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Chemical Additives in Food—A Review of the Regulatory Processes Governing Their Control and the Procedures for Evaluating Their Safety in Use

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ABSTRACT

This paper reviews the regulatory processes of control and evaluation of the safety of chemicals added to foods (commonly termed food additives). It endeavours to identify modifications in the official documentation and uses this as a discussion basis for tracing developments in the field of toxicity studies. It examines the criticisms that have been levelled against existing procedures and the extent of official acknowledgement of these objections. Finally, it explores the necessity to weigh the possible risks to health from the use of food additives with the difficulties inherent in supplying food to an ever expanding urbanised society, from the point of view of the authorities and the consumer.

LEGISLATIVE BACKGROUND

Introduction

The development of food legislation in the United Kingdom appears to show a definite progression from attempts to control commercial malpractice (Giles, 1976) to today's controls in which the major principle is the control of the risk to health. The current Food Act of 1984, which, for England and Wales, contains the provisions of the original Food and

TABLE 1
The Control of Food Additives in the United Kingdom

Additive category	*Reference*
Controlled by Regulations	
Antioxidants	SI (1978)
Colouring matter	SI (1973)
Emulsifiers and stabilisers	SI (1980*a*)
Mineral hydrocarbons	SI (1966)
Miscellaneous additives (includes the following categories: acid, anti-caking agent, anti-foaming agent, base, buffer, bulking agent, firming agent, flavour modifier, flour bleaching agent, flour improver, glazing agent, humectant, liquid freezant, packaging gas, propellant, release agent or sequestrant)	SI (1980*b*)
Preservatives	SI (1979)
Solvents	SI (1967)
Sweeteners	SI (1983)
Recommended for control	
Enzyme preparations	FACC (1982*b*)
Flavouring agents	FACC (1976)
Modified starches	FACC (1980)

Drugs Acts, provides the framework for the legal controls of food production and marketing and prevents the manufacture of food which could provide a risk to health (as well as preventing adulteration for fraudulent purposes). Similar controls are applied in Scotland and Northern Ireland by the relevant Food and Drugs Acts of 1956 and 1958, respectively. The detailed controls which now encompass most food additives are contained in regulations made under the Acts. Table 1 provides the details of those classes of additives currently controlled by regulations and those which have been reviewed and recommended for control.

With additives, the objective has been to produce statutory permitted lists of all classes of additives which may be used and the maximum levels of use. To date, all except flavourings are controlled by specific regulations, or are likely to be controlled in the near future. Flavourings present particular problems which are proving difficult to surmount. In addition to the additive regulations, the use of additives may be restricted

by regulations relating to the composition of certain foods which contain provisions limiting the use of additives in those particular foods.

The Rôle of the Food Advisory Committee

Before a substance is listed it is submitted to an evaluation by an independent committee of experts in the relevant scientific disciplines which advises the Ministers concerned on the use of the additive. Until 1983, two committees were involved in the evaluation of food composition and the use of additives. The two were:

Food Standards Committee (FSC), which advised on the composition, labelling and advertising of food.

Food Additive and Contaminants Committee (FACC), which advised on the need, safety-in-use of additives and levels of contaminants permitted in food.

The functions of these two committees have now been combined, with the formation of a single committee, the Food Advisory Committee (FAC), which has responsibility for the functions of both the original two committees (Bunyan *et al*, 1984).

Food additives can be considered for several reasons:

(1) A new additive will be considered before it can be used.
(2) Each class of additive will be reviewed on a regular basis to ensure that they represent the current state of knowledge.
(3) Further research may become available nationally or internationally and give rise to concern regarding the safety of the additive in question.
(4) The consideration of a further class of additives, not previously reviewed, may become necessary.

Upon referral to the FAC the need for, and safety-in-use of, each substance is considered with particular emphasis on the latter aspect. Figure 1 shows the approach to consideration adopted and the lengthy process required prior to the adoption of an additive by regulation. It can be seen from the Figure that the FAC may, in turn, take advice from various other committees including:

Committee on Toxicity of Chemicals in Food, Consumer Products and the Environment (COT).

Committee on Medical Aspects of Food Policy (COMA).

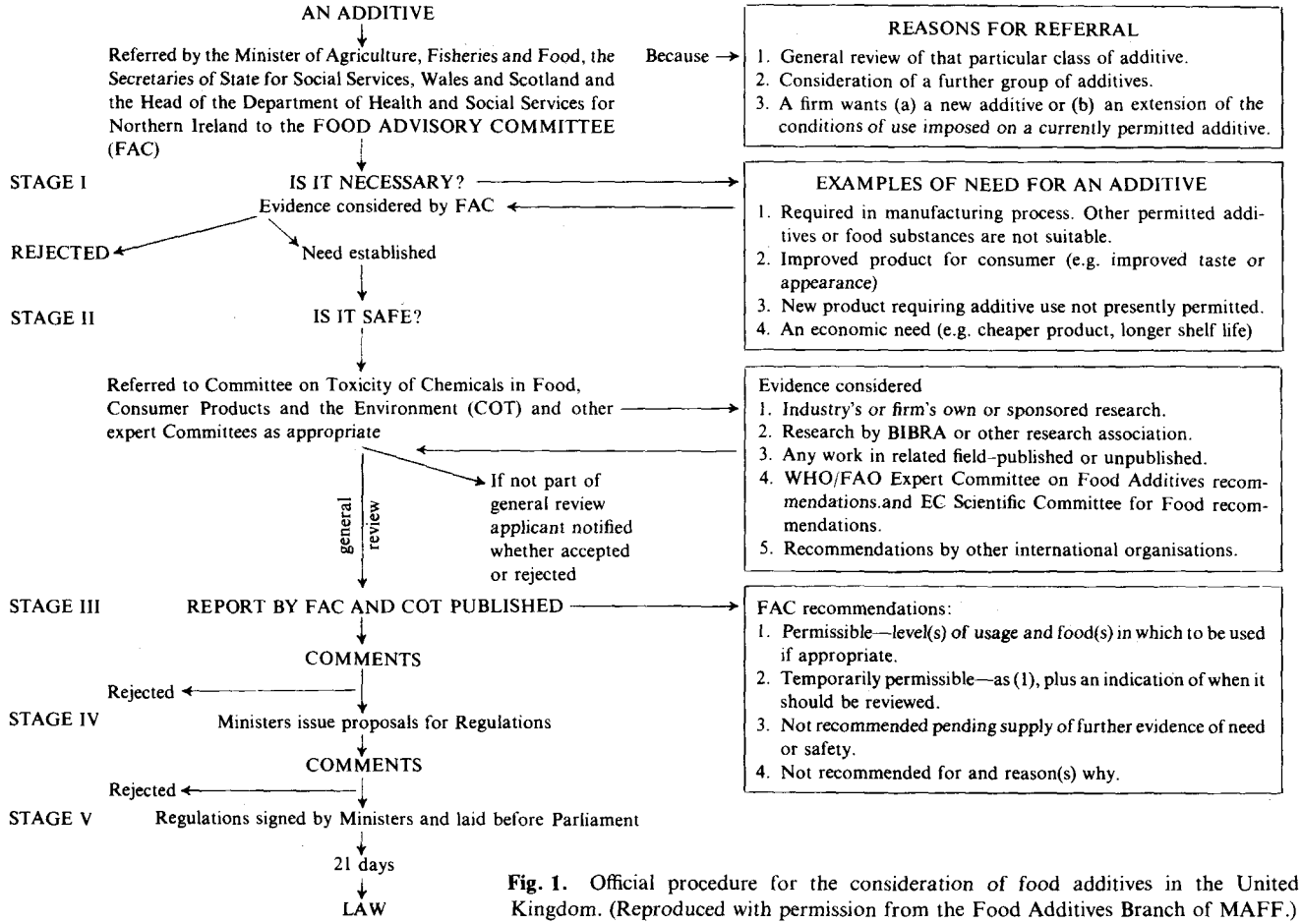

Fig. 1. Official procedure for the consideration of food additives in the United Kingdom. (Reproduced with permission from the Food Additives Branch of MAFF.)

Committee on Carcinogenicity of Chemicals in Food, Consumer Products and the Environment.

Committee on Mutagenicity of Chemicals in Food, Consumer Products and the Environment.

The committees have no facilities for toxicity testing but consider reports of relevant investigations carried out largely by the industry/manufacturer concerned, research associations and international organisations. Recommendations are made as to safety status, level(s) of usage and food(s) in which the additive is to be used where appropriate.

The system of evaluation is, by necessity, protracted to enable opportunities for comment from all interested parties. However, the process can be accelerated considerably, as is illustrated in the case of the banning of cyclamates (Crampton, 1970).

International control

Membership of the European Economic Community (EEC) has had implications for the existing UK regulations. The EEC initiates legislation with the purpose of reducing barriers to trade. In the area of food, legislation is evolving with the aim of harmonising the different compositional requirements of member states to enable food legally produced in one country to be accepted by another. Thus, the legal controls on additives are one area in which the Commission of the EEC (the CEC) has taken an interest. The development of Community legislation, as illustrated in Figure 2, again provides opportunities for consultation with interested parties. The Commission, which initiates Community policy, takes impartial advice on the composition and safety of both food and food ingredients from the Scientific Committee for Food (SCF). This committee was instituted in 1974 and is composed of fifteen members chosen from nationals of member states and covering a range of appropriate scientific disciplines. Its advice is published as SCF reports. The increasing rôle of the SCF in reviewing the safety of additives was one of the reasons which led to a merger of the FSC and the FACC in the United Kingdom (to produce the FAC).

The SCF (and the FAC) may also take note of advice published by various international groups. These are many in number but of particular importance are the following:

Joint FAO/WHO Expert Committee on Food Additives (JECFA):

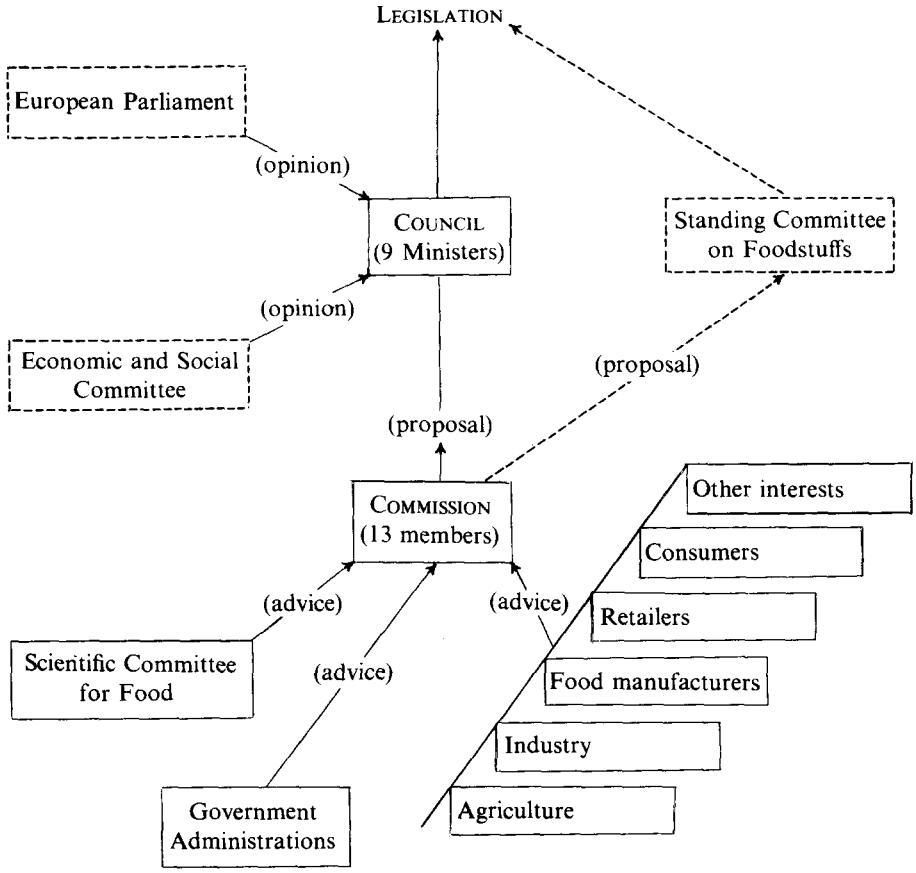

Fig. 2. Consultative process in the development of EEC legislation (Haigh, 1978).

concerned with the technical and administrative aspects of the problems associated with the use of additives in food.

Codex Alimentarius Commission (CAC): has an extensive programme, including food composition and food ingredients.

Organisation for Economic Co-operation and Development (OECD): decides upon consumer policy aspects of the environment and of chemicals such as pesticides and food additives.

OFFICIAL SAFETY EVALUATION PROGRAMMES

It has long been acknowledged by the Government and other regulatory bodies that, conceptually, there is no such thing as absolute safety.

Kolbye and Schaffner (1979) remind us that, in connection with food safety, toxicologists know that 'the dose makes the poison'. Hence, all foods and food ingredients are potentially toxic if consumed at sufficiently high levels. Safety is therefore seen as a value judgement which involves evaluating risks and, when the risk for harm is considered acceptable, then something is deemed 'safe'. Such a judgement is based on the interpretation of complex data from three areas, namely, potential toxicity, human exposure and susceptibility.

Official guidance

In the United Kingdom guidelines have been published on the evidence required for submission and the methodology to be followed. A Memorandum had been issued in 1965 on the Procedure for Submissions on Food Additives and on Methods of Toxicity Testing (MAFF, 1965). It was mainly concerned with the principles of testing and reference is made to the techniques set out in the Second and Fifth Reports of the JECFA Committee (FAO/WHO, 1958, 1961). More recently, the Scientific Committee on Food of the EEC issued Guidelines for the Safety Assessment of Food Additives (CEC, 1980*b*).

The details of toxicity testing contained in the 1965 Memorandum have been superseded by three recent Department of Health and Social Security (DHSS) Guidelines. These now encompass the range of chemicals relevant to the health of man and therefore include those chemicals used as food additives. The issuing of these more extensive Guidelines was necessary to take account of recent improvements in methodology. These Guidelines are:

Guidelines for the Testing of Chemicals for Mutagenicity, 1981. (The Mutagenicity Guidelines) (DHSS, 1981)
Guidelines for the Testing of Chemicals for Carcinogenicity, 1982. (The Carcinogenicity Guidelines) (DHSS, 1982*a*)
Guidelines for the Testing of Chemicals for Toxicity, 1982. (The Toxicity Guidelines) (DHSS, 1982*b*)

The intention of this last document is again to provide general information only and attention is directed to the detailed recommendations on protocols drawn up by the OECD (1981*a*) and the EEC Commission (EEC, 1984). Whilst the procedure for submissions on food additives contained in the 1965 Memorandum still officially exists, it is

anticipated that a new document, specifically dealing with this aspect, will be drawn up in the next few years (Bunyan *et al.*, 1984).

It is not the purpose of this review to describe in detail the content of these Guidelines. However, as the rationale upon which control is based is often criticised, it is worth taking consideration a stage further. In addition, a comparison between the 1965 Memorandum and the recent Guidelines does indicate that changes have occurred, resulting from a greater appreciation of the difficulties of assessing food additives.

Rationale of the testing procedures

The basic approach to the evaluation of the safety of any chemical involves toxicological testing. Obviously, human studies involving deliberate exposure to new additives are unethical. Even studies of exposure to old additives are difficult to interpret unless part of an epidemiological study. Further, man's genetic construction may be regarded as random and statistical interpretation of observed effects is difficult unless many assumptions are made. Although not an ideal solution, laboratory and animal experimentation are used to assess risk and the conclusions are extrapolated to man. Inherent in the process are several rationales or assumptions. These include the following.

(a) That the administration of a chemical compound will result in some effect on a biological system in some circumstances. These effects may occur within a relatively short period or may take several years to become apparent. These eventualities are provided for by the requirement for short-term and long-term studies.

(b) That the administration of a chemical to an experimental animal throughout its lifetime can be equated with, or extrapolated to reflect that of, a lifetime exposure in man. Ideally, a species of animal should be selected which metabolises the chemical similarly to man.

(c) That there exists a dose–effect relationship describing the effect of a chemical compound on a biological system. This is the basis used to establish the LD50, which, in turn, is used to assess the general order of toxicity and to identify target organs for toxic effect.

(d) That, as a corollary, there must exist a threshold dose below which no effect occurs. Thus, the 'No Effect Level' (NEL) is determined in experimental animals and expressed in milligrams per kilogram in the diet. Suitable conversion factors must be applied to establish the intake in milligrams per kilogram of body weight per day.

(e) That safety can be assumed by the statistical absence of a detectable effect. Statistical advice is recommended during the planning stage of studies.

(f) That safety factors can be applied to take account of interspecies variation and the heterogeneous susceptibility of the exposed human population. The concept of 'Acceptable Daily Intakes' (ADIs) has been calculated on this basis and is defined as the dose, in milligrams of product per kilogram of body weight of the consuming subject, which can be administered without damage to the health of the consumer.

Changes in the UK recommendations

A comparison of the 1965 Memorandum (MAFF, 1965) and the recent Guidelines (DHSS, 1981; 1982*a*, 1982*b*) reveals similarities in the general approach to safety evaluation. Two stages are discernible. The first is

TABLE 2

Factors to be Considered in the Evaluation of the Acceptability of a Chemical (DHSS, 1982*b*)

(1)	Chemical structure.
(2)	Specification and purity: including formulation and processing details.
(3)	Use and exposure: involving consideration of likely routes, levels and duration of exposure in man and on comparative pharmacokinetic and metabolic data.
(4)	Data on human exposure: from studies designed to investigate metabolic rate or to assess tolerance and from observations made in people subjected to industrial or accidental exposure.
(5)	Toxicological data from animal experiments: including studies on acute toxicity and target organ studies (up to 28-day studies) sub-acute toxicity (for example, 90-day studies) long-term toxicity/carcinogenicity (for example, rat study of 2 years minimum duration) embryotoxicity/teratogenicity/reproduction studies metabolism mutagenicity studies additional special studies
(6)	*In vitro* tests: including studies on mutagenicity, cardiotoxicity, neurotoxicity
(7)	Risk/benefit analysis: involving weighing of potential risks with benefits and to assure minimum risk to health and the environment.

concerned with establishing adequate data describing the biological activities of the substance under examination. The second is concerned with the interpretation and extrapolation of this data to estimate levels of acceptable human exposure. Whilst the basis is similar, certain points do stand out as having changed. Thus, the recent Guidelines:

(a) place a greater emphasis on some areas of study regarding specifications and purity criteria;
(b) appreciate the problems involved in reliable animal experimentation;
(c) acknowledge a sequential approach to the testing programme;
(d) incorporate advances in testing techniques including pharmacokinetics, carcinogenicity, mutagenicity, *in vitro* studies, structure-activity prediction, etc;
(e) show awareness of the factors which influence susceptibility of the human population;
(f) give voice to the concept of risk/benefit analysis. The general considerations for safety evaluation, as outlined in the 1982 Guidelines, are given in Table 2.

OBJECTIONS TO SAFETY EVALUATION PROGRAMMES

As outlined in the previous section, safety is regarded as a value judgement based on certain imprecise parameters. Therefore, the reliability of the system can be readily challenged on various grounds, including precision, validity and incomplete data. The major disagreements can be split into the two main areas of study—toxicity studies and carcinogenicity studies.

Toxicity studies

One of the major points of attack regarding toxicity testing relates to the plethora of opinions that can and are expressed. Thus, although the multidisciplinary approach to toxicity testing has led to significant advances in procedures for evaluation, paradoxically, it has meant that it is more difficult to reach recommendations (FAO/WHO, 1981). At the same time, there have been a large number of objections levelled against the rationale and methodological approaches of such a programme. The

situation has been compounded by the failure of scientists to agree on points, possibly because of misinterpretation of data and over-emphasis of isolated data (Emerson, 1981). The numerous opinions of researchers have been reviewed and, where there appears to be a consensus of opinion, are presented in the following subject groupings.

(a) Dose levels

The objective of classical quantitative toxicity studies is to establish the level of a substance that can be included in the diet of man without toxic effects. The conventional practice has been to expose experimental animals to increasing quantities of the test substance and to monitor the effect on development and health. Typically, the response depends on the dose administered and gives a sigmoid curve with a fairly straight middle section. From the curve it is hoped to establish a feeding level at which there is no observed adverse effect—the 'No Effect Level' (NEL)—and then to reduce this level by the application of appropriate safety factors to establish a dose which presents virtually no risk to man (Hall, 1979). However, with some food additives no toxic effects are observed even at high dose levels and, for such substances, the 'Maximum Tolerated Dose' (MTD) is used (Vettorazzi, 1980).

The highest dose levels are deliberately chosen in order to produce some adverse effects. Much criticism has, however, been levelled against such high dose levels as results may be difficult to interpret (FAO/WHO, 1981). The dose may result in a seriously reduced food intake and so introduce the added complication of nutritional imbalance. Additionally, early serious toxicity may occur, resulting in premature death, so that long-term manifestations do not have a chance to develop (Hall, 1979). There may be a change in the metabolic pathway being followed when compared with that followed upon low level dose administration (Fairweather & Swann, 1981).

The Guidelines for Toxicity Testing of 1982 consider that such acute toxicity tests are of value in defining the general order of toxicity but that their precision may be limited by a number of uncontrolled factors including those above. Further, they say that sub-acute tests should involve the use of substances administered at realistic levels (i.e. a minimum of three dose levels approximating to multiples of anticipated or known maximum exposure levels). Ideally, the highest dose levels should not exceed the minimal toxic dose range as determined by the acute toxicity tests.

(b) Animal experimentation

Inevitably, since little data is available from observations on man, the results of animal experimentation play a major part in safety evaluation programmes. However, there are many limitations in using animal studies to generate toxicological data.

The validity of data can be questioned unless the results of comparative metabolic studies are available to establish the degree of similarity between the metabolism of the test species and man. Table 3 illustrates some examples of species differences due to rate of absorption and metabolic pathway. A species must therefore be selected which reflects man's metabolic profile. However, it is very difficult to simulate, in test species, the large range and combination of factors which may influence an individual's metabolic pathway: dosage, mode, frequency, age, sex, dietary factors, genetic deficiencies, hormonal imbalance, etc. (Gangolli, 1983). In addition, certain species are precluded due to the expense of their maintenance and long lifespan.

A major criticism concerns the use of small numbers of experimental animals necessitated by economic and practical restrictions. Reference to relevant statistical principles indicates that several hundred animals at each dose level are needed to have a 99% certainty of detecting one abnormal reaction in a test group of 100. Obviously, to advocate the use of such large numbers would be unrealistic and, instead, reliance is given to the observation of adverse responses in the majority of test animals given high dose levels (Vettorazzi, 1980).

Many aspects of animal husbandry, including dietary intake, merit

TABLE 3

Examples of Species Differences in Metabolic Disposition and Toxicity (Gangolli, 1983)

Compound	*Toxic effect*	*Species*	*Effect* + = *positive* − = *negative*	*Causes*
Degraded carageenan	Bowel ulcers	Guinea-pig	+	Gut absorption
		Rat	−	
Orange RN	Methaemoglobin in red cells	Rat	+	Microflora metabolism and formation of aniline
		Ferret	−	
Coumarin	Liver injury	Rat	+	Difference in hepatic metabolic pattern
		Mouse	−	
		Baboon	−	

further investigation. It is usual to feed the same diet to animals of all ages on an *ad libitum* basis. This frequently results in the development of obese, sluggish laboratory animals which are prone to serious endocrine abnormalities. Roe (1981) questions the validity of following such a regime in toxicity tests. He suggests that *ad libitum* feeding is unsuitable and that some diet restriction may be more appropriate.

The influence of nutritional imbalance is well documented. In order to obviate these effects, the policy has been to provide standard feed, suitable for the species, designed to maintain the animals in a good nutritional state. However, there may well be merit in instituting studies using imbalanced diets to produce effects which were previously masked by a balanced dietary intake (CEC, 1980*b*). Indeed, it would seem reasonable to design studies to reflect common nutritional imbalances in man.

Despite the queries raised in connection with animal studies, the recent Toxicity Guidelines still regard them as the best available method for the evaluation of safety-in-use. Also, they allow for flexibility in the choice of numbers of species and test animals, depending on the results of comparative testing and the extent of human exposure, provided that they meet the requirements of valid toxicological data. Animal husbandry and diet are emphasised and reference is made to further documents which should be consulted, namely; 'Guidance Notes from the Home Office Inspectorate of the Cruelty to Animals Act, 1876' (Home Office, 1971) and the 'Final Report of the Expert Committee on Good Laboratory Practice' published by the OECD (1981*b*).

(*c*) *Potentiation and other possible modifying effects*

The CEC, in its information document, 'Food Additives and the Consumer', (CEC, 1980*a*) highlights several factors which should be taken into account when considering the effect of food additives within the body.

The human diet frequently includes a number of additives ingested simultaneously either in one product or in a number of products consumed together. However, toxicity tests are usually carried out on an isolated additive. The possibility of interaction is raised. Do they cancel out, have an additive effect or potentiate each other? Whilst recognising that it would be impossible to test all possible combinations, it is suggested that the most frequent should be investigated.

The possibility of interaction with other toxins (e.g. alcohol or

medicine) exists. It is unlikely that one would not be prescribed drugs at some point throughout one's lifetime due to the trend towards preventative medicine and increased life expectancy. It is possible that two substances, harmless by themselves, may react to form a toxic product. Particular attention is drawn to the use of additives in alcoholic drinks and to those individuals or countries where alcohol consumption is high. It should also be remembered that alcohol can modify the absorption of certain substances from the gastro-intestinal tract.

There is an increasing awareness that diet plays a central rôle in health (Coomes, 1983). However, toxicity studies are usually carried out on animals fed on balanced, or even vitamin-supplemented, diets and it may be advisable to investigate effects when fed imbalanced diets. This can be illustrated by reports of deaths among heavy beer drinkers in the USA, Canada and Belgium. Rats fed diets containing cobalt did not manifest signs of cardiotoxicity. However, malnutrition, especially thiamine deficiency, appears to have potentiated the effect of cobalt causing human cobalt–beer cardiomyopathy (Berglund, 1978).

The Guidelines for Toxicity Testing (DHSS, 1982*b*) recognises that the susceptibility of population sub-groups may be influenced by their nutritional status and consumption of drugs or alcohol. It recognises the possibility of chemical interactions but considers that the practical difficulties of investigating all such eventualities are prohibitive except in the instance where two chemicals are commonly used together. It believes that a substantial margin of safety is afforded by the calculation of ADIs from NELs and the use of maximum permitted levels.

(d) Calculation of acceptable daily intakes

From toxicity studies a dose level is established that causes no demonstrable effects in the test animal. The data, where appropriate, have then to be extrapolated to man, taking account of a large range of factors including the various differences between the animal test and the human exposure. A number of the differences which are important are given in Table 4.

The extrapolation is achieved by the application of an arbitrary safety factor to provide an adequate margin of safety and will result in the establishment of an acceptable daily intake (ADI) for man. This term was originally defined by JECFA as 'the daily dose of a chemical that appears to be without appreciable risk (to man) on the basis of all the known facts at the time' (FAO/WHO, 1967). However, in practical terms it has become the average daily amount of a substance, expressed in milligrams

TABLE 4
Factors which Need Consideration when Evaluating Animal Test Data (Preussman, 1978)

Animal exposure	*Human exposure*
20 to 200 animals	Thousands to millions of humans
High doses	Minimal quantities
Single compound	Combinations of compounds
Genetically homogeneous	Genetically heterogeneous
Standardised experimental conditions	Healthy adults, children, ill people, etc.

per kilogram of body weight, which is acceptable for lifelong exposure without damage to health. It is calculated as:

$$\text{ADI (mg/kg body weight man)} = \frac{\text{NEL mg/kg body weight animal species}}{\text{Safety factor (usually 100)}}$$

The safety factor applied is normally 100, proposed on the following basis:

× 10 allows for increased sensitivity in man
× 10 takes account of heterogeneous response of individuals

The concept has been generally acknowledged although the method of calculation has been questioned (CEC, 1980*a*).

Criticisms which are commonly expressed in reviews of food additive safety include the following points (Berglund, 1978):

(1) Is adequate account taken of the amount of the substance naturally present in the food?
(2) Is sufficient consideration given to hypersensitivity reactions exhibited by a small proportion of the population?
(3) Is the expression of ADIs in terms of body weight (BW) as valid as expressing it in terms of metabolic mass ($BW^{0.75}$) in order to reflect the relative exposure to animals of different size?

Consideration of the testing procedures can also lead to points of discussion although some may provide further safety factors. The following can be mentioned (Bunyan *et al*, 1984):

(1) The NEL is a subjective experimental decision.
(2) Test diets can vary by factors of 10. An experimentally determined NEL could therefore be set considerably below the actual NEL.

(3) A rat may eat 5% of its body weight in dry food per day whereas man usually consumes about 2·5% of his body weight in food which contains between 30 and 40% water.
(4) Extrapolation from animal to man may involve factors which are not determined for the specific diet or animal strain used.
(5) Safety factors are not normally quoted when ADIs are stated.

The Government appreciates that the safety factor of 100 does not provide an invariable guarantee of safety and that it may be necessary to increase the safety margin considerably in certain instances (MAFF, 1965). It is also obvious that, for substances used at > 1% of the diet, it is inappropriate.

(*c*) *Dose for incorporation into foodstuffs*
Once the ADI has been established the toxicity evaluation programme, strictly speaking, has been completed but the relevant authorities have yet to set the dose to be incorporated into foodstuffs. Information detailing food consumption of the population is essential.

Surveys are frequently used to give a general idea of consumption but, ideally, they should provide a breakdown into different sub-groups. Experience has shown that certain sub-groups will preferentially consume certain foods and it is therefore particularly important when setting the permitted dose in these foods. Also it is advisable to monitor food intake and check observance of permitted levels to ensure that the ADI is not being exceeded (CEC, 1980*a*).

In the United Kingdom the National Food Survey is used to provide a profile of the national average diet. MAFF acknowledges that the information appertaining to minority groups is sparse but claims that, where it is conscious of the lack of data, a hypothetical 'worst' case is used. Programmes of food monitoring are undertaken by the Steering Group on Food Surveillance established by MAFF in 1971. It has several Working Groups which constantly review and assess the food chain, including the presence and safety of direct and indirect additives (Coomes, 1983).

Carcinogenicity studies

Before discussing criticisms of carcinogenicity studies it is necessary to outline how a chemical carcinogen may cause cancer, although the mechanisms are not fully understood.

Cancer is thought to be a multi-step process involving tumour initiation, possibly promotion and ultimately resulting in the formation of a malignant cell. Frequently, the chemical must be metabolised before it is reactive (Garner, 1981). Traditionally, carcinogenicity was included as part of long-term studies on toxicity (MAFF, 1965). Increased incidence of tumour development is a manifestation of chronic toxicity and it seemed logical to study these parameters in the same experiment. However, concomitant with discoveries in the cancer field has been a growing disillusionment with some of the techniques used, arising from some of the following problems associated with traditional carcinogenicity studies (Golberg, 1982):

Spontaneous tumour incidence
Maximum tolerated dose
Distinction between initiators and promoters
Epigenetic promotion mechanism
Pathogenesis of end result
Mounting cost versus uncertain outcome
Availability of preferable alternatives.

Three of these are worth considering in more detail.

(*a*) *Spontaneous tumour incidence*

Some strains of certain animal species are susceptible to 'spontaneously' occurring tumours (FAO/WHO, 1981). The susceptibility of outbred strains can be reduced by the use of inbred strains or F1 hybrids. However, this may introduce an element of unreliability since a resistant strain may, by chance, be selected. Further, the incidence of such tumours is known to be influenced by a range of factors including type of feed, quantity, stress and other non-specific factors. The carcinogenic potential of a test substance may be masked by the development of tumours in a control group caused by factors other than the test agent. Also, tumour incidence enhanced by non-specific factors in the test group may be incorrectly attributed to administration of the test agent.

In the recent relevant Guidelines the Government shows an appreciation of these problems and recommends that the following measures should be adopted:

(1) Strains should be avoided which are susceptible to spontaneous tumour incidence.
(2) Where F1 hybrids are used, several strains should be selected.

(3) Outbred strains, if used, should come from closed stock where the spontaneous disease incidence is known.
(4) Test and control groups should be kept under similar environmental conditions so that they are subject to the same non-specific factors.

(*b*) *No effect level*

The generally accepted view is that there is no threshold level for a carcinogen as continuous exposure leads to a linear dose and dose time relationship which holds even at low dose levels. Single small doses are additive and summation will occur. Therefore, even low doses of carcinogens are a low, but definite, health risk (Preussman, 1978). In practice, a NEL is taken as the dose level which produces no detectable increase in tumour formation from a lifetime's exposure. However, precancerous cells may exist with a potential for progression under the influence of an appropriate stimulus (Coomes, 1983). To guard against this possibility it has been suggested that the safety factor of 100 should be increased when extrapolating data on chemical carcinogens (Preussman, 1978).

(*c*) *Maximum tolerated dose*

For food additives, particularly those of low toxicity, it may prove difficult to establish a dose level that is toxic. The MTD is then used in chronic studies. It is defined as 'the highest dose of the test agent that can be predicted not to alter the animal's normal longevity from effects other than carcinogenicity ... and that causes no more than a 10% weight decrement' (DHSS, 1982*a*).

However, administration of the MTD has been the subject of much criticism. Should this approach be used *per se* or should it be modified when anticipated human exposure is low (Preussman, 1978)? In addition, administration at this level may result in major alterations in the dietary intake and introduce non-specific effects (Emerson, 1981). The recent relevant Guidelines recognise that dose administration in excess of 5% of the diet is undesirable and, in such cases, suggest that it should arbitrarily be set at 5% of the diet.

DEVELOPMENTS IN TOXICITY TESTING

The conventional toxicity studies required by the regulatory authorities for the clearance of a food additive are expensive and time-consuming.

They cost a minimum of £300,000 and take up to 3–4 years to complete. This is in spite of the fact that toxicologists have expressed reservations, as previously discussed, as to the validity of existing procedures. Along with these factors the emergence of new scientific understanding has prompted a re-examination of the whole approach and of specific techniques of testing. These developments, some of which have led to modifications in the regulations, will now be discussed.

Alternative approaches

Various alternative approaches have been suggested including the Frawley (1967) proposals relating to the regulation of food packaging materials. He suggested that any food packaging additive, if present at 0·2% or less, was safe beyond reasonable doubt provided that:

(a) it was not carcinogenic
(b) there was a maximum migration into food of 0·1 ppm
(c) the NEL was not less than 1 g/kg body weight

In an attempt to simplify existing legislation he suggested that such additives should not be subject to government regulations. The main criticism of these proposals was that the conclusions were based upon the results of short-term exposure tests and no provision was made for genetic or chronic effects revealed from long-term exposure tests.

The importance of chemical structure in the prediction of biological activity was the basis of the scheme proposed by Cramer *et al.* (1978). Whilst the relevance of this approach is readily acknowledged, it has limitations due to the lack of information which relates chemical structure to biological activity. Thus, it has a limited range of use. Nevertheless, it is included in the Guidelines for Toxicity Testing (DHSS, 1982*b*) as a useful method of predicting toxic potential.

The 'Decision-Tree' approach, which was recommended by the Food Safety Council (1978) in the USA, organises the tests into a logical sequence so that, at each stage, information is generated enabling a decision to be made: accept, reject, carry on testing. Figure 3 shows a flow chart which illustrates this approach. It can be envisaged that this approach should produce economies in testing but clearly the success of the programme will be limited by the adequacy of key test procedures. The scheme has found widespread acceptance throughout the United States and has influenced other international regulatory agencies and

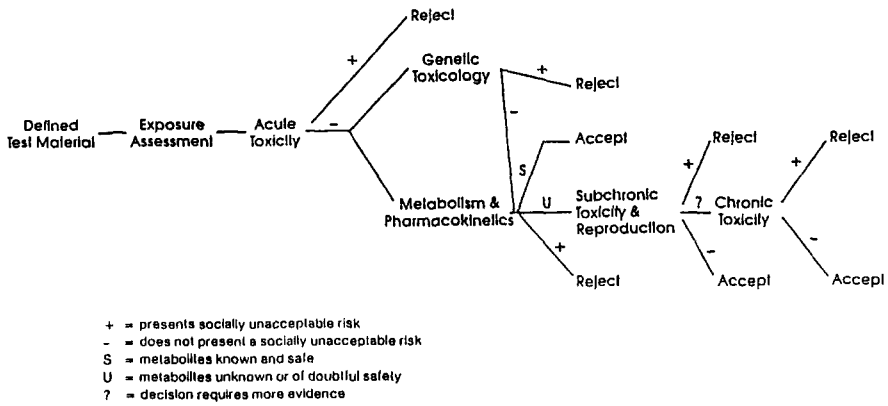

Fig. 3. 'Decision-tree' approach in the evaluation of food additives (Food Safety Council, 1978).

organisations (Seligsohn, 1982). The DHSS have used a similar basis to update their safety evaluation procedures. The following extract, taken from the Guidelines for Toxicity Testing (DHSS, 1982*b*), acknowledges this sequential approach to testing:

'The programme of tests on a chemical should be designed to progress logically in the light of all the relevant information available at each stage, starting with a knowledge of chemical structure and properties and the likely routes of human exposure and continuing with appropriate studies in animals and possibly human volunteers.'

Both the 'Decision-Tree' approach and the updated Toxicity Guidelines show awareness of, and incorporate new understanding and investigative techniques in the field of toxicity. Some examples are outlined below.

Specifications and purity

Clearly, it is of paramount importance to have at hand the identical material which is in use, or which is proposed for use, when commencing a programme of toxicity assessment. This may seem obvious but it should be remembered that not all food additives are simple, pure chemicals but, rather, mixtures of related chemicals, and most contain impurities. The Memorandum (MAFF, 1965) appreciated the problem and noted that the primary task must be to provide a specification detailing:

(1) composition
(2) standard of purity

(3) nature and quality of contaminants

Also, appropriate methods of analysis to determine these characteristics should be included. Prior to membership of the EEC the specific purity criteria were largely contained in the following:

Food Chemicals Codex
European Pharmacopoeia
British Pharmacopoeia
British Pharmaceutical Codex
British Standards

The implementation of harmonisation directives has resulted in a change-over to largely EEC Directives of purity criteria.

However, these specifications have, on occasions, been insufficiently specific and may have provided unreliable results. A notorious example of a food additive whose reputation may have suffered in this way is saccharin. In its 19th report (FAO/WHO, 1975), JECFA notes that impurities may be present in a food additive as a result of the manufacturing process and gives *o*-toluene sulphamide in saccharin as an example. The EEC, in its consumer information document (CEC, 1980*a*) states that the toxicity of saccharin may be due to the presence of an impurity since, if sufficiently pure, it does not cause cancerous lesions. The SCF, in its Report on Guidelines for testing (CEC, 1980*b*), acknowledges the importance of the method of manufacture by observing that an alteration in the method may result in changes in the nature and or amount of impurities. These must be determined and a revised specification produced if considered necessary. In addition, consideration must be given to changes which may occur during storage and possible reaction with other food components. The Guidelines for Toxicity Testing (DHSS, 1982*b*) again emphasise the need for compliance with a defined specification and the desirability of chemicals with a high degree of purity.

Metabolic, including pharmacokinetic, studies

Metabolic studies have long been regarded as essential in a programme of toxicity testing as the metabolic behaviour of a food additive can be used as an indicator of safety (MAFF, 1965).

However, pharmacokinetics (or toxicokinetics) has been recognised as

TABLE 5
Excretion of Orange G and its Metabolite. (Values are Expressed as Percentage of the Administered Dose of Orange G.) (Carpanini and Crampton, 1972)

Species	*Excreta*	*Free Orange G*	p-*Aminophenol*
Rat	Urine	Trace	72%
	Faeces	Trace	—
Ferret	Urine	32%	0%
	Faeces	61%	0%
Man	Urine	3%	54–95%

having an increasingly important rôle in this field of investigation. Karlog *et al* (1978) define the term as the study of the absorption, metabolism and excretion of toxic materials in a living organism which can be described by zero- or first-order kinetics. In particular, these specific processes have been shown to be dose related. These studies have been proved important in:

(1) The study of differences in response to the administration of toxic compounds both between species and strains and between individuals.
(2) Studies of interactions of toxic agents with potential ingested compounds (e.g. foodstuffs, drugs, alcohol).
(3) The identification of species which metabolise toxic compounds in a similar manner to man.
(4) The selection of species and strains which most closely resemble the metabolic handling of the chemical in man.

Clearly, the ideal situation is to select and use a species which handles the chemical similarly to man. An example can be seen with an investigation into the metabolism of Orange G in rat, ferret and man, as indicated in Table 5. It is clear that the excretion of free Orange G and its major metabolite, *p*-aminophenol, differs with animal species. The studies show that the rat would be the most suitable animal species on which to test the additive.

However, it is recognised that it may be impossible to select a corresponding species due to the limitations of pharmacokinetics and the large range of factors that may affect metabolism (DHSS, 1982*b*). Nevertheless, information generated by comparative testing is still

considered to be of value in the design and interpretation of animal toxicity studies.

Metabolism in the gastro-intestinal tract

A further salient aspect of metabolism is the variety of reactions which a food chemical may undergo in the gastro-intestinal tract. A useful example to illustrate the importance of this can be drawn from investigations into the artificial sweetener, cyclamate. Philp (1981) reviews the studies which established the conversion of cyclamate to cyclohexylamine by gut microflora in the gastro-intestinal tract prior to absorption.

Test materials may undergo degradation by reaction with hydrolytic enzymes found in the gastro-intestinal juices. In addition, they may undergo metabolism as a result of the action of intestinal bacterial enzymes found in the microflora which reside in the gastro-intestinal tract and the small intestine mucosa (Gangolli, 1983). The wide range of metabolic capabilities of gut microflora can have toxicological consequences. First, detoxication of some contaminants has been shown to be affected, such as the conversion of toxic methyl mercury to metallic mercury which has a low oral toxicity. Secondly, reductive and degradative metabolism may occur to produce toxic, carcinogenic or mutagenic metabolites (Rowland, 1981). Synthesis is rare, with the notable exception of nitrosamine formation (Preussman, 1978).

The Guidelines for Toxicity Testing (DHSS, 1982*b*) draw attention to the significant rôle of gut microflora in metabolism. Further, species differences in gut flora exist and may be determined by features such as diet. Rowland (1981) cites the following features to explain differences in metabolism and toxic effects:

(1) Species, strain and individual differences in gut flora composition.
(2) Species differences in distribution of flora.
(3) Dietary modification of flora.
(4) Metabolic adaptation.
(5) Effects of disease and gastro-intestinal disorders on composition and distribution of flora.

Again, this stresses the importance of considering interspecies variation, dietary modification and state of health in test animals.

Carcinogenicity studies

Further insight into the mechanism of carcinogenesis has emerged since the early Memorandum (MAFF, 1965) and also new methods of detecting potential carcinogens have been proposed. These advances have recently been reviewed by the Government and, where considered appropriate, have been incorporated into the Guidelines for Carcinogenicity Testing (DHSS, 1982*a*). Although it is not considered relevant to deal at length with this subject, attention will be drawn to the most promising advances relevant to the field of safety evaluation.

The most striking developments are to be seen in the field of short-term *in vitro* tests. Most of the current tests are based on the shared property of carcinogens to react with DNA. These tests involve biological monitoring of the DNA reaction (Garner, 1981). The tests should aim both to establish whether the chemical has the potential to be a carcinogen and also whether man is susceptible.

The limitations of these tests have been recognised (Hall, 1979). In short, the test may give false negatives as no single test system can possibly bring about effective activation, provide all target molecules or take into account metabolism by intestinal bacteria. Also, false positives may be found as they cannot reproduce the detoxication mechanisms that may interpose in a higher organism.

Due to these limitations, short-term testing cannot be regarded as the definitive test. Nevertheless, it is considered to be of value when considered in conjunction with the data from long-term testing (DHSS, 1982*b*). Long-term testing in laboratory animals is probably the most reliable method of determining carcinogenicity but the short-term tests can be particularly useful when used at the screening stage (Fairweather & Swann, 1981).

Mutagenicity studies

Mutagenesis is the process by which changes occur in the genetic material (mutations) in individuals or cells, spontaneously or as the result of the actions of chemicals or radiation. The mutations are transmitted to successive generations and, although some have importance in the evolutionary process, the majority are thought to produce deleterious effects in the offspring. In addition, there is growing evidence that somatic cell mutations may be important. It is widely accepted that chemicals

capable of inducing mutations (mutagens) may also be able to cause cancer. Mutagens are thought to produce cancer by inducing mutations in somatic cells which lead to changes in the cell and, finally, to tumour production (Anderson & Purchase, 1983).

Recently, the Government considered the relationship between mutagenicity and carcinogenicity and the methods for testing for mutagenic potential. Its findings were published in 1981 as the Guidelines for the Testing of Chemicals for Mutagenicity (DHSS, 1981). The importance of mutagenicity studies has been recognised and the Guidelines for Toxicity Testing (DHSS, 1982*b*) consider that they should be included in toxicological evaluations where the following are particularly relevant:

(1) to screen for the potential to cause mutagens
(2) to alert for the possibility of carcinogenicity

Short-term tests for assessing the mutagenic potential have evolved in recent years and look for evidence of interactions with DNA. The most widely used of these is in the *in vitro* Ames test which seeks to quantify the mutagenic effect of a chemical on a bacterial strain, particularly *Salmonella typhimurium*. The test can also be adapted to assess for carcinogenic potential. A liver microsomal suspension of rat is added to the *in vitro* system so that carcinogenic metabolites derived from the compound can be detected (Farmer, 1982). However, these tests do not give satisfactorily reproducible results and the information from one test only should not be relied upon. Rather, a battery of overlapping standardised tests should be used as a preliminary screening procedure before commencing long-term toxicity studies in animals (DHSS, 1982*b*).

SPECIFIC SENSITIVITIES

There are a large number of factors which may influence an individual's sensitivity on exposure to a chemical so that, within a population as a whole, a heterogeneous pattern of response can be predicted. The Guidelines for Toxicity Testing (DHSS, 1982*b*) gives examples of particularly susceptible sub-groups and these are summarised below:

(1) Individuals with genetically determined or acquired abnormalities.
(2) Individuals consuming special diets, e.g. diabetics.

(3) Individuals in a state of nutritional imbalance.
(4) Individuals consuming drugs or alcohol.
(5) Individuals showing allergic responses.
(6) Elderly people.
(7) Infants and children.
(8) Fetuses.
(9) Smokers.

Allowance for the possibility of such sensitivities is made in the calculation of ADIs, the limitations of which have previously been discussed. Factors (5) and (7) will be discussed more fully as they have had consequences on current regulatory control.

Infants and children

Special consideration has been given to the particular susceptibility of infants and children. It is postulated that they may have a different complement of detoxifying enzymes from adults which, in turn, may render them more or less susceptible to certain chemicals. In addition, since food intake may initially be restricted to a few commercial formulae, the importance of their composition cannot be overstated.

In the 1981 FSC Report on Infant Formulae (FSC, 1981), COMA referred to the use of additives in such products. They acknowledged the necessity for their use due to the requirements of preservation. However, they recognised the possibility of increased susceptibility by advising that:

(1) Their use, especially in infant formulae consumed during the first 3 months of life, should be restricted as far as practicable.
(2) Manufacturers should seek to develop their processing and packaging techniques so as to eliminate the use of additives wherever possible.

In addition, the specific additive regulations show awareness of the situation, particularly when dealing with additives of questionable safety. The following examples, taken from existing regulations, serve to illustrate this point. First, the FACC Report on the Review of Flavour Modifiers (FACC, 1978) proposed that this class of additives should not be permitted in foods intended for consumption by infants or young children. This was incorporated into the regulations. Secondly, the Sweeteners in Food Regulations (SI, 1983) prohibit the use of saccharin in

infant foods. Saccharin is an intense sweetener whose safety is under question and, as such, has been given a Grade B status (provisionally acceptable for use in food pending further information) by the COT in the FACC Report on the Review of Sweeteners in Food (FACC, 1982*a*).

Individuals showing allergic responses

Adverse reactions to certain foods have long been recognised and attention has been drawn in recent years to the allergenic potential of certain food additives. Pottage & Nimmo (1977) cite the following additives:

Colouring agents —tartrazine, sunset yellow
Antibiotics —tylosin
Antioxidants —ethoxyquin, BHA, BHT
Flavour enhancer—MSG

Also, there are indications that natural food additives may be responsible for similar reactions; in particular, the colouring agent annatto (Mikkelson *et al.*, 1978).

The term 'allergy' is often used to describe any adverse reaction which arises on ingestion of a particular food or food additive. However, food reactions can be divided into two main categories; Mansfield (1983) describes these as being:

(i) classic allergic response or hypersensitivity involving an immunological-type response;
(ii) food intolerance or idiosyncrasy involving a non-immunological-type reaction.

Although the clinical manifestations of both types of reaction are similar, most adverse reactions to food additives are clinically thought to be intolerances, rather than allergies.

It is sufficient for traces of an additive, on gaining access into the body of a sensitised individual, to trigger signs of allergy or intolerance. The clinical picture may vary widely from mild or moderate severity to severe discomfort requiring intensive treatment. The EEC Consumer Information Document (CEC, 1980*a*) notes the following likely manifestations:

(1) Skin reactions—with itching, small eruptions, urticaria, eczema and sometimes large-scale generalised eruptions or rashes.

(2) Respiratory troubles—may develop into asthma.
(3) Digestive reactions—in particular, vesicular or colitic reactions may occur, as well as purpura (i.e. small punctiform haemorrhages scattered throughout the body).

Parrish (1983) also notes other, less supported, manifestations of headache, urinary incontinence or urgency, hyperkinesis and psychological disturbances.

It is difficult to assess the frequency of adverse reactions to food additives due to the problems inherent in diagnosis. Subjective methods involving history taking, elimination diets and challenge studies are difficult to standardise. Hill (1982) reports that, for the most common manifestations, a frequency of 0·03 %–0·15 % of the adult population has been suggested but other reports suggest a higher incidence.

At present, data on animal toxicity infrequently include tests for allergic potential. This is largely due to the lack of understanding of the mechanisms involved. Diagnostic tests, including animal models and *in vitro* tests, will have to be developed which both distinguish between the immunological and non-immunological type reactions and can predict the likelihood of an adverse reaction due to either allergy or intolerance.

Hyperkinesis

One particular adverse reaction has received much attention in the popular press, namely, hyperkinesis in children. The term hyperkinesis, as described by Auty (1982), can be applied to disorders with diverse symptoms but with the main emphasis on overactivity accompanied by lack of concentration, learning problems, aggression, cognitive impairment and lower IQ. Various causes have been put forward, including food additives. Feingold (1973) speculated that food additives, in particular colouring matter, are pharmacologically active substances that can aggravate or induce hyperkinesis in children. In later investigations he implicated artificial flavours, antioxidants and salicylates. The 'Feingold Diet' was developed excluding all foods which contain these additives and this form of dietary treatment has found widespread acceptance among parents of hyperkinetic children.

However, the validity of Feingold's findings has been questioned by researchers as he presented little evidence of control data and further scientific evaluations have been provoked. Taylor (1979) reviews their

findings and observes that the evidence is inconclusive. The SCF Report on adverse reactions to ingested additives (CEC, 1982) states that there is no good evidence to support Feingold's hypothesis but includes a disclaimer that it might be unwise to clear all food additives. Clearly, the question remains open!

Adverse reactions to food additives—regulatory implications

In 1979 the *Interim Report on the Review of the 'Colouring Matter in Food Regulations 1973'* (FACC, 1979) noted that there had been several reports of hypersensitive reactions to food colours. However, as the incidence of such reactions seemed rare and hypersensitivity to food constitutes a general problem, it was considered advisable to await reliable evidence from controlled studies in man.

The Scientific Committee for Food drew the attention of the EEC Commission to the problem in its report, in 1979, on Certain Colouring Matter for use in Foods (CEC, 1979). Concern over the use of colouring matter in food and the realisation that other additives may have similar effects prompted the Committee to recommend to the Commission that a working party should be convened to consider the question of adverse reactions to ingested additives present in food and pharmaceuticals. The findings of the working group were presented in 1981 and published in 1982 (CEC, 1982). Several of the conclusions have repercussions on regulatory control and can be summarised as follows:

(1) The Committee considered that there was sufficient evidence to indicate that a problem did exist and that the frequency of possibly 1 in 1000 merited additional regulatory consideration.
(2) The presence of all food ingredients, including additives, should be clearly indicated by informative labelling to enable sensitive subjects to avoid them.
(3) Test systems to detect allergenicity should be included in a programme of toxicity assessments. New additives should be screened and those already in use suspected of provoking adverse reactions should be investigated.
(4) There should be a move towards reducing the total quantity ingested either by lowering the permitted levels or by limiting the foods in which they are permitted.

The European Community registered its concern in the Council

Directive 1978 on Labelling, Advertising and Presentation of Foodstuffs requiring specific labelling (EEC, 1978). However, a derogation allowing generic labelling until 1983 was taken up by the United Kingdom. The Food Labelling Regulations, 1980 (SI, 1980*c*) which became compulsory on 1st January, 1983, required that additives should be declared in the labelling by the appropriate category name of the function, followed, in certain cases, by the ingredient's specific name or serial number (if any), or both. The cases which were exempted from stating the specific name or serial number did, however, include several important categories (antioxidants, colours, emulsifiers, flavourings, preservatives and stabilisers). These exemptions are being withdrawn for all the categories except flavourings following the issuing of the Food Labelling Regulations 1984 (SI, 1984).

RISK/BENEFIT ANALYSIS

Risk/benefit analysis is a necessary stage in the safety evaluaton programme of a food additive. It involves weighing the likely risks to health or life against the likely benefits to health, supply, organoleptic appeal or convenience.

The concept

The concept is given official recognition in the Guidelines for Toxicity Testing (DHSS, 1982*b*). However, it also acknowledges that the concept should not be taken to imply an exact science as risks and benefits are difficult to compare due to the problems inherent in quantifying and measurement. Hall (1979) explains that risks are almost invariably remote and uncertain. Furthermore risks have to be assessed from animal data and, as previously discussed, there will be a degree of uncertainty associated with such assessments. Finally, the risks are not easily measured in economic terms whereas the benefits, typically an 'improved' product, have economic consequences which can be measured. But even this is not as easy as it sounds since it is difficult to attribute increased consumer acceptance solely to the presence of a particular additive as other sales considerations, such as packaging, promotion or availability of alternative products, may be involved.

In addition, in some instances, risk/benefit assessment may be a matter of weighing one toxic risk against another. A typical example which

illustrates this approach is the use of nitrates as preservatives in fish or meat. Grasso (1983) describes how nitrites, added directly or derived indirectly by the reduction of nitrates, may react with secondary or tertiary amines produced by the natural degradation process of the protein constituents. Interaction yields nitrosamines which are potentially carcinogenic in animals even at low doses. Although he states that the risk would appear small he does agree that nitrosamines—and so, by implication, nitrites—do pose a potential risk. However, against this must be weighed the possible risk from the growth of micro-organisms in the food. It should be remembered that nitrite alone, or used in combination with sodium chloride, has important antimicrobial properties. Nitrites used as a curing agent provide protection against *Clostridium botulinum* and may also be important in the inhibition of other food poisoning micro-organisms such as *Cl. perfringens*, *Bacillus cereus*, *Staphylococcus aureus* and *Salmonella* (Sinskey, 1979).

Consumer acceptance of risk inherent in the use of food additives

While scientists and their respective governments may be prepared to accept that it is impossible to assume zero risk, does it necessarily follow that the general public will show a similar willingness? Judging by the reactions to possible scares reported in the popular press it would appear that the answer is 'no'.

Starr (1969), investigating consumer attitudes towards technological risk, concluded, first, that there are indications that the public's willingness to accept 'voluntary risks' is approximately a thousand times greater than that for 'involuntary risks' and, secondly, that the risk of death from disease appears to be a psychological yardstick for establishing acceptability of other risks. Therefore, as food additives could be described as an involuntary risk and, since their use may involve a risk to health, this may help to explain the public's attitude. Coomes (1983) goes even further, suggesting that the average man or woman in the population is not prepared to accept any risk in the use of food additives.

The actual risks associated with food additives have often been stated to be considerably less than the other possible hazards associated with food. Thus, Wodicka (1977) gave the possible major hazards the following ranking (most important first):

> microbiological, nutritional, environmental contaminant, natural toxicant, pesticide residue, food additive.

TABLE 6
Examples of the Toxicant Risks of Natural Foods (Taylor, 1980)

Constituents of natural food products:	
Oxalates	Cyanogens
Safrole	Goitrogens
Lathyrogens	Solanine
Trypsin inhibitors	Haemaglutinins
Amines	Hypoglycins
Microbiological contaminants of natural food products:	
Aflatoxin	Ergot
Non-microbiological contaminants of natural food products:	
Saxitonin	Tetradoxin

Any ranking produced to indicate the level of concern of the public or media is likely to show a very different ranking (Gray, 1985). Although lack of understanding may partially excuse the consumers' attitude it would seem incongruous when compared with the other hazards of life. Whilst it is acknowledged that it is difficult to quantify the contribution made by food additives to specific diseases, a study of deaths in Great Britain in any year would highlight the absurdity of a situation where the population is willing to participate in an activity such as smoking which has a high risk of death from lung cancer and yet is unwilling to accept the use of additives with a low level of risk.

Natural versus synthetic

The situation is compounded by the current tendency to associate safety with natural ingredients (Emerson, 1981). While the intention is not to raise alarm over the popular misconception that all foods are *per se* safe, it is hoped, in this section, to rationalise the situation in comparison with the safety of food additives.

It has been calculated that we consume yearly, on average about 1,500 pounds of foodstuffs of which approximately 1 pound is contributed by food additives (IFT Expert Panel, 1975). Roughly a half of these additives are consumed in quantities of less than 0·5 mg. Therefore, it is clear that by far the greatest quantity of chemical substances consumed by man are the normal, natural constituents.

Although human experience of lifetime ingestion of many natural

foods demonstrates that they can be safely consumed in normal dietary amounts, the disquieting fact remains that many natural foods are also composed of chemicals, some of which are toxic or carcinogenic. Some of the toxicant risks of natural foods are indicated in Table 6. Whilst the human body can usually deal with small quantities ingested in a varied diet, the potential risk can become apparent where

(1) a detoxification procedure has not been carried out;
(2) excess food is ingested;
(3) food is eaten by those people who react abnormally.

CONCLUSION

This examination has highlighted several points which can be summarised as follows:

(1) The review of the legislative process of control of food additives serves to emphasise the wealth of available scientific knowledge that may be called upon when evaluating the safety-in-use of a particular food additive. It also shows that the legislation is sufficiently flexible to encompass new evidence and initiate prompt action where considered appropriate.
(2) The Government is evidently aware of, and concerned with, the health aspects of chemicals, including food additives. It seeks to provide informed guidance for the evaluation of safety and has endeavoured to incorporate developments in methodological approaches and extrapolation. Further, it recognises that all conclusions are provisional and may be subject to alteration as a result of new data or new understanding of the mechanisms involved.
(3) Safety is regarded as a value judgement based on certain imprecise parameters and, as such, is open to criticism. The Government recognises that the classical approach, in its modified form, should not be regarded as an absolute guarantee of safety. Whilst appreciating the limitations of the evaluation programme it still considers animal experimentation to be the most appropriate means available of evaluating public health risks. In addition, when combined with adequate food surveillance systems, it is thought to provide an acceptable level of consumer protection.

(4) The economic and practical limitations imposed by toxicity testing have prompted reappraisal of the overall approach. Several proposals have been put forward of which the examination of chemical structure / biological activity relationships is regarded as valid but having limited applicability. However, the sequential approach to testing based on the Decision-Tree proposal has found widespread acceptance and indeed has been adopted in modified form in the most recent Guidelines.

(5) Investigations into the mechanisms of toxicology have revealed the importance of impurities and have resulted in greater emphasis being given to specific purity criteria. Metabolic studies including pharmacokinetics are of use in identifying a species which handles the test chemical similarly to man. The important rôle of hydrolytic enzymes and microflora in the gastro-intestinal tract is being elucidated. Great strides have been made in developing short-term *in vitro* tests for assessing carcinogenic/mutagenic potential and are regarded as particularly valuable screening procedures prior to commencing long-term toxicity studies if included as part of a battery of tests.

(6) Sub-groups particularly susceptible to exposure to a chemical have been identified within a population. The overview of two such groups indicates that there is still much investigation required to clarify the situation. In addition, whilst a blanket protection against the heterogeneous pattern of response is included in the formulation of ADIs, further specific regulatory controls may be expected as the nature of specific sensitivities is revealed.

(7) Risk/benefit analysis is an essential, but intrinsically difficult stage in a safety evaluation programme even when tackled by Government experts. The consumer's willingness to accept the concept is hampered by lack of knowledge, irrational fears and the natural versus synthetic question. The availability of more reliable information would encourage a more open minded attitude to the possible risks involved with the use of food additives.

The present safety programme would appear to offer the best practical solution to the problem of safeguarding the health of the public against the possible adverse effects of food additives. The existing regulations, combined with food monitoring, afford a reasonable degree of protection. Finally, the flexible and responsible attitude of the authorities

ensures that advances in methodology and extrapolation factors will be incorporated into the legislation so that the consumer can expect an even further reduction of risk in the future.

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