Dose is the amount of a substance administered at one time.

Other parameters are needed to characterize the exposure to xenobiotics.

The most important are

the number of doses

frequency

total time period of the treatment.

For example:

650 mg acetaminophen (Tylenol® products) as a single dose.

500 mg penicillin every 8 hours for 10 days.

10 mg DDT per day for 90 days.

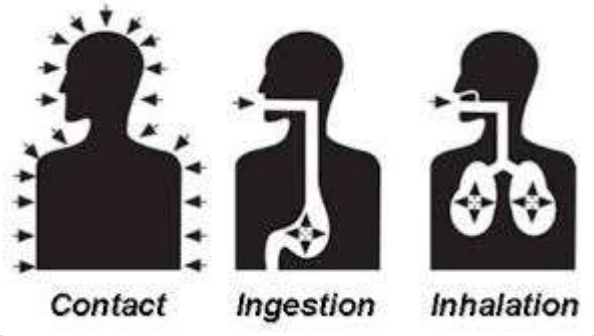
Xenobiotics can travel into the body through the skin, eyes, lungs, and digestive tract.

Exposure to a xenobiotic can occur in any environment where a substance can enter the:

Skin through dermal absorption (air and water).

Respiratory tract through inhalation.

Digestive tract through ingestion.



A person’s age and body size affect the clinical and toxic effects of a given dose. Age and body size usually are connected, particularly in children.

This relationship is important because a person's body size can affect the burden that a substance has on it.

For example, a 650-mg dose of acetaminophen is typical for adults but it would be toxic to young children. Therefore, a tablet of an acetaminophen product designed for children (Children's Tylenol®) contains only 80 mg of the drug.

One way to compare the effectiveness of a **dose** and its **toxicity** is to assess the amount of a **substance** administered with respect to **body weight**. A common **dose** measurement is **mg/kg** which stands for **mg** of **substance** per **kg** of body weight.

Another important aspect is the **time** over which a dose is administered. That is especially important for exposures that occur over several days or that are chronic. Because the most common time unit is 1 day, the usual dosage unit is **mg/kg/day**.

Dose Estimates

Dose-response curves are used to derive dose estimates of chemical substances.

Historically, **LD50** (Lethal Dose 50%) has been a common dose estimate for acute toxicity. It is a **statistically derived maximum dose** at which 50% of the group of organisms (rat, mouse, or other species) would be expected to die. LD50 testing is no longer the recommended method for assessing toxicity because of the ethics of using large numbers of animals, the variability of responses in animals and humans, and the use of mortality as the only endpoint. Regulatory agencies use LD50 only if it is justified by scientific necessity and ethical considerations.

Lethal Doses/Concentrations

Lethal Dose 0% (LD0) — represents the dose at which no individuals are expected to die. This is just below the threshold for lethality.

Lethal Dose 10% (LD10) — refers to the dose at which 10% of the individuals will die.

Lethal Concentration 50% (LC50) — for inhalation toxicity, air concentrations are used for exposure values. The LC50 refers to the calculated concentration of a gas lethal to 50% of a group. Occasionally LC0 and LC10 are also used.

Effective Doses (EDs)

Effective Doses (EDs) are used to indicate the effectiveness of a substance.

Normally, effective dose refers to a beneficial effect such as relief of pain.

It may also stand for a harmful effect such as paralysis. Thus, the specific endpoint must be indicated.

The usual terms are: ED0, ED10, ED50, ED90.

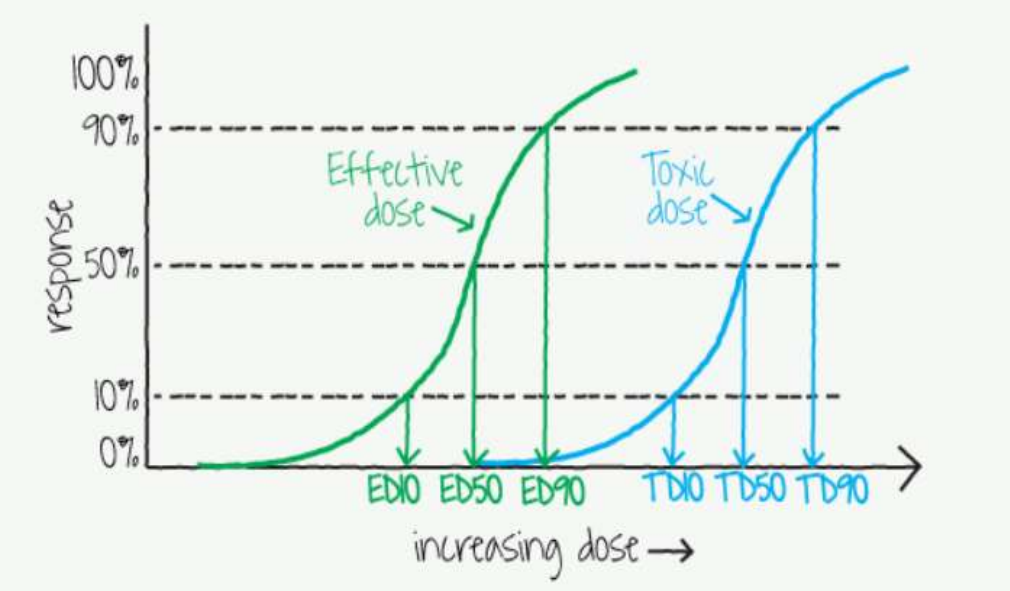
Toxic Doses (TDs)

Toxic Doses (TDs) are used to indicate doses that cause adverse toxic effects. The usual dose estimates include: TD0, TD10, TD50, TD90.

Determining the Relative Safety of Pharmaceuticals

Toxicologists, pharmacologists, and others use **effective** and **toxic dose** levels to determine the relative safety of pharmaceuticals.

As shown in Figure, two dose-response curves are presented for the same drug, one for effectiveness and the other for toxicity. In this case, a dose that is 50% to 75% effective does not cause toxicity. However, a 90% effective dose may result in a small amount of toxicity.



Dose-response curves

Therapeutic Index

The **Therapeutic Index (TI)** is used to compare the therapeutically effective dose to the toxic dose of a pharmaceutical agent. The TI is a statement of relative safety of a drug. It is the ratio of the dose that produces toxicity to the dose needed to produce the desired therapeutic response. The common method used to derive the TI is to use the 50% dose-response points, including TD50 (toxic dose) and ED50 (effective dose).

$$\mathbf{TI} = \frac{\textbf{\textit{Toxic dose}}}{\textbf{\textit{Dose for Therapeutic response}}} = \frac{\mathrm{TD50}}{\mathrm{ED50}}$$

For example, if the **TD50** is 200 and the **ED50** is 20 **mg**, the **TI** would be 10.

$$\mathbf{TI} = \frac{\mathrm{TD50}}{\mathrm{ED50}} = \frac{200}{20} = \mathbf{10}$$

A clinician would consider a drug safer if it had a **TI** of 10 than if it had a **TI** of 3.

However, the use of the **ED50** and **TD50** doses to derive the **TI** may be misleading about a drug's safety, depending on the slope of the dose-response curves for therapeutic and toxic effects. To overcome this deficiency, toxicologists often use another term to denote the safety of a drug: the Margin of Safety.

The **Margin of Safety (MOS)** is usually calculated as the ratio of the toxic dose to 1% of the population (TD01) to the dose that is 99% effective to the population (ED99).