Exposure, Dose, and Response Relations

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Exposure, Dose, and Response Relations

• Definitions review, toxicological paradigm, fundamental principles, application to risk
• Exposure assessment (getting to dose)
• Dose measurements and outcomes
• Dose-response curves and interpretations
• Interactions of chemical exposures (and doses)
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Definitions Review

• 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 or carrier (the environmental media: air, water, soil, food)

(continued)
Definitions Review (cont.)

• 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

The Toxicological Paradigm
(biological mechanisms and individual variation)

- Exposure
- Internal dose
- Biologic effective dose
- Early biologic effects
- Altered structure & function
- Clinical disease

Susceptibility
- Genetic factors

Effect modifiers
- Diet
- Habits
- Health
- Medication
- Co-exposure
The Toxicological Paradigm
(Toxicological Mechanisms)

- exposure
  - internal dose
    - biologic effective dose
      - early biologic effects
        - altered structure & function
          - clinical disease

TOXICO-KINETICS

TOXICO-DYNAMICS

Risk Assessment Activities

1. Hazard identification
   - Is the agent innately toxic?
2. Exposure assessment
   - What is the intensity, frequency, and duration of human exposure to the agent, and what is (are) the route(s) of exposure?
3. Dose-response assessment
   - What is the relationship between varying doses and incidences (and severity) of adverse effects in exposed populations?
4. Risk characterization
   - What is the actual risk of adverse health effects in the specific population(s) of concern?
Bradford-Hill Criteria for Causality and Association

- Strength of association
- Consistency
- Specificity
- Temporality
- Biological gradient
- Plausibility
- Coherence
- Experiment


Key Characteristics of Carcinogens (IARC, 2019)

- THE KEY CHARACTERISTICS OF HUMAN CARCINOGENS

  1. Is Electrophilic or Metabolically Activated
  2. Is Genotoxic
  3. Alters DNA Repair or Genomic Instability
  4. Induces Epigenetic Alterations
  5. Induces Dedifferentiation
  6. Induces Chronic Inflammation
  7. Is Immunosuppressive
  8. Modulates Receptor-mediated effects
  9. Causes Immortalization
  10. Alters Cell Proliferation, Cell Death, or Nutrient Supply

Guyton et al. Carcinogenesis, 39: 614-622, 2018
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Exposure Assessment

exposure = intensity x frequency x duration

(exposure = how much x how often x how long)
Patterns of Exposure

- Continuous
- Intermittent
- Cyclic
- Random
- Concentrated

Exposures and Time

- Instantaneous
  - 1945: Atomic Bomb
- Intermittent
  - 1950 - 1975: Uranium mining
- Continuous
  - Cigarette smoking
Vectors for Exposure in Context of Environmental Health

Issues in Understanding “Exposure”

• Distinction between agents and vectors
• Time-activity patterns
  – what did the agent do in environment with time?
  – what did the host do in environment with time?
• Homogeneous versus heterogeneous exposures
  – mixed exposure scenario
• Factors influencing biodistribution
  – same exposure may not yield the same dose

Moeller DW (adapted)
Hierarchy of “Exposure” Data or Surrogates (best to worst)

- Quantitative personal dosimeter measurements
- Quantitative ambient measurements in the vicinity
- Quantitative surrogates of exposure
  - e.g., estimates of drinking water or food consumption x conc.
- Residence or employment in proximity to the source of exposure
- Residence or employment in the general geographic area of the source of exposure

Moeller DW (adapted)

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### Intrinsic Toxicity

<table>
<thead>
<tr>
<th>Agent</th>
<th>LD$_{50}$ (mg/kg)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ethyl alcohol</td>
<td>10,000</td>
</tr>
<tr>
<td>Sodium chloride</td>
<td>4,000</td>
</tr>
<tr>
<td>Ferrous sulfate</td>
<td>1,500</td>
</tr>
<tr>
<td>Morphine sulfate</td>
<td>900</td>
</tr>
<tr>
<td>Sodium cyanide</td>
<td>15</td>
</tr>
<tr>
<td>Strychnine sulfate</td>
<td>2</td>
</tr>
<tr>
<td>$d$-Tubocurarine</td>
<td>0.5</td>
</tr>
<tr>
<td>Tetrodotoxin</td>
<td>0.1</td>
</tr>
<tr>
<td>Dioxin (TCDD)</td>
<td>0.001</td>
</tr>
<tr>
<td>Botulinum toxin</td>
<td>0.00001</td>
</tr>
</tbody>
</table>

- **9 orders of magnitude**

Casarett and Doull's TOXICOLOGY, 2008

### Uncertainties in Toxicology

- High to low dose extrapolation:
  - How well do our high dose experiments inform us about risks from ambient exposures?
  - This is the data to extrapolation for risk issue.

- Interspecies comparisons:
  - Are studies conducted in rodents or other test models (yeast, worms, fish, etc.) appropriate surrogates for humans?

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Cancer Endpoint: No Safe Dose -- Regulate to an “Acceptable” Level of Risk

UK Million Women Study Mortality Ratio

Lung Cancer

Emphysema

Measurement of *Acute* vs. *Cumulative* Exposure or Dose

- What exposure or dose time duration does the measurement reflect?
- Example: lead in the body
  - Clearance half-time in blood = 30 days
  - Clearance half-time in bone = 30 years

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Early on in any toxicology study: Define dose-response relationship

- The relationship between the quantity of response and the dose of drug or toxicant

- **Rationale:**
  - *Response is due to the agent (sometimes a drug)*
  - *Degree of response is due to the compound concentration*
  - *Have a quantifiable (measurable) response parameter*

- Observe dose-related change in intensity of response. Example: enzyme inhibition, blood pressure change

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**Example dose-response relationship**

- Example: drug for control of blood pressure
  - groups of 10 patients
  - one dose of drug per group
  - administer 8 doses of drug and then measure blood pressure
  - "response" = \( \geq 20 \) mm Hg drop in blood pressure
  - plot % of patients responding versus log of dose
- Sigmoidal dose-response curve is typical
- Similar to ligand-receptor binding curve, cell response curve, etc.
Dose curves let you compare different agents

- **Definitions** - Effective dose (for a drug) = \( ED \); Lethal dose = \( LD \)
- **Potency** - Range of doses over which a drug produces increasing responses
- **Efficacy** - Maximal response; plateau of the dose-response curve

Comparison to two compounds that achieve the same potency and efficacy, but at different doses

Lethality or Toxicity Curve (want to avoid this)

No Threshold Model

- **Risk (probability) of response is a function of dose**
  - assumes no threshold
  - no dose is safe
  - any dose increases the risk (not severity)
  - e.g., cancer
    - implies that any exposure increases the risk of cancer, with larger exposures producing a greater risk (but not a bigger tumor)
Threshold Response 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 (PCBs exposure)

Dose-Response Curves

Response = Risk

Response = Severity

Cancer

All other health effects
Non-cancer Endpoints: “Safe” Dose

LOAEL (lowest-observed-adverse-effect level)
NOAEL (no-observed-adverse-effect level)
UF (uncertainty factor)

\[
RfD = \frac{NOAEL}{UFs}
\]

“Safe” Doses

- Reference Dose (RfD) = NOAEL/UF
- Acceptable Daily Intake (ADI) = NOAEL/UF
- Uncertainty Factor(s) (UF) = factors of 10
  - 10 for animal to human extrapolation
  - 10 for short duration instead of chronic
  - 10 for individual variability
  - 10 for LOAEL instead of NOAEL
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Interactions of chemicals

• Mechanisms alter one or more of these processes
  • Absorption
  • protein binding
  • biotransformation (xenobiotic metabolism)
  • Excretion
• Interactive Responses (and two chemicals simplistic view of reality)
  • Additive (2 + 4 = 6)
  • Synergistic (2 + 5 = 20)
  • Potentiation (0 + 4 = 10)
  • Antagonism (2 + 6 = 3; 4 + 1 = 0)
Interactions of chemicals

- **Additive** \((2 + 4 = 6)\)
  - 2 chemicals - same mechanism of action
  - two different organophosphates interacting with cholinesterase receptor
  - As if having more of the same chemical!

  ![Specific receptor or very specific interaction](image)

  - **Malathion**
  - **Acetylcholinesterase**
  - Very specific molecular binding

- **Synergistic** \((2 + 5 = 20)\)
  - Carbon tetrachloride with ethyl alcohol
Synergism

Lung Cancer & 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

Report of the Surgeon General, 1985
Interactions of chemicals

- **Potentiation** \((0 + 4 = 10)\)
  - Only one chemical has toxic effect at site of action

**Isopropyl alcohol** (rubbing alcohol, antifreeze, deicing fluid, solvent)
- Not toxic to liver
- CNS depression with gastritis, pain, nausea, vomiting

**Acetone**

<table>
<thead>
<tr>
<th>Pretreatment</th>
<th>CCl₄ Challenge</th>
<th>Fold Increase in Liver Toxicity (AST)</th>
</tr>
</thead>
<tbody>
<tr>
<td>None</td>
<td>Yes</td>
<td>1</td>
</tr>
<tr>
<td>Ethanol</td>
<td>Yes</td>
<td>6</td>
</tr>
<tr>
<td>Isopropanol</td>
<td>Yes</td>
<td>25</td>
</tr>
<tr>
<td>Acetone</td>
<td>Yes</td>
<td>20</td>
</tr>
</tbody>
</table>

- Both potentiate CCl₄

- The hepatotoxicity of carbon tetrachloride is greatly enhanced by the presence of isopropanol. Such exposure may occur in the workplace.

Normally, warfarin (a widely used anticoagulant in cardiac disease) is bound to plasma albumin so that only 2% of the warfarin is active. Drugs which compete for binding sites on albumin increase the level of free warfarin to 4% causing fatal hemorrhage.
Interactions of chemicals

- **Antagonism** \( (2 + 6 = 3) \) (Mostly good!!!!)
  - **Functional mechanism**
  - 2 chemicals counterbalance each other
  - Chemical producing convulsions plus Anticonvulsant drug (e.g., diazepam)

- **Disposition mechanism** alters concentration or residence time of toxin
  - e.g. Absorption: ipecac, charcoal

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Interactions of chemicals

- **Antagonism** \( (2 + 6 = 3) \)
  - **Receptor Block** mechanism

  competitive inhibitors

<table>
<thead>
<tr>
<th>Poison</th>
<th>Receptor</th>
<th>Blocker drug</th>
</tr>
</thead>
<tbody>
<tr>
<td>morphine, heroin</td>
<td>( \mu )-opioid</td>
<td>naloxone</td>
</tr>
<tr>
<td>estrogen (estradiol) of mammary tumor</td>
<td>estrogen receptor</td>
<td>tamoxifen (pro-drug)</td>
</tr>
<tr>
<td>organophosphate insecticide</td>
<td>acetylcholinesterase</td>
<td>atropine</td>
</tr>
</tbody>
</table>
Artificial Intelligence (AI) and Drug Metabolism

Lamisil (terbinafine) toxicity: Determining pathways to bioactivation through computational and experimental approaches
Duane A. Barnette¹, Mary A. Davis¹, Na L. Dang², Anirudh S. Pidugu³, Tyler Hughes³, S. Joshua Swaminathan⁴, Gunnar Boysen⁵, Grover P. Miller⁶,*

Time-Course of Response

better

EXPOSURE
PERIOD

Health

Reversible
Irreversible
Progressive

worse

Time, years

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Key Points

- Exposure is outside the body; dose is inside the body.
- Cumulative or total exposure = intensity x frequency x duration (how much x how often x how long).
- Environmental media (air, water, soil, food) serve as the vectors that transport environmental agents (chemical, biological, physical) into the body.
- In a random dose-response relation, risk is a function of dose. Cancer and genetic changes are random processes.
- In a deterministic dose-response relation, severity is a function of dose. All non-cancer, non-genetic endpoints represent deterministic processes.
- Mixed exposures can lead to synergistic interactions.