

***The 2005 Cancer Guidelines with
Particular Focus on the Treatment of
Mode of Action Information***

William P. Wood, Ph.D.
Executive Director
Risk Assessment Forum
Office of Research and Development

Key Features of Cancer Guidelines

- Analyze data **before** invoking default options.
- Framework for mode of action
- Weight-of-evidence narrative **and** descriptor replaces the previous alpha-numeric
- Two-step dose-response process separates
 1. modeling the observed data, **from**
 2. extrapolation to lower doses.
- Linear and nonlinear extrapolations are considered.
- Differential risks to susceptible populations and lifestages are considered.



Mode of Action Consideration: A Main Focus

- “These cancer guidelines view a critical analysis of all of the available information that is relevant to assessing the carcinogenic risk as the starting point from which a default option may be invoked if needed to address uncertainty or the absence of critical information.”
- “The use of mode of action in the assessment of potential carcinogens is a main focus of these cancer guidelines.”



Important Definitions

- **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
- **Key Event:** Empirically observable precursor step that is itself a necessary element of the mode of action or is a biologically based marker for such an element



Use of MOA Information

- Assess the relevance of laboratory animal results to human environmental exposures
- Provide insight into whether the dose-response curve is likely to be linear or nonlinear at low doses
- Identify susceptible populations and lifestages
- Quantify the relative sensitivity of laboratory animals and human populations



MOA Framework

- Description of the hypothesized mode of action
- Analytic tool for judging whether there's sufficient experimental support for the hypothesized mode of action
- Is neither a checklist nor a list of required criteria, the type and amount of information will depend on the mode of action postulated
- Useful for organizing thinking about aspects of causation, and consistent with the scientific method of developing hypotheses and testing those hypotheses experimentally
- Is based upon considerations for causality in epidemiologic investigations originally articulated by Bradford Hill

EPA's framework is consistent with others, e.g., the International Programme on Chemical Safety and by the International Life Sciences Institute.



Mode of Action Framework

- Summary description of the hypothesized mode of action.
- Identification of key events.
- Strength, consistency, specificity of association.
- Dose-response concordance.
- Temporal relationship.
- Biological plausibility and coherence.
- Consideration of the possibility of other MOAs.

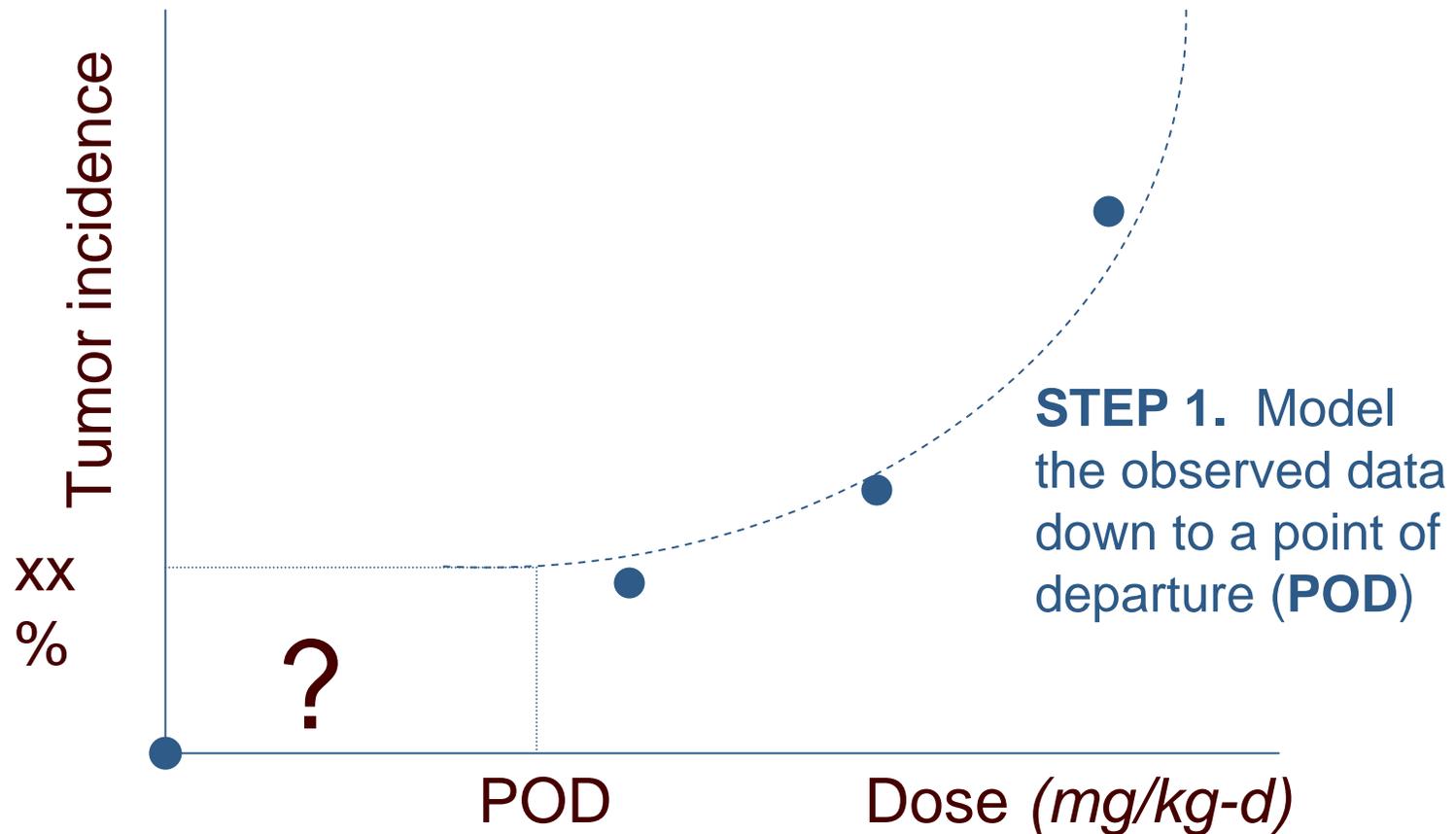


Conclusions about the MOA

- Is the mode of action sufficiently supported in the test animals?
- Is the mode of action relevant to humans?
- Which populations or lifestages can be particularly susceptible to the mode or action?
 - *Question is both qualitative and quantitative*
 - *Quantitative differences can be used in the dose-response assessment*



Two-step approach to dose-response

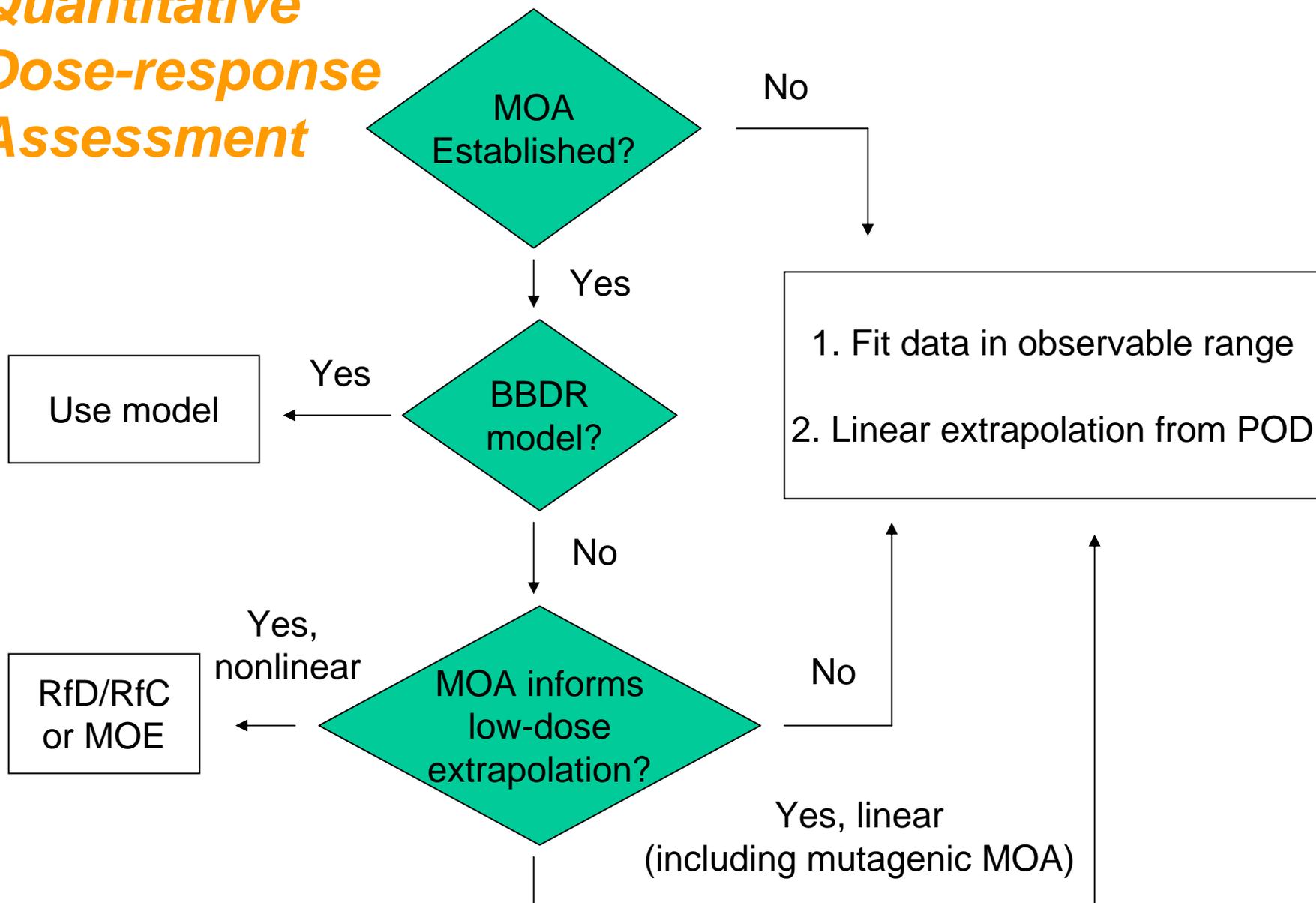


Point of Departure (POD)

- Starting point for subsequent extrapolations and analyses
- Is the lowest point that is adequately supported by the data
- “The POD for extrapolating the relationship to environmental exposure levels of interest, when the latter are outside the range of observed data, is generally the lower 95% confidence limit on the lowest dose level that can be supported for modeling by the data.”



Quantitative Dose-response Assessment



More than One MOA

- Both linear and nonlinear approaches may be used when there are multiple MOAs.
- If there are multiple tumor sites, then the appropriate extrapolation is used for each site.
- If there are multiple MOAs at a single tumor site, then both approaches can be used to decouple and consider the respective contributions of each MOA in different dose ranges.
- Where alternative approaches with significant biological support are available for the same tumor response and no scientific consensus favors a single approach, an assessment may present results based on more than one approach. One procedure may be given greater weight or preference.

