Short-term Toxicity Tests for Non-genotoxic Effects
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CHAPTER 1

*Introduction, General Conclusions and Recommendations**

1.1 INTRODUCTION

The safety evaluation of chemicals depends heavily on the use of animal tests from which inferences are drawn about the degree of risk to human health and the environment. There is now general agreement on the principles and methods for testing and evaluating chemicals (World Health Organization, 1978, 1984; Vouk and Sheehan, 1983; OECD, 1981; IARC, 1980). However, the methods involved are costly, require skilled manpower and specialized facilities, and take several years to complete. Furthermore, there is a growing number of examples of chemical toxicity in man that were not predicted by routine toxicity tests involving lifetime rodent bioassays. This is particularly the case for chemical agents that cause direct toxic effects on the endocrine, immune and nervous systems and on the developing organism.

It is also difficult to detect, by established, routine methods, subtle damage to organs and systems that have a large functional reserve or which display tolerance to toxic insults. Examples include effects on the liver and kidney, on the intestinal tract and on haematopoietic and immune response processes.

For these reasons, there is a continuing and justifiable interest in new approaches that may be able to provide more specific information concerning the effects of chemicals on particular organs or biological systems. Recent advances in biology and chemistry have opened up the possibility to study the effects of chemicals on living matter at the cellular and subcellular level. Better knowledge of the relationship between chemical and physical characteristics of toxic substances and their biological activity has opened up possibilities for predicting toxicity based on a study of these relationships. In consequence, new procedures and techniques have been developed that provide much useful information about the mechanisms whereby chemicals exert their toxic actions. Some of these appear to have potential as bioassay techniques that yield results more rapidly than the traditional methods now

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used in toxicology. Accordingly, tests of this type are often referred to as 'short-term tests'.

Best known and most widely applied of the short-term tests are those that serve as indicators of mutagenic activity and are predictive of carcinogenic potential. The Workshop excluded these short-term tests for genotoxic effects from its cosideration since this group of tests has been recently reviewed and evaluated elsewhere (International Agency for Research on Cancer, 1980; International Life Sciences Institute, 1984). This report reviews current short-term tests other than those based on genotoxicity, with a view to describing their potential as predictive methods for toxicity and ecotoxicity and their current limitations.

The choice of this subject for study by a SGOMSEC workshop arises from a need for rapid and inexpensive methods that can be used to set priorities for testing a large number of substances present in our environment, to make it possible to rapidly screen new products in order to concentrate industrial research and development efforts on those with the least potential for toxicity, and to enable preliminary, but important, decisions to be made about chemicals in order to institute control procedures without the delay that would be required for complete toxicological assessment.

The Workshop concentrated on those tests, procedures and techniques that produce results within a few weeks rather than the two or three years required for traditional safety testing procedures usually applied to chemicals. It was noted that many tests of this type have the merit of low cost, and are easily manageable although it must be acknowledged that this is not always the case.

1.2 GENERAL CONCLUSIONS AND RECOMMENDATIONS

(1) Short-term tests provide a great deal of information relevant to the evaluation of the safety of chemicals, particularly the mechanism(s) of action, but are not yet developed to the stage where they can replace long-term animal tests as a basis for safety judgement.

(2) The prospects for developing *in vitro* tests for acute, local effects are encouraging. For example, recent developments indicate that it may be possible to develop an *in vitro* battery of tests to identify substances which cause acute irritation in the eye (Nardone and Bradlaw, 1983) as an alternative to the Draize test which has been used since the 1940s.

(3) A relatively simple set of *in vitro* cytotoxicity tests will identify most substances likely to cause acute systemic toxicity; progress is being made toward quantitation of these techniques. However, the full potential of such assays will require a better understanding of the proportion of chemicals exerting an effect through general cytotoxic action compared with those affecting 'organizational aspects' of the whole organism.

(4) Chronic effects are unlikely to be detected using currently-available *in vitro* procedures.

(5) While there are no true short-term tests for ecosystem function, two major areas show substantial promise for the shortening of time-to-decision in the ecotoxicological evaluation of chemicals: quantitative structure–activity relationships (QSAR), particularly for environmental behaviour; and multi-species test systems.

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