Australian Government
Department of Health
Therapeutic Goods Administration

Toxicity of tartrazine

Scientific review report

Version 1.0, February 2014

TGA Health Safety Regulation

About the Therapeutic Goods Administration (TGA)

- The Therapeutic Goods Administration (TGA) is part of the Australian Government Department of Health, and is responsible for regulating medicines and medical devices.
- The TGA administers the *Therapeutic Goods Act 1989* (the Act), applying a risk management approach designed to ensure therapeutic goods supplied in Australia meet acceptable standards of quality, safety and efficacy (performance), when necessary.
- The work of the TGA is based on applying scientific and clinical expertise to decision-making, to ensure that the benefits to consumers outweigh any risks associated with the use of medicines and medical devices.
- The TGA relies on the public, healthcare professionals and industry to report problems with medicines or medical devices. TGA investigates reports received by it to determine any necessary regulatory action.
- To report a problem with a medicine or medical device, please see the information on the TGA website <http://www.tga.gov.au>.

Version history

Version	Description of change	Author	Effective date
V1.0	Original publication	Office of Scientific Evaluation	Feb 2014

Contents

1. Introduction

The TGA and MedSafe are engaged in several ANTZPA harmonisation activities under the Common Regulatory Framework Programme. One of these involves the development of a common list of colouring substances allowed for use in medicines. A comparison of the two lists of colouring substances allowed in Australia and New Zealand revealed that the New Zealand list contains tartrazine allowed for both oral and external use in New Zealand but is only allowed for external use in Australia. When used in products for internal use in New Zealand, the product label has to state that the product contains tartrazine. Tartrazine is a permitted food colour in both Australia and New Zealand.

In the interest of harmonisation, a proposal was put forward to the ANTZPA Trans-Tasman Senior Officials Group (TTSOG) that:

> *"Australia should consider adding tartrazine to its list of colours allowed in medicines for oral use and, consistent with international practice, require the medicine label to state that the product contains tartrazine".*

In response to this proposal, this review of tartrazine was undertaken by the TGA.

2. Historical background in Australia

In 1983, in response to media reports and published papers, the then Australian Drug Evaluation Committee (ADEC) recommended a ban on the use of tartrazine for oral ingestion due to potential hypersensitivity reactions. At its 109th meeting (1983/2), ADEC recommended that no new applications for products containing tartrazine should be accepted (Res No 2374B). Since that time it has been the policy of the TGA not to accept such products.

The restriction was not extended to topical or lipstick products because of the relative lack of absorption through the skin. At the time, there were no animal toxicity data on the subject. A detailed literature search failed to reveal any convincing clinical or scientific evidence to support a ban for topical products. The use in sunscreens and 'chapsticks' and the very low level of reported incidences of sensitivity added support to ADEC's decision.

3. Review criteria and search terms

With the help of the TGA library, the TGA undertook a thorough search of the literature from the 1970s to the present for peer-reviewed publications dealing with the toxicity of tartrazine and consumption of tartrazine and its possible correlation with hyperactivity and behavioural changes. The search included both animal and human studies.

The review is based on several published papers (up to May 2013), as well as on reviews of international authorities in the public domain as listed in the Bibliography. The following databases were searched: TOXLINE, TOXNET, PUBMED, Medline, Embase, Biosis, and a Dialog search on a large number of medical and pharmaceutical databases.

4. Use in other products

Many processed foods contain the dye, including dairy products, juices, pickles, candies and cake mixes, as well as cosmetics and toiletries. It is also found in many drug products that were approved prior to ADEC's 1983 recommendation. The amounts range between 0.001 to 2.5 mg.

Tartrazine is included in the Food Standards Code; Schedule 4 of Standard 1.3.1 Food Additives. Schedule 4 allows tartrazine in certain foods and beverages up to maximum 0.29 mg/g and 0.07 mg/mL, respectively. It also states that certain beverages (such as carbonated, mineralised and soda waters specified in Schedule 1) are exempted from this quantity restriction.

The acceptable daily intake (ADI) is the amount of a substance that can be taken every day for an entire lifetime without any adverse effect. Tartrazine has an ADI of up to 7.5 mg/kg bodyweight, which was established by Joint FAO/WHO Expert Committee on Food Additives (JECFA) in1964. Recent reviews have concluded that a revision of the ADI based on the available data is not warranted. A dietary exposure assessment predicted that tartrazine consumption for children aged between 2 and 16 years in Australia, even at the highest daily consumption, would be between 0.21 and 0.38 mg/kg bodyweight (which corresponds to between 3 and 5% of the ADI). Elhkim *et al*. (2007) recently conducted a toxicological assessment and their bibliographical review of animal studies confirmed the initial hazard assessment conducted by JECFA (1964) and the ADI of 7.5 mg/kg bw. They calculated that in France the estimated maximum theoretical intake of tartrazine in children is 37.2% of the ADI at the 97.5th percentile.

5. International regulatory status

Colouring agents have a unique status as pharmaceutical excipients and most regulatory agencies hold lists of colours that may be used in medicinal products. Restrictions or bans on the use of some colouring agents have been imposed in some countries, while the same colours may be permitted for use in a different country. As a result, the same colour (including tartrazine) may have a different regulatory status in different territories of the world.

5.1 European Union

Tartrazine (E 102) is authorised as a food additive in the EU[1] and is allowed to be used in medicines for oral use. The primary legislation governing colouring agents that may be used in medicinal products is Council Directive 78/25/EEC of 12 December 1977[2]. This Directive links pharmaceutical requirements with those of foods in the EU. There is a clause in EEC Directive 78/25 that states, "*Experience has shown that on health grounds there is no reason why the colouring matters authorized for use in foodstuffs intended for human consumption should not also be authorized for use in medicinal products.*" The Scientific Committee on Medicinal Products and Medical Devices (SCMPMD) on 21 October 1998 alluded to this clause in respect of other colourants; there is no specific opinion of the this committee (SCMPMD) on the use of tartrazine. But the European Commission has provided guidance on cross references to the current food colour legislation as contained in Council Directive 94/36/EC[3].

In the EU, Directive 89/107/EEC as well as Regulation (EC) 1333/2008 of the European Parliament and of the Council of 16 December 2008 on food additives, which has applied from 20 January 2010, require that food additives must be monitored and re-evaluated whenever necessary in the light of new scientific information. Accordingly, a re-evaluation of tartrazine (E102) was undertaken by the European Food Safety Agency (EFSA) in 2009.

[1] http://eur-lex.europa.eu/LexUriServ/LexUriServ.do?uri=OJ:L:2009:006:0020:0063:EN:PDF
[2] http://ec.europa.eu/health/files/eudralex/vol-1/dir_1978_25/dir_1978_25_en.pdf
[3] http://ec.europa.eu/food/fs/sfp/addit_flavor/flav08_en.pdf

5.2. UK

Tartrazine is permitted for use in oral medicines and must always be declared on the label.

5.3. Canada

Permitted in drugs for internal and external use (Food and Drug Regulations [C.R.C., c 870, Section C.01.040.2])[4].

5.4. USA

In the USA, 21 CFR 74.1505, 82.51 and 82.705 clearly state that "FD&C Yellow #5 (and associated lakes) may be safely used for coloring drugs generally, including drugs intended for use in the area of the eye, in amounts consistent with current good manufacturing practice."

There is a restriction in 21 CFR 74.1505 for prescription drugs that states that the labels for these products must bear the following warning statements: "This product contains FD&C Yellow #5 (tartrazine) which may cause allergic-type reactions (including bronchial asthma) in certain susceptible persons. Although the overall incidence of FD&C Yellow #5 (tartrazine) sensitivity in the general population is low, it is frequently seen in patients who also have aspirin hypersensitivity".

6. Toxicological assessment in animal studies

There have been several comprehensive reviews of the safety of tartrazine. The first risk assessment of tartrazine was conducted by JECFA followed by at least three evaluations by the EU Scientific Committee on Food (SCF, now known as EFSA) in 1975, 1984 and 2009 (EFSA 2009; EFSA 2010). Independently, reviews were also conducted by the National Health and Welfare Canada (Khera & Munro 1979) and by the Nordic Council of Ministers (2002) in Europe.

The sections below are a brief summary of salient features of the toxicology profile of tartrazine from a variety of animal studies.

6.1. Toxicokinetics

The absorption, distribution, metabolism and excretion of tartrazine have been studied in animals and humans. The majority of these studies were originally evaluated by JECFA (1966). Except for a few studies describing azoreduction by intestinal bacteria, no new data has been published since the JECFA review.

At a range of doses, absorption of orally administered intact tartrazine in humans and laboratory animals is less than 5%. The absorbed tartrazine is secreted in urine largely, unchanged. The remaining tartrazine is extensively metabolised by intestinal microflora; of which some metabolites are absorbed through the intestine. (JECFA 1964; Khera & Munro, 1979; reviewed by Elhkim *et al*. 2007, Watabe *et al*., 1980, EFSA 2009). Of these metabolites, sulfanilic acid is predominantly secreted by urine. Kuno & Mizutani (2005), using bovine liver microsomes that mimic human liver microsomes, showed that tartrazine is not a substrate for CYP2A6 and UDP-glucuronosyltransferase.

[4] http://laws-lois.justice.gc.ca/Search/Search.aspx?&h1dd3n1d=K8P9R3AAIINK-5&h1tNumb3r=1&ddC0nt3ntTyp3=ActsRegs&h1dd3nPag3Num=1&txtS3archA11=tartrazine&h1ts0n1y=0#results

6.2. Acute and chronic toxicity

Acute oral toxicity was assessed in rodents. In mice, the LD50 value was determined to be 12750 mg/kg bw (EFSA 2009; JECFA 1966) and in rats it was >2000 mg/kg/bw (EFSA 2009; Sasaki *et al*., 2002).

Several short-term and sub-chronic toxicity studies in rats, cats and dogs were reviewed by JECFA (1966). No tartrazine-related effects were reported for doses up to 500 mg/kg bw. A more recent rat study by Abdel-Zahab *et al*. 1997 (reviewed by EFSA 2009) examined the effects of two mixtures of colouring agents (up to 800 mg/kg/ bw), including tartrazine. However, the composition of the mixtures were not reported due to commercial-in-confidence issues. The EFSA panel concluded that it was difficult to assess the results of this study as the exposure of the animals to the individual food colours could not be determined.

Tartrazine was reported to produce neurotoxicity and deficits in learning and memory in animals (Gao 2011) at doses in excess of the acceptable daily intake (ADI) of tartrazine (0-7.5 mg/kg/day). However, it could not be excluded that exposure to tartrazine together with other dyes exerted toxicity by mechanisms involving synergistic process.

Long-term toxicity studies in rodents were reviewed by JECFA (1966). As confirmed by EFSA (2009), these studies were all conducted prior to the introduction of OECD guidelines and the establishment of Good Laboratory Practice. In the majority of these studies, when examined, there were no consistent or dose-related effects on behaviour, morbidity, mortality, haematology or the general physical observations.

6.3. Genotoxicity

Available evidence shows that tartrazine has no mutagenic potential in the majority of studies (reviewed by EFSA 2009; Elhkim *et al*, 2007; JECFA 1966; Rafii *et al*., 1997). However, other studies demonstrated that tartrazine has potential clastogenic activity. It was shown to induce chromosomal aberrations in Chinese hamster (Ishidate *et al*., 1981, 1984) and rat (Giri *et al*., 1990) somatic cells, but not in mice (Durnev *et al*., 1995). Sasaki *et al*. (2002), using the Comet assay, showed that tartrazine may induce transient DNA damage in the colon of mice at doses slightly above ADI. EFSA (2009) reviewed these latter studies and concluded that the transient DNA damage observed could be partly attributed to local cytotoxicity of the dye. However, in a more recent study, tartrazine did not reveal any genotoxic effect in the micronucleus assay in mice at doses up to 2000 mg/kg bw (Poul *et al*., 2009 reviewed by EFSA 2009).

The biological significance of the positive genotoxicity results is uncertain in view of the negative carcinogenicity studies.

6.4. Carcinogenicity

No evidence of carcinogenicity was observed in studies reviewed by JECFA (1964) nor in recent studies conducted in mice and rats (Borzelleca & Hallagan 1988; Maekawa *et al*., 1987; Moutinho *et al*., 2007).

Tartrazine in drinking water (1-2%) showed no carcinogenic effects in two-year toxicity study of rats (Maekawa *et al*., 1987). In the studies reported by JECFA (1964), tartrazine was administered orally at doses up to 5% of the diet to rats and 1% to mice. Maekawa *et al*. (1987) administered tartrazine *ad libitum* in the drinking water at levels ranging from 0.1% to 2% for as long as two years while those described by Borzelleca & Hallagan (1988) mice were exposed to dietary levels of 0-5%.

6.5. Reproductive toxicity

Reproductive studies show that tartrazine does not have teratogenic effects on rats or rabbits and no adverse effects on reproductive parameters were recorded in one-generation studies at doses up to 2% in the diet (JECFA 1964; reviewed by Elhkim *et al*., 2007; Tanaka 2006). Behavioural development of offspring was not affected in any of these studies. The No Adverse Effect Level in rats was 5% tartrazine in the diet (2641 and 3348 mg/kg/day in male and female rats, respectively; Borzelleca & Hallagan 1988b) and 1000 mg/kg/day in rabbits (FDA 1972 in Collins *et al*. 1990).

Reproductive parameters were also examined in the chronic toxicity and carcinogenicity studies referred to above and reviewed by EFSA (2009). No treatment-related effects were observed.

7. Hypersensitivity and intolerance in humans

7.1. History

The major controversy in the field of artificial food colours is the suggestion first made in the 1920s that artificial food colours and additives, including tartrazine, may have detrimental effects on children inducing 'hyperactivity' (Burrows 2009, cited by Arnold *et al*., 2012). A specific hypothesis relating to this relationship was developed in 1973 by Feingold (1975) who proposed that hyperactivity and learning problems in children were due to certain foods and food additives as well as foods containing natural salicyclates. The work was criticised by the medical profession. However, his hypothesis was accepted by many parents following media reports (comprehensively reviewed by Arnold *et al*., 2012).

Subsequent investigations failed to demonstrate a link with hyperactivity due to deficiencies of many of these studies (Arden & Ram, 2001; Arnold *et al*., 2012; Conners *et al*., 1976; Dipalma 1990; Khera & Munro 1979; Levy *et al*., 1978; Rowe 1988; Settipane 1977). In trying to identify the biological process(es) underlying this potential relationship, several hypotheses were put forward based on neurochemical, genetic or allergic/immunological mechanisms. However, no definitive biological process was established (reviewed by FDA/CFSAN 2011).

Over the years, interest waned but was revived in 2004 with a study published by Schab & Trinh (2004; see below).

7.2. Recent human studies

The following are brief summaries of reviews or studies conducted during the last 12 years.

In 2001, Ardern & Ram reviewed 18 relevant studies in humans, but found they were inconclusive as none of them conducted tartrazine challenge or avoidance in diet nor did they significantly alter asthma outcomes. Schab & Trinh (2004) conducted a meta-analysis of findings from previously conducted clinical trials that attempted to show a definitive relationship between consumption of artificial food colours, including tartrazine, and behavioural changes in children. The study was, however, deficient in analysing objective measures of behaviour such as clinical/psychological evaluations, activity monitoring or behavioural testing; and was universally criticised for its emphasis on behaviour ratings as reported by parents, teachers or clinicians (Arnold *et al*., 2012; Elhkim *et al*., 2007; FDA/CSAN 2011; Watson 2008).

Thus, no clear relationship between ingestion of food colours (including tartrazine) and the development of attention deficit hyperactivity symptoms in children (Arnold *et al*., 2012) or development of intolerance reaction (Elhkim *et al*., 2007) was established. The use of non-standardised diagnosis, questionable sample selection, imperfect blinding and non-standardised outcome measures utilised by previous investigators may have been key factors contributing to the ambiguity surrounding tartrazine consumption and these reactions.

Interest in the relationship between food colours and hyperactivity in children was revived again in 2007 when McCann *et al*. (2007) published a study conducted at the Southampton University. The study implied that mixtures of certain artificial food colours and sodium benzoate could increase the mean level of hyperactivity profile behaviours in two age groups of children (3–4 years old and 8–9 years old) from the general population. However, lack of consistency in the results with respect to the age and sex of the children and the type of observer (parent, teacher, or independent assessor); the unknown clinical relevance of the effects measured; the use of mixtures in the study and lack of information on dose-response resulted in the European Food Safety Authority (EFSA) rejecting suggestions of a direct link between artificial food colours and hyperactivity (Watson 2008).

Furthermore, in response to a petition from the Center for Science in the Public Interest (CSPI 2008) arising from the Southampton study, the FDA also conducted a thorough review of the McCann *et al*. 2007 study as well as publications of previously conducted clinical trials (33 trials), including the 2004 meta-analysis by Schab and Trinh (2004).

The concerns of the FDA neurotoxicology/toxicology panel were in line with the previously identified deficiencies of McCann *et al*. 2007 study by the EFSA (Watson 2008). Thus, the FDA concluded that a causal relationship between exposure to tartrazine (and other colour additives) and hyperactivity in children in the general population could not established.

Neither EFAS nor the FDA found any compelling evidence to alter current regulations on acceptable daily intakes of tartrazine in foods, drugs and cosmetics.

8. Conclusions and recommendations

From a toxicological point of view, tartrazine does not appear to represent a risk for the consumer. It is recommended that the TGA allow the use of tartrazine for oral use and to label those products as to tartrazine content in line with New Zealand.

Bibliography

Includes additional reference material consulted but not cited herein.

Ardern KD & Ram FS (2001) Tartrazine exclusion for allergic asthma [Review]. *Cochrane Database of Systematic Reviews*. (Not possible to provide firm conclusions as to the effects of tartrazine on asthma control)

Arnold LE, Lofthouse N & Hurt E. (2012) Artificial food colors and attention-deficit/hyperactivity symptoms: conclusions to dye for. *Neurotherapeutics*. 9: 599–609.

Bartle WR (1976) Tartrazine-containing drugs. *Canadian Medical Association Journal*. 115: 332–333.

Borzelleca, J.F., Hallagan, J.B. (1988a) Chronic toxicity/carcinogenicity studies of FD & C Yellow No. 5 (tartrazine) in rats. *Food Chem. Toxicol*. 26: 179–187.

Borzelleca, J.F., Hallagan, J.B. (1988b). A chronic toxicity/carcinogenicity study of FD & C Yellow No. 5 (Tartrazine) in mice. *Food Chem. Toxicol*. 26: 189–194.

Burrows A. Palette of our palates: a brief history of food coloring and its regulation. (2009) *Compr Rev Food Sci Food Saf*. 8:394–408.

Center for Science in the Public Interest (CSPI0; 2008). Petition to Ban the Use of Yellow 5 and Other Food Dyes, in the Interim to Require a Warning on Foods Containing These Dyes, to Correct the Information the Food and Drug Administration Gives to Consumers on the Impact of These Dyes on the Behavior of Some Children, and to Require Neurotoxicity Testing of New Food Additives and Food Colors. Available at: http://www.fda.gov/downloads/AdvisoryCommittees/CommitteesMeetingMaterials/FoodAdvisoryCommittee/UCM248005.pdf.

Collins, T.F., Black, T.N., Brown, L.H., Bulhack, P. (1990) Study of the teratogenic potential of FD & C Yellow No. 5 when given by gavage to rats. *Food Chem. Toxicol*. 28, 821–827.

Collins, T.F., Black, T.N., O'Donnell Jr., M.W., Bulhack, P. (1992) Study of the teratogenic potential of FD & C yellow No. 5 when given in drinking-water. *Food Chem. Toxicol*. 30: 263–268.

Conners CK, Goyette CH, Southwick DA. (1976) Food additives and hyperkinesis: preliminary report of a double-blind crossover experiment. *Psychopharmacol Bull*. 12:10–11.

Desmond RE & Trautlein JJ. (1981) Tartrazine (FD&C Yellow No 5) anaphylaxis: a case report. *Ann Allergy*. 46: 81–82.

Dipalma JR. (1990) Tartrazine sensitivity. *Am Fam Physician*. 42: 1347–1350.

Directive 2008/128/EC

Durnev, A.D., Oreshchenko, A.V., Kulakova, A.V., Beresten, N.F. (1995) Analysis of cytogenetic activity of food dyes. *Vopr. Med. Khim*. 41: 50–53.

EFSA (European Food Safety Authority) Panel on Food Additives and Nutrient Sources added to food (ANS; 2009) Scientific Opinion on the re-evaluation of tartrazine (E 102) on request from the European Commission. EFSA Journal. 7: 1331–1383. Available online: http://www.efsa.europa.en

EFSA (European Food Safety Authority) Panel on Dietetic Products, Nutrition and Allergies (NDA; 2010) Scientific Opinion on the appropriateness of the food azo-colours Tartrazine (E 102), Sunset Yellow FCF (E 110), Carmoisine (E 122), Amaranth (E 123), Ponceau 4R (E 124), Allura Red AC (E 129), Brilliant Black BN (E 151), Brown FK (E 154), Brown HT (E 155) and

Litholrubine BK (E 180) for inclusion in the list of food ingredients set up in Annex IIIa of Directive 2000/13/EC. *EFSA Journal* 8:1778. Available online: http://www.efsa.europa.eu/efsajournal.htm

Elhkim M, Heraud F *et al*. (2007) New considerations regarding the risk assessment on tartrazine. An updated toxicological assessment, intolerance reactions and maxiumum theoretical daily intake in France. *Regulatory Tox Pharmacol*. 47: 308–316.

FDA/CFSAN (2011) Interim Toxicology Review. Available online. Memorandum http://www.fda.gov/downloads/AdvisoryCommittees/CommitteesMeetingMaterials/FoodAdvisoryCommittee/UCM248102.pdf

Feingold BF. (1975) Hyperkinesis and learning disabilities linked to artificial food flavors and colours. *Am J Nurs*. 75: 797–803.

Gao Y, Li c, Huaxian J-S *et al*. (2011) Effect of food azo dye tartrazine on learning and memory functions in mice and rats, and the possible mechanisms involved. *J Food Sci*. 76:2011–2015.

Giri, A.K., Das, S.K., Talukder, G., Sharma, A., 1990. Sister chromatid exchange and chromosome aberrations induced by curcumin and tartrazine on mammalian cells in vivo. *Cytobios* 62, 111–117.

Himri I, Bellahcen S *et al*. (2011) A 90-day oral toxicity study of tartrazine, a synthetic food dye, in Wistar rats. *Int J Pharmacy & Pharmac Sci*. 3: 159–169.

Ishidate, M., Sofuni, J., Yoshikawa, K., 1981. Chromosomal aberration tests in vitro as a primary screening tool for environmental mutagens and/or carcinogens. *Gann Monogr. Cancer Res*. 27, 95–108.

Ishidate, M., Sofuni, T., Yoshikawa, K., Hayashi, M., Nohmi, T., Sawada, M., Matsuka, A., 1984. Primary mutagenicity screening of food additives currently used in Japan. *Food Chem. Toxic*. 22: 623–636.

JECFA (Joint FAO/WHO Expert Committee on Food Additives; 1964) Specifications for identity purity and toxicological evaluation of food colours in FAO nutrition. Meetings Report Series No 38B, WHO, Geneva.

JECFA (NMRS 38/TRS 309-JECFA 8/14, FAS 66.25/NMRS 38B-JECFA 8/88. 0-7.5. FU. R)

Kanarek RB. (2012) Artificial food dyes and attention deficit hyperactivity disorder. *Nutrition Rev*. 69: 385–391.

Khera KS & Munro IC (1979) A review of the specifications and toxicity of synthetic food colors permitted in Canada. *CRC Critical Review in Toxicology*. 6: 81–133.

Levy F, Dumbrell S, Hobbs G *et al*. (1978) Hyperkinesis and diet: a double-blind crossover trial with a tartrazine challenge. *Med J Australia*. 1: 61–64.

Lockey SD (1959) Allergic reactions due to FD&C Yellow No 5, tartrazine, an aniline dye used as a colouring and identifying agent in various steroids. *Ann Allergy*. 17: 719-721. NO ABSTRACT AVAILABLE

McCann D *et al*. (2007) Food additives and hyperactive behaviour in 3-year old and 8/9-yearold children in the community: a randomized, double-blinded, placebo-controlled trial. *The Lancet*. 9598: 1560–1567.

Maekawa, A., Matsuoka, C., Onodera, H., Tanigawa, H., Furuta, K., Kanno, J., Jang, J.J., Hayashi, Y., Ogiu, T., 1987. Lack of carcinogenicity of tartrazine (FD & C Yellow No. 5) in the F344 rat. *Food Chem. Toxicol*. 25: 891–896.

MacCara ME (1982) Therapeutic Review: Tartrazine: a potentially hazardous dye in Canadian drugs. *Canadian Medical Association Journal*. 126: 910–914.

Moutinho, ILD, Bertges LC & Assis RVC. (2007) Prolonged use of the food dye tartrazine (FD&C Yellow No 5) and its effects on the gastric mucosa of Wistar rats. *Braz J Biol*. 67: 141–145.

Nordic Council of Ministers (2002) Food additives in Europe. In TemaNord, pp 53-60. (Cited by Elhkim M, Heraud F *et al*., 2007).

Pestana S, Moreira M & Olej B (2010) Safety of ingestion of yellow **TARTRAZINE** by double-blind placebo controlled challenge in 26 atopic adults. *Allergol Immunopathol* (Madr) 38: 142146.

Race S. (2012) Tartrazine (FD&C Yellow no 5). Tigmor Books.

Rafii F, Hall JD & Cerniglia CE (1997) Mutagenicity of azo dyes used in foods, drugs and cosmetics before and after reduction by Clostridium sp. From the human intestinal tract. *Food Chem Toxicol*. 35: 897–901.

Sasaki, Y.F., Kawaguchi, S., Kamaya, A., Ohshita, M., Kabasawa, K., Iwama, K., Taniguchi, K., Tsuda, S. (2002) The comet assay with 8 mouse organs: results with 39 currently used food additives. *Mutat. Res*. 59: 103–119.

Schab DW & Trinh NT. (2004) Do artificial food colours promote hyperactivity in children with hyperactive syndromes? A meta-analysis of double-blind placebo-controlled trials. *J Dev Behav Pediatr*. 25: 423–434.

Settipane GA (1977) Tartrazine sensitivity and aspirin intolerance. *Comprehensive therapy*. 3: 15–20.

Speer F, Denison TR, Baptist IE: (1981) Aspirin allergy. *Ann Allergy*. 46:123–126

Stevens JJ, Kuczek T, Burgess JR *et al*. (2013) Mechanisms of behavioural, atopic and other reactions to artificial food colors in children. *Nutrition Rev*. 71: 268–281.

Tanaka, T. (2006) Reproductive and neurobehavioural toxicity study of tartrazine administered to mice in the diet. *Food Chem. Toxicol*. 44: 179–187.

Tse CST & Bernstein IL (1982) Adverse reactions to tartrazine. *Hosp Formul*. 17: 1635–1637.

Watson R. (2008) European agency rejects links between hyperactivity and food additives. *BMJ*. 336: 687.

Watabe T, ozawa N, Kobayashi F *et al*. (1980) Reduction of suphonated water-soluble azo dyes by microorganism from human feces. *Food Cosmet. Toxicol*. 18: 349–352.

Young E. (1997) Prevalence of intolerance to food additivies. *Environ Toxicol Pharmacol*. 4: 111–114.

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