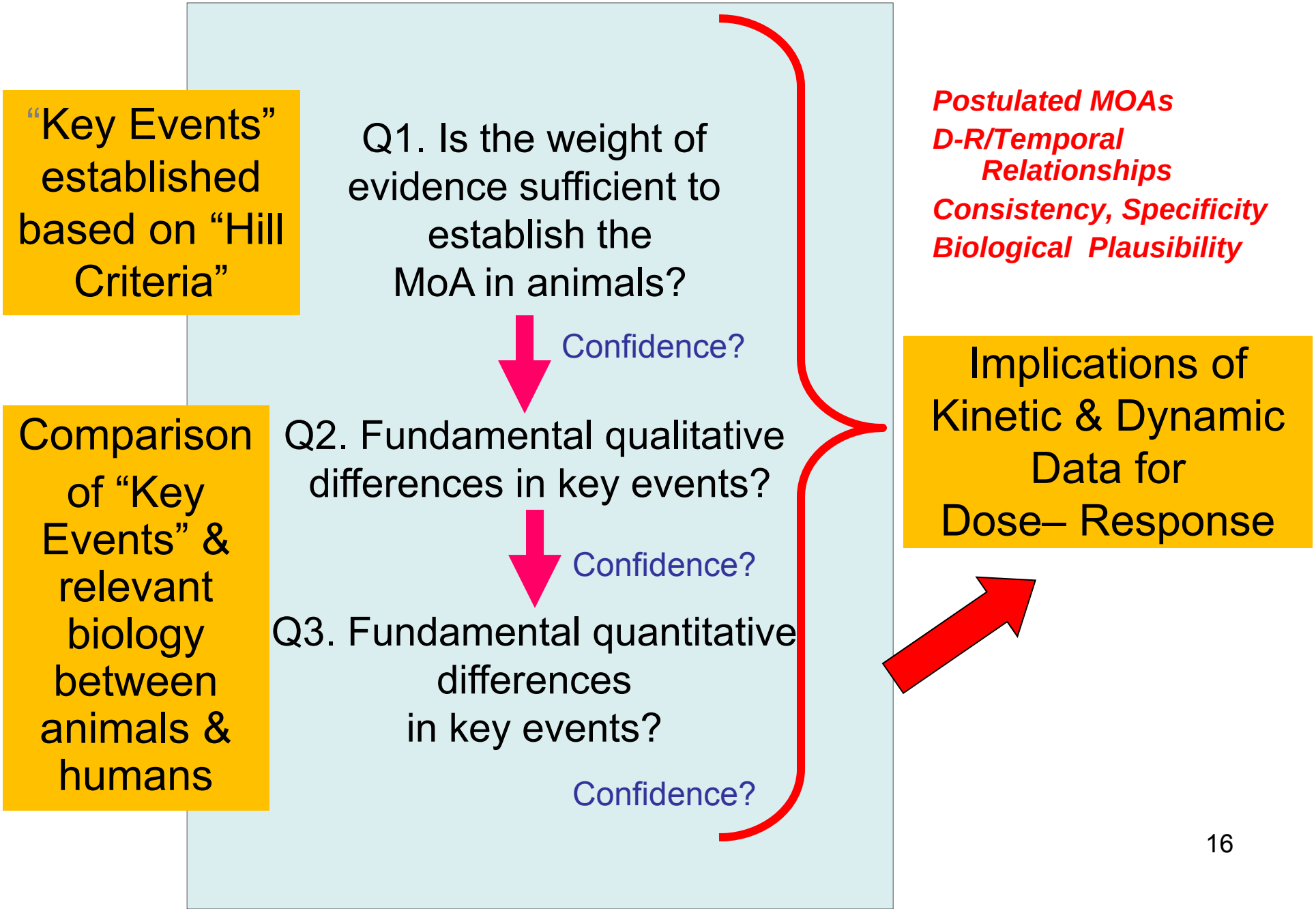
- Genotoxicity and Cancer ≠ Mutagenic Mode of Action
- Tumours induced by a mode of action where mutation is an early and influential primary key event
- Early consideration (integration) of patterns of data in a hazard characterization context (MOA) can help



Genetic Activity Profile C



IPCS/ILSI MOA/HR (WOE) Framework



Examining an Individual Key Event (KEDRF)

Considering impact on dose-response of factors that determine outcome of individual events:

- Dose (level, frequency and duration)
- Physiological mechanisms (e.g., homeostasis, repair, immune response, compensatory pathways)
- Host factors (life-stage, disease state, genetic makeup, nutritional status, co-exposure)

MoA: Implications for Interspecies Differences and Human Variability

PbPK Modeling or Simple Kinetic Parameters

Interspecies Kinetics (4)	Human Variability in Disposition (3.2)
Interspecies Dynamics (2.5)	Human Variability in Sensitivity (3.2)
Default = 10X	Default = 10X

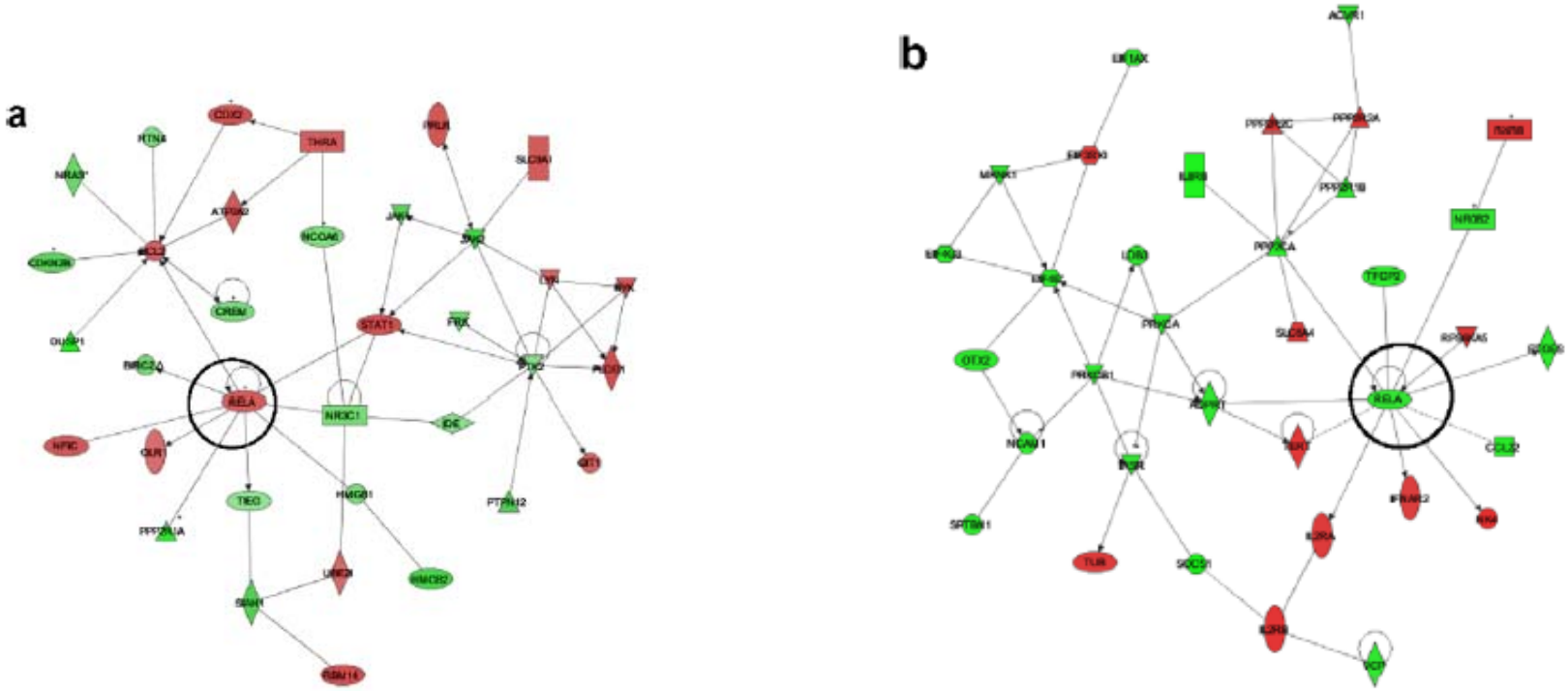
In vitro data in target tissue

International Guidance for CSAF available since 2005; Draft EPA Guidance on DDUF now available

For Example: Integrating Information from Evolving Technologies Proposed Key Events

- Nuclear receptor activation (***transcriptional profile)***
- Induction of P450 enzymes (***transcriptional profile*** confirmed by ***biochemistry***)
- Inhibition of Cyp 51 (site of action of fungicide)
- Decreased cholesterol synthesis (***transcriptional profile*** confirmed by ***clinical chemistry***)
- Mitogenesis (***histology***)
- Altered mitosis (suggested by ***inhibition of cholesterol synthesis***)
- Oxidative stress (***transcriptional profile***)

Chemical D - Biological Interactions amongst Genes in a) Rat and b)Human Urothelial Cells



Downregulated genes **Upregulated genes**

Similar networks altered suggesting common responses across species.

Sen et al., Toxicol In Vitro 21:1513-1529, 2007

Focus on MOA/HR Analysis Increasing predictive capacity and utility of risk assessment

- Drawing maximally and early on the most relevant information
  - data on kinetics/dynamics and the broader biology base
- Transparency
  - Rigor & consistency of documentation
  - Explicit separation of science judgment on weight of evidence from science (public) policy considerations
- Doing the right research/testing
  - Chemical Specific: Iterative dialogue between risk assessors/researchers
  - Developing more progressive testing strategies

Recent Developments
ECETOC Workshop, October, 2009

- Catalogue documented modes of action for human health
  - Connecting ongoing initiatives
- Map against chemical categories
- Collect & compile information on early key events as predictors
- Develop guidance for testing and assessment

Recent Developments (cont'd)

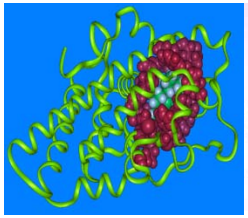
- Extending MOA and MOA/HR framework concepts as the coordinating construct between:
  - The ecological & health risk communities
  - The QSAR modelling and risk assessment communities
    - OECD workshop in December, 2010
    - IPCS coordinating steering group on mode of action (constituted in October, 2010)
      - Revision of the MOA/HR framework – evolving methodologies
      - Database on MOAs/key events/"codification" of Bradford Hill criteria
      - Training

Application to Levels of Organization Based on Source to Outcome

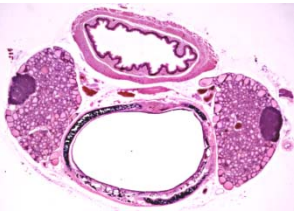
Source

Environmental Contaminant

Exposure



Molecular Initiating Event



Cellular Effects

Individual

Population

Community

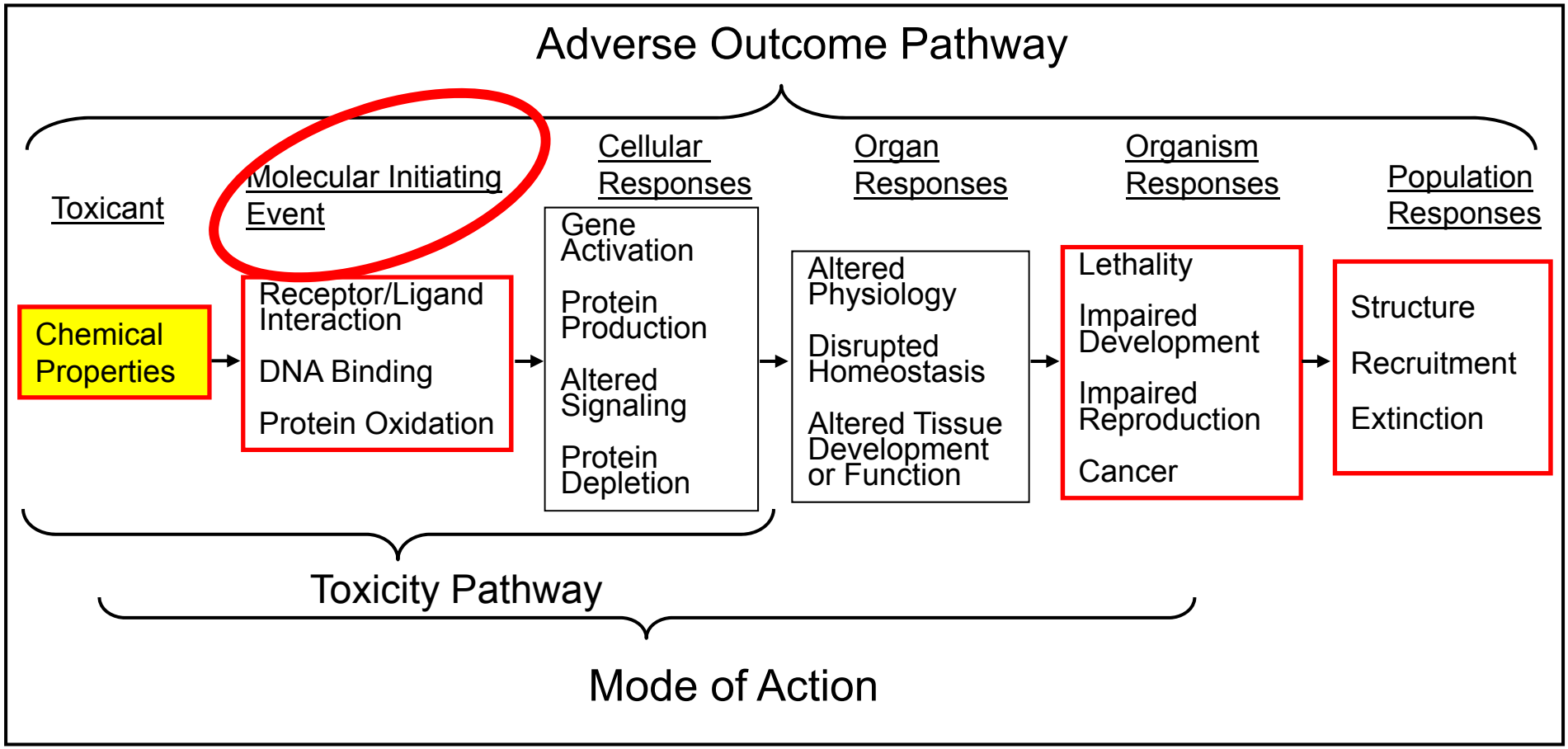
Toxicity Pathway

Mode of Action

Adverse Outcome Pathway

Source to Outcome Pathway

General Template



Modified from Ankley et al 2010

Terminology

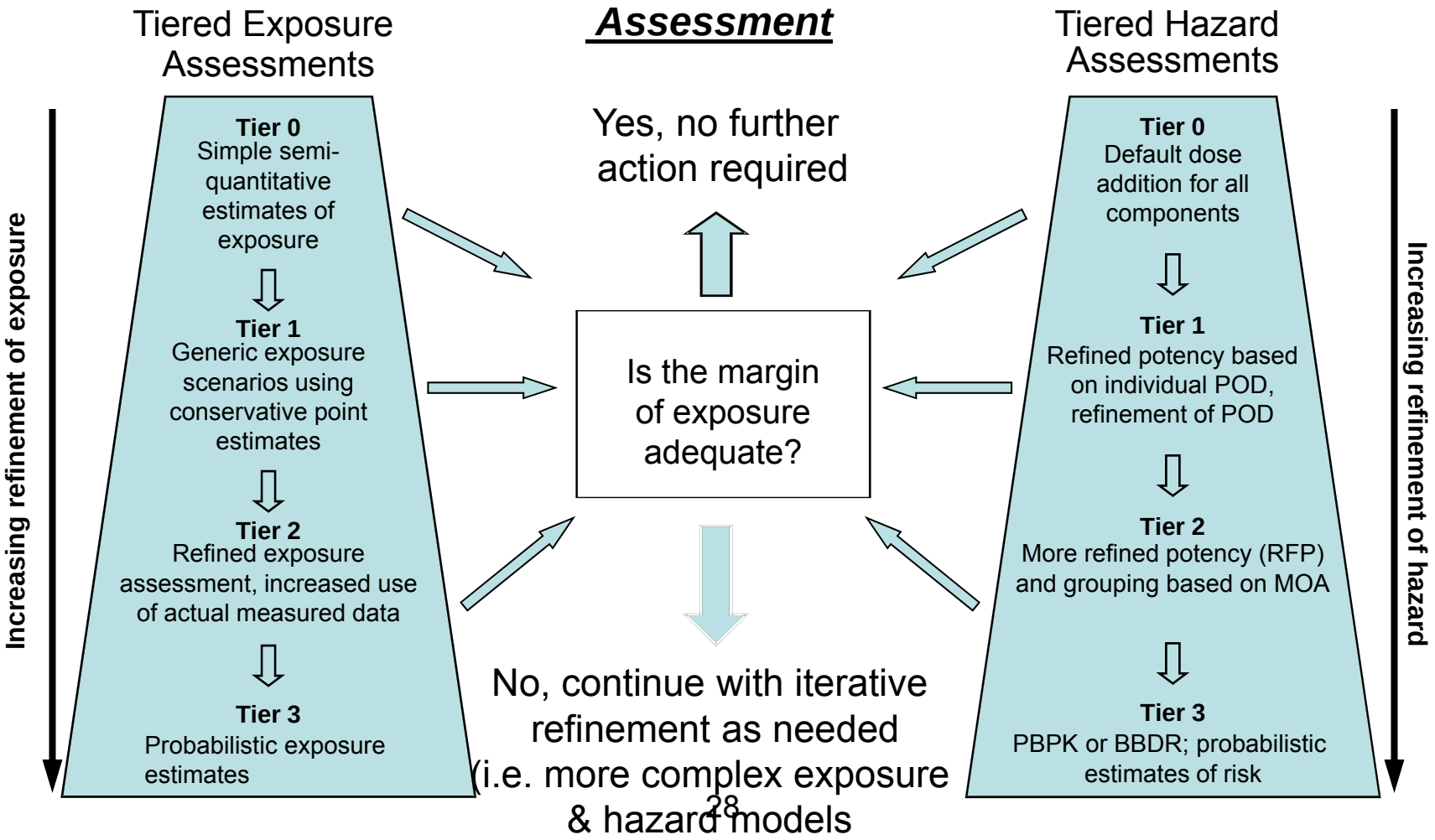
- Key Event/Mode of Action
  - More ***traditional biomarkers*** of exposure and effect with mechanistic underpinning, e.g.,
    - Specific metabolic transformation
    - Cytotoxicity
  - Resulting from perturbation of toxicity pathways
- Molecular Initiating Event
  - ***Initial*** point of ***chemical-biological interaction*** with the organism that starts the pathway
- Adverse Outcome Pathway
  - Linkage between the molecular initiating event and the adverse outcome at the individual or ***population*** levels

Continuing Improvement of MOA/HR Analysis

- Better characterization of uncertainty vs. yes/no decisions
- Earlier/more informed options analysis for potentially relevant MOAs
  - ***At relevant dose levels***
- Better integration of D-R/temporal concordance for key events with subsequent D-R analysis for risk characterization
- Integrating chemical-related information with disease process
  - Moving to a more systems-biology understanding of toxicity
    - cascading failures of control mechanisms
- Considering process/engagement
  - multidisciplinary

Problem Formulation

Nature of exposure?
Is exposure likely?
Co-exposure within a relevant timeframe?
Rationale for considering compounds in an assessment group?



Selection and Use of Defaults

- "EPA should develop clear, general standards for the level of evidence needed to justify the use of agent-specific data and not resort to default"
- This is helpful to increase transparency as a basis to separate science ***judgment*** from science ***policy***
- ***However:***
- It rather sets up "default" as representing something other than:
  - what we use when we don't have more informative data about how chemicals induce their effects
- Fails to acknowledge the significant contribution that EPA/international community have made in this area
  - MOA/HR
  - CSAF/DDUF

Forward Looking Assessment

- Public problem formulation with proposal for “fit for purpose” assessment
  - Assimilated Overview of Data
  - Proposed Focus
  - Efficiency
  - Proposed Process
- Tiered assessment options drawing on predictive tools in early tiers
  - Importance of mechanistic underpinning

More Information?

Evolution of the ILSI/IPCS Frameworks – Mode of Action

- Meek & Klaunig (2010) Chemico-Biological Interactions 184:279–285

The Key Events/Dose Response Framework

- Boobis et al. (2009) Crit Rev Food Science Nutrition 49(8): 690 – 707

Guidance for CSAF

- ***http://www.who.int/ipcs/methods/harmonization/areas/uncertainty/en/index.html***

Combined Exposures

- Meek et al. (2011) Reg Tox Pharm 60: S1-S14

ECETOC Workshop

- Critical Reviews in Toxicology, 2011; 41(3): 175–186

WHO/IPCS Harmonization Initiative

- http://www.who.int/ipcs/methods/harmonization/index.html