SAFETY EVALUATION OF XENOBIOTICS

Xenobiotics exposed to organisms, including those of human beings, always pose certain risks. To assess the risk posed by a chemical, certain toxicity tests are conducted. These tests are initially performed on laboratory animals and the data so obtained are then extrapolated for human beings. If the risk posed by a chemical in a given set of conditions is acceptable, chemical is considered to be safe. Although, it is known that none of the xenobiotics is completely safe under all the conditions of exposure. But, most of them can be used in a way relatively safe to organisms including the human beings.

According to REACH, which is a European Community Regulation on chemicals and their safe use, concerning the Registration, Evaluation, Authorisation and Restriction of Chemicals, legislation, a **chemical safety assessment** (**CSA**) "*has to be performed by registrants for substances manufactured and imported in quantities starting at 10 tonnes per year and by downstream users if their uses are not addressed by their supplier*." *The **safety** may be defined as value judgement of acceptability of risk* (Maki and Bishop, 1985). The safety evaluation of xenobiotics is done on the basis of information on dose-response relationship and no observed effect level. It is also customary to evaluate safety of a chemical using appropriate safety factor or a mathematical model. The safety factor or model is selected on the basis of scientific knowledge and judgment. The safety evaluation programme consists of two main steps :

(1) Evaluation of potential risk to animals and finally to human beings.

(2) Value assessment regarding the acceptability of risk.

1. Process of Risk Assessment

The information related to chemical needed for the assessment of risk posed by the same may be outlined as follows:

(*i*) Information about toxicological properties of the chemical, and

(*ii*) Information of environmental fate of the chemical (Figure 22.1).

The risk assessment process of any chemical essentially involves the correlation between two parallel lines of scientific investigations, *i.e.* (*i*) observed biological effects, and (*ii*) expected environmental fates. In principle, upto a certain level, the chemical causes no adverse effect on survival, growth and reproduction. This level of chemical is referred to as *No Observed Effect Level (NOEL).* The value of NOEL is determined by performing whole life cycle chronic toxicity tests.

FIGURE 19.1 AS FIGURE 22.1 from page 251

Similarly, certain highest level of the chemical is expected to be present in the environment on account of its handling, such as, manufacture, transport and consumer use. This level is termed as, *Expected Environmental Level* (EEL).

One important step in the process of risk assessment is to accurately measure the values of NOEL and EEL of chemical, so that a comparison may be made between known biological

effects and environmental levels of the chemical. The accurate estimates of these two parameters are often made by sequential series of tests.

FIGURE 19.2 AS FIGURE 22.2 from page 251

Figure 22.2 depicts these two levels of chemical as parallel lines. The wide and overlapping range of confidence limits of these values suggest that additional tests are required to be conducted to know whether the difference between these values are statistically significant. Further improvement in testing programme may be made as per experience to narrow the range of confidence limits of known biological effects and environmental fate of the chemical and thereafter, to infer with reasonable certainty that the difference between the levels of biological effects and the environmental fate of chemical is statistically significant.

2. Safety Evaluation Programme

Effective and efficient safety evaluation programme requires due attention to be paid on various factors and their appropriate combinations. The conceptual and generalized safety evaluation programme may be presented with the help of a flow chart (Figure 22.3). The flow-chart provides an insight into the nature of safety evaluation programme. The safety evaluation programmes are still emerging and none of the presently existing programmes is applicable for various uses of all chemicals.

FIGURE 19.3 AS FIGURE 22.3 from page 252

As evident from the flow chart, the safety evaluation programme of a chemical consists of a number of distinct phases. Each phase accomplishes certain scientific purpose and is designed to acquire certain scientific information. On the basis of information certain decision is made. The testing programme starts from simple screening tests to increasingly complex and confirmatory investigations. The type and amount of information needed in each phase is largely independent of other phase though these phases are closely integrated.

The entire safety evaluation programme may be divided into ten distinct steps. The overall process may be grouped into two main lines, one is meant for human safety whereas the other for environmental safety. The informations from both the directions are utilized for making certain decisions. The various components of a generalized safety evaluation programme is being dealt with separately.

(*i*) *Physico-chemical Properties of Chemical* The risk posed by any chemical is greatly dependent on physical and chemical properties of the compound. Therefore, safety evaluation programme starts with examination of physical and chemical properties of the xenobiotic.

Each chemical is identified on the basis of its common and chemical names, chemical registry number, molecular and structural formulae and molecular weight. The important physical properties are physical form, colour, odour, density, melting- and boiling points, vapour pressure and solubility in water and other organic solvents. The relevant chemical properties of toxicological interest are acidity or alkalinity, ionization properties, nature of complexation, susceptibility to oxidation, hydrolysis, thermal degradation and photolysis. Many of these characteristics of chemical may be procured from literature or directly from the investigators, if possible. In case of otherwise, these characteristics may be determined in the laboratory. In the early stages, screening of literature may be sufficient, but for more precise information, the development and application of analytical procedure may be necessary.

(*ii*) *Usage Pattern* The usage pattern, such as, manufacture, transport and disposal of chemical besides amounts and types of use greatly affect the human and environmental exposures. Therefore, for the selection and interpretation of tests as a component of safety evaluation programme these points must be considered. The informations regarding manufacture, transport, storage, usage and disposal of chemical required for effective safety evaluation programme are outlined below:

(*a*) The informations required regarding the chemical are intermediates/ raw materials used for the manufacture, place and quantity to be manufactured, expected loss/escape of chemical and measures adopted to control the exposure of the chemical.

(*b*) The informations required regarding the transport of chemical are nature of transport and quantity of chemical to be transported, expected environmental exposure, accidental spillage and the measures adopted to control the exposures of chemical.

(*c*) The informations required pertaining to the storage of chemicals is place and conditions of storage, quantity of chemical to be stored, expected environmental exposure and accidental spillage and control measures adopted for such exposure.

(*d*) The informations related to usage pattern of chemical are purpose of use, suitable properties of chemical, use of chemical, such as substitute of another chemical, conditions restricting its escape into the environment and alterations, if any, in the parent chemical after use.

(*e*) The informations pertaining to the disposal of a chemical are routes and nature of disposal, quantity to be disposed, expected accidental spillage, expected environmental levels, chemical transformations, if any, and nature of products.

(iii) Environmental Levels The expected level of chemical in various compartments of the environment may be predicted on the basis of information regarding physico-chemical properties of the chemical and the usage patterns. The estimates of environmental levels of chemical are helpful in assessing the types and amounts of exposure to plants and animals including the human exposure. It also suggests the level of tests to be conducted to determine the environmental fate of the toxicant. The environmental fate tests are helpful to have accurate estimates of environmental levels. The accurate estimates may be used to predict more accurate human exposure and environmental effects.

(iv) Environmental Fate A number of test methods consisting of both the screening and confirmatory tests may be used to determine the environmental fate of chemical. The environmental fate test reveals that what happens to a chemical when it is released into the environment. These tests are useful in deriving accurate estimates of environmental levels of chemical. The latter is an important factor in determining the estimates of human exposure.

(v) Human Exposure The informations pertaining to manufacture, transport, usage patterns and disposal of chemicals, and estimation of their levels in the environment are valuable for evaluating the expected human exposure. The exposure to human beings may either be occupational exposure, such as, those to factory workers or intentional or accidental exposure to the consumers or incidental exposure through drinking water and air. The exposure may be through dermal, ocular, oral or respiratory routes. Therefore, in order to assess human exposure from such a diverse exposures, a variety of screening and confirmatory tests are needed. The estimates of human exposure are essential and helpful in deciding as to which health-effect test should be performed as also in evaluating the findings of such tests.

(vi) Health-Effects Tests for health-effects are used to evaluate the possible effects of chemical on human-health. As stated earlier, such tests are conducted on laboratory animals. The data from health-tests on laboratory animals are employed to predict the possible effects of chemical on human-health. On the basis of information on the possible health effects and the doses or concentrations of chemical required to produce those effects, the presumably safe level of chemical for human beings may be derived or determined.

(vii) Environmental Effects The environmental effect tests include acute and chronic tests, which are performed with certain representatives of a particular environment. For instance, in aquatic environment, environmental effect tests are performed on one plant (*e.g.* alga), one invertebrate (*e.g.* crustacean or insect larvae) and at least one vertebrate (*e.g.* fish).

These tests provide informations on the possible effects of expected environmental level of chemical on: (*a*) the environment, especially to its biotic component, (*b*) the type of adverse effect caused by a particular level of chemical, and (*c*) the susceptible species, which is likely to be, affected the most.

(viii) Decision making Based on the findings of various tests and certain basic informations from the literature, a comparison is made between the expected environmental levels of chemical on account of handling and use of the material and its harmful effects to laboratory animals and environment. From this comparison the possible risks of harmful effects are evaluated. Thereafter, a decision is made regarding the acceptability of the risk. For the evaluation of acceptability of risk, it is not necessary to carry out all possible tests for each chemical. But, often scientific decisions are made regarding the necessity and types of the test for the assessment of risk on account of exposure of chemical. Finally, on the basis of these informations a decision is made regarding use of the chemical.

(ix) Monitoring, Surveillance and Follow-up If the decision is to use the chemical, a systematic monitoring is necessary to estimate whether the levels of chemical in the environment arising on account of its use corresponds to the expected environmental levels of chemical determined by laboratory tests. To further check the relevance and correctness of the decision regarding the use of chemical medical follow up of consumer complaints and surveillance of employee's health are also necessary.

(x) Restrictions on Use If on the basis of informations gathered from various tests and literature, the risk associated with a chemical has been found to be unacceptable, certain restrictions are imposed on the use of chemical. On account of imposition of restrictions, the anticipated exposure may diminish and in turn the risk is lowered. The restriction may consists of following steps: (*a*) low use of chemical, (*b*) use of warning labels, like cigarette smoking is injurious to the health, (*c*) handling of chemical in smaller containers, (*d*) alteration in physical form of the product, (*e*) introduction of more stringent measures of industrial hygiene, and (*f*) use of means to confine or neutralize spills.

In addition to these, other appropriate restriction measures specifically suitable for chemicals under specific conditions may be devised. After the imposition of certain restrictions, the process of decision-making should be reviewed to further assess the acceptability of the risk.