

Tartrazine, Azo, and Non-azo Dyes

Donald D. Stevenson

KEY CONCEPTS

- By the standard of the Food and Dye Coloring Act, 10 coal tar dyes, including tartrazine, have been approved for consumption by humans.
- Most humans do not have any adverse effects from ingesting these dyes, which are found in food, drink, and color-coded medications.
- Rarely some individuals have urticaria or asthma after ingesting tartrazine or other azo dyes but the relationship is generally overestimated based on poorly designed older studies.
- There is no evidence to support the idea that tartrazine and aspirin cross-react.
- Well-designed studies rarely document any associations between hyperkinesia and ingestion of tartrazine, despite the belief of parents that a cause and effect relationship exists.
- Contact dermatitis to tartrazine has been reported in a few case reports.
- Rarely, atopic dermatitis worsens after ingesting tartrazine.

Ten coal tar derivatives have been approved under the Food Dye and Coloring Act (FD & C) for use as dyes in food, drink, and color coding of capsules and tablets [1]. All of these dyes contain aromatic rings and some contain azo linkages ($-N=N-$). Azo dyes include tartrazine (FD & C yellow no. 5) (Fig. 31.1), sunset yellow (FD & C yellow no. 6), ponceau (FD & C red no. 4), and carmoisine (FD & C red no. 2). By contrast, the non-azo dyes do not contain the $-N=N-$ linkages. A few examples of non-azo dyes include brilliant blue (FD & C blue no. 1) (Fig. 31.2), erythrosine (FD & C red no. 3), and indigotin (FD & C blue no. 2). Since all of these dyes have been approved for use in humans, addition of dyes to processed food and drink occurs routinely in the developed countries of the world and is perfectly legal under the regulatory requirements of these countries, including the United States. Therefore, from a practical standpoint, the issue is not whether populations of humans are exposed to these chemicals in our food and drink but rather what harm if any do they cause. Some claim that all “chemicals” are harmful and should be banned from the diet, ignoring the fact that “natural chemicals” are found in most food and drinks consumed by humans. The regulatory agencies do not

agree with the above position and concluded long ago that azo and azo dyes were generally regarded as safe (GRS), thus allowing their addition to food, medications, and beverages. Are there some persons who are harmed by these dyes? If so, how many and in what manner are they harmed? Assuming

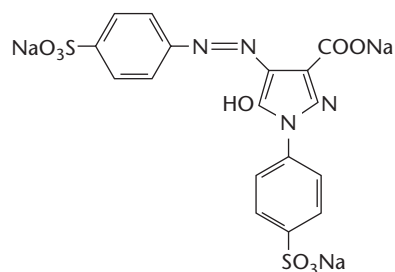


Figure 31.1 An example of an azo dye (tartrazine or FD & C yellow no. 5; note azo linkages).

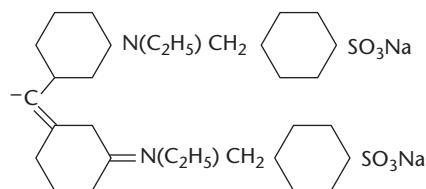


Figure 31.2 An example of a non-azo dye (brilliant blue or FD & C blue no. 1).

the answers are yes, what mechanisms are involved in reactions to these dyes? The purpose of this chapter is to review the relevant literature and attempt to understand the answers to the above questions. Tartrazine is selected for special emphasis because an extensive literature on this azo dye exists. However, other azo and non-azo dyes are also described in the literature as being harmful to humans and therefore will be covered, but in less detail.

In 1984, Simon reviewed the subject of generalized adverse effects of dietary dyes on humans and unequivocally took the position that the evidence supporting the claim that azo and non-azo dyes were harmful to the general population of humans was “speculative” [2]. Despite a constant stream of criticism in the lay press by health food advocates and physicians who practice environmental medicine, there is no credible evidence to support global claims that these dyes cause injury, mental disease, or other known chronic diseases in the general population. Such a conclusion is not to rule out occasional reactions to azo dyes in genetically vulnerable individuals, who might experience immune, pseudo-immune, or biochemical alterations responses to these chemicals. This chapter is organized into sections dealing with azo and non-azo dyes as propagators of urticaria and angioedema, asthma, anaphylaxis, various cutaneous reactions, and hyperkinesia.

Urticaria/angioedema reactions associated with tartrazine and other dyes

In 1959, Lockey described three patients who gave a history of developing a rash after ingesting yellow-color-coded medications [3]. The author conducted unblinded challenges with dilute solutions of tartrazine and concluded that the itching and other subjective complaints, which the patients experienced over the next few hours, were evidence of allergic reactions to tartrazine. In 1972, Juhlin *et al.* [4] reported a prevalence of tartrazine-associated urticaria that ranged between 49% and 100% of subjects who ingested 1–18 mg of tartrazine. During the remainder of the 1970s, others reported tartrazine-associated urticarial reactions [5,6]. In 1981, Juhlin reported that 18/179 (10%) patients with chronic urticaria reacted to tartrazine during single-blind challenges [7]. Challenge doses reflected the belief at that time that tiny concentrations of tartrazine (0.1 mg) in color-coded medications were capable of inducing urticarial reactions. During single-blind challenges in patients with chronic urticaria, antihistamines were discontinued before the placebo challenges, which were always conducted first. By the time tartrazine was given, the therapeutic effects of antihistamine dissipated. Thus, the appearance of hives could have been spontaneous and due to withdrawal of the therapeutic effects of antihistamines. It is difficult to understand how the same author could report a prevalence of tartrazine-induced urticaria of 100% in 1972 and 9 years

later in a second study of patients, from the same city and medical practice and report a prevalence of 10%.

Doeglas [8], Thune and Granholt [9], and Gibson and Clancy [10] reported tartrazine-associated urticarial reactions in 21%, 30%, and 34% of patient populations with chronic urticaria who underwent single-blind challenges with tartrazine. In the six studies reviewed above, all challenges were single-blinded with placebo challenges conducted first. Antihistamines were always withheld in two studies and no information on the use of antihistamines was provided in the other four studies.

Up through 1976, there were three studies, which relied upon double-blind and placebo-controlled oral challenge techniques. In a study by Gibson and Clancy [10], 26/76 (34%) patients with chronic idiopathic urticaria were recorded as having reacted to tartrazine during double-blind, placebo-controlled tartrazine challenges. Three of the 26 reactors were re-challenged with tartrazine 1 year later and no longer experienced an urticarial reaction to tartrazine. The authors interpreted this change in reactivity to be secondary to the institution of a tartrazine exclusion diet, which these three patients believed they were following during the year. In 1975, Settupane and Pudupakkam [11] conducted double-blind, placebo-controlled challenges in 2 patients with chronic urticaria and 18 patients with aspirin-induced urticaria. In 1/2 patients with chronic urticaria, ingestion of 0.22 mg of tartrazine correlated with an urticarial flare during a double-blind challenge. In the aspirin-induced urticarial patients, 2/18 (11%) experienced a flare of urticaria during double-blind challenges with tartrazine. In a 1976 report, the same authors conducted double-blind tartrazine challenges in 38 patients with chronic urticaria [12]. Of these 38 patients, 10 experienced flares of urticaria after ingesting aspirin. Using tartrazine doses of 0.22 mg during double-blind challenges, 3/38 (8%) experienced a tartrazine-associated flare of acute urticaria.

Of the nine studies reviewed, only the last three were double-blind and placebo-controlled. In seven studies, the study population had chronic idiopathic urticaria, including the three double-blinded studies. In the remaining two studies, the study population was never described. Antihistamine therapy was withheld in five studies but the timing of withdrawal, relative to the beginning of the challenges, was not clearly stated. The remaining four studies did not provide any information about treatment with antihistamines. The presence or absence of aspirin-induced urticaria in the study populations was not clarified in most studies, with the exception of the studies by Settupane [11,12]. Nevertheless, in three studies tartrazine-associated urticaria occurred in at least some patients with chronic idiopathic urticaria whose urticaria was not flared by aspirin. Therefore, a tight linkage between aspirin-induced urticaria and tartrazine-induced urticaria was not established.

In 1986, Stevenson *et al.* [13] reported the results of tartrazine challenges in 10 patients suspected of having flares of

urticaria, in which the patients believed that their urticaria was caused by ingestion of tartrazine. None of these patients had chronic idiopathic urticaria and all were classified as having acute intermittent urticaria. Most were not taking regular antihistamines because they were not having chronic urticaria. For the challenge study protocol, antihistamines were not allowed before or during the study. A screening single-blinded, placebo-controlled tartrazine challenge was conducted first, using doses of 25 and 50 mg. If this challenge was negative, a double-blind challenge was not conducted. If the screening challenge with tartrazine was positive, the protocol called for a confirmatory double-blind challenge. At the beginning of the challenges, all 10 patients were free of urticaria or angioedema. The results were that one patient developed hives 30 minutes after ingesting tartrazine 25 mg during the single-blind challenge. She was re-challenged 5 days later using a double-blind, placebo-controlled challenge with 25 mg of tartrazine and two placebos. During this second challenge, her urticaria also flared 30 minutes after ingesting 25 mg of tartrazine. At a later date, she underwent a single-blinded aspirin challenge with doses up to 650 mg and aspirin did not induce urticaria.

In a second group of nine patients with chronic idiopathic urticaria, antihistamines were continued during the challenges [13]. None of these patients experienced an urticarial flare during single-blind challenges with 25 and 50 mg of tartrazine. While continuing the same doses of antihistamines, 5/9 patients developed flares of urticaria during challenges with aspirin. Finally, in a separate group of five aspirin-sensitive urticaria patients, challenges with tartrazine again failed to induce urticarial reactions but the next day aspirin challenges induced generalized urticarial reactions.

Murdoch and colleagues [14] studied 24 patients who were suspected of having dye-induced urticaria because their disease was in remission while consuming a diet free of dyes and additives. During multiple double-blind challenges with a variety of drugs and additives, the following results were recorded. Fifteen of the 24 (63%) did not react to any challenge substance. Four patients experienced urticarial reactions during aspirin challenges, two reacted to sodium benzoate, and three reacted to a panel of azo dyes (tartrazine, sunset yellow, amaranth, and carmoisine). Thus, only 4/24 (17%) reacted to the substances that they were avoiding with presumed therapeutic success. Furthermore, 3/4 subjects were admitted to hospital for more extensive challenge studies. Two of the three experienced urticarial reactions to each of the four dyes during double-blinded, placebo-controlled challenges. The third patient did not react during any of the in-hospital challenges. However, plasma and urine histamine levels increased during the challenges in all three patients. Simultaneously, prostaglandins were measured in the urine during the challenges. It was fascinating to note that even though patient #3 did not have clinical reactions, his plasma and urine histamine

rose and prostaglandins were found in the urine during the active dye exposures. Shock organ responsiveness appeared to diminish in this patient, even though mediators were released during interactions with some dyes.

Nettis *et al.* [15] pointed out that tartrazine-induced urticaria is incredibly rare (<1%) in patients being evaluated for food-associated urticaria. Furthermore, the other 99% of their study population had positive immediate hypersensitivity to food proteins in their diets. Thus, focusing incorrectly on dyes as the cause of chronic urticaria can divert attention from the real diagnosis of IgE-mediated food allergy.

In conclusion, yellow dye no. 5 (tartrazine) and several azo dyes are associated with urticarial reactions in a very small number of patients [16]. It seems unlikely that tartrazine and other azo dyes are the hidden “cause” of chronic urticaria in the vast majority of patients afflicted with chronic urticaria. Even in the carefully controlled Murdoch study, 83% of patients who eliminated dyes and additives in their diet and experienced “improvement,” nevertheless did not react to these compounds during double-blind challenges. Finally, there does not appear to be any cross-reactions between tartrazine and aspirin or the other non-steroidal anti-inflammatory drugs (NSAIDs) with respect to tartrazine-associated urticaria [16].

Asthma associated with tartrazine and other dyes

In 1958, Speer [17] wrote in his book that “agents used in artificial coloring were the cause of asthma in sick children.” Data supporting this claim were not presented. In 1967, Chafee and Settupane [18] discovered a patient who believed that food dyes were worsening her asthma. Using a double-blinded protocol, they introduced a new dye or placebo, each day for 6 days. On the day, she ingested tartrazine, coughing occurred. Objective measures of lung function were not presented and the challenge with tartrazine was not repeated at another time. The possibility of coincidental coughing could not be excluded in this study.

Samter and Beers attempted to link tartrazine sensitivity to aspirin intolerance [19,20]. In their first report of 80 asthmatic patients with Samter’s Triad, challenges with unknown doses of tartrazine, using unknown challenge protocols, produced three “reactions” to tartrazine [19]. In their second report, 14/182 (8%) aspirin-sensitive asthmatic patients were said to have “reacted” to tartrazine [20]. The report did not indicate how many subjects were aspirin sensitive, by what criteria this fact was established, and how many of the 14 experienced urticaria or asthma during tartrazine challenges.

In 1975, Settupane and Pudupakkam conducted double-blind, placebo-controlled tartrazine challenges in 20 asthmatic patients [11]. Using small doses of tartrazine (0.44 mg), they reported that 3/20 (15%) experienced a 20% drop in forced expiratory volume in 1 second (FEV1) values during

challenges with tartrazine. Whether or not asthma medications were withheld during the challenges was not stated.

Stenius and Lemola conducted oral challenge studies using small doses of tartrazine (0.1–10 mg). Following ingestion of tartrazine, 25/114 (22%) unselected asthmatics dropped their peak flow measurements by 20% from baseline values. In the same study, a separate population of 25 aspirin-sensitive asthmatics underwent tartrazine challenges and 12 (50%) reacted with a >20% decline in peak flow values.

It is generally agreed that peak flow measurements are less reproducible than timed flow/volume measurements [21,22]. Most investigators use flow/volume spirometry and obtain FEV1 values during repetitive measurements of lung function. This subject was reviewed in detail by Stevenson [23]. During placebo challenges, in patients with irritable airways, FEV1 values have been documented to decline by as much as 43%. Therefore, it is incumbent upon the investigator to treat the underlying asthma, demonstrate that the FEV1 values do not vary by more than 10% during placebo challenges even before beginning single- or double-blind challenge studies. Most investigators use a 20% or more decline in FEV1 as evidence of bronchospasm during challenge studies, assuming that the baseline challenge with placebo was stable [23]. Despite everything stated above, in a 1977 report by Freedman, a 14% decline in FEV1 was used as an endpoint for “an asthmatic reaction to tartrazine” and was provided as proof that a tartrazine-induced bronchospastic reaction had occurred [24].

Spector and co-workers conducted one of the largest studies investigating the prevalence of tartrazine-associated bronchospasm [25]. In their studies, bronchodilators were withheld for 6–12 hours before beginning double-blind oral challenges with one challenge substance (or placebo) each day during inpatient hospitalizations. A 20% decline in FEV1 values, when compared to the placebo day, was considered to be evidence of a bronchospastic reaction. Tartrazine provoking doses ranged from 1 to 50 mg. The results of their study are summarized as follows. There were 277 asthmatic patients in their study. All were challenged with aspirin and 44/277 (16%) experienced respiratory reactions. Of the remaining 233 aspirin-tolerant patients, none experienced a 20% decline in FEV1 values on the days they ingested tartrazine. By contrast, when the 44 aspirin-sensitive asthmatics were challenged with tartrazine, 11 (25%) experienced a 20% decline in FEV1 values. Unfortunately, of the 11 tartrazine reactors, “5 did not undergo placebo challenges” (i.e. did not have a placebo challenge baseline day with proven airway stability before challenges with tartrazine). Thus the authors, stopped anti-asthmatic medications in a group of aspirin-sensitive asthmatics, whose asthma was severe enough to be admitted to National Jewish Hospital, failed to consistently perform baseline placebo challenges and then noted a 20% decline in FEV1 values during challenges with tartrazine. Were these changes in lung function due to

discontinuing anti-asthmatic medications, inherent hyperirritability of the airways or did these patients have tartrazine- and aspirin-induced asthma?

The most revealing study in this area of controversy was performed by Weber and associates [26]. Using standard single-blind oral aspirin challenges, they identified 13 of 44 asthmatic patients as having aspirin-sensitive asthma. After challenges with tartrazine, in doses ranging from 2.5 to 25 mg and withholding morning bronchodilators, 7/44 (16%) of the patients experienced a 20% decline in FEV1 values. Tartrazine challenges were repeated in the same 7 patients 1 week later and this time they received their morning bronchodilator medications. During these follow-up challenges, using the same “provoking dose” of tartrazine, FEV1 values remained steady throughout the testing period and therefore none could be categorized as having tartrazine-induced asthma. These patients were also challenged with six other azo dyes and did not experience any reactions. If one took the position that morning bronchodilator treatment prevented the tartrazine reactions, one is faced with the task of explaining why 13/44 (30%) of these patients experienced a 20% or more decline in their FEV1 values during oral challenges with aspirin while taking the same bronchodilators. In a study by Vedanthan and associates, 49 aspirin-tolerant children and 5 aspirin-sensitive asthmatic children underwent oral challenges with tartrazine [27]. Standard asthma medications, including cromolyn, theophylline, and corticosteroids, were continued during the challenges. None of the subjects reacted to tartrazine. The 5 aspirin-sensitive asthmatics, during aspirin challenges, experienced a >20% decline in FEV1 values. Therefore, the endpoint of a 20% decline in FEV1 values, as evidence of induced bronchospasm, was sensitive enough to detect changes in bronchial airways during aspirin challenges. If tartrazine was comparable to aspirin and could actually provoke bronchospasm, might we have expected this to occur in some of the 5 aspirin-sensitive asthmatic children?

In a study of adult asthmatics by Tarlo and Broder bronchodilators were continued. One of 26 aspirin-tolerant asthmatics experienced a “wheezing reaction” and a >20% decline in FEV1 values during a double-blind challenge with tartrazine [28]. The first point of this chapter is the disassociation between aspirin sensitivity and tartrazine-induced asthma. Secondly, the authors stated that elimination of tartrazine from the diet in this patient did not have any effect on the course of her asthma. This chapter is instructive, since the original premise of detecting tartrazine-induced asthma was to then advise the patient to avoid tartrazine and improve their asthma. Although, one patient provides only an anecdotal report, proponents of the theory that “dietary tartrazine causes asthma” did not gain support from this patient’s clinical course [17,20,25].

In the largest series of aspirin-sensitive asthmatics undergoing single-blind, tartrazine challenges, Stevenson and

associates were unable to detect tartrazine-induced asthma in any of 150 aspirin-sensitive asthmatics [13]. The protocol for this study was as follows. All patients were admitted to an inpatient General Clinical Research Center. Regular asthma controller medications were continued (inhaled corticosteroids, theophylline, long-acting bronchodilators, and in a minority of patients systemic corticosteroids). All patients underwent single-blind, placebo-controlled oral challenges. If the baseline placebo challenges were stable ($<10\%$ change in FEV1 values over 3 hours), tartrazine 25 mg in a green capsule was given. If FEV1 did not decline by 20% from baseline at 3 hours, 50 mg of tartrazine was given and FEV1 values were obtained every hour for an additional 3 hours. If FEV1 values dropped by 20% during one of the tartrazine challenges, patients were re-scheduled for a repeat double-blind tartrazine challenge at a later date. However, if the single-blind tartrazine challenge was negative ($<15\%$ change in FEV1), the patient was classified as not having tartrazine-induced asthma. After tartrazine challenges were completed, all 150 patients underwent single-blind oral aspirin challenges on the next day while taking the same four controller medications. Asthmatic reactions ($>20\%$ decline in FEV1) occurred in all 150 patients. Only those patients with a positive oral aspirin challenge were classified as having aspirin-sensitive asthma and were included in this study.

Of the 150 patients, 6 experienced a 20% or more drop in FEV1 values, compared to placebo challenges during the single-blind screening challenges with tartrazine (either coinciding with the 25- or 50-mg tartrazine doses). These six patients were re-challenged with the same provoking dose of tartrazine in a double-blind, placebo-controlled oral challenge protocol at a later date. None reacted to tartrazine during these double-blind challenges. At the time of re-challenge, none of the patients were participating in aspirin-desensitization treatment and all were taking the same or less asthma controller medications as they were during the first tartrazine challenges. These studies were extended when another 44 aspirin-sensitive asthmatic patients underwent oral single-blind tartrazine challenges at the same institution [29]. Again, none of the patients reacted to 25 and 50 mg of tartrazine.

A 1986 study from Poland identified tartrazine sensitivity during oral challenges in 16/51 (31.4%) of aspirin-sensitive asthmatic patients [30]. The authors reported that 5 of the 18 aspirin-sensitive asthmatics also experienced reactions (dyspnea) to tartrazine and when these same 5 were desensitized to aspirin they could then take tartrazine without adverse effects. Obviously, there was something radically different about the results of this study and the study by Stevenson *et al.* [13]. If the study from Poland was accurate, with a tartrazine cross-challenge rate of 31.4% [30], Stevenson *et al.* [13,29] should have identified 61/194 (31.4%) tartrazine-sensitive patients in order to equal the percentage identified by this Polish study.

In a large multi-institutional study in Europe, including patients from Poland, 156 known aspirin-sensitive asthmatic patients underwent screening single-blind oral challenges with tartrazine [31]. Of the 156 participants, 4 (2.6%) reacted to 25 mg of tartrazine with a 25% decline in FEV1 values during single-blind challenges. At another time, these four patients were re-challenged with the same dose of tartrazine. Again, the four patients experienced a 25% decline in FEV1 values during double-blind tartrazine challenges. A full day of placebo challenges may have been performed for each patient before starting tartrazine single-blind challenges but was not reported in their paper. However, comparative placebo challenges were conducted as part of the double-blind, placebo-controlled follow-up challenges. The authors of this study are well-known investigators with extensive experience in conducting oral challenges. The extremely low prevalence of positive single- and double-blind challenge studies with tartrazine (2.6%) in the 1988 European study contrasts sharply with the 31.4% prevalence in the 1986 study from Poland. Assuming that Polish patients were equally represented in the 1988 study, within 2 years, the prevalence of tartrazine sensitivity appeared to drop by 29%. Such a decline seems unlikely.

On the basis of scientific facts, what conclusions can be drawn from the literature on this subject? First, many of the early studies reporting large numbers of asthmatics with tartrazine reactions were actually measuring spontaneous asthma in patients whose anti-asthmatic medications were inadequate or had been discontinued before the challenges. Most of the high prevalence rates of positive respiratory reactions to tartrazine are simply not credible. Even the very large study by Spector *et al.* [25] where 11/44 (25%) aspirin-sensitive asthmatics were said to have tartrazine-induced asthma had serious methodological flaws in the performance of the challenges.

Second, there are probably a few patients with reactions to tartrazine, which include urticaria [13] and or bronchospasm [28,31]. Whether or not these reactions are IgE mediated is unknown. However, such a mechanistic explanation is more attractive than the idea that tartrazine participates in COX-1 inhibiting cross-reactions. In fact, it has been shown that tartrazine does not inhibit cyclooxygenase *in vitro* [32]. Since inhibition of COX-1 is the mechanism by which NSAIDs and aspirin cross-react, the Gerber data [32] eliminate any possibility that tartrazine and aspirin are cross-reactors. COX-1 inhibiting NSAIDs, on a dose-dependent basis, cross-react in aspirin-sensitive asthmatics 100% of the time and the weak inhibitors of COX-1, acetaminophen and salsalate, cross-react 34% and 20% when given in usually therapeutic doses, respectively [33–37]. Since all the NSAIDs that cross-react with aspirin inhibit COX-1 and tartrazine does not inhibit COX-1, there is no rational reason to suspect cross-reactivity between aspirin and tartrazine.

Except for the Samter study in 1968 [20], Spector study in 1979 [25], and the 1986 Polish study [30], the link

between aspirin-sensitive asthma and tartrazine-induced asthma is not supported by any of the more recent and larger studies [23,29,31]. Furthermore, the study by Tarlo and Broder [28], where tartrazine-induced asthma was found in an aspirin-tolerant asthmatic, and the two studies by Stevenson and colleagues [13,29], where tartrazine-induced asthma was not found in 194 aspirin-sensitive asthmatics, make it difficult to link aspirin sensitivity with tartrazine-induced asthma attacks. Even the European study of tartrazine-induced asthma found only 4/156 (2.6%) aspirin-sensitive asthmatics that also reacted to tartrazine. Their reported incidence of 2.6% is too low to qualify as a cross-reacting chemical.

Finally, with respect to recommendations to patients, it is logical to warn all aspirin-sensitive asthmatics and chronic urticaria patients to avoid cross-reacting NSAIDs, acetaminophen, salsalate [38,39]. However, to make the same recommendation for tartrazine is not logical. Arguably, in the entire medical literature, there are only five proven cases of tartrazine-induced asthma, where double-blind challenges were conducted [28,31]. In 194 aspirin-sensitive asthmatics [13,29] there were no patients who experienced asthmatic reactions to tartrazine. In the Tarlo and Broder report, even when a case of tartrazine-induced asthma was discovered, elimination of tartrazine in the diet of that individual did not change the course of her ongoing asthma [28]. In an extensive online review of 90 articles on the subject of tartrazine challenges and avoiding tartrazine in the diet of asthmatics, only 18 articles were potentially relevant. None of these articles presented evidence in which either challenge with tartrazine or avoidance of tartrazine in the diet significantly altered asthma outcomes in the study subjects [40]. Therefore, rather than making generalized recommendations regarding tartrazine avoidance in any population of asthmatic patients, my recommendation would be to screen patients on the basis of history and conduct oral challenges with tartrazine in those who gave a positive history. In those rare patients who experienced bronchospasm during double-blind, placebo-controlled tartrazine challenges, one could consider, with no literature support for such action, recommending avoidance of tartrazine on a trial basis. Reporting the results of such a rare occurrence and potential dietary manipulation in a letter to the editor of an allergy journal would be helpful and appropriate in view of the rarity of these reactions.

Rhinitis associated with ingestion of dyes

There are patients with allergic and non-allergic rhinitis who have observed that rhinitis symptoms are worse, when ingesting diets which contain tartrazine, monosodium glutamate, *p*-hydroxybenzoate, sodium metabisulfites, and monosodium benzoates. Furthermore, preservative-free diets have been used to improve nasal symptoms in some

patients. Are these effects real and if so how commonly does it occur? In 226 patients with both allergic and non-allergic rhinitis, an additive-free diet was prescribed as a baseline for 1 month. They were then switched to an additive-rich diet for the next 2 weeks. Of the 226 patients only 20 (8.8%) showed improvement while on the preservative-free diet and exacerbation on the additive-rich diet. This group of 20 then became the study group. Patients reported to the clinic in Verona, Italy, and underwent double-blind, placebo-controlled challenges with symptoms plus nasal peak inspiratory flow (NPIFR) measurements: The results showed that acute nasal symptoms and change in NPIFR occurred in 19/20 (95%) with monosodium benzoate, 3/20 (15%) with *p*-hydroxybenzoate, 2/20 (10%) with tartrazine, 7/20 (35%) with erythrosine, 6/20 (30%) with sodium metabisulfite, and 8/20 (40%) with monosodium glutamate. For tartrazine, a 2/226 (0.08%) incidence in a general population of patients with allergic and non-allergic rhinitis is obviously quite low and makes tartrazine ingestion an unusual cause of nasal symptoms. However, nasal congestion and rhinorrhea did occur in two patients and for those two individual, with exacerbation of nasal symptoms while ingesting tartrazine in the diet, this discovery was significant. From a practical standpoint, a preservative-free diet (all fresh foods) for 2–4 weeks is a reasonable way to screen for these unusually preservative, additive, tartrazine-induced rhinitis patients.

Anaphylaxis from ingestion of dyes

There is a case report by Caucino *et al.* [41] of anaphylaxis after ingesting an estrogen tablet with FD & C red no. 40 and FD & C yellow no. 27. A puncture prick test of the skin with a suspension of the ground up estrogen tablet, including the dyes and other excipients, induced a wheal and flare cutaneous response. Prick tests to the estrogen and other excipients was negative. Oral challenges with the two azo dyes were not performed. This case then becomes at best a probable dye-induced anaphylaxis. Other reports of anaphylaxis in the literature could not be found and a review of the subject found no causal connection between anaphylaxis and azo dyes [42].

Atopic dermatitis reactions

In a small study of 12 children, ages 1–6 years, with atopic dermatitis, multiple double-blinded challenges with tartrazine 50mg were performed [43]. The 12 children were selected for the study because they had severe and intractable atopic dermatitis and a parental history that tartrazine ingestion caused flares of their dermatitis. In one child, flares of dermatitis occurred during the three tartrazine challenges but not when placebos were administered. Both the symptom scores and the physician observer scores were

significantly and consistently increased only after tartrazine challenges. In a sample of 12 patients, the fact that three positive challenges with tartrazine and three negative challenges with placebo would occur by chance alone was 0.46. Balanced against the fact that tartrazine sensitivity was probably observed in 1/12 patient is the striking prevalence of non-reactions in other 11/12 atopic children. In all 12 patients, the parents were convinced that tartrazine was a provoking agent. This is consistent with a desire on the part of parents to fix their child's chronic disease by eliminating something. Since dyes and preservatives are found in many foods, drinks, and color-coded pills, there is a strong chance that a flare of dermatitis will coincidentally occur at the same time as a remembered ingestion of a dietary dye. Advertising of this relationship in the lay press has further increase the chances that the parents will notice dyes as the perceived "cause" of their child's atopic dermatitis. The above discussion is not designed to say that tartrazine can never exacerbate atopic dermatitis but to realize that the relationship is over-diagnosed, helped along by a willing Internet, newspaper, and magazine reporting system.

From Berlin, Germany, Prof. Worm and colleagues [44] stimulated peripheral leukocytes from patients with atopic dermatitis, using food additives and dyes. Only in the patients with positive itch rash response to additives, there was synthesis of leukotrienes (LTs) *in vitro* when specific dyes and additives were added to the leukocytes mixture. Only 1/9 patients synthesized LTs *in vitro* after addition of tartrazine. Other food additives which induced *in vitro* synthesis of LTs were benzoate and nitrites. This investigation is interesting because it provides a biochemical explanation for why these rare events might occur.

Contact dermatitis to tartrazine and azo dyes

Azo dyes are skin sanitizers and can induce delayed hypersensitivity reactions of the skin in a small number of patients [45]. Positive patch tests to tartrazine and other azo dyes have been documented in a few patients [46]. Skin contact with azo dyes is most likely to occur in textile workers [47] or in customers who wear clothes that are new and have been colored with azo dyes.

Other cutaneous reactions to tartrazine and azo dyes

Purpura after ingestion of tartrazine has been reported [48–50]. In addition hypersensitivity vasculitis has been documented in patients who were ingesting tartrazine on a regular basis [51]. Discontinuing tartrazine was associated with disappearance of vasculitis in some cases [52]. A case report of fixed drug eruption from eating cheese crisp (containing tartrazine) has been reported [53].

Hyperkinesis and tartrazine

Hyperkinesis and learning disorders have been attributed to ingestion of tartrazine in children [54,55]. There is considerable controversy surrounding this subject and some authors do not believe that tartrazine has any effects on either hyperkinesis or learning disorders [56]. In reviewing the literature it is difficult to draw a definitive conclusion. This is largely because reports of tartrazine-induced effects on mental function and behavior are plagued by poorly designed studies, imprecise definitions of hyperactivity, and poor reliability of behavioral outcome measures. Furthermore, it has been difficult to define study populations and segregate them from the background noise of a larger heterogeneous population of children. Placebo effects, as detected by vigilant parents, have consistently reflected parental attitudes and bias in favor of tartrazine as a perceived cause of their child's problems. A number of articles, where poorly performed studies of tartrazine and hyperkinesis were reported, were not selected for mention in this review.

Despite this gloomy introduction, there are a few studies that address most of the investigative issues and present a reasonable case in support of occasional children having tartrazine-induced mental abnormalities. Swanson and Kinsbourne [57] conducted oral tartrazine challenges in 40 hyperactive children with up to 150mg of tartrazine in 1 day. The performance of the hyperactive children was impaired on the days they received tartrazine but not on the days when they received placebos. The control children, without a diagnosis of hyperkinesis, did not experience any differences in behavior on any days, whether ingesting the dye or placebo.

In another study, Rowe examined 220 children referred because of suspected dye-induced behavior problems [58]. After interviewing all 220 children, the author admitted 55 to the study as a core group of suspected tartrazine-induced behavioral disorders. Further screening was then employed by restricting the children's diets to avoid dyes and preservatives over a study period of 6 weeks. By the end of this screening period, 40/55 (73%) of the parents reported improvement in their child's behavior. Of these 40 children, 14 were said to strongly exhibit abnormal behavior, when ingesting foods containing azo coloring. For eight of these highly selected children, the parents agreed to enroll them in a double-blind, placebo-controlled crossover challenge study. Each day, the children received placebo, tartrazine, or carmoisine, over a study period of 2 weeks. When the codes were broken, only 2/8 (25%) showed any correlation with ingestion of the dyes and abnormal behavior. The remaining six subjects did experience behavioral changes but such changes occurred on placebo days as well as days when the dyes were given. In summary, of 220 subjects, whose parents thought that tartrazine induced behavioral changes; in only 2 subjects double-blind, placebo-controlled dye challenges correlated with behavior changes.

The authors extended their studies in a group of 24 patients, selected during challenge studies, from a referral population of 800 children, suspected by their parents of having hyperkinesia secondary to ingestion of tartrazine [59]. A dose-response effect was discovered during double-blind, placebo-controlled challenge tests in these 24 study subjects. The minimal dose of tartrazine associated with hyperactivity in affected children was 10 mg/day. However, some children did not become hyperactive until they received much larger doses.

Their first conclusion was that only a small number of children, suspected of having dye-induced behavioral problems, are actually affected by the dyes. Second, a dose of at least 10 mg of tartrazine was required before any behavioral changes in the affected population of children were observed. This makes it difficult to implicate color-coded tablets and capsules, where the total dose of dye is <1 mg. Finally, although the evidence is rather persuasive that dye-induced behavioral changes can occur in an occasional child, who ingests moderate to large doses of dyes, the claim that most children with behavioral disorders are the victims of dye-induced reactions is not supported by the facts.

Conclusions

Although a few well-designed studies have been conducted, the azo dye literature is filled with studies that are not of high quality and report dye-induced pathologic events, sometimes in large numbers of patients. After sifting through the maze of claims against tartrazine and other azo dyes, the paucity of documented adverse events caused by these dyes is apparent. Except for rare patients who experience mild asthma or urticaria and a few other rashes as a consequence of exposure to azo dyes, the vast majority of humans tolerate these chemicals without any problem. In fact the overwhelming majority of claims against azo dyes, and particularly the well-advertised tartrazine yellow no. 5, are mistaken identity and misdirected blame.

References

- Simon RA, Stevenson DD. Adverse reactions to food and drug additives. In: Middleton Jr E, Reed CE, Ellis EF, Adkinson Jr NE, Yunginger JW, Busse WW (eds.) *Allergy, Principles and Practice*. St. Louis, MO: Mosby, 1993;2:1687-1704.
- Simon RA. Adverse reactions to drug additives. *J Allergy Clin Immunol* 1984;74:623-30.
- Lockey S. Allergic reactions due to FD & C yellow #5 tartrazine, an aniline dye used as a coloring agent in various steroids. *Ann Allergy* 1959;17:719-25.
- Juhlin L, Michaelsson G, Zetterstrom O. Urticaria and asthma induced by food and drug additives in patients with aspirin sensitivity. *J Allergy Clin Immunol* 1972;50:92-102.
- Michaelsson G, Juhlin L. Urticaria induced by preservatives and dye additives in food and drugs. *Br J Derm* 1973;88:525-32.
- Ros A, Juhlin L, Michaelsson G. A follow up study of patients with recurrent urticaria and hypersensitivity to aspirin, benzozates and azo dyes. *Br J Derm* 1976;95:19-27.
- Juhlin L. Recurrent urticaria: clinical investigation of 330 patients. *Br J Derm* 1981;104:369-81.
- Doeglas H. Reactions to aspirin and food additives in patients with chronic urticaria, including physical urticaria. *Br J Derm* 1975;93:135-43.
- Thune P, Granholt A. Provocation tests with antiphistologics and food additives in recurrent urticaria. *Dermatologica* 1975;151:360-4.
- Gibson A, Clancy R. Management of chronic idiopathic urticaria by the identification and exclusion of dietary factors. *Clin Allergy* 1980;10:699-705.
- Settipane G, Pudupakkam RK. Aspirin intolerance III: subtypes, familial occurrence and cross-reactivity with tartrazine. *J Allergy Clin Immunol* 1975;56:215-21.
- Settipane G, Chafee H, Postman M, Levine MI. Significance of tartrazine sensitivity in chronic urticaria of unknown etiology. *J Allergy Clin Immunol* 1976;57:541-6.
- Stevenson DD, Simon RA, Lumry WR, Mathison DA. Adverse reactions to tartrazine. *J Allergy Clin Immunol* 1986;78:182-91.
- Murdoch R, Pollack I, Young E, Lessof MH. Food additive induced urticaria: studies of mediator release during provocation test. *J R Coll Phys Lond* 1987;21:262-6.
- Nettis E, Colanardi MC, Ferrannini A, Tursi A. Suspected tartrazine induced acute urticaria/angioedema is only rarely reproduced by oral rechallenge. *Clin Exp Allergy* 2003;33:1725-9.
- Simon R. Adverse reactions to food additives. *N Engl Reg Allergy Proc J Med* 1986;7:533-42.
- Speer K. *The Management of Childhood Asthma*. Springfield, IL: Charles C Thomas, 1958.
- Chafee FH, Settipane G. Asthma caused by FD & C approved dyes. *J Allergy* 1967;40:65-9.
- Samter M, Beers RF. Concerning the nature of the intolerance to aspirin. *J Allergy* 1967;40:281-93.
- Samter M, Beers Jr R. Intolerance to aspirin: clinical studies and consideration of its pathogenesis. *Ann Int Med* 1968;68:975-83.
- Kory R, Hamilton LH. Evaluation of spirometers used in pulmonary function studies. *Am Rev Respir Dis* 1963;87:228-36.
- Fitzgerald M, Smith AA, Gaensler EA. Evaluation of electronic spirometers. *N Eng J Med* 1973;289:1283-6.
- Stevenson DD. Oral challenges to detect aspirin and sulfite sensitivity in asthma. *N Engl Reg Allergy Proc* 1988;9:135-42.
- Freedman B. Asthma induced by sulfur dioxide, benzoate and tartrazine contained in orange drinks. *Clin Allergy* 1977;7:407-11.
- Spector SL, Wangaard CH, Farr RS. Aspirin and concomitant idiosyncrasies in adult asthmatic patients. *J Allergy Clin Immunol* 1979;64:500-6.
- Weber RW, Hoffman M, Raine DA, Nelson HS. Incidence of bronchoconstriction due to aspirin, azo dyes, non-azo dyes, and preservatives in a population of perennial asthmatics. *J Allergy Clin Immunol* 1979;64:32-7.

- 27 Vedanthan PK, Menon MM, Bell TD, Bergin D. Aspirin and tartrazine oral challenge: incidence of adverse response in chronic childhood asthma. *J Allergy Clin Immunol* 1977;60:8–13.
- 28 Tarlo S, Broder I. Tartrazine and benzoate challenge and dietary avoidance in chronic asthma. *Clin Allergy* 1982;12:303–12.
- 29 Stevenson DD, Simon RA, Lumry WR, Mathison DA. Pulmonary reactions to tartrazine. *Pediatr Allergy Immunol* 1992;3:222–7.
- 30 Grzelewska-Rzymowska I, Szmidi M, Kowalski ML, Rozniecki J. Sensitivity and tolerance to tartrazine in aspirin-sensitive asthmatics. *Allergol Immunopathol (Madr)* 1986;14:31–6.
- 31 Virchow CH, Szczeklik A, Bianco S. Intolerance to tartrazine in aspirin-induced asthma: results of a multicenter study. *Respiration* 1988;53:20–3.
- 32 Gerber JG, Payne NA, Oelz O, *et al.* Tartrazine and the prostaglandin system. *J Allergy Clin Immunol* 1979;63:289–94.
- 33 Mathison DA, Stevenson DD. Hypersensitivity to non-steroidal anti-inflammatory drugs: indications and methods for oral challenge. *J Allergy Clin Immunol* 1979;64:669–74.
- 34 Stevenson DD. Cross-reactivity between aspirin and other drugs/dietary chemicals: a critical review. In: Pichler WJ, Stadler MM, Dahinden CA, Pecoud AR, Frei P, Schneider CH, deWeck AL (eds.) *Progress in Allergy and Clinical Immunology*. Lewiston, New York: Hogrefe and Huber, 1989;1:462–73.
- 35 Stevenson DD, Simon RA. Aspirin sensitivity: respiratory and cutaneous manifestations. In: Middleton E, Reed CE, Ellis EF (eds.) *Allergy: Principles and Practice*, 3rd edn. St. Louis, MO: CV Mosby, 1988;2:1537–54.
- 36 Settipane RA, Shrank PJ, Simon RA, *et al.* Prevalence of cross-sensitivity with acetaminophen in aspirin-sensitive asthmatic subjects. *J Allergy Clin Immunol* 1995;96:480–5.
- 37 Stevenson DD, Hougham A, Schrank P, *et al.* Disalcid cross-sensitivity in aspirin sensitive asthmatics. *J Allergy Clin Immunol* 1990;86:749–58.
- 38 Stevenson D. Approach to the patient with a history of adverse reactions to aspirin or NSAIDs: diagnosis and treatment. *Allergy Asthma Proc* 2000;21:25–31.
- 39 Stevenson DD, Sanchez-Borges BM, Szczeklik A. Classification of allergic and pseudoallergic reactions to drugs that inhibit cyclooxygenase enzymes. *Ann Allergy Asthma Immunol* 2001;87:177–80.
- 40 Arden K, Ram FS. Tartrazine exclusion for allergic asthma. *Cochrane Database Syst Rev* 2001;4:460.
- 41 Caucino J, Armeneka M, Rosensteich DL. Anaphylaxis associated with a change in Premarin dye formulation. *Ann Allergy* 1994;72:33–5.
- 42 Rues KE, Houben GM, Stam M, Dubois AE. Food additives as a cause of medical symptoms. *Ned Tijdschr Geneeskde* 2000;144:1836–9.
- 43 Devlin J, David TJ. Tartrazine in atopic dermatitis. *Arch Dis Child* 1992;67:709–11.
- 44 Worm M, Vieth W, Ehlers I, *et al.* Increased leukotriene production by food additives in patients with atopic dermatitis. *Clin Exp Allergy* 2001;31:265–73.
- 45 Theirbach M, Geursen-Reitsma AM, Van Joost T. Sensitization to azo dyes. *Contact Derm* 1992;27:22–6.
- 46 Roeleveld C, Van Ketel WG. Positive patch test to the azo dye tartrazine. *Contact Derm* 1976;2:180–3.
- 47 Hatch KM, Maibach HI. Textile dermatitis. *J Am Acad Dermatol* 1995;32:631–9.
- 48 Criepp L. Allergic vascular purpura. *J Allergy Clin Immunol* 1971;48:7–12.
- 49 Michaelsson G, Pettersson L, Juhlin L. Purpura caused by food and drug additives. *Arch Dermatol* 1974;109:49–53.
- 50 Kubba R, Champion RH. Anaphylactoid purpura caused by tartrazine and benzoates. *Br J Dermatol* 1975;93:61–8.
- 51 Lowry M, Hudson CF, Callen JP. Leukocytoclastic vasculitis caused by drug additives. *J Am Acad Dermatol* 1994;30:854–5.
- 52 Parodi G, Parodi A, Rebora A. Purpuric vasculitis due to tartrazine. *Dermatologica* 1985;171:62–3.
- 53 Orchard DC, Varigos GA. Fixed drug eruption to tartrazine. *Australas J Dermatol* 1997;38:212–14.
- 54 Finegold B. Hyperkinesia and learning disabilities linked to artificial flavors and colors. *Am J Nurs* 1975;75:797–803.
- 55 Colins-Williams C. Clinical spectrum of adverse reactions to tartrazine. *J Asthma* 1985;22:139–43.
- 56 David T. Reactions to dietary tartrazine. *Arch Dis Child* 1987;62:119–22.
- 57 Swanson J, Kinsbourne M. Food dyes affect performance of hyperactive children on a laboratory learning test. *Science* 1980;207:1485–91.
- 58 Rowe K. Synthetic food colorings and hyperactivity: a double blind cross-over study. *Aust Paediatr J* 1988;24:143–7.
- 59 Rowe K, Rowe KJ. Synthetic food coloring and behavior: a dose response effect in a double blind, placebo controlled, repeated measures study. *J Pediatr* 1994;125:691–8.