Introduction to Toxicology:

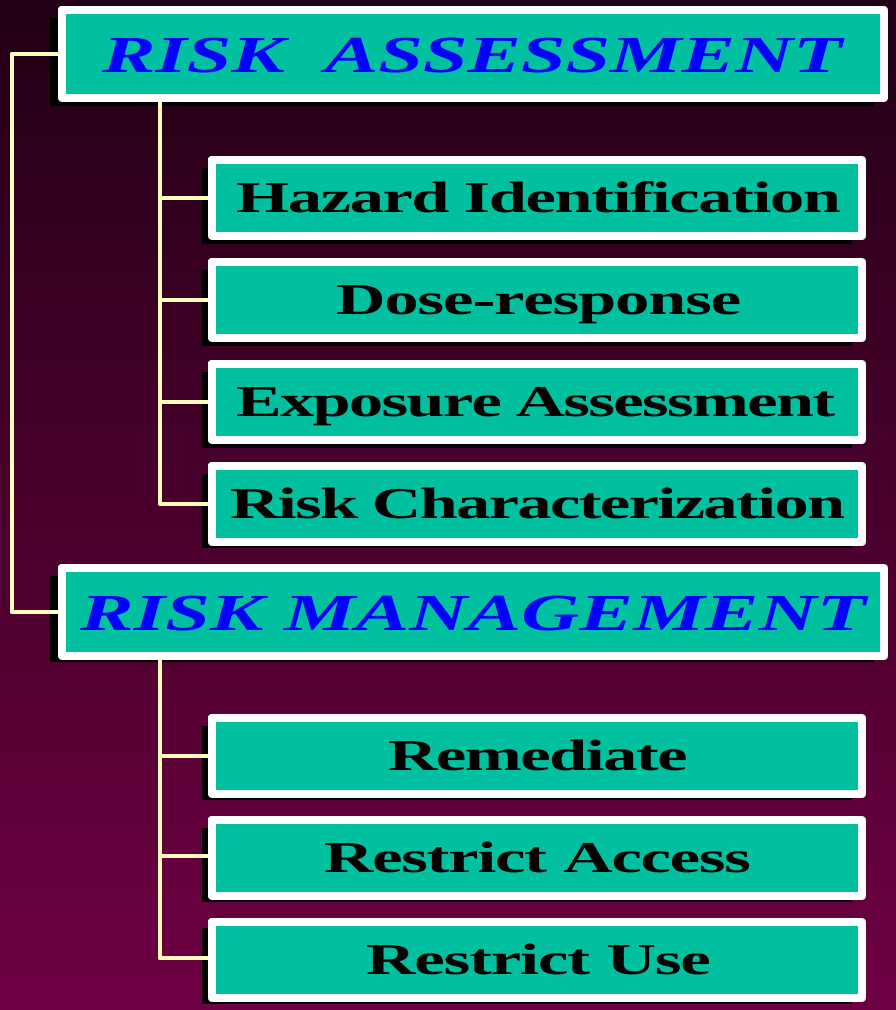
A Presentation to the Sludge Management Advisory Committee

Paul R. Harp, Ph.D.

NH Department of Health & Human Services
Bureau of Health Risk Assessment

October 25, 1999

The Role of Toxicology in Risk Assessment



Ü **Toxicology**

What is Toxicology?

- The study of the adverse effects of natural and man-made materials on biological systems.
- Toxicology investigates exposure vs. disease.

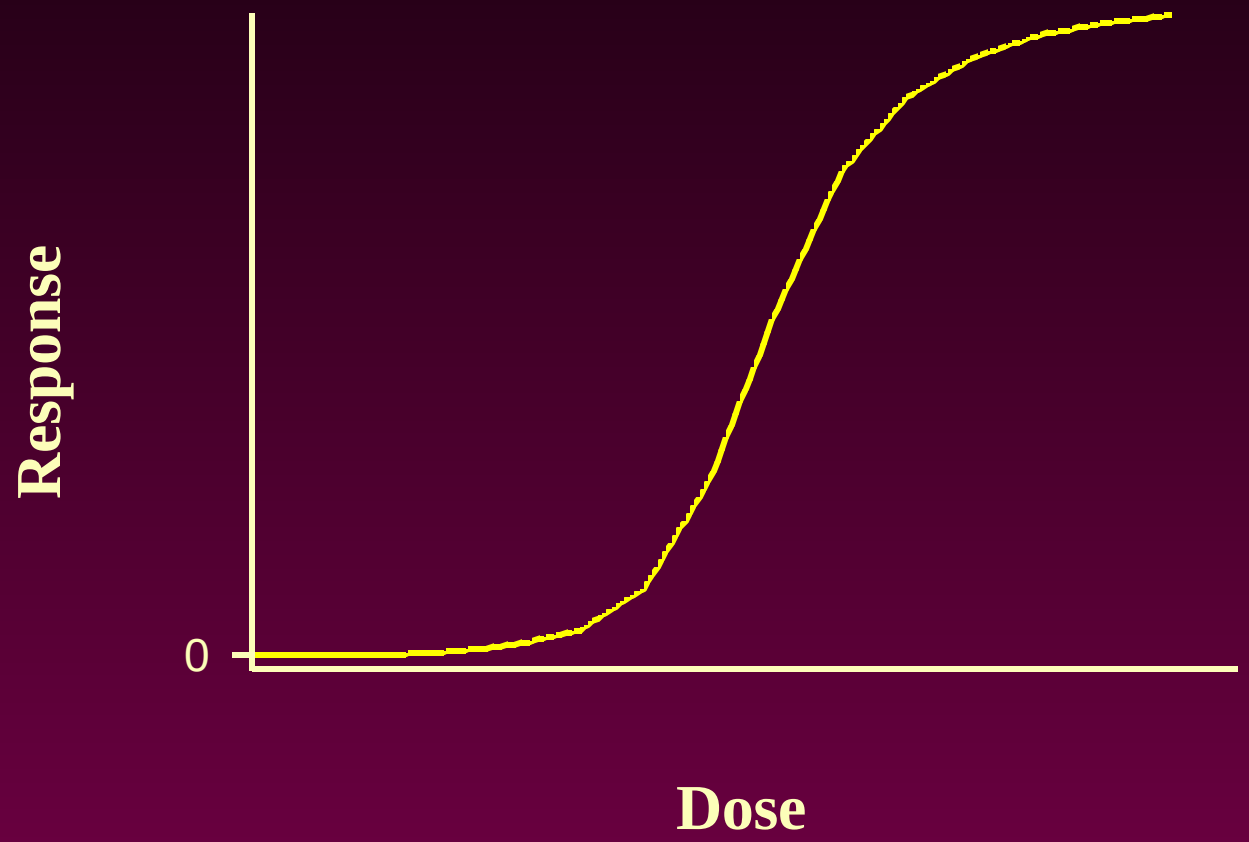
The Dose-Response Relationship

- A fundamental concept in toxicology which describes the quantitative relationship between the amount of exposure (dose) to a toxicant and the incidence of adverse effects (response).

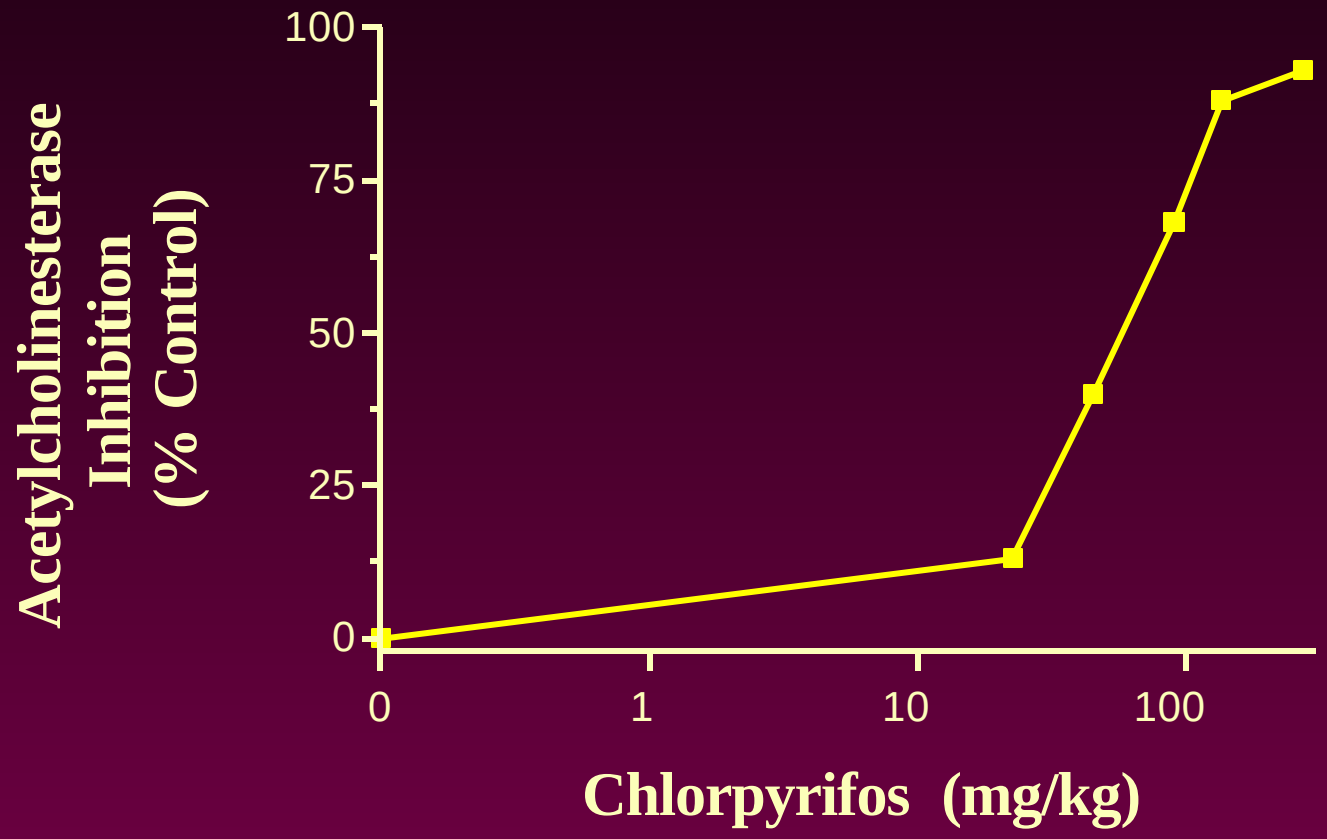
- Sources of Information:
  - Animal studies
  - Human epidemiology studies

Typical Dose-Response Curve

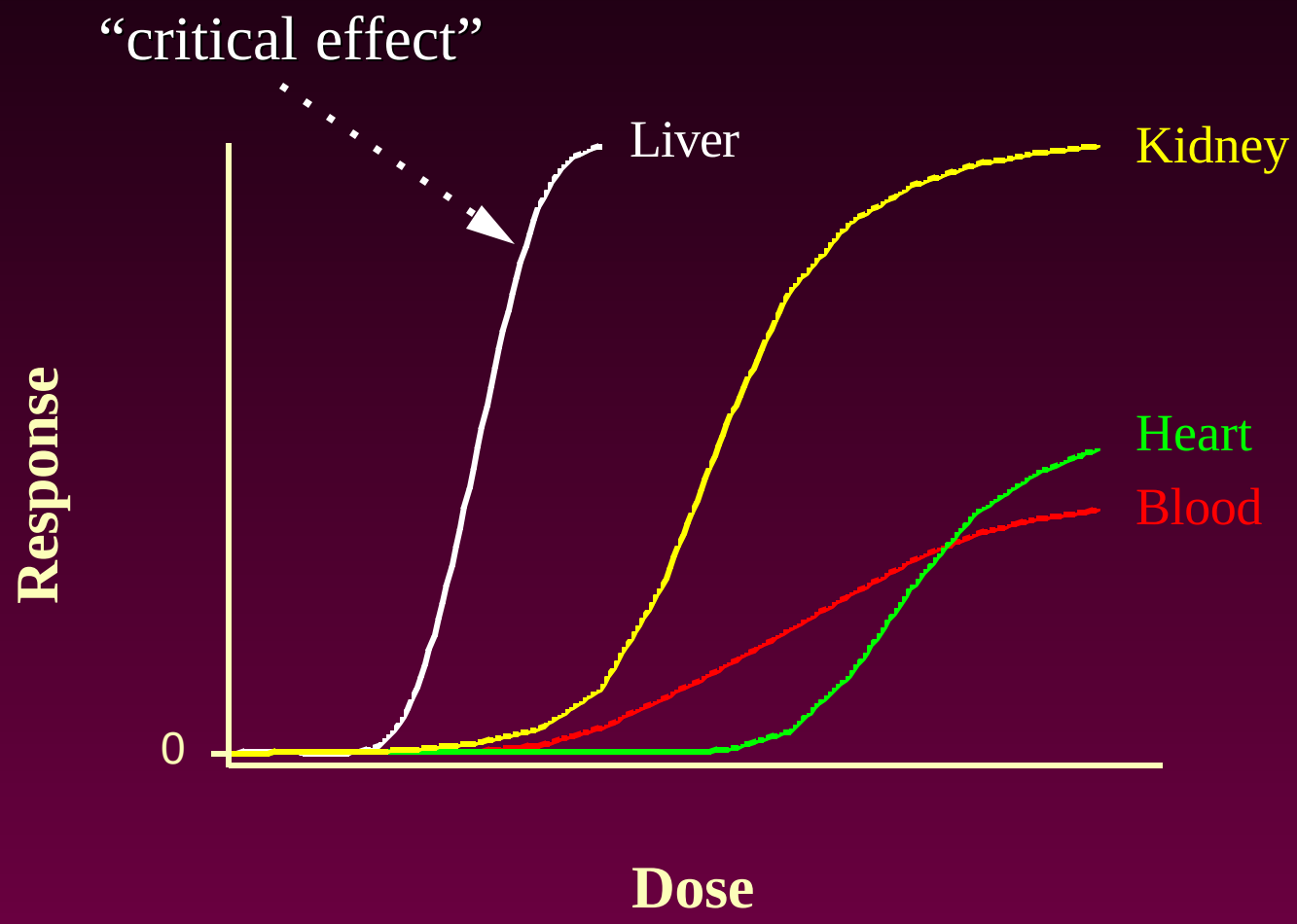
Non-Cancer Endpoints



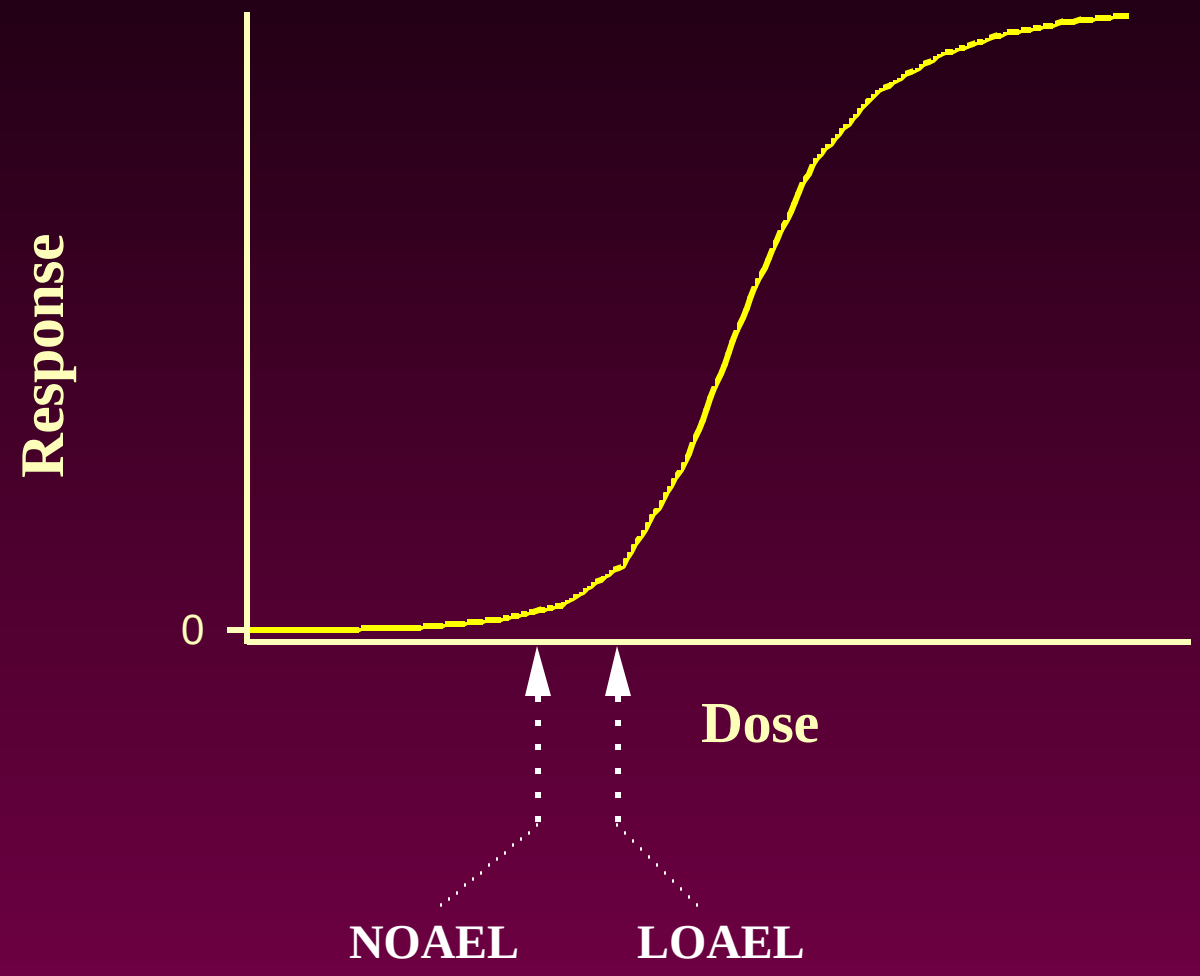
Acetylcholinesterase Inhibition by the Organophosphate Insecticide Chlorpyrifos



Multiple Target Organs



DR Curve & Regulatory Toxicology



Reference Dose (RfD)

- An estimate of a daily exposure to the human population (including sensitive subgroups) that is likely to be without an appreciable risk of deleterious effects during a lifetime.

Reference Dose (RfD)

- Established by EPA
  - available in IRIS
- Based on the most sensitive endpoint
- Chronic or subchronic exposure studies
- RfD = NOAEL / (UF x MF)

Standard Uncertainty Factors

10-fold factors that account for:

- intraspecies sensitivity in humans (10H)
- interspecies sensitivity (10A)
- less than chronic NOAEL values (10S)
- use of LOAEL rather than NOAEL (10L)

Modifying Factor

- Additional UF greater than 0 and less than or equal to 10.
- Allows professional assessment of additional uncertainties not accounted for by the UF.
- Default is 1.

Example of RfD Calculation

- Experimental Design:
  - 60-day oral exposure in mice
  - 4 exposure levels: 0, 1, 5, 25 mg/kg/day
  - 25 animals / exposure level
- Results
  - NOAEL = 5 mg/kg/day

Example of RfD Calculation

UF = 10H x 10A x 10S = 1000

MF = 2.0 (low number of animals)

RfD = NOAEL / (UF x MF)

= 5 mg/kg/day / (1000 x 2.0)

= 0.0025 mg/kg/day

Additional Considerations

- Route of Exposure
  - Influences occurrence and type of toxicity
  - Toxicokinetic differences
  - Oral “first pass” effect

Additional Considerations

- Toxicokinetics
  - Absorption - entry into body
  - Distribution - delivery to various tissues
  - Biotransformation - metabolic conversion
  - Excretion - elimination from body

- External vs. Internal vs. “Effective” Dose

Additional Considerations

- Mechanism(s) of Action (MOA)
  - biochemical interactions of toxicant and "target" tissue
  - ex: Chlorpyrifos
    - inhibits acetylcholinesterase
    - allows accumulation of neurotransmitter
    - overstimulation of nervous system

Carcinogens vs. Non-Carcinogens

- Toxicokinetic processes are similar.
- Mechanisms of toxicity are different.
  - ex: Benzo(a)pyrene
  - "One-hit" model of carcinogenesis
- Thresholds assumed not to exist in carcinogen DR relationships.

Carcinogen DR Relationships

- Carcinogen DR curves indicate probability or risk of tumor formation.
- Risk from low-dose exposures cannot be directly measured.
- Mathematical models are used to extrapolate low-dose risk from high-dose exposures.

Average Number Animals Needed to Detect an Increase in Tumor Incidence

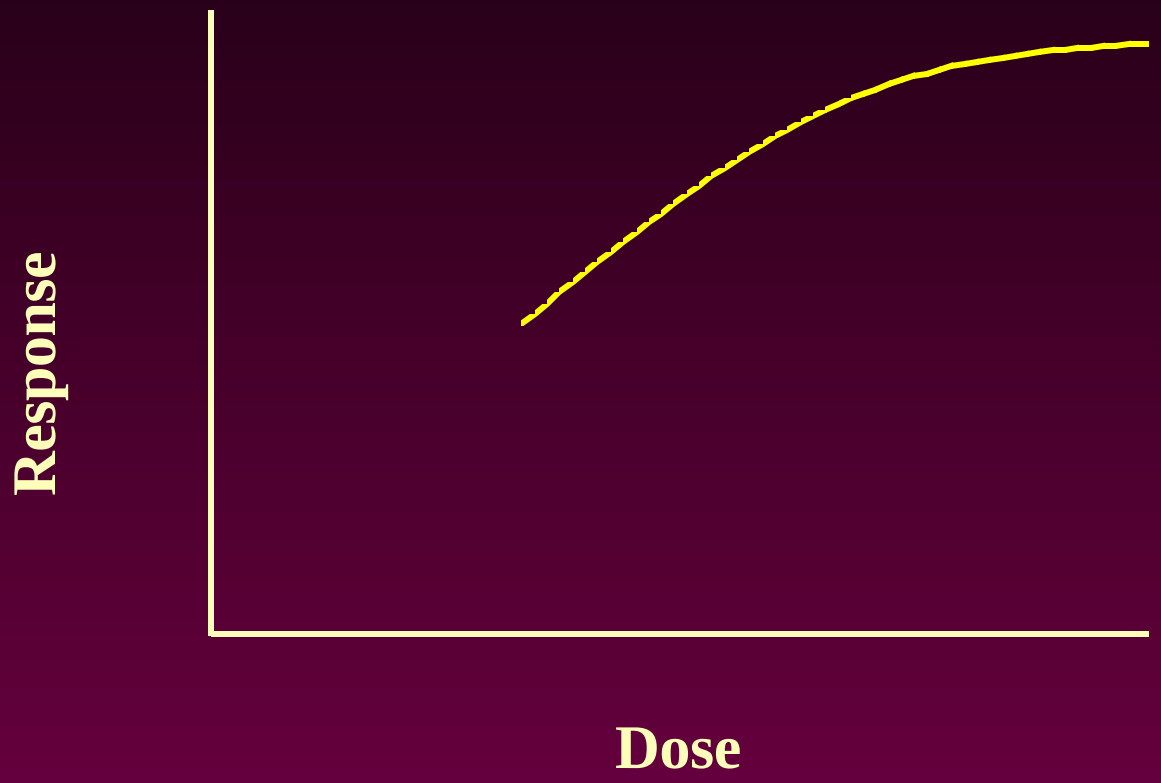
Increase	# Animals*
1:10	46
1:100	4600
1:1000	460,000
1:10,000	46,000,000

* Based on 0% Background Incidence

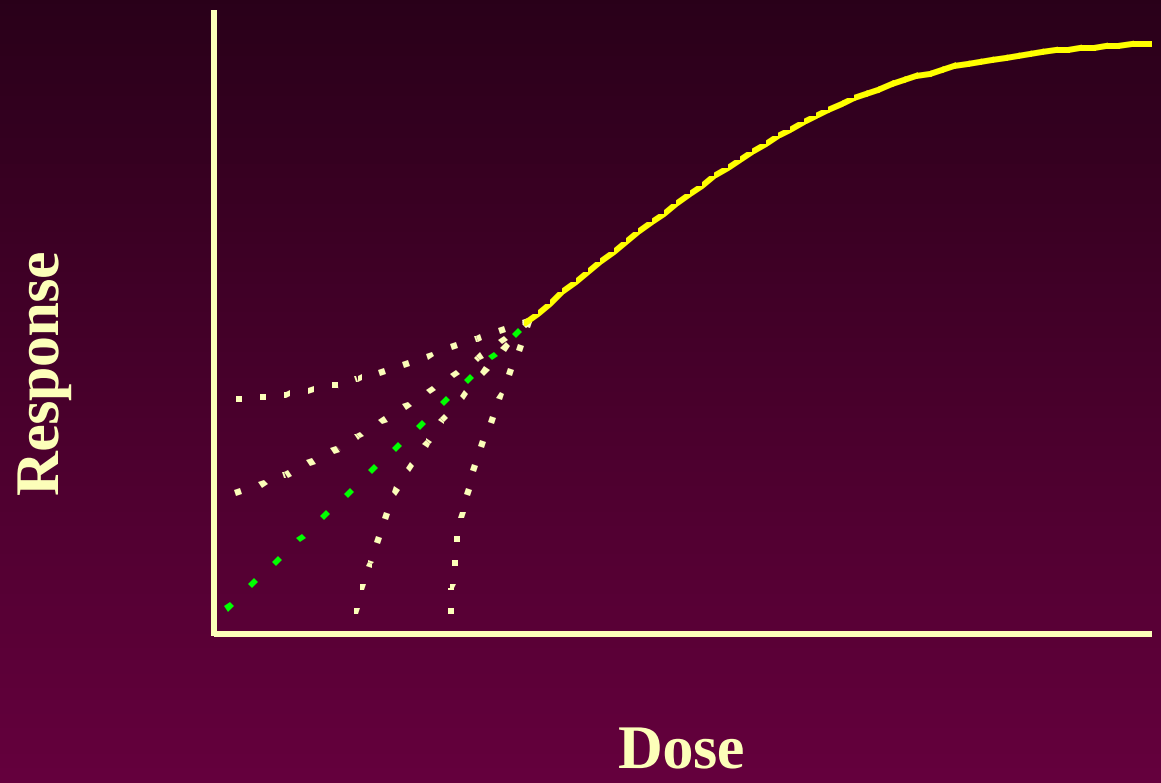
Toxicity Testing for Carcinogenesis

- Choose appropriate animal model
- Determine appropriate route of administration
- Expose animal for majority of lifetime (2 yrs)
- Look for increase in incidence of tumors

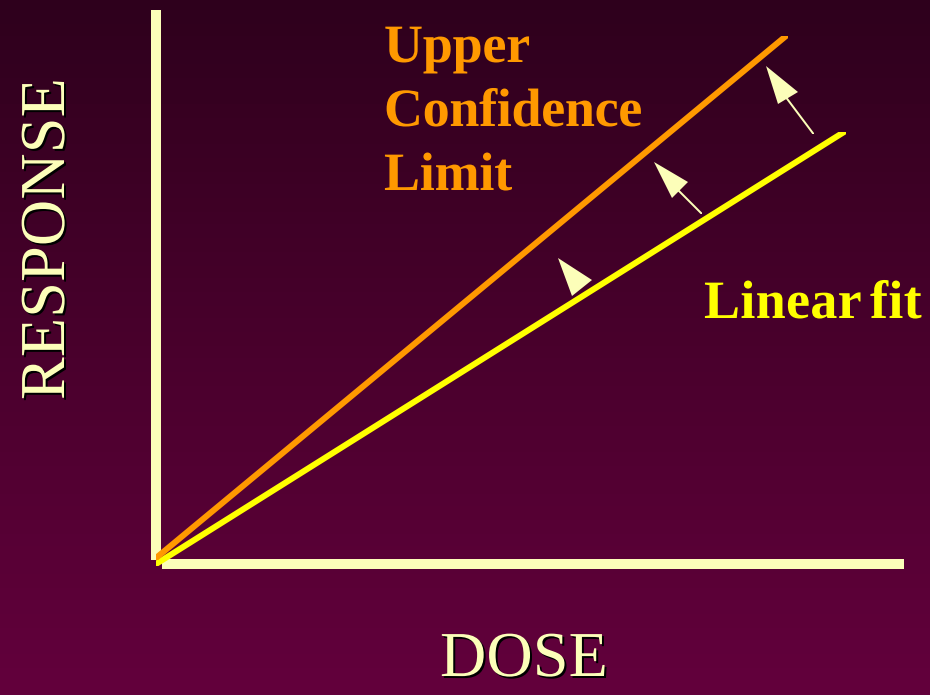
Hypothetical Carcinogen Dose-Response Curve



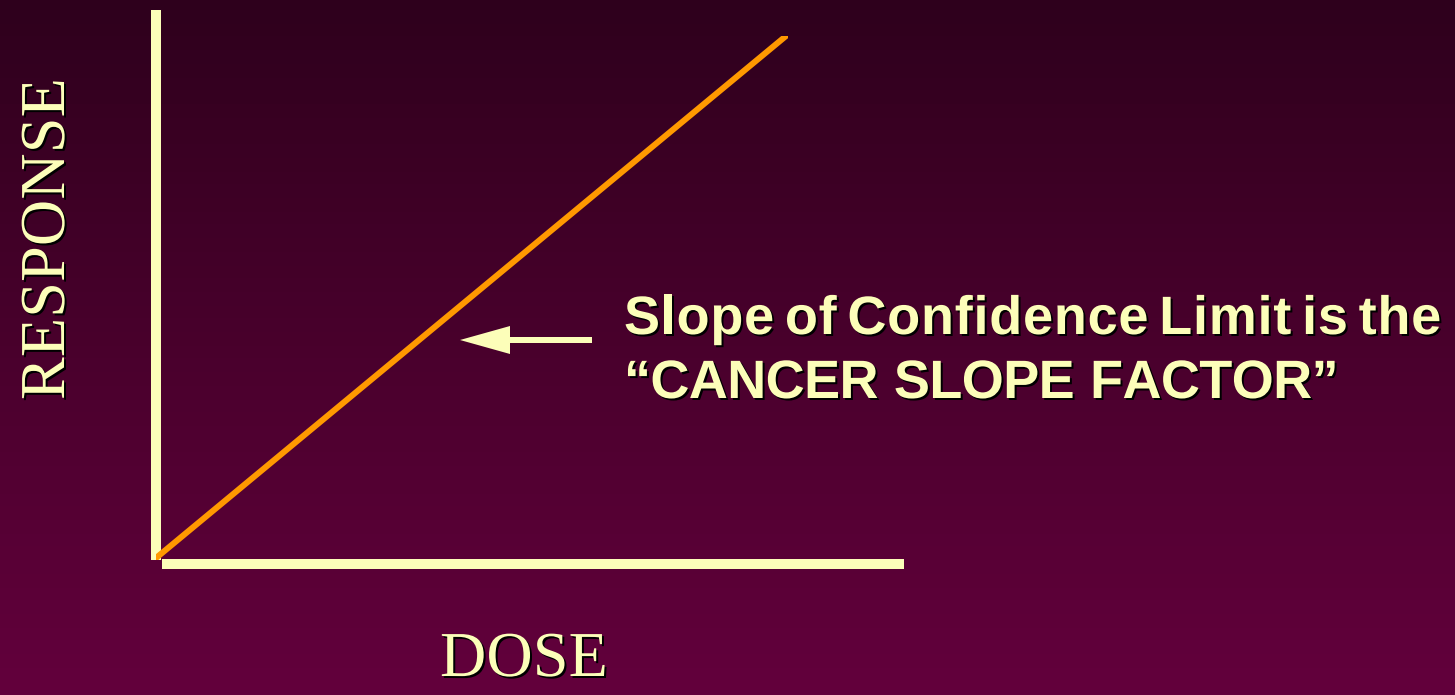
Hypothetical Carcinogen Dose-Response Curve



Low-Dose Risk Extrapolation



Cancer Slope Factor



How These Toxicology Values are Applied in Risk Assessment

- Exposure is divided by RfD to determine hazard.
- Exposure is multiplied by CSF to estimate cancer risk.

Summary of "Safety" Factors in Regulatory Exposure Limits

- Reference Doses (RfDs)
  - Uncertainty factors
  - Modifying factors
- Cancer Slope Factors (CSFs)
  - Linearized Model
  - Upper Confidence Limit

Conclusions

- RfDs & CSFs are based on studies with animal and available human epidemiology data.
- Safety factors and methods provide values that are conservative, even for sensitive subgroups.
- Allow the risk of harm from exposures to be assessed.