

Dose – response

The relationship between degree of response of the biological system and the amount of toxicant. There are two types of dose – response relationships

A. Individual or Graded Dose – response relationships:-

Individual dose – response relationships are characterized by a dose – related increase in the severity of the response. For example figure (1) shows the dose – response relationship between different dietary dose of the organophosphate insecticide chlorpyrifos and the extent of inhibition of two different enzymes in the brain and liver; acetyl cholin esterase and carboxyl esterase. In the brain the degree of inhibition of both enzymes is clearly dose – related and spans a wide range, although the amount of inhibition per unit dose is different for the two enzymes from the shapes of these two dose – response curves it is evident that in the brain cholin esterase is more easily inhibited than carboxyl esterase.

The toxicology response that results is directly related to the degree of cholinesterase enzyme inhibition in the brain . It should be noted that most toxic substances have multiple sites or mechanisms of toxicity , each with its own " dose – response " relationship and subsequent adverse effect .

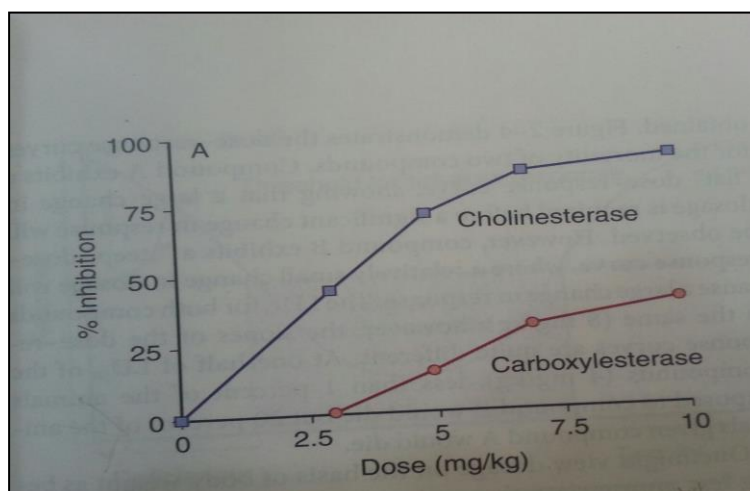


Figure 1- Dose- response relationship between different doses of the organophosphate insecticide chlorpyrifos and esterase enzyme inhibition in the brain

B. Quantal Dose – response relationship:-

A quantal dose – response relationship, which characterized the distribution of response to different doses in a population of individual organisms. Figure (2) shows the relationship between dose and effect. The bars represent the percentage that died at the immediately lower dose. One can clearly see that only a few animals responded to the lowest dose and the highest dose, larger number of animals responded to doses intermediate between these extremes and the maximum frequency of response occurred in the middle portion of the dose range. Thus we have a bell – shaped curve known as a normal frequency distribution.

The reason for this normal distribution is that there are differences in susceptibility to chemicals among individuals . Animals responding at the left end of the curve are referred to as hypersusceptible , and those at the right end of the curve are called resistant .

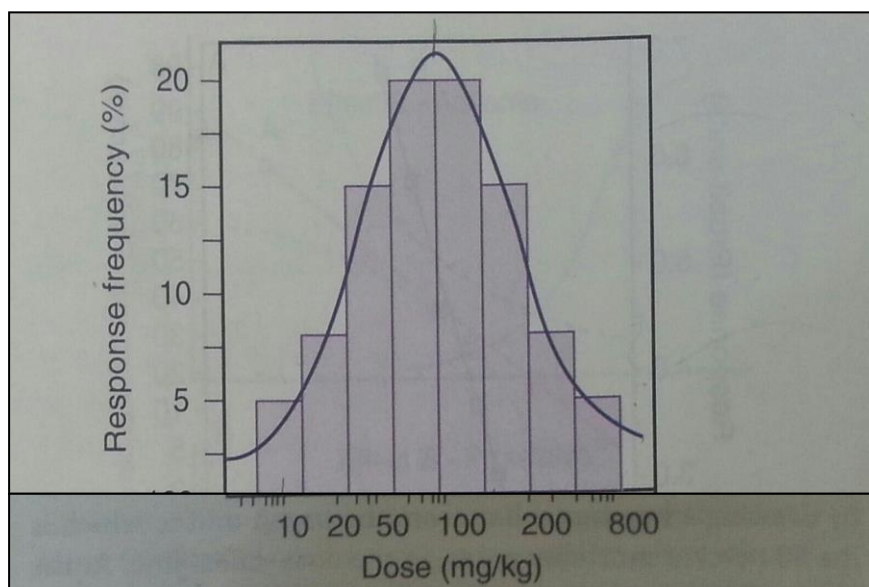


Figure 2 –Diagram of a quantal dose – response relationship (mortality frequency)

Evaluation the toxicity of the substances:

There are many testes to determined the toxicity of any agent;

1. **Acute lethality**:-The first toxicity test performed on a new toxin (chemical is acute toxicity);

- **Determined of lethal dose (LD₅₀)**:- Single dose a substance that can be expected to cause death in 50% percent of the animals tested.

Ex.:- Five laboratory animals group (mouse) treated with five doses toxin A (0 , 25 , 50 , 75 , 100 mg/Kg)through the oral. Daily examination of the animals and tabulated of the number of animals died in (14 days) period after a single dosage occurs, the result was the following;

Dose (mg/Kg)	<u>NQ.</u> of animals death	A	b	a*b
0	0	25	0	
25	0	25	0	
50	1	25	0.5	12.5
75	2	25	1.5	37.5
100	5	25	3.5	87.5
				137.5

The LD₅₀ calculated according to the following formula;

$$LD_{50} \text{ (mg/Kg)} = \text{Biggest dose} - \sum a*b/n$$

$$= 100 - 137.5/5$$

$$= 72.5 \text{ mg/Kg}$$

a- Contrast between of the doses

b- The number mean animals death between each two doses

n = The animals number were treated with each tested dose.

2. **Sub acute dose**:- Sub acute toxicity tests are per formed to obtain information on the toxicity of a chemical after

repeated administration for typically (14 days) and as an aid to establish doses for sub chronic studies .

3. **Sub chronic dose:-** *Sub chronic exposure usually test for (90 days). The principle goals of the sub chronic study are to establish a lowest observed adverse effect level (LOAEL) and identify and characterize the specific organ or organs affected by the test compound after repeated administration.*
4. **Chronic dose:-** *Long – term or chronic exposure studies are per formed similarly to sub chronic studies except that period of exposure is usually for (6 month to 2 years) chronic toxicity test are often designed to assess both the accumulative toxicity and the carcinogenic potential of substances (chemicals).*