Short-term Toxicity Tests for Non-genotoxic Effects
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CHAPTER 4

Methods to Predict Toxicity

4.1 QUANTITATIVE STRUCTURE–ACTIVITY RELATIONSHIPS

Quantitative structure–activity relationships (QSAR) are quantitative models which relate the variation in measures of activity in a series of chemical compounds to the variation in chemical structure between compounds in the series. The use of QSAR in the study and identification of potentially toxic chemicals is receiving increased attention, as demonstrated by several recent reviews (for example, McKinney, 1985; Hansch, 1985; Enslein, 1984; Birge and Cassidy, 1983).

Although most extensively applied to drug design, QSAR is now being effectively exploited by other fields from anticancer research (Nasr *et al.*, 1984) to aquatic toxicology (Birge and Cassidy, 1983). The major limiting factor in the application of QSAR systems appears to be the inability to delineate biological responses quantitatively to the same degree of precision as is possible for molecular descriptors (Birge and Cassidy, 1983). This is due to the fact that many of the biological responses so far used in QSAR systems are the result of the interaction of a variety of toxic manifestations and, therefore, are not as absolute as physiochemical parameters used to define molecule descriptors.

The models used in QSAR range from simple additivity models where each parameter is independent of all others (e.g. the Free–Wilson model (Free and Wilson, 1964)), to complicated models of pattern recognition where multivariate activity data are related to different chemical structures and physiochemical parameters. These models provide both qualitative classifications (indicating the existence of an effect or its likelihood of occurring) and quantitative data (i.e. an index of the probable severity of an effect). However, qualitative classification must be done at the same time or prior to any quantitative analysis.

In qualitative predictions, each compound is assigned to a class (active *vs.* non-active, synergist *vs.* antagonist, etc.). Usually, a compound is given a value for its probability of belonging to each class. Some method of pattern recognition—discriminant analysis—is used to determine a relation between the class assignment and the molecular descriptor which indicates physiochemical values and/or structural features of the chemical.

QSAR has potential for use in priority setting, toxicity evaluation and hazard analysis, but much more development is necessary. There are inadequacies in the toxicity data bases that are available for QSAR studies and inadequacies in the

methods used for encoding chemical structures and quantifying biological activities for computer analysis which must be overcome before QSAR can be fully exploited in toxicology.

4.2 PREDICTING SAFE LEVELS OF EXPOSURE TO CHEMICALS

A major goal of toxicology is the establishment of levels of chemical exposure which will not cause irreversible harm to man. Safe levels of exposure are usually determined by extrapolation of mammalian toxicological data to the human situation.

It is often advantageous to predict safe levels of chemical exposure based on short-term test results, or before a full safety evaluation has been completed. Such situations include:

- the laboratory and pilot production stage in the development or manufacture of a new chemical;
- when only very small quantities of a chemical are to be produced;
- when short-term or limited exposure is expected during the use of the chemical;
- when accidental release of or exposure to a chemical occurs before the safety evaluation is completed.

A variety of methods have been proposed for estimating safe exposure levels for chemicals (see Sanockij, Chapter 20, this volume). However, these methods are restricted to families of chemicals with well understood properties and which are not suspected of having delayed or long-term effects. The primary limitation to the routine establishment of safe exposure levels from short-term tests is the lack of sufficient validation of the correlation of short-term tests with long-term effects. It is often difficult or impossible at present to extrapolate dose–effect (response) relationships in the whole organism from short-term tests, with any degree of precision or confidence.

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