PRINCIPLES OF TOXICOLOGY

INTRODUCTION

Toxicity testing is paramount in the screening of newly developed drugs before it can be used on humans. Toxicity testing is the determination of potential hazardsa test substance may likely produced and the characterization of its action, most ofthe toxicity testing is carried out on experimental animals.The advantages of usinganimal models in toxicity testing are enormous. These advantages include the possibility of clearly defined genetic constitution and their amenity to controlled exposure, controlled duration of exposure, and the possibility of detailed examination of all tissues following necropsy.. The information obtained canserves as the basis for hazard classification and labeling of chemicals in commerce[.The essence of toxicity testing is not just to check how safe a test substance is; but to characterize the possible toxic effects it can produce. Toxicity testing was given much attention following early 1960s thalidomide catastrophe; with thousands of children born worldwide with severe birth defects2. After this incidence many countries of the world have resolved to go for toxicity testing and teratogenicity in both sexes so as to prevent further tragedies.

Importance of toxicity studies

- To establish a dose response curve.
- To ensure safety of new chemicals for use as pesticides, drugs, or foodadditives before they are registered for general use in industry or doctors clinics.
- To establish the mode of action or mechanism for a toxic effect that may have been seen in other studies.
- To produce epidemiological studies to explain observations in the population,

for instance, the long investigation into the association of smoking with lung

 To validate new methods of testing or investigation, particularly those conducted in vitro rather than in animals.

The two basic principles guiding toxicity test in animals

 To check the effect of the test substances on laboratory animals and its direct toxic effect on human.

 Exposure of laboratory animals to high doses in order to evaluate its possible hazard on human that are exposed to much lower doses

Toxicity studies are divided into:

Acute toxicity studies

This is a short term assessment and evaluation of potential hazard test substance or consequences of single dose of a test substance.Acute toxicity testing may be used in risk assessments of chemicals for humans and non-target environmental organisms. Acute toxicity study is better described as LD50, which is defined as the dose which kills 50% of animals. LD50 is used for the estimation of the toxicity of the chemical agents. Acute toxicity provides guidelines on the dose to be use in more prolonged studies and it also provides the basis for which other testing program can be design. In acute toxicity studies rodent are mostly used because they are economical and readily available and easy to handle. This test is carried out in each species of animal as the same route as intended to be use in treatment

Importance of acute toxicity testing

 To identify the target organ of toxicity.

 To provides safety measures and monitoring guild lines for workers involved in the development and testing of test substances.

 To provides information needed for the dose selection in prolonged toxicity studies.

 To generate data containing the adverse effects of a substance on human, animal health and environment.

 To provides the basis for which other testing program can be design.

 For academics and regulating purpose; classification, labelling and

transportation of chemical agents

Sub-acute toxicity studies

This study is conducted to determine organs affected by different dose levels. This study access the nature of toxic dose under more realistic situation than the acute toxicity studies. Three dose levels are normally used[2].

- Dose that is high enough to elicit definite signs of toxicity but not to kill many of the animals.
- Low dose that is expected to induce no toxic effect.
- Intermediate dose.

Doses are generally selected on the basis of information obtained in acute toxicity studies using both LD50 and the slope of the dose response curve. The duration of sub-acute toxicity studies depend on intended duration of the test substance.

Chronic toxicity studies

This study is basically to determine the organs affected and to check whether the drug is potentially carcinogenic or not. This test extends over a long period of time and it involves large groups of laboratory animals. Chronic toxicity is the development of adverse effects as the result of long term exposure to a toxicant or other stressor. It can manifest as direct lethality but more commonly refers to sublethal endpoints such as decreased growth, reduced reproduction, or behavioral changes such as impacted swimming performance.

Common aquatic chronic toxicity tests

Chronic toxicity tests are performed to determine the long term toxicity potential of toxicants or other stressors, commonly to aquatic organisms. Examples of common aquatic chronic toxicity test organisms, durations, and endpoints include:

- Fathead minnow, *Pimephales promelas*, larval survival and growth
- Daphnia, *Daphnia magna*, 21-d survival and reproduction
- Green algae, *Raphidocelis subcapitata*, 72-h growth
- Amphipod, *Hyalella azteca*, 42-d survival, growth, and reproduction

GENOTOXICITY AND MUTAGENICITY- TERATOGENICITY

- – **Genotoxicity** covers a broader spectrum of endpoints than mutagenicity, includes DNA damage assessments. DNA damage are not themselves necessarily transmissible to the next generation of cells, pre-mutagenic
- – **Mutagenicity** refers to the production of transmissible geneticalterations. Somatic cell genotoxicity may lead to cancer. Germ cell genotoxicity may lead to infertility or diseased children
- TERATOGENICITY Capacity of a drug to cause foetal abnormalitites when administered to the pregnant mother. Placenta does not consider astrict barrier and any drug can cross it to a greater or lesser extent. The embryo is one of the most dynamic biological systems Genotoxicity • Genotoxicity tests can be defined as in vitro and in vivo tests designed to detect compounds that induce genetic damage by various mechanisms. • These tests enable hazard identification with respect to damage to DNA and its fixation. Genotoxins can be of the following category depending on its effects 1) Carcinogens or cancer causing agents 2)Mutagens or mutation causing agents 3)Teratogens or birth defect causing agents. Agents that can cause direct or indirect damage to the DNA • Reactive oxygen species. • UV and ionizing radiations. • Nucleoside analogues . • Topoisomerase inhibitors . • Protein synthesis inhibitor