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

Exposure -> Dose -> Response

Source -> Host -> Adverse Health Effect

Transport
Air, Water, Soil, Food -> Humans -> Disease
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!**
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 \times Frequency \times Duration

Exposure = \textit{How much} \times \textit{How often} \times \textit{How long}
Patterns of Exposure

- Continuous
- Intermittent
- Cyclic
- Random
- Concentrated
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
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

<table>
<thead>
<tr>
<th>Types of Data</th>
<th>Approx. to Actual Exposures</th>
</tr>
</thead>
<tbody>
<tr>
<td>1. Quantitative personal dosimeter measurements</td>
<td>Best</td>
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<tr>
<td>2. Quantitative ambient measurements in vicinity of residence or activity</td>
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<tr>
<td>3. Quantitative surrogates of exposure, e.g., estimates of drinking water or food consumption</td>
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<td>4. Residence of employment in proximity of source of exposure</td>
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<tr>
<td>5. Residence or employment in general geographic (e.g., county) of site or source of exposure</td>
<td>Poorest</td>
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Adapted from Moeller, D. W.
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

The graph illustrates a direct proportionality between dose and response, with the response increasing linearly as the dose increases. The x-axis represents the dose, ranging from 0 to 10, and the y-axis represents the response, ranging from 0 to 10.
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

![Graph showing a linear relationship between dose and risk. The x-axis represents dose ranging from 0 to 10, and the y-axis represents risk ranging from 0 to 10. A straight line runs through the origin, indicating that risk increases linearly with dose.]
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

![Graph showing the relationship between dose and severity. The graph is a linear function with dose on the x-axis and severity on the y-axis. The line shows an increase in severity as dose increases.]
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

Linear relationship
(risk = dose)

Quadratic relationship
(risk = 0.1 dose + 0.1 dose^2)
Dose-Response Curve

Linear relationship
(risk = dose)

Quadratic relationship
(risk = 0.1 dose + 0.1 dose^2)
Dose-Response Curve

- **Carcinogens**
- **All other chemical agents**
Dose-Response Curve

Observable Range

Range of Inference
Additivity
Synergism

The graph illustrates the dose-response relationship for A and B. The response increases linearly with the dose for both A and B. The graph suggests a synergistic effect when both A and B are administered together, as indicated by the steeper slope compared to the individual responses of A and B.
Lung cancer and asbestos compared with the risk of dying from lung cancer for a nonsmoker not exposed to asbestos.

- Non-smoking asbestos worker: 5
- Smokers not exposed to asbestos: 11
- Smoking asbestos workers: 53
- Asbestos workers smoking 1 pack/day: 87

Lung Cancer and Radon

Section C

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

Exposure

Internal dose

Biologically effective dose

Early biologic effects

Altered structure and function

Clinical disease

Exposure/Dose Relationships

Susceptibility

Genetic factors

Biological Responses
Sequence Leading to Neoplasia

- Procarcinogen
  - Direct carcinogen

Ultimate carcinogen

Initiated cell

Preneoplastic lesion

Malignant tumor

Clinical cancer

Relapse and secondary tumors

Exposure

Internal dose

Biologically effective dose

Transfer

- Direct carcinogen
  - Procarcinogen

Bioactivation

- Ultimate carcinogen
  - Genotoxic
  - Epigenetic
Toxicological Paradigm, Neoplasia, and Intervention

<table>
<thead>
<tr>
<th>TOXICOLOGICAL PARADIGM</th>
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<td>Exposure</td>
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<tr>
<th>SEQUENCE LEADING TO NEOPLASIA</th>
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<td>Pro-/Direct Carcinogen</td>
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<tr>
<th>INTERVENTION STRATEGIES</th>
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<td>Primary Prevention</td>
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<td>Avoid Exposure</td>
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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
<table>
<thead>
<tr>
<th>Epidemiology</th>
<th>Mechanistic Research</th>
<th>Behavioral and Engineering</th>
<th>Regulatory Process</th>
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<tbody>
<tr>
<td>Identify risks</td>
<td>Understand role of tobacco</td>
<td>Design risk communication strategy</td>
<td>Regulate sales</td>
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<tr>
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<td>Understand carcinogenesis and design early diagnostics</td>
<td>Design smoking cessation techniques</td>
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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”