Chapter 6

Dose and Response
Dose Response

• The most fundamental of all principles in toxicology is that of the relationship between the amount of a toxicant that is received by the organism (the dose) and the effect(s) that results from that dose (the response).

• The basis for establishing this relationship comes primarily from experimental data using laboratory animals, in vitro studies, and information from humans.
Dose Response Relationship

• Can establish the lowest dose where an objectively measurable effect first occurs (threshold level)
• Establishes a quantitative relationship between the dose and the response
• Provides the basis for establishing a causal relationship between the dose and the response
• Provides information to assess the relative toxicity of a chemical when compared with others tested under similar conditions of exposure
Dose

• The *administered* or *applied dose* is the amount presented to an absorption barrier and available for absorption (although not necessarily having yet crossed the outer boundary of the organism). This is the dose referred to in toxicity testing unless otherwise specified.

• The *absorbed dose* is the amount crossing a specific absorption barrier (e.g., the exchange boundaries of the skin, lung, and digestive tract) through uptake processes.
Dose

• The *internal dose* is a more general term denoting the amount absorbed without respect to specific absorption barriers or exchange boundaries.

• The *delivered dose* is the amount of the chemical available for interaction with any particular organ or cell.
## Table 6-1 The Gram

<table>
<thead>
<tr>
<th>Unit</th>
<th>Gram Equivalents</th>
<th>Exponential Representation</th>
</tr>
</thead>
<tbody>
<tr>
<td>Kilogram (kg)</td>
<td>1000.0 g</td>
<td>$1 \times 10^3$ g</td>
</tr>
<tr>
<td>Milligram (mg)</td>
<td>0.001 g</td>
<td>$1 \times 10^{-3}$ g</td>
</tr>
<tr>
<td>Microgram (µg)</td>
<td>0.000001 g</td>
<td>$1 \times 10^{-6}$ g</td>
</tr>
<tr>
<td>Nanogram (ng)</td>
<td>0.0000000001 g</td>
<td>$1 \times 10^{-9}$ g</td>
</tr>
<tr>
<td>Picogram (pg)</td>
<td>0.00000000000001 g</td>
<td>$1 \times 10^{-12}$ g</td>
</tr>
</tbody>
</table>
Relating Dose to Response

For a dose–response relationship to be scientifically valid in toxicology, a number of conditions must be satisfied:

1. A method is needed to objectively measure an adverse response.
2. The adverse response occurs after the dose is administered.
3. The adverse response is due solely to the dose.
Relating Dose to Response

For a dose–response relationship to be scientifically valid in toxicology, a number of conditions must be satisfied:

4. The type of adverse response(s) measured is the same or similar for each individual or \textit{in vitro} system that is used for testing.

5. The intensity of the adverse response is proportional to the dose.
Relating Dose to Response

• The lowest dose that produces an adverse effect can be considered a *threshold dose*.

• At this dose level the first appearance of an adverse effect can be causally linked to the chemical.

• Doses above the threshold result in the same type of adverse effect(s) but at correspondingly higher levels of intensity.
Figure 6-1 Arithmetic vs. semilog D-R plot.

Shape of Arithmetic Plot vs. $\log_{10}$ Plot of Dose
Relating Dose to Response

- The slope of a dose–response curve is the most rapidly rising portion and represents the change in the intensity of the response per unit of increase in the dose.
- Different chemicals may have very different slopes.
- Chemicals with similar thresholds do not need to have correspondingly similar slopes.
- Each toxicant has its own characteristic progression of toxicity.
Relating Dose to Response

• The slope of a dose–response curve reveals something about the potency of the chemical.
• Potency is a measure of the strength of a chemical relative to that of other chemicals.
• The sharper the rise in toxicity of one chemical compared with another (or the larger the numerical value of the slope), the more potent the chemical.
Figure 6-2 Dose–response curves for two toxicants showing the thresholds for responses.
How Individuals may respond in a Population

• In a population of individuals, you can observe biological variation in response to the same dose of chemical.

• Consider hypothetically that the concentration of that chemical in the air is the same for each person and that each person receives the same internal dose.

• We see a bell-shaped distribution curve that theoretically never reaches 0 or 100%.
How Individuals may respond in a Population

• This bell-shaped curve demonstrates that within this hypothetical population, the majority of responses to the toxicant are similar (some coughing and eye irritation); however, because of biological variability some individuals may be more or less susceptible to the effects of exposure.
Figure 6-4 Responses of individuals to the same dose


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Responses to the Same Dose

• The individuals toward the left of the curve may have only a barely perceptible sensation of eye irritation, with no tears or coughing.
• These individuals appear to be less susceptible and we can refer to them as “resistant” or as “hyporesponsive.”
Responses to the Same Dose

• There are other individuals who are very susceptible to this exposure and respond intensely; they are shown on the right of the curve, and they will likely experience severe coughing, tightness in the chest, and difficulty breathing.

• We refer to these individuals as being “sensitive” or as “hyperresponsive.”
The Dose Must Be Referenced to Time

• The way that time is referenced with respect to dose can greatly impact our assessment about toxicity.
• A dose can be a single event or multiple events over a specified period of time.
  – For example, an adult male may take a total dose of 400 mg of ibuprofen 1 time over the course of a month or he may take a dose of 500 mg of amoxicillin three times a day (1,500 mg/day) for 10 consecutive days over the course of a month (total dose, 15,000 mg or 15 g).
Dose must be referenced to Time, cont.

• The antibiotic, if properly taken by this individual, should have therapeutic value.
  – If he were to take the total dose on day 1, then there would be little therapeutic value and indeed there may be adverse effects, including injury to the liver and kidneys.
  – If this individual weighed 70 kg and the antibiotic was correctly taken, then a daily dose (1,500 mg) would have been approximately 21.4 mg/kg of body weight (1,500 mg/70 kg).
Dose must be referenced to Time, cont.

– Compare this with all the antibiotic taken as a single total dose of 214 mg/kg of body weight (15,000 mg/70 kg), or a dose 10 times greater than the daily therapeutic level.

– If we were to reference the doses over an 8-hour period instead of a 24-hour period, then if correctly taken the therapeutic dose becomes 7.14 mg/kg (500 mg/70 kg) compared with 214 mg/kg (15,000 mg/70 kg) if all the antibiotic is taken as a single dose.

– This latter dose is approximately 30 times greater than the therapeutic dose.
Dose Standardization Based on Body Weight

- For both efficacy studies and toxicity studies, doses are standardized based on body weight.
  - Consider a single daily dose of 0.1 mg/kg of a pharmaceutical has been shown to be efficacious in men
    - a 120-kg male should receive a daily dose of 12 mg
    - a 70-kg male would require only 7 mg.
Dose Standardization Based on Body Weight

– If these same two men were drinking at a pub and each consumed the same amount of the toxicant ethanol, over the same period of time they would have very different blood alcohol concentrations based on weight differences alone, assuming that their blood alcohol levels were similarly determined.

– For the lighter man a blood alcohol level at the legal threshold, which establishes presumptive impairment, would occur with fewer drinks than for the heavier man.
<table>
<thead>
<tr>
<th>Toxicity Rating</th>
<th>Probable Lethal Oral Dose For “Average” Adult</th>
</tr>
</thead>
<tbody>
<tr>
<td>Practically nontoxic</td>
<td>&gt;1 liter</td>
</tr>
<tr>
<td>Slight</td>
<td>0.5–1 liter</td>
</tr>
<tr>
<td>Moderate</td>
<td>30–500 milliliters</td>
</tr>
<tr>
<td>Very</td>
<td>3–30 milliliters</td>
</tr>
<tr>
<td>Extremely</td>
<td>7 drops–3 milliliters</td>
</tr>
<tr>
<td>Supertoxic</td>
<td>&lt;7 drops</td>
</tr>
</tbody>
</table>
Referencing Dose to Environmental Media

• A dose may be represented as:
  – an “exposure dose”
  – the concentration of a chemical present in a medium

• A dose may be expressed as a gram unit of a chemical per cubic meter of air, liter of water, kilogram of soil, or kilogram of a consumable (e.g., vegetable, fruit, fish).
For inhaled chemicals we typically discuss exposure concentration in parts per million (ppm) or milligrams per cubic meter of air (mg/m3).

- This is not equivalent to the actual dose because it does not tell us how much of the chemical has entered the body.

- A chemical present in the air at 3 mg/m3 may represent an exposure concentration, but the actual absorbed dose depends on factors such as the amount of time spent breathing the air, body weight, pulmonary retention, etc.
It is possible to estimate the inhaled dose using equations that incorporate these factors.

The total dose of any chemical may be the result of combined individual doses, from different media, over a specified period of time.
The dose of an inhaled aerosol may be described by the following formula:

\[
D = \frac{\alpha \times (V_T \times f \times C) \times t}{M}
\]

where \( D \) represents the dose (mg/kg), \( \alpha \) is the fraction of aerosol deposited in the lungs (% retained), \( V_T \) represents the tidal volume (ml of air moved with each breath), \( f \) is the ventilation frequency (breaths per minute), \( C \) is the exposure concentration of the chemical (mg/m3), \( t \) is the exposure duration (minutes), and \( M \) represents body weight (kg).
### Table 6-3 Benzene Consumption and Oral Daily Dose

<table>
<thead>
<tr>
<th>Body Weight (kg)</th>
<th>Amount of Media Consumed</th>
<th>Amount of Benzene Consumed</th>
<th>Total Benzene Consumed (μg)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Water (l)</td>
<td>Fish (mg)</td>
<td>Soil (mg)</td>
</tr>
<tr>
<td>Dad</td>
<td>80</td>
<td>3</td>
<td>500</td>
</tr>
<tr>
<td>Mom</td>
<td>60</td>
<td>2</td>
<td>300</td>
</tr>
<tr>
<td>Child</td>
<td>25</td>
<td>1</td>
<td>200</td>
</tr>
</tbody>
</table>