

Adverse Reactions to the Antioxidants Butylated Hydroxyanisole and Butylated Hydroxytoluene

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KEY CONCEPTS

- Butylated hydroxyanisole (BHA) and butylated hydroxytoluene (BHT) are synthetic antioxidants widely used in packaged foods, cosmetics, and other manufacturing.
- Animal toxicology reveals protective as well as deleterious effects on the circulation, pneumonitis, and gut-related tumors.
- In doses currently used in human consumption, no risk of gastrointestinal malignancy has been found.
- Adverse reactions in the upper and lower respiratory tract are not well documented.
- European studies have previously greatly overestimated the prevalence of urticarial reactions to BHA/BHT due to flaws in study design. Such reactions do occur but are very uncommon.
- Delayed hypersensitivity reactions have been well described.
- Double-blind oral challenge is the preferred mode of diagnosing adverse reactions.

Foods containing vegetable or animal fat turn rancid through chemical changes induced by exposure to oxygen, heat, moisture, or the action of enzymes. The rapidity with which rancidity develops depends on the source and storage conditions of the fats or oils. Unsaturated fats have carbon-carbon double bonds in their structure, and these sites are susceptible to chemical changes causing rancidity. Saturated fats are more resistant. Vegetable oils have more unsaturated fats, but also contain naturally occurring protective antioxidants such as tocopherols. Animal fats are more saturated, but have lower amounts of natural antioxidants, and are at greater risk for spoilage [1,2]. Similar factors may cause the "browning effect:" fruits and vegetables losing their freshness and turning color. Antioxidants block these events, and may even restore "freshness" in some cases.

The phenolic antioxidants butylated hydroxyanisole (BHA) and butylated hydroxytoluene (BHT) are used in a large number of foods that contain oil and fat. Other chemicals having antioxidant activity are frequently used

in combination with BHA or BHT to enhance their activity: such agents include propyl gallate, citric acid, phosphoric acid, and ascorbic acid. Additionally, there is a group of naturally occurring antioxidant compounds called tocopherols, which have varying amounts of vitamin E action. About eight forms occur naturally in foods such as vegetable oils, cereals, nuts, and leafy vegetables, and are used commonly in baked goods, cereals, soups, and milk products.

BHA and BHT are synthetic compounds and do not occur in nature. BHT, also termed 2,6-di-*tert*-butyl-4-methylphenol or 2,6-di-*tert*-butyl-*p*-cresol, is manufactured from *p*-cresol and isobutylene [3]. BHA is a mixture of two isomers, 85% 2-*tert*-butyl-4-methoxyphenol and 15% 3-*tert*-butyl-4-methoxyphenol (see Fig. 32.1) [4]. BHT was initially patented in 1947. These substances were originally developed as antioxidants for petroleum and rubber products, but were quickly discovered to be effective antioxidants for animal fats.

In 1949, BHA appeared on the new Class IV preservative allowed list of the Health Protection Branch of Health and Welfare Canada, and usage was restricted to levels under 0.02% [5]. Animal studies from the manufacturers were submitted to the US Food and Drug Administration (FDA) in 1954 and 1955, and permission was granted prior

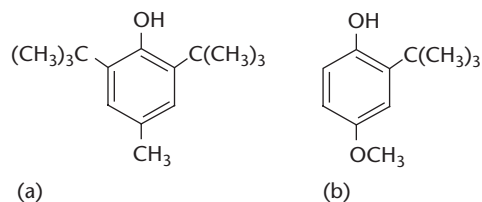


Figure 32.1 (a) Butylated hydroxytoluene (BHT, 2,6-di-*tert*-butyl-4-methylphenol). (b) Butylated hydroxyanisole (BHA, 2-*tert*-butyl-4-methoxyphenol). Commercial BHA also contains 15% 3-*tert*-butyl-4-methoxyphenol.

to the 1958 Food Additives Amendment. Therefore BHA and BHT were given “generally recognized as safe” (GRAS) status and no additional studies were required. However, a number of items on the GRAS list have come under further scrutiny, and BHA and BHT remain on the list with provisional status. The FDA limits their use in food, either alone or in combination with other antioxidants, to $\leq 0.02\%$ of the total fat and oil content [1].

These compounds are commonly added to various foods, cosmetics, and pharmaceuticals to prevent oxidation of unsaturated fatty acids, and are considered more potent than other antioxidants. They are less expensive than some other antioxidants such as nordihydroguaiaretic acid (NDGA) [5]. BHA is used more than BHT because it is more stable at higher temperatures. They are used in breakfast cereals, chewing gum, snack foods, vegetable oils, shortening, potato flakes, granules and chips, enriched rice, and candy [1]. By 1970, the total amount of BHT used in foods was near 600,000 pounds, twice that used in 1960. By 1976, the total annual production of BHT in the United States was 19.81 million pounds, of which 10.95 million pounds were for non-food uses, and 8.86 million for food use. In addition to human food, BHT is added to animal feeds, such as fish meal in poultry feed [3]. Turkeys are particularly susceptible to *Aspergillus* aflatoxin B(1), and dietary BHT protects against deleterious effects of the mycotoxin [6]. This protection is mediated through interference with conversion of aflatoxin B(1) to a toxic metabolite [7]. Passive food exposure in humans to BHA/BHT may occur through their use in food-packaging materials like pressure-sensitive adhesives, paper and cardboard, lubricants, and sealing gaskets for food containers [1,3].

The United States average daily intake per person of BHT alone was estimated as 2 mg in 1970, while intake in the United Kingdom was estimated at half that rate [3]. With the greater present reliance of the North American diet on processed, packaged foods, more recent daily intakes of BHA and BHT are substantially larger. In 1986, the mean intakes for BHA ranged from 0.13 to 0.39 mg/kg body weight/day. The intake for teenage males was 12.12 mg/person/day, with the average for both sexes of all ages at 7.40 mg/person/day [5]. In 1974, the Joint Food and Agriculture Organization

of the United Nation/World Health Organization Expert Committee on Food Additives had recommended 0.5 mg/kg as the acceptable daily intake of BHA, BHT, or their sum [4]. A 2000 study from the Netherlands reported in older adults mean daily intake of BHA as 105 μg and BHT as 351 μg [8].

BHT is used in cosmetics as an antioxidant, in concentrations ranging from 0.0002% to 0.5%. Skin penetration does occur, but the systemic absorption from the skin is considered too low to be a risk. The Cosmetic Ingredient Review Expert Panel concluded that BHT is safe as used in cosmetic formulations [9].

Toxicology

Animal toxicology studies have revealed a variety of adverse events, which may be related to their actions as antioxidants. BHA and BHT act as lipid-soluble chain-breaking agents, delaying lipid peroxidation by scavenging intermediate radicals such as lipid peroxy radicals [10]. In the process, however, the antioxidant has lost a hydrogen atom, thus becoming a radical. The antioxidant radical is generally less reactive than the peroxy free radical, but under some circumstances can show pro-oxidant properties, frequently due to interactions with iron ions.

Single doses of BHT have been shown to induce interstitial pneumonitis and pulmonary fibrosis in mice, while BHA and other antioxidants did not appear to have this action [11]. This BHT effect can be potentiated by oxygen given early, but not late [12,13]. High-dose corticosteroids additionally may significantly worsen lung damage if given early, while late administration may alleviate the injury [14,15]. Whether the lung injury is mediated through some unique property of BHT, rather than through an antioxidant pathway is unclear; it does appear that the extent of damage is dependent on several factors interweaving both dose and timing. Recent research demonstrates that there are distinct mice strain differences in the chronic response to BHT, part of which may be due to cytochrome P450 conversion of BHT to the more pneumotoxic metabolite *tert*-butyl hydroxylated BHT (BHT-BuOH) [16]. CXB H mice became tolerant to the chronic administration of BHT, while BALB/cBy mice showed a chronic inflammatory process with activated alveolar macrophages and increased lung tumor multiplicity. Acute effects demonstrated 2- to 5-fold decreases in protein kinase C α and calpain II (calcium-dependent protease isozyme II).

Impact of dietary antioxidants on cancer prevention has received much scientific and media attention. BHA and BHT have been shown to both protect from and enhance tumor development in different systems. BHA, BHT, and NDGA have been shown to decrease skin tumor promotion by 12-*O*-tetradecanoylphorbol-13-acetate (TPA), benzoyl peroxide, and ultraviolet light. BHA achieves this result through decreased gene expression of ornithine decarboxylase, an indicator of skin tumor promotion and hyperproliferation

[17]. BHT, however, increased the incidence of liver tumors in male C3H mice [18]. The same study showed increased colon cancer in BALB/c mice following one chemical carcinogen, dimethylhydrazine, but not another, methylnitrosourea. BHA, on the other hand, appeared to protect against the acute liver toxicity of a colon-specific carcinogen, methylazoxymethanol acetate [19]. However, high-dose BHA was shown several years ago to produce cancers of the forestomach in rats [5]. Since man does not have a forestomach, and doses about 10,000 times higher than likely human consumption were used, it was felt by the FAO/WHO Joint Expert Committee on review of the data that the benefits of BHA outweighed the potential risks [5]. The Netherlands Cohort Study found no significant association with stomach cancer risk with usual intake levels of BHA and BHT [8].

BHT may have anti-atherogenic effects. Using a cholesterol-fed rabbit model, Xiu and colleagues showed BHT prevented decreased blood flow and vessel diameter in the microcirculation [20]. The same group more recently demonstrated that this effect is mediated through induction of increased triglyceride levels [21].

Using human lymphocytes, Klein and Bruser demonstrated BHT cytotoxicity with concentrations $>100\mu\text{g/ml}$ [22]. At $50\mu\text{g/ml}$, BHT inhibited the mixed lymphocyte reaction, but not phytohemagglutinin (PHA) stimulation. A synergistic effect of PHA suppression was seen with co-incubation with either cortisol or prednisolone.

In mice studies, BHA inhibited several microsomal enzymes, but long-term administration also induced specific P450 cytochrome enzymes [23]. In humans, BHA 0.5 mg/kg for 10 days had no appreciable effects on biotransformation capacity [24]. Antipyrine and paracetamol (acetaminophen) metabolism were unaffected. Urinary excretion of BHA metabolites was significantly increased on days 3 and 7 compared to day 1, suggesting either an inhibition of BHA metabolizing enzymes or bioaccumulation of BHA and/or its metabolites in the body.

Asthma/rhinitis

Despite a wealth of animal toxicology literature on these antioxidants, there are only scattered reports of adverse reactions to BHA and BHT in humans. In 1973, Fisherman and Cohen reported on seven patients with asthma, vasomotor rhinitis with or without nasal polyps, or the combination, who were suspected of intolerance to BHA and BHT [25]. There were no clinical details given as to why BHA and BHT were suspected. These patients were identified following open challenge with capsule ingestion of 125–250 mg of BHA/BHT and reproduction of symptoms of worsening vasomotor rhinitis, headache, flushing, asthma, conjunctival suffusion, dull retrosternal pain radiating to the back, diaphoresis, or somnolence. No objective measures were noted. BHA/BHT intolerance was additionally

documented by a doubling of a Duke earlobe bleeding time (termed the sequential vascular response by the authors) in all cases. No rationale for the reported effect on the bleeding time was given, other than a supposed similarity to aspirin intolerance. In a follow-up paper the same year, dealing with aspirin cross-reactivity, these authors had apparently found 21 patients with intolerance to BHA/BHT via the bleeding time, of which 17 had clinical symptoms on challenge, with no clinical details given [26].

The following year, in an unsuccessful attempt to duplicate Fisherman and Cohen's initial findings, Cloninger and Novey performed a similar study using oral ingestion of 300–850 mg BHA in five asthmatics and two rhinitics [27]. They reported that the baseline earlobe bleeding time was not reproducible. None of the patients had clinical exacerbations, changes in peak flows, or more than a 50% change in the bleeding times; there was a non-dose-related effect of drowsiness noted in four of seven patients. These authors questioned the validity of clinical BHA intolerance as well as the validity and reproducibility of the sequential vascular response. Goodman and colleagues, as discussed further below, in a case of well-documented BHA/BHT-induced chronic urticaria, could not demonstrate a positive effect of either BHA 250 mg or placebo on the earlobe bleeding time in either the patient or two controls [28].

Weber and colleagues, in a study where single-blind challenges were validated by subsequent double-blind challenges, found no asthmatic responses of $>25\%$ drop in forced expiratory volume in 1 second (FEV1) in 43 moderately severe perennial asthmatics undergoing single-blind capsule challenges with sequential doses of 125 and 250 mg of BHA and BHT [29]. Aspirin sensitivity was documented in 44% of the patients, and reactivity to *p*-hydroxybenzoic acid, sodium benzoate, non-azo or azo dyes in 2–5%. The author is aware of one unpublished case of a drop of pulmonary function following double-blind challenge with BHT 250 mg in a patient with food anaphylaxis and oral allergy syndrome, but this was not validated with additional blinded challenges. Therefore, at the present time, there are no published reports of BHA or BHT challenges resulting in well-documented, reproducible asthmatic responses.

Urticaria

In 1975, Thune and Granholt reported 100 patients with recurrent urticaria evaluated with provocative food additive challenges [30]. Sixty-two patients had positive challenges, with two-thirds reacting to multiple substances. Positivity rates for individual dyes, preservatives, or anti-inflammatory drugs ranged from 10% to 30%. Most reactions occurred within 1–2 hours, with a number occurring between 12 and >20 hours. Six of 47 (12.7%) tested to BHA reacted, and 6 of 43 (13.9%) reacted to BHT; it is unclear whether these were the same six patients. Test doses were given in two to

three increments, with the total dose of BHA and BHT being 17 mg. The provocative challenges were not blinded, nor did the authors state criteria for a positive challenge.

In 1977, Fisherman and Cohen reported the results of provocative oral or intradermal challenges of a large number of suspected agents on the bleeding time (sequential vascular response) in the assessment of 215 patients with chronic urticaria [31]. Medications were withdrawn 12 hours prior to challenge, with the exception of hydroxyzine, which was held for 72 hours. Intolerance was found in 19 patients with challenges of 250–500 mg of BHA and BHT. Slight details of four reactors challenged with 250 mg each of BHA and BHT were included in a table: in addition to doubling of the earlobe bleeding time, two developed nasal congestion, and three had urticaria, although it is not clear whether this was increased over baseline. These authors felt they made a determination of “single or partial etiologies” in 203 of the 215 patients (94.4%), an astounding success rate in a clinical entity known for its resistance to defined etiology. Obviously, the same criticism of the lack of conceivable mechanism and the non-reproducibility of the test in other hands holds for these authors’ urticaria evaluations as well as the asthma challenges.

Juhlin mentioned in a review on urticaria in 1977 the results of provocative challenges with a mix of BHA and BHT in 130 urticaria patients [32]. Incremental doses of 1, 10, and 50 mg each of BHA and BHT resulted in nine positive and five probably positive challenges (6.9–10.8%). Details as to the nature of the patients’ symptoms, criteria for positive response, or the blinding of the challenges were not given. Four years later, Juhlin published the results of an evaluation of 330 patients with recurrent urticaria [33]. He used a 15-day single-blind challenge battery of dyes, preservatives, and placebo. Antihistamines were withheld from 4 to 5 days before the commencement of the challenge sequence. Testing was accomplished when patients had “no or slight symptoms.” Tests were judged positive if “clear signs of urticaria or angioedema” occurred within 24 hours. Slightly less than half of the 330 patients (156) received a BHA/BHT challenge with cumulative doses of 1, 10, 50, and 50 mg given (total dose 111 mg). Fifteen percent had positive reactions, and 12% had equivocal reactions. Lactose placebo was given in two doses on days 1, 3, 9, and 12, although modifications in the order did occur. Active substances were given in single to six divided doses at hourly intervals. Most patients did not undergo the entire challenge schedule; one third did not receive a placebo challenge.

In 1986, Hannuksela and Lahti published their results of an extensive double-blind challenge study [34]. They evaluated 44 patients with chronic urticaria of >2 months duration, 91 atopic dermatitis patients, and 123 patients with resolved contact dermatitis. They used wheat starch as their placebo rather than lactose since Juhlin had reported positive responses to lactose placebo. Patients were challenged to

sodium metabisulfite 9 mg, benzoic acid 200 mg, BHA and BHT mixture of 50 mg each, and β -carotene and β -apo-carotenal mixture 200 mg each. Positive reactions were repeated 4 days later to validate the response: challenges were rated as positive if the patient responded both times, and as equivocal if the repeat was negative. Of the 44 urticaria patients none had reproducible positive reactions to BHA/BHT; two responded to the first challenge but not the second. The same response occurred with the atopic dermatitis patients; two had equivocal reactions to BHA/BHT. None of the contact dermatitis patients reacted to the antioxidants. One urticaria patient had reproducible responses to the wheat placebo, and another to benzoic acid, and one had an equivocal response to metabisulfite. One atopic dermatitis patient had positive reactions to carotenal/carotene, and another had an equivocal reaction to metabisulfite. One contact dermatitis patient had an equivocal reaction to the wheat placebo (second challenge not done). The authors contrasted their results to those of Juhlin, and cited challenge differences to explain their lack of responses. They also wondered whether a prolonged refractory period following the initial positive challenges could account for the negative follow-up trials, since they had waited only 4 days. In general, however, the authors felt that ordinary amounts of food additives do not provoke urticaria or influence atopic dermatitis [34].

In 1990, Goodman and colleagues reported the first double-blind, placebo-controlled multiple challenge protocol documenting the link of BHA and BHT with chronic urticaria [28]. The demonstration of symptom aggravation did not rest on single challenges: two patients with chronic urticaria and angioedema of 3–4 years duration underwent oral challenges with several agents performed 2–3 times for verification. The patients had demonstrated improvement on restricted diets, but had lost 20–30 pounds in the process. Both patients were admitted, placed on an elemental diet formula, and observed for 5–7 days to establish baseline activity. The patients ranked pruritus severity, and skin lesions were ranked from 0 to 4+ based on degree of body distribution. Only challenges inducing lesions within 12 hours of ingestion and involving an entire extremity or body area, or generalized, were considered positive. Those occurring 12–24 hours were considered equivocal. A mixture of 125 mg each of BHA and BHT was given, with 250 mg of each given 2–4 hours later if no major reaction had occurred. One patient was additionally challenged to BHA 250 mg alone. Placebo capsules were either dextrose or lactose. The patients were also challenged to sodium benzoate, *p*-hydroxybenzoic acid, tartrazine, and other azo dyes. Both patients reacted within 1–6 hours to BHA and BHT at all times, and did not react to the other additives or placebo on numerous trials. There were no delayed reactions.

Oatmeal one patient had been routinely ingesting for breakfast contained BHA and BHT. Both patients were placed on diets specifically avoiding BHA and BHT, resulting in

sustained diminution of frequency and severity of urticaria. The first patient, at 7-year follow-up, continued to rigidly adhere to his diet, and noted exacerbations of his urticaria when unexpected exposures occurred. The other, at 1-year follow-up, also continued to follow his diet, noting only two minor exacerbations, again after ingesting foods containing BHA and BHT. These two episodes lasted under 12 hours, and required no medication. Each patient returned to his pre-illness weight and was able to resume his normal occupation.

The first patient assessed had serial plasma determinations throughout the challenge period for CH50, activated C3 and factor B, and PGE2, PGF2 α and dihydroxy-ketoPGF2 α . Blood was drawn at baseline, and half-hour intervals after the first dose to 2 hours, and hourly intervals until 6 hours after the second dose. After the initial challenges were completed on the first patient, and the code broken, the patient as well as two normal controls underwent an additional double-blind session, using BHA 250 mg and placebo. This was done to evaluate the predictive value of the sequential vascular response test (SVR) of Fisherman and Cohen. As commented above, this test is basically an earlobe bleeding time, but had been advanced as diagnostic in adverse reactions to BHA/BHT, aspirin, and other chemicals. Prick skin tests with serial dilutions of BHA, BHT, sodium salicylate, and OHBA were also performed, which were uniformly negative.

Serial complement and prostaglandin determinations during the challenges were unrewarding. CH50 was seen to decrease 30–35% randomly on both placebo and active compound days. Activated C3 and factor B were sporadically elevated on four occasions, twice with placebo and once during the pre-challenge baseline period. The prostaglandin levels all decreased as the day progressed, with both placebo and active challenges. Despite the extensive evaluation, the mechanism of action is uncertain. An immunological process was not supported by the inconsistent changes in complement components, negative immediate skin tests, and lack of vasculitis on biopsy. The strict elimination diets did not totally ablate lesions in either patient. It may be that the antioxidants acted as potentiators of an underlying unrelated process, similar to the action of aspirin in chronic urticaria [35]. Serial earlobe bleeding times were all unchanged with both placebo and BHA in the patient and control subjects, despite the patient having a brisk urticarial response to the BHA.

Osmundsen reported a case of contact urticaria due to BHT contained in plastic folders [36]. Contact with the folders on unbroken skin resulted in a strong urticarial reaction within 20 minutes. The patient had positive wheal and flare responses to 1% BHA and BHT in ethanol.

The importance of these antioxidants causing or aggravating chronic urticaria is not clear. The true incidence of urticarial adverse reactions to BHA/BHT is unknown. Identification of triggers in a disease of waxing and wan-

ing nature may be difficult, especially when a background of urticarial activity persists during challenges. A sharp definition of what constitutes a positive reaction is necessary. Additionally, the observer rating the severity of the reaction must be blinded as well as the subject, since he is just as susceptible to expectation bias. The studies of Thune and Granholt, and Juhlin fail on these counts [30,32,33]. The 13–15% incidence of BHA/BHT reactions reported in these studies is most surely an overestimate. Preliminary results of single-blind, placebo-controlled food additive panel challenges at Scripps Clinic have been unrewarding [37]. In evaluating somewhat over 20 chronic urticaria patients, a panel including tartrazine, potassium metabisulfite, monosodium glutamate, aspartame, sodium benzoate, methylparaben, BHA, BHT, and sunset yellow (FD&C yellow #6) has revealed no responders. Additionally, the importance of double-blinding in such studies has been pointed out by Weber and colleagues [29], and reinforced by Stevenson and associates [38]. In the former study, of 15 patients who reacted to dyes or preservatives on open challenge, only 3 responded under repeat double-blind conditions.

Dermatitis

A variety of non-urticarial skin eruptions have been attributed to food additives. Contact dermatitis may occur to a large number of food additives, especially antioxidants, spices, gums, and waxes. Evidence for such responses can be objectively obtained through patch testing for delayed hypersensitivity.

Tosti and colleagues reported two cases of contact dermatitis due to BHA in topical agents for psoriasis and eczema [39]. Patch testing was positive for BHA but not BHT in both cases. The concentration of BHA in the preparations was 0.1% and 0.2%, respectively. As of 1987, the authors cited 14 cases of BHA contact dermatitis in the literature. Contact sensitivity to latex gloves is an ever-increasing problem; one recent report, however, revealed sensitivity not to the usual rubber allergens, but to antioxidants, one being BHA [40]. Acciai and co-workers found one case of contact dermatitis from BHA in a pastry cook during the investigation of 72 caterers with eczema [41]. In an evaluation of contact sensitivity in 69 women with pruritus vulvae, which revealed patch positivity of clinical significance in 40 (58%), one demonstrated sensitivity to BHA (2% in petrolatum) [42]. The importance of these instances of contact sensitivity to food considerations is that in some cases, once the hypersensitivity has been initiated through cutaneous exposure, dermatitis symptoms could be flared by ingestion of the causative agent. Roed-Petersen and Hjorth found four patients with eczematous dermatitis who had positive patch tests to BHA and BHT [43]. Dietary avoidance of the antioxidants resulted in remissions in two of their

patients. When challenged with ingestion of 10–40 mg BHA or BHT both patients had exacerbations of the dermatitis.

Cutaneous vasculitis from food additives in chewing gum has been induced by ponceau (FD&C red #4), and also by BHT [44,45]. The case of acute urticarial vasculitis due to BHT was reported in 1986 by Moneret-Vautrin and associates. Biopsy revealed a heavy perivascular lymphoid infiltrate of the upper dermis, with immunofluorescence revealing IgM, C1q, C3, C9, and fibrinogen. Lesions resolved with discontinuation of chewing gum. A series of single-blind challenges showed a reproduction of the lesions with ingestion of BHT and not other ingredients.

Mechanisms

The reports of Roed-Petersen and Hjorth, Osmundsen, and Moneret-Vautrin suggest that certain adverse reactions to BHA and BHT may be mediated through immunological mechanisms in addition to that seen in typical contact delayed hypersensitivity. Histamine release from leukocytes has been described following aspirin, benzoate, BHA/BHT, and azo dyes [46]. The authors studied 12 urticaria patients as well as 18 healthy subjects. BHA and BHT caused histamine release 1 time each in an urticaria patient, but 4 healthy subjects reacted to BHT and one to BHA, raising the question of clinical relevance in these *in vitro* tests. These studies suggest that immune effector cells are probably involved in at least some of these adverse effects, and that different mechanisms are operant. The majority of data to date, however, does not support that these are immunologically specific reactions.

Several authors have felt that adverse cutaneous reactions in humans to BHA or BHT were akin to skin lesions induced by aspirin and non-steroidal anti-inflammatory drugs, and represented alterations in the arachidonic acid–prostaglandin cascade. There is no data at present supporting such an action of the phenolic antioxidants. The evaluation of the single patient of Goodman and associates did not reveal obvious perturbations of prostaglandin metabolites despite clinical exacerbation [28]. It appears reasonable that BHA and BHT are acting in these circumstances in a pharmacological manner, but the mode continues to be unclear.

Unsubstantiated effects

In addition to the purported adverse effects of BHA and BHT advanced by Fisherman and Cohen based on the non-reproducible earlobe bleeding time prolongation, these two antioxidants have gained notoriety in the health food lay press in the past as life prolongation agents. Claims for their benefit in increasing life span are apparently based on mice studies performed 25 years ago [3]. Unfortunately, these studies had contradictory results, and it appears unclear whether the improved life span in the mice could not also be

achieved by optimum normal diet. Recommendations have been made for the ingestion of 2 g of BHT daily as a counteragent for disordered nutrition, age-related problems, and genital herpes [4]. As pointed out by Llauro, however, the dosing recommended by these health food advocates is only an order of magnitude, 10-fold lower, than the lethal concentration noted in certain rat toxicology studies [4]! Obviously, such careless dosing is to be strongly discouraged.

Summary

BHA and BHT are ubiquitous food additives found in a variety of foods, but to the greatest degree in food that contain larger amounts of fats or oils which may become rancid. Additionally, these phenolic antioxidants are also added to plastic or paper products, which may come in contact with food items, as well as in cosmetics and medications that may come in contact with the skin or mucosa. They continue to be widely used despite concerns over animal toxicity studies. Continued provisional status on the GRAS list reflects that the toxicology studies in animals are with greatly larger doses than that utilized in the food industry. Nevertheless, consumption appears to be creeping up over the past three decades.

Adverse reactions in humans to date are best substantiated in the skin. Delayed hypersensitivity contact dermatitis through a variety of occupational or medicinal exposures is well documented, but not common. The true incidence of antioxidant sensitivity in chronic urticaria is presently unknown. High reaction rates of adverse reactions to food additives have not been substantiated by carefully done double-blind studies. Earlier European reports suggesting a 1–15% incidence of BHA/BHT intolerance in chronic urticaria patients suffer from weakness in study design. There appears to be the strong likelihood that a number of positives were due to random fluctuations of disease activity, and not true reactions to the antioxidants or other food additives. To date, there are no convincing reports of human respiratory adverse responses. Therefore, the true prevalence of adverse reactions to BHA and BHT remains unclear.

Oral challenges, preferably double-blinded, remain the desired approach to verifying suspected adverse reactions to these antioxidants. The recommended schedule used is a truncated incremental challenge. The doses used may be considered high, and certainly far exceed an average daily intake. However, such doses are more likely to provide a definitive reaction. Clinical relevance can then be ascertained by elimination of the incriminated agent from the diet. It must be noted that such doses, while appropriate for urticaria evaluations, could be dangerous if one were examining potential asthmatic responses.

Considering the lack of success in identifying causes in chronic urticaria, a search for additive sensitivity is probably warranted, even considering the anticipated low yield. Strict

elimination diets or the use of elemental formulas are difficult and poorly tolerated by patients. Open or single-blind challenges could identify possible aggravants, which should then be further authenticated with double-blind testing. The diet restrictions could then be rationally addressed.

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