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Principles of Exposure, Dose, and Response

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Section A

Overview and Definitions

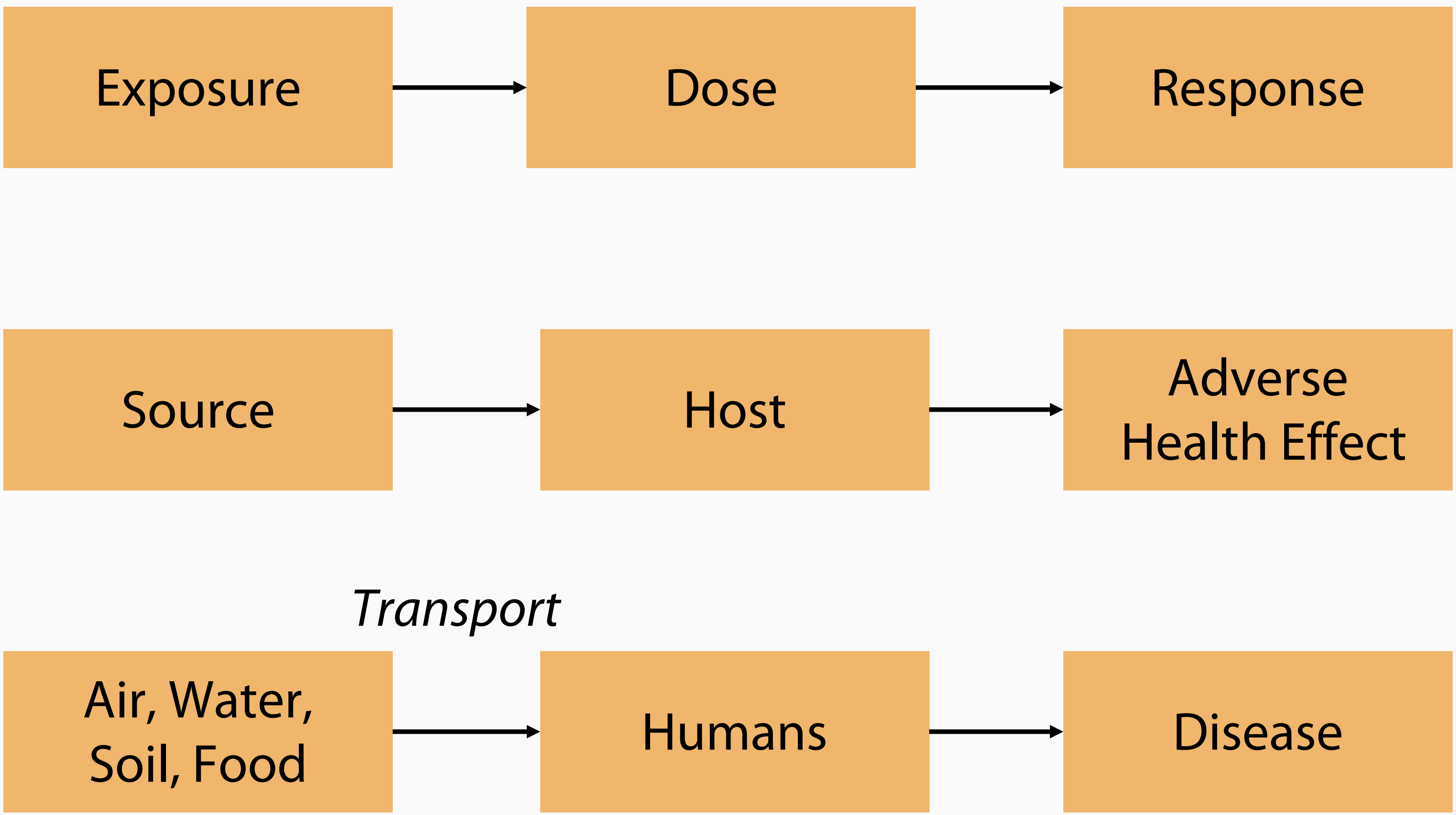
Definitions: Exposure and Agent

- Exposure
  - Any condition which provides an opportunity for an external environmental agent to enter the body
- Agent
  - Any chemical, biological, or physical material capable of eliciting a biological response
  - Different than the vector carrier (air, soil, water, food)

Definitions: Dose and Response

- Dose
  - The amount of agent actually deposited within the body
  - Typically, the distinction between exposure and dose is blurred, although in reality, significantly different doses can result from the same exposure
- Response
  - The biological response to an agent

Exposure-Response Paradigm



Risk Assessment and Management

- Risk assessment
  - The determination of the probability that an adverse effect will result from a defined exposure
- Risk management (science and value judgements)
  - The process of weighing policy alternatives and selecting the most appropriate intervention strategy based on the results of risk assessment and social, economic, and political concerns
- Factors influencing environmental health problems and their solutions are both technical/scientific and non-scientific in character!

Risk Assessment Activities

1. Hazard identification
   – Characterize the innate toxic effect of the agent
2. Exposure assessment
   – Measure or estimate the intensity, frequency, and duration of human exposure to the agent
3. Dose-response assessment
   – Characterize the relationships between varying doses and incidences of adverse effects in exposed populations
4. Risk characterization
   – Estimate the incidence of health effects under the various actual conditions of human exposure

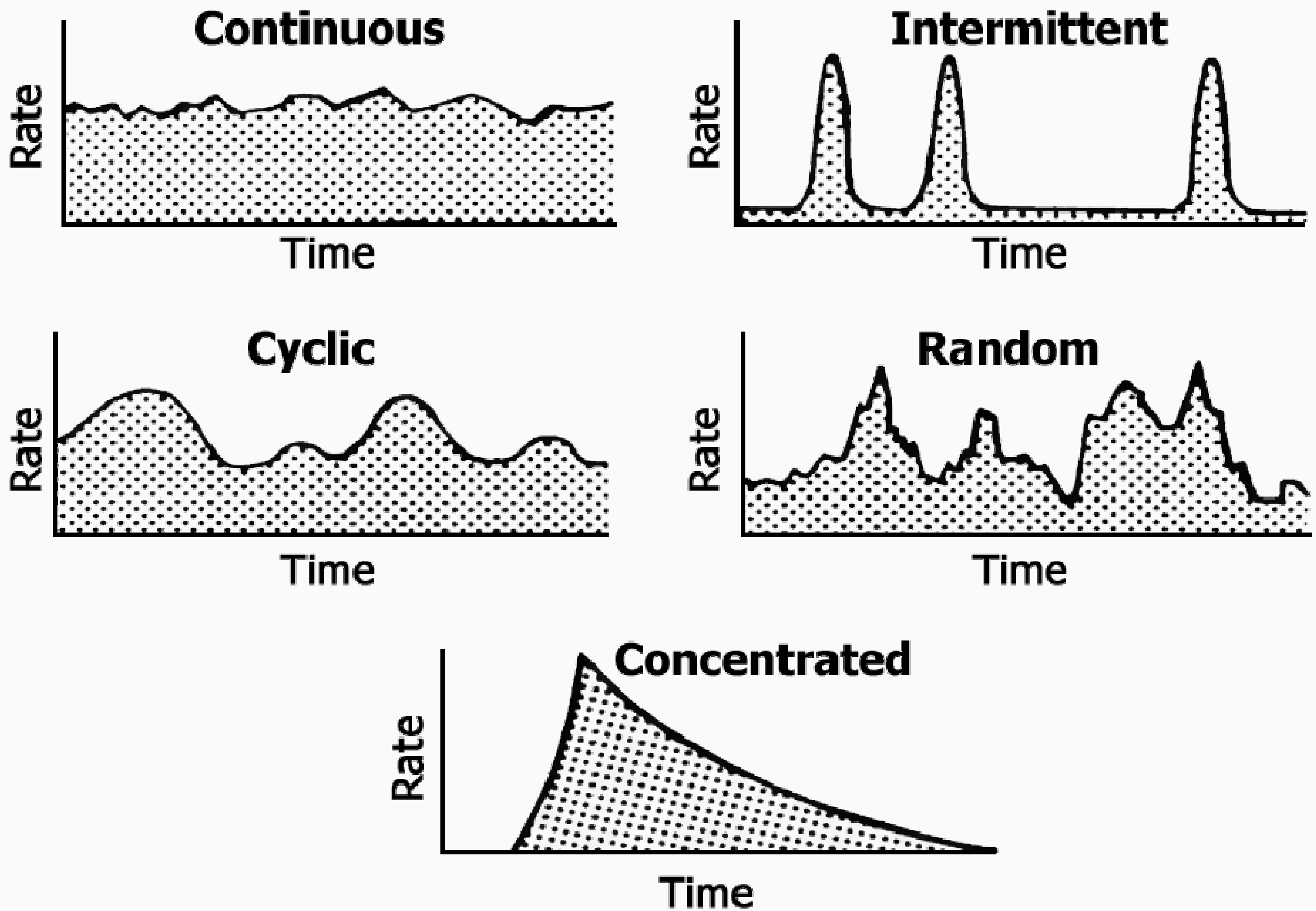
Exposure Assessment

- Characterization of the exposure setting
- Identification of the exposure pathway
- Quantification of exposure

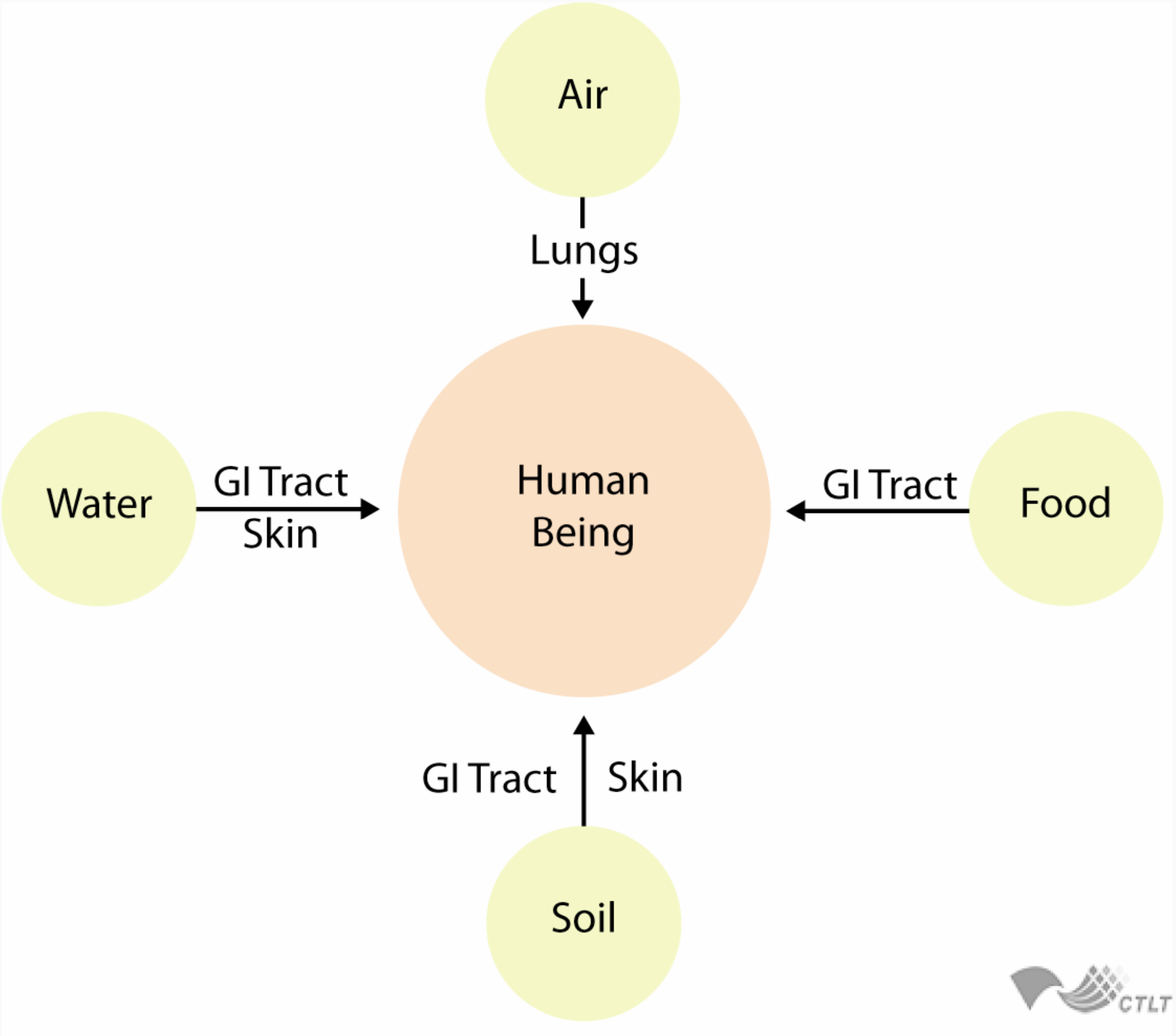
Exposure = Intensity x Frequency x Duration

Exposure = How much x How often x How long

Patterns of Exposure



Vectors for Exposure



Adapted by CTLT from Moeller, D. W.

Air: Liquid and Solid Suspensions

- Aerosols
  - Characterized by particle size, which influences physical interactions (coagulation, dispersion, sedimentation, impaction)
  - Aerodynamic properties depend on dimensions, shape and density
    - Dust—mechanical division of bulk material
    - Smoke—condensation of combustion products
    - Mist—mechanical shearing of a bulk liquid
    - Fog—condensation of water vapor on atmospheric nuclei
    - Smog—combination of smoke and fog

Air: Gases and Vapors

- True solutions
  - Present as discrete molecules; vapors are the gaseous phase of a substance that is normally a solid or liquid at room temperature
  - Generally form mixtures so dilute that physical properties (e.g., density, viscosity) are indistinguishable from those of clean air
  - All molecules of a given compound dispersed in air are essentially equivalent in their size and capture properties

Water and Soil

- Chemical contaminants in solution or as hydrosols
  - Immiscible solid or liquid particles in suspension; liquid particles in suspension = emulsion (water equivalent of an aerosol)
- Dissolved contaminants
  - Solids, gases, and suspended particles
  - Behavior is like that of water
- Soil
  - Intrinsic biological or physical agent
  - Chemical contaminants

Food

- Toxic agents can be acquired during production, harvesting, processing, packaging, transportation, storage, cooking, serving
- Agents are naturally occurring toxicants or those that become toxicants on conversion by chemical reactions (with other constituents or additives) or by thermal or microbiological conversion

Examples of Exposure

- Contaminated groundwater
  - Ingestion (drinking water)
  - Dermal contact (bathing)
  - Inhalation of VOCs (during showering)
- Contaminated surface water
  - Incidental ingestion or dermal absorption of chemical or biological contaminant

Examples of Exposure

- Contaminated surface soil
  - Ingestion or dermal absorption of contaminants
- Contaminated food
  - Ingestion of contaminated muscle tissue or vegetables and fruits grown in contaminated soil or covered with contaminated dust
- Contaminated air
  - Inhalation of “fugitive dusts” or VOC emissions by nearby residents or on-site workers

Issues in Understanding "Exposure"

- Distinction between agents and vectors
- Time activity patterns
  - What did agent do in environment with time?
  - What did host do in environment with time?
- Homogeneous versus heterogeneous exposures
  - Mixed exposure scenario
  - Difficult to quantitate putative agent
- Factors influencing biodistribution
  - Same exposure may not yield the same dose

Hierarchy of Exposure Data or Surrogates

Types of Data	Approx. to Actual Exposures
1. Quantitative personal dosimeter measurements 2. Quantitative ambient measurements in vicinity of residence or activity 3. Quantitative surrogates of exposure, e.g., estimates of drinking water or food consumption 4. Residence of employment in proximity of source of exposure 5. Residence or employment in general geographic (e.g., county) of site or source of exposure	Best ↕ Poorest

Adapted from Moeller, D. W.

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Section B

Dose-Response Relationships

Dose-Response Relationships

- Quantitatively characterize the association between previous exposure to an environmental agent and subsequent development of disease
  - Frequently “stuck” with exposure-response relationships
  - Association versus cause and effect
  - Plausible biologic mechanism (one prerequisite for cause and effect)

Important Issues

- Distinction between exposure and dose
  - Exposure is “outside” the body
  - Dose is “inside” the body
- Definition of ***response***
  - Change in structure or function, morbidity, or mortality
    - Define and characterize endpoint

Important Issues

- Challenges in obtaining dose-response relationships
  - Characterization of exposure or dose
  - Assessment of response
  - Selection of dose-response model to fit the observed data

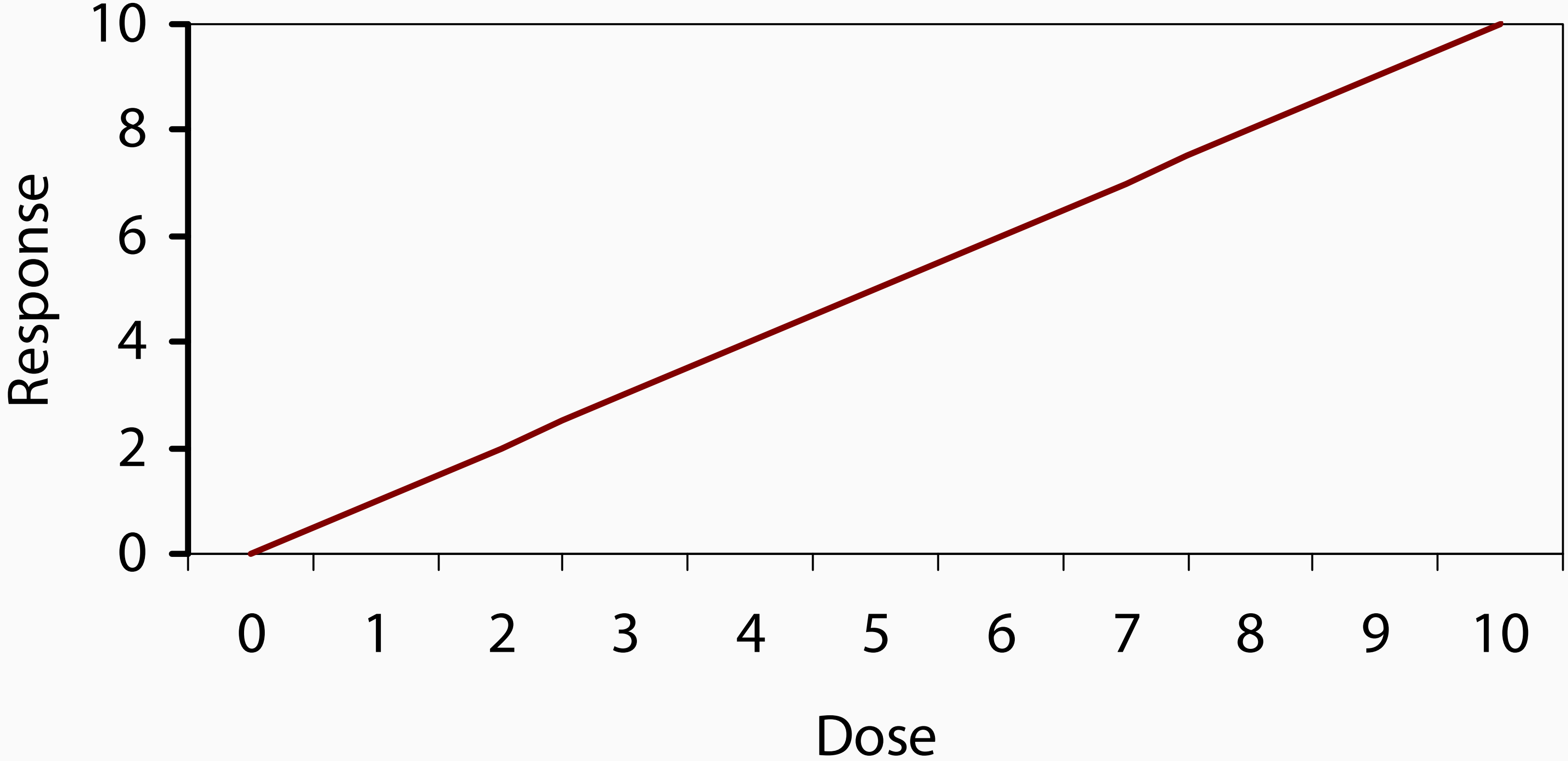
Issues in Understanding "Response"

- Acute versus delayed onset
  - Latent period confounds many epidemiologic studies
- Short-term versus chronic disease
  - Irreversibility
- Spontaneous incidence
  - Function of age
  - Tease out agent-produced component from background
  - Hundreds of causes of "nonspecific" effects

Dose-Response Models

- Model
  - A mathematical description of the relationship between exposure or dose and response
  - The mathematical model or “function” may be plotted on a graph (with exposure or dose on the x-axis and response on the y-axis)

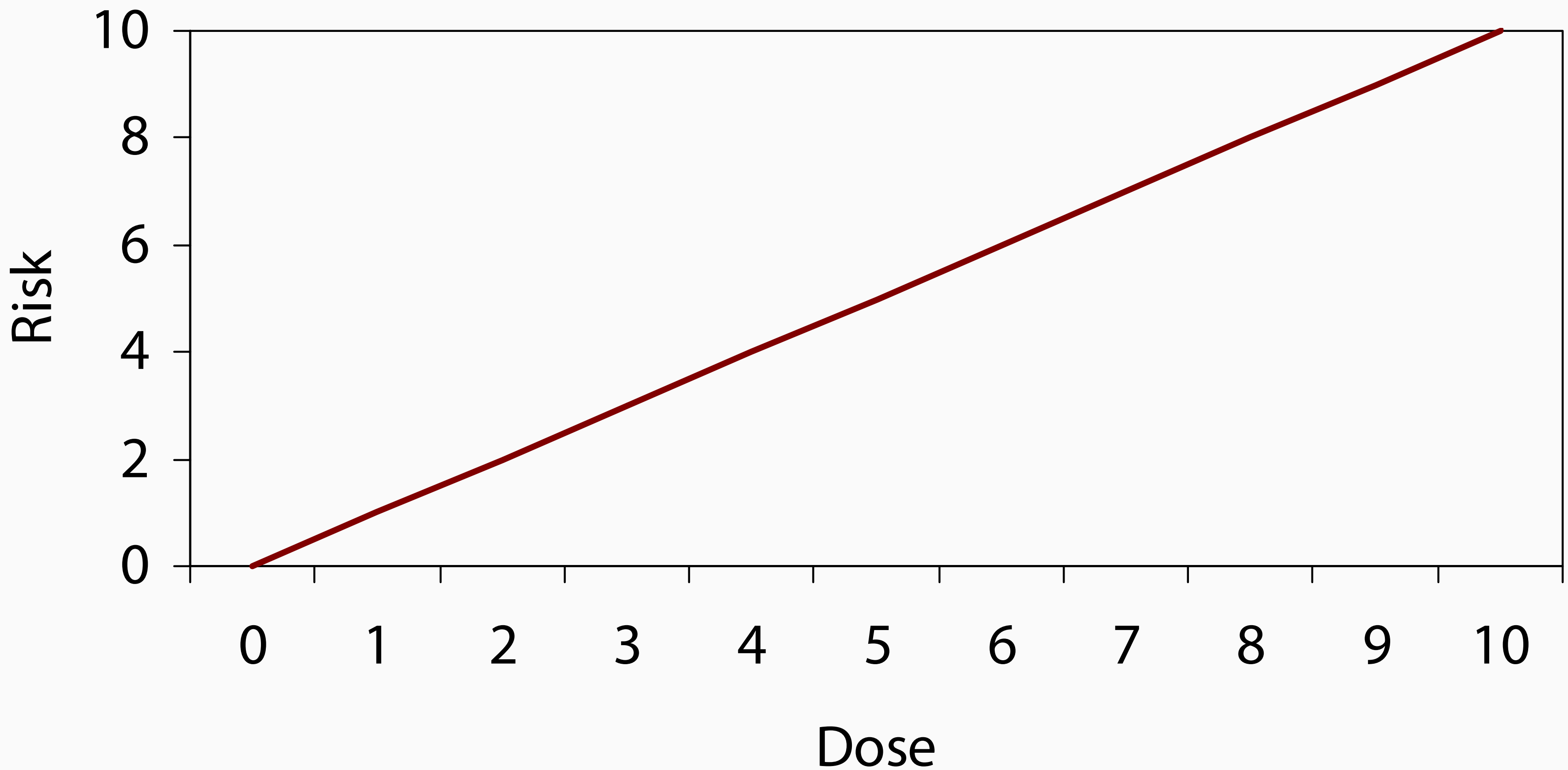
Dose-Response Curve



Stochastic ("Random") Model

- Risk (probability) of response is a function of dose
  - Assumes no threshold
  - No dose is safe
  - Any dose increases the risk (not severity)
  - For example, cancer
    - Implies that any exposure increases the risk of cancer, with larger exposures producing a greater risk (but not a bigger tumor)

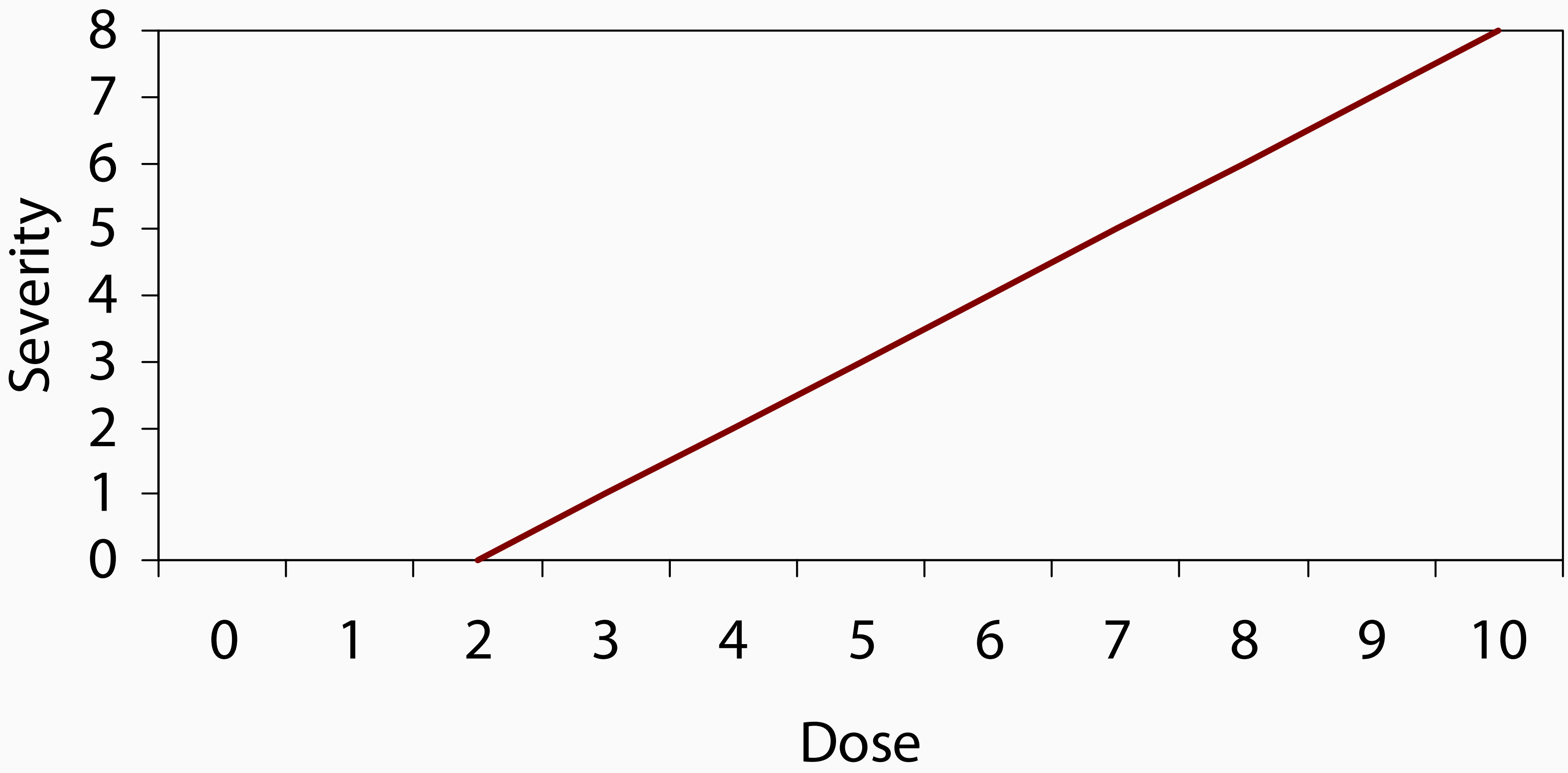
Stochastic ("Random") Process



Non-Stochastic ("Deterministic") Model

- Severity of response is a function of dose
  - Assumes a threshold
  - A "safe" dose exists
  - Examples
    - Radiation
      - Cataractogenesis
      - Mental retardation following in utero irradiation
    - Chloracne

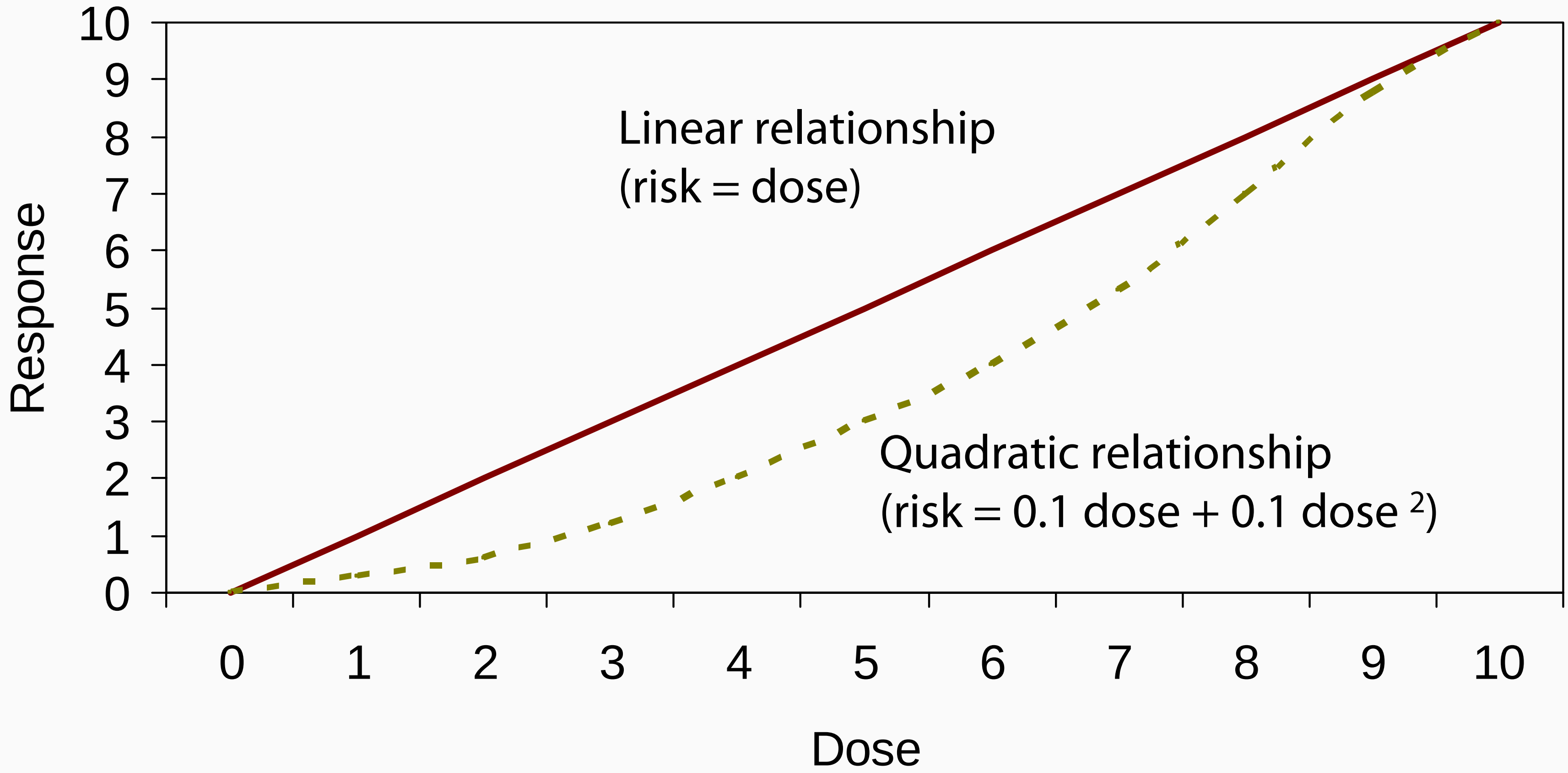
Non-Stochastic ("Deterministic") Process



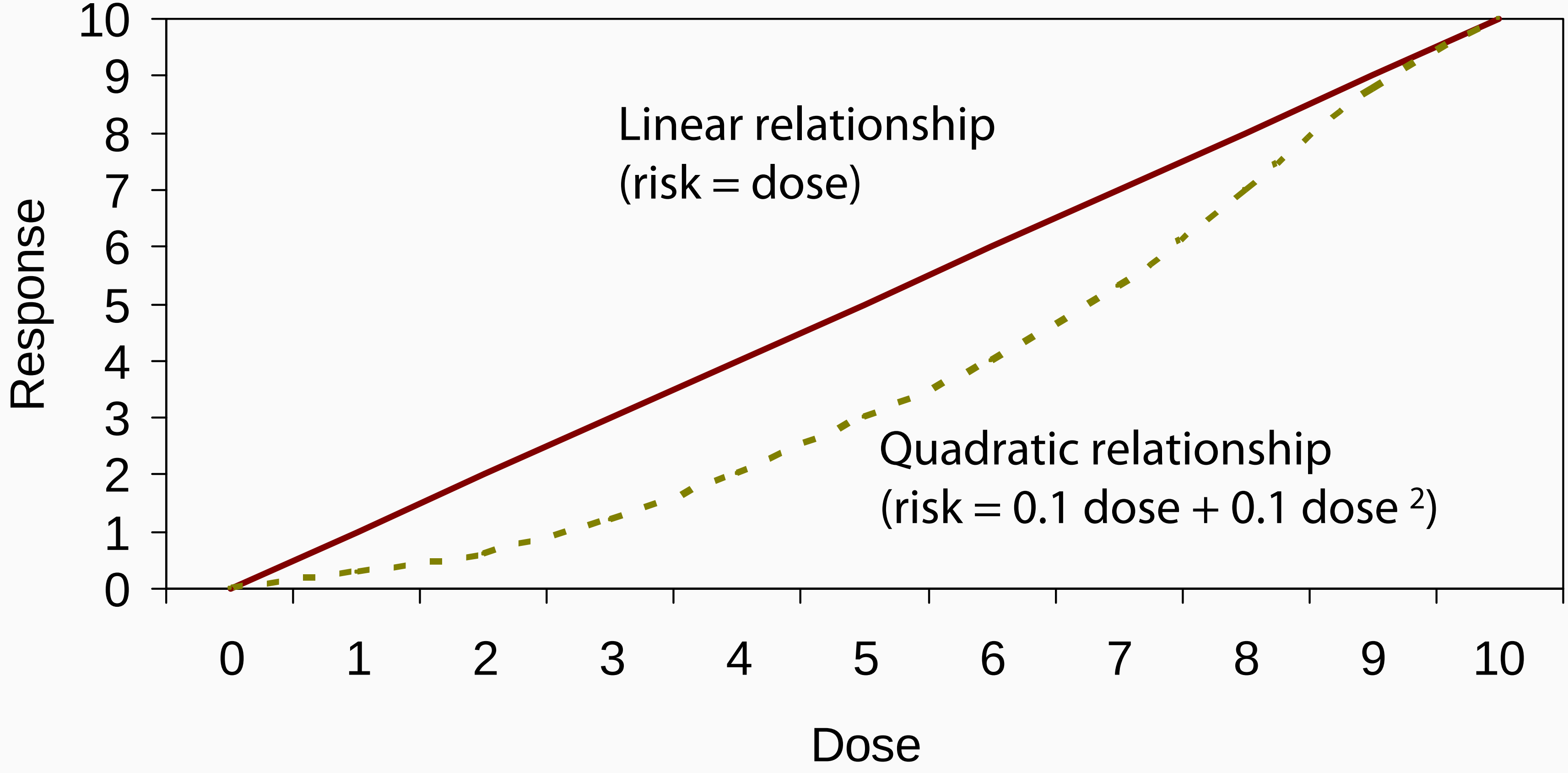
Major Issues in the Choice of a Model

- Random or deterministic model
- Actual mathematical function
  - The shape of the curve
- Presence or absence of a threshold
  - An exposure or dose below which there is no effect

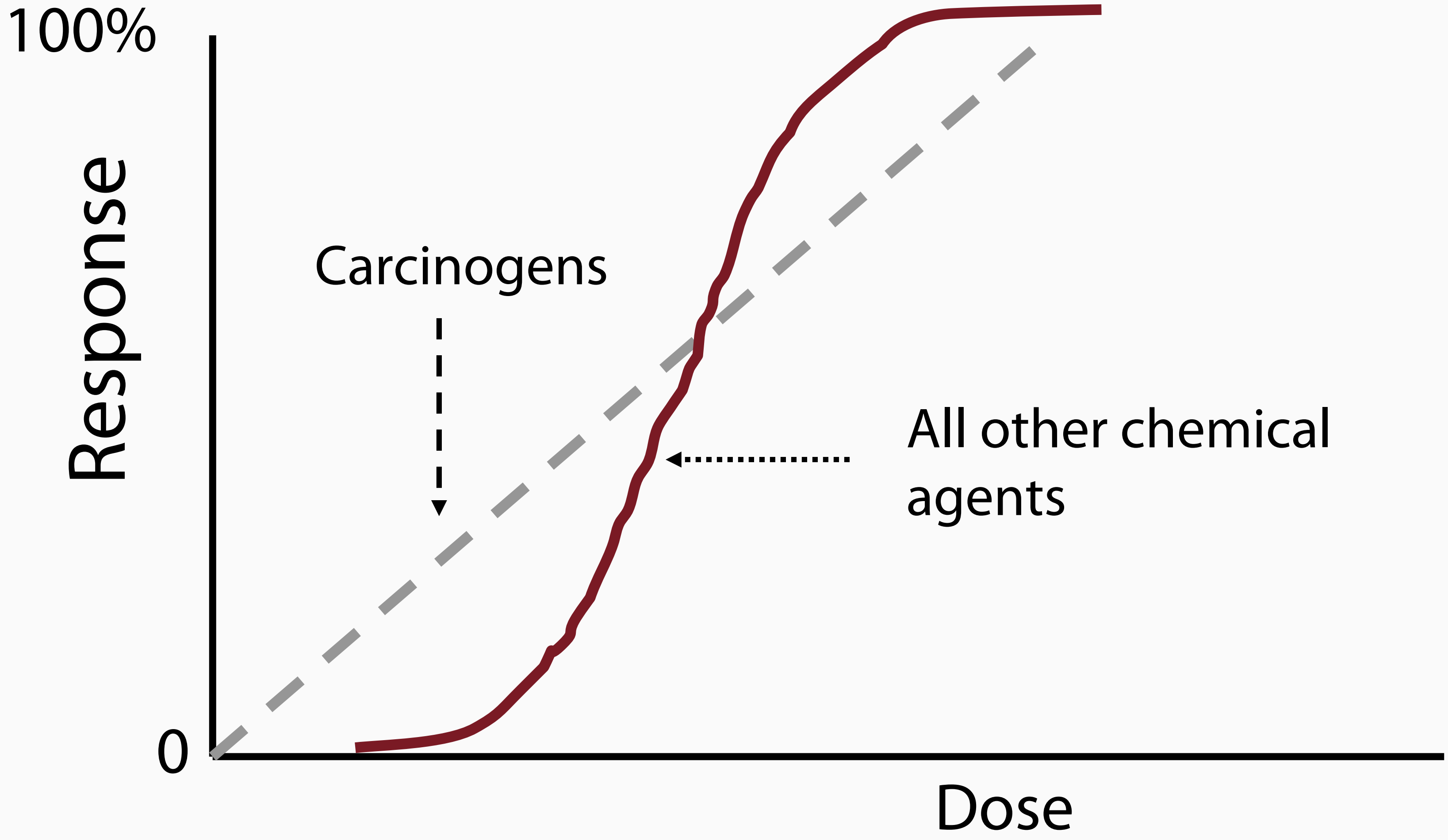
Dose-Response Curve



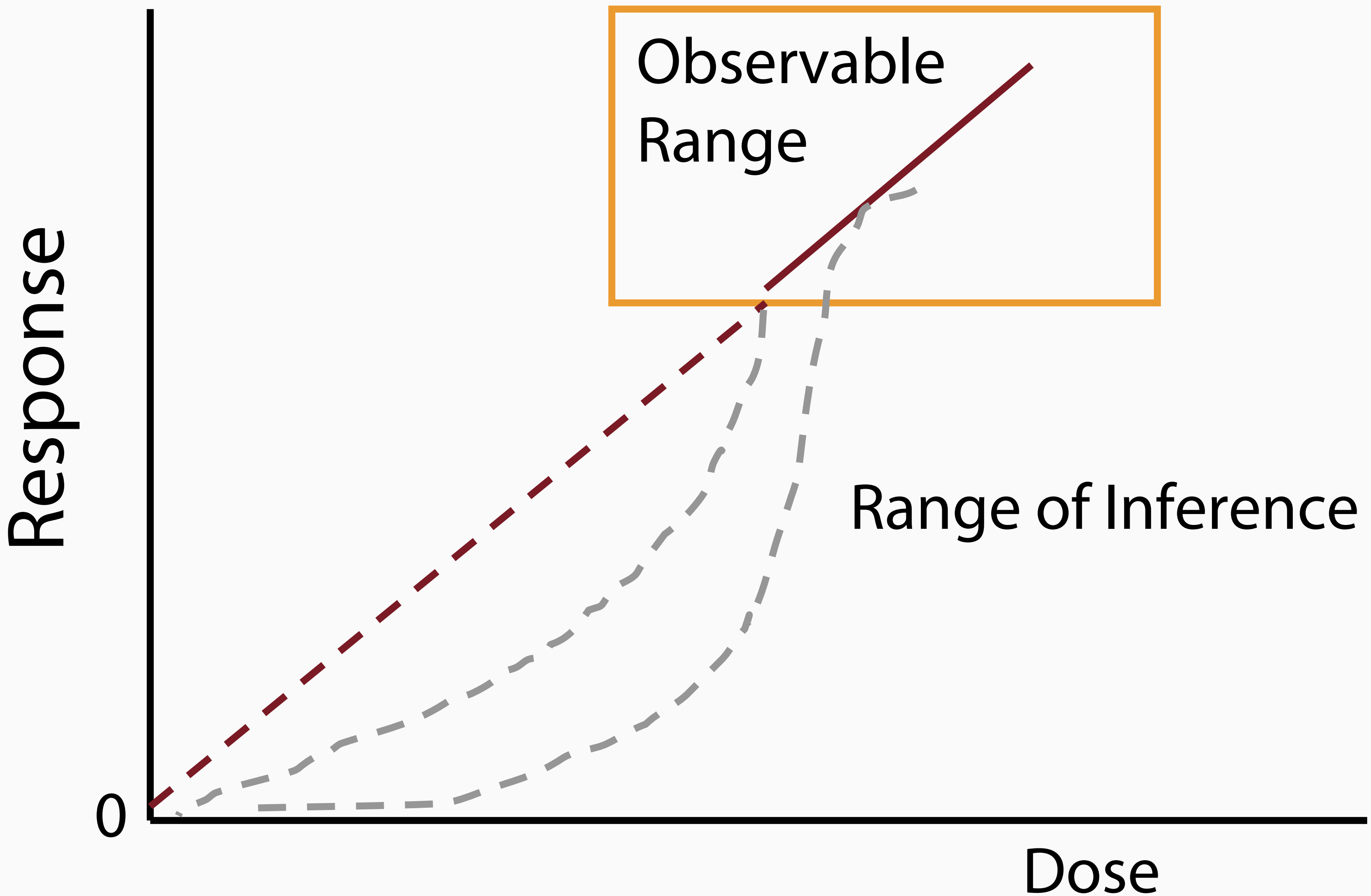
Dose-Response Curve



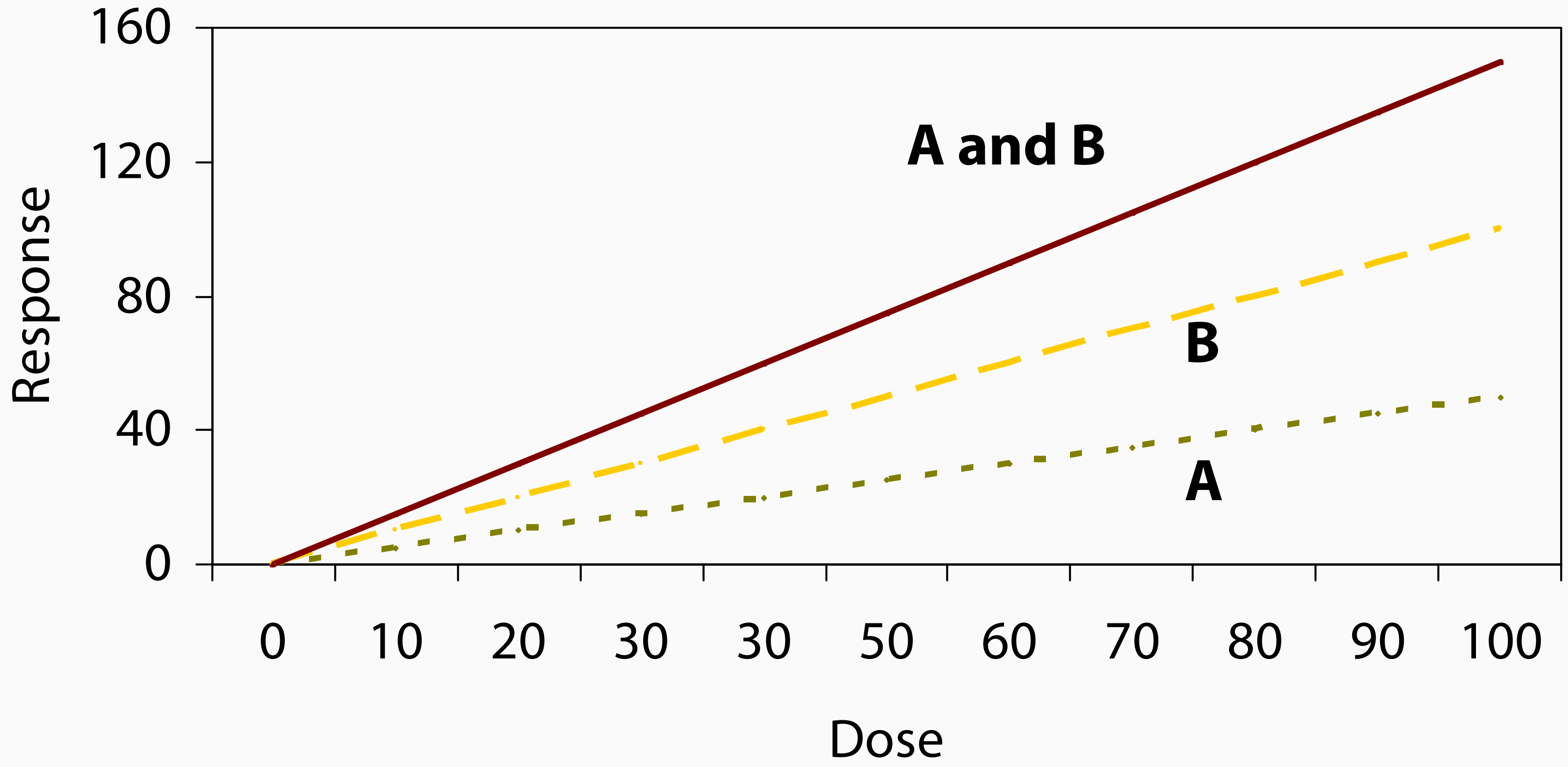
Dose-Response Curve



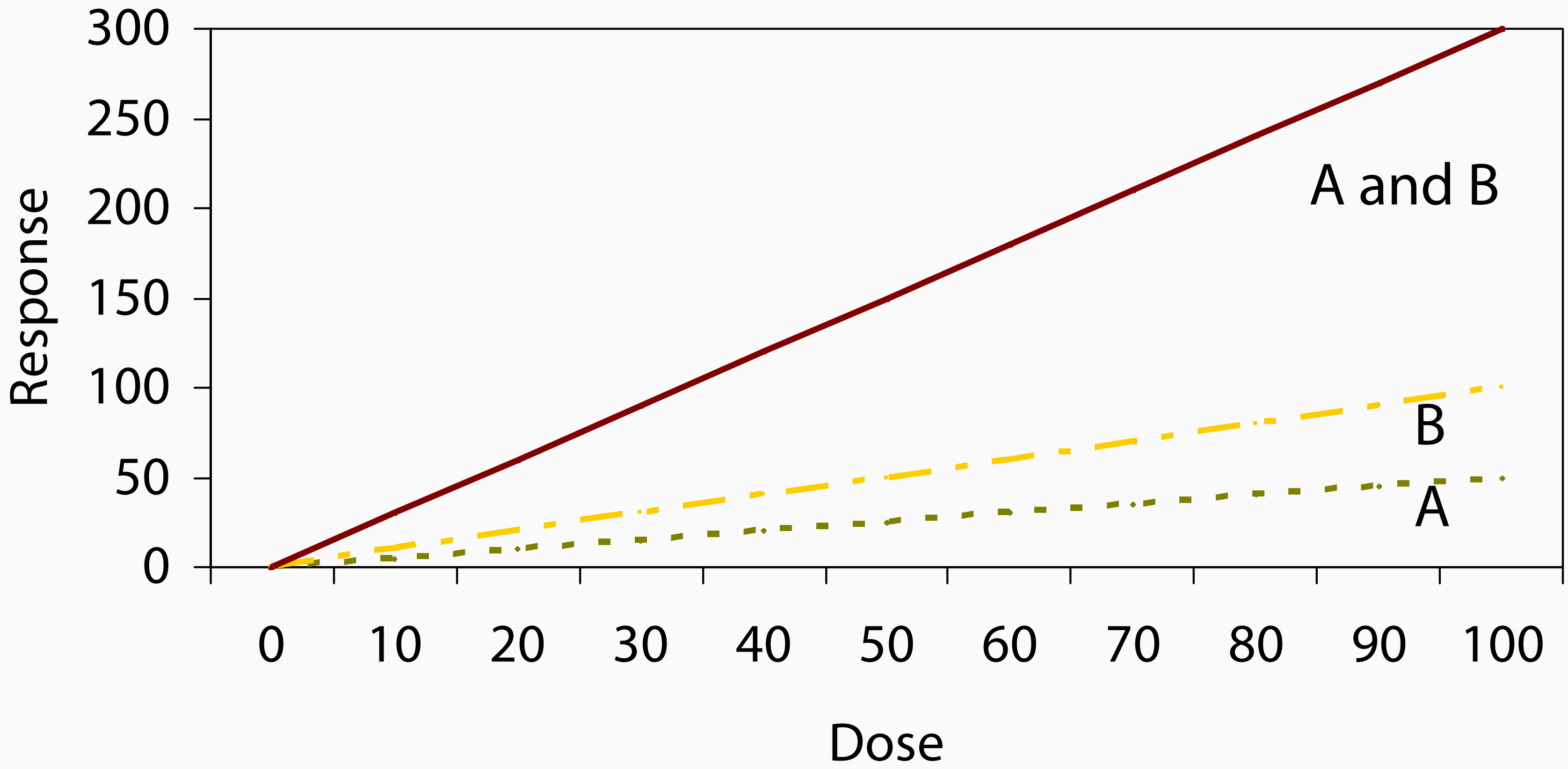
Dose-Response Curve



Additivity


160
120
80
40
0
Response
A and B
B
A
0
10
20
30
30
50
60
70
80
90
100
Dose

Synergism



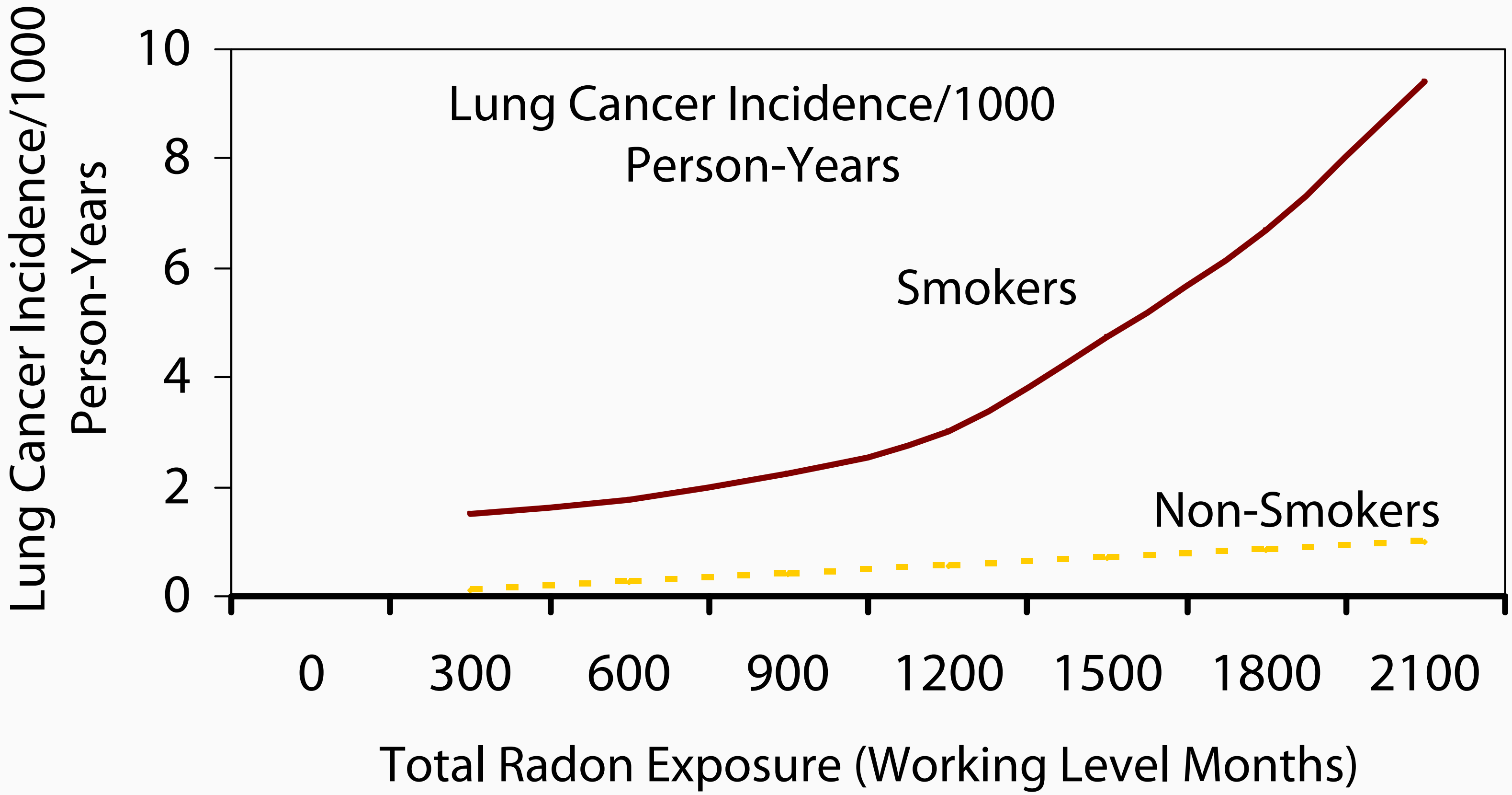
300
250
200
150
100
50
0
Response
A and B
B
A
0
10
20
30
40
50
60
70
80
90
100
Dose

Lung Cancer and Asbestos

- Lung cancer and asbestos compared with the risk of dying from lung cancer for a nonsmoker not exposed to asbestos

Source: Report of the Surgeon General, 1985.

Lung Cancer and Radon



Adapted from: Archer, Gillam, Wagoner. (1976). NY Acad Sci, 271.

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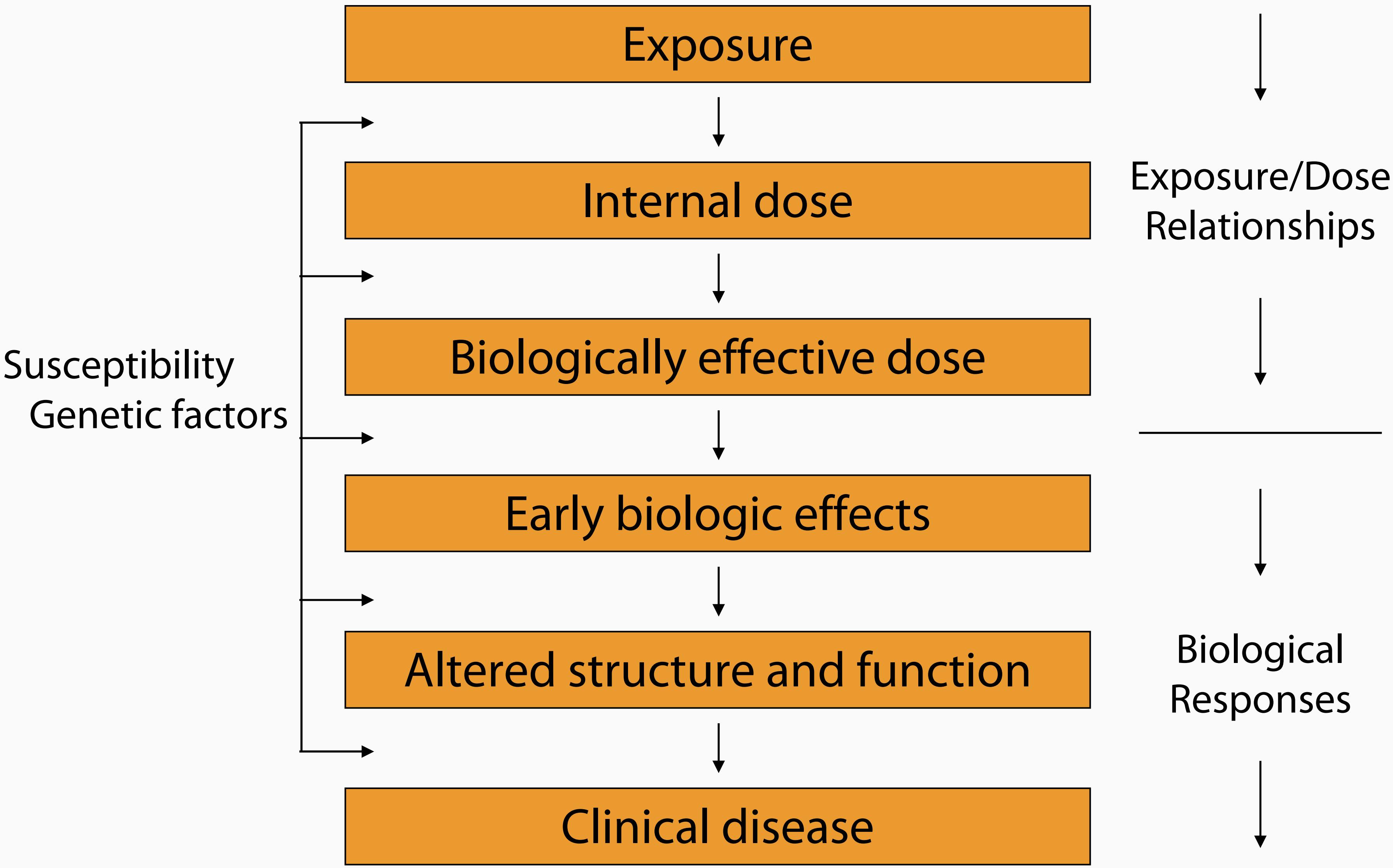
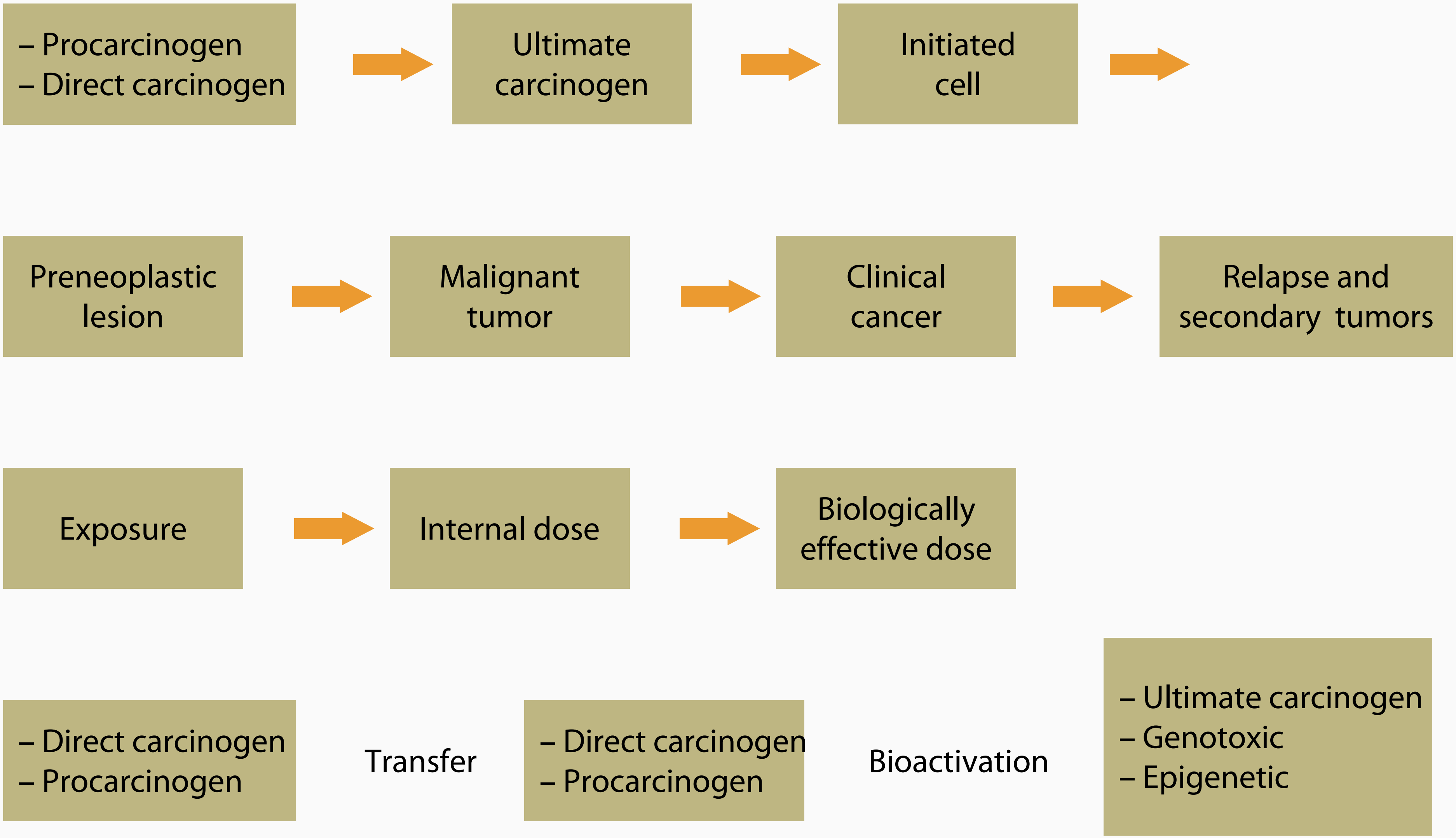
Section C

The Toxicological Paradigm, the Public Health Paradigm, and the Environmental Health Paradigm

Toxicological Paradigm



Sequence Leading to Neoplasia



Toxicological Paradigm, Neoplasia, and Intervention

TOXICOLOGICAL PARADIGM						
Exposure	Internal Dose	Biologic Effective Dose	Early Biologic Effect	Altered Structure or Function	Clinical Disease	Prognose Signify
SEQUENCE LEADING TO NEOPLASIA						
Pro-/Direct Carcinogen	Ultimate Carcinogen	Initiated Cell	Pre-neoplastic Lesion	Malignant Tumor	Clinical Cancer	Relapse & Secondary Tumors
INTERVENTION STRATEGIES						
Primary Prevention		**Chemo-Protection**		**Secondary Prevention**	**Therapy**	**Tertiary Prevention**
Avoid Exposure	Prevent Formation of Carcinogens	Block Interactions with Genome	Suppress Growth	Early Diagnosis	Surgery Radio-Rx Chemo-Rx	Prevent Relapse & 2° Tumors

Lung Cancer in the United States

- Lung cancer accounts for more 25% of all cancer deaths
- Lung cancer deaths have increased about 30% in men and 200% in women over the age of 65 since 1973
  - Women took up smoking decades later than men
- Most lung cancer deaths are the result of cigarette smoking

Steps in Lung Cancer Mortality Reduction: 1

- Identify risk factors and associated factors
- Identify and characterize susceptible groups
- Identify the effects of secondhand smoke (ETS)
- Understand the role of tobacco smoke in carcinogenesis
- Understand intermediate stages of the carcinogenic process

Steps in Lung Cancer Mortality Reduction: 2

- Design early diagnostic procedures
- Understand the effects of secondhand smoke
- Understand the addictive nature of nicotine
- Design effect-risk communication strategies
- Design effective smoking cessation techniques
- Promote negative social feedback mechanisms
- Design ventilation systems to reduce ETS
- Regulate the sale of cigarettes
- Tax the sale of cigarettes

Public Health Paradigm

Epidemiology	Mechanistic Research	Behavioral and Engineering	Regulatory Process
Identify risks	Understand role of tobacco	Design risk communication strategy	Regulate sales
Identify susceptibles	Understand carcinogenesis and design early diagnostics	Design smoking cessation techniques	Tax sales
Identify ETS effects	Understand ETS effects	Design ventilation systems	
	Understand nicotine addiction		

Public Health and Environmental Health Paradigms

Public Health Paradigm			
Epidemiology	Mechanistic Research	Behavioral and Engineering Sciences	Regulatory Process

Risk Assessment | *Risk Management*

Environmental Health Paradigm			
Environmental Epidemiology	Toxicology	Environmental Engineering	Environmental Regulation

Key Points: Exposure, Dose, and Response

- Exposure
  - Refers to any condition which provides an opportunity for an external environmental agent to enter the body
- Dose
  - Refers to the amount of agent actually deposited within the body
- Response
  - Refers to the biological effect of the agent

Key Points: Paradigms

- The relationship between previous exposure to an environmental agent and subsequent development of clinical disease can be represented as a six-stage "toxicological paradigm"
- Consideration of the toxicological paradigm leads to a general "public health paradigm," which can be directly related to a corresponding "environmental health paradigm"
  - The activities or stages in this paradigm may be broadly grouped into "risk assessment" and "risk management"