Food Toxicology — Real or Imaginary Problems?

Edited by
G. G. Gibson and R. Walker

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FOREWORD

Whilst there is little doubt that, generally speaking, the human food supply is safer now than at any time in the evolution of the species, it is equally true that dietary components play a significant part in the aetiology of human disease. Epidemiological studies on migrant populations have indicated that changes in dietary habits can lead to different patterns of disease and mortality and have helped to identify some of the risk factors involved. In relative terms, the hazards associated with natural toxicants, such as the mycotoxins, and with 'overnutrition' would appear substantially greater than those resulting from modern technological practices in the agricultural and food processing industries which, in many cases, have made a positive contribution to food safety. However, this in itself is not grounds for complacency; the benefits of modern food technology must be evaluated against any associated risks and the latter minimised as far as is practicable without prejudicing food supplies.

The benefits against which the risks need to be balanced are many. Modern methods of amplifying agricultural food production, of controlling losses on storage and distribution, of eliminating pathogenic micro-organisms by improved hygienic practices and of preventing re-infection or contamination by the use of packaging materials have all contributed to a reduction in nutritional deficiency diseases and in food-borne infections and microbial intoxications. These undoubted benefits inevitably are associated with some potential problems: with contamination of food and water supplies by fertilizers, pesticide residues, veterinary drugs and growth promoters or by packaging migrants; with the presence in food of the additives used in controlling spoilage, preservatives and anti-oxidants, or which are used for other technological, economic or aesthetic reasons. Whether these potential problems constitute a real risk to human health is not readily established, depending on appropriate toxicological methodology to assess the likely toxicity to man and data on actual levels of human exposure in order to relate toxicity to actual hazard. Regulatory measures to control the hazards depend critically on the availability of relevant toxicological information and up-to-date surveillance data, both in the drafting of legislative controls and in monitoring their effectiveness against a backcloth of changing eating habits and exposure levels.

The purpose of the Symposium on which this volume is based was, as implied in the title 'Real or Imaginary Problems', to examine the current issues facing food toxicologists and regulatory bodies with a view to identifying where the 'real' problems lie. This is an essential prelude to the allocation of priorities since the resources available for food safety evaluation are limited, not least by the number of trained researchers in this field.

Food safety evaluation has as its foundations a battery of toxicological tests performed very largely in experimental animals. But how secure are these foundations? The first session of the Symposium addressed this question and the paper by Professor Conning suggests ways in which current methodology might be developed to improve its predictive value for man. The difficulties posed in the evaluation of major food ingredients and the potential loopholes in current routine toxicity testing were also examined in this session. The obsession with carcinogenicity, which is a hallmark of current protocols and leads to such philosophical absurdities as 'zero tolerance' in some legislation, has tended to divert attention from other important issues, such as allergies and idiosyncratic responses or behavioural toxicology where the required methodology is still to be developed and applied to the prediction of hazard. The papers dealing with the potential loopholes serve as a timely reminder that there are other forms of toxicity than cancer which are known to affect the food consumer and other methodologies than chronic toxicity tests in rats and mice.

The approach to legislative control of food additives and contaminants was examined from the point of view of the U.K., E.E.C., U.S.A. and Canada and it is clear from the papers addressing this issue that a common aim of safety assurance can be approached in significantly different ways. These reflect not only alternative philosophies, as embodied in, e.g. U.K. Guidelines or the F.D.A. 'Red Book', but also differing responses to the various interest groups which exert conflicting pressures on the legislatures. The problem of reconciling the various scientific and political inputs is a very real one, with inevitable consequences for international trade, but the scientific community cannot avoid its responsibility to ensure that it does not compound the problem by failing to respond quickly enough to scientific advances in toxicology. It was perhaps a salutory lesson that resistance to the proposed ban on saccharin in the United States came from consumer groups rather than the scientific fraternity, who were still arguing about the relevance to man of bladder tumours in rats fed several per cent of the compound in the diet.

Following these general issues, the Symposium turned its attention to the more specific topics of carcinogens in food, food additives and contaminants, and interaction products in processed foods. There is no doubt that the presence of low levels of potent carcinogens in the diet is a real problem but whether it represents a real hazard to man is less readily established unequivocally. Mutagenicity tests (Dr. Anderson) and carcinogenicity bioassays (Dr. Clayson) were considered in relation to the prediction of risk and the multi-stage process of carcinogenesis was emphasised; different regulatory approaches might be adopted for 'complete carcinogens' and for those compounds which modify discrete events in the process whilst not themselves being 'genotoxic'. On the one hand lie the aflatoxins, nitrosamines, polycyclic aromatic hydrocarbons and some of the heterocyclic pyrolysis products which are potent mutagens while on the other there are saccharin and butylated hydroxyanisole which undoubtedly lead to tumours of the bladder or forestomach respectively in rat bioassays but only at relatively high dietary dose levels. It is clearly inappropriate to consider all these compounds as equivalent, or even to measure them by the same yardstick, and a rational basis for making distinctions between them will very much depend on a clearer understanding of the mechanisms of carcinogenesis

and their modulation by environmental factors. The papers and discussions in this area represent progress on the road to a rational assessment of the risks posed by low levels of 'carcinogens' in the food supply.

In the papers dealing with food additives, contaminants from agriculture, animal husbandry, food processing and packaging, many of the current issues were discussed arising from individual case studies or from such difficulties as allocating priorities for investigation of the hundreds of compounds used as flavours. Whilst it is easy to feel complacent in the belief that the measures being taken to evaluate and control additives and contaminants are effective in protecting the consumer, as indeed they usually are, a review of the Spanish 'toxic oil' episode proved a useful, sharp reminder of the need for constant vigilance and the failure to identify the factor(s) responsible for the intoxication demonstrates that even retrospective toxicology has its limitations.

The Symposium ended with a stimulating paper by Professor Golberg entitled 'Food Toxicology - Time for an Agonising Reappraisal' in which attention was drawn to the shortcomings and misdirected emphases in safety evaluation which have resulted in as many 'Imaginary Problems' being created as 'Real Problems' solved. As a fitting end to a thought-provoking meeting, we were left each performing our own 'agonizing reappraisal' - a painful but necessary process if progress is to be made in this important area of preventive medicine.

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FOOD SAFETY ASSESSMENT, LEGISLATION AND SURVEILLANCE

ALLOCATION OF PRIORITIES - WHERE DO THE REAL RISKS LIE?

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Introduction

My job as chairman in giving the initial talk is to set the scene and to pose some questions. Subsequent speakers will, I trust, be providing some of the answers.

To strike a personal note, I have myself been fairly closely involved with food safety assessment, legislation and surveillance for over 12 years, since I first joined the Ministry of Agriculture, Fisheries and Food as Chief Scientific Adviser (Food) in January 1971. Prior to that I have been the Director of a Food Research Association, and prior to that I had been in academic life, so I had never before been a civil servant. I remember that the first problem I got - on my first day -was to set up an official committee to determine and report on levels of mercury, and especially methylmercury, in the British diet and their significance. We worked very closely then, as we still do now, with our colleagues in the Department of Health and Social Security. It was not an easy job, but we reported with despatch - within a few months - and since then there have been problems with food contaminants such as lead, cadmium, nitrosamines, aflatoxin, radionuclides, pesticides, PCBs and vinylchloride, and food additives such as nitrites, saccharin and BHA, to mention but a few. My colleagues from other parts of the world could all tell similar stories about the problems which they have experienced in the past decade or so.

I think it is now recognised that most of the substances to which I have referred pose, at their present levels in the UK diet, risks which are low or negligible, although we naturally want to keep the amounts of many of the contaminants to the lowest practicable level. But for none of them, with the possible exception of radionuclides, can we quantify the risk to the average - or even the non-average - consumer. Do the present levels of cadmium in the UK food supply reduce the expectation of life of the average man or woman?; do the present levels of dimethylnitrosamine in the UK food supply actually cause an increase in cancer levels? In both cases the answer is that we do not know, although the evidence suggests that any effect which might exist is probably very small. Needless to say, all food is a collection of chemicals; for some of these the chemistry and toxicology is well-known, others we know little about. Man has come to eat his present diet by a process of trial and error, and there is no guarantee that every one of our traditional foods poses no toxicological risk.

Risk Assessment

The whole of this Conference is concerned with assessment of risks to the consumer. Until we can quantify risks from ingestion of food components, or of additives or contaminants, we are in no position to say whether or not they are appreciable in relation to normal risks of life. As you will know, a Royal Society Study Group (Royal Society 1983) published a report entitled "Risk Assessment" which is a mine of information on risks of many types. For example, the average annual accidental death rates at work in the UK per million at risk is 5 for the manufacturing of clothing and footwear, 110 for agricultural employees and 1650 for off-shore oil and gas; while the risk of death per 10^9 km travelled is 0.45 for rail passengers, 1.4 for scheduled airline passengers, 8 for car drivers and 85 for pedal cyclists. How do the risks, for example, of eating bacon containing 1 part per thousand million of dimethylnitrosamine, or drinking tea containing saccharin, compare with these? The answer is, of course, that it is impossible to say, partly because the risks which have been best quantified are those in which people are killed directly by an acute accident. With food, the situation is similar - there are some short-term risks, e.g. of choking on a fish bone, or of getting acute food poisoning which will show up a short time after the meal. But if a person dies from a particular type of cancer at the age of 60, there is no way of telling how far the composition of his diet has contributed to this. For assessment of long-term risks from food, therefore, we have to rely upon the results of animal experiments usually using exaggeratedly high doses of the substances to be studied, in order to get results in a reasonable time, with a reasonable number of animals. We then need to do at least two extrapolations (a) from high dose levels in the rat (say) to realistic levels in the rat; and (b) from the rat to man. Both of these extrapolations are, of course, fraught with complex difficulties, some of which will be discussed in this Symposium.

Short-Term Risks - Acute Food Poisoning

Additives with a high short-term chemical toxicity are not permitted for use in the food supply, and acute chemical toxic effects from contaminants very rarely occur except in most unusual accident situations. On the other hand, there is no doubt that contamination of food with pathogenic micro-organisms does cause a lot of illness and sometimes, but rarely, death. In fact, the WHO publication (O'Neill, 1982) entitled "Health Crisis 2000" reports that food poisoning is the second largest cause of illness today. One reason is the increase in consumption of food outside the home. Over half of all the meals eaten in Sweden are consumed in public places, such as cafeterias or works canteens (the corresponding figure for Britain is about one fifth). The average stay of a worker in the kitchens of Heathrow Airport, one of the world's largest, is six weeks. There are stringent tests on the hygiene of catering staff - without constant vigilance, airports could become the biggest and fastest exporters of food poisoning in the world.

Food poisoning is a notifiable disease in the UK and usually some 10,000 cases of food poisoning during the year are notified to the authorities by medical practitioners in England. As far as risk quantification is concerned, if 50 million people each eat 1,000 meals per year and 10,000 cases of food

poisoning are notified, the average person has one chance in 5 million of becoming a notified case for every meal he eats, or one chance in 5,000 every year. Relatively mild cases of stomach upsets, of course, are not even reported to the doctor, so it is safe to say that many more than 10,000 people each year in England are made ill by bacterial food poisoning, which is often caused by poor hygiene in the kitchen, shop or restaurant, or by failure to cook food adequately. The majority of food poisoning cases and due to Salmonellae, including Salmonella typhimurium, plus significant contributions from Clostridium welchii, Staphylococcus aureus and Campylobacter. At least in this area there has been great improvement in the past century, e.g. through the proper use of preservatives, packaging and refrigeration. Furthermore, the lines for further improvement, mainly through improving hygiene education, and reduction where possible of Salmonella infection in livestock, are clear.

Long-Term Risks from Food

If we regard radionuclides in food as potential carcinogens, or at least as capable of promoting the development of potential carcinogenic changes, then we can calculate risks from ingesting food containing them, provided that we know the types of nuclide present, their concentration, retention time in the body and other relevant factors. For consumers of fish taken from the Irish Sea, for example (Hunt, 1980), Table 1 shows the radiation dose equivalent as a percentage of the ICRP recommended dose limit (International Commission on Radiological Protection, 1977) for various groups.

Typical members of the fish-eating public in 1978 were receiving no more than 1.2% of the recommended ICRP dose limit, while heavy eaters of fish in the local fishing community were estimated to receive 26% of the recommended dose limit. This limit is aimed to ensure that the average dose equivalent to members of the population from all sources, including natural and medical irradiation, will not exceed 0.1 millisievert (1 sievert = 100 rem). This is in turn equivalent to about 1/10th of the natural background radiation of 1 mSv, corresponding to about 200 ionising events per year for every cell in the body. Radionuclides are in a special position because of our knowledge of dose/response relationships from early human experience with ionising radiation following the discovery of x-rays and radium, and more recently with medical uses of radiation, exposure from nuclear weapon tests and the peaceful uses of atomic energy. For chemical carcinogens such as nitrosamines or mycotoxins, such dose/response data are not usually available.

Nutritional Factors

A further complicating factor is that the health of the population at large depends at least partly on the general composition of the diet, and the diet of individuals within a given country may vary widely. As Sir Richard Doll has pointed out (Doll, 1977), variation of cancer incidence from one country to another is well known, and is only partly genetic in origin. Diet almost certainly plays a part; for example, there is a strong correlation

Table 1 Individual Radiation Exposures due to Consumption of Irish Sea Fish and Shellfish 1978

Exposed population	Consumption rate used in assessment	Radiation dose equivalent (as % of ICRP-recommended dose limit for members of the public		
			Effective (ICRP-26)	
Consumers in local fishing community	170 gd^{-1} fish 15 gd^{-1} crustaceans 6 gd^{-1} molluscs	26	^{90}Sr ^{106}Ru ^{134}Cs ^{137}Cs $^{239}Pu + ^{240}Pu$ ^{241}Am	0.6 1.5 2.0 16.8 0.9 3.7
Consumers associated with commercial fisheries (Whitehaven, Morecambe Bay)	360 gd^{-1} fish 70 gd^{-1} crustaceans 50 gd^{-1} molluscs	15	^{90}Sr ^{106}Ru ^{134}Cs ^{137}Cs $^{239}Pu + ^{240}Pu$ ^{241}Am	0.9 0.4 1.4 12.1 0.04 0.2
Typical member of the fish-eating public consuming fish landed at Whitehaven Fleetwood	40 gd^{-1} fish	1.2	^{134}Cs ^{137}Cs	0.1 1.0

between the intake of fat per head in various countries and the incidence of colon cancer ($r = 0.78$), breast cancer ($r = 0.79$) and endometrial cancer ($r = 0.85$), although these correlations do not prove a cause/effect relationship. Furthermore, the undoubted fact that calorie restriction inhibits the formation of various types of tumours in mice and rats (Carroll, 1975) implies the possibility that risks from a given level of a particular carcinogen in the diet may vary from one human population to another. At least as far as rats are concerned, aflatoxins seem to be more dangerous in an ample diet than in a frugal one. We also have to take into account the possibility that some substances which are apparently more or less harmless by themselves, may be converted into mutagens or carcinogens in the human gastrointestinal tract.

The problem then in assessing the possible effect on health of a new food additive or contaminant is to judge the possible long-term effects on

humans against a background of other health effects due to environment, genetic differences, life style, etc. Doll (1979) has concluded in a recent study that "the removal of additives cannot be expected to do much to reduce the current incidence of cancer in man". He believes that much greater dietary risks come from:

(a) consumption of alcohol, especially in conjunction with smoking;

(b) general over-eating;

(c) contamination of food by fungi in hot moist climates;

(d) lack of sufficient fibre in the diet.

Some Problems for Research

At a recent Toxicology Forum in Vancouver (Elton, 1981) I spoke about some of the questions which we need to address in seeking to improve our assessments on the safety of the food supply. Perhaps I can just list some of these questions briefly; later speakers in this Symposium will deal with most of them in more detail:

(a) In attempting to use experimental animals to assess long-term hazards to man, how do we take into account inter-species variation in sensitivity? Do qualitative differences exist, e.g. are some compounds carcinogens in some species and not in others, or are the differences only quantitative? Obviously, if a compound is metabolised differently in the test animal from its metabolism in man, the validity of any extrapolation becomes questionable.

(b) When trying to assess the carcinogenicity of dietary components in test animals, what should be base line be? For a given group of animals this might be the diet which produced the lowest incidence of tumours, all other things being equal. The quantity of food consumed, as well as its composition, will probably be important. It is not necessarily true that the standard laboratory rat diet is the best possible "control diet" to use.

(c) In assessing hazards to man, should we assume that the dose/response parameters for man are the mean of the dose/response parameters for the animals studied, or should we be more conservative and assume that man is as sensitive as the most sensitive of the animal species tested, and then incorporate a substantial safety factor in setting regulatory limits? And what about time factors? Generally speaking, time-to-tumour in a given species rises as dose level falls. If for low doses the time-to-tumour extrapolated by some valid method were to exceed greatly the life-span of the species, should we worry about it at all?

(d) Can we evolve a satisfactory system of expressing a quantitative indication of potency of a carcinogen? Dr. Leon Golberg (Golberg, 1979) has suggested that for human exposure to known carcinogens, potency might vary by a factor of 10^7, whereas exposure (including occupational exposure) might vary by a factor

of 10^8. For a given exposure time, therefore, the risks posed by two different carcinogens might differ by a factor of 10^{15}. Peto (1979) has calculated that the hazards from many carcinogens may vary with the fourth or fifth power of the exposure time, so that doubling the exposure time to a particular carcinogen could multiply the risk by a factor of the order of 20 or 30.

(e) How do we assess the safety of food components which may form a substantial part of the diet? For trace components we may establish a control limit such as an acceptable daily intake (ADI) which should be exceeded only in exceptional circumstances, and which would normally incorporate a conservative safety factor based on no-effect levels in animal experiments. However, for a substance likely to be a major component of the diet (i.e. to be used at 1% or more) the safety factor obtainable in an animal feeding experiment is going to be very small. This could well pose problems in the future in assessing the safety of novel foods, or novel food processing methods. To quote one example, the FAO/WHO Joint Expert Committee on Food Irradiation (JECFI) has recommended clearance for use of ionising radiation treatment of foods at a rate of 1 Megarad. At 0.1 Megarad the dose is so low that radiolytic products are insignificant. But various studies have indicated that at 1 Megarad, treatment of various foods (e.g. chicken, sugars) leads to the production of detectable amounts of mutagenic substances; but the levels of mutagens present are unlikely to show up any toxicological effects when the foods are fed at any reasonable attainable level in the diet. The extent of safety testing required is currently still a matter of international debate, although it seems probable that permitted levels of irradiation for various foods will be gradually raised as improved knowledge allows.

Conclusions

In relation to acceptability of risk, the Royal Society Study Group on Risk Assessment (Royal Society, 1983) pointed out that if the average expectation of life is 70-75 years, then the imposition of a continuing annual risk of death to an individual of 10^{-2} seems unacceptable. The Study Group judged that levels of annual risk in the region of 10^{-6} might be regarded as trivial, while an annual risk ten times as great as this (10^{-5}) in travelling by train does not cause the ordinary traveller any concern. Unfortunately, we are not in a position of putting figures like this on risks associated with food consumption. Nor can we assume that a risk which an individual is prepared to take as a result of travelling in a train or smoking a cigarette is the same as the risk which he is prepared to take in relation to something as fundamental as his food supply. Perhaps the thing which really matters is what people think the risk is, and this may be easier to measure than the real risk, although, of course, it is subject to change, e.g. due to improved education and understanding.

I started my talk with a list of some of the problems I met 12 years ago. Listed below are some of the nutritional/toxicological problems under discussion internationally today: