4.2: Dose Level and Applied Toxicology

Learning Objectives

After completing this lesson, you will be able to:

- 1: Assess toxicity in response to dose levels.

As students of toxicology it is critically important to understand that everything including water and oxygen has the potential to act as poison. It is only the dose that determines the toxic/beneficial effect.

Dose level and Applied Toxicology

While traditional toxicology approaches in many academic laboratories and also in industry utilized very high dose levels of xenobiotics in order to study various mechanisms of toxicity, it has been identified recently that this is not a very ideal approach especially for industrial applications.

Step 1 Title

- Using very high dose levels may saturate the physiological processes in a living system and hence may cause “forced toxicity” which is not very relevant in terms of real life exposures (could be valid in case of overdose/accidental overexposure).

In industry, a lot of preliminary research is conducted in order to determine dose levels for toxicology experiments. Typically, in case of pharmaceutical compounds a lot of pharmacokinetic modeling and simulations is performed to come up with exposure levels that are multiples of the real drug exposure level in humans. In the chemical industry relevant exposure levels that human beings may be exposed to based on the use of the chemical is determined.

Dose Level Selection

- 1: Traditional toxicity testing involved using a large number of animals and using very high dose levels. Study designs such as LD 50 (Lethal Dose for 50% animals in the study) are no longer used. It is not feasible from a scientific or animal welfare point of view
- 2: Nowadays, dose level selection often involves mathematical simulation and modeling utilizing various forms of in vitro data that are analyzed with the help of medium and high-throughput modeling tools. This is a systems toxicology approach where data from different platforms is utilized to come up with relevant dose levels that are scientifically justifiable and also to refine and minimize animal experiments.

Schematic Approach: Systems Toxicology

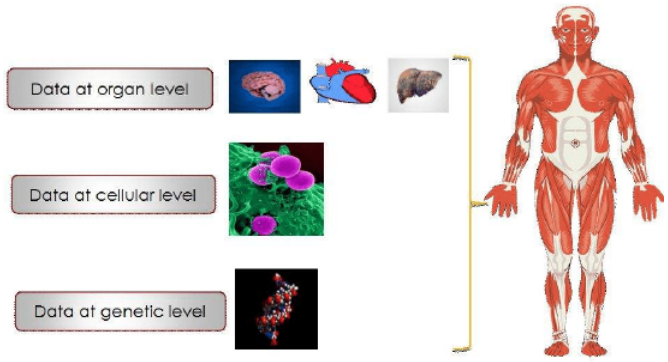

Figure 4.2.1: Schematic Approach: Systems Toxicology. Credit: pixabay.com

Key Points

In this section, we explored the following main points:

- 1: The understanding of how toxicity is driven strongly by the dose response relationship.

Knowledge Check

1. Utilizing very high dose levels in animal models are not useful because

It causes forced toxicity due to saturation of the absorption and elimination processes

It is too toxic and no meaningful information is available from such data

It is necessary for planning acute studies

It causes a lot of wastage of test article

Answer

It causes forced toxicity due to saturation of the absorption and elimination processes

2. Traditional LD 50 studies evaluated...

Adverse effects in 50 animals per dose group

Death in 50 % of the population

Effects in 50% of the animal population

Doses to be used in subsequent chronic studies

Answer

Death in 50% of the population