2.SELECTIVE TOXICITY

Various toxicants differ in their chemical constitutions, as they may possess various functional groups (chemical diversity) that are largely responsible for their different modes of action. On the other hand, there is a great difference in different forms of life (biological diversity). These variations may be due to differences in morphological, anatomical, histological, cytological and biochemical features of organisms. Owing to great variations in the structure and function of organisms, it is very difficult to predict the toxic effects of a chemical to human-beings on the basis of experiments performed on the laboratory animals. The biological diversity, on the other hand, is advantageous in developing specific drugs or toxicants (*e.g.* pesticides, *etc.*), which are effective against a certain group of organisms or certain individuals.

The selective toxicity may be defined as *adverse effect of a chemical to one form of life (cell or organism) without affecting other form of life, even though the two may exist in intimate contact* . Albert (1965) defines selective toxicity as toxic effect of one kind of living matter without affecting the other form of living matter, though the two may exist in intimate contact. The living matter injured is termed as *uneconomic form* and the matter prevented is said to be *economic form*. Both the injured and prevented forms of living matter may be present in the same organism or in different organisms, which may be related to each other, like a parasite and host. If the affected and non-affected cells are present in different organisms, the toxic action of chemical is said to be *species specific*.

The selective toxicity is of great significance in the field of agriculture, and human and veterinary medicines. For instance, in agriculture different forms of life (*e.g*. weeds, insects, fungi, *etc*.) damage our crops as weeds, pests or pathogens and finally affect the agricultural production. To regulate the population of these organisms without having any adverse effect on the crops, the selective poisons are needed and in fact such poisons are available. Similarly in human and animal medicine, selective drugs are required, which are effective only against harmful organisms (*e.g.* parasites and pathogens) without affecting human beings and their livestock.

As described earlier, the toxicity of a chemical is function of its concentration at the specific site(s) (*i.e.*at the site of receptors). The concentration at the specific site is affected by the translocation and biotransformation of the chemical. It is also known that toxicant induces adverse affect on account of its interaction with a specific receptor. Thus, the selective toxicity of a chemical may be based on any of the following three mechanisms:

(i) due to differences in translocation;

(ii) due to differences in biotransformation reactions; and

(iii) due to presence or absence of receptors.

The first two of these mechanisms are concerned with increase or decrease in effective concentration of the drug or toxicant at the site of specific receptor(s).

(i) Selective toxicity due to differences in translocation of chemicals

Gross morphological, anatomical and cytological variations among various groups of organisms largely account for the differential absorption, distribution and accumulation of chemicals, which in turn may cause selective toxicity. For instance, insects have large surface area in comparison to mammals with respect to per unit weight. The large surface area of insects causes greater absorption and accumulation of toxicant exposed. This may lead to greater effect

on insects without any effect or similar effect to other forms of life. An organochlorinated pesticide, DDT has been reported to be readily absorbed through the chitinous exoskeleton of insects whereas the same pesticide is poorly absorbed through mammalian skin, having relatively low surface area. Thus, it causes greater effects to insects than those to mammals.

Spraying of 20% aqueous solution of sulphuric acid was practised in many parts of world for the control of dicotyledonous weeds in some cereal crops before some decades. Although the acid is equally harmful to all the living forms, it is accumulated more in the leaves of weeds owing to their rough surface, whereas the leaves of cereals are smooth surfaced. Thus, greater accumulation of sulphuric acid causes greater damage to the weeds, at the same time it has very little or no effect on cereals.

Some other modern synthetic herbicides (*e.g.* 2, 4-D salts) are used for the control of dicotyledonous weeds in the fields of cereals. The leaves of cereal crops are waxy and upright, which prevent the penetration of these synthetic herbicides, whereas the same are accumulated in quantities sufficient to selectively kill the dicotyledonous weeds from the fields that are rough and wax free, without affecting the cereals.

Tetracyclines and other antibacterial substances have been used to treat bacterial infections in mammals including the human beings. These drugs inhibit ribosomal protein synthesis of bacteria at doses that do not affect the vertebrate hosts hosts. This selectivity in action of these chemicals occurs as a result of favourable distribution of the drug in bacteria. Bacteria concentrate these antibiotic drugs on account of selective permeability of their cell membranes whereas the mammalian cells do not concentrate them. Hence, the concentrated drug affects the process of protein synthesis in bacteria without any effect or such effect to host cells.

Radioactive iodine has been used in the treatment of goiter in human beings. The thyroid gland cells accumulate iodine whereas the cells of other organs and glands do not accumulate it. Hence, iodine causes desired effect only on thyroid cells.

Barriers to translocation of a chemical may be present in some species whereas the same may be absent in others, thereby influencing the concentration of chemical in different species. For instance, study of toxicity of an anti-cancer drug, N-N'-Bis-(-methane sulphonyloxy propionyl) 1,2, propanediamine, has revealed that exposure of 10 mg/kg dose of drug per day either by oral route or by intravenous route to dogs caused severe depression in white blood cells (WBCs) formation at the end of five days. On the other hand, exposure of 100 to 500 mg/kg per day dose of drug to rats and monkeys by oral route for 1-3 months caused no effect on WBC formation. However, if the same drug was given at the rate of 10 mg/kg per day for five days by intravenous route to either of these animals, it caused significant depression in WBC formation. This report clearly revealed that the selective toxicity of chemicals in different species may be due to differential translocation of the chemicals.

Sometimes, the chemicals combine with certain macromolecules of the body, such as proteins, and form complexes. These complexes are stored in inactive forms in certain species. Therefore, active form of the chemical is not available in specific tissues of those species, even though sufficient concentration of the chemical is present in inactive form in other tissues (storage depots). Thus, the toxicants cause no effect to the organisms of one species whereas the same level of chemical may be toxic to other species or tissues.

The chemicals applied against organisms are often transported to the organs of excretion where some part of these may be resorbed and the rest may induce adverse effects to the excretory organs. Thus, the substances may cause selective toxicity to a specific organ of the organism without any effect to the other organs or tissues of the body. For instance, when

mammals are exposed to uranium bicarbonate, it is filtered from the blood circulation through glomerulus of the kidney for excretion. The kidney tubules resorb bicarbonate, thereby free uranyl ions are liberated. The uranyl ions interact with the tubular cells and cause selective renal tubular toxicity.

(*ii*) *Selective toxicity due to different biotransformation reactions*

Selective toxicity of chemicals can also be achieved owing to differences in biotransformation processes. Biotransformation is the biocatalytic conversion of one form of toxicant into another in the body of organisms. As a result of biotransformation the toxicants may be converted into more active forms, which may in turn increase their toxicity in one group of organisms whereas in other group of organisms the same chemicals may be converted into inactive forms and the toxicity of parent compounds may decrease. Thus, the chemicals may become nontoxic to other group of organisms. The biotransformation of toxicant may also alter the translocation of the chemical, hence the toxicity.

The biotransformation mechanisms vary in relation to genetic variations. Thus, one chemical may be toxic to certain strains and at the same time may be nontoxic to some other strains of a species. For instance, antibiotic penicillin is not effective against certain strains of bacteria, particularly the gram-negative bacteria because they possess an enzyme, ***penicillinase***, which converts the antibiotic into inactive form. Similarly, malathion is ineffective against certain strains of houseflies and mosquitoes because they possess a specific enzyme (***esterase***) that biotransforms malathion into inactive form, which causes no harm to these insects.

The various biotransformation reactions take place at different rates in different species, which may cause selective toxicity of a chemical to one species without having such effect to the other. Heath (1961) pointed out the importance of rates of biocatalytic activation and inactivation of organophosphorus pesticides as determinants of their selective toxicity to insects. These pesticides cause toxicity on account of inhibition of Acetylcholinesterase (AChE) activity. The organophosphorus pesticides may be broadly grouped into two types:

(*i*) those containing P=S group, and

(*ii*) those containing P=O group.

The pesticides having P=O group possess the ability to directly inhibit AChE activity, whereas those having P=S group are first oxidized into active form (*i.e.* P=O form) by microsomal mixed function oxidases in order to cause inhibition of enzyme. The activated derivatives are then hydrolyzed into inactive form by some other enzymes (*i.e.* esterases). The rates of oxidation and hydrolysis of indirect type of AChE inhibitors differ in different species. The species in which the rate of oxidation of OP compounds is rapid and the rate of hydrolysis is slow, the active form of compound would accumulate which may induce the toxicity. On the other hand, in other species if the rate of hydrolysis is rapid in comparison to the first species, the activated form of chemical is rapidly converted into inactive form, hence the toxicity is decreased.

In figure 12.1 biotransformation of malathion and relative rates of various steps of biotransformation in insects and mammals have been shown. Malathion is oxidized into an active form, ***malaoxon***, which is then hydrolyzed into inactive products. Malathion may also be directly converted into inactive products by hydrolysis and binding. The rate of oxidation in insects is

rapid whereas the rate of hydrolysis and binding is very slow. Consequently, the active form (*i.e.* malaoxon) is accumulated by insects, which kills them. On the other hand, the rates of oxidation, hydrolysis and binding are rapid in mammals, hence active form is rapidly converted into inactive products that cause no harm to mammals. Thus, malathion is selectively toxic to insects while causing no harm to mammals.

(iii) Selective toxicity due to presence or absence of receptors

In previous two mechanisms, the selective toxicity has been shown to be the function of active concentration of the chemical at specific site(s), may be either different cells of an organism or different organisms. But, in this mechanism, all the cells or organisms are exposed to the same concentration and the toxicants are selective in their action due to the spresence or absence of the receptors. It is already known that toxicants induce adverse effects on account of their interactions with certain receptors. It is also known that owing to cytological and biochemical differences in different groups of organisms, the specific receptors may be present in some whereas the same may be wanting in others. Thus, a chemical may be toxic to one form of life possessing appropriate receptors, at the same time may be nontoxic to other organisms, which are devoid of such receptors.

The organophosphorus and carbamate poisons owe their toxicity to interaction with AChE. These poisons are similar in structure with that of natural substrate, Acetylcholine (Ach). Hence, they have good affinity for enzyme and bind to its active site. This binding involves strong covalent bonding forces leading to almost irreversible, AChE-poison complex. Consequently, enzyme is not available for reaction with natural substrate, thereby normal neurophysiological function is impaired. Thus, these poisons affect the nervous system without affecting other systems. In this way these substances cause selective effects.

Some other toxicants are selectively toxic because they are sufficiently similar to normal enzyme substrates, like OP and carbamate pesticides, and compete with normal substrates for the active sites of enzymes in the body of animals. These toxicants also occupy the active sites of enzymes much in the same manner that normal substrate occupies and thus the enzyme does not remain available for interaction with the natural substrate. One of the example of such selectively toxic chemical is sodium fluoroacetate. In the body of organisms, it forms fluorocitrate by condensation with oxaloacetate (Figure 12.2) The fluorocitrate then competes with citrate and binds at the active site of the enzyme, ***aconitase*** leading to its inhibition. Thus, sodium fluoroacetate blocks the citric acid cycle in tissues and alters the body functioning of organisms, ultimately leading to their death.

Another chemical, d-tubocurarine induces toxicity by causing paralysis of skeletal muscle. It interacts with ACh receptors and forms d-tubocurarine-ACh receptor complex, which is sufficiently stable. Therefore, ACh receptor is not available for the normal physiological mechanism. Tubocurarine-receptor complex does not trigger response of muscle, normally triggered by ACh-receptor complex (Figure 12.3) and thus normal physiological mechanism is altered. d-tubocurarine causes this specific action only for ACh receptor of neuromuscular membrane without any effect on the receptors of smooth muscles and heart cells. However, it can be displaced from the complex or the site of receptor by excess of ACh.

There is great difference between plants and animals. The plant cells have rigid cell wall and mostly the photosynthetic machinery, which are usually absent in animal cells. But, the plant cells are devoid of muscles, nervous system and circulatory system. The organophosphorus and carbamate pesticides are nerve poisons and owe their biological activity to the inhibition of AChE activity, which works as receptors for these poisons. The plants lack nervous system, hence the enzyme AChE. Therefore, mostly these pesticides have very little or no phytotoxicity, hence they are often used as systemic poisons.

Certain antibiotics cause selective toxicity by selectively interacting with certain receptors of bacteria that are essential for their maintenance and reproduction. The same receptors are either absent or not so important in the normal functioning of their mammalian hosts. For instance, penicillin interacts with rapidly multiplying bacteria by interfering with the synthesis of mucopeptide and teichoic acid. These two substances are structural components of bacterial cell wall. Thus, penicillin induced defective cell walls lead to bizarre and fragile forms, eventually causing death of these bacteria. The action of penicillin is an example of interspecific selective toxicity.