CURRENT APPROACHES IN TOXICOLOGY

Edited by
Bryan Ballantyne

WRIGHT

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PREFACE

Modern toxicology involves a multidisciplinary approach to the study of the interaction between chemicals and biological systems in an attempt to define the likelihood of producing adverse effects in the intact organism; and if potentially harmful changes do occur, to investigate their nature, incidence, detection, mechanism of production, and reversibility. Although arbitrary, it is convenient to consider applied toxicology as covering three overlapping areas, each being partly determined by the type and application of the chemicals, the nature and extent of human involvement, and the expertise necessary; these three areas are forensic and clinical toxicology, environmental toxicology and economic toxicology. Forensic and clinical toxicology deals with the diagnosis, treatment and medicolegal aspects of adverse effects of chemicals on man. Of prime importance in this area is the detection, quantitation and confirmation of the presence of toxic substances or their metabolites in body tissues and fluids, precise considerations on cause–effect relationships, and detailed studies on the reversibility of toxic effects. Environmental toxicology is principally concerned with the adverse effects that may be caused to plants and animals from chemicals gaining access to the organism from the atmosphere, water, food or contact with surrounding media during normal activities. Economic toxicology, a rapidly evolving area and the basis of a growing industry, deals with the adverse consequences that may arise in both the short and long term from exposure to, and interaction between, synthetic and naturally occurring chemicals used for specific purposes; groups of compounds covered include medicinal products, food additives, agrochemicals, and cosmetics. There is clearly a considerable overlap between economic and environmental toxicology in terms of the nature of the chemicals and the investigational approach.

At the present time there is a proliferation of requirements, some sensible and some not so sensible, in order to satisfy the needs of legislation in defining the framework for acceptability of chemicals, and their formulations, used for specific purposes. Introduction of legislation in terms of, for example, the Medicines Acts 1968 and 1971 and the Health and Safety at Work, etc. Act 1974, whilst based on sociably desirable attitudes and acceptable motives, is, unfortunately, leading to some unsatisfactory trends. Already there is an attitude in some minds of the 'check-list' type of toxicity testing, a tendency to official dogmatism, and, even more a cause for concern, a lack of informed communication between assessor and notifier. It is perhaps more than by chance that the U.K. Pesticides Safety Precautions Scheme, which enjoys the unqualified support of government and industry, is non-mandatory.

Another unfortunate consequence of the necessary intense current interest in the possible adverse consequences to man and the environment from exposure to synthetic and natural chemicals is the appearance of a group of instant, unqualified, 'experts'; these individuals not only use the language of science in a totally uninformed way, but in addition, have introduced a conceptually meaningless synthetic language, particularly noticeable in the area of environmental toxicology. It is unfortunate that the ill-informed and scientifically illogical comments of the self-styled 'environmentalists' have been given excess and unbalanced publicity by the sensational copy-seeking popular journals.

This volume deals with certain aspects of economic and environmental toxicology. It is the intention to present an overall approach to the requirements for toxicity testing, to draw attention to the various factors influencing the reaction between chemicals and biological materials, to discuss the interpretation of the results of toxicity tests, to describe and critically analyse particular aspects of toxicology of current interest, and to indicate the trends and likely future developments. It is hoped that this volume will not only present a general approach to economic and environmental toxicology and emphasize the necessity that with each particular problem the details of design of approach require specific considerations, but will also demonstrate the requirements for toxicological investigations involves more than is conveyed in the current jargon phrases of 'safety evaluation' and 'hazard assessment'.

In order to obtain the widest and most representative collection of opinions, contributors have been drawn from university and government departments, industry, and independent and commercial research and advisory groups. I have been asked to state that the contributions from individuals working in government departments represent the views of the authors and not the department, and that any statement must not be interpreted as representing departmental policy.

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Chapter 1

EVALUATION OF THE SAFETY OF CHEMICALS

M. Sharratt

We are constantly made aware of the increasing numbers of chemical substances prepared by the chemical industry and of our high degree of dependence on them in everyday life. The large number of synthetic medicinal products now available, the improved quality of food crops resulting from the widespread use of pesticides, fertilizers and animal husbandry products, the presence in shops of convenience foods containing chemical additives, the wide range of detergents, cleaners, polishes, cosmetics, toiletry products and other consumer goods and the appearance of plastics in everything from food packaging and toys to cars and building materials, all provide convincing proof that extremely large quantities of an immense variety of chemical substances are synthesized, imported, transported and generally made available in this country; all come in contact with particular sections or with the whole of the community. Chemicals or products containing them may have direct effects on health or find their way by various routes into the air, water or soil where they may damage animal and plant life or simply inhibit enjoyment of our environment by polluting it. It is hardly surprising, therefore, that individual members of the public, groups with particular interests in health or the environment, and the news media tell of the concern felt about possible ill-effects these chemicals might have on health or on the environment, if not immediately then in the long term.

It is the responsibility of Government to see that the appropriate action is taken to ensure that chemical substances do not cause ill-health during and after their manufacture and that they do not adversely affect the environment. Although an extensive organization exists for these purposes, many people do not know of its existence or understand how it is intended to work. In particular, it is frequently not appreciated which Government Departments carry the responsibility for ensuring that chemicals of various types are safe or that particular groups of people are protected, or how these departments obtain medical and toxicological advice on which to base their decisions to allow or refuse the use of a chemical or to issue instructions on how it can be used safely. In this paper the existing arrangements for assessing the safety of chemicals by United Kingdom Authorities are outlined, the attitude to toxicological assessment and the ways in which human exposure is controlled and the environment protected are discussed,

and the degree of protection which can be expected to be achieved is commented upon.

RESPONSIBILITY OF DEPARTMENTS

Responsibility for the safety of chemicals is not, as might at first seem logical and desirable, in the hands of a single department or agency, but is spread throughout many departments as can be seen from *Table* I. This lists the areas of responsibility of each Government Department and the source of their toxicological advice. Some departments obtain advice from their own medical staff and advisory committees who specialize in areas of particular interest to the departments; for example the Ministry of Defence has its own medical advisory service and the Department of Health and Social Security a specialist section advising on the safety of human medical products. Most departments, however, consult the Division of Environmental Health and Chemical Hazards of the Department of Health and Social Security for advice. This division consists of Government employed consultants, but it has available and makes use of the expertise of independent consultants from universities and other research organizations and medical institutions, as well as of the toxicological expertise from other departmental groups.

Responsibility for the safety of chemicals is scattered among many departments. Because of the special interests of each, several may bear the responsibility for ensuring the safety of the public from the possible adverse effects of a single chemical substance. For example, the Health and Safety Executive has to see that the production of sulphur dioxide or its use in chemical processes will not lead to illness in workers. The Department of the Environment has an interest in its adverse effects as an air pollutant, and the Ministry of Agriculture, Fisheries and Food for its safety when used as a food preservative. The Department of Prices and Consumer Affairs would become involved if sulphur dioxide produced ill-effects when used as a preservative in cosmetic and toiletry products. In the case of lead, the safety of workers producing and using the metal and its salts is in the hands of the Health and Safety Executive, while lead pollution of the air, water, land and sea is handled by the Department of the Environment. The Ministry of Agriculture, Fisheries and Food controls lead in food, while the Department of Prices and Consumer Affairs deals with lead in consumer goods such as glazes on pottery, toys and graphical instruments. Any hazard relating to the carriage of lead-containing compounds by land and sea is in the province of the Department of Trade, while the Department of Education and Science would be concerned with any possible exposure of children to hazardous amounts of lead in schools. The Department of Health and Social Security interests are in the incidence of lead poisoning and in research on its biological effects as well as in providing toxicological advice to other departments and to Local Authorities.

With the involvement of so many departments it would not be impossible for the actions of one, in looking after its own interests, to

Table 1. Departmental responsibilities for hazardous chemicals

Department	*Areas of Responsibility*	*Medical/Toxicological Advisers*
Ministry of Defence	Chemicals used by the Armed Services	A combination of departmental and independent medical advice
Health and Safety Executive	Substances produced and used in employment.	Employment Medical Advisory Service (1)
	Pesticides used for non-agricultural purposes	Advisory Committee on Pesticides and other Toxic Products (3)
Ministry of Agriculture, Fisheries and Food	Food additives	DEHCH (2)
	Food contaminants	DEHCH (2)
	Food packaging	DEHCH (2)
	Pesticides	Advisory Committee on Pesticides and other Toxic Products (3) and DEHCH (2)
	Veterinary products	Veterinary Products Committee (4)
Department of the Environment	Air, water, marine and soil pollution, disposal of 'toxic' wastes, chemicals used in water treatment	DEHCH (2)
Home Office	Sale of acute poisons	Poisons Board
Department of Prices and Consumer Affairs	Cosmetics, toys, and graphical instruments, other consumer goods	DEHCH (2)
Department of Education and Science	Chemicals used in schools	DEHCH (2)
Department of Trade	Carriage of dangerous goods	DEHCH (2)
Department of Health and Social Security	Human medicines	Committee on the Safety of Medicines
	Some medical devices	Committee on the Safety of Medicines and Committee on Dental and Surgical Materials
	Some medical equipment	Supplies division and DEHCH (2)
	New smoking materials	DEHCH (2)
	Acute poisoning treatment	National Poisons Information Service

(1) Advice available from DEHCH through this group.
(2) Division of Environmental Health and Chemical Hazards of the Department of Health and Social Security.
(3) A Committee of the Department of Education and Science.
(4) With advice from DEHCH, Ministry of Defence medical staff and executive of the Committee on Safety of Drugs.

endanger health or the environment by creating a problem which was the province of another department. For example, if the concentration of a chemical vapour was above that considered safe for workers in a factory, the Factory Inspectorate may recommend that it should be lowered by increasing the ventilation to the atmosphere directly or through a scrubber to remove the chemical into water. In either case the problem of the Health and Safety Executive would be solved at the expense of creating a potential air and pollution problem for the Department of the Environment. Similarly, if an antimicrobial substance is being considered for use in maintaining the health of trout in a fish farm, not only its possible ill-effects on the health of the fish has to be considered, but also that it may influence the value of the antibiotic in human medicine, that it may end up in drinking water or damage the microbial flora of sewage works, or that it may produce undesirably high residues in fishmeat. The potential hazard could thus involve three Departments.

The possibility that the action of one department, in controlling the dangers of a particular chemical, will not create dangers that others have the responsibility to control is obviated by close co-operation between the administrators of each department and by liaison between the doctors and toxicologists of the various advisory groups. Frequently liaison is maintained by toxicologists and administrators of one department joining the advisory group of another department, or at least sitting in on discussions. For example, on the Department of Education and Science's Advisory Committee on Pesticides and Other Toxic Products and its various subcommittees, which have the responsibility of advising the Ministry of Agriculture and Health Departments on the safe use of pesticides, are Government and independent scientists who assess and advise on the risks of handling pesticides, on the possible dangers of residues which can occur in food crops, on the hazards to wildlife, on the risks to man of any contamination of the soil, air and surface waters, on the disposal of waste pesticides, and on the treatment of cases of accidental poisoning. All departments which have responsibilities in these areas, including those for Scotland, Wales and Northern Ireland are represented to ensure that some aspect has not been forgotten, or that control in one area has not caused problems in another.

It would be a valueless exercise to assess separately the potential ill-effects of each of a number of sources of a particular chemical. The major source of exposure to lead in the ordinary population is food, but in assessing the hazard of lead in food the possibilities that a person may be exposed to lead while at work, from car exhaust fumes, from drinking water, paint or cooking utensils, have to be taken into consideration. While separate departments are best equipped to determine and monitor exposure of people and the environment to chemicals within their own areas of interest, there is every merit in the assessment of health risks being organized by a central body or group of well co-ordinated bodies. In the case of lead the risks to public health have been assessed by the Division of Environmental Health and Chemical

Hazards and its several advisory committees which, because of the close contact with all responsible departments, has been able to take account of all sources of exposure to the chemical.

Although, therefore, the responsibility for controlling chemicals is spread widely among Government Departments, by co-ordination by administrators and by close liaison between medical, toxicological and scientific advisers, all aspects of any problem that might follow the release of a chemical on to the market can be considered and, if necessary, control devised in all or in particular areas.

TOXICOLOGICAL ASSESSMENT IN THE UNITED KINGDOM

Those who advise on the safe use of chemicals are frequently asked what types of test are required by Government Departments before the use of a particular chemical can be allowed, and detailed protocols of the tests which are required are sometimes demanded. For many groups of chemical products no official permission is needed before release on to the market. It is up to the manufacturer to decide how much testing and what type of testing is necessary both to ensure safety and to protect himself from any legal action that might result from any illness his product causes (for example under section 6 of the Health and Safety at Work, etc., Act 1974). This is so, for example, with cosmetics, packaging, household cleaners and fertilizers.

Where Government Departments do demand evidence of safety either through a legally enforced or a formally agreed scheme as with medicines, veterinary products, food additives or pesticides, no attempt is made to detail specific toxicological tests which have to be carried out. Instead guidelines are issued which indicate the areas of concern in relation to health for each group of chemicals and the type of information which assessors expect to see in any investigation done. Guidelines have been issued for medicines (Department of Health and Social Security, 1971, 1974), veterinary products (Ministry of Agriculture, Fisheries and Food, 1971a), pesticides (Ministry of Agriculture, Fisheries and Food, 1971b), and food additives (Ministry of Agriculture, Fisheries and Food, 1965) and also for investigating the carcinogenic potential of chemicals (Department of Health and Social Security, 1968). Other guidelines may be prepared and several are under revision at the present time.

Possible hazards to health of a chemical depend not only on its toxicity, but also on the way it is used, the frequency of use, the amounts to which people are exposed, the period of exposure, the type of person exposed, the form of the product and many other factors. It is sometimes suggested that for a group of chemicals which are all used in the same way and for which all these variables are therefore similar, a standard set of toxicological test criteria could be laid down which would pass or fail a substance. For example, in a report discussing the methods of assessing the possible toxic hazards from the use of

fire-resistant hydraulic fluids in mines the use of five simple toxicological tests was advocated. The results of these tests were to be scored numerically and the scores added after a weighting procedure; any fluid exceeding a certain score would fail the toxicological test (Mines Safety Commission, 1971). In a later report (Mines Safety Commission, 1974) the contrast of the United Kingdom approach to the problem is evident; this lists the possible hazards of the fluids to miners and the environment, states that appropriate data will be assessed by a Government-controlled group of toxicologists and technologists and then merely gives guidelines which refer to the published methods for investigating the particular toxic hazards. The design of the actual tests is left, as it should be, to the investigating toxicologist.

The 'laundry list' and 'pass–fail' approaches are unacceptable for many reasons. They are likely to inhibit the development of new toxicological techniques and of new ideas on toxicological assessment. The toxicologist would be led away from designing the most appropriate studies to investigate each problem and provide the most suitable information from which it can be assessed, to the mere performance of routine tests. This could eventually produce gaps in our knowledge and a subsequent risk to the public. Each toxicological investigation should be designed bearing in mind everything that is previously known about the chemical; one experiment leads to the next. While the commonly done toxicological investigations (the LD_{50}, 90-day tests, long-term tests, reproduction, metabolic and other studies) are looked upon by some as 'routine tests', they should be recognized as pilot studies designed to give information on which definitive studies can be based. Although in many cases the pilot studies tell enough to discourage a manufacturer from putting a product on the market and in other cases show substances to have such a low biological activity that no further work is necessary, in many cases much further study is needed to investigate any of a multitude of factors. It is impossible to foresee and lay down in official protocols all investigations which may be necessary for all substances; where toxicological data are submitted for assessment by a Government body, that body must have freedom to ask for further studies to elucidate any point on which there is doubt in relation to the safety of the chemical.

While all aspects of the likely hazard of every chemical have to be assessed, not all aspects need to be investigated experimentally. For example, the fact that the possible carcinogenic hazard of every organophosphorous insecticide has to be assessed does not mean that long-term tests of each one will be demanded; tests would be asked for if the structure, similarities to known carcinogens or early toxicological data were suggestive of carcinogenic activity.

On rare occasions tests are laid down in great detail for the investigation of a particular aspect of the toxicity of a compound. For example, a specific method for investigating the delayed neurotoxic action of an organophosphorous insecticide is prescribed under the Pesticides Safety Precautions Scheme. This method has been shown to be the

most sensitive available so far, but others could be used as long as they could be demonstrated to be equally or more sensitive.

The assessment of the toxic hazard of a chemical and its relationship to the benefit the chemical produces in an individual or in the community, demands close co-operation between the toxicologist and those who understand the needs for the chemical and all technical aspects of its production and use. Technological advisers are therefore associated with all Government assessing bodies. For example, clinicians, pharmacologists and pharmacists advise in relation to drugs, food technologists advise on the need for food additives and on the amounts likely to be consumed, and those who understand the mechanisms of chemical plants work alongside medical advisers when the safety is being considered of workers exposed to chemicals.

The question is sometimes raised by overseas regulatory authorities about the sources of toxicological data which are acceptable to United Kingdom authorities. An implication is made, even now, that the reliability of toxicological data from the manufacturer's own laboratory must be suspect, while that produced by independent commercial organizations should be more acceptable, and trustworthy data can only come from sources controlled by Government. This has never been the opinion in the United Kingdom where the majority of information comes from industrial sources. Increasing amounts are produced by independent laboratories, but relatively little is produced by Government-controlled laboratories, although a considerable amount of basic toxicological research is sponsored by the Government. It is not our experience that data from one source is any less or more reliable than from another. It might be that the confidence in manufacturers' data is a result of personal contacts between official and industrial toxicologists. In relation to food additives, drugs and pesticides, for example, discussions are encouraged on toxicological problems during various stages of a submission of a chemical for clearance by the official bodies. In this way industrialists get to know the way Government advisers think and the advisers can understand the practical difficulties often met by investigators.

CONTROL OF TOXIC HAZARDS

Since the aim of a toxicological assessment is to enable advice to be given on the precautions necessary to ensure and minimize pollution, a brief mention of control measures is appropriate. Restriction of production, sale or distribution of some chemicals is essential in order to reduce or eliminate hazards. Substances which are so acutely toxic that they can kill or make men or animals ill must have their availability to the general public restricted and this has been done for many years (Pharmacy and Poisons Act, 1933). The substances which have to be available to the public but which may cause injuries if not properly used also have to be controlled; for example, with medicines availability is limited to those who have a doctor's prescription. Substances

which may be consumed, often unknowingly, by all sections of the public over long periods, for example, food additives and pesticide residues, also need to have their use carefully regulated and this is done in most countries. There are, however, many products which are not a hazard under normal circumstances and others which, although they may cause mild inconvenience to a few people, seldom do serious harm to the vast majority of the population.

Controls on the use of chemicals should be appropriate to the type and degree of hazard, to the particular people at risk and to many other factors. Because these factors vary considerably the basis of control also shows a wide variation; there are five broad types:

1. Strict legislative control; for example with medicines and veterinary products (Medicines Act, 1968), acute poisons (Pharmacy and Poisons Act, 1933), industrial carcinogens (Carcinogenic Substances Regulations, 1967), and food additives and contaminants (Food and Drugs Act, 1955).
2. Formal control schemes agreed between Government and Industry; for example, the Pesticides Safety Precautions Scheme (Ministry of Agriculture, Fisheries and Food, 1971b).
3. Codes of Practice or British Standards; these may have statutory or quasi-statutory backing, may be simply a vehicle for Government advice, or may have been developed by Industry, for example, the BPF/BIBRA Code of Practice on Packaging Materials (1973).
4. Informal schemes; for example, the control of the safety of medical supplies which lays down the standard of safety expected for equipment supplied to the National Health Service.
5. Control by manufacturers and (the threat of) common law; for example, cosmetics and many other consumer goods.

The systems of control show considerable variation from simple refusal of permission to allow production, importation or sale of a chemical or restriction of supply to particular responsible groups, to simple advice on how to use the chemical safely for insertion on the product label or in a code of practice. Restrictions that are imposed must be capable of enforcement and it is desirable that the degree of exposure and any ill-effects should be monitored. These factors are relevant when considering the degree to which any control scheme can guarantee the safety of a chemical.

MONITORING THE SUCCESS OF TOXICOLOGICAL ASSESSMENTS

Ideally for each use of every chemical which man might contact or which escapes in the original or an altered form into the environment a guarantee of absolute safety should be available. In fact, all chemical substances carry some degree of risk, albeit an extremely low one, and what has to be done in practice is to ensure that any risk remaining, when all reasonable safety precautions have been taken, can be justified by the benefit the substance confers on individuals or on the nation as