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INFLUENCE OF FOOD ADDITIVES AND CONTAMINANTS (NICKEL AND CHROMIUM) ON HYPERSENSITIVITY AND OTHER ADVERSE HEALTH REACTIONS – A REVIEW

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This article is focused mainly on the influence of food additives such as natural and artificial food colouring, conservative agents, antioxidants, flavour enhancer, sweeteners and unintentional trace contaminants present in food, such as nickel and chromium, which cause serious disorders of a human organism.

Food additives may induce an adverse reaction of atopic patients and provoke clinical symptoms including first of all dermatitis, rhinitis and asthma, urticaria, angioneurotic edema, and contact urticaria. Systemic and respiratory reactions to food colorants and benzoates have been claimed to occur more frequently in acetylsalicylic acid-sensitive patients than in the non-reactors. Hypersensitivity reactions in organs other than the skin and respiratory tract are rare or poorly documented. The literature data indicate that food additives are suspected to stimulate hyperactivity and psychoneurotic reactions too.

INTRODUCTION

Food additives and preservatives have been used for thousands of years. In industrialized nations, the last 50 years have seen a significant increase in the number of preservatives and additives introduced to foods before they go to market. The growth in the use of food additives has increased enormously in the past 30 years, totaling now over 200,000 tonnes per year. Therefore it has been estimated that as today about 75% of the Western diet is made up of various processed foods, each person is now consuming on average 3.6-4.5 kg of food additives per year. With the great increase in the use of food additives, there also has emerged considerable scientific data linking food additive intolerance with various physical and mental disorders, particularly with childhood hyperactivity and hypersensitivity [Feingold, 1973; Smith, 1991]. Processed foods usually contain additives of some sort. The hypothesis that some of these additives can cause behavior and attention problems is continuously discussed. A wide range of adverse reactions is associated with food additives in approximately 0.03 to 0.23% of people and diagnosis is usually based on placebo-controlled oral provocation tests [Madsen, 1994; Wüthrich *et al*., 1993]. Prevalence of food additive intolerance in children is estimated at 1 to 2% and is mainly found in atopic children in whom the additive aggravates the existing hypersensitivity to some other substances [Fuglsang *et al.*, 1994; Madsen, 1994]. It is supposed that food additives or preservatives may induce symptoms of physical illness or intolerances, but a majority are not acknowledged by the medical community. Most adverse reactions to food additives do not involve the immune system and not provoke IgE reactions. Well-known are some forms of food intolerance, *e.g.* lactose intolerance. Generally, the elicit mechanisms are not well understood, but possibly involve direct mast cell and basophil histamine release.

FOOD ADDITIVES IN THE LIGHT OF FEINGOLD HYPOTHESIS

Food additives are substances added to food in order to preserve its flavour or improve its taste and appearance. Some of them have been used for centuries, *e.g.* in preserving food by pickling with vinegar, salting meat or fish, adding sugar, or using sulphur dioxide in wines. Lately many new additives of both natural and artificial origin have been introduced to food. The application of some of the additives to food is open to debates and disagreements whether they should be allowed at all. Moreover, many claim that certain substances may be the cause of different health disturbances such as allergies, migraines, hyperactivity in children, and several other adverse reactions. The exact mechanism of the influence of food additives on health has not been fully recognized yet.

Many causal hypotheses for childhood hyperactivity have been addressed in both medical and psychiatric literature including; genetic factors, implications of the central nervous system dysfunction, improper embryological development or subtle chromosomal irregularities, birth complications, and unforeseen interactions in a human body [Kuntsi & Stevenson, 2001; Tanaka *et al*., 2008].

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Benjamin Feingold, M.D., was one of the first physicians to speak out against food additives [Young, 1997; Schab & Trinh, 2004]. His special interest was the effect of food chemicals on children's behaviour and the role of nutrition in treating learning disabilities. In 1973 he announced that salicylates, artificial colours, and artificial flavours caused hyperactivity in children. Actually, hyperactivity is medically classified as Attention Deficit Disorder (ADD) or Attention Deficit Hyperactivity Disorder (ADHD). To treat or prevent this condition, Feingold suggested a diet that was free of any chemical substances. Many parents who followed Feingold's recommendations have reported improvement in their children's behaviour but now there is a lot of controversial information concerning this approach. After collecting evidence based on over 1,200 cases, de la Rey [http://www.healthyoptions.co.nz] found that hyperactivity, including other neurophysiological disturbances, can be induced in some children when they consume certain chemicals such as food additives, as well as some naturally occurring salicylates. Feingold arrived at this conclusion by observing that certain children, who seem to react neurophysiologically to aspirin, reacted also in a similar manner to natural foods containing salicylates [Feingold, 1973]. Studies undertaken at that time pointed out to the still controversial problem of health consequence of food additives. Below there are described the most popular substances added to food and some health problem connected with them.

FOOD COLOURING

The colour of food products is extremely important because it influences directly the perception of both the flavour and quality of a food product and improves its sensory properties, especially when processed food loses an attractive appearance due to high temperature or enzymatic modification. In 1960 the US Congress passed the Color Additive Amendment [Burrows, 2006]. This was a federal law that required all the dyes and colorants in food, drugs, or cosmetics to be tested for safety before being used in any item sold. Accordingly, out of many additives used nearly 200 substances were withdrawn. Today, there are fewer than 35 dyes approved by the FDA. Scientists have concluded the color additive may cause hives in fewer than one out of 10,000 people.

Natural colour additives

The immune mechanism involved in cases of adverse reaction to natural colour additives has not been investigated, but sometimes reports may be found on an IgE-dependent reaction directed to residue proteins present due to technological process [Lucas *et al*., 2001].

Carotenoids (E 160) as a group include above 600 different compounds soluble in oils and non-polar solvents. At present, there are 43 dyes known as red colouring additives used in foodstuffs, including among others beta-carotene and xanthophyll [Francis, 2000]. Reported cases of adverse reactions to natural colours belonging to the carotenoid colour family are rare. Juhlin study [1981] described 112 patients suffering from angioedema and recurrent urticaria who were orally administered 50 and 100 mg of carotene and 10 and 200 mg of canthaxanthin in open fashion during provocation tests to a variety of substances. Of the patients examined 10% had a positive challenge to carotene, but 14% had uncertain results; in turn 14% of the patients reacted positively to canthaxanthin, while 24% had uncertain results [Juhlin, 1981]. Carotenoids can cause allergic reactions especially in patients allergic to some kinds of vegetables. Most likely the main reason is the cross-reactivity between epitopes originating from carotenoids and some vegetables.

Annatto (E 160b) is a carotenoid-based dye extracted from seeds of a tropical tree *Bixa orellana* found by Spanish conquistadores in the New World. Incidents of an anaphylactic shock to annatto have been reported for a 62-year-old male after ingestion of a cereal mix which contained heat bran, corn bran, aspartame, corn syrup, vitamins A, C, D, B6, B12, thiamine, and annatto extract color [Nish *et al.,* 1991]. Within minutes, the patient developed symptoms characteristic of the anaphylactic shock, including generalized pruritius, generalized urticaria, angioedema of the eyes and lips, undetectable blood pressure, and loss of consciousness. A skin prick test for annatto, at the 1:10,000 dilution was negative while the test at 1:1000 dilution and full-strength tests were positive. The patient's serum was positive for the presence of an annatto-specific IgE when analysed by immunoblot. Nevertheless, the allergic reaction seems to be primarily because of the protein impurities rather than of the pigment fraction itself [Giuliano *et al.,* 2003].

Saffron is a perennial stemless herb of the *Iridaceae* family. The yellow dye saffron originates from the plant *Crocus sativus L,* cultivated in Spain, France and Greece. In the ancient times saffron was used as an anticancer agent. Saffron is used not only as a dye but also in unconventional medicine in conditions such as painful menstruations, lumbar pains, atonic dyspepsias, coughs, bronchial spasms, asthma and teething problems [Rios *et al.,* 1996]. The analysis of saffron protein allowed to identify specific IgE antibodies for saffron proteins, potential allergens, with molecular weights between 40 and 90 kDa and a relevant one in 15.5 kDa with profiline nature by SDS-PAGE followed by immunoblotting [Feo *et al.,* 1997].

Carmine (E120, Natural Red 4) is cochineal dye originating from dried and powdered secretions of gravid female Cochineal scale insects *Coccus cacti* (*Dactylopius coccus)*. The most probable mechanism involved in an adverse reaction to carmine is IgE-mediated allergy. Baldwin *et al.* [1997] described a woman who experienced anaphylaxis after ingestion of a popsicle coloured with carmine. Additional evidence was provided by the Prausnitz-Kustner test using patient's husband as a recipient to prove that the adverse reaction was IgE-mediated.

A number of cases of allergy to Campari wine coloured with carmine have been reported, too [Wüthrich *et al.,* 1997; Acero *et al.,* 1998; Steurich & Feyerabend, 2001]. In Wüthrich study four cases of adverse reactions were reported after the consumption of alcoholic beverages containing carmine. For instance, a 33-year-old atopic woman experienced urticaria and angioedema as a consequence of consuming Campari-Orange. Skin prick tests were positive for carmine supplied by diluted (1:1) Campari and weakly positive for a commercially available 0.5% carmine solution. Skin prick tests with carmine can be compromised on occasion by the solubility of carmine proteins. The RAST test for carmine was posi-

tive too. The second case reported was a 43-year-old woman who after drinking Campari-Bitter or Campari-Orange had rhinorrhea, eyelid edema, pruritus, and dyspnea. In the third case, an atopic 25-year-old woman reported sneezing, rhinitis, nasal obstruction, angioedema, widespread urticaria and dyspnea within 30 min since the consumption of a Campari--Orange beverage. Skin prick tests were positive with Campari and carmine, but negative with commercially available carmine. The RAST for carmine was positive. In the fourth case, after drinking Campari-Orange, a 39-year-old woman developed acute urticaria with angioedema of the face within 30 minutes. After 30 minutes, skin prick tests performed using Campari carmine were positive. Skin prick tests using commercially available carmine were negative. The RAST for carmine was positive [Wüthrich *et al.,* 1997].

Sensitization to carmine may take place by oral intake, by inhalation or *via* the skin. Food intolerance and occupational asthma following exposure to carmine in sausage manufactures were showed in the study by Ferrer *et al.* [2005].

Curcumin (E100) is the major component of turmeric rhizomes of the *Curcuma longa,* a popular perennial plant cultivated in India, China and Indonesia, becoming also increasingly popular in the Western society in products such as nutritional food supplements. The active component of turmeric is curcumin, a polyphenolic photochemical with anti-inflammatory, antiamyloid, antiseptic, antitumour and antioxidative properties. There is some information about its antiallergenic properties with an inhibitory effect on histamine release from the mast cells. Curcumin downregulates Th 2 response through decreased recruitment of eosinophiles, reduced IgE antibody and cytokine production and lesser inflammatory responses [Kurup & Barrios, 2008]. On the other hand, there are a few studies concerning allergic contact dermatitis among people who worked with animal fur dyes [Swartz *et al.,* 1957] and in pasta factories [Kiec-Świerczynska & Krecisz, 1998]. There were also reported a couple of cases of allergic contact dermatitis caused by curcumin classified as IV type of hypersensitivity. Two cases of contact urticaria were apparently produced by two completely different mechanisms: one immunologic and the other non-immunologic. With the increasing use of this spice one can expect a rise in the number of curcumin allergy cases [Liddle *et al.,* 2006].

Enocianina (E163) origins from grape. Numerous adverse reactions, sensitivities and confirmed allergic reactions following ingestion of grapes and the products thereof have been reported in literature [Guinnepain *et al.,*1998; Sbornik *et al.,* 2007; Brito *et al.,* 2008], but it did not concern a grape skin extract or a grape colour extract. Wine is the most popular product containing a grape extract along with such food proteins as casein, milk, egg white, or fish-derived isinglass, and particularly trace amounts of these proteins can cause allergenic reactions. Therefore, international legislation requires labelling wines revealing the potential allergenic source of food proteins since there were reported patients with confirmed immunoglobulin E-mediated relevant food allergy [Rolland *et al.,* 2006]. The cases of occupational asthma in grape farm workers in the Western Cape originate mainly from the contact with spider mite, *Tetranychus urticae*, quite popular in this region [Jeebhay *et al.*, 2003].

Artificial food colourants

The adverse reaction, first time described in 1959 as asthma, hypersensitivity and urticaria caused by the synthetic aniline dye tartrazine pointed out to the influence of artificial food colourants as factors which may initiate clinical health problems including migraine, blurred vision, itching, and rhinitis [Rangan & Barceloux, 2009].

Tartrazine/ E 102/Yellow No. 5 is used as the yellow and orange colourant for food and drugs, but can also be used with Brilliant Blue FCF or Green S to produce various green shades. The prevalence of food intolerance to azo-dyes has been estimated to range between 0 and 0.12%. Neuman *et al*. [1978] found that an oral administration of 50 mg of tartrazine to 122 patients suffering from allergy-related disorders evoked the following reactions: feeling of suffocation, weakness, heat sensation, palpitations, blurred vision, rhinorrhoea, pruritus and urticaria. Even though 50 mg could be considered as a substantial dose, such a quantity of tartrazine could easily be consumed by an individual drinking only a few bottles of soft drinks per day. Until recently tartrazine has been perceived as the most common allergy trigger, especially among patients with aspirin intolerance and asthma. In Virchow study, in which one hundred and fifty-six German, Italian and Polish patients with confirmed aspirin-induced asthma underwent open oral challenges with increasing doses of tartrazine up to 25 mg, only 4 out of 156 patients (all Polish) had positive reactions in a double-blind test [Virchow *et al.,* 1988]. Actual opinion is that there is no scientific evidence that tartrazine provokes asthma attacks or that people who react to aspirin have a cross-sensitivity to it as it has been claimed in the past. But tartrazine can be an aggravating factor in atopic dermatitis. Some research has linked Yellow No. 5 to Early Childhood Obsessive-Compulsive Disorder and hyperactivity [Ward, 1997]. Tertrazine is banned in Austria and Norway, but is still legally used in the UK.

There are suggested a few immune mechanisms of tartrazine intolerance. The most popular one concerns the inhibition of cyclo-oxygenase, characteristic for aspirin intolerance, in which intolerance is explained as possible cross-reactivity between aspirin and E102 [Kurek & Grubska-Suchanek, 2001]. Other possibilities include the inhibition of platelet aggregation and increase in leucotriene synthesis, but they are less popular. A recent study carried out in the Clinical and Laboratory Investigation Circle for Food Allergy Medicine in France reported only one case of tartrazine intolerance among 703 declarations of food intolerance or food allergy [Elkhim *et al.,* 2007]. Whenever added to foods, it must be listed on the product's label.

Blue No. 1/Brilliant Blue FCF/ E133 creates a medium blue shade. This colourant was banned in Austria, Belgium, Denmark, France, Germany, Greece, Italy, Norway, Spain, Sweden, and Switzerland, but has since been allowed back into most of the EU countries. Blue No. 1 can be found in some dairy products, sweets, and drinks. Coal tar is one of its components; therefore, many organizations and circles are speaking out and boycotting it due to its carcinogenic properties shown in studies reporting tar induced tumours in lab rats. There were no observed any cases of hyperactivity after ingestion of foods containing Blue No. 1. Zillich with

coworkers [2000] reported a case of a 11-year-old girl who developed pseudocyanosis after consuming food containing FD&C Blue No. 1 (Brilliant Blue FCF).

Green No. 3/Fast Green FCF can be used for tinned green peas and other vegetables, jellies, sauces, fish, desserts, and dry bakery mixes at the level of up to 100 mg/kg. It is poorly absorbed by the intestines. Although it is certified for use in foods, it may cause chromosomal aberrations upon oral exposure in mice and inhibit the release of neurotransmitters in rats [Van Hoff, 2002].

Indigotine (E133)/Blue No 2 is commonly used in pharmacy to coat tablets and capsules, but is also added to ice cream, sweets, baked goods, confectionery, and cookies. There have been observed allergic reaction cases to Blue No. 2. (*e.g.* occupational asthma), [Miller *et al.,* 1996].

Allura Red AC (E129)/Red No. 40 has the appearance of dark red powder. Red No. 40 can be found in sweets, drinks, condiments, medications, and cosmetics. Allura Red is banned in Denmark, Belgium, France, Germany, Switzerland, Sweden, and Austria and in the USA. It was once feared as carcinogenic, but this has since been disproved [http://ec.europa.eu]. It has, however, caused allergic reactions in people as well as hyperactivity in children. The studies on reproduction and embryotoxicity including teratogenicity revealed no significant adverse effects in the two species investigated [http://www.inchem.org/].

Erythrosine/ E 127/ Red No. 3 is a cherry-pink coal tar-based food dye. It has been found to cause all possible clinical forms of allergic reactions, sensitivity to light and also learning difficulties, increase thyroid hormone levels and lead to hyperthyroidism. In a study of Jennings and co-workers [1990], it was shown to cause thyroid cancer in rats, so the lipid-soluble formulations of erythrosine were banned because of the increased incidence of thyroid tumors in male rats fed this dye. Water-soluble derivatives of erythrosine are permitted in foods and oral medications because the gastrointestinal absorption of these compounds is very low [Lakdawalla & Netrawali, 1988]. Erythrosine has been found to act as a potent neurocompetitive dopamine inhibitor of dopamine uptake by nerve endings when exposed *in vitro* on a rat brain. Other studies showed that erythrosine can act as an inhibitor also on other neurotransmitters, resulting in an increased concentration of neurotransmitters near the receptors, thus functionally augmenting the synaptic neurotransmission. There is now some evidence that a reduced dopamine turnover may lead to childhood hyperactivity. Similar findings have been linked with a reduction of noradrenaline [Tuormaa, 1994]. Erythrosine also has been found to have a potential carcinogenic action when tested on animals [Tuormaa, 1994].

Sunset Yellow FCF/ E110 is an orange coal tar-based food dye. It is capable of causing allergic reactions such as abdominal pain, hyperactivity, hives, nasal congestion, and broncho-constriction as well as kidney tumours, chromosomal damage, and distaste for food when fed to laboratory rats. It has also been found to be carcinogenic when fed to animals [Rangan *et al.,* 2009].

The information about intolerance induced by the consumption of food additives provoked the United Kingdom Food Standards Agency (UK FSA) to commission the Southampton University researchers to arrange a programme concerning the effects of consuming foods with colourants [Sunset yellow (E110), Quinoline yellow (E104), Carmoisine (E122), Allura red (E129), Tartrazine (E102) and Ponceau 4R (E124)] and sodium benzoate]. The study was carried out on 137 children aged three and 130 children aged from eight to nine. The results, announced in September 2007, reported that both the colourants and the sodium benzoate produced signs of hyperactivity in both groups of children [McCann *et al.,* 2007]. There was created a special new website called "Action on Additives" coordinated by the Food Commission. Up to now more than 1,000 such products have been found in the UK alone and entered into the list. The information published on the 3rd June 2008 in "Food Magazine" [http://www.foodmagazine.org.uk] announces that the UK food manufacturers will be called upon to voluntarily remove six artificial food colourants from all food and drinks by the end of 2009 if advice from the Food Standards Agency is acted upon by Ministers. Yet, the experts at the European Food Safety Authority (EFSA) from Milan, Italy, decided the results of the study were controversial and too inconclusive and the European evaluation of the influence of food additives on human health is still in progress [Larsen, 2008].

PRESERVATIVES

Benzoates (E 210-219) belong to the most commonly chemicals used as food preservatives to prevent the growth of yeast and moulds. Maximum concentrations of benzoic acid and sodium benzoate used as food preservatives range up to 2000 mg/kg. The content of benzoic acid occurring naturally in plant and animal products (*e.g.,* milk) is about 40 mg/kg [International Programme on Chemical Safety, World Health Organization 2000]. Allergic reactions caused by them have different clinical development. Benzoates have been found to provoke urticaria, angioedema and asthma. Furthermore, they have also been directly linked with childhood hyperactivity [Pacor *et al.,* 2004]. The dose of sodium benzoate capable of inducing that disease is 250 mg/kg body weight up to 500 mg/kg daily for several years. The most common adverse responses to this treatment are anorexia and vomiting [Kubota & Ishizaki, 1993]. However, adverse responses resulting from the use of these doses of sodium benzoate are difficult to separate from the effects of the disease. Some individuals who have asthma suffer from tight chest, scratchy feeling at the back of their throats and rashes.

Benzoic acid and sodium benzoate cause animal toxicities in extremely high doses; human toxicities primarily involve rare case reports of mild hypersensitivity reactions such as urticaria and pruritus [Parke & Lewis, 1992; Walker, 1990].

Sulphites, in general, are added to foods as preservatives and sometimes are formed during natural fermentation in beverages, beer and wine. Due to the adverse reaction observed in atopic patients the European Directive 95/2/EC3 [http://www.fsai.ie] has been issued that states that the maximum level of sulphites in food items expressed as SO_2 should not be higher than 10 mg/kg or 10 mg/L and that all packaged and processed foods containing sulphites should be labelled.

Sulphite-induced hypersensitivity is the most well-established adverse response to a food additive. The prevalence

of sensitivity to sulphites in the general population is unknown. The FDA estimates that one in a hundred people is sulphite sensitive, and that 5% of those who have asthma are also at risk of suffering an adverse reaction to the substance [Papazian, 1996]. Four to 8% of asthmatic patients develop sensitivity to sulfites. Literature data indicate that frequently occurring reactions to sulphites are bronchospasms, occasionally severe, occurring within minutes after ingestion of sulphite-containing foods, urticaria, angioedema, hypotension [Simon 1992; Habenicht *et al.,* 1983; Schwartz, 1983, Yang & Emerson, 1985] and anaphylactic shock [Lester, 1995]. The predicting mechanism indicate that the hepatic enzyme, sulfite oxidase, catalyzes the conversion of sulphites to inorganic sulphates. Some sulphite-sensitive patients lack sulphite oxidase, possibly leading to an accumulation of sulphite and subsequent conversion to sulphur dioxide, a known pulmonary irritant [Gunnison & Jacobsen, 1987]. Some sulphite-sensitive patients have a positive skin test to sulphite, suggesting a relationship with an IgE-mediated response in selected patients. The clinical presentation is an anaphylactic or anaphylactoid reaction with acute bronchospasm. Sulphite sensitivity occurs more commonly in patients with asthma, but sulphite-induced symptoms may develop in patients without documented asthma or other allergy-related disorders. Symptoms include urticaria, angioedema, and IgE-mediated anaphylaxis [Sokol & Hydick, 1990]. Although the FDA banned the use of sulphites in raw foods, sulphites are permitted in processed foods.

One of the most known examples of allergy to sulphites is wine-induced asthma. Wine is made from many components and is a complex of ingredients any of which can induce allergic symptoms and several mechanisms can be involved and play a role [Vally *et al.,* 1999]. Sulphites are also components of some medicines which can be particularly dangerous in the case of allergic patients.

One of the hypotheses accounting for the mechanisms of sulphites intolerance in the human organism ascribes it to their aspirin-like properties [Williams *et al.,* 1989]. Intolerance to sulphites is more common among asthma patients and particularly among asthmatics who are also intolerant to aspirin, with a prevalence of up to 20% in this group.

Sulphites are safe for most people. But in 1986 the FDA imposed a ban on their use in on fresh fruits and vegetables (except potatoes) intended to be sold or served raw to consumers.

ANTIOXIDANTS

Butylated hydroxyanisole (BHA, E320)) and butylated hydroxytoluene (BHT, E321) are synthetic phenol-derivatives used as common antioxidants protecting food lipids from spoilage by inhibiting lipid peroxidation and preventing the disintegration of lipid-soluble vitamins. They have been related with cosmetic and chewing-gum contact dermatitis. BHA and BHT are associated with exacerbations of urticaria in patients with chronic urticaria [Goodman *et al.,* 1990]. High doses of BHT that far exceed the dose of BHT in food can cause human toxicity. Shlian with coworkers [1986] described a case of acute gastroenteritis with epigastric pain, vomiting, weakness, confusion, syncope after ingestion of 4 g of BHT, while the ingestion of 80 g of BHT induced lightheadedness, slurred speech, unsteady gait, and lethargy. Reports of carcinogenicity from BHA and BHT free-radical metabolites are limited to rodent squamous cells of the fore stomach, an organ that does not have a human counterpart [Altman *et al.,* 1986]. BHA was found to be an animal carcinogen as it induced tumor in rats [Ito *et al.,* 1989].

FLAVOUR ENHANCER

Monosodium glutamate (MSG/E621) is added as a flavour enhancer to soups, sauces, and meat-preparation products. Its popularity originates from the tastiness of the Far East cuisine [Populin *et al.,* 2007]. Its use has been controversial in the past 30 years because of reports of adverse reactions in people who ate foods containing MSG and were involved in severe food reactions. In 1968 there appeared the first report about the so-called "Chinese Restaurant Syndrome" described as a triad of palpitations, generalized weakness, and sensory numbness originating at the nape of the neck with radiation to the arms and back [Kwok, 1968]. Controlled clinical trials have not confirmed this response to MSG, suggesting that MSG may cause symptoms only in selected populations, *e.g*. asthmatic or atopic patients [Geha *et al.,* 2000]. Short-term responses to MSG occurred in one double-blind trial of healthy patients ingesting 5 g of MSG on an empty stomach, and in patients with severe asthma. Transient symptoms (MSG symptom complex) associated with MSG consumption included numbness, burning sensation, tingling, facial tightness, chest pain, headache, nausea, palpitations, drowsiness, and weakness as an effects of peripheral nerve receptors in the esophagus stimulation [Yang *et al.,* 1997]. Although some epidemiological studies demonstrated correlations between MSG and adverse responses in severely asthmatic patients, a single-blind, placebo-controlled challenge study did not detect symptoms of wheezing or reduction in forced expiratory volume in 100 asthmatic patients ingesting 2.5 mg of MSG [Woessner *et al.,* 1999]. Long-term health effects do not usually occur or are difficult to find. MSG remains on the list of GRAS ingredients, but the US FDA requires manufacturers to list MSG and related compounds (monopotassium glutamate, monoammonium glutamate) on the food label. MSG was banned from the production of infant foods because of the occurrence of irreversible retinal lesions in neonatal rodents [Stricker-Krongrad *et al.,* 1998], however, it can be found as a natural component of human bodies. It can elicit mild adverse reactions in some individuals, which may include: headache, sometimes called MSG headache, flushing, sweating, sense of facial pressure or tightness, numbness, tingling or burning in or around the mouth, rapid fluttering heartbeats (heart palpitations), chest pain, shortness of breath, nausea, or weakness. The Acceptable Daily Intake (ADI) for MSG is 120 mg/kg/d, but also lower doses can be associated with acute syndrome in sensitive individuals [Rangan & Barceloux, 2009]. A randomized-controlled trial found a 33% occurrence of headache, numbness, tingling, and weakness following the ingestion of single doses of 2.5 g MSG [Yang *et al.,* 1997]. Some studies have found that people who suffer from allergies or severe and poorly controlled asthma may be prone to MSG sensitivity. There have also been reports of people with asthma having more severe asthma attacks after consuming MSG [Stevenson, 2000].

SWEETENERS

Aspartame E 951 (L-aspartyl-L-phenylalanine methyl ester) is a low-calorie, intense sweetener, approximately 200 times sweeter than sucrose [EFSA, 2006]. Unfavourable information about harmfulness of aspartame appeared in the middle 1990s. The misinterpretation of studies concerning cancer incidence data in the mice brain was the main reason for the bad reputation of aspartame. Further studies using aspartame doses hundreds times higher than the 90th percentile intake by humans proved that aspartame was not carcinogenic [Butchko *et al.,* 2002]. Also some regulatory and government agencies from different countries (the FDA, NCI, ANZFA, United Kingdom Department of Health, Food Standards Agency, European Commission) confirmed that aspartame was not associated with brain tumours and that it was safe for human consumption [Renwick & Nordmann, 2007]. Aspartame is digested in the gastrointestinal tract into three components: aspartic acid (40%), phenylalanine (50%), and methanol (10%) [Karim & Burns, 1996], which are absorbed and then utilized by the metabolic pathways of the body. The same components are present in foods such as eggs, milk, meat, fish, cheese, fruits and vegetables consumed daily.

No relation was found between the symptoms of asthma and exposure to aspartame [Butchko *et al.,* 2002]; nor is it involved in the allergic type of reactions. Nevertheless, over 90 different adverse reactions and side effects were reported in relation to aspartame: from severe itching without rashes, through severe lip and mouth reactions, urticaria (hives), severe genital itching, rash, or both, lupus erythematosis-type eruption, other rashes, marked thinning or loss of hair, aggravation of respiratory allergies, to dual sensitivity to MSG.

The study carried out with rats showed that aspartame was found to double the level of phenylalanine in their brains, which involved a great rise in brain tyrosine, followed by a considerable reduction in brain tryptophan levels. Low tryptophan levels have been directly linked with both aggressive and violent behaviour [Rangan & Barceloux, 2009].

CONTAMINANTS (NICKEL, CHROMIUM)

Apart from food additives which are intentionally added to different kinds of food products there occur also cases of incidental contaminations, which can also cause severe reactions including allergic ones. A well-known example is allergy to nickel, chromate and cobalt found in food or systemic contact dermatitis caused by metal present in food [Jellesen *et al.,* 2006]. The highest concentrations of nickel were found in canned vegetables, sugar, bread and cereal products, which suggests a contribution from food processing equipment and possibly canning. A detailed study from the North American Contact Dermatitis Group (NACDG) revealed that 16.2% of the US population showed a positive reaction to nickel, in Central Europe 12.9%, with the highest prevalence in Italy (32.2%), and lowest in Denmark (9.7%) [Torres *et al*., 2009].

It was observed that oral nickel exposure elicited skin reactions in nickel sensitive individuals, but some other studies suggest that oral intake of small amounts of nickel could apparently prevent the development of nickel allergy probably involving immunotolerance mechanism [Sosroseno, 1995].

Chromium plays an essential role in maintaining normal carbohydrate, lipid and protein metabolism [Krzysik *et al.,* 2008]. It also improves glucose tolerance and lipid profile by increasing the level of high density lipoprotein cholesterol and decreasing total serum cholesterol [Anderson, 1997]. Chromium is usually present in food as Cr (III) and its bioavailability depends on the chemical and physical properties of Cr compounds and complexes; its absorption from the gut is low, ranging from 0.5% to 2% [Anderson & Kozlovsky, 1985]. The highest concentrations of chromium were found in shellfish, meat, fish, fruit, and sweets.

CONCLUSIONS

The problem of the presence of food additives and some contaminants in an everyday diet and their influence on human immune system is still discussed. In some countries (*e.g*. UK), campaigns against using them in the food industry are continued. The general conclusion is an important recommendation: when buying food products it is necessary to be vigilant and always check labels. If there are any doubts, we should discards such products since this is the only safe way to avoid allergens.

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