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Toxicology Lec.(2)

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DOSE–RESPONSE RELATIONSHIP

- The characteristics of exposure and the spectrum of toxic effects come together in a correlative relationship referred to as the dose–response relationship.
- Whatever response is selected for measurement, the relationship between the degree of response of the biological system and the amount of toxicant administered assumes a form that occurs so consistently as to be considered the most fundamental concept in toxicology.

From a practical perspective, there are two types of dose–response relationships:

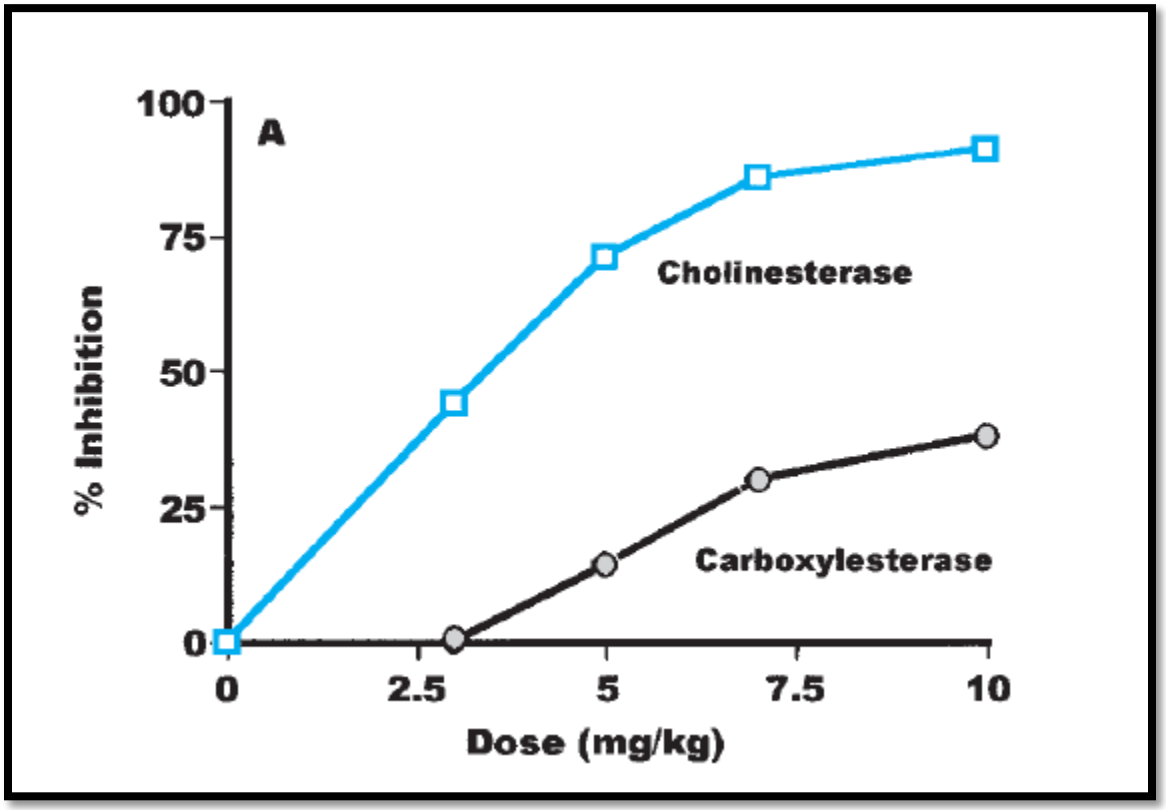
- (1) The individual dose–response relationship, which describes the response of an individual organism to varying doses of a chemical, often referred to as a “graded” response because the measured effect is continuous over a range of doses.
- (2) A quantal dose–response relationship, which characterizes the distribution of individual responses to different doses in a population of individual organisms.

Individual, or Graded, Dose–Response Relationships

- Individual dose–response relationships are characterized by a dose related increase in the severity of the response.
- The dose elatedness of the response often results from an alteration of a specific biochemical process.

- For example, Fig. 2-3 shows the dose–response relationship between different dietary doses of the organophosphate insecticide chlorpyrifos and the extent of inhibition of two different enzymes in the brain and liver: acetylcholinesterase and carboxylesterase.
- In the brain, the degree of inhibition of both enzymes is clearly dose-related and spans a wide range, from the shapes of these two dose–response curves it is evident that, in the brain, cholinesterase is more easily inhibited than carboxylesterase.

Figure 2-3. Dose–response relationship between different doses of the organophosphate insecticide chlorpyrifos and esterase enzyme inhibition in the brain.



Quantal Dose–Response Relationships

- In contrast to the “graded” or continuous-scale dose–response occurs in individuals, the dose–response relationships in a population are by definition quantal—or “all or none”—in nature ; that is, at any given dose, an individual in the population is classified as either a “responder” or a “nonresponder.”

- A widely used statistical approach for estimating the response of a population to a toxic exposure is the “Effective Dose” or ED
- Generally, the mid-point, or 50%, response level is used, giving rise to the “ED50” value.
- However, any response level, such as an ED01, ED10 or ED30 could be chosen.
- A graphical representation of an approximate ED50 is shown in Fig. 2-4.
- Note that these data are quantal. Even continuous variables can be converted to quantal responses if desired.

- For example, an antihypertensive drug that lowers blood pressure might be evaluated in a population by assigning a “responder” as an individual who’s blood pressure was lowered by10 mm Hg or more.
- Note that, in this example, an individual that responded to a change in blood pressure of 50 mm Hg would classified the same as an individual with a change in only 10 mm Hg, yet an individual with a change in 8 mm Hg would be classified as a“ non-responder”.
- The top panel of Fig. 2-4 shows that quantal dose responses typically exhibit a normal or Gaussian distribution.

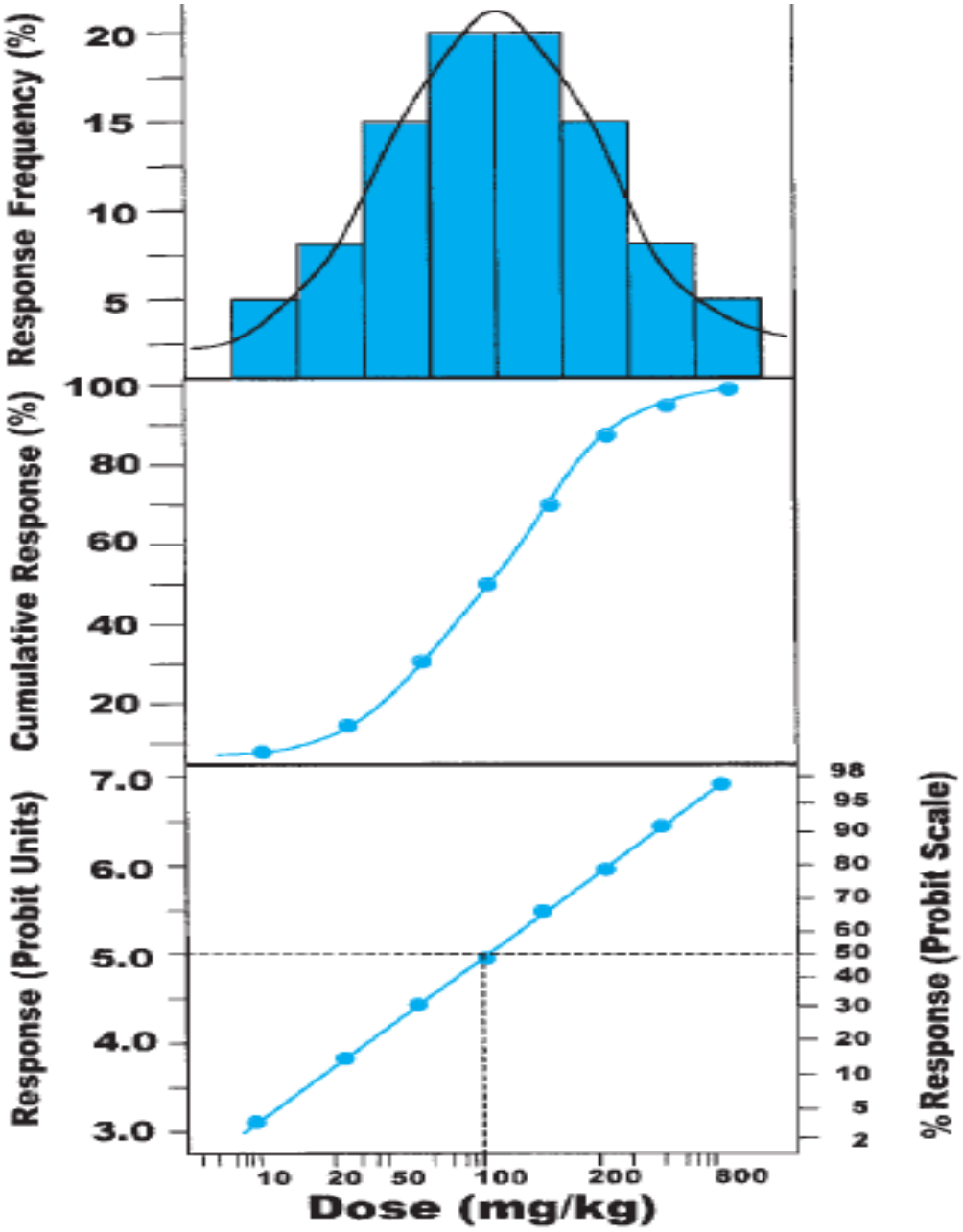


Figure 2-4. Diagram of quantal dose–response relationship.