TERA
Toxicology Excellence for Risk Assessment
a nonprofit corporation dedicated to the best use of toxicity data for risk values

Incorporation of Mode of Action Understanding of Hormesis into Dose Response Assessment

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What is Hormesis?

- How does definition help understand the phenomenon and its implications?

- **Solution:** Focus on mechanistic understanding – informs implications for risk assessment

What is Hormesis - Revisited

- Focus on shape of dose- response curve – biphasic, U-shaped, J-shaped
  - Interest in statistically or biologically significant biphasic dose-response curves
- Separate dose-response shape from beneficial/not beneficial/adverse
- Separate description of the phenomenon from implications for risk assessment
- Recognize multiple modes of action
- Potentially different implications for medical applications vs. environmental risk assessment
- Separate dose-response curve for individual chemicals from issue of interactions

Key Considerations for Use of Biphasic Curves

- Is it statistically or biologically significant? (meta-analyses allowed)
- Confirm that response metric of interest has been identified
- Determine units of y axis
- Determine mode(s) of action and whether truly biphasic
- Address susceptible populations
- Consider background response and implications of other exposures

Case Studies

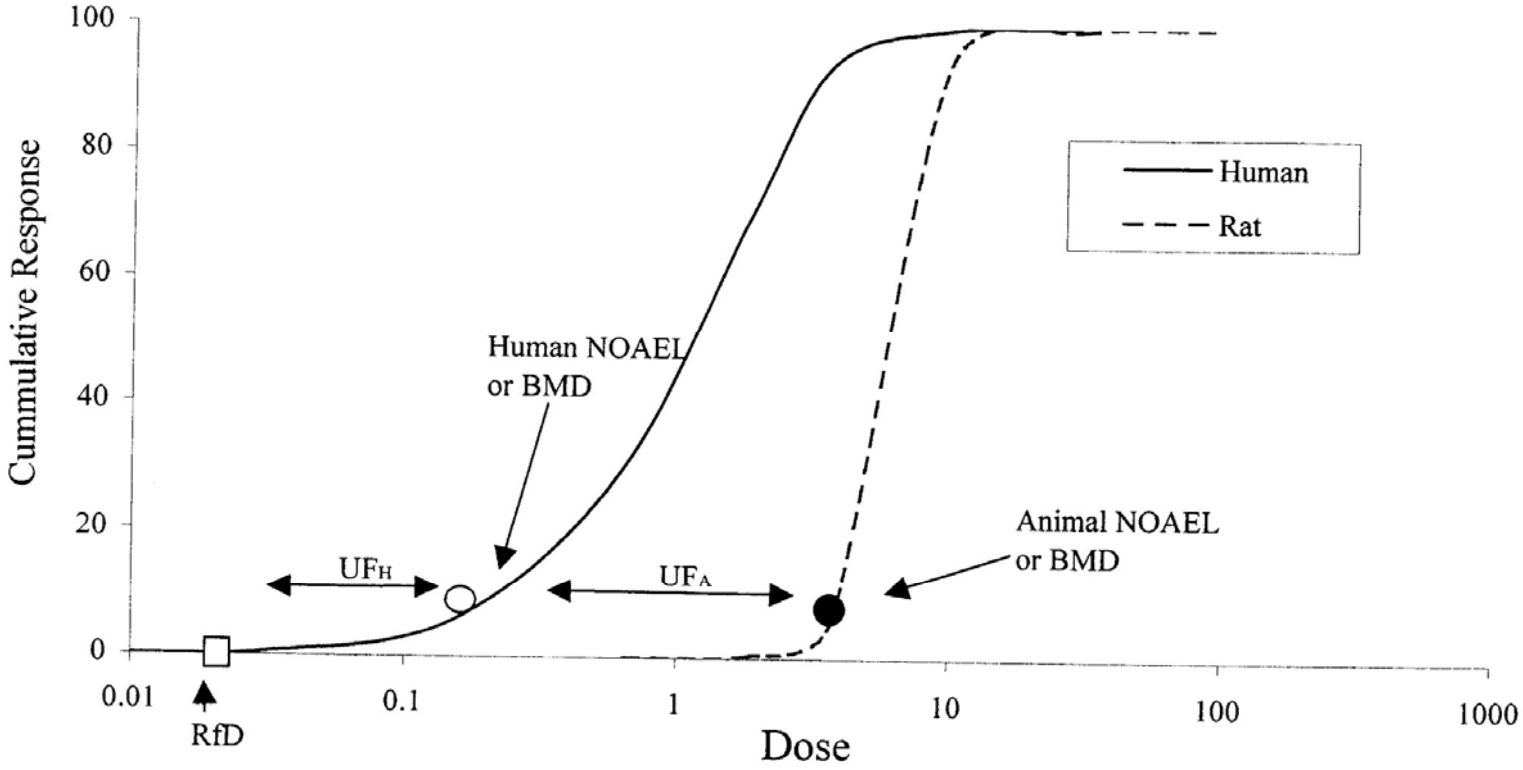
- Essential elements and nutrients
- Difference in target and mechanism for toxicity and benefit
- Modified spectrum of response
- Stimulatory and inhibitory receptors within the same organ
- Multiple modes of action for cancer
- Protein induction (e.g., metabolic or repair enzymes)

General Method for Noncancer Assessment

- Identify critical effect
  - "The first adverse effect, or its known precursor, that occurs to the most appropriate or sensitive species as the dose rate of an agent increases."
- Identify point of departure (POD) – NOAEL, LOAEL, BMD
- Identify uncertainty factors (interspecies, intraspecies, LOAEL to NOAEL, subchronic to chronic, database)
- RfD = POD/total UF

Extrapolation from Animal Data

Figure 5a. Cumulative Response as a function of Dose for Humans and Rats. Data are hypothetical, but approximate real situations.

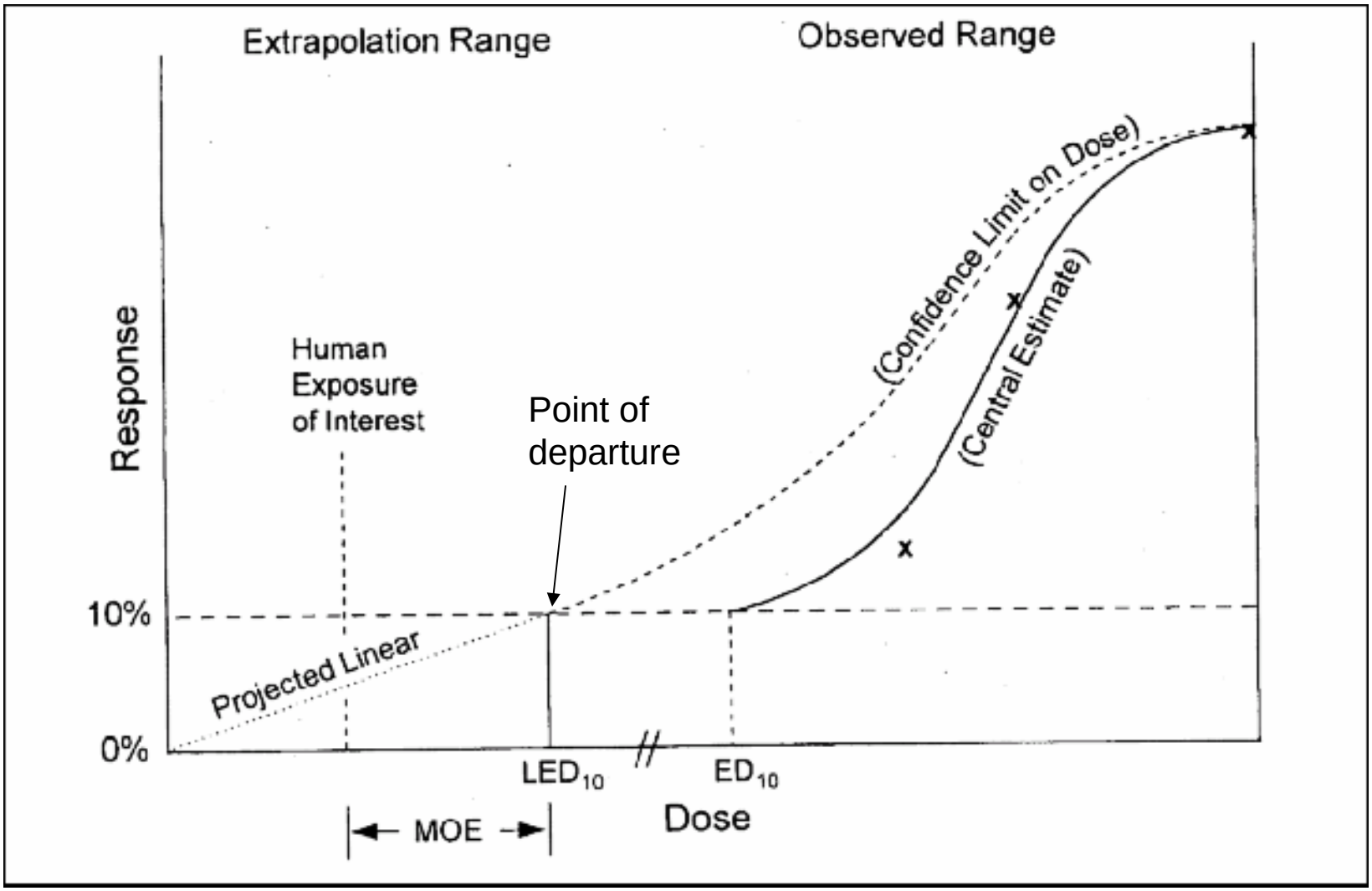


(Dourson et al., 2002)

General Method for Cancer Assessment

- Identify tumors with statistically significant increases and evaluate weight of evidence for carcinogenicity
- Evaluate Mode of Action, including identification of key events and human relevance
- Model data in experimental range and determine point of departure
- Low dose extrapolation
  - If acts via direct DNA reactivity or not enough information – low dose linear
  - If MOA consistent with nonlinearity, develop RfD based on key event

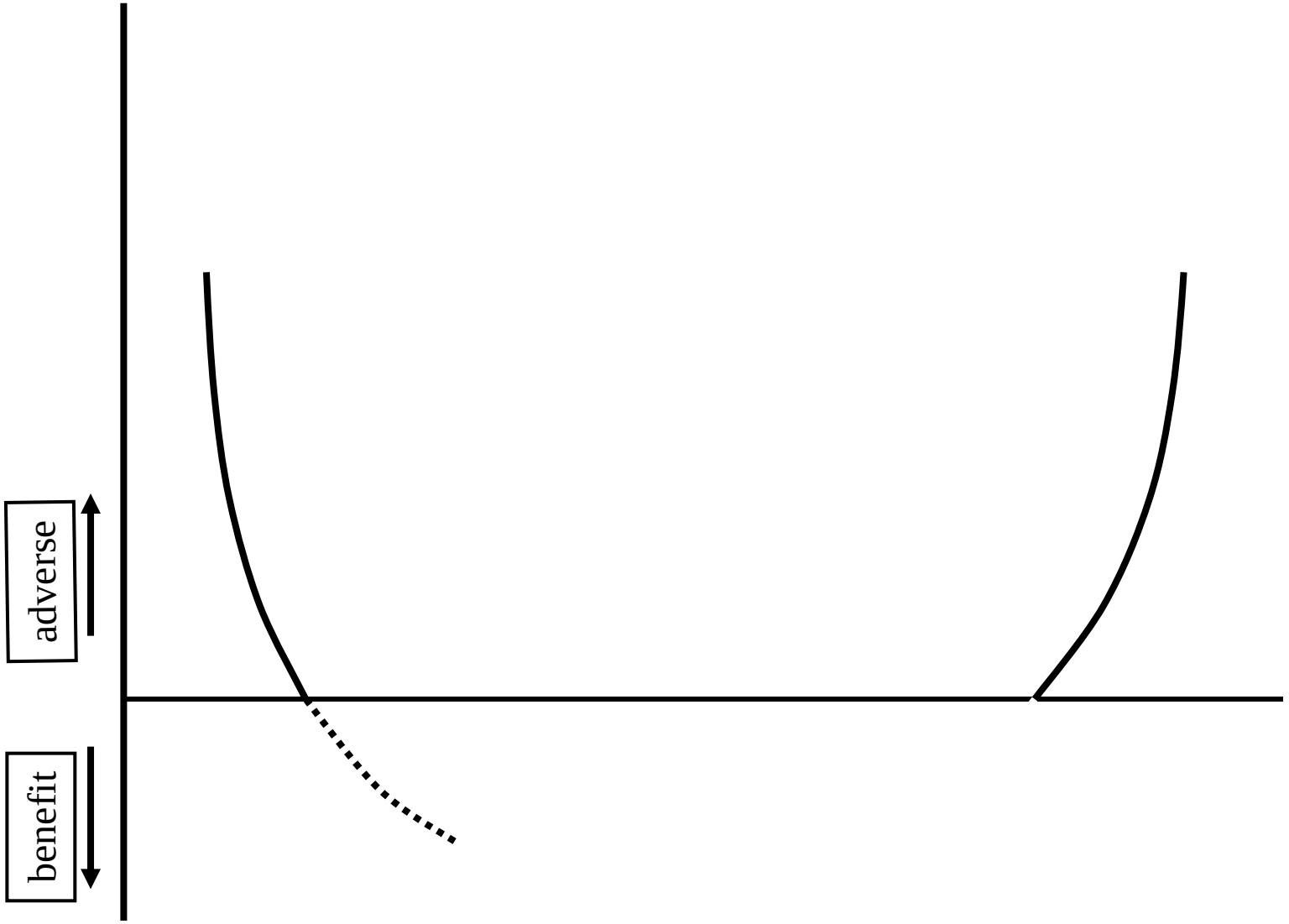
Graphical Representation of Data and Extrapolation



Case Study: Essential Elements

- Typically homeostatically controlled
- Multiple targets effects when move into deficiency or toxicity range
- Deficiency and excess (toxicity) may have different modes of action

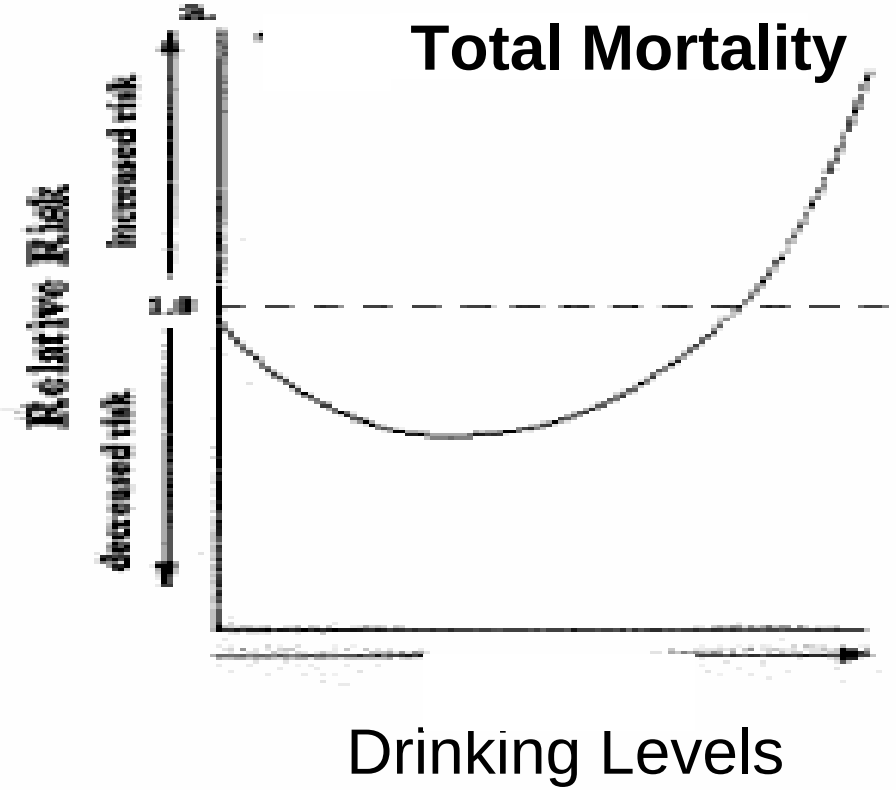
Case Study: Essential Elements

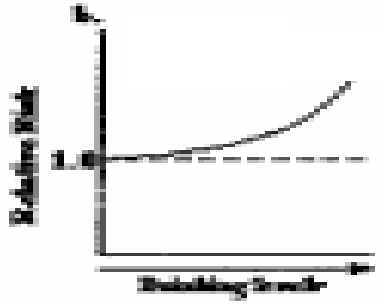


Case Study: Essential Elements

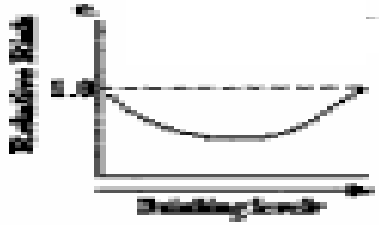
- Risk assessment approach – modify UFs so that RfD is above the RDA;
  - Anticipate no overlap in curves
  - Different groups may have different RDAs
  - Some groups with increased nutritional needs may have RDA above RfD *for general population*
- Exceptions: hypersusceptible individuals – may need to label or otherwise restrict exposure

Ethanol Dose – Responses: Different Targets

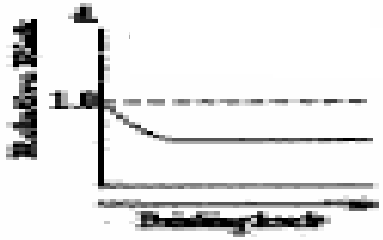




Cancer



Cardiovascular Disease

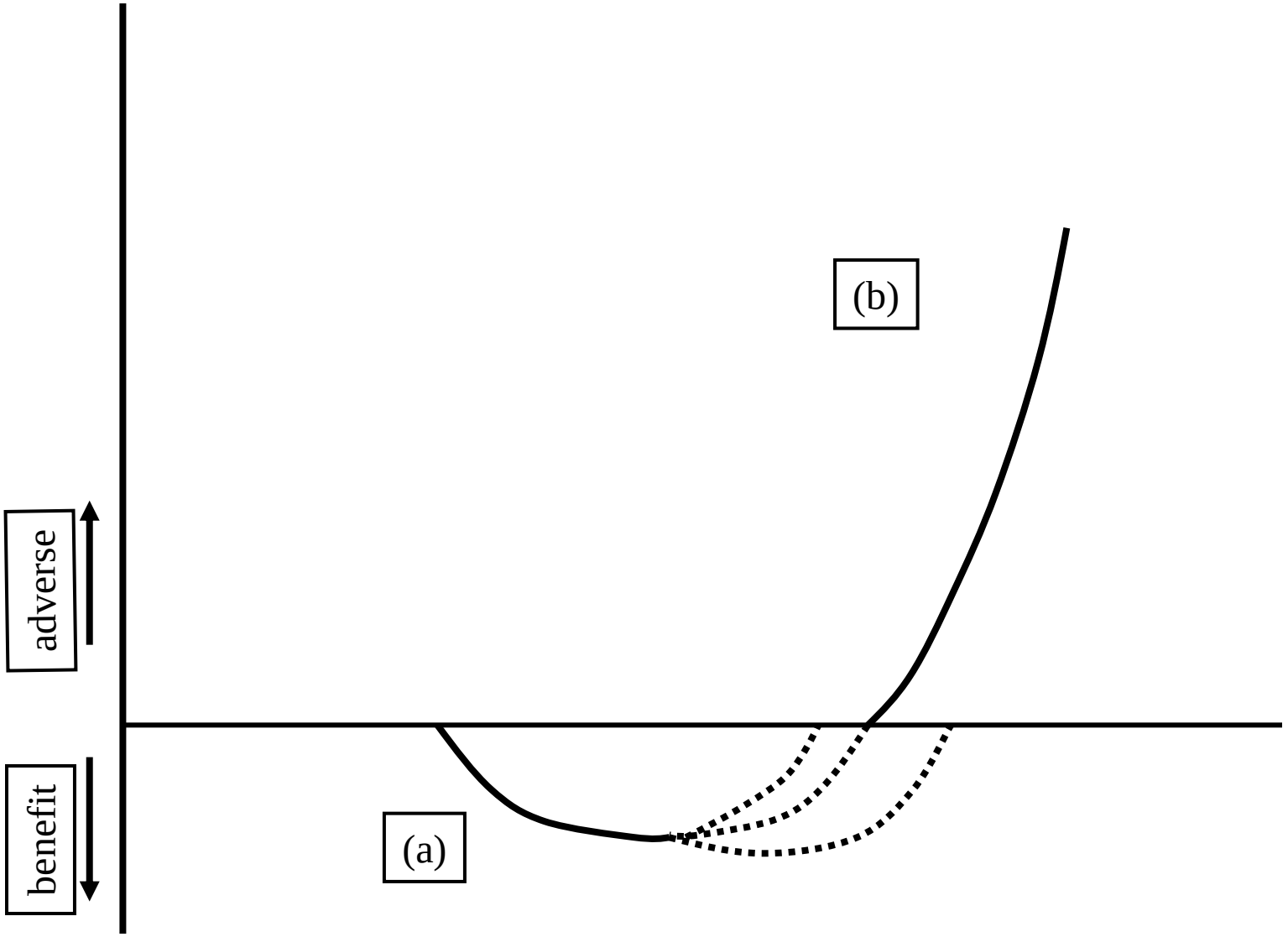


Coronary Heart Disease

Case Study: Different Targets

- Example – ethanol
- Low dose cardiovascular benefits
- Higher dose acute CNS and chronic liver effects, developmental effects
- Different dose-response curves and modes of action for risk and benefit

Case Study: Different Targets



Case Study: Different Targets

- Different target populations – pregnant women and people with chronic liver disease may choose to forgo cardiovascular benefits because they are sensitive populations for the effects of excess.
- Protection of sensitive populations would require RfD to be set below value that may benefit some
- Full information on dose-response curve can inform risk management decisions
- Is the role of risk assessment to maximize benefit or minimize harm?

Case study: Modified Spectrum of Response

- Cyclophosphamide – inhibitor of protein synthesis that stops cell division
- Causes shift in immune cell populations, increases in some aspects of acquired immunity (attributed to greater sensitivity of T suppressor cells compared to other parts of immune system) but decreasing NK cells (part of innate immune system)
- Looks like J-shaped curve if only look at subset of all parameters (e.g., PFCs in SRBC assay)
- Endpoints – flu vs. cancer
- Implication: Need to look at entire spectrum of response; low-dose effect may be adverse

Case study: Stimulatory and Inhibitory Receptors

- Often seen with pharmaceuticals
- Overall dose-response appears biphasic
- Dose response is composite of 2 phenomena – binding to stimulatory and inhibitory receptors – or multiple binding to same receptor
- Need to differentiate
  - Is it different endpoints or same endpoint via different mechanisms?
  - Two different receptors may both provide input to same regulatory gene that integrates total response

Case study: Stimulatory and Inhibitory Receptors

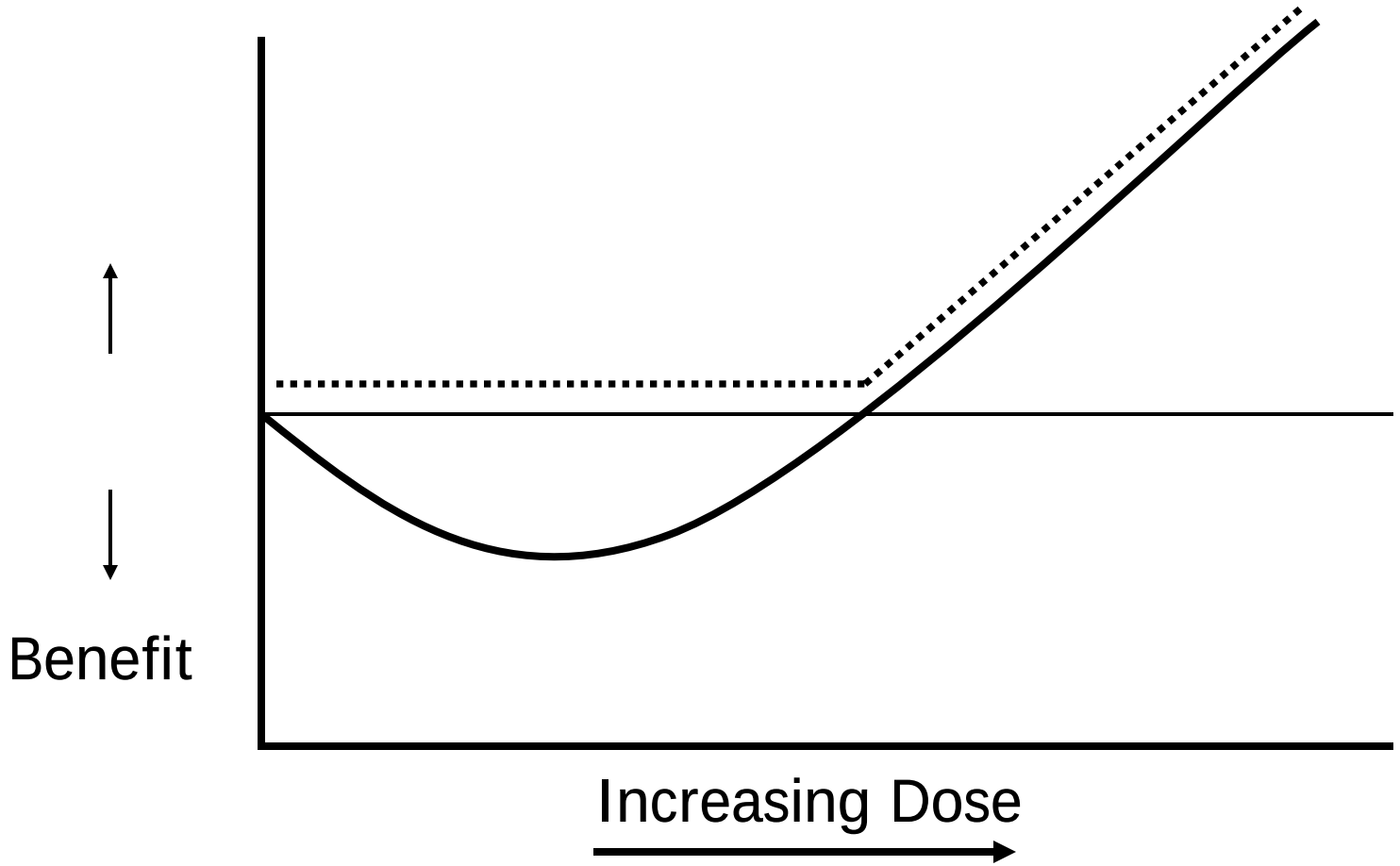
- Risk assessment perspective:
- Both phases may be adverse, as departures from normal (e.g., altered motor activity)
  - If stimulatory effect adverse and sufficient magnitude, is critical effect. Otherwise, critical effect is inhibitory one.
- If different receptors provide input to same regulatory molecule, integrated response is endpoint of interest
  - Still need to consider background and timing issues

Case Study: Cancer – Multiple MOAs

- Formaldehyde - well-studied; biologically-motivated dose-response model exists
- DNA-protein crosslinks formed, may lead to mutations – low-dose linear
- Cytolethality/regenerative cell proliferation- J-shaped curve, may be hockey stick
- 2-stage clonal growth model linked mode of action with mutation accumulation and tumor formation

Case Study: Formaldehyde (cont.)

- Predicted tumor response very sensitive to shape of regenerative cell proliferation dose-response
  - If J-shaped, tumor response is J-shaped
  - If hockey-stick, tumor response is low-dose linear
- Risk assessment implications:
  - Sensitivity to uncertainties
  - Importance of background of regenerative cell proliferation – effect of other exposures


Benefit
Increasing Dose

Case Study: Protein Induction

- Examples: adaptive response; induction of metallothionein; glutathione synthesis; heat shock proteins; metabolic enzymes
- Note background damage of oxidative stress and DNA damage from endogenous reactive species
- May result in J-shaped curve or hockey stick, depending on other exposures

Considerations

- Increased metabolic enzymes may decrease toxicity of some other chemicals (decreasing background), but increase toxicity of others (increasing background)
- Net benefit depends on combination of background exposure and exposure to chemical of interest
- Importance of timing – chronic low-level exposure may protect against later higher exposures, but risk managers can't assume previous (inducing) exposure. Uninduced population needs protection of traditional approach
- Doses beneficial to general population could be adverse to sensitives, and doses beneficial to sensitives could be below beneficial range for general population

Conclusions

- Consideration of mechanistic factors often affects the shape of the dose-response curve and should be considered in deriving risk values and in risk management decisions
- Current research is helping to elucidate these mechanisms
- Mechanisms that can result in biphasic curves may also warrant modifying some default assumptions in the future, particularly for cancer assessment.
- Hormesis should not yet be the principle dose-response default assumption in risk assessment