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# THE ROLE OF FLAVORING SUBSTANCES IN FOOD ALLERGY AND INTOLERANCE[1]

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## I. INTRODUCTION

Flavorings are concentrated preparations, with or without flavor adjuvants, used in foods to impact flavor. Flavorings are not intended to be

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consumed as such, but rather used at low levels in finished consumer foods to enhance or improve quality. Flavoring substances are either chemically defined or natural products, the primary function of which is to impart flavor.

Food allergies and intolerances are an increasingly important concern to consumers and food manufacturers alike. Flavoring substances are rarely implicated as causative factors in food allergies and intolerances. Since thousands of different flavoring substances are used in foods, usually at very low levels, the likelihood of allergies or intolerances triggered by these substances is quite small.

However, some cases of adverse reactions to foods remain idiopathic or unexplained. In some such cases, the major ingredients listed on the incriminated product's ingredient listing have been clinically tested and eliminated as possible causative agents. The physician is then left to consider the possible role of minor ingredients, such as flavoring substances. This review provides a perspective of the likelihood that flavoring substances could be involved in allergy. The review also provides a diagnostic approach to evaluating the role of flavoring substances in adverse reactions.

## II. FOOD ALLERGIES AND INTOLERANCE

### A. DEFINITIONS AND PERCEPTIONS

Food allergies and intolerances are adverse reactions that affect some, but not all, individuals in the population. These individualistic adverse reactions to foods can occur through a variety of different mechanisms. Food allergies involve abnormal immunological reactions in which the person's immune system overreacts to ingestion of ordinarily harmless substances, usually naturally occurring proteins in foods (1–4). In contrast, food intolerances do not involve the immune system. Nonimmunological food intolerances include non-IgE-mediated histamine release (anaphylactoid reactions), metabolic food disorders, and a host of food idiosyncrasies (5). Although food allergies and intolerances are manifested in only a minor proportion of the population, the public views such illnesses as a major health concern and fails to distinguish between the different types of illnesses that fall within this general category. As many as 10–20% of all consumers believe that they have food allergies (6), although only 1–2% of the population are truly afflicted with these conditions.

## B. TRUE ALLERGIC REACTIONS

Two types of allergic reactions to foods can be distinguished (Table I), reflecting differences in the immune mechanisms involved in the course of the reaction. Allergic reactions may involve either an antibody-mediated or a cell-mediated response. Antibody-mediated responses are associated with IgE antibodies and are designated *immediate allergic reactions* because symptoms are experienced within minutes or hours following exposure of the sensitive individual to the allergenic food. The IgE-mediated mechanism is involved in other types of environmental allergies such as reactions to pollens, mold spores, animal danders, insect venoms, and drugs. Cell-mediated reactions are mediated by T lymphocytes and are designated *delayed-type allergic reactions* denoting the delay in the onset of symptoms

TABLE I

CLASSIFICATION OF ALLERGIC REACTIONS OF FOODS

| Descriptive name | Initiation time | Mechanism | Typical manifestations |
|---|---|---|---|
| IgE-mediated hypersensitivity | 2–30 min | Antigen cross-links IgE bound to mast cells and basophils with release of vasoactive mediators (histamine and many others) | Systemic anaphylaxis (anaphylactic shock)<br>Localized anaphylaxis<br>Respiratory<br>asthma, wheezing, rhinitis, bronchospasm<br>Cutaneous<br>dermatatis or eczema (rash), urticaria (hives), angioedema, pruritis<br>Gastrointestinal<br>vomiting, nausea, diarrhea, abdominal cramps<br>Other<br>hypotension, palatal itching, oral swelling, include tongue and larnyx |
| Cell-mediated hypersensitivity | 24–72 hr | Sensitized T lymphocytes release cytokines that activate macrophages, which mediate direct cellular damage | Localized tissue damage (especially in the intestinal tract with food) |

of 24–72 hr following exposure to the allergenic food. Cell-mediated reactions can also occur with agents from sources other than foods, such as medications and cosmetics. The term "food allergy" should be applied only to immunologically based adverse reactions invoked by food, but this convention is not always followed by consumers or even some physicians.

### *1. IgE-Mediated Allergies*

The primary mechanism involved in food allergies is the antibody-mediated allergic reaction involving the formation of the IgE class of antibody. The mechanism of IgE-mediated food allergies has been thoroughly reviewed (3,7). Briefly, in IgE antibody-mediated allergic reactions (Figure 1), the offending food protein (allergen) triggers production by the B lymphocytes of specific IgE antibodies. IgE binds in a highly specific fashion to certain high-affinity IgE receptors on the membranes of blood basophils and tissue mast cells. Upon a second exposure to the same allergen, the allergen cross-links two membrane-bound IgE molecules, initiating the

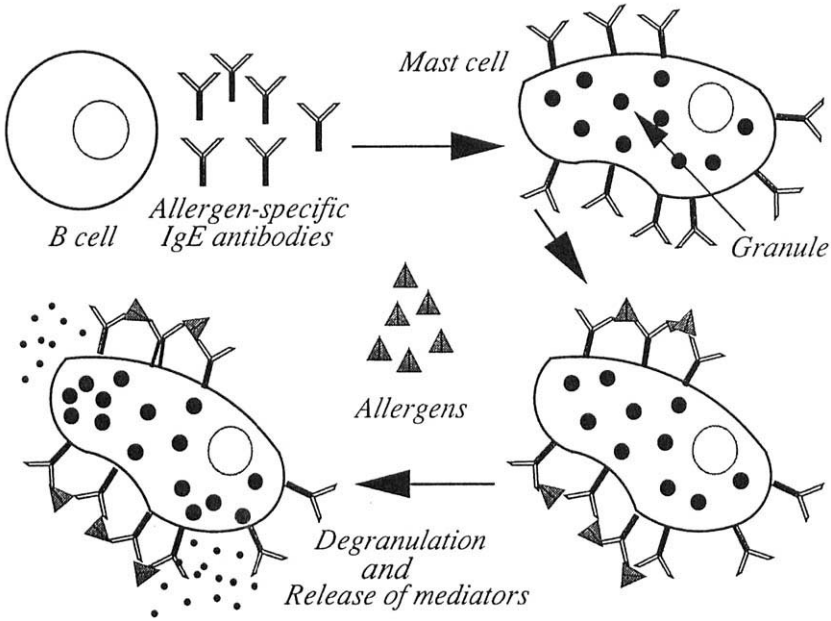


FIG. 1. Mechanism of an IgE-mediated allergic reaction.

release of a large number of different mediators, including histamine, prostaglandins, and leukotrienes (3).

Mediators released from mast cells and basophils interact with a variety of tissue receptors, causing numerous symptoms (Table I), primarily involving the gastrointestinal tract, skin, and respiratory system (2). Not all of these symptoms are experienced by any one allergic individual. Most affected individuals experience only mild symptoms, although severity can increase with frequent exposure. The severity of the symptoms varies depending on the sensitivity of the allergic individual, the amount of the offending food ingested, and the length of time since the last previous exposure. On rare occasions, life threatening anaphylactic shock responses occur upon exposure to the offending food (8,9). Anaphylactic shock is the most common cause of death in the rare fatalities associated with true food allergies (9). However, the most common manifestation of IgE-mediated food allergies is the so-called "oral allergy syndrome," in which symptoms such as swelling, itching, and hives are confined to the oropharyngeal area. These reactions are typically associated with fresh fruits and vegetables.

The prevalence of IgE-mediated food allergies is not precisely known in the total population. Studies have demonstrated that the prevalence in young infants ranges from 4 to 8% (10). However, food allergies, especially to certain foods including cow's milk and eggs, are commonly outgrown (11,12). While the prevalence of IgE-mediated food allergies in adults is not precisely known, it has been estimated to affect <1% (2,12). Any food or food ingredient that contains protein has the potential to cause allergic reactions in some individuals. However, the protein constituents of only a few foods are responsible for the majority of food allergies (Table II) (3). Perhaps 90% of allergic reactions in the United States are caused by the foods on this relatively short list (12). Foods often implicated by consumers as causes of food allergies such as chocolate, strawberries, and citrus fruits do not give positive results in double-blind, placebo-controlled food chal-

TABLE II

COMMON ALLERGENIC FOODS

| |
|---|
| Cereals containing gluten (wheat, rye, barley, oats, spelt or their hybridized strains and products of these) |
| Crustacea and products of these (shrimp, crab, lobster) |
| Eggs and egg products |
| Fish and fish products |
| Milk and milk products (lactose included) |
| Peanuts, soybeans, and products of these |
| Tree nuts and nut products |

lenges (13). However, the prevalence of allergic sensitivities to specific foods varies from one country to another depending on the frequency with which the food is eaten in that country and the age at its introduction into the diet. For example, peanuts are a much more frequent cause of food allergies in the United States than in most other countries because U.S. citizens eat peanuts more often and introduce peanut butter into the diets of children at an early age. For similar reasons, the Japanese seem to experience more soybean and rice allergies than other cultures, and Scandinavians have a very high prevalence of codfish allergy.

The major mode of treatment for all food allergies and intolerances is the specific avoidance diet. The construction of avoidance diets and the difficulties faced by consumers with such diets have been extensively reviewed (14,15). The effectiveness of avoidance diets is dependent on the patient's ability to identify the offending food or the ingredients derived from that food. Therefore, ingredient labeling is critical for effective avoidance. Food labels, especially certain labeling terms, can sometimes be confusing to patients, who need to be educated in the proper use of label information. Careful scrutiny of the ingredient lists on food labels will usually reveal the presence of the offending food.

Trace levels of the offending food can elicit adverse reactions. The safe level of the offending food that can be tolerated by individuals with true food allergies is unknown, but likely to be very low and variable. Allergic reactions have occurred from the inadvertent ingestion of milligram levels of the offending food (16). Foods may also become contaminated with trace amounts of other foods through a wide variety of means. Errors in processing and preparation of foods can result in the contamination of foods with allergenic foods. Examples of processing errors include use of shared equipment or facilities, use of work (i.e., material from one batch blended with material from another batch), formulation errors, and packaging or labeling mistakes. Food preparation practices, including use of shared utensils or cooking equipment, use of the same frying oil for more than one type of food, and creative formulation (e.g., peanut butter in chili) can also lead to the unsuspected presence of an allergenic food, especially in food service situations. Furthermore, restaurant foods are not labeled, so allergic individuals must inquire about the presence of specific foods in specific menu items.

When considering the allergenicity of a food ingredient, the presence of protein is important. If the protein is removed or rendered nonallergenic by processing, the resultant food product is safe for allergic individuals to consume. However, food allergens tend to be quite stable to processing treatments, especially heat treatments (17–20). For example, a study by Nordlee *et al.* (17) showed that the extracts of most processed peanut

products retained their ability to bind specific IgE from peanut-allergic sera, indicating that peanut allergens are highly heat-stable. One exception is the allergens present in certain fresh fruits and vegetables, which are quite heat-labile. The allergens in fresh fruits and vegetables are also sensitive to digestion. Hence, these proteins tend to elicit primarily oral symptoms, the oral allergy syndrome. Proteolysis has been suggested as a more effective way to destroy food allergens but most of these proteins also tend to be resistant to proteolysis (20–22). While casein hydrolysates are frequently used in hypoallergenic infant formulas, allergic reactions have been associated in a few cases even to this highly hydrolyzed protein (23). Soy products, such as hydrolyzed soy protein and soy sauce, which are subjected to considerable proteolysis during processing, remain unsafe for soy-allergic consumers in many cases because allergenic fractions of protein may remain in the final consumer product (20). Allergens can be effectively removed from some food ingredients. Herian *et al.* (20) determined that some highly refined soy products such as soy oil, which does not normally contain soy protein, may be safe for consumption by soy-allergic individuals. Double-blind challenge tests to determine the allergenicity of peanut, soybean, and sunflower oils indicate that the highly refined oils did not cause allergic reactions in sensitive individuals (24–26). Allergenic activity was lost because the protein fraction is typically removed from the oil during the refining process.

Virtually all food allergens are proteins. However, foods, even commonly allergenic foods, contain enormous numbers of proteins, and only a few of these proteins are food allergens. The nature of the IgE-mediated reaction, especially the need for cross-linking, conveys certain structural requirements on food allergens, including the presence of multiple IgE-binding sites. Although most allergens are proteins having a molecular weight between 10 and 60 kDa (27), attempts to identify some common chemical property of these proteins, for example, one that conveys allergenicity, have failed. It appears that allergenicity is a consequence of a complex series of interactions involving not only the allergen but also the dose, the sensitizing route, sometimes an adjuvant, and most importantly, the genetic constitution and immunological status of the consumer. The nature of the proteins involved in most food allergens has not been identified and characterized. The nature of the well-characterized food allergens has been reviewed elsewhere (12).

Only a few contaminants or food additives are implicated in true food allergies, and the overall impact of allergic reactions to these categories of food-borne chemicals is quite small in comparison to that of naturally occurring substances. One (perhaps the only) food additive associated with true food allergies is papain (28). This proteolytic enzyme from papaya, a

component of meat tenderizers and not a flavoring, is a known although not very common allergen. Food additives and ingredients derived from allergenic foods such as wheat starch may contain residues of the protein fraction of the food and thus would be allergenic. Penicillin, a veterinary antibiotic sometimes found in the milk or meat of treated animals, is one of the few nonprotein food contaminants associated with true, IgE-mediated food allergies (29,30). In this case, penicillin acts as a hapten by binding to proteins and eliciting the formation of IgE antibodies specific to the penicillin–protein complex. A hapten is a low-molecular-weight compound that is not allergenic by itself, but when coupled with a carrier protein, can elicit immune responses. Where naturally occurring proteins exist as components of food additives or inadvertent, unlabeled contaminants of other foods, a risk exists to those consumers with food allergies. It is unlikely that flavoring substances could be associated with true IgE-mediated food allergies unless the flavoring substances contain proteins, or can act as significant haptens. There are no nonproteinaceous flavoring substances associated with true IgE-mediated food allergies.

### 2. *Cell-Mediated Allergies*

Cell-mediated allergies or delayed hypersensitivities occur without the direct involvement of antibodies. Cell-mediated reactions develop when allergens activate sensitized T lymphocytes. Activation of T lymphocytes by allergen on appropriate antigen-presenting cells results in the secretion of various lymphokines (cytokines produced by activated lymphocytes). At the cellular level, the overall effect of these lymphokines is to attract macrophages and other cells into the area. Due to the local environment, these cells are activated, promoting increased phagocytic activity and increased concentration of lytic enzymes for more effective killing of foreign cells. As lytic enzymes leak out of the activated phagocytic cells into the surrounding tissue, localized tissue destruction can ensue. These reactions typically take 48–72 hr to develop, the time required for initial T lymphocyte activation and lymphokine secretion to mediate accumulation of additional cells and the subsequent release of their lytic enzymes (31).

Evidence for the involvement of cell-mediated immune reactions in food allergies is sparse but reasonably compelling (32–37). No estimates of the prevalence of cell-mediated food allergies have been made. The symptoms of cell-mediated food allergies are likely to be more localized than those of systemic IgE-mediated reactions. Thus, life-threatening responses, such as anaphylactic shock, are not known to occur in cell-mediated allergic reactions.

Celiac disease is probably the best characterized example of a cell-mediated food reaction. There is increasing evidence to support an immunologic basis of gluten sensitivity in this condition (38). However, even in this case, the mechanism has not been proven. Celiac disease, also known as celiac sprue or gluten-sensitive enteropathy, is an inherited malabsorption disease that occurs in certain individuals following the ingestion of the naturally occurring protein fraction of wheat, rye, barley, triticale, and perhaps oats (39–41). Following ingestion, the absorptive epithelial cells in the small intestine become damaged. This results in a decreased number of epithelial cells that are critical for digestion and absorption. The mucosal enzymes necessary for digestion and absorption are also altered in the damaged cells. The absorptive cells are thus functionally compromised. This process results in severe malabsorption characterized by diarrhea, bloating, weight loss, anemia, bone pain, chronic fatigue, weakness, muscle cramps, and, in children, failure to gain weight and growth retardation (42).

The treatment of celiac disease typically involves the total avoidance of wheat, rye, barley, triticale, oats, and all products produced from these grains (40). As with other food allergies, the symptoms of celiac disease are thought to be triggered by ingestion of rather small quantities of these grains. A safe tolerance level cannot yet be established, so complete avoidance is still advised. However, adherence to these strict avoidance diets can be quite difficult. Flavorings are not involved in celiac disease except in the rare circumstance where the flavoring contains proteins from wheat, rye, barley, oats, or triticale.

### *3. Contact Sensitivities*

Contact sensitivity is another common form of cell-mediated allergy. Many contact sensitivity reactions are mediated by T lymphocytes or Langerhans cells in the skin. Most of the causative substances are small molecules that can act as haptens and complex with skin or perhaps mouth mucosal proteins. This complex is internalized by antigen presenting cells in the mucosa, causing activation of sensitized lymphocytes or Langerhans cells and an ensuing cell-mediated reaction as detailed above. Contact sensitization reactions are most common with consumer products that are in frequent and/or prolonged contact with the mucosa. Several flavoring substances are known to cause contact sensitivity reactions, but primarily in the skin only from cosmetic uses. Such reactions are not relevant to most food uses where mucosal exposure is short. In products such as chewing gum or hard candy, there is prolonged and frequent exposure of the flavoring substances to the mucosal cells of the oral cavity. Contact sensitivity reactions in the mouth should be distinguished from the oral allergy syndrome, which

involves IgE antibodies and exposure to proteins without the need for prolonged exposure.

## C. INTOLERANCES

In contrast to true food allergies, many of the individualistic adverse reactions to food do not involve the immune system. Food intolerances, like food allergies, affect a limited number of individuals. Food intolerances occur through a number of nonimmunologic mechanisms. The three major classes that we discuss are (1) non-IgE-mediated histamine release (referred to as anaphylactoid reactions, to be distinguished from systemic anaphylaxis), (2) metabolic food disorders, and (3) idiosyncratic reactions. Intolerances can be distinguished from true food allergies both by the lack of immune system involvement and by the degree of tolerance for the offending food or food ingredient. With food intolerances, the affected individual can typically tolerate ingestion of a much greater amount of the offending substance than is the case with true food allergies.

Most of the nonimmunological food intolerances are caused by food-borne substances other than proteins. These substances may be naturally present in the food or from constituents added to foods. However, the situation is complicated by the fact that the evidence supporting the existence of some of these illnesses is far from complete. Food additives appear to be a focus of concern for unexplained maladies, but the possible role of naturally occurring substances in these conditions has received considerably less attention.

### *1. Non-IgE-Mediated Histamine Release (Anaphylactoid Reactions)*

Non-IgE-mediated histamine release reactions are the result of substances in food that cause mast cells and basophils to release spontaneously histamine and other mediators of allergic reactions. However, unlike food allergies, there appears to be no involvement with IgE or other immunoglobulins, and prior exposure is not a prerequisite (2).

Occasionally, histamine poisoning, also known as scombroid fish poisoning, is included as an example of a non-IgE-mediated release reaction (43) or as a separate category of nonimmunological food intolerance (44). However, histamine poisoning is actually a food-borne intoxication associated with the ingestion of foods containing unusually high levels of histamine, which is formed during bacterial spoilage (45). Everyone is susceptible to histamine poisoning, so it does not truly fit into this review of food allergies and sensitivities.

In non-IgE-mediated histamine release reactions, it is presumed that some substance in the implicated food destabilizes the mast cell membranes causing a spontaneous release of the histamine and other mediators. Actually, none of these histamine-releasing substances has ever been isolated or identified in foods, although this mechanism is well established with certain drugs. Therefore, the only evidence for the existence of anaphylactoid reactions from foods is highly circumstantial.

The most often cited example is strawberry "allergy." Strawberries are known to cause adverse reactions (frequently urticaria) in some individuals. Yet, strawberries contain little protein, no strawberry allergen has ever been identified, and no evidence has been obtained for the existence of strawberry-specific IgE. Since the symptoms of strawberry "allergy" are reminiscent of a true food allergy, *in vivo* release of histamine and other mediators seems a plausible mechanism. However, it must be emphasized that this mechanism has not been proven in strawberry "allergy" or any other food sensitivity.

There is no evidence that flavoring substances are involved in non-IgE-mediated histamine release reactions. This is likely due to low use levels of flavoring substances since significant dosage levels are likely required for this type of reaction.

### 2. *Metabolic Food Disorders*

Metabolic food disorders are adverse reactions to a food or food additive that occur through some effect of the substance on the metabolism of the individual (5). Metabolic food disorders involve genetically determined enzyme deficiencies that either affect the host's ability to metabolize a food component (e.g., lactose intolerance) or enhance the sensitivity of the host to some food-borne chemical via an altered metabolic pattern (e.g., favism). Lactose intolerance and favism are by far the most common metabolic food disorders. Lactose intolerance is caused by a deficiency of the enzyme $\beta$-galactosidase in the intestine, which results in an inability to digest and absorb lactose. Favism is caused by a deficiency of the enzyme glucose-6-phosphate dehydrogenase in erythrocytes, which results in hemolytic anemia upon ingestion of fava beans, which contain several otherwise innocuous hemolytic agents. Metabolic food disorders have a very defined tolerance level (most lactose-intolerant individuals can safely ingest 5 g or less of lactose, a level that exceeds by orders of magnitude the levels of use as flavor ingredients), although the degree of tolerance may be individually variable. Flavors do not contain the substances that cause these disorders and have not been linked to metabolic food disorders.

### *3. Idiosyncratic Reactions*

Idiosyncratic reaction is the general term used to describe a variety of food intolerances thought to have nonimmunological, but unknown, mechanisms (2). Many of the reported adverse reactions to food additives are placed in this category owing to the lack of understanding of their modes of action. Although consumers may wrongly refer to idiosyncrasies as food allergies, physicians should explain this aspect to patients. Food idiosyncrasies fall into three categories: (1) illnesses whose association with specific foods or food ingredients is well documented, (2) illnesses whose association with specific foods or food ingredients have not been firmly established or, in some cases, remain controversial, and (3) illnesses widely believed by consumers to be associated with specific foods or food ingredients despite considerable evidence to the contrary.

While some illnesses such as the involvement of sulfites in asthma are well documented (46,47), other associations such as chocolate in migraine headaches (48–50), food coloring agents and sugar in hyperkinesis (48–50), butylated hydroxyanisole (BHA) and butylated hydroxytoluene (BHT) in hives (53,54), and monosodium glutamate in headache, facial flush, and chest pain (55,56) are unproven.

In the vast majority of food idiosyncrasies, the role of specific foods or food ingredients remains to be established. Although tests have been done to prove the existence of some reactions, for the most part, carefully controlled challenge studies have not been conducted to examine the role of foods or food ingredients in these situations. The existence of many of these illnesses is based primarily on unconfirmed, anecdotal reports, or poorly designed clinical trials that leave the cause and effect relationship in doubt. Some of these illnesses may exist, but others may be psychosomatic or attributable to causes other than foods. The role of psychological disorders in perceived reactions to foods has been the subject of several notable studies (56–61). In some cases, including food-induced migraines and monosodium glutamate (MSG)-induced headache and flushing, the symptoms are so subjective that the confirmation of the responses is difficult. In other cases, such as the alleged roles of tartrazine (FD&C Yellow No. 5) in asthma and BHT and BHA in chronic urticaria (54), the results of several challenge studies are not in agreement. The design of the studies, especially the withholding of medications for the chronically ill patients involved in the studies, is a particularly critical factor.

Sulfite-induced asthma is the best example of a well-established idiosyncratic illness of food-borne origin. Sulfites have been widely used in

foods for a variety of purposes, and sulfite residues are present in a variety of foods at levels ranging from a few ppm to >1000 ppm in dried fruits (62). Sulfites can also occur naturally in foods, especially fermented foods, but the residues of naturally occurring sulfites are usually low (62). The pathogenesis of sulfite-induced asthma is not understood, although several mechanisms have been hypothesized including IgE-mediated reactions, hyperreactivity to inhaled $SO_2$, and sulfite oxidase deficiency (54,62,63). In controlled challenges with capsules and/or acidic beverages, the threshold level of sulfite ranges from 3 to 130 mg of $SO_2$ equivalents (62). Thus, sulfite-sensitive asthmatics must avoid highly sulfited foods (64).

Flavoring substances, with the exception of MSG, have not been implicated in idiosyncratic reactions. MSG is a widely used food ingredient and is best characterized as a flavor enhancer. MSG and various protein hydrolysates, which contain glutamate, are used widely as ingredients of flavor formulations. However, as noted later in this review, the role of MSG in food-borne illness remains controversial and unproven.

## III. TYPES AND USES OF FLAVORING SUBSTANCES IN FOODS

Many aspects of flavoring substances must be examined when assessing the allergenic potential of these substances, including their chemistry, the presence of protein, the manufacturing of the substance, and the typical usage level.

Flavors are composed of many materials, chemicals, although most are present in extremely low amounts. In the United States, flavors are composed of almost 2000 substances of which over 400 are well-characterized products of natural origin containing numerous individual components, while approximately 1600 are structurally defined substances. Flavors can be classified by physical appearance (liquid, solid, or paste) as summarized in Table III (65). The physical characteristics of the flavor must be compatible with the product in which it is to be used. Flavors can also be classified as either simple or compounded (65). Simple flavors are those consisting of a single ingredient or a single substance diluted in an appropriate neutral carrier. Compounded flavors are blends of several substances. Flavors can also be classified as natural or artificial, a common distinction on the package label. However, artificial flavors can, and often do, contain natural ingredients. Flavoring substances meet the specifications for identity and purity of the Food Chemicals Codex, established by a committee of experts for the National Academy of Science.

TABLE III
PHYSICAL CLASSIFICATION OF FLAVOR INGREDIENTS

| Solids | Liquids | | Pastes |
|---|---|---|---|
| Crystals | Essential oils | Tincture | Soft extracts |
| Powders | Folded | Infusions | Resins |
| Freeze dried | Recitified | Distillates | Natural |
| Spray dried | Terpeneless | Spirits | Prepared |
| Dried extracts | Sesquiterpeneless | Soluble essences | Resinoids |
| Plated | Oleoresins | Emulsions | Concretes |
| Encapsulated flavors | Absolutes | Fractions and isolates | Emulsions (creams) |
| | Fluid extracts | Concentrated juices | |
| | Compounded oils | Single-strength juices | |
| | Alcoholates | | |

## A. NATURE AND COMPOSITION OF FLAVORING SUBSTANCES

The flavor characteristics of a food are derived mainly from its volatile components. Volatile substances, while often intense flavors, are seldom major components of food (carbohydrates, proteins, and fats), although they may be considered to be derived from these major components (66). Flavors may be naturally occurring in foods or generated from precursors during the cooking or processing of foods. Flavors can be produced by thermal reactions between naturally occurring compounds in foods, such as the creation of meat flavor by the thermal reaction of certain amino acids and sugars. Flavors may also be generated by enzymatic reactions or enzymatic modification, as is cheese flavor, or by microbial fermentation, as is butter flavor. The most important classes of flavors in various foodstuffs and the mode of their formation from precursors are summarized in Table IV. In general, these and all other flavoring substances are low-molecular-weight substances.

The classes of flavoring substances listed in Table IV are unlikely to elicit allergic reactions except when they act as haptens. These reactions are usually manifested as contact sensitivity reactions. Antibodies are elicited for the hapten and the carrier protein. Hapten–protein complexes can elicit either antibody-mediated or cell-mediated immune responses. For example, cinnamic aldehyde may act as a hapten through its reactivity with protein. Therefore cinnamic aldehyde can produce contact allergy and urticaria under some conditions (67). However, digestive processes

TABLE IV

MAJOR CLASSES OF FLAVORING SUBSTANCES IN VARIOUS FOODS AND THEIR MODE OF FORMATION FROM PRECURSORS

| Food | Precursors | Main mode of formation | Classes of flavoring substances |
|---|---|---|---|
| Fruit | Sugars | Natural formation | Terpenes, terpenoids, acids, furans, pyrans, esters |
| | Fats | Natural formation | Aldehydes, ketones, esters, lactones |
| Vegetables, spices, herbs | Sugars | Natural formation | Terpenes, terpenoids, isoprenoids, phenols |
| | Fats | Natural formation | Lactones, aldehydes |
| | Amino acids, sugars | Natural formation | Pyrazines |
| | Amino acids, sugars | Enzymes | Sulfur compounds, aldehydes |
| | Amino acids | Heat | Sulfur compounds, cyanides |
| Wine, beer | Sugars | Fermentation | Esters, acetals |
| | Amino acids | Fermentation | Lactones, amines |
| Dairy products | Fats | Enzymes, heat | Ketones, lactones, aldehydes |
| | Amino acids | Fermentation | Acids, amines |
| Meat | Amino acids, sugars | Heat | Acids, aldehydes, ketones, furans, pyrazines, phenols, sulfur compounds |
| Fish | Amino acids | Enzymes, heat | Amines, sulfur compounds |
| | Fats | Enzymes | Aldehydes, ketones |
| Coffee, cocoa | Amino acids, sugars | Heat | Heterocyclic amines, aldehydes, ketones, phenols, sulfur compounds |
| Bread | Amino acids, sugars | Heat | Pyrroles, pyrazines, pyridines |
| Roasted nuts | Amino acids, sugars | Heat | Pyrazines, aldehydes, ketones, sulfur compounds |

commonly destroy the hapten–protein complexes. Thus, low-molecular-weight chemicals in foods are unlikely to be effective haptens in systemic reactions.

Process flavors are created by the combination of reducing sugars with amine compounds at elevated temperatures. In the case of process flavors, proteins or peptides may be used as the nitrogen source materials. Thus, the process flavors could contain protein residues and potentially be allergenic (see next section).

## B. MANUFACTURING OF FLAVORING SUBSTANCES

There are many general methods for preparation of flavoring substances (Table V). Each method can be modified or combined with other methods. When manufacturing a flavoring substance, many processing methods are utilized, including chemical synthesis, distillation, expression, solvent extraction, concentration, microencapsulation, vacuum drying, and spray drying.

Distillation is a process requiring heat to volatilize the components at elevated temperature. Each component boils at a different temperature, depending on molecular weight, functional groups present, molecular composition, structure, etc. The resulting distillate leaves the protein behind in the source material. Therefore the distillate is not likely allergenic.

Expression is a process by which oils and juices are removed from plant sources by applying external pressure. If the source of extraction contains allergens, the extract may also contain allergens.

Solvent extraction is a procedure in which solvents are used to extract selectively desirable ingredients. Extracted natural flavor substances generally consist of rather dilute solutions in which the solvent may or may not contribute to the overall flavor strength. Proteins, if any, would be present at very low levels.

The process of concentration results in an increase in organoleptic principals resulting from the partial elimination of the inert solvent.

Microencapsulation consists of forming capsules that envelope the flavor substances when added gum solidifies. Microencapsulation will not remove or change any allergen if present.

Vacuum drying of liquid extracts takes place under vacuum with removal of solvents as the main objective. The moisture content of vacuum-dried products is approximately 3 to 4%.

TABLE V

GENERAL MANUFACTURING METHODS FOR FLAVORING SUBSTANCE PREPARATION

| |
|---|
| Distillation |
| Expression |
| Concentration |
| Crystallization |
| Lyophilization |
| Vacuum drying |
| Spray drying |
| Microencapsulation |

Spray drying is an operation in which the product is mixed with a carrier and sprayed into a stream of hot air. If allergens are present in the flavor source, drying will not remove them or render them nonallergenic. In fact, the drying process would concentrate any allergens present in the liquid extract. However, it must be emphasized that the source materials for production of distilled, concentrated, extracted, encapsulated, and dried flavors seldom contain allergenic components.

Process flavors are generated by enzymatic or thermal treatment, or combined treatments, of various materials. Enzymes, especially lipases and proteases, are added to food materials and incubated at appropriate temperatures to create such products as hydrolyzed proteins and enzyme-modified cheeses. Alternatively, fermentations with bacterial or yeast cultures can be used to create similar products. The thermal processes used to create reaction flavors typically involve extensive nonenzymatic browning, the reaction of reducing sugars with amino acids, to create unique flavors. The nature of precursor materials used in the creation of process flavors dictates the type of flavor that will evolve. For example, the most prominent methods in which the various classes of sulfur-containing flavor substances are formed from their natural precursors are summarized in Table VI (66). As noted below, process flavors are often prepared from proteinaceous sources, for example, meat, and do contain protein residues. But, because extensive conditions (typically 100°C for 15 min) and other reactions occur in the processing of process flavors, the allergenicity of the protein may be diminished or destroyed. Some food allergens are known to be quite heat-stable. Therefore, process flavors should be assumed to be allergenic if the source protein is a known allergen unless testing proves otherwise.

## C. PROTEIN CONTENT OF FLAVORING SUBSTANCES

Nonproteinaceous substances make up the majority of flavors. For most flavoring substances, protein residues are not allowed in Food Chemicals Codex specifications. Most flavoring substances contain little, if any, protein. Even fewer of these proteins are derived from commonly allergenic foods. Yet, virtually all allergens are proteins, so the protein content of flavors is a key indicator of its possible allergenicity. Table VII lists the common protein sources that are used in the production of flavors, especially process flavors. Several of these sources, including eggs, peanuts, milk, sea foods, soybeans, tree nuts, and wheat, are considered to be common allergenic foods. However, some of the substances derived from such sources (e.g., refined oils) are free of protein residues. The protein content of reaction flavors is highly variable depending on the source materials used in the

TABLE VI

SULFUR-CONTAINING FLAVOR COMPOUNDS FORMED FROM NATURAL PRECURSORS

| Class of sulfur compound | Precursor | Formation | Food |
|---|---|---|---|
| Hydrogen Sulfide | Cysteine | Enzymes | Seafood, yeast |
| | Cysteine/cystine | Heat | Meat, eggs |
| | Thiamine | Heat | Meat |
| Thiols | Methionine | Enzymes | Yeast |
| | Methionine | Heat | Meat, fish |
| | Thiamine | Heat | Meat |
| Monosulfides | Methionine | Enzymes | Yeast, milk |
| | Methionine | Heat | Vegetables, meat, seafood |
| | *S*-Methylmethionine | Heat | Vegetables |
| | Dimethyl-*b*-propiothetin | Bioformation | Seafood |
| | Disulfide | Heat | Vegetables |
| Disulfides | Sulfide | Heat, oxidation | Meat, vegetables |
| | Thiosulfinates | Heat | *Allium* vegetables |
| Trisulfides | Disulfide | Heat, oxidation | *Allium* vegetables |
| Thiosulfinates | *S*-Alkylcysteine sulfoxide | Enzymes | *Allium* vegetables |
| Isothiocyanates | Glucosinolate | Enzymes | *Cruciferae* vegetables |
| Thiocyanates | Isothiocyanate | Enzymes, heat | Vegetables |
| Methional (derivatives) | Methionine | Enzymes | Yeast, soy sauce |
| | Methionine | Heat | Vegetables, meat, milk |
| Thiazoles | Cysteine (?) | Bioformation | Tomato |
| | Cysteine/cystine | Heat | Meat, coffee, nuts, bread |
| | Thiamine | Heat | Meat |
| Thiophenes | Disulfide | Heat | Onion |
| | Cysteine/cystine | Heat | Meat, coffee, nuts, bread |
| | Thiamine | Heat | Meat, milk |
| | Furanones + $H_2S$ | Heat | Meat |
| Thiolanes, thianes, thiepanes | Peptides (?) | Bioformation | Asparagus |
| | Peptides | Enzymes, heat | Mushroom |
| | Hydrogen sulfide | Heat, oxidation | Potato, meat |

formulation, the protein content of these substances, processing conditions (especially in the case of reaction flavors), and extraction conditions, where applicable. Identifying these proteins on flavor labels is an appropriate means of informing the food processor of their presence. The use of such flavors would determine if subsequent identification of the protein on the consumer product label is warranted.

TABLE VII

PROTEINACEOUS SOURCE MATERIALS USED AS INGREDIENTS IN FLAVOR MANUFACTURING

| Protein source | Substances used in flavor manufacturing |
|---|---|
| Egg and egg products | Dried egg albumen, egg yolk solids, egg yolk extract, and frozen egg products. |
| Meat and meat products | In meat, the characteristic flavor compounds are formed in thermal reactions from sugars and amino acids. For sulfur-containing volatiles, the paramount source of sulfur is cysteine, either in the free form or as a part of the meat proteins. |
| Milk and milk products | Butter, butter oil, buttermilk solids, nonfat dry milk, enzyme modified milk powders, casein (dry and hydrolyzed), whey, sour cream, sour cream solids, cheese (including enzyme-modified cheeses), butter starter distillates (as defined by 21 CFR), lipolyzed butter oil, and butter powders. Note that butter esters, although the name implies dairy, are often mistaken to be a butter product. These esters tend to be those flavor chemicals known to be present in butter. |
| Peanut and peanut products | Peanuts extracts, peanut distillates, and peanut oils, which may or may not be refined. |
| Seafood | For the most part, seafood ingredients include extracts of cod, shrimp, crab, lobster, oyster, scallop, crayfish, and molluscs. Some of these ingredients are available in powdered form. |
| Seeds | These ingredients tend to be the oils derived from the seed. In particular, both refined and unrefined oils of sesame and sunflower as well as the partially hydrogenated oils of these seeds. |
| Soybean or soybean-containing products | As with seeds, these ingredients tend to be the oil and partially hydrogenated oil. The oil is often used in concentrations up to 0.5% to eliminate dusting from ingredients such as autolyzed yeast extract. Also included in this category is soy sauce and soya flours. |
| Tree nuts | As with peanuts, the tree nut products (Brazil nut, walnut, hazelnut [filbert], cashew, almond, pinenut, pistachio, pecan, macadamia) include the extracts and distillates. |

(*continues*)

TABLE VII (*Continued*)

| Protein source | Substances used in flavor manufacturing |
|---|---|
| Wheat and wheat-containing products, and other grains | Barley, bran, cereals, gluten, and oats; starch ingredients used in flavor production tend to be modified cornstarch, maltodextrin, and barley malt flour as carriers. |
| Enzymes | Various enzymes are used to prepare hydrolyzed products including lipolyzed butter and enzyme-modified cheeses. The enzymes include proteases, lipases, and peptidases. |
| Hydrolyzed plant proteins | Various degrees of hydrolysis of various sources of plant proteins fall under this category. Included are corn gluten, wheat gluten, wheat protein, and soy protein. |
| Yeast extracts | Yeast extracts prepared from bakers yeast, brewer's yeast, Torula yeast, and other yeast extracts as well as autolyzed yeast extracts. |

## D. USAGE LEVELS OF FLAVORING SUBSTANCES

When considering the allergenic potential of flavoring substances, usage levels should also be taken into consideration. Because flavoring substances are used at low levels, ranging from parts per million (ppm) to perhaps 1% of the total product, very small amounts of many flavoring substances are present in finished food products. The wide variety of uses for flavoring substances makes it impossible to establish firm rules defining their usage levels, but many are self-limiting at high levels. In some cases, the use of a substance to impart a dominant note may be at a level more than 1000 times that of the same substance used as a trace ingredient (69). It is reasonable to conclude that in actual manufacturing practice, a level of 5 times the average maximum use will include nearly all normal applications of the ingredient (69). Table VIII provides examples of the average maximum use levels of some ingredients reported by food category. As noted earlier, an enormous variety of flavoring substances is allowed for use in foods. Thus, exposure to any single flavoring substance would be quite limited, especially given the low levels of typical use. Thus, allergic sensitization to most food flavors is rather unlikely due to the chemical composition and low level of use.

## E. LABELING OF FLAVORING SUBSTANCES

Information required to be on the label of U.S. food products is itemized in Section 403 of the Food, Drug and Cosmetic Act. Among the required

disclosures is the need to list ingredients used in fabricated food, in descending order of predominance. This requirement was by no means meant to be rigidly comprehensive. From the start, Congress recognized that reasonable limits to any such required disclosure are essential to preserving an efficient and competitive food industry and the concomitant benefit of an abundant food supply. The intent of Congress is clear: the labeling provisions of the FDC Act do not reflect a consumer right-to-know orientation. Even on issues as sensitive as food ingredients, Congress has specifically exempted the identification of certain ingredients and provided the agency authority to, in its sound judgment, exempt further ingredients from disclosure requirements.

The purpose of Section 403(I)(2) of the FDC Act is to ensure that the consumer obtains "reasonable information regarding the composition of the food he buys." This section of the Act generally excludes spices, flavors, and certain colors from its identification requirements. Congress also recognized that trade secret information regarding formulas falls outside the scope of "reasonable" information needed to inform the consumer.

Section 201(n) recognizes that certain foods or food ingredients may present risks for some consumers that can and should be averted through affirmative labeling. Under this authority, the FDA has required declarations identifying the presence of ingredients such as sulfiting agents (21 CFR 101.100(a)(4)), FD&C Yellow No. 5 (21 CFR 74.705(d)(2)), and other ingredients that the agency has concluded possess the potential to trigger adverse reactions in people sensitive to such ingredients.

The Code of Federal Regulations has outlined terms describing the physical or technical functional effects for which direct human food ingredients may be added to foods (Table IX). In Europe and many other countries, if any compounded ingredient (an ingredient composed of two or more ingredients) contains an ingredient that is less than 25% of the compounded ingredient, it need not be listed separately (70).

In some cases, when a flavoring substance is used for a function other than imparting flavor, the substance may be used at higher levels. If a known allergenic protein is added to the flavor in a larger quantity for such dual functional purposes, such as using whey as a flavor carrier, the likelihood of an allergic reaction is increased.

## IV. REVIEW OF REPORTED ALLERGIC REACTIONS TO FOOD FLAVORING SUBSTANCES

Allergens are typically proteins of natural origin. As previously noted, flavors and flavoring substances rarely contain proteins. Most frequently,

## TABLE VIII

AVERAGE MAXIMUM USE LEVELS REPORTED BY FOOD CATEGORY (IN PPM [MG/KG])

| Substance | Nonalcoholic beverages | Alcoholic beverages | Frozen dairy desserts | Candy | Baked goods | Gelatins and puddings | Meat and meat products | Condiments, relishes | Other category uses | | Misc. unclassified |
|---|---|---|---|---|---|---|---|---|---|---|---|
| Anethole | 42.5 | 723 | 53.5 | 531 | 495 | 52.8 | 10 | | Sweet sauce | 86 | 3261 |
| | | | | | | | | | Gravies | 5 | |
| Anise oil | 31.3 | 570 | 61.3 | 681 | 182 | 46.3 | 27.1 | 180 | | | 5 |
| Balsam of Peru | 6.04 | 6.99 | 9.46 | 15.33 | 15.1 | 8.88 | | | | | 6.15 |
| Carvone | 41 | 145 | 497 | 226 | 115 | 90 | 0.1 | 60 | Cheese | 0.2 | |
| Cassia | 1947 | 2 | 1940 | 140 | 14,006 | 4000 | 4021 | 1198 | Sweet sauce | 1400 | |
| | | | | | | | | | Soups | 200 | |
| | | | | | | | | | Gravies | 2.35 | |
| Cassia bark oil | 48.6 | 228 | 123 | 375 | 469 | 99.8 | 237 | 264 | Fats and oils | 15 | 742 |
| | | | | | | | | | Processed fruit | 4 | |
| | | | | | | | | | Gravies | 19.4 | |
| Cinnamon | 57 | | 616 | 155 | 12,967 | 1429 | 1570 | 214 | Breakfast cereals | 5103 | 200 |
| | | | | | | | | | Fats and oils | 324 | |
| | | | | | | | | | Milk products | 700 | |
| | | | | | | | | | Cheese | 15 | |
| | | | | | | | | | Processed fruit | 771 | |
| | | | | | | | | | Conf. and frost. | 20,000 | |
| | | | | | | | | | Jams and jellies | 1050 | |
| | | | | | | | | | Sweet sauce | 5000 | |
| | | | | | | | | | Soups | 371 | |
| | | | | | | | | | Gravies | 60 | |
| Ciannamic acid | 175 | 712 | 263 | 356 | 384 | 290 | | | | | |
| Cinnamaldehyde | 68.7 | 499 | 78 | 550 | 367 | 109 | 59.3 | 31.9 | Gravies | 800 | 3693 |
| Cinnamyl alcohol | 8.06 | 8.97 | 10 | 21.3 | 17.9 | 14.8 | | | | | 76.1 |
| Clove stem oil[a] | 52.6 | 600 | 129 | 414 | 40.9 | 125 | 525 | 60.3 | | | |
| Ethyl vanillin | 29.7 | 10 | 26.6 | 89.6 | 92.9 | 39.9 | 3.9 | 13 | Breakfast cereals | 300 | 910 |
| | | | | | | | | | Fats and oils | 0.153 | |
| | | | | | | | | | Milk products | 1403 | |
| | | | | | | | | | Conf. and frost. | 270 | |
| | | | | | | | | | Sweet sauce | 173 | |

| | | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|
| Eugenol | 2.18 | 1 | 3.79 | 14.9 | 21.3 | 2.75 | 102 | 100 | Conf. and frost. | 750 | 814 |
| Fennel, sweet, oil | 55.4 | 234 | 70 | 67.9 | 84 | 61.9 | 185 | 95.6 | | | 2 |
| *d*-Limonene | 199 | 812 | 437 | 512 | 500 | 452 | 79.7 | 20 | Gravies | 3 | |
| *d*-Menthol[b] | 16.1 | 15.9 | 63.5 | 591 | 53.2 | 70 | | | | | |
| Phenyl salicylate | 1.21 | 1.9 | 2.07 | 3.25 | 4.86 | 1.8 | | | | | |
| Peppermint oil | 47.4 | 282 | 175 | 1040 | 327 | 145 | 17.1 | | Processed fruit | 150 | 2127 |
| | | | | | | | | | Conf. and frost. | 800 | |
| | | | | | | | | | Jams and jellies | 730 | |
| | | | | | | | | | Sweet sauce | 300 | |
| Propylene glycol | 1239 | 5885 | | 1401 | 2441 | 685 | 534 | | Other grains | 8.4 | 5275 |
| | | | | | | | | | Fats and oils | 318 | |
| | | | | | | | | | Milk products | 377 | |
| | | | | | | | | | Cheese | 620 | |
| | | | | | | | | | Poultry | 100 | |
| | | | | | | | | | Egg products | 4.2 | |
| | | | | | | | | | Processed fruit | 5000 | |
| | | | | | | | | | Conf. and frost. | 50,858 | |
| | | | | | | | | | Sweet sauce | 4207 | |
| | | | | | | | | | Soups | 0.4 | |
| | | | | | | | | | Snack foods | 920 | |
| | | | | | | | | | Nut products | 63 | |
| | | | | | | | | | Gravies | 980 | |
| | | | | | | | | | Seas. flavoring | 151,990 | |
| Spearmint oil | 136 | 154 | 130 | 560 | 1318 | 95.4 | | 250 | Jams and jellies | 550 | 1796 |
| | | | | | | | | | Sweet sauce | 98.7 | |
| | | | | | | | | | Seas. flavoring | 66,668 | |
| Vanillin | 97.4 | 47 | 55.2 | 408 | 186 | 117 | 2.72 | | Breakfast cereals | 353 | 2092 |
| | | | | | | | | | Fats and oils | 100 | |
| | | | | | | | | | Milk products | 314 | |
| | | | | | | | | | Conf. and frost. | 768 | |
| | | | | | | | | | Sweet sauce | 363 | |
| | | | | | | | | | Snack foods | 200 | |

[a] The data used were from clove stem oil (vs clove bud or leaf oil) as it appeared to have the highest maximum use levels.

[b] The data used were from *d*-menthol (vs *l*-form) as the average maximum use levels reported are greater than those of the racemic mixture.

TABLE IX

TERMS DESCRIBING THE PHYSICAL OR TECHNICAL FUNCTIONAL EFFECTS FOR WHICH DIRECT HUMAN FOOD INGREDIENTS MAY BE ADDED TO FOODS

| | | |
|---|---|---|
| Anticaking agents | Flavoring substances and adjuvants | Processing aids |
| Antimicrobial agents | Flour texturizing agents | Propellants, aerating agents, gases |
| Antioxidants | Formulation aids | Separation/filtration aids |
| Colors and coloring adjuncts | Free-flow agents | Sequesterants |
| Curing and pickling agents | Fumigants | Solvents and vehicles |
| Dough strengtheners | Humectants | Stabilizers and thickeners |
| Drying agents | Leavening agents | Surface-active agents |
| Emulsifiers and emulsifier salts | Lubricants and release agents | Surface-finishing agents |
| Enzymes | Nonnutritive sweeteners | Synergists |
| Firming agents | Nutrient supplements | Texturizers |
| Flavor | Nutritive sweeteners | Tracers |
| | Oxidizing and reducing agents | |
| | pH control agents | |

flavor formulations are mixtures of many small-molecular-weight chemicals. Thus, it is not surprising that flavors have rarely been implicated in allergic reactions. Yet, several published examples of oral allergic reactions to flavors exist, and these are reviewed here.

## A. PUBLISHED EXAMPLES OF ALLERGIC REACTIONS TO FLAVORING SUBSTANCES

Most of the few published cases of allergic reactions to flavors have been reactions to flavoring substances found in toothpaste, dental supplies, tobacco products, hard candy, and chewing gum (Table X). These cases do not reflect the situation that exists for most flavored food products.

These reactions are contact sensitivity reactions resulting from the flavor acting as a hapten and binding to mucosal proteins in the mouth, thus eliciting a cell-mediated immune response. These contact sensitivity reactions require repeated exposure to comparatively higher concentrations of the offending substance and prolonged contact with the affected tissue. The reactions are localized and are likely delayed hypersensitivity reactions.

Balsam of Peru is the most notable of the many flavoring substances in its ability to induce such reactions. The major components of Balsam of

TABLE X

DOCUMENTED CASES OF ORAL SENSITIVITIES TO FLAVORS OR FLAVORING SUBSTANCES

| Substance | Patient reacted to substance found in | Reference |
|---|---|---|
| Anethole<br>found in oil of anise, star anise, and fennel | toothpaste | 71 |
| Anise oil | denture cream | 72 |
| Balsam of Peru | dentures, toothpaste | 73 |
| Carvone<br>main constituent of spearmint oil; also found in caraway oil | toothpaste | 71 |
| Cinnamon (cassia) and cinnamic compounds: cinnamon/cassia oil, cinnamic aldehyde, cinnamic acid, cinnamic alcohol | toothpaste, chewing and bubble gum, mouthwash tablets, breath spray, hard candy, antacid, dental cleaner | 74–82 |
| Clove oil | dental cleaner | 80 |
| Eugenol<br>integral part of oil of carnation, oil of bay, and other essential oils | oral postsurgical dressing, temporary cavity preparation, dental cement, impression paste | 83, 84 |
| Menthol | toothpaste, cigarettes, hard candy | 83–88 |
| Peppermint oil<br>free menthol (45%), limonene, pinene | toothpaste | 71–86 |
| Spearmint oil<br>carvone (50%), limonene, pinene | toothpaste | 72–86 |

Peru are listed in Table XI (89,90). Several components of Balsam of Peru (cinnamic aldehyde in particular) are notorious contact sensitizing agents (74). Most reported reactions to Balsam of Peru occur from its use in cosmetics (90) and over-the-counter (OTC) drugs where frequent and prolonged exposure enhances the likelihood of contact sensitization.

Thus, reactions in the oral cavity associated with the use of Balsam of Peru in toothpaste and dental materials are not surprising. Similar com-

TABLE XI

COMPONENTS OF BALSAM OF PERU

| | |
|---|---|
| Cinnamic aldehyde | 2% |
| Cinnamic alcohol | 2% |
| Cinnamic acid | 5% |
| Methyl cinnamate | 0.5% |
| Eugenol | 5% |
| Vanillin | 10% |

ments could be made about the other flavor substances involved in oral contact sensitivities noted in Table X. Balsam of Peru is also allowed for use as a food flavoring substance, although it is not commonly used. Foods containing Balsam of Peru include products containing citrus peel (marmalade, baked goods, juice), products flavored with essences (baked goods, candy, chewing gum), ice cream, some nonalcoholic beverages, and products made with cinnamon, cloves, or vanilla. Contact sensitivity reactions to foods containing Balsam of Peru have been documented (91–93). Typical usage levels are listed in Table VIII, with the highest concentrations used in chewing gum and hard candy. Sensitization to Balsam of Peru almost certainly occurs through dermal exposure. The individuals described in earlier studies of sensitivities to Balsam of Peru in foods (91–93) were likely sensitized through exposure to Balsam of Peru in cosmetics and OTC drugs, although they do react to Balsam of Peru in ingested foods thereafter in some cases (91–93). A cook who was sensitized to cinnamon was observed by Fisher (94). The patient's chronic hand eczema cleared upon avoidance of contact with cinnamon, but he suffered from a subsequent flare of dermatitis and from urticaria whenever he drank vermouth, which contains cinnamates. Another individual was observed who had marked positive reactions to Balsam of Peru, oil of cinnamon, and cinnamic aldehyde, and suffered from generalized urticaria whenever he drank soft drinks containing these substances (94). The mechanism of these adverse reactions to Balsam of Peru is not known but several of the active components, for example, cinnamic aldehyde, are known to act as haptens. Thus, these are likely cell-mediated, delayed hypersensitivity reactions.

IgE-mediated allergic reactions resulting from other flavoring substances in typical food products are even more rare, and in such cases the flavoring contained well-known allergens from milk or peanuts. While the principal examples involve milk, similar situations could arise with the use of proteins from other prominent allergenic foods (soy, wheat, eggs, peanuts, tree nuts, etc.) found in Table II. In a report by Gern *et al.* (95), four patients had reactions after eating foods that were labeled "nondairy" or "pareve" (containing no milk products), either a beef hot dog (two cases) or a bologna product (two cases). Traces of milk protein were found in these products. On each occasion, a parent had carefully read the product label in order to avoid exposing the child to foods containing milk or milk proteins. Each of the patients had subsequently eaten different brands of similar foods without experiencing adverse reactions. The manufacturer of the hot dog and bologna stated that the "natural flavorings" component of the product formulation had recently been changed from yeast autolysate to hydrolyzed sodium caseinate. Since hydrolyzed sodium caseinate was considered a "natural flavoring" by this manufacturer, it was determined that it was

unnecessary to specifically list the flavoring ingredient on the label. However, enough milk allergen existed in the product to elicit allergic reactions in milk-allergic individuals. Under current FDA regulations, hydrolyzed sodium caseinate must be labeled on such consumer products.

St. Vincent and Watson (96) documented the cases of two patients who developed allergic reactions after ingesting an unsuspected source of cow's milk protein found in dill pickle-flavored potato chips. The package label listed "dill pickle seasoning," but not milk or milk products as an ingredient. Information from one manufacturer showed that the dill pickle seasoning contained whey as an ingredient. Another manufacturer who makes dill pickle-flavored chips did not list milk as an ingredient, but includes lactose and "spices." The lactose was derived from cow's milk, and may contain residues of milk proteins (96).

In 1993, the Food Allergy Network and Kellogg's Company (97) jointly alerted allergic individuals that the new Kellogg's Rice Krispies Treats Cereal contained natural and artificial flavorings that may contain milk proteins, in an effort to prevent milk-allergic individuals from inadvertently consuming a product that contained milk proteins but was not labeled as such. The ingredient statement originally reflected only the presence of natural and artificial flavorings.

In 1996, a similar episode occurred involving a soup product sold by Fantastic Foods, Inc. (98). The flavoring in the soup contained peanut flour and elicited an allergic reaction. The ingredient statement revealed only the presence of natural flavors.

Persons allergic to milk and peanuts, including those who read product labels carefully, may consequently continue to be exposed to quantities of milk and peanut proteins sufficient to cause generalized reactions. Physicians should therefore consider this possibility in patients with milk and peanut sensitivity who have adverse reactions of unclear origin.

Some of the most commonly used flavoring substances are spices. The most common spice allergy is mustard; the allergens from mustard have been identified (99–102). Other spices that have been known to cause allergic reactions are allspice (103), anise (101,104,105), caraway (106), cardamon (107), clove (103), coriander (105–107), cumin (104), curry (103–105), dill (100), fennel (104–108), ginger (103–105), mace (109), nutmeg (104), paprika (103), parsley (110), pepper–cayenne (106), pepper–red (104), and pepper–white (103–105).

Difficulties in distinguishing between irritant and allergic reactions from spices are well noted. Skin tests from some spices are notorious for false-positive responses. Even in modest amounts, putting cinnamon on the skin can cause a wheal and flare in a nonallergic individual due to irritation caused by the spice. Thus, while some of the reported adverse reactions

to spices are probably true IgE-mediated reactions, others may be irritant reactions with false-positive skin tests. While allergic reactions to spices have been reported more frequently than allergic reactions to other flavoring substances, such sensitivities are still considered rather rare.

## B. LIKELIHOOD OF ALLERGIC OR INTOLERANCE REACTIONS OF FLAVORING SUBSTANCES

### *1. Allergic Reactions*

IgE-mediated allergic reactions to flavor substances are unlikely for several reasons: (1) virtually all allergens are proteins (3,4) and proteins are infrequently used in flavors, (2) when proteins are used as a flavor or flavoring substance, the proteins used are rarely allergenic proteins, (3) in some cases, if an allergenic protein is used, the manufacturing process will remove the protein fractions through refinement or distillation, and (4) if an allergenic protein is used and the protein survives the manufacturing process, in most cases it will be at such a low level that it would not elicit a reaction from an allergic individual. If the source of the flavoring substance is not allergenic, then the flavoring substance will not be. If the source is allergenic then it must be determined if any protein survived the manufacturing of the flavor, and if it remains allergenic. As noted above, few flavor substances contain allergenic proteins.

Delayed hypersensitivity or cell-mediated allergies are also unlikely to occur with flavor substances except in a few special circumstances. Cell-mediated reactions involving proteins, such as celiac disease, are highly unlikely due to the reasons noted above.

It also must be determined if the ingredient can act as a hapten. Nonproteinaceous, low-molecular-weight flavoring substances can sometimes act as haptens. Haptens will more frequently elicit cell-mediated reactions than IgE-mediated sensitivities. Cinnamic aldehyde is an outstanding example. However, to cause a cell-mediated response, the flavoring ingredient (1) must be reactive with proteins; (2) must be present in comparatively large amounts in the food product; (3) as the protein–hapten complex, must survive digestion or react in the oral cavity; and (4) must have a long residence time in the oral cavity for localized oral reactions. Contact sensitivity, a form of cell-mediated reaction, has occurred in the oral cavity with highly reactive flavoring substances in toothpaste, chewing gum, or hard candy. These cases are limited to the few flavoring substances that can act as haptens, bind to proteins, and elicit immune responses in the oral mucosa. However, such reactions have not been documented with other food applications of these same flavoring ingredients. Substances

used as flavoring substances that are associated with contact sensitization are listed in Table XII. However, the contact sensitization reactions are primarily associated with cosmetic use and not with the use of flavors in foods. Such reactions in food would be more likely to occur in prolonged exposure situations as with cosmetics, toothpaste, dental materials, and perhaps chewing gum and hard candy. Contact sensitivities could also conceivably occur from handling of flavor preparations in occupational settings. The low concentrations of flavoring substances in food, the diversity of flavoring substances used in foods, and the comparatively short contact time with specific tissues argues against contact sensitivity as a mechanism for adverse rections to food flavor substances, except in a few unique circumstances.

Contact dermatitis to flavors was first described in 1993 by Hutchinson (111), who mentioned a skin eruption caused by vanilla. Later case reports identified flavors in toothpastes, dental preparations, and cosmetics as causes of allergic contact dermatitis in cheilitis, gingivostomatitis, or hand eczema. Some of the allergic reactions described in Table X, especially those involving toothpaste and various dental and denture products, are most likely contact sensitivity reactions.

TABLE XII

SOME COMMON FLAVORING SUBSTANCES REPORTEDLY ELICITING MUCOSAL CONTACT SENSITIZATION REACTIONS

| Substance | Reference |
|---|---|
| Anise oil (anethole) | 71, 72, 112 |
| Balsam of Peru | 73, 76, 79, 89, 90, 92, 113–133 |
| Carvone | 71 |
| Cinnamic acid | 89, 125 |
| Cinnamic alcohol | 125, 126, 134 |
| Cinnamic aldehyde | 71, 74, 77, 79–81, 89, 125, 126, 135, 136 |
| Cinnamon (cassia) | 74, 78, 79, 82, 118 |
| Cinnamon (cassia) oil | 75, 76, 80, 81, 129, 130, 136 |
| Ethyl vanillin | 129, 130 |
| Eugenol (oil of clove) | 76, 80, 84, 125, 134 |
| Fennel oil (anethole) | 71, 72 |
| *d*-Limonene | 129, 137 |
| Menthol | 71, 82, 85–88, 138, 139 |
| Peppermint oil (menthol) | 71, 86 |
| Phenyl salicylate | 140, 141 |
| Spearmint oil (carvone) | 71, 86 |
| Vanillin | 88, 90, 125, 131 |

### 2. *Intolerances*

Other types of food intolerances are unlikely to occur with flavoring substances. Known metabolic food disorders do not involve flavoring substances. In addition, such reactions display high thresholds, and the low concentrations of flavoring substances would not likely exceed these thresholds. The identities of food-borne substances involved in non-IgE-mediated histamine release reactions remain unknown, but no evidence exists for an association with food additives, including flavoring substances. The role of flavoring substances in idiosyncratic reactions is also speculative since the association with food remains to be established with most of these reactions. In these cases as well, high threshold responses have been noted with the well-documented idiosyncratic reactions, such as sulfite-induced asthma, and the low concentrations of flavoring substances would not likely exceed such thresholds. Sulfites are not widely used in flavoring formulations.

Adverse reactions to flavor enhancers, such as monosodium glutamate, and related flavor enhancers, such as hydrolyzed vegetable protein and yeast autolysate, would be classified as idiosyncratic reactions. Flavor enhancers may be defined as compounds exhibiting little or negligible odor and taste, but they magnify, usually manyfold, the characteristic flavor of certain food substrates when used in small or even trace amounts. The flavor enhancers used in food are primarily MSG, yeast autolysate, hydrolyzed proteins made from soy, wheat, corn, gelatin, casein, and other sources, and several nucleotides. The involvement of MSG in these idiosyncratic reactions remains to be proven. While numerous adverse reactions have been attributed to MSG, especially in the lay media, a recent and extensive review of MSG conducted by a group of independent scientists under the auspices of the Federation of American Societies for Experimental Biology (FASEB) helped put these safety concerns into perspective and reaffirmed the Food and Drug Administration's belief that MSG and related substances are safe ingredients for most people when eaten at customary levels (142). Some evidence exists to suggest certain people may develop short-term reactions (flushing, etc.) when they consume large doses (3 g or more) of MSG (142). No evidence was found linking the "MSG Symptom Complex" to consumption of low levels of MSG (142). There may be a small subgroup of people with severe asthma who respond to large doses of MSG (3 g or more) (145). However, the mechanism is unknown, and the role of MSG in asthma has not been confirmed (55,56,143). While a complete discussion of MSG and its possible role in idiosyncratic reactions is beyond the scope of this review, the level of MSG in the diet originating from flavor formulations would be insufficient (far below 3 g) to elicit the adverse reactions noted in the FASEB report.

The FASEB report indicates that no evidence exists for allergic reactions to such ingredients as hydrolyzed proteins and yeast autolysates (142). Fully hydrolyzed proteins would be mixtures of amino acids, including glutamate, and would be unlikely to elicit adverse reactions in the levels used in flavoring formation (see the preceding MSG discussion). Thus, reactions from MSG and fully hydrolyzed proteins (1) have not been proven, (2) remain highly controversial, and (3) would not be true allergic reactions in any case but fall under the category of idiosyncratic reactions (56,142,143). Furthermore, allergic reactions to yeast autolysates would not be expected except on rare occasions, because few individuals have IgE directed toward yeast protein. However, the partially hydrolyzed proteins from commonly allergenic sources such as soy, wheat, and casein could induce true IgE-mediated allergies if the allergenic epitopes remained intact after hydrolysis. In the United States, hydrolyzed proteins must be listed and declared by source when used as flavor enhancers or for other technological functions, including flavoring.

Thus, both scientific logic and experience dictate against a major role for flavoring substances in allergic and other sensitivity reactions, except in those cases when a large quantity of a known allergen is added to the flavor formulation.

### C. OCCUPATIONAL SENSITIVITIES

Occupational sensitivities to flavor substances are unlikely to occur. Furthermore, they would not provide clues to adverse reactions in consumers exposed to much lower amounts of these substances. If occupational sensitivities due to flavor substances existed, it would be found in flavor manufacturing sites where the workers would be exposed to higher levels, rather than in food manufacturing. Hand eczema due to contact allergy to spices was found in growers and handlers of spices and people who have frequent contact with spices such as bakers, confectionery/candy makers, chemists, cooks, and homemakers (74,103,129,131,134,144). Garlic, onion, lettuce, endive, parsley, and carrots were reported to be responsible for most hand contact dermatitis in homemakers and catering workers (145). Very few, if any, occupational sensitivities due to inhalation of flavoring substances have been reported. Garlic and onion sensitivity has been documented only at high levels found in dehydration facilities (145–147).

## V. APPROPRIATE DIAGNOSTIC TESTS FOR INVESTIGATION OF SENSITIVITY TO FOOD FLAVORING SUBSTANCES

Allergists frequently encounter patients who provide histories of recent adverse reactions to a specific food product. If the historical account is

convincing and if the patient has a known food allergy, the physician should suspect that the patient has inadvertently ingested that food even if a source of that food is not clearly identifiable on the package label. Cross-contamination can occur in the food and food service industries from the use of shared equipment or inadequate clean-up procedures. For example, Yunginger *et al.* (148) described reactions to peanut residues remaining in sunflowers seed butter from the use of shared equipment. A determination can be made regarding the presence of that particular allergenic food in the incriminated product using the RAST inhibition assay or some similar test (149). If this patient does not have a known food allergy or if the known allergenic food is not detected in the incriminated product, the physician must first confirm a cause and effect association between the incriminated food product and the alleged adverse reaction using challenge procedures as documented below. If a positive response is observed in the challenge test, then the search for the causative ingredient in the food product must commence. Since the ingredients are listed in descending order of prevalence on the label, the obvious strategy would involve testing these ingredients in their descending order of prevalence. Skin testing could be conducted initially if an IgE-mediated reaction was suspected. However, a challenge test is again the best means of establishing a cause and effect relationship.

Since flavors are grouped and usually appear at or near the end of the ingredient list on a food label, they are the least prevalent ingredients in most foods. However, the physician occasionally encounters negative results from evaluation of the more prevalent ingredients, which results in a desire to evaluate the flavoring substances in the product. An approach for evaluating the likelihood of the involvement of flavoring substances in allergic reactions is provided in Table XIII. The assessment strategy detailed in Table XIII presumes that alternative explanations as noted above have been considered and eliminated. Since flavor formulations are proprietary and are quite complex in most foods, physicians should seek information from the food manufacturers and flavor suppliers in such assessments. Flavor formulations are confidential information that is the "life-blood" of the flavor industry. However, there are certain conditions under which the flavor industry must be willing to disclose enough formula information for a physician to treat a patient. Normally verbal communication between the physician and the manufacturer will suffice. If the patient has known food allergies, celiac disease, or contact sensitivity, then the physician may be able to make a probable diagnosis, without need for further testing, if sources of known offending substances are found in the flavor formulation. Flavor manufacturers should be able to provide information on the protein content and origin of flavors. Skin tests, patch tests, and double-blind,

## TABLE XIII

APPROACH TO THE DIAGNOSIS OF ALLERGIC REACTIONS TO FOOD FLAVORS

I. Systemic reactions (anaphylactic shock, generalized urticaria, dermatitis, gastrointestinal symptoms, etc.)
   A. Does the patient have a history of known IgE-mediated food allergy?
      If yes, continue and answer parts a–d. If no, go to No. 2.
      1. Does the food contain any dual-functional flavors?[a]
         a. What is the flavor source material?
         b. Was it derived from an allergenic source?
         c. Does it contain proteins from that source?
         d. Does the source match with the sensitivity of the patient?
            If yes, the diagnosis is confirmed. If no, go to No. 2.
      2. Was the flavor formulation derived in whole or in part from an allergenic source?[b]
         If yes, continue and answer parts a–c. If no, the likelihood of involvement of the flavors in the allergic reaction is remote.
         a. What is that source?
         b. Does it contain proteins?
         c. Does the source match with the sensitivity of the patient?
            If yes, the diagnosis is confirmed. If no, do skin tests to assess allergenicity to other known allergenic sources in the formulation. Consider DBPCFC to confirm positive skin test. Positive skin tests confirm the diagnosis.
   B. If the patient has a history of celiac disease, answer the following:
      1. Does the food contain any dual functional flavors?[a]
         If yes, continue and answer a and b. If no, go to No. 2.
         a. Was the ingredient derived from wheat, rye, barley, triticale, or oats?
         b. Does it contain proteins from that source?
            If yes, the diagnosis is confirmed. If no, go to No. 2.
      2. Was the flavor derived in whole or in part from wheat, rye, barley, triticale, or oats?[b]
         a. Does it contain proteins?
            If yes, the diagnosis is confirmed. If no, consider other sources in the patient's diet for this delayed type of hypersensitivity.

II. Localized oral reactions
   A. If the patient has a history of known IgE-mediated food allergy, repeat parts 1 and 2 from Part I,A.
   B. If the patient has a history of contact sensitivity to cosmetics, answer the following:
      1. Does the flavor formulation contain any known contact sensitizing substances? (see Table XII)[b]
      2. Does the flavor formulation contain any substances that are highly reactive with proteins?[b]
         If yes, continue and answer part a and consider patch tests of those substances to confirm diagnosis. If no, the involvement of the flavors in the allergic reaction cannot be confirmed.
         a. Is this substance present in high proportion in the flavor formulation?

[a] The food manufacturer should be able to answer this question in most cases. Dual functional flavors are ingredients used for more than one purpose.

[b] The food manufacturer can only answer this question after consultation with flavor supplier(s).

placebo-controlled challenge tests can be considered to suggest and confirm possible diagnoses of the role of flavors in allergic reactions, but are unlikely to be necessary except in very unusual circumstances. The preferred approaches to challenge testing and skin testing for the causative agent are provided below.

## A. CHALLENGE TESTS

The double-blind, placebo-controlled food challenge (DBPCFC) is considered the "gold standard" for the diagnosis of adverse reactions to foods (150). This procedure should have similar status in the evaluation of the adverse reactions to food ingredients including flavoring substances. The best use of the DBPCFC is to confirm or refute a cause and effect association between the adverse reaction and the specific food product. Any challenge tests should be conducted using the oral route of exposure since the alleged adverse reaction also involved that route of exposure. If the incriminated food is available, the double-blind challenge should be done with the product. If the actual incriminated food is not available, an identical product purchased from the marketplace is the next best choice. The physician may wish to conduct a skin test using a freshly prepared extract of the whole food before conducting the challenge test. A positive response in the skin test may indicate the presence of an allergenic food in the product, whether acknowledged on the label or not. If the patient has a known food allergy, the physician may want to search for the presence of that allergenic food in the product before conducting a direct challenge test. If the patient does not have a known food allergy, a positive skin test may indicate the existence of an IgE-mediated allergy to one of the ingredients in the specific food product. With a positive skin test, the physician should approach the challenge test with some caution since patients with positive skin tests are more likely to react in the challenge trial. Extra precautions would need to be exercised in the challenge test especially if severe reactions are thought possible. Challenge studies will have some serious limitations for the evaluation of adverse reactions to flavors and flavoring substances. It will be especially difficult to identify the specific flavoring substance responsible for any adverse reaction. It is, in general, only necessary to determine the protein content and source. Flavoring formulations are also difficult to disguise so adequate placebo controls are difficult to obtain. Finally, flavors are typically used at rather low concentrations, so the amount used in the DBPCFC should be similar to the level encountered in food applications. Since flavor formulations are difficult to acquire and use in such challenge tests, their use is not advocated in the approach outlined in Table XIII.

Where they are used, the evaluation of adverse reactions to the flavoring formulation rather than the individual flavoring substances would suffice for diagnostic purposes.

## B. SKIN TESTS

The skin pick test is probably the most frequently used test for the diagnosis of IgE-mediated allergies including food allergies. The skin prick test is typically conducted by the prick/puncture method with diluted (1 : 10 or 1 : 20) extracts of the specific food or food ingredient. A positive skin test is indicated by the development of a wheal at the puncture site that is 3 mm or larger in diameter than a diluent control wheal measured within 10–30 min of treatment. The proper application of the skin prick test in the evaluation of food allergies has been described by Bock *et al.* (151).

Skin tests may be quite useful for the detection of allergenic foods in a food product incriminated in a specific incident. If the patient is known to have food allergies, then a search should be made for sources of those specific foods in the product. If the patient does not have a history of food allergies, a positive skin test may indicate the existence of such an allergy to some component of the incriminated food product.

However, the use of skin tests in the evaluation of adverse reactions to food flavoring substances or formulations is limited. Skin tests identify the presence of IgE-binding allergens, which are typically proteins of natural origin. As discussed earlier, flavors and flavoring substances will not often contain such ingredients. Most frequently, flavors will be mixtures of small-molecular-weight chemicals that are not likely allergens. If the patient has a known food allergy, a skin test with the product's flavoring formulation could be used to confirm the presence of an allergenic protein, probably from that source in the formulation. If other sources of proteins are identified in the suspect flavor through the assessment approach outlined in Table XIII, skin tests could be used to assess the possible existence of allergic sensitivity to those foods. However, in any other situation, the use of skin tests must be approached with care because of the likelihood of false-positive reactions. Many of the chemicals used in flavors may be irritating to the skin even in modest amounts. Therefore, the injection of small amounts of an undiluted flavor may cause an irritational response, which can be easily read as a false positive. Even with dilution, this possibility will exist. Control skin tests must be conducted on nonsensitive individuals to identify such false-positive responses. The ideal diluent for flavor or flavoring substance is buffered physiological saline. Histamine is used as a positive control substance for skin testing.

### C. PATCH TESTS

Patch tests are used in the diagnosis of contact sensitivity reactions. A patch test involves applying a specific substance to the skin with the intention of producing a small area of allergic contact dermatitis. The patch test is generally placed on the skin for 48–72 hr and then observed for the appearance of localized dermatitis. The test material is applied to a small area of the skin and covered by gauze held in place with tape. The concentration of the test material is critical, but, in the case of flavors, the concentration should not exceed the level found in the suspect food by more than severalfold. False-positive reactions can occur with patch testing especially with irritant substances. Since some flavoring substances likely have irritant properties, precaution must be taken to avoid misinterpretation of the results. The use of relevant concentrations is one reasonable precaution. The comparison to results obtained with normal, control individuals should also help to identify false positives. Patch tests could be extremely useful in the diagnosis of contact sensitivity reactions to flavors found in food products such as chewing gum and hard candy where the exposure to the flavor might be sufficiently long and frequent to induce such reactions.

## VI. CONCLUSIONS

Flavoring substance in food are highly unlikely to elicit adverse reactions among consumers. The extremely low amounts of individual flavoring substances used and the wide variety of such flavoring substances in foods argues against any significant role for these substances in the adverse reactions of foods. The nonprotein nature of most flavoring substances implies that these substances will not likely be involved in IgE-mediated allergic reactions or celiac disease. While some of these chemicals could possibly act as haptens to initiate an IgE-mediated response, this mechanism is unlikely given the low usage levels of flavoring substances and the effect of digestion on protein–hapten complexes. However, contact sensitivity reactions may occur in some situations where prolonged oral exposure occurs to a flavoring substance, for example, chewing gum or hard candy. Other forms of food intolerances are unlikely to be triggered by flavoring substances because affected consumers typically have a finite tolerance for the offending food with these illnesses. The small amounts of flavors used in foods would argue against the involvement of flavoring substances in such food intolerances.

Flavors do occasionally contain food proteins in small quantities. If these proteins are obtained from known allergenic foods such as peanuts or

cows' milk, listed in Table II, then these particular flavors might trigger IgE-mediated allergic reactions in allergic consumers. However, the very low quantities of proteins from the flavors in the final product would in most instances likely result in a mild adverse reaction by comparison to other types of inadvertent exposures to the same protein, except in the cases when higher levels are added for dual functionality as mentioned earlier.

The term "food allergy" should only be applied to immunologically based adverse reactions invoked by food. In cases where the patient has a known food allergy, the presence of that allergenic food should be sought in the incriminated food product before any consideration is given to possible adverse reactions to flavoring formulations. The role of flavoring substances in any adverse reaction should be confirmed by DBPCFC using appropriate dosages of the flavoring substance(s) and effective blinding approaches with the objective assessment of symptoms wherever possible.

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