TOXICOLOGICAL ASPECTS OF FOOD

Edited by
KLARA MILLER

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FOREWORD

There are enormous geographical inequalities in the amount and variety of foodstuffs available to the consumer and, while famine or threat of famine afflicts many third-world countries, the developed countries enjoy an abundance of relatively cheap food in almost bewildering variety. The success of the more affluent countries in meeting the increasing food demands of their populace has been achieved in a number of ways including: (a) amplification of agricultural food production, (b) control of losses during storage, (c) control of losses during distribution and in the home, i.e. increased shelf-life, and (d) more efficient use of available resources. In all these areas, new chemicals and new technologies have played an indispensable role.

Amplification of food production is exemplified by the increase in yield of maize in the USA from 2·3 tons/ha to 5·5 tons/ha in the period 1945–1970. These increased yields have only been achievable by the use of agrochemicals: fertilizers, pesticides and herbicides. It has been a major achievement of the agricultural industry to make two or three ears of corn grow where one grew previously, but an achievement heavily reliant on the associated agrochemical industry. Nor is increased efficiency necessarily confined to production of plant foods; by use of anabolic agents and veterinary drugs, production of animal products also may be enhanced.

In many third-world countries, an already parlous situation is made worse by the substantial proportion of food lost between production and consumption due to vermin or microbial spoilage. Even foods which may still appear edible to the consumer may be contaminated by mycotoxins elaborated by field or storage fungi, with consequent hazards to health. Once again, in more fortunate areas, such losses and contamination have been minimised by the use of chemicals (fungicides, fumigants) or new technologies such as irradiation in controlling germination in stored food-

stuffs. Extension of shelf-life by means of, *inter alia*, preservatives and anti-oxidants has facilitated the feeding of vast urban populations with minimal losses while reducing the health hazards from pathogenic micro-organisms or chemical spoilage products.

New technologies have also emerged to meet the increasing demands for food, leading to more efficient use of food raw materials, e.g. in re-formed meat products, and the development of novel foods to meet general nutritional needs or specific dietary goals. Using such new technologies and additives, it is also now possible to exploit novel sources of nutrients and convert these into palatable foods, further opening up possibilities for increasing food supplies from hitherto unconventional sources.

While nostalgia might have us wish that we could return to earlier methods of agriculture and food preparation, this is clearly an impracticable proposition; it would be quite impossible to meet current and future demands for food using only 'organically grown' raw materials (whatever that means) distributed in completely unprocessed form. However, once adequate supplies of food are assured and at a price that the consumers can afford, the broader issues of food safety also need to be addressed. Indeed, food safety assurance has assumed an increasing importance in the field of food science and technology, and would always be a consideration whenever new processes or new chemicals are introduced into the food chain. Both at national and international level, regulatory agencies have been established with the express purpose of ensuring that the safety of food supplies is not compromised and, where necessary, legislative procedures have been adopted to control potential hazards. Implicit in this regulatory activity is a need objectively and scientifically to establish the nature and quantitative dose-dependence of the potential toxic hazard; from this need has grown, over the past thirty years or so, the developing and increasingly mature science of food toxicology. The requirements of this scientific discipline and the problems encountered in the safety evaluation process are dealt with in the first section of this book, which also helps to put into perspective the relative hazards from sources other than food additives and contaminants.

The current debate on food safety has had an important emotional dimension which has, to some extent, clouded the real issues. The emphasis has been most heavily placed on man-made chemicals used in agriculture and food processing to the neglect of other, and in some cases more serious, hazards. In this climate, risk–benefit assessments have not always been seen in context. Whilst the concept of 'zero hazard' from chemicals used in food production and processing is attractive, it is both

unrealistic and irrational. There can be no doubt that food-borne microbial infections and intoxications constitute a hazard to the consumer of far greater magnitude than the properly controlled use of the chemicals, fungicides and preservatives used to combat them. It is ironic that higher levels of potently toxic and carcinogenic mycotoxins have been found in so-called 'health foods' produced without the benefits of anti-microbials than in comparable conventional food products. In this situation, even an imprecise assessment of residual hazard would clearly indicate that, although the net hazard might not be zero, it is significantly reduced by the use of fungicides in production and storage. Similarly, the benefits accruing from the use of anti-oxidants in controlling food spoilage and associated loss of nutrients, or accumulation of toxic oxidation products, may be seen as outweighing any net risk associated with their use.

The very toxicological techniques, both experimental and epidemiological, which have been applied to assessment of the safety-in-use of food additives and man-made contaminants have also helped to identify and quantify hazards arising from the presence of natural toxicants which are, and always have been, present in traditional food sources. A very great number of quite highly toxic components have been identified even in staple foods, particularly of plant origin, and are known to have caused death and morbidity in some circumstances. Examples such as favism, lathyrism, tropical ataxic neuropathy or even deaths from eating 'greened' potato serve to remind us that foods which may be valuable and innocuous in most circumstances are not totally without risk. However, any attempt to exclude such foods from the diet in pursuit of zero-risk would lead to a much more serious problem of food shortage and malnutrition. While such issues are not directly addressed in this book, they do impinge on the safety evaluation of foods from novel, non-traditional sources. There is no doubt that, if the potato were not a well-established food and was being evaluated as a novel food source, it would not pass the stringent safety requirements which are currently applied; the levels of glycoalkaloids such as solanine would be considered unacceptably high. It follows, as is pointed out in the section on novel foods later, that new foods/processes currently being evaluated will be safer than some of those which they replace. It also follows that, if the standards applied are too rigorous, potentially valuable and safe food sources may be lost. On a more positive note, knowledge of naturally occurring toxicants in plant foods has enabled the plant breeder to be alerted to the dangers and to develop low-toxicant varieties such as the low-glucosinolate, low-erucic acid strains of rape. In this instance, novelty has been linked to safety and irrational neophobia would have led

to a higher risk or the abandonment of a very valuable food crop. Critics of scientific progress in the field of food and agriculture would be well advised to learn from these examples; mankind has *not* learned from historical experience to select a safe diet which carries no risk, and new technologies can give increased margins of safety.

Suspicion of processed foods has led to a suspicion of the processes themselves and a firm belief in some quarters that 'good' food equates with domestically prepared food. This belief does not stand close examination in the light of the discovery of a number of potent mutagens and carcinogens in foods subjected to high temperatures in such traditional cooking procedures as roasting, grilling and frying. There is at least circumstantial evidence to suggest that polycyclic aromatic hydrocarbons and other pyrolysis products like the amino imidazoarenes may be implicated in the aetiology of human cancer and any proposed novel food process which carried such risks would be considered a non-starter. A valuable result of research in this area is the identification of the types of food materials and cooking procedures which carry the greatest potential for the formation of mutagens, and sound advice can now be given on how to reduce the hazard. Unfortunately, old habits die hard and the domestic cook is not subject to the same regulatory constraints as the commercial food processor!

While the foregoing might be taken as somewhat reassuring, and there can be no doubt that advances in food toxicology have played and continue to play a part in assuring the safety of the food supply, there are still a number of problems which require fundamental research towards a solution. One such problem, albeit a multi-faceted one, is that of food intolerance, whether of an immunological nature or resulting from other mechanisms. It has to be admitted that, at present, there is no suitable predictive model for the food toxicologist to apply prospectively, and most knowledge in this area has been derived from retrospective case studies, not always well founded. It is little comfort to the sufferer to point out that the consequences are only rarely of a life-threatening nature and that the incidence of intolerance to natural dietary components is probably greatly in excess of that to food additives. While one regulatory approach is to ensure that, by adequate labelling, the presence of the components or additives responsible can be identified and exposure avoided, improvements on this position are clearly needed.

Another problem facing the regulatory toxicologist is the undue weight placed on some toxicological end-points, such as cancer, at the expense of a more balanced overall evaluation. This has in large measure been dictated

by a response to political pressure and ill-considered legislation in some countries. A reappraisal is needed in order to put other toxic manifestations into a proper context, particularly those which relate to major causes of human morbidity such as cardio- and cerebro-vascular disease, while recognising the comparative irrelevance of some lesions seen in common laboratory animal species which seem to have no counterpart in man. Better experimental models and a clearer understanding of the mechanisms of pathogenesis are needed in order to discharge the duty of ensuring that the safety evaluation process is soundly based.

This book addresses all the problems referred to above and which face the regulatory toxicologist when considering the potential hazards posed by food contaminants, natural and man-made, and when evaluating the safety of new foods, food additives or technological processes. Distinguished experts in the various specialist fields have provided their insight into the nature of the problems and how they might be attacked. There is clearly no room for complacency as the industrialised world becomes more and more complex, but the success of the scientific approach to identifying and controlling potential hazards in the food supply may be judged by the availability of adequate amounts of generally safe, wholesome and nutritious food.

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Chapter 1

THE IMPORTANCE OF TOXICOLOGY IN FOOD SCIENCE

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INTRODUCTION

The enormous popularity of toxicology among the life sciences in the years following the United Nations Conference on the Human Environment in 1972 (UNEP, 1978) has resulted in a general feeling that all the problems caused to man and his biosphere by natural and man-made pollution will be healed or mended by the outright application of the principles and advances of toxicology. Today, however, toxicology as a discipline appears to be undergoing a moment of reflection and, recently, it has been pointed out that most difficulties in the field are not technical but political, psychological and sociological (Chenoweth, 1985).

Toxicology, from a trivial discipline buried in medical school curricula, suddenly emerged in the 1970s as a leading developmental specialty at the very forefront of science. Then, because of its inherent multidisciplinary character, it split inevitably into an array of associations with many cognate sciences. Thus, in addition to some of the well-established fields such as clinical (Conso, 1984; Temple, 1984), forensic (Cravey and Baselt, 1981; Maes, 1984; Oliver, 1980; Pohl, 1984), and environmental toxicology (Duffus, 1980; Guthrie and Perry, 1980; Somani and Cavender, 1981), a

variety of branches have been developed for which clear lines of demarcation were often difficult to draw.

Today many areas of specialization are open to the basically trained toxicologist. Here is a list that by no means should be interpreted as being exhaustive: analytical (Everson and Oehme, 1981), aquatic (Pearson *et al.*, 1980), chemical (Galli *et al.*, 1978), ecological toxicology (Hammons, 1981; Truhaut, 1977), environmental genotoxicology (Sawicki, 1982), evaluative (Kassel, 1984), experimental (Bertelli, 1979; WHO/EURO, 1984), food regulatory and regulatory (Vettorazzi, 1978, 1980, 1981), genetic (Thilly and Liber, 1980), industrial toxicology (Lauwerys, 1982; Lewis, 1984), neurotoxicology (Blum and Manzo, 1985), nutritional (Hathcock, 1982; Truhaut and Ferrando, 1978), ophthalmic toxicology (Ballantyne *et al.*, 1977), phytotoxicology (Kingsbury, 1980), preventive (Preziosi *et al.*, 1984), relay toxicology (Ferrando *et al.*, 1978), reproductive toxicology (Dixon, 1983), toxicovigilance (Roche, 1979) and tropical toxicology (Schvartsman, 1976; Smith and Bababunmi, 1980). An attentive reader of the current literature might also come up against certain folklore, such as barefoot toxicology (Abbou, 1979), courtroom toxicology (Houts *et al.*, 1981) or shuttle toxicology (Miller, 1984).

Important associations of toxicology are undoubtedly food science and nutrition; in this regard, if the science of toxicology has developed fast during the last decades, food science and technology as well as nutrition have equally advanced at a very rapid pace. These advances brought about the appearance of a large number and variety of foodstuffs on the market shelves. Highly organized curricula have made food science a multidisciplinary academic specialty which incorporates the sciences of chemistry, biochemistry, nutrition, bacteriology, engineering, etc. and which concerns itself with production, processing, composition, nutrition, acceptability and safety of food. There is today sufficient documentation to show that food is an extremely complex chemical mixture (even without considering the presence of extraneous materials), and the impact of these chemicals on the metabolic and homeostatic mechanisms of the human body is still in many respects the object of speculation, in spite of the great advances of physiological and medical sciences. It will thus be difficult to ignore the contributions of the food scientist when food safety evaluations are carried out (Vettorazzi, 1975). Food science interfaces with toxicology in many aspects which are all geared towards a common goal: the safety and acceptability of food. This chapter will describe briefly some of these aspects which are today of significance for the advances of toxicology as a food science. They will be described only in their essential elements with

the objective of identifying important operational interactions in the activities and responsibilities of the food scientist and food toxicologist.

MICROBIAL AND PARASITIC ENTITIES

The presence in food of bacteria, rickettsia, viruses, molds and parasitic protozoa/metazoa may cause human illness, characterized as food 'poisoning' or food 'intoxication' if the responsible agent grew in or on food and produced a toxin, or it may cause a food 'infection' if a parasite is ingested with the food and chooses the human organism as its host. Most food-borne illnesses of this type are well known and have been thoroughly characterized and extensively reviewed (Marth, 1981; Mundt, 1982; Rechcigl, 1983*a*; Riemann and Bryan, 1979). Efforts in this field are today mainly directed towards the establishment of control measures which would eliminate or reduce the incidence of these diseases. It is the responsibility of the food toxicologist to ensure that adequate technical and scientific support is developed and provided to those in charge of this control. Today this is mainly carried out by actively promoting investigations on new methods of detection and quantification of microbial contaminants which will be more effective, in terms of accuracy, time and cost, and by optimizing processing conditions such as dehydration and ultra-high temperature sterilization to ensure destruction or inhibition of microbial growth, including microbial toxic metabolites and enzymes. The outcomes of these trends are of great value in evaluating the role of microbiological criteria for foods and food ingredients (NRC/NAS, 1985). In addition to the development of methodology and dynamic optimization of conditions, there are two other aspects of growing importance today which underline the interface of toxicology and food science: one is the host/gut flora interaction and the other is the safety assessment of enzyme preparations of microbial origin used in food technology in mobilized and immobilized forms.

The gut microflora may influence the outcome of toxicity in a number of ways, reflecting their importance in relation to the nutritional status of the host animal, to the metabolism of xenobiotics prior to absorption, and to the biliary conjugation products. This was recognized by the Joint FAO/WHO Expert Committee on Food Additives (JECFA) on several occasions when it drew attention to the need for studies on metabolism involving the intestinal microflora in toxicological evaluation of food additives and contaminants (WHO/FAO, 1971, 1975). Diet and gut flora

interactions in toxicology today form a topic of broad interest (Hentges, 1983; Rowland and Walker, 1983; Mallett, 1984; WHO, 1987*a*).

The increasing use of enzymes in food technology has made it imperative that consideration be given to the toxicological evaluation of enzymes as a class of food additives. More and more enzymes derived from microbial sources are used today. These enzyme preparations are generally not single enzymes but often have enzymatic activities besides that of the main principle and also contain non-enzymatic proteins, metabolites, and other residues from the source material. In addition, residues of substances used in their manufacture and adjuncts such as buffers, inorganic salts, diluents, or stabilizers are often present. Consequently, for toxicological evaluation the expression of the amount of the enzyme preparation used in terms of activity is less relevant than a statement in terms of weight. In addition to concern regarding the possible hazard arising from the presence of toxins associated with enzyme preparations from micro-organisms, particularly with reference to mycotoxins (Moreau, 1979; Kurata and Ueno, 1984) and the possible allergic reactions following inhalation or dermal application, there is also the possibility of mutations accruing in the organism which could affect the food enzyme adversely through the emergence of new, potentially toxic products. Furthermore, the increasing use of immobilizing enzymes calls for the evaluation of the immobilizing substrates as well as the immobilizing techniques (WHO/FAO, 1971, 1974, 1978). Guidelines for the evaluation of these substances as well as principles helping to establish specifications for identity and purity were formulated (WHO, 1982, 1986); the food scientist and the food toxicologist ought to be cognizant of these advances.

TOXICANTS FROM NATURAL SOURCES

Many apparently wholesome and healthful foods contain naturally occurring substances which have undesirable effects on humans and animals. The ingestion of these foods can bring about toxic outcomes which may become evident in the form of aspecific acute reactions, such as in the case of inborn intolerances in hypersensitive individuals, or they can manifest their presence through well-characterized clinical syndromes, as in instances of mushroom poisoning, skeletal deformities, aortic ruptures and neoplastic phenomena.

Furthermore, early in the history of scientific investigation of ailments it was noticed that certain foods contained small amounts of materials whose

effects, although not toxic, were nevertheless interfering with the nutritional quality. These factors, today of primary concern to the nutritional toxicologist, became known as co-nutrients, and include substances such as antienzymes, antivitamins and estrogens.

The interest in naturally occurring toxic factors in food is as old as medicine, and man has learned through the years the laborious task of refraining from edibles which, by experience, caused obvious objectionable consequences to his well-being. Today this problem becomes even more arduous with the discovery that the amounts of the harmful substance consumed daily may be very minute, and no observable physiological effect can be obtained from a single intake. Consequently, careful studies are now directly aimed towards the evaluation of long-term impact on animals, and extrapolation of results obtained in laboratory animals to those anticipated in man has become the normal procedure. In this manner, several toxic factors already have been characterized (NAS, 1973; Liener, 1980; Rodricks and Pohland, 1981; Rechcigl, 1983*b*). Many more, however, are still awaiting basic biochemical and pharmacological investigations as well as extensive epidemiological studies. The task of ascertaining more clearly and systematically the role of food-borne toxicants in human pathology is of relatively recent date.

There are signs of renewed interest in contaminants from natural sources, especially because of the importance of the recurrent problems they cause in developing areas of the world. The International Programme on Chemical Safety (IPCS) is presently preparing an extensive review on pyrrolizidine alkaloids and their role as causative agents of veno-occlusive diseases (Tandon *et al.*, 1977, 1978; WHO, 1987*b*). The food scientist and the food toxicologist in the developing world are continuously challenged by the appearance of new fields of investigation from toxicants found in common foods of natural origin. It should, however, be recognized that the problem generally affects localized areas and, with the exception of a very few (e.g. mycotoxins), contaminants from natural sources are not commonly found in foods circulating in international trade at levels which may cause public health concern.

An interesting field of expansion is today represented by the presence of 'pressor' amines in a number of common foods either naturally or as a result of processing. As an example, baby foods containing banana may contain up to 25 ppm of 5-hydroxytryptamine (serotonin). Thus a baby of 7 kg consuming 200 g of such a food would ingest 0·7 mg/kg body weight, and about 70% of this amount would be absorbed from the intestine (Vettorazzi, 1972, 1974). Amines related to the common aromatic amino