AOPs and Regulatory Decisions: Problem Formulation, Development and Acceptance

AOP WORKSHOP 09/04/14

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Disclaimer

- The views expressed in this presentation are those of the author and do not represent the policy of the U.S. EPA.

So What Is EPA Policy?

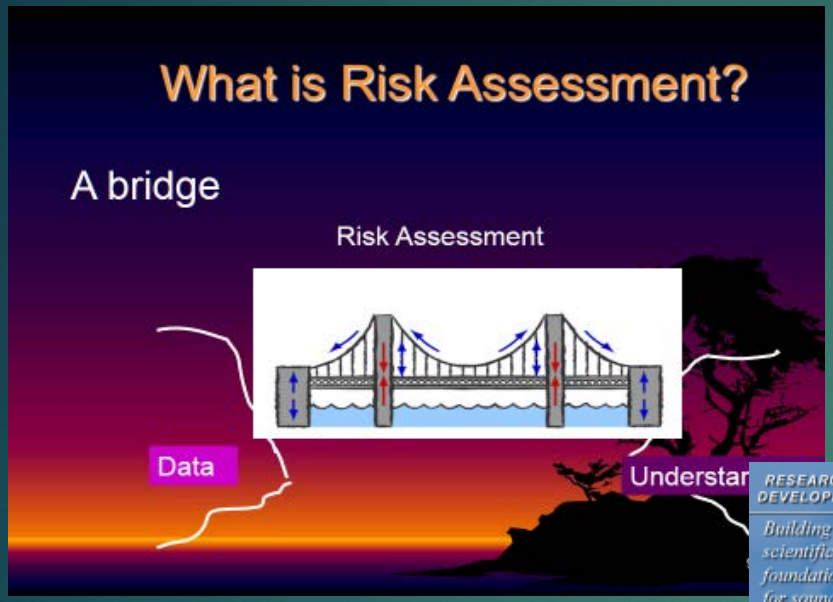
- Science Policy
  - Defaults, methods, Guidelines
  - Used when there are data or methodology gaps
  - Peer reviewed
  - Lots of documentation, which is publicly available
- Policy based on science
  - May be set by EPA Executive Level
  - Generally involves regulations or other risk management choices; science is peer reviewed, action involves public comment; May be subject to Federal Advisory Committee Act
  - Lots of documentation; may be docket; publicly available

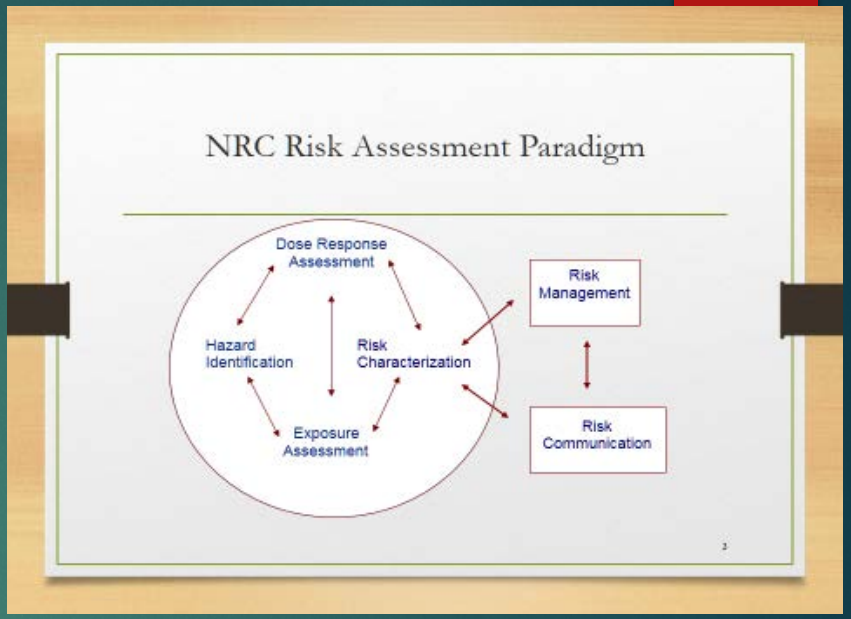
Examples

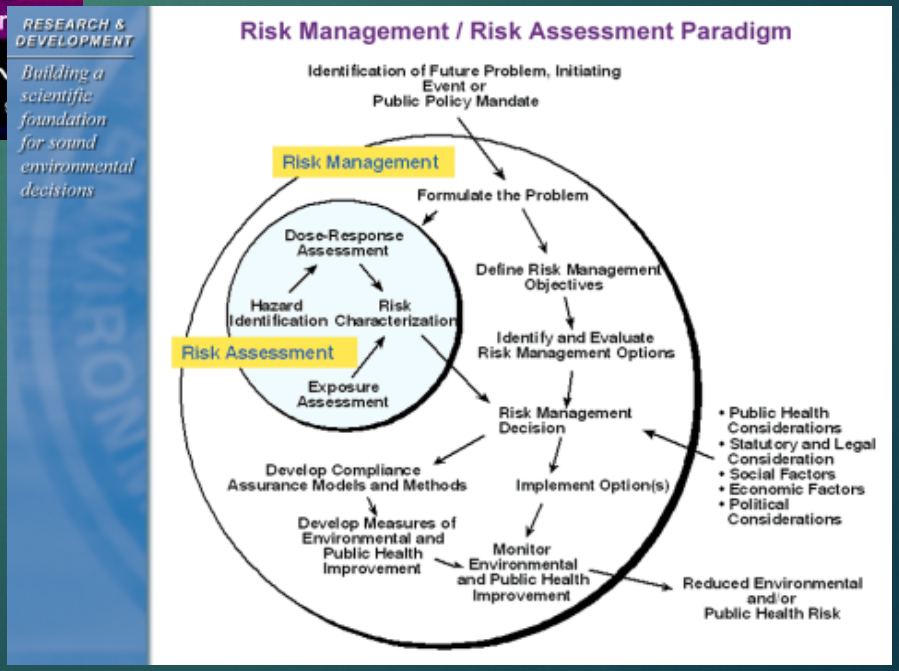
- Science policy
  - *Cancer Guidelines* 2005
  - Set a reference dose for effects which are likely to have a threshold
  - Quantitative adjustment to cancer risk for early life exposure
  - Animal data are relevant to humans unless demonstrated otherwise

These all deal with risk assessment

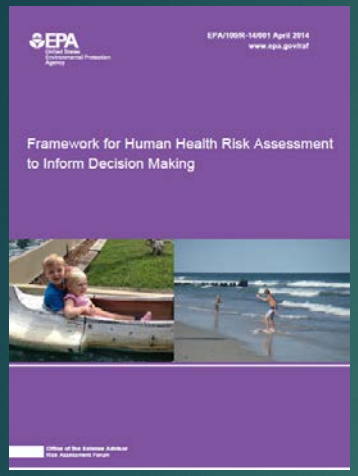
Risk Assessment



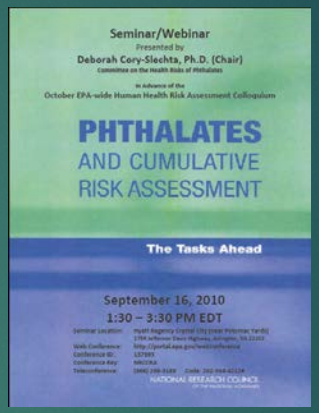


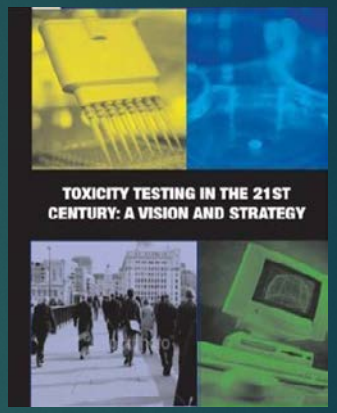


A lot has changed since ‘83



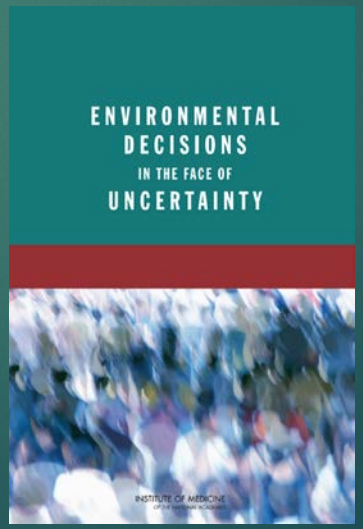
Exposure Science in the 21st Century: A Vision and A Strategy

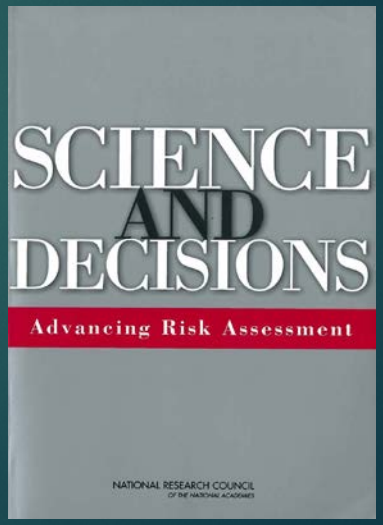




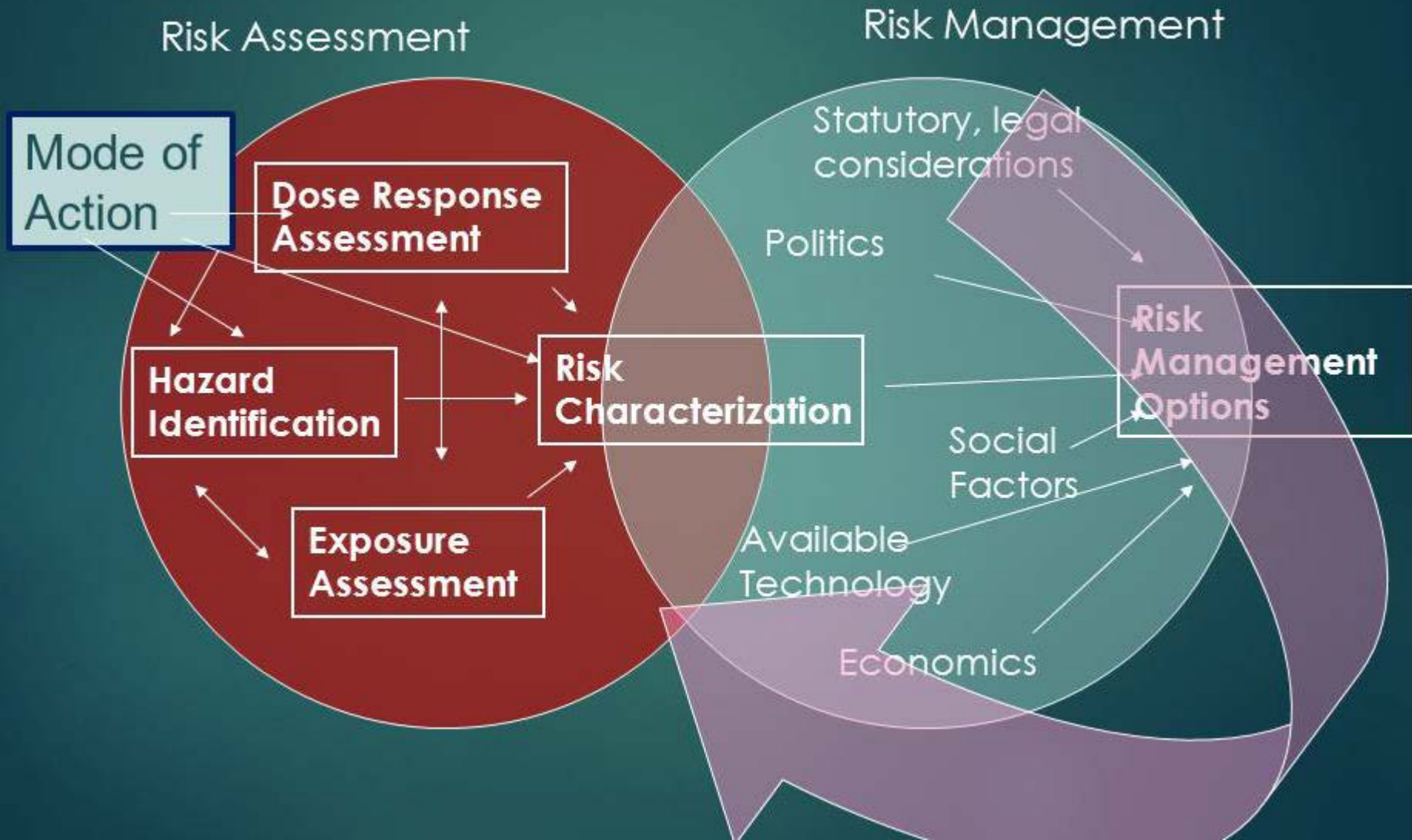
IPCS FRAMEWORK FOR ANALYSING THE RELEVANCE OF A CANCER MODE OF ACTION FOR HUMANS

World Health Organization



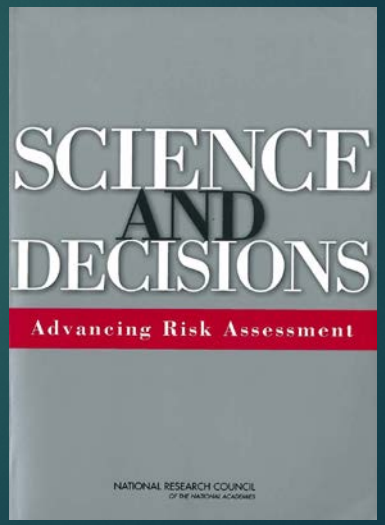


’83 Risk Assessment Paradigm ’14?



Why Do Risk Assessment?

- ". . . risk assessment should be viewed as a method for evaluating the relative merits of various options for managing risk . . . " (Science and Decisions 2009)
- To provide support for decisions to protect public health and the environment.
  - Complex and controversial
  - Risk assessment summarizes the science



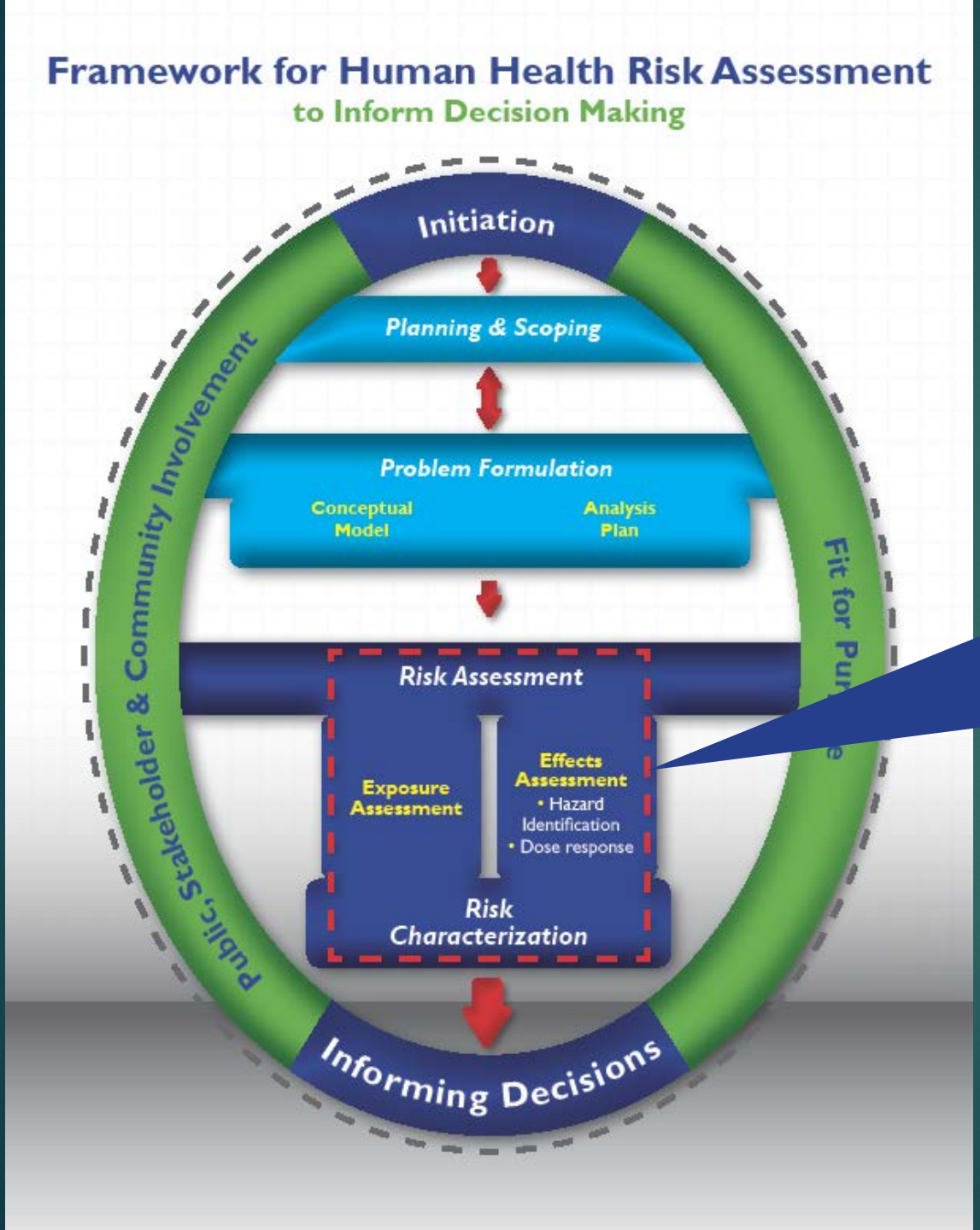
TAKE HOME MESSAGE # 1: It's all about better decisions

- Committee recommends an important extension of the Red Book model—that risk assessment should be viewed as a method for evaluating the relative merits of various options for managing risk rather than as an end in itself.
- Risk assessment should continue to capture and accurately describe what various research findings do and do not tell us about threats to human health and to the environment, but only *after* the risk-management questions that risk assessment should address have been clearly posed, through careful evaluation of the options available to manage the environmental problems at hand.

Thomas Burke; presentation 09/10

NRC Silver Book Recommendation

- NRC Silver Book recommendation (Chapter 8 “Improving Utility of Risk Assessment”)
  - *To make risk assessments most useful for risk management decisions, the committee recommends that EPA adopt a framework for risk-based decision-making . . . that embeds the Red Book risk assessment paradigm into a process with initial problem formulation and scoping, upfront identification of risk-management options and use of risk assessment to discriminate among these options.*



Risk Assessment in the Federal Government: Managing the Process (NRC 1983)

The Red Book Risk Assessment Paradigm showing by the red dashed lines.

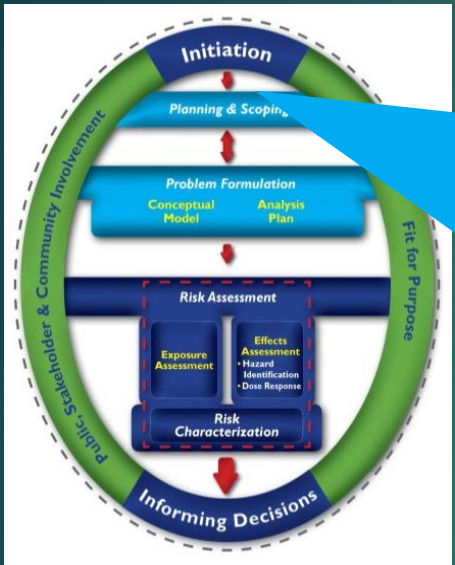
Overarching Considerations

Children's Environmental Health Protection

Cumulative Risk Assessment

Environmental Justice

Sustainability



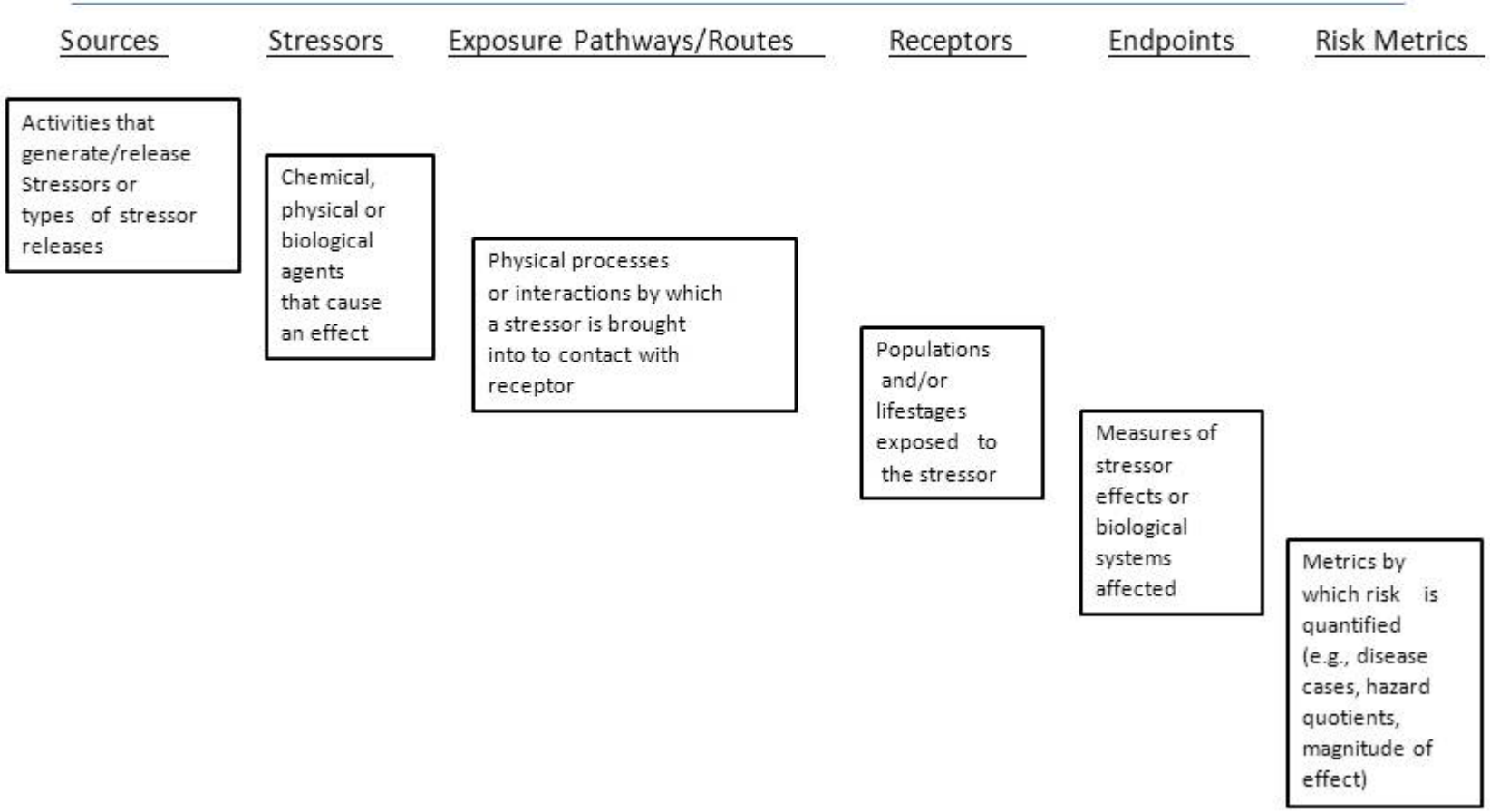
Key Considerations for Planning and Scoping

- What decision is to be informed by risk assessment, when is the decision anticipated, and what are the risk management options?
- What legal/statutory requirements affect risk management options and level/type of analysis?
- What other considerations (e.g., environmental justice, life stage, cumulative risk, sustainability) or countervailing risks may influence risk management options and analyses?
- What assessments (e.g., risk, economic) are needed to address decision-making needs?
- What expertise, resources and timelines are available to conduct the assessments(s)?

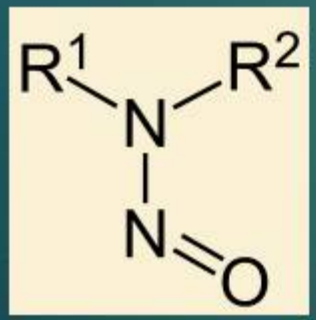
Problem Formulation

A Generalized Conceptual Model

(adapted from USEPA, 2002; 2003)

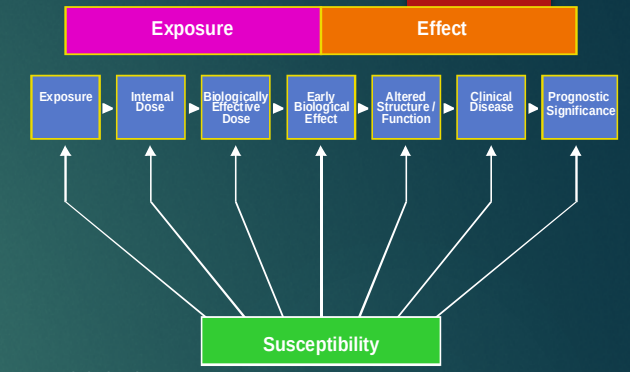


Sources Pathways/ Routes	Stressors	Exposure	Receptors	Endpoints	Risk Metrics
Drinking water disinfection	Variable mixture nitrosamines; dependent on treatment & source water.	Ingestion of nitrosamine mixture in drinking water	Consumers of drinking water; includes sensitive populations &life stages	Cancer, any site or type	Combined risk of cancer from subset nitrosamines in mixture



Conceptual Model
Nitrosamines in Drinking Water

How high the bar?



Source: Schulte (1989).

- Several continua
  - Increasing cost – economic, social
    - Lower → Higher
  - Voluntary action → Command and control
  - Information → Regulation
  - Prioritizing research → Required testing

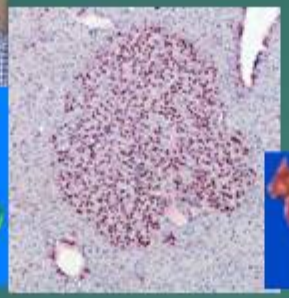
  - Less evidence → Lots of evidence
  - AOP seems plausible → "Validated"

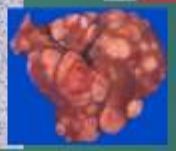
Application to Levels of Organization Based on Source to Outcome

Source

Environmental Contaminant

Exposure





Molecular Initiating Event

Cellular Effects

Individual

Population

Community

Toxicity Pathway

Mode of Action

Adverse Outcome Pathway

Source to Outcome Pathway

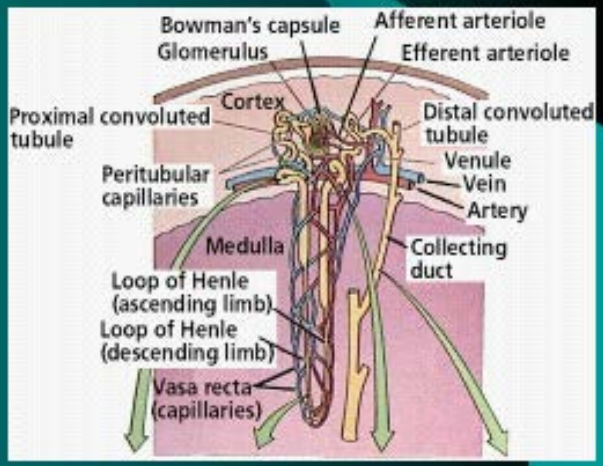
Uses of AOP -- Hazard ID

- Relevance of animal data: e.g. α2μ globulin

α2u-Globulin

- The main story
  - Protein produced by male rats
  - MOA– functional changes in epithelial cells of proximal tubules

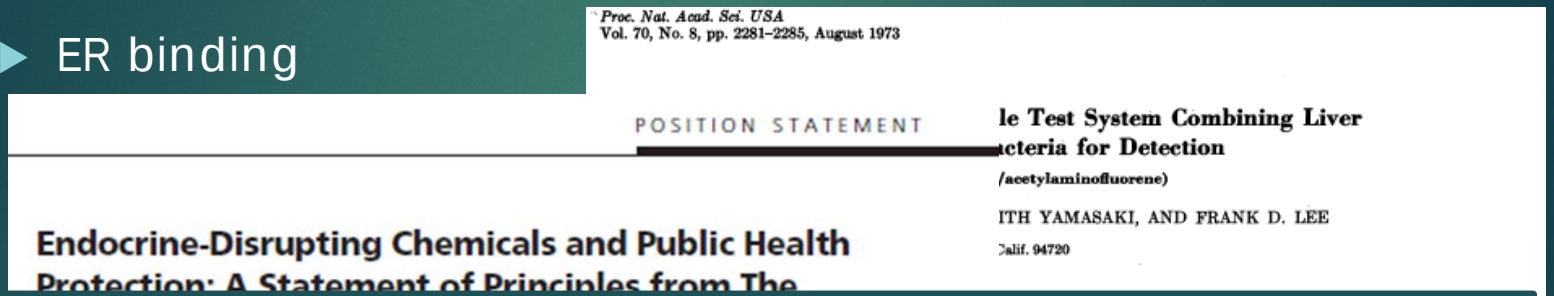
- Hyaline droplets accumulate
- Tubule cell degeneration
- Regenerative cell proliferation
- Expansion of initiated renal tubule cells



8/27/2014

Uses of AOP -- Hazard ID

- Prediction of AO from early step in AOP
  - Genotoxic carcinogens
  - ER binding

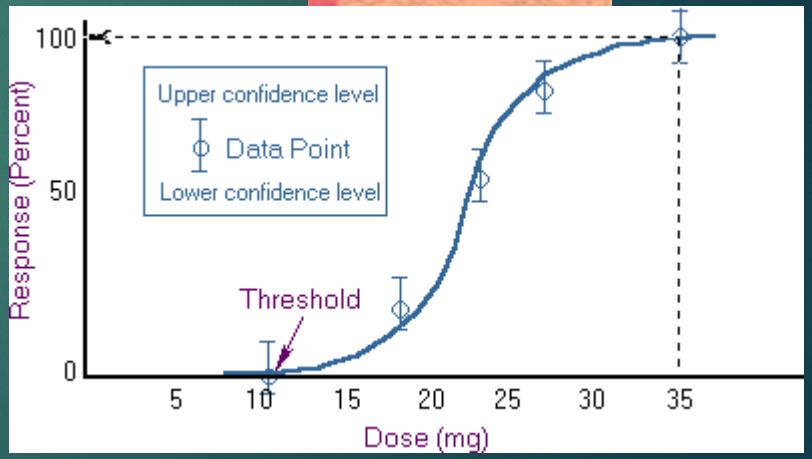


"We propose that the ability of a chemical to interfere with hormone action is a clear predictor of adverse outcome, much like mutagenicity is a predictor of carcinogenicity." p. 4099

"Environmental chemicals that interfere with any aspect of hormone action should be presumed to cause adverse effects." p. 4107. (Zoeller *et al.* 2012.)

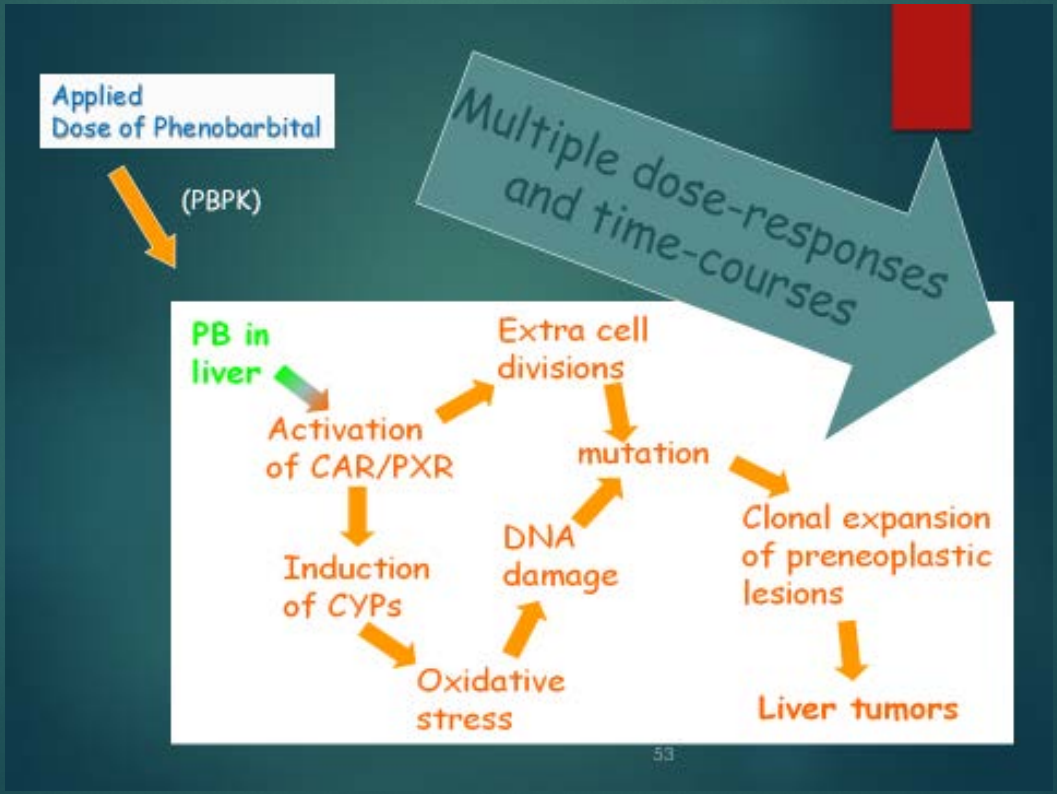
Uses of AOP -- Hazard ID

- Conditions under which agents produce toxicity
  - Route of exposure
  - High dose only?
  - Life stage
- Prioritizing
  - For testing
  - For assessment

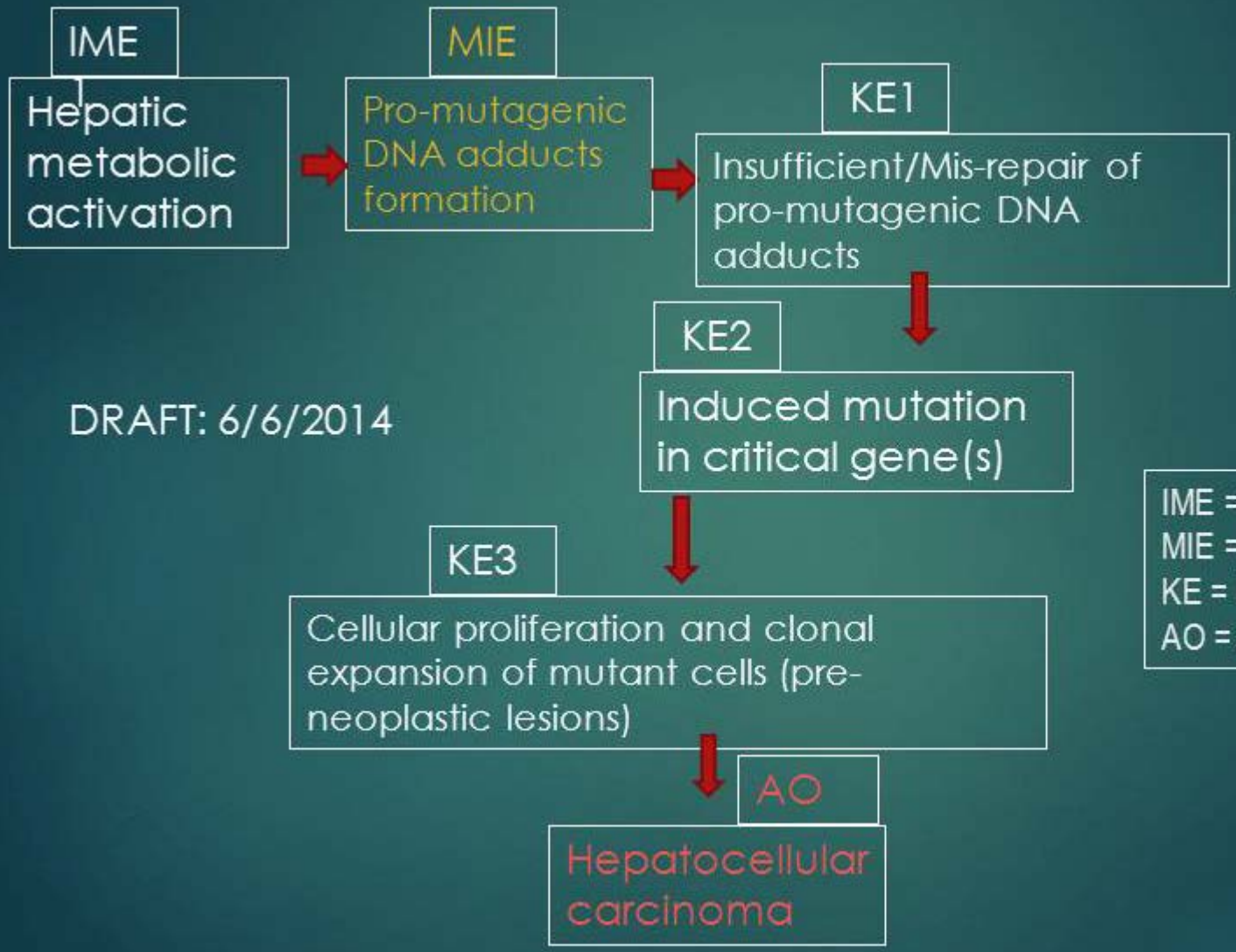


Uses of AOP Dose Response

- Quantitative KER in Biologically Based Dose Response models (BBDR)



Mutagenic MOA for Cancer: AFB1-induced HCC



DRAFT: 6/6/2014

IME = Initial Molecular Event
MIE = Molecular Initiating Event
KE = Key Event
AO = Adverse Outcome

Can KER Be Quantified?

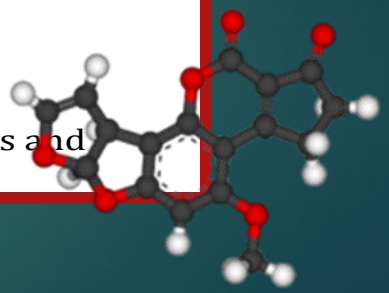
Quantitative Understanding of the Linkage[edit]

Oltipraz is a chemoprotective agent that increases GST activity in cells. [57-61] Oltipraz also appears to increase nucleotide excision repair, the primary error-free DNA repair mechanism that acts on both types of AFB1-DNA adducts. [62] Kensler suggested the use of aflatoxin-albumin adducts as a biomarker of AFB1 exposure and demonstrated the oltipraz administration reduced both albumin adducts and HCC incidence. [63] Scholl derived a relationship between albumin adducts in rats as a function of cumulative AFB dose. [64] That relationship is:

$$Adduct\ Burden\left(\frac{pg\ LYS-AFB1}{mg\ Albumin}\right) = 0.3\ dose^2 + 39.6\ dose$$

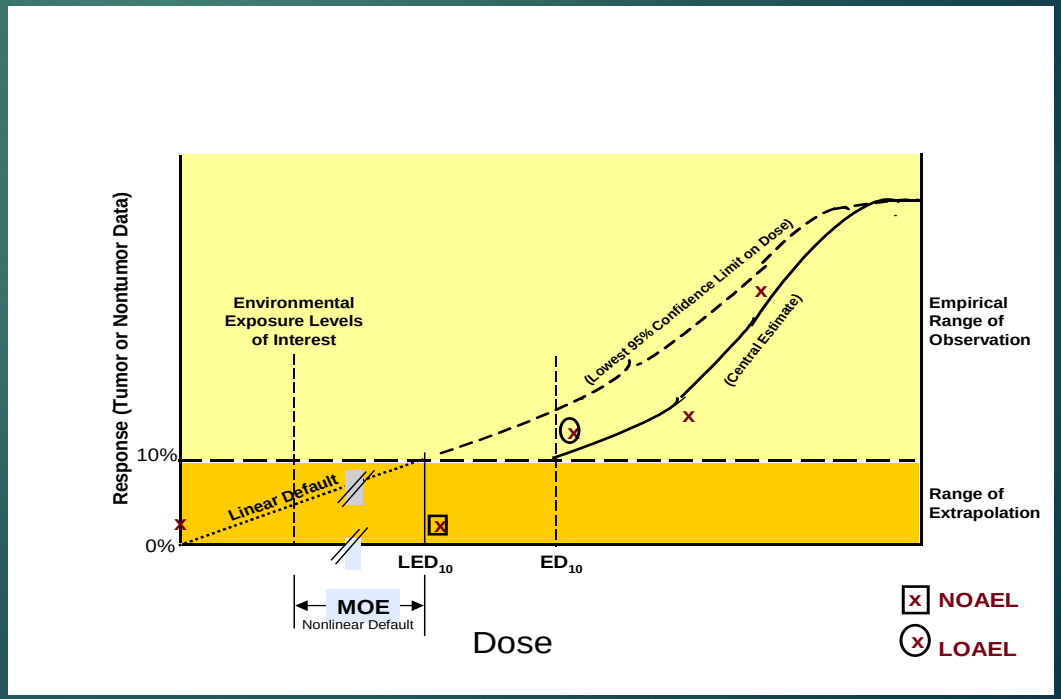
where dose = μg AFB1 / kg BW

It may be possible to use the relationship between AFB1 albumin adducts and mutations based on the work of Scholl et al. (2006).



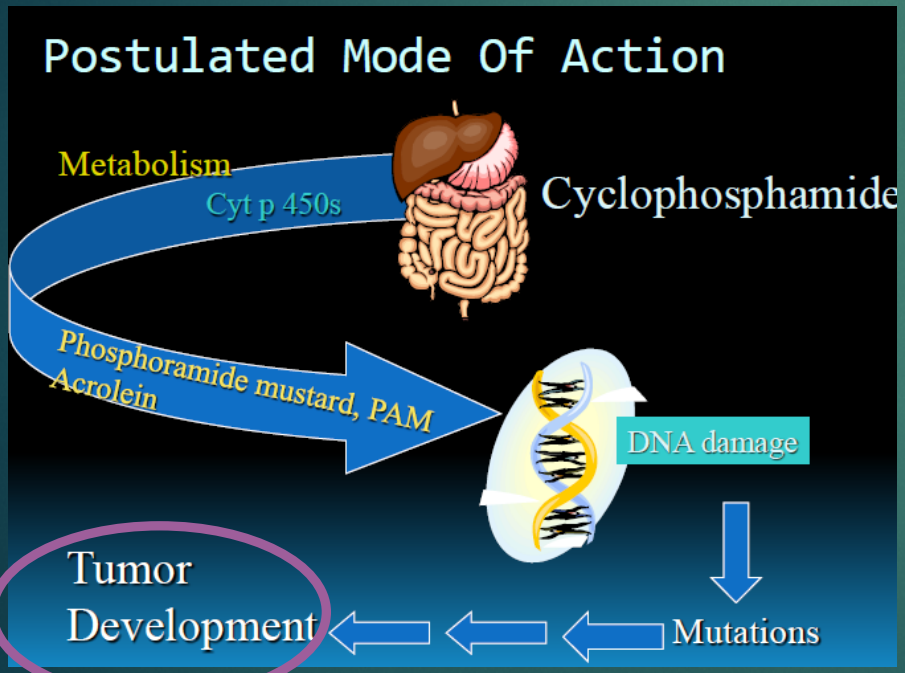
Uses of AOP Dose Response

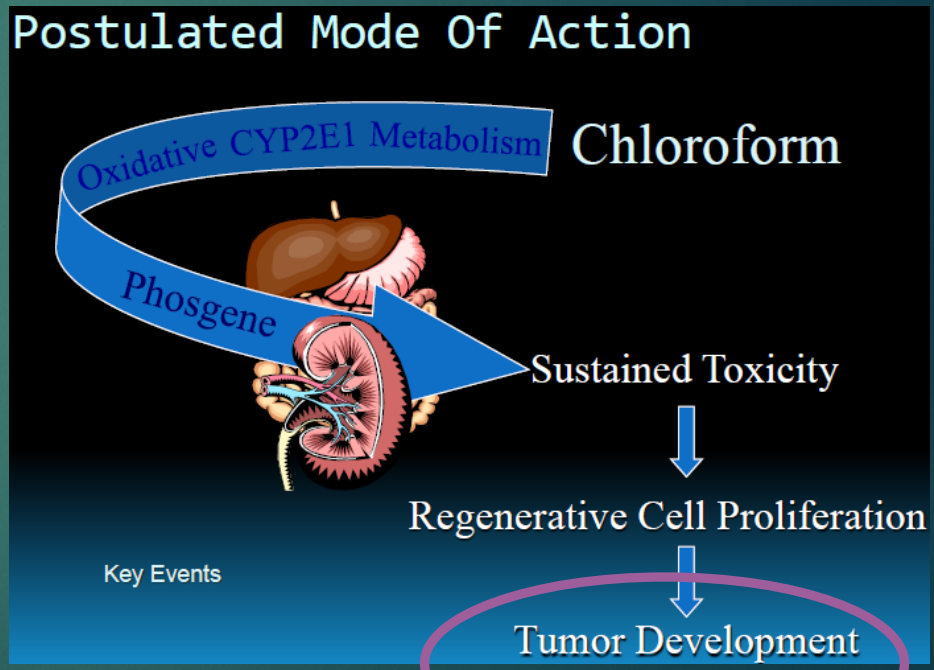
- Choice of POD
- Choice of extrapolation method
- Life Stage adjustment?



Use of AOP Grouping

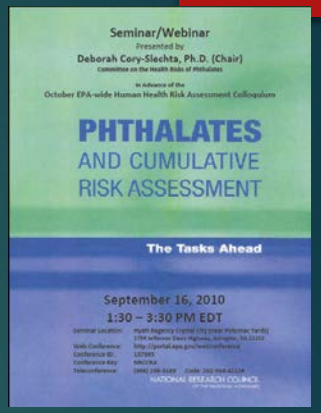
- For Cumulative Risk Assessment
  - By MOA, AOP



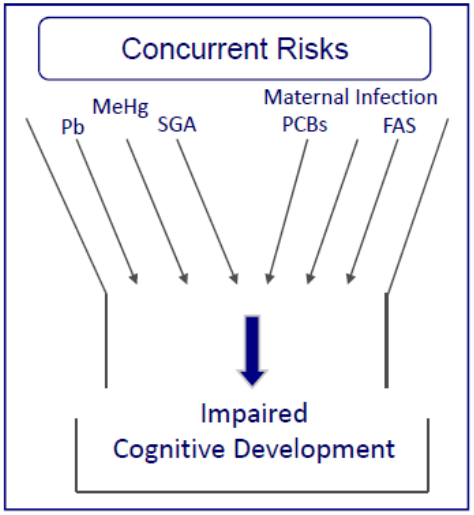


Use of AOP Grouping

- For cumulative risk assessment
  - By common adverse outcome



Cumulative Risk Assessment Broadly Viewed



Why Should This Only Apply to Reductions in Androgen?

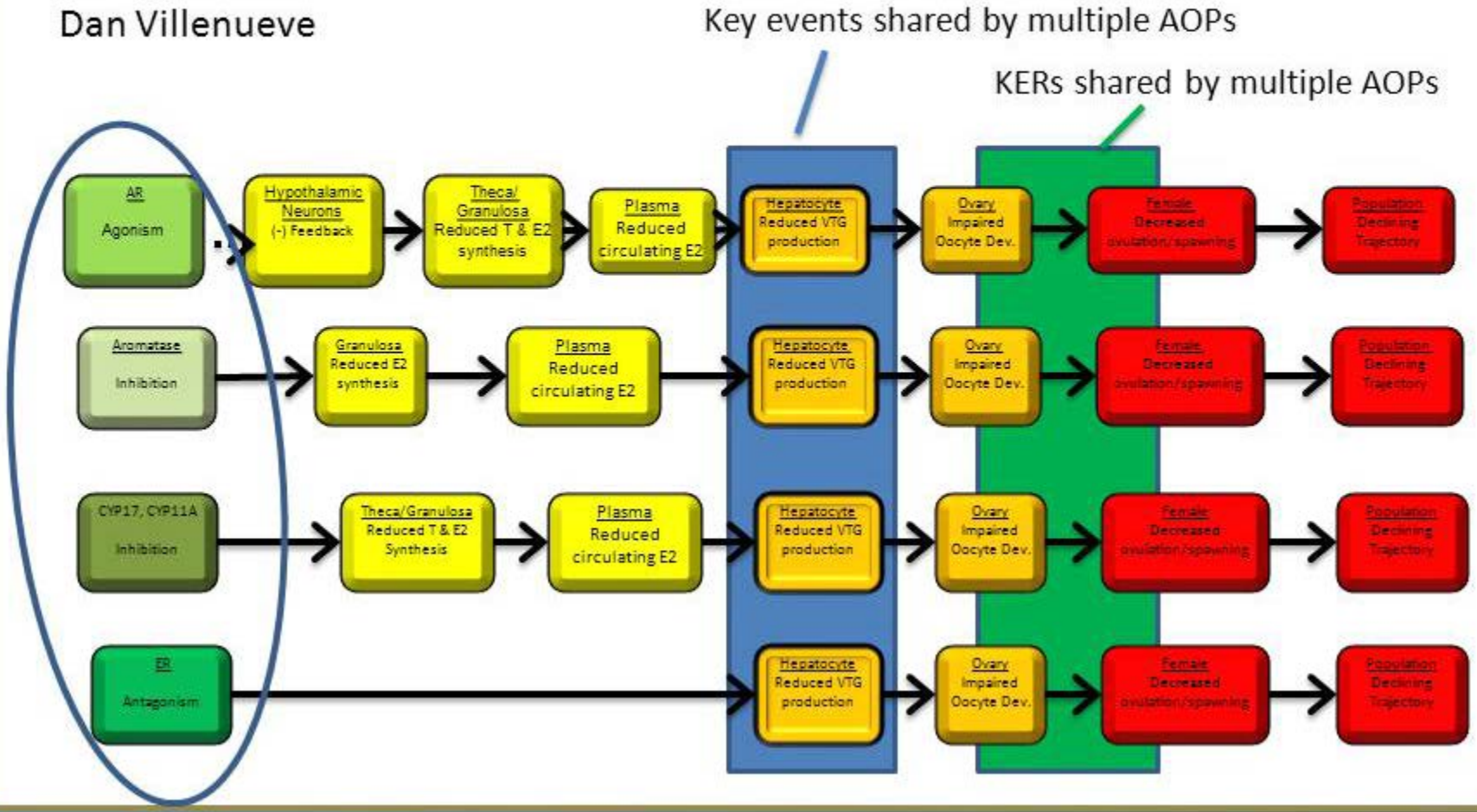
- "To cite another example, EPA could evaluate combined exposures to lead, methylmercury and polychlorinated biphenyls because all contribute to the cumulative risk of cognitive deficits associated with IQ reductions in children, although the deficits are produced by different mechanisms of action."

Principles of AOP Development

CSS

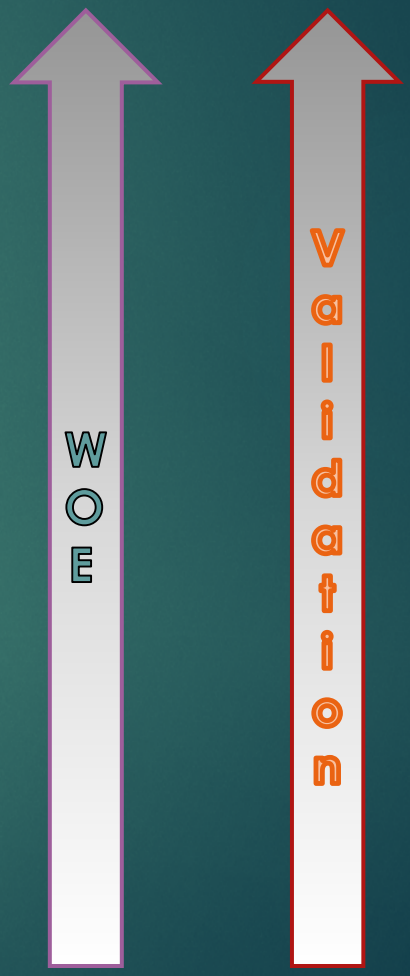
For most real-world applications, AOP networks are the functional unit of prediction

Dan Villenueve



Use of AOP Grouping

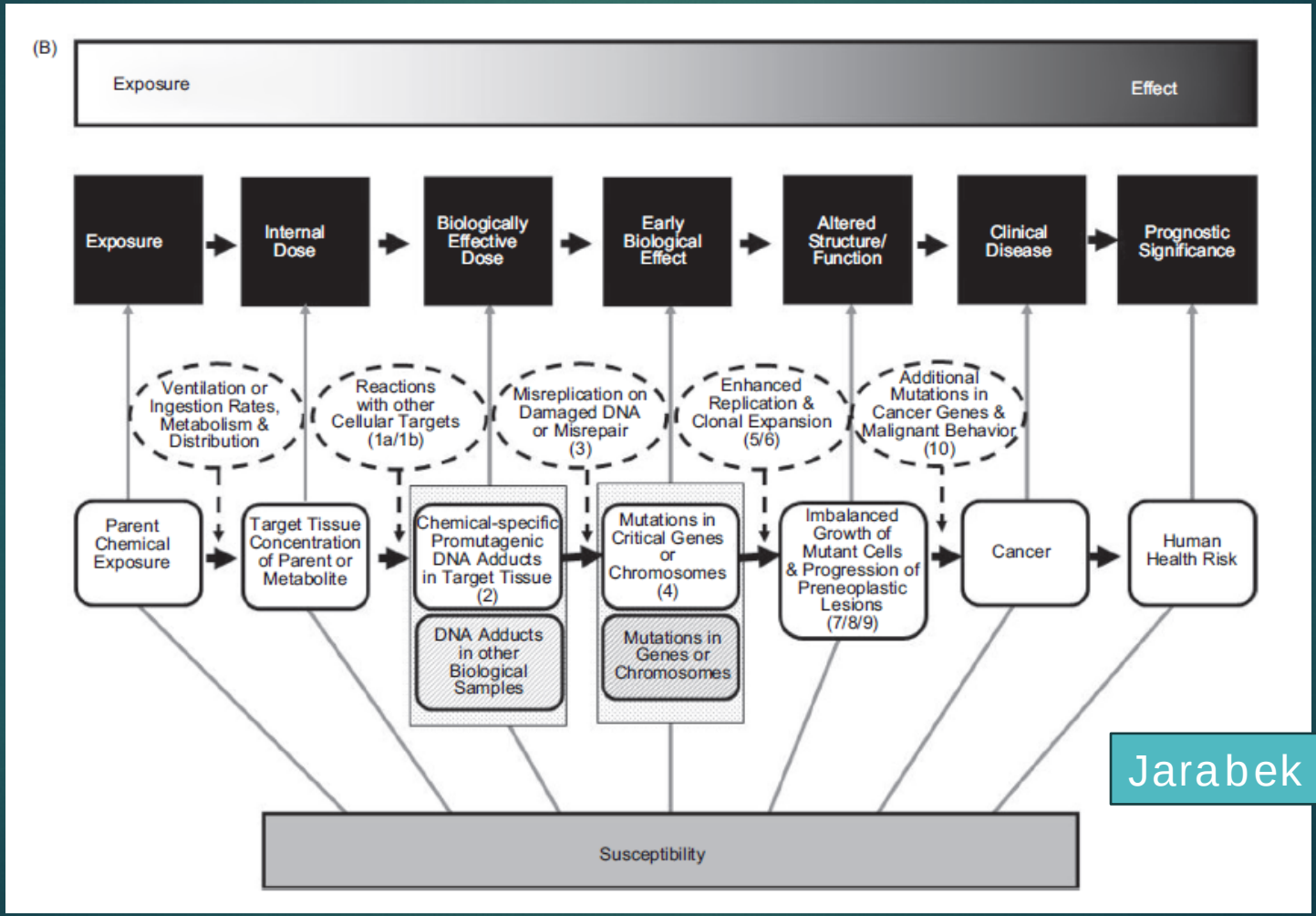
- Cumulative risk assessment
  - For scoping, qualitative assessment
  - For regulation, clean up
- Prioritize for testing
- Prioritize for assessment



What Does "Validation" Mean?

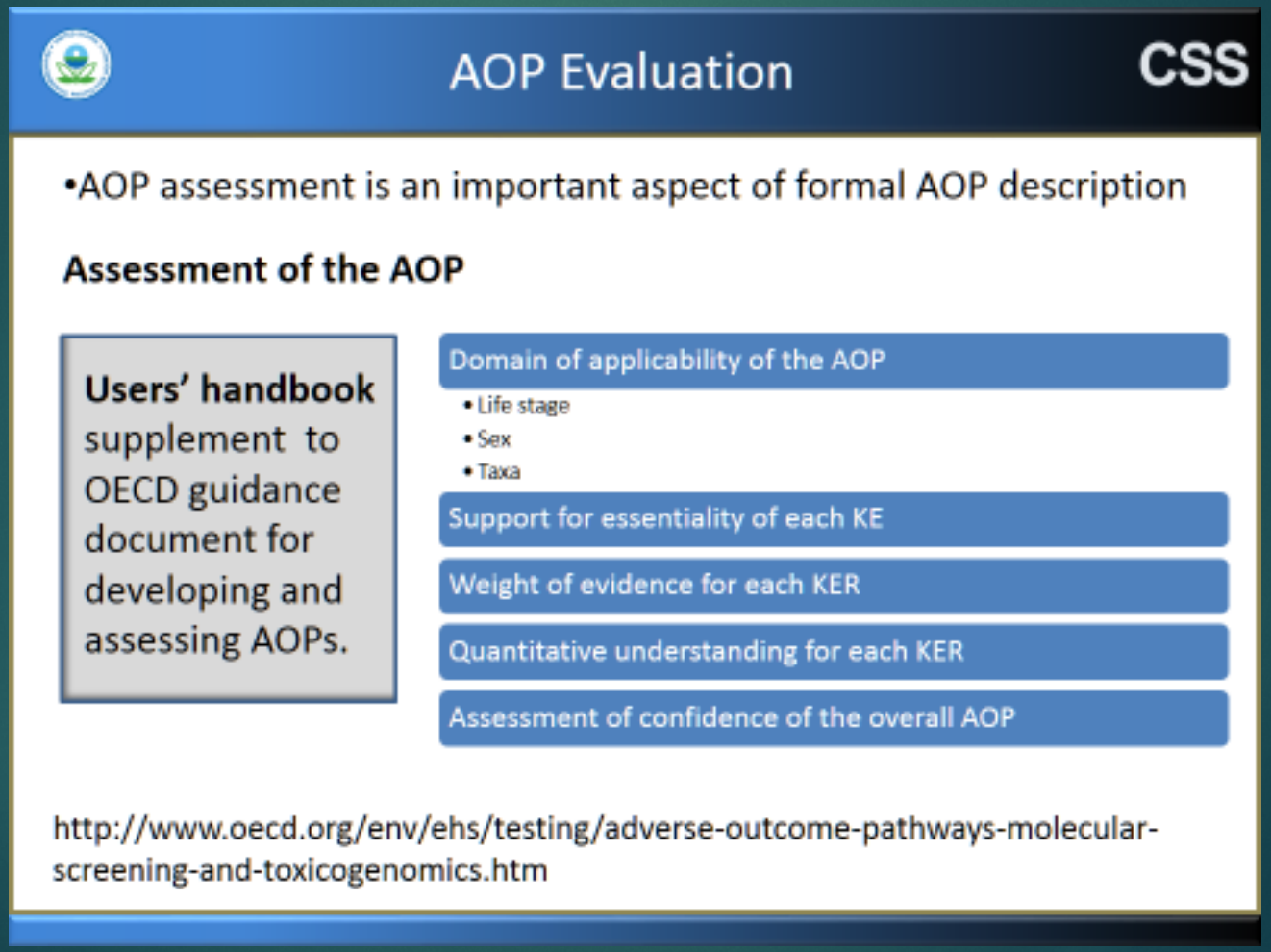
- "Validating New Tools/ Assays Against Carcinogenicity AOPs to Support Regulatory Decisions"
- Some meanings are defined by statute or court
- Often means comparison to a standard set of results
  - Comparison of HTP assays to lifetime assay results
    - Specificity and sensitivity

Validated biomarkers

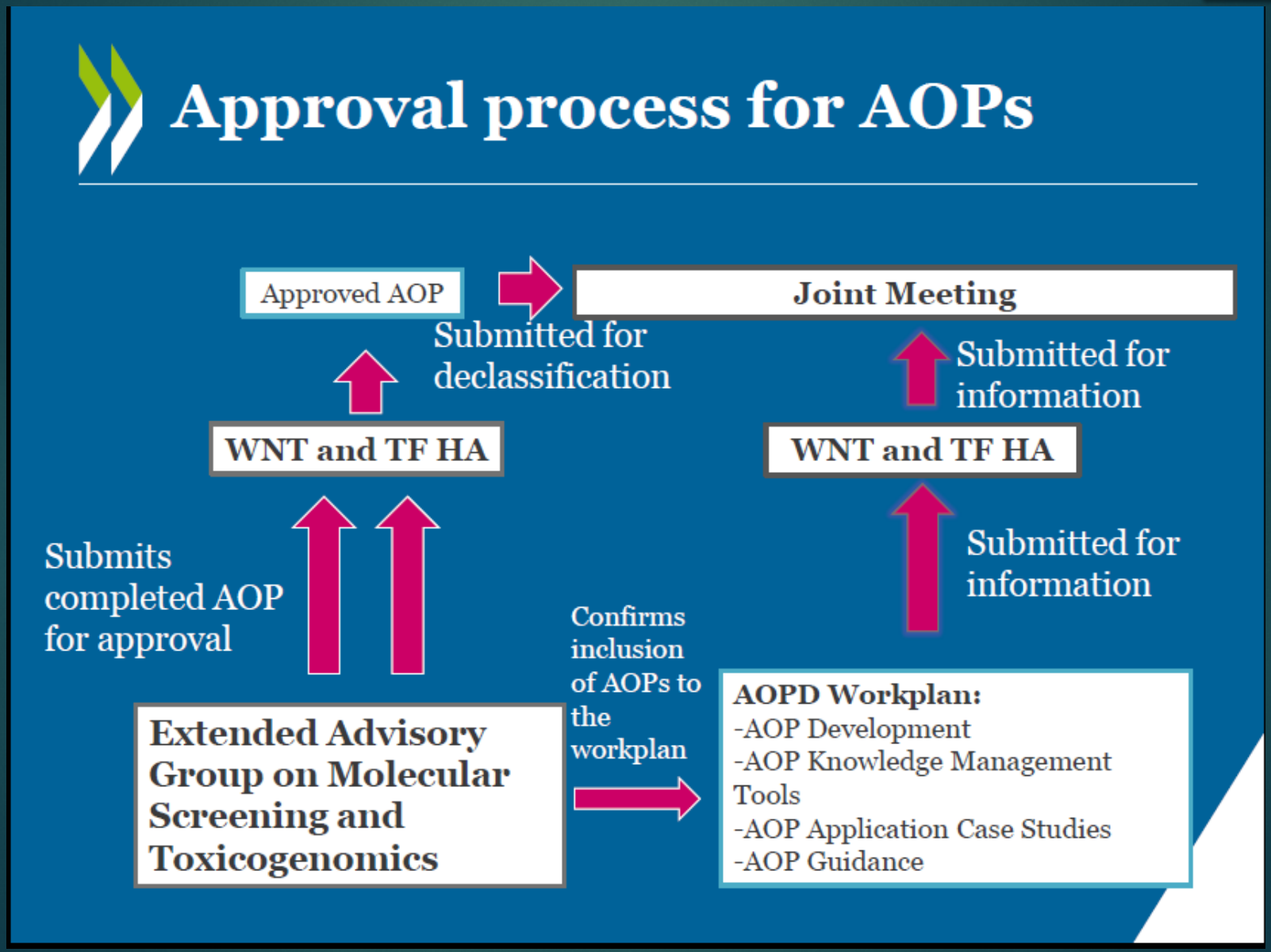


Jarabek *et al.* 2009

Validation in OECD Handbook

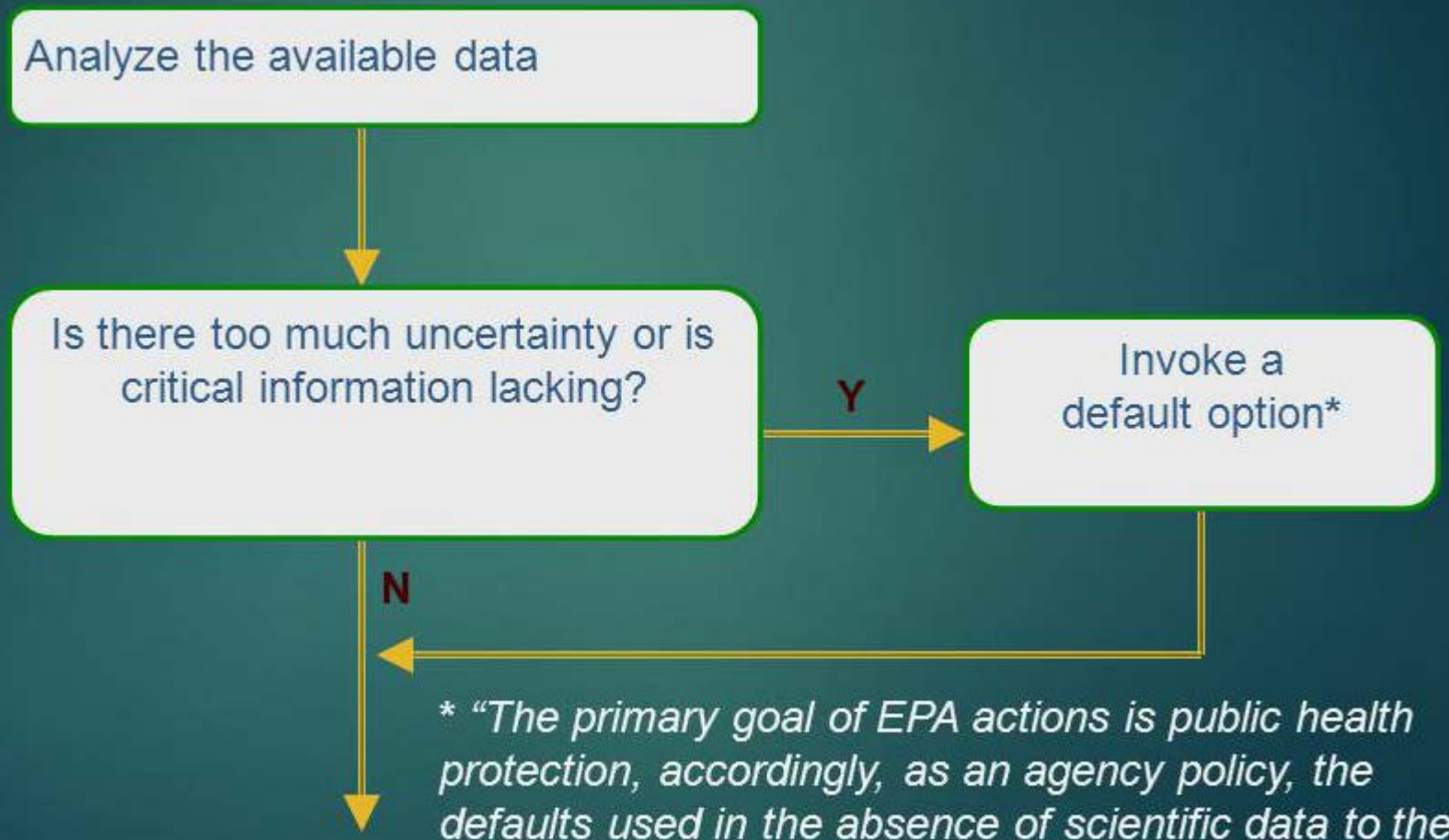


OECD "validation"



Use of Default Options

The Guidelines emphasize analysis of all the data before use of default options.



Conclusions

- Progress in changing basis for regulation can move at glacial speed
  - Glacier melting appears to be accelerating
  - Bad for climate change; maybe good for acceptance of new approaches
- Most terms have meaning only when defined in a particular context
  - e.g. “validate”
- Problem formulation, planning and scoping is critical for any assessment
- Knowledge beats information beats data