Toxicology:

Modern toxicology is concerned with the behavior of chemicals in the body (*Toxicokinetics*)(Lec.3), the effects of the chemicals on the body (*Toxicodynamics*)(Lec.4).

Basic Concepts in Toxicodynamics:

1.Exposure:

-Any condition which provides an opportunity for an external environmental agent to enter the body.

2.Agent:

−Any chemical, biological, or physical material capable of eliciting a biological response.

−Different than the vector carrier (air, soil, water, food).

3.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.

4.Response:

−The biological response to an agent.

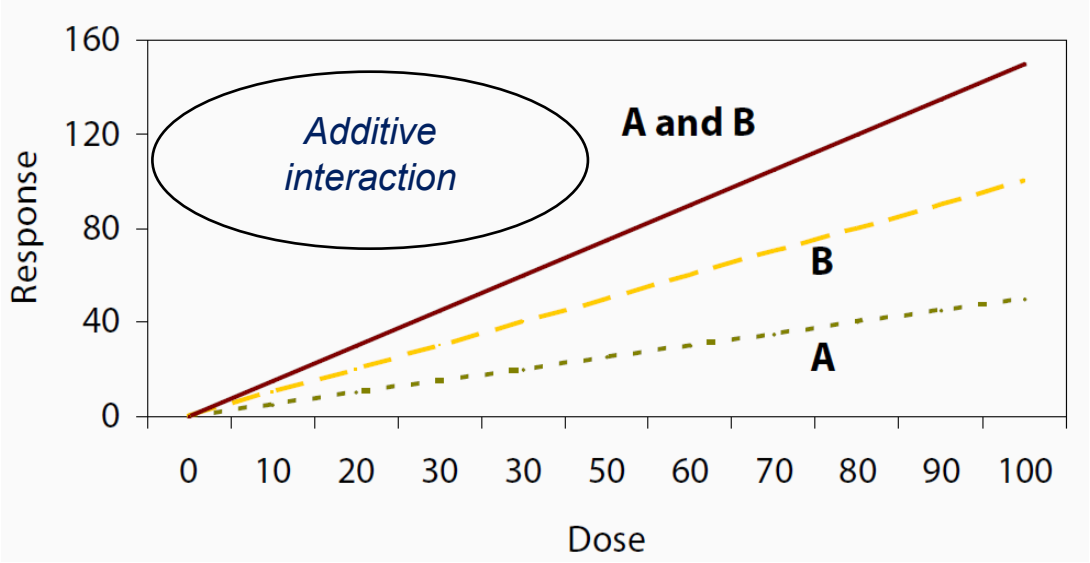
Toxicodynamics

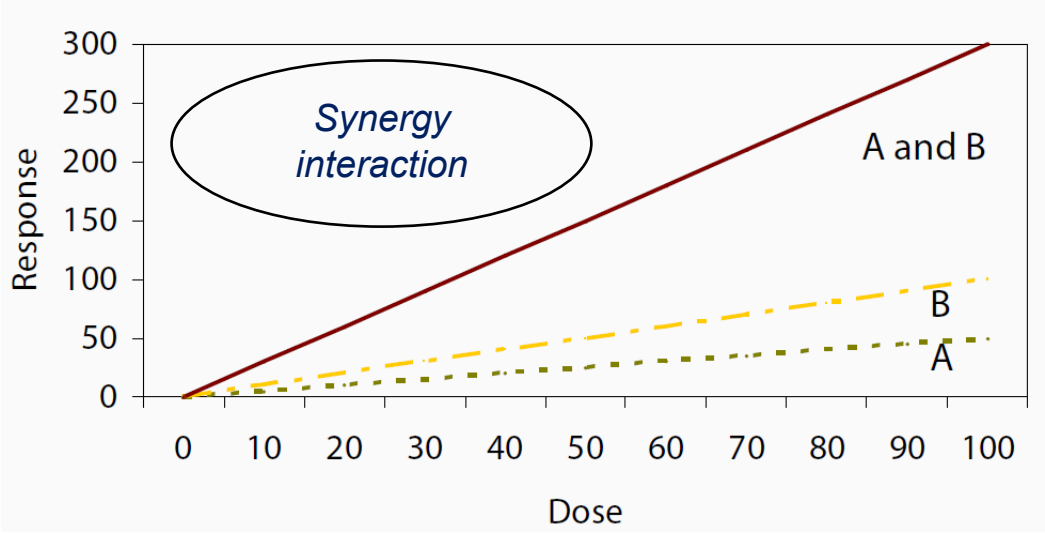
Toxicodynamics refers to how the chemicals affect the body. Now, it is well understood that all chemicals have the potential for toxicity at some level of exposure, but at very low levels of exposure any chemical can be safe.

-Chemicals can interfere with every natural process in the body. However, there are some general rules. The dose, or intensity of exposure, to a chemical determines whether exposure results in toxicity, how much toxicity results (from barely detectable to death), and how many people (or animals)

in a community or group suffer from the toxic effect. Therefore, the dose-response, or exposure response, relationship (usually plotted as a curve) is one of the most important principles of toxicology and defines the action of a chemical for a particular effect on a particular species (human or animal).

-Toxic exposures may interact, when two chemicals act the same way to produce the same result, their effects are typically *Additive*—the same as the combined effect of one on top of the other. When two chemicals act in different ways to produce a similar or related effect, or one modifies the way the other acts, together they may produce a much greater response, called *synergy* or a *positive interaction.*





One important example is that of cigarette smoking: Cigarette smoking interacts with exposure to asbestos to produce more lung cancer in exposed workers than the combined effect of either smoking or asbestos alone. Another example is *potentiation* of liver damage by combined exposures: Carbon tetrachloride is highly toxic to the liver; ethanol can also damage the liver when ingested in excess, but normally not in small quantities; however, when a nontoxic dose of ethanol is added to exposure to carbon tetrachloride, the combination causes much worse liver damage that would be predicted from adding together their individual effects.

Xenobiotics exert toxic effects by interfering with the normal functions of the body. These effects occur at the molecular and cellular levels. Thus, an understanding of normal function and biochemistry is essential for understanding toxicodynamics.

The liver, kidney, lungs, skin, and bladder are particularly susceptible to toxic effects. These organs are often affected by environmental and organic carcinogens because:

- They may be the first to encounter a toxic exposure,
- Receive a large blood flow,
- Are highly active metabolically,
- Actively metabolize xenobiotics themselves,
- Concentrate toxic substances or their metabolites.

The *exposure-response relationship* is fundamental to toxicology and was one of the first great insights contributed to modern toxicology. All chemicals have toxic properties that may only become apparent as increasing quantities are consumed or absorbed.

Dose is the total quantity of a toxic substance that has been administered within a relevant period.

Exposure is the level of concentration available for absorption by any or all routes at or over a given period of time. Thus, dose is best understood as total or cumulative exposure over a relevant time period. If the dose is given all at once, the dose-response relationship is most meaningful, as it is when the toxic substance is accumulated in the body. If the exposure takes place over a prolonged period of time, the internal dose at any given time tends to vary, and it is more useful to think of an *exposure-response relationship.* When a xenobiotic such as lead accumulates and persists in the body over a period of weeks, or dioxin and pesticides over a period of months and years, cumulative exposure approximates dose in toxicological terms.

When a xenobiotic does not readily accumulate and is quickly eliminated, cumulative exposure over a long time period does not equal effective dose in toxicological terms.

The three distinct varieties of the exposure-response relationship that need to be distinguished conceptually are shown in Figure 4.3. These are the toxicological dose-response relationship, the clinical dose—or exposure—response relationship, and the epidemiological exposure-response relationship.

The most fundamental building block of toxicology is the dose-response relationship demonstrable in the laboratory, often called the *toxicological* dose—or exposure-response relationship. The fundamental principle is that the physiological response depends on the amount of the agent in the blood and presented to the tissue. As exposure increases at the tissue level, the response (for example, smooth muscle contraction, inflammation, cell injury or other outcomes) increases up to the maximum that the tissue can sustain.

This gives rise to another type of dose- or exposure-response relationship, which might be termed the *clinical* exposure-response relationship. At a given level of exposure, often referred to clinically as a *threshold*, one can usually expect a given constellation of symptoms and signs. This clinical exposure response relationship depends importantly on susceptibility. In a given exposure situation, one person because of personal susceptibility may show one symptom and another, a different symptom. At relatively low levels of lead toxicity, some patients show elevated uric acid levels because of reduced renal clearance; however, many do not. The detection of the expected clinical response depends on the sensitivity of clinical examination and laboratory tests. Clinical tests are often inadequate for early detection of equivocal cases because they are designed to make specific diagnoses in people known to be sick in a way that strongly suggests a particular type of disease.

Exposure Assessment:

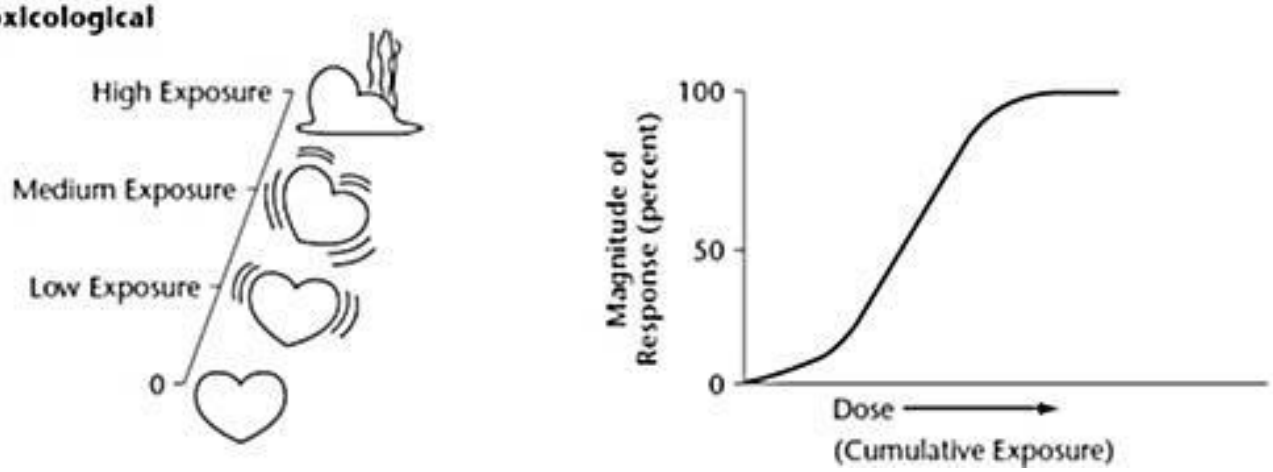
- Characterization of the exposure setting.
- Identification of the exposure pathway.
- Quantification of exposure.

Exposure = Intensity x Frequency x Duration

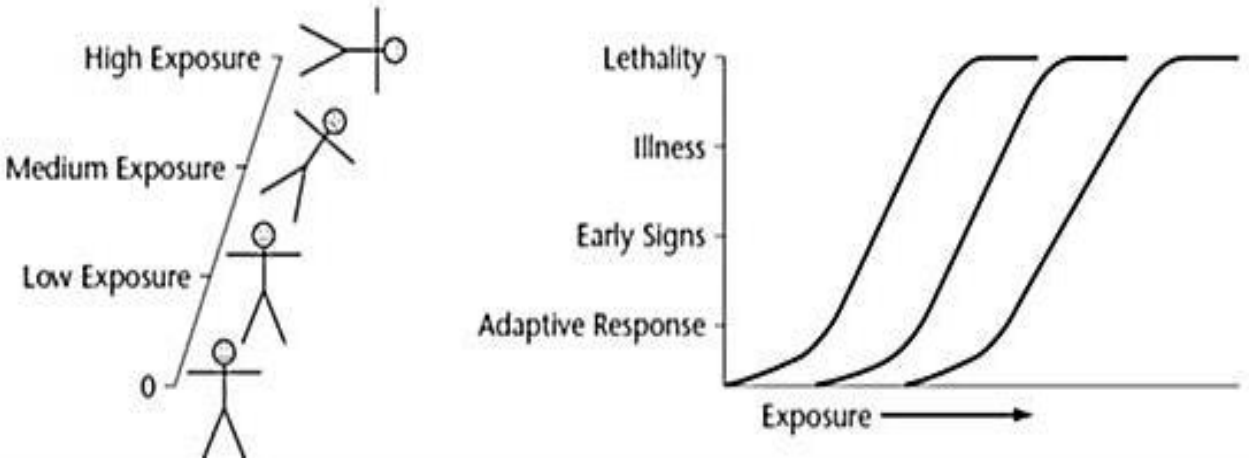
Exposure = How much x How often x How long

FIGURE 4.3. EXPOSURE-RESPONSE RELATIONSHIPS.

Toxicological



Clinical



Epidemiological