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REPORT OF THE SCIENTIFIC COMMITTEE FOR FOOD ON THE SENSITIVITY OF INDIVIDUALS TO FOOD COMPONENTS AND FOOD ADDITIVES

(Opinion expressed 22 October 1981)

TERMS OF REFERENCE

To complete the review of the topic of hypersensitivity and intolerance to food additives and to advise on the relevance of this subject to public health.

BACKGROUND

It has been well established for a number of years that various "allergic"* reactions may be caused in sensitized individuals following the ingestion of food additives. Since the initial observations of these effects there has been an increasing number of scientific publications on the subject. The Committee has drawn the attention of the Commission to this problem particularly in its report on Certain colouring matters for use in food (opinion expressed 23 March 1979)[1]. Indeed opposition has been expressed within the Committee to the addition to food of any colour alleged to cause allergic reactions, although this has been countered by the argument that where the incidence of allergic reactions is low, acceptability might be considered. In 1979 the Committee recommended to the Commission that it should convene experts in this specialised field to advise on the latest scientific information relating to such adverse reactions due to ingested food additives and drew attention to the parallel problems that might arise in the case of pharmaceuticals, and, in some cases, cosmetics. The present opinion is adopted in the knowledge of the conclusions of the working group set up by the Commission.

DISCUSSION

It should be stressed that in the present opinion the Committee has restricted its comments to food components and food additives but it is the total exposure from food, pharmaceuticals and cosmetics that pose the potential problem. The Committee reiterates its recommendation that competent bodies in these fields should be reminded of this fact.

The Committee was impressed by the information presented in the report of the Commission's working group on adverse reactions to ingested additives and concluded that this report should be annexed to the present report because it surveyed comprehensively the most recent scientific and medical information available. The Committee does not intend to repeat the detailed findings in its own report. It also approves the tenor of the recommendations in the report, but believes that more precise recommendations should be formulated by the Scientific Committee for Food in respect of food ingredients and particularly food additives.

In recent time much of the debate about sensitivity of individuals to food components and ingredients has concentrated on adverse reactions arising from the ingestion of food additives. Individuals learn by experience which foods are likely to cause disagreeable effects, but the susceptible subject is less easily able to identify the causative agent for the adverse reaction experienced if this is a food additive in a manufactured food.

The Committee is aware that the Council Directive on the approximation of the laws of the Member States relating to the labelling, presentation and advertising of foodstuffs for sale to the ultimate consumer[2] prescribes a complete list of ingredients for foods. The Committee endorses this principle but notes that for specific individuals sensitive to particular food components some of the relevant information might be lacking. These problems might well be resolved by Directives applying to specific foodstuffs principles of the Council Directive on the approximation of the laws of the Member States relating to foodstuffs for particular nutritional uses[3].

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*the term "allergy" is used to denote both true allergy (or hypersensitivity) and intolerance (or idiosyncracy)

[1] Reports of the Scientific Committee for Food, 8th Series, 1979

[2] OJ L 33 of 8.2.1979, p. 1

[3] OJ L 26 of 31.1.1977, p. 55

The Labelling Directive includes food additives in the definition of ingredient and thus these too must be indicated. In most cases this indication must be by the name of the category to which the additive belongs followed by a specific indication of the individual additive. The Committee has recommended in the past that there should always be clear and appropriate labelling of food additives so that the consumer can be aware of the contents of the food. It is especially important, with relation to individuals sensitized by food additives, that the wording is not only visible and understandable to the lay person but also meaningful to the medical practitioner.

The advantage of the "EEC No." is its simplicity, but many members of the Committee felt that the consumer in general was not aware of what this system entailed and that the medical profession in particular was not conversant with the details of the lists. The Committee stresses the importance of finding some way of informing consumers and their doctors in an objective manner on what the "EEC numbering system" involves.

The evidence presented to the Committee clearly demonstrates that in many cases of adverse reactions to food a dose/effect relationshop exists. It is evident therefore that a reduction in the total ingestion of the particular additive by the person likely to be affected by the additive would be beneficial. Reduction of intake can, in general terms, be brought about either by limiting the categories of food permitted to contain the additive or by lowering the amount of the additive in a particular foodstuff.

It seems to the Committee that for some additives the use level is in excess of that necessary to achieve the desired effect and the Committee supports the working group in its recommendation that a more rigorous appraisal of technological need should be undertaken in defence of the health of individuals sensitized by food additives. This problem is not only relevant to "allergy" and has been discussed in detail in the Committee's Guidelines for the Safety Assessment of Food Additives[4].

However, the Committee is not advocating a general lowering of present levels of additives unless a fundamental appreciation of the effects is understood. In this context the Committee has some grounds for believing that the use of additives whose role appears mainly to be organoleptic (e.g. colouring matters) is too widespread and there are good grounds for reducing their ingestion to the absolute minimum necessary. This is particularly relevant for substances causing the adverse reactions of the type presently under discussion

Where the effects noted are particularly severe or where the effects are widespread in the population, the Committee is of the opinion that a total ban on the substance in question should be envisaged as the ultimate reduction in use.

Each food additive represents a special problem as the socio-economic factors surrounding its use have to be taken into account by the legislative authorities in deciding on the appropriate measures to be taken. For this reason the Committee has taken a deliberate decision to limit its advice to questions of principle.

For practical reasons the Committee decided that it had to make a distinction between additives of long usage and additives to be introduced in the future.

Although the very nature of the problem and the limitations of the available testing techniques make it difficult to perform a complete assessment of potential allergenicity of chemicals, the Committee believes that all existing food additives suspected of provoking adverse reactions should be tested for allergenicity. Moreover the Committee considers that it would be reasonable to suggest to manufacturers that where there are grounds for suspicion - without scientific proof - that an additive already permitted in food is causing severe or widespread effects, manufacturers and users have a responsibility to provide proof that the suspicion is invalid, or to phase out or at least significantly reduce the uses of such an additive.

For new food additives a more strict attitude is to be envisaged. Test systems to detect "allergenicity" should be included routinely in toxicity assessments of new food additives.

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[4] Reports of the Scientific Committee for Food, 10th Series, 1980, EUR 6892

At present the existing methods should be applied, even though the results of these tests are in some cases not sufficiently predictive.

The Committee considers it essential that new methods are devised and developed to assess the reactions of hypersensitivity and intolerance that might be provoked by such additives so that a meaningful evaluation of their acceptability is more easily made. Moreover the Committee endorses the conclusion of the working group that there is an immediate and fundamental need for research to be carried out on the epidemiology of, and basic mechanisms concerned, in adverse reactions to food additives.

As has often been stated, in any toxicological evaluation the material tested should conform to an adequate specification. In the case of "allergy" particular attention should be given to the possible effects of specific impurities present in the additive and to metabolites associated with it since their presence could be the factor determining the adverse effect.

SUMMARY OF CONCLUSIONS

1. The Committee endorses the conclusions of the Commission's working group on adverse reactions to ingested additives.

2. The presence of additives in food should be mentioned by a specific indication for each additive which is informative to the consumer and the medical practitioner.

3. A more rigorous appraisal should be undertaken on the technological need for food additives with a view to a reduction in the total ingestion either by lowering permitted levels or by limiting the numbers of foodstuffs in which they are permitted.

4. In respect of food additives to be introduced and additives already in use suspected of having an effect on sensitized individuals, tests systems to detect "allergenicity" should be included in toxicity assessments.

5. New methods should be developed to assess adverse reactions of hupersensitivity and intolerance.

6. There is an immediate and fundamental need for research into the epidemiology and basic mechanisms concerned in adverse reactions to food additives.

ANNEX

Report of a working group on adverse reactions to ingested additives

CONTENTS

1. INTRODUCTION

Allergic reactions to certain foods are a long recognised problem. Often an individual will 'feel' that a particular food does not agree with him and will avoid eating that food (e.g. eggs, milk, shellfish or strawberries). The increasing replacement of fresh foods by manufactures 'convenience' foods has been accompanied by the use of food additives (e.g. preservatives, antioxidants and colouring agents). The realisation that similar adverse reactions can also be caused by such additives, in susceptible subjects, has resulted in questioning their continued use. Prompted by the preoccupations of its scientific advisers in the food, pharmaceutical and cosmetic sectors the Commission decided to set up this working group to review and report on hypersensitivity. Adverse reactions to food additives also involves drugs and cosmetics, since most components used in the formulation of drugs and several used in cosmetics are selected because of their toxicological clearance for safety-in-use as food additives. Discussion in this paper will deal mainly with adverse reactions from ingestion of food additives, in the hope that it will be possible to derive a common policy applicable to all food additives, but much that is said will be applicable to pharmaceutical products and cosmetics. The term allergy is often used for any adverse reaction resulting from ingestion of a particular food or additive. However it has been established that, despite their clinical similarity, such reactions are of two different types - true allergy (or hypersensitivity) which results from an immunological mechanism, and intolerance (or idiosyncracy) when no immunological basis is apparent. Our understanding of these mechanisms is incomplete and limited by a lack of appropriate laboratory tests. Nevertheless, it seems that most adverse reactions to food additives are manifestations of intolerance rather than allergy Therefore we have used this more specific terminology whenever possible. But these adverse reactions to food are still likely to be considered as "allergy" in any general discussion of the problem.

Definitions of the terms used in this report are attached in Annex I.

2. CLINCIAL PICTURE

When the additive gains access into the body of a susceptible subject, irrespective of whether it triggers off an immunological or other mechanism, it produces clinical manifestations which cause a very variable degree of discomfort. The most common manifestations of intolerance or hypersensitivity occur in the respiratory tract, skin a and gut, but other systems such as the nervous and vascular systems may be affected. In any individual the target organ pattern is likely to be rather constant.

Skin

It is probable that hypersensitivity or intolerance to food additives can be manifested in the skin in a variety of ways. Rashes which should be considered as possible skin manifestations of such reactions include eczema, purpura, erythema multiforme and fixed drug eruption. A relationship between quinine ingestion and purpura has been documented in occasional patients (e.g. Belkin, 1967; see also review by Baylon, 1979). A case of recurring purpura due to tartrazine (Criep, 1971), tartrazine and benzoates (Kubba and Champion, 1975), and seven patients with purpura following ingestion of azo-dyes and benzoates (Michaelsson et al, 1974), have also been reported. In the outbreak of 'Dutch margarine disease' in the late 1950s the erythema multiforme-like eruption which developed in patients consuming a particular brand of margarine was attributed to the use of a novel emulsifier (Mali and Malten, 1961).

Contact dermatitis due to additives in food and drugs has been described but is rare (Fischer, 1973). It is more common from additives used in topical medications and cosmetics (Wilkinson, 1972). But it is possible, and in some instances demonstrable, that ingestion of the sensitiser (or a related cross-reacting compound) may produce a flare-up in the contact dermatitis. Such a situation may occur with azo-dyes, antioxidants (e.g. BHA and BHT), preservatives (e.g. parabens, sorbic acid), flavourings (e.g. cinnamon, quinine) or stabilisers (e.g. ethylene diamine hydrochloride) where the sensitising additive is used in pharmaceutical preparations and/or cosmetics as well as in food.

The only well defined, common dermatoses in which present evidence suggests food additives play a significant part are chronic urticaria and angio-oedema.

Urticaria is a common symptom, likely to affect one in five persons at some time. The weals are due to histamine release, which in acute urticaria is often the result of an allergic reaction to a drug or food. In recurrent or chronic urticaria, the situation is more complicated. Certain foods and drinks are mentioned by 40% of patients as possible agents which worsen or provoke their urticaria (Juhlin, 1981). Several studies, testing for such hypersensitivity by provocation tests, have now been published. An urticarial reaction to an azo-dye, tartrazine, was first reported by Lockey (1959). Samter and Beers (1968) found that some of their aspirin-sensitive patients with urticaria also reacted to tartrazine. Juhlin et al (1972) found this true for 7 out of 10 patients with aspirin intolerance. Some also reacted to benzoic acid and its derivatives. Half of 52 patients with chronic urticaria reacted, with urticaria, to different azo-dyes and benzoic acid compounds (Michaelsson and Juhlin, 1973). The doses used for provocation tests can be exceeded by normal daily consumption of food and drugs. Investigation of 330 patients with chronic urticaria from 1974-1979 (Juhlin, 1981), with various coded food additives and placebo, showed at least 31% with positive provocation tests. Azo-dyes (18%), benzoates (11%), aspirin (22%), annatto (10%), BHA, BHT (15%), quinoline yellow (13%) and yeast (16%) formed the bulk of the positive reactions. A breakdown of positive reactions obtained in a similar group of patients by Mikkelson et al (1978) showed the following percentage proportions: 26% for annatto, 11% for tartrazine, 17% for Sunset Yellow, 16% for Food Red 17, 9% for Amaranth, 15% for Ponceau 4R, 12% for erythrosine and 14% for Brilliant Blue. There are many other reports of reaction to food colours in patients with chronic urticaria. It should be noted that although most attention has been paid to tartrazine these studies show that it is not only tartrazine that causes skin reactions. Patients with chronic urticaria have been shown to improve on a diet free from azo-dyes and preservatives (Thune and Granholt, 1975; Ros et al, 1976; Warin and Smith, 1976; Douglas, 1977; Freedman, 1977; Rudzki, 1977; August, 1979).

Respiratory tract - asthma, rhinitis and nasal polyps are the main symptoms. Aspirin has been known to cause serious reactions in some patients with asthma since 1919 (Cooke). Patients may have rhinitis and nasal polyps preceding the bronchoconstrictor type of (asthmatic) intolerance to aspirin by months or years. Aspirin sensitive patients often show intolerance to other analgesics (Smith, 1971). Speer (1958) reported that colouring matters can precipitate an asthmatic attack. Cross reaction to tartrazine in about 8 to 15% of aspirin-sensitive asthmatic patients has been reported by several authors (e.g. Settipane et al, 1967 and 1975). Similar cross reactions with various benzoates have also been found (e.g. Juhlin et al, 1972). Rosenhall (1977) tested 504 patients, with asthma and rhinitis, for hypersensitivity to food colouring matters, preservatives and analgesics. Reaction to at least one of the substances occurred in 106 patients. In 33 patients reacting to tartrazine, 42% showed intolerance to aspirin and 39% to sodium benzoate. Although dietary treatment was found to be effective in some patients, in preventing exacerbation of the disease, on the whole it did not influence the course of the disease, or the need for medication. Stenius and Lemola (1976) tested 140 asthmatics for reaction to aspirin and tartrazine. Most of the patients who reacted to tartrazine also reacted to aspirin, and about one third of them were able to give a history of reaction to colouring matters in food and drinks. While investigating patients with asthma who experienced attackes shortly after ingestion of orange soft drinks, and agreed to undergo challenge tests, Freedman (1977b) found that of a total of 14 patients, 8 gave positive tests to sulphur dioxide, 4 to sodium benzoate and 1 to tartrazine. This is the first report of asthma following ingestion of a beverage containing sulphur dioxide.

Investigation of children with asthma suggests that hypersensitivity or intolerance to food additives may be less common. Speer (1958) described reactions to tartrazine in children, but Vedanthan et al (1977) found no such adverse response after tartrazine provocation in 56 asthmatic children. Østerballe et al (1979) found that only 3 out of 46 asthmatic children had positive reactions to aspirin, benzoates or dyes. Similar results were obtained by Weber (1979) among 45 children. Only Syvanen and Backman (1978) have reported a situation similar to that obtained in adult asthmatics: of 32 children, 33% showed intolerance to aspirin, 18% to sodium benzoate and 20% to tartrazine.

Other clinical manifestations

Although there is definite evidence that allergic or idiosyncratic reactions involving the skin and respiratory tract can result from ingestion of food additives, this is not the case for adverse reactions involving other systems, such as the digestive or nervous system. It must be emphasised that in most of the following clinical situations there is little data to support the diagnosis of adverse reactions to food, and even less evidence that the symptoms are the result of hypersensitivity or intolerance to food additives.

a) Anaphylaxis is a very serious form of immediate immune reaction in which a state of generalised shock occurs and the outcome can be fatal. Anaphylactic reactions do not often result from food ingestion. They are known to have occurred after eating fish, eggs and celery for example; and very exceptionally have been attributed to particular food additives (Lockey, 1971).

b) Gastro-intestinal tract

The consideration that adverse reactions may easily affect the site of entrance of the food or additive, suggests that the gastro-intestinal tract may be a major target in hypersensitivity or intolerance to food and food additives. Nausea, vomiting, diarrhoea, abdominal distension, pain and bleeding are the commonest symptoms ascribed to such adverse reactions to food. These symptoms may occur alone or in association with respiratory and/or skin disturbances. When only gastro-intestinal symptoms occur, the diagnosis of an adverse reaction to food may not be at all obvious, since identical symptoms may result from chemical or microbiological contamination of food, or some psychological problem - furthermore mild gastro-intestinal upsets are part of everyone's experience and often ignored. There is therefore virtually no information about the incidence of uncomplicated gastro-intestinal manifestations of food allergy or intolerance associated with additives.

c) Nervous system

"Allergy" has long been reported to be a cause of headache and migraine. Out of 100 patients suffering from "allergic" headache, food was found to provide a relevant allergen in 87 (Rowe and Rowe, 1972). In patients with chronic migraine (2 to 3 attacks a week), diets avoiding the most common allergens may be effective in 85% of cases (Grant, 1979) - and use of the RAST, to detect specific antibodies has been suggested as a guide to appropriate dietary exclusion (Monro et al, 1980). But additives have not been specifically implicated.

Hyperkinesis

Purposeless overactivity with concentrating and learning difficulties may be present in from 0.09% (Rutter et al, 1969), to 1.19 to 5% of young children (Lambert, et al, 1978). Both non-scientific and scientific speculation on this condition stems from Feingold's suggestion in 1973 that dyes, preservatives and other additives could be responsible. His claim that a diet free from artificial food colouring matters and flavourings produced a dramatic and rapid improvement in 25 to 50% of hyperactive children, has not been substantiated in double-blind trials with food colouring matters. Flavourings have not been similarly tested. The evidence is well reviewed by Lipton (1979). Even studies in hyperactive children using bolus doses from 26 to 150 mg of colouring matters lend no support for Feingold's hypothesis, although it was apparently possible to demonstrate impairment of visual tracking performance (Conners et al, 1976) and concentrating ability (Swanson and Kinsbourne, 1980).

Various other neurological syndromes and symptoms have been reported due to food "allergy" (e.g. "allergic" tension-fatigue syndrome; mood and behavioural disturbances, transient paresis and paraesthesiae, vision and speech abnormalities, etc.). There is little evidence to support these suggestions. Weiss et al (1980) reported that out of 22 children with behavioural problems (other than hyperkinesis) who had previously shown improvement on an elimination diet, one child aged just under 3 years old was assessed by its mother to have responded positively to challenge with a blend of 7 artificial colouring matters.

It would therefore be fair to state that there is no good evidence to support Feingold's hypothesis; but it is perhaps not possible to give all food additives a completely clean bill in terms of behavioural toxicity. (See Report of the National Advisory Committee on hyperkinesis and food additives, 1980).

d) Urogenital allergy

Since the original report of Duke in 1922, the possibility that bladder urgency, frequency and strangury may be caused by "allergy" to food and additives has been repeatedly reported (Horesh, 1976; Dickey, 1977). The oedema and spasm of the bladder resulting from allergic reactions have been claimed to be responsible for incomplete emptying with subsequent recurrent infections and enuresis (Gerrard and Zaleski, 1977).

The presence of IgE in glomeruli of some patients with nephrotic syndrome (Paronetto and Gerber, 1971) has interested those who believe that dietary allergies may be of importance to urogenital pathology.

e) Articular and muscular allergy

"Allergy" to food and food additives as a cause of arthritis and arthralgias, as well as of muscular pain and fatigue, is often reported. Varying degrees of improvement with elimination diets have been described in patients with intermittent hydroarthrosis, palindromic rheumatism and even rheumatoid arthritis (see Rowe and Rowe, 1972). Recently, hypersensitivity to tartrazine as shown by positive RAST on synovial fluid, and by positive challenge with the dye, has been demonstrated in a patient with asthma and pain and swelling in the knee joints. Symptoms were completely relieved by avoidance of tartrazine in the diet, drinks and chewing gum (Wraith, 1980).

f) Ocular allergy

Contact dermatitis of the eyelids resulting from additives, as well as oedema of the eyelids, conjuctivitis and corneal pathology caused by food allergy have been reviewed by Rowe and Rowe (1972).

g) Ear allergy

Food allergy has been invoked as the cause of such conditions as chronic exudative serous otitis externa, Meniere's syndrome, and impaired hearing due to oedematous blockage of the Eustachian tubes.

3. FREQUENCY OF ADVERSE REACTIONS TO FOOD ADDITIVES

It is obvious from the previous sections that it is difficult to assess the number of cases of food allergy and intolerance since diagnosis is largely dependent on the subjective methods of history taking, elimination diets and challenge studies. A minimum of 0.2% for food allergy is suggested in a recent Danish Report (Poulsen 1980). Moneret-Vautrin and Grilliat (1979) suggest that if 15% of the population have allergic problems 6% will be cutaneous, 5% ENT, 3% bronchial and only 0.5 to 1.0% digestive in origin. This last figure agrees with Smiths estimations (1974) of less than 1%. When it comes to trying to assess the frequency of allergy, or intolerance, to certain food additives the problem is even greater; yet those who have to regulate the use of these additives need to know the size of the problem. Most of the good studies have been carried out in selected populations; and more information is available on the colouring matters in general and tartrazine in particular than for other food additives. The frequency of tartrazine sensitivity amongst the allergic population, as determined by skin or challenge tests, is very variable. Juhlin has reviwed the literature for information and used this with his own data to calculate the frequency of adverse reactions to some of the food additives. But he points out that when the diagnosis of intolerance or hypersensitivity depends upon provocation tests, then the recorded frequency is bound to vary with selection of patients, and dosage, and on the observation times used in the tests.

Food additives induced urticaria or angio oedema in about one third to half the patients with chronic urticaria. From this it was calculated that in a population of 10 million, additives will cause urticaria each day in 2,200 people, and that each year about the same number of patients will be referred to a specialist because of their sensitivity to additives. Of the individual additives, tartrazine is the most commonly tested azo-dye - it gave positive reactions in from 5 to 46% of patients. Other azo-dyes gave from 5 to 20% positives, and the natural colouring matters, annatto, from 8 to 26%. Amongst preservatives, benzoates are the most frequently tested, and gave positive reactions in from 3 to 44%; sorbic acid positive reactions were found in 6% of patients, and the antioxidants BHA and BHT gave from 14-15% positive results.

When considering asthma the facts can be summarised:- The prevalence of asthma in adult and childhood populations is very similar (2-6% and 0.5-10% respectively). Intolerance to aspirin is well recognised amonst asthmatics - the frequency increases with increasing age. About 8-10% of patients show intolerance; unless severe asthmatics are treated separately, when 16-18% are intolerant. Some 8-44% of aspirin intolerant asthmatics

show cross-reactivity with tartrazine, and 14% with various benzoates. Amongst 32 children with asthma, aspirin intolerance was found in 33%, and sensitivity to sodium benzoate in 18% and tartrazine in 20% (Syvanen and Backman, 1978). These figures have to be compared with a zero incidence of adverse reactions to tartrazine found by Vedanthan et al (1977), and those of Østerballe et al (1979) whose initial testing suggested that 24% of children with asthma showed intolerance to aspirin, benzoates or dyes, but on double-blind retesting with placebo found only 6.5%. From this background information it was roughly calculated that in every 10 million people, about 40,000 will have intolerance to aspirin (0.4%), 6,000 to tartrazine (0.06%) and 5,000 to benzoates (0.05%). Estimates of the incidence of tartrazine sensitivity in the whole French population have been made by Pellegrin (1979): 0.15%; and Moneret-Vautrin et al (1980): 0.03%.

In the Danish study reported by Poulsen (1980) a more systematic approach was used in an attempt to assess the frequency of reactions to food additives.

First the frequency (one year prevalence) in the general adult population, of asthma, all year rhinitis and chronic urticaria was determined as being 3.8%, 1.9% and 0.5% respectively. Subsequently the frequency of adverse reactions to food additives in these selected population groups was established by reference to previous provocation tests with food colouring matters and benzoates, on the basis of cross reactivity with aspirin. From these investigations, the frequency of intolerance to food additives in the Danish population (aged above 16 years) was calculated to be of the order of 1,000 per million (0.1%) for both tartrazine and benzoates. These frequencies were considered high by Danish allergy specialists (and an explanation was offered in the facts that there was a high frequency of chronic urticaria, and that the doses of colourings matters, other than tartrazine, used in the provocation tests were above expected levels of daily intake). But they agree with a combination of Juhlin's figures, calculated from food additive sensitivity in chronic urticaria, and tartrazine and benzoate sensitivity in asthma. Therefore when attempting to quantify the problem of adverse reactions to food additives, it is only possible, on the basis of present information, to suggest a wide range of possible frequencies (and only for the most common manifestations) of 0.03% to 0.15%.

4. MECHANISMS OF PRODUCTION OF ADVERSE REACTIONS

Understanding of the mechanisms of food additive allergy or intolerance does not seem necessary for ascertaining the frequency of this condition, and thus providing some basis for regulatory decisions. However, because the diagnosis of such "allergy" is usually imprecise, information about frequency has not been easily obtained. This situation will only be improved when diagnostic tests become readily available which are simpler and more accurate than the present subjective methods. This in turn will depend on better understanding of the cause of the adverse reaction. Furthermore development of animal and/or in vitro model systems to test food components for potential allergenicity (and intolerance) depend on understanding of the processes involved. Therefore from both a regulatory and a purely scientific viewpoint, it is important to try to elucidate the mechanisms of food hypersensitivity and intolerance.

The obvious first line of enquiry is to look for evidence of immunological mechanisms causing true allergic reactions. The basic concept in activation of the immunological system is that only large molecular weight substances, such as proteins, can act as allergic antigens and induce an immune response. It has been suggested that some food additives of small molecular weight can act as haptens and combine with proteins before acting as specific allergens. Exposure to the allergen stimulates the production from plasma cells in susceptible (atopic) individuals of specific antibodies which are distinctive in type (IgE), but may also show other patterns of antibody response to absorbed foreign protein. These specific IgE antibodies bind to basophils in the blood or mast cell results in the rapid release of histamine, serotinin, etc., which is responsible for the symptoms of immediate (reaginic) hypersensitivity (or atopy). Such reactions occur within minutes or several hours of ingesting food. Alternatively, a less well understood type of hypersensitivity can be produced: the onset of symptoms is typically 6-24 hours after food ingestion, but differentiation between immediate and delayed types of hypersensitivity cannot satisfactorily be made on the basis of the time interval but requires appreciation of the immunological differences involved. There has been much debate about the contribution of delayed hypersensitivity reactions to food allergy - it is a difficult condition to demonstrate - and the wide variation between some estimates of the overall frequency depends on whether or not delayed hypersensitivity type reactions are included. Resolution of this problem will be facilitated when tests

other than the standard subjective history taking and elimination/challenge procedures for the diagnosis of delayed hypersensitivity to food become generally available. Objective tests used to detect immediate hypersensitivity reactions include skin tests, RAST, and basophil degranulation. Unfortunately the results from these tests do not always agree (e.g. Pellegrin et al, 1978). It appears that molecules such as acetylsalicylic acid and tartrazine do not act as haptens; and IgE antibodies do not seem to be involved in adverse reactions to them (Weltman et al, 1978; Bernstein et al, 1978). However Weliky et al (1978, 1979) have found evidence of correlation between serum levels of an IgD tartrazine specific antibody and the clinical sensitivities of a group of patients.

The extact mechanism(s) for adverse reactions to food additives such as azo-dyes and benzoates is not understood. Since cross-reaction to various analgesics and anti-inflammatory drugs occurs, as well as to aspirin (e.g. indomethacin, phenylbutazone, methanamate, ibuprofen) intolerance seems probable for most patients. A chemical resemblance can clearly be seen between benzoates and salicylate. It may be relevant that tartrazine undergoes cleavage in the intestine into sulphanilic acid and a pyrazalone derivative. Moneret-Vautrin et al (1980) suggest that the latter substance may be concerned in the reaction rather than tartrazine. Some azo-dyes can form aniline compounds which could explain their cross-reaction with preservatives (Walker, 1970). In asthmatic aspirin intolerance, an abnormal blocking of prostaglandin E2, (which is a broncho-dilator) has been proposed as a possible explanation (Settipane et al, 1974). Such a mechanism in asthma seems logical since drugs which like aspirin induce urticaria and asthma are also good inhibitors of microsomal prostaglandin synthetase, but weaker inhibitors of this enzyme (like acetamidophen and salicylamide) often fail to produce symptoms (Szozeklik et al, 1975, 1977). To explain why some people react adversely to aspirin-like drugs while others improve, an underlying abnormaity in a metabolic pathway or of a particular receptor must be postulated in sensitive patients. The adverse reactions to tartrazine seem not to be mediated though an inhibition of prostaglandin synthesis (Gerber et al, 1979). The latter believe that tartrazine sensitivity is co-existent with that of aspirin and might have an allergic basis. Obviously, much work needs to be done before diagnostic tests for hypersensitivity and intolerance to food additives will operate from a firm factual basis.

In the context of intolerance to aspirin and to tartrazine, there is some evidence that commercial impurities may perhaps be responsible for the effects produced in sensitive subjects. Bungard and de Weck (1974, 1975) have shown that two impurities (acetylsalicylic anhydride and acetylsalicylsalicylic acid) commonly present in commercial aspirin are capable of producing the formation of salicyloyl-specific antibodies in experimental animals. They suggest that similarly the antibodies detected in a number of patients with aspirin intolerance are due to these impurities and not to acetylsalicylic acid itself. However Juhlin et al (1972) found that acetylsalicylic anhydride did not provoke urticaria in aspirin sensitive patients. Menoret (1979), in a paper submitted by the EEC Industries' Colours Group to the Commission, described skin sensitisation in the guinea-pig with impurity in a preparation of tartrazine; but the clinical relevance of this finding is doubtful.

One final point concerning the mechanisms of production of food allergy or intolerance. Although the abnormal genetic bases postulated to exist in sensitive subjects may include for example an inherent tendency to produce IgE antibodies, and/or a defect in the metabolic pathway of prostaglandin synthesis, there can be little doubt that conditions in the gastro-intestinal tract itself must influence the fate of ingested "allergens". It may not require deficiency of IgA to have an impaired local defence system in the gut. If the normal secretions are inadequate or if the mucosa is hyperaemic or damaged, it can be surmised that "allergens" may more readily gain access to the gut epithelium or absorption into the body. Attention should therefore be paid to such factors as dietary habits, alcohol intake, medicaments, etc. when considering the production or aggravation of food intolerance or hypersensitivity and the possibility of mitigating its effects in sensitive individuals.

5. ASSESSMENT OF THE INFORMATION AVAILABLE AND PRESENT UNCERTAINTIES ABOUT ADVERSE REACTIONS TO FOOD ADDITIVES

A satisfactory basis for regulatory decision requires information on the extent of the clinical manifestations and the frequency of adverse reactions to food additives in the general population. Uncertainties exist in both areas.

There is no doubt about the existence of allergy or intolerance to food additives, particularly in the form of urticaria and respiratory reactions, which can be provoked by several commonly used food colouring matters, preservatives and antioxidants. Investigation so far suggests in a reasonably convincing manner that the azo dye, tartrazine, is the most commonly implicated additive - but some allowance must be made for the relative usage and frequency of testing of different additives. Although the reactions produced by this colouring matter are usually of mild or moderate severity, occasionally severe asthmatic symptoms have been produced requiring intensive treatment (Pellegrin et al, 1978). The extent of clinical manifestations of food additive hypersensitivity or intolerance to food additives in general, other than dermatological and respiratory disorders, is uncertain. For example, the relationship between food additive ingestion and behaviour problems in children must be questioned. It is possible that the problem is one of very much wider implication than seemed likely initially, and one which would be resolved more satisfactorily by means other than extensive dietary elimination.

A second question of clinical importance is whether food additives are capable of intially causing hypersensitivity or intolerance, or merely of provoking a reaction in certain predisposed or sensitised individuals. If additives were shown to be aetological agents in the general population then this would greatly influence the decision about what course of action to recommend.

There is no direct information about the incidence and prevalence of hypersensitivity or intolerance to food additives in the general European population. The available evidence is derived from case reports and studies of highly selected populations. Furthermore it has not been established (though often supposed) that some additives such as tartrazine are more likely to provoke adverse reactions than others. The information required here would have to include data on the relative use and amounts ingested of individual additives, as well as the results of challenge tests.

Much of the reason for this lack of information lies in the present incomplete understanding of the mechanisms involved in adverse reactions to food additives, and the resulting absence of suitable diagnostic tests. The mechanism underlying a reaction may be immunological (allergy) or non-immunological (intolerance), but the clinical manifestations are similar and the tests at present available do not necessarily distinguish between these two types of reaction. The presence of a threshold effect, found in challenge tests with some food additives is likely to indicate intolerance. The fact that there seems to be a higher incidence of intolerance to additives in adults than children is thought to indicate that accumulation may also occur. This might be of importance in children in respect of neurological manifestations of intolerance to food additives.

6. RESEARCH PROPOSALS

i) Epidemiology

Although the ability of food additives to provoke a variety of clinical manifestations is widely recognised, there is a surprising dearth of fact. As has already been noted such evidence as there is derives largely from isolated case reports and studies of highly selected populations. Accordingly, it is of prime importance to establish the incidence and prevalence of intolerance or hypersensitivity to these substances in the general European population. Several population cohorts should be studied on a geographical basis e.g. France, Britain, Germany, Italy. If an area exists in which no additives are used, then it would be helpful also to carry out investigations in such a population. The cohorts studied should be as representative of the general population as possible. Ideally, randomly selected volunteer individuals from general practitioners' lists should be included. Both prevalence (the number of individuals at a single point in time suffering from adverse reactions to food additives) and incidence (the number developing symptoms over a defined period of time) should be determined, to avoid errors due to clustering in time. The size of cohorts and their selection should be determined after detailed discussions with epidemiologists and statisticians.

Detailed case histories of skin or respiratory symptoms and possible relationships to food factors should be made using standardised questionnaires. Any history of associated diseases (eczema, asthma, migraine, contact allergic dermatitis, rhinitis, drug reactions, etc.) should be noted. In addition to case histories, use will have

to be made of diagnostic tests despite their present limitations. Hopefully research into basic mechanisms (see below) will result in better diagnostic tests being developed which clearly distinguish between reactors and non-reactors.

ii) Basic mechanisms involved in food additive intolerance or hypersensitivity:

a) Understanding of the basic mechanisms may be helped by looking for specific differences in, for example, genetic and immunological factors between members of the local population who show a reaction and those who do not. 'Markers' could include HLA type and serum levels of IgE, complement factors, immune complexes, rheumatoid factor, and auto-antibodies including anti-nuclear factor; also levels of circulating antigens. Similarly, investigation of pharmacological mediatros for possible information about non-immunological mechanisms is required.

Perhaps these and the epidemiological surveys will throw some light on the problem of whether food additives are primary aetiological factors or aggravating factors in sensitive subjects.

b) Specific information about the mechanism(s) involved may be obtained from the following investigations in reactors:

Histology and immunopathology - Biopsy with direct immunofluorescence studies for immunoglobins and complement, and special stains for mast cells, in addition to routine histological examination.

Immunology - Isolation of haptens; isolation and purification of antigen (the consistent presence of a particular impurity may be relevant); immunodiffusion precipitin and haemagglutination tests for specific circulating IgG/IgM antibodies; radio-immunoassay for IgE (reaginic) and IgD antibodies; lymphocyte transformation tests, and tests based upon release of macrophage inhibition factor (MIF) in situations where a cell-mediated immune response is queried.

Pharmacology - To study the reactions involved in the intermediate stages of a response:- pharmacological analysis of venous blood, during lung and skin reactions initiated by systemic challenge, for kinins and other vasoactive peptides, slow reacting substance of anaphylaxis (SRSA), histamine, prostaglandin, serotonin; incubation of patients' leucocytes with food additives, and acetyl salicylic acid, and measurement of the release of histamine, prostaglandins, SRSA, hydroxy fatty acids and lysomal enzymes; analysis of skin exudate (obtained during onset, development and regression of lesion evoked by systemic challenge) for levels of such factors.

Pharmacodynamics of acetyl salicylic acid and tartrazine - The influence of aspirin and tartrazine on pharmacological mediator release or formation in vitro and in vivo need to be studied. Appropriate in vitro models should include antigen provoked histamine release from human skin and leucocytes and rat peritoneal mast cells, and biosynthesis of prostaglandins and related compounds (SRSA) from arachidonic acid by cyclo-oxygenase and lipoxygenase from seminal vesicle and skin. In vivo, measurement of pharmacological activity in venous blood, as outlined above, should be carried out after oral challenge.

Pharmacokinetics of acetyl salicylic acid and tartrazine - The absorption, distribution, plasma half life and urinary excretion of tartrazine and acetyl salicylic acid should be compared in control and reactive individuals.

Biotransformation - Attempts should be made to identify the metabolites of additives which can provoke adverse reactions. An attempt should also be made to correlate pharmacokinetic findings with genetic factors (see earlier section). The influence of non-covalent bindings to macromolecules such as albumin on the reactivity of tartrazine and other additives should be studied.

Structure-activity relationships - Characterisation of metabolites and conjugates and identification of in vitro models showing specific reactivity with food additives or derivatives should enable detailed structure-activity relationships to be established.

The possible influence of any consistent impurity(ies) in an additive, on pharmacological, as well as immunological processes, should be investigated.

iii) Development of animal models

Although animal toxicity data on food additives are available, these studies do not often include tests for allergenic potential. Evaluation of local irritant potential can be achieved using the Draize test (1944) or a modification of it. The readiness with which a food additive can induce delayed cell mediated immunity can be evaluated using the guinea pig maximisation test (Magnusson and Kligman, 1969). Animal models can also be used for detecting the production of immediate (IgE-mediated) hypersensitivity of the anaphylactic type and to reveal induction of complement-dependent immune complex-mediated and cytotoxic immune allergic reactions.

However the actual importance of allergic mechanisms in food additive-evoked clinical states is uncertain. There is considerable evidence to suggest that, on the contrary, non-immune mechanisms may be involved. The ability of aspirin to exacerbate wealing in patients with chronic urticaria is a widely recognised fact, but no evidence of an immune basis for this phenomenon is recognised. It seems probable that an interaction between aspirin and the arachidonate-prostaglandin cascade is involved (Sullivan and Parker, 1979 ; Marone et al, 1979).

Thus new animal models and in vitro test systems will have to be devised. These models would be useful not only for studying the mechanism(s) of clinically indistinguishable intolerance or hypersensitivity reactions but would also form an essential step in the safety-in-use assessment of proposed new food additives. It will be necessary to have models which can predict the likelihood of a particular additive causing a reaction due to either allergy or intolerance.

7. DISCUSSION

Label? or Ban?

Although insufficient information is available on the frequency in the general population of adverse reactions to food additives, or of the extent of the clinical manifestations which may be so provoked, to provide an ideal basis for regulatory decision making, it has been established that several food additives are capable of causing symptoms of allergy or intolerance in susceptible individuals who may constitute about 0.03 to 0.15% of the population. Everyone has the right to know what ingredients and additives are present in food, drug formulations and cosmetics. Information on the occurrence of additives in food and drugs is a matter of the utmost importance for individuals who are susceptible to adverse reactions. It seems a basic precaution therefore to give adequate warning by labelling. It is important that the wording is not only clearly visible, but also readily understandable to the lay person i.e. chemical formulae are not required, but a conventional name (e.g. erythrosine) or abbreviation (e.g. BHA), together with the appropriate E number (in brackets) should be employed. Thus a general requirement exists for information to be provided about all additives and ingredients present in food, but consideration needs to be given to certain problems associated with the use of labelling as a means of giving information about additives in foods: for instance it is not readily apparent how food labelling can help the individual eating out in a restaurant.

It cannot be emphasised too strongly that what is required is labelling to indicate all additives used - not just those which appear at present to be most frequently involved in provoking adverse reactions to food. It is likely that amongst the less frequently used and investigated additives are some with an equal potential to provoke adverse reactions due to intolerance or hypersensitivity. Furthermore, such a complete declaration might indirectly serve to question the need for the presence of numerous additives in some foods - so that stimulus might be given to apply more rigorously the principle of only using additives when a definite case of technological need exists.

Is labelling enough; or should more be done? Ideally from the point of view of the nutritional scientist, food additives with a purely "aesthetic" effect, such as colouring matters; and which provoke symptoms of allergy or intolerance, should not be used and it would perhaps be reasonable enough to ban the use of such colours in food. However, in drugs, the use of different colouring agents can afford an additional element of

safety in discriminating between different drugs but other methods are also possible. In this case banning could perhaps only satisfactorily be contemplated if it were possible to prove that the risk was one of inducing rather than aggravating a disease state, or if it were possible to be certain that the benefit derived from the use of colours in medicines could be preserved by substituting colours which were not similarly capable of provoking adverse reactions. At the moment neither of these premises is valid. However, bearing in mind the facts that a) a dose response relationship exists for the type of intolerance with which colours such as tartrazine seem to be associated and b) that the amount of a colour used can vary widely, it would be reasonable to suggest that the amount of colour permitted could be restricted both in foods and on/in different drug formulations. Furthermore, tartrazine (or any colouring agent similarly able to provoke adverse reactions) should be removed from the formulation of any drug likely to be prescribed for allergic subjects (e.g. antihistamines, beta-stimulators, antibiotics) or customarily taken daily over a long period of time by large sections of the population (e.g. contraceptive pills, tranquilisers). Of course, removing, reducing the quantity of, or labelling colours would not dispose of the similar but smaller problem with preservatives and antioxidants (in food, drugs and cosmetics), nor the common risk of allergic symptoms arising from natural food ingredients.

8. CONCLUSIONS

a) On the basis of currently available evidence, it is considered that the presence of all food ingredients, and additives in food, drugs and cosmetics should be clearly indicated by labelling. Furthermore it is suggested in the case of food colouring matters that the amounts used could be considerably reduced; and that no colouring matter which can provoke an adverse reaction in a sensitive individual, should be included in the formulation of drug preparations prescribed for the treatment of allergic conditions, or for large sections of the population on a long term basis.

   When further information is available from the research suggested in c) below, it may be advisable to consider if further action is indicated.

b) Action is required to try to prevent new additives being introduced into food, drugs or cosmetics with a potential for provoking reactions due to intolerance or hypersensitivity. Appropriate animal and/or in vitro test systems (for detecting such potential "allergenicity") should be adopted in future toxicity assessments. Ideally all existing food additives should also be tested for allergenicity, but this would be quite impracticable; however, those suspected of provoking adverse reactions should be investigated.

c) Finally, there is an immediate and fundamental need for research to be carried out on the epidemiology of, and basic mechanisms concerned in adverse reactions to food additives. This will include development of idagnostic tests for allergy and intolerance to food additives.

ANNEX I

DEFINITIONS

(NB It is difficult to give definitions which are universally acceptable in different languages for many of the terms used in discussing hypersensitivity and intolerance. The following definitions explain the meanings intended in this paper, and are based on Dorland's Medical Dictionary, 25th Edition.)

1. Basic Mechanisms

allergen	a foreign substance which provokes a harmful immune response
allergy	a hypersensitive state acquired through exposure to a particular allergen, reexposure bringing to light an altered capacity to react by an immune response
"allergy", "allergen", "allergic"	the use of quotation marks implies that in the particular context (of e.g. a reference from the literature) it is unclear whether an immunological or other process is involved
anaphylaxis	an unusual exaggerated allergic reaction to a foreign protein or other substance
antibody	an immunoglobulin which reacts in the (humoral) immune response specifically with the antigen, allergen or hapten which induced its synthesis in lymphoid tissue
antigen	any substance which is capable of inducing the formation of antibodies and of reacting specifically with them
atopy	an hereditary predisposition to develop some form of allergy (hypersensitivity) such as asthma or hay fever: an unusual type of antibody (reaginic, IgE class) is involved
delayed hypersensitivity	a specific immune response mediated by predominantly small lymphocytes of thymic origin (but also involving macrophages and antibody).
hapten	a simple protein free substance which is only capable of causing an immune response if it becomes coupled to a carrier protein
hypersensitivity	an abnormal (exaggerated) reaction to a foreign agent effected by the immune response or chemical mediators Type I - immediate hypersensitivity reaction Type II - injury is produced by an antibody against tissue antigens Type III - injury is produced by antigen-antibody complexes Type IV - delayed hypersensitivity reaction
immediate hypersensitivity	an immune response mediated predominantly by IgE antibodies, and characterised by lesions resulting from the release of histamine and other vasoactive substances
immune response	normal immune reaction to foreign antigen; manifested as antibody production or cell-mediated immunity

immunoglobulin (Ig)	protein with antibody activity, responsible for humoral aspects of immunity
IgA	antibody predominantly in secretions
IgD	antibody present in small amount in the blood. Its biological function has not yet been clearly defined
IgE	antibody of importance in immediate hypersensitivity
IgG, IgM	antibodies predominantly in blood and tissues
idiosyncracy	an abnormal, but non-immune reaction to a foreign substance, which is determined by a particular characteristic of certain individuals (e.g. enzyme abnormality)
intolerance	non-immunologically determined abnormal clinical response to a foreign substance
lymphocytes	specialised white cells which mediate immune reactions both humoral and cell mediated
macrophages	scavenger cells
mast cells and basophils	cells which release inflammatory substances (e.g. histamine, heparin) in immediate hypersensitivity reactions
plasma cells	lymphocyte derived white cells which synthesise immunoglobulins
radioallergosorbent tests (RAST)	laboratory tests using radio-immunoassay to detect IgE antibody to specific allergens in patients with immediate hypersensitivity

2. Clinical

challenge tests for immunological hypersensitivity	suspected allergens can be ingested, applied sublingually, inhaled or given as a skin test (superficially, intradermally or subcutaneously)
angio oedema (giant urticaria, angio neurotic oedema)	a condition closely related to urticaria in which the swellings occur in the subcutaneous tissues instead of in the skin: pain is common and itching less so
eczema	an inflammatory condition of the skin which may be extensive or patchy in distribution. In its acute form it is characteristically a papular, blistering, exudative eruption which is accompanied by intense redness, itching, pain and swelling. In the chronic form, thickening, dryness, cracking, scaling, persistent itching and excoriation are the main features
erythema	redness of the skin due to dilation of the blood vessels
erythema multiforme	a symmetrical eruption of red macules, papules and blisters, usually with purpura. Accompanying ulceration of the mucous membranes is common and the patient may be febrile

fixed drug eruption	an acute inflammatory reaction to systemically administered drugs, often with blistering, but always at the same site or sites
oedema	swelling due to the presence of abnormally large amounts of fluid in the intercellular tissue spaces of the body
purpura	a rash due to haemorrhages into the tissues which are visible through the epidermis. Small (less than 3 mm) purpuric lesions are called petechiae, and larger ones echymoses. Purpura occurs as a result of damage to walls of small blood vessels, which may be of an inflammatory or non-inflammatory type. When the purpura is due to inflammatory change in blood vessels, the term vasculitis is used to describe the eruption
rhinitis	consists of oedema of, and increased secretion from the nasal mucosa, with itching and obstruction. It may be accompanied by loss of taste and smell
urticaria (hives, "nettle rash")	transient, circumscribed swellings (weals) surrounded by erythema, associated with itching, and of generalised distribution. Swellings rarely last more than 24 hours, and usually last only 2-4 hours. Several clinical varieties are recognised. Chronic urticaria, when there are recurrent episodes, is by far the commonest variety.

ANNEX II

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The Scientific Committee for Food was established by Commission Decision 74/234/EEC of 16 April 1974 (OJ L 136 of 20.5.1974, p. 1) to advise it on any problem relating to the protection of the health and safety of persons arising from the consumption of food, and in particular the composition of food, processes which are liable to modify food, the use of food additives and other processing aids as well as the presence of contaminants.

The members are independent persons, highly qualified in the fields associated with medicine, nutrition, toxicology, biology, chemistry, or other similar disciplines.

The present series relates to hypersensitivity and intolerance to food additives.