Food Dyes and Our Health

Before you let her eat that … read this book!

A collection of studies and reviews

edited by Shula Edelkind

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Research on the Relationship of Diet to Behavior & Health

February 15, 2019

Ms. Anna Smith, Food Dye Study
Office of Environmental Health Hazard Assessment
1515 Clay Street, 16th Floor
Oakland, CA 94612

Dear Ms. Smith,

I am happy to attach a list of the research that may be of help in the review of food dyes.. The documents include everything I have relating food dyes to health and behavior. Most are linked to their full text, but those that aren't open-access will require the username "**private**" and the password **"papers**".

Below each citation is some explanation of the paper's contents. Where I have an opinion or additional comment, it is in italics and prefaced with "**Note:"** I hope this will help your committee choose relevant papers that deserve more study.

Reviews published in the past 20 years are included alphabetically with the studies, but I have segregated the 81 reviews prior to 1999 into an "Old Reviews" section, which may be of historical interest.

A slide-show (with voice-over) of my 9-minute presentation to the 2011 FDA Food Advisory Committee is at: https://youtu.be/NIYygfXNKXM One of the slides links to an old page at www.diet-studies.com. If you should need the username/password for any links on that page, use **"myfile / 4Studies"**

Please contact me if you have any questions.

Sincerely,

Shula Edelkind
www.TalkingAboutTheScience.com
Phone: 678-640-9853

FOOD DYES AND OUR HEALTH

Links go to full text when available
*if username/password is requested, use **"private/papers"***
(May not work on a phone)

LEGEND

(FDA)	Provided by the FDA to the Food Advisory Committee in 2011
(*)	NOT reviewed by the FDA Food Advisory Committee in 2011
(Review)	Review, meta analysis, editorial, letter to the editor, etc.
(Study)	Clinical study, controlled trial, epidemiological study
(Case)	Case study, case report
(Lab)	Studies in animals, tissues, cells, or molecules
(Allergy)	Allergic or hypersensitivity reactions - asthma, urticaria, etc.
(Extra)	Paper is about something indirectly related but interesting
(Medical)	Study showing potential medical benefit of a food dye.

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BLOOD BRAIN BARRIER (BBB)

Some studies illustrate the permeability of the BBB under different conditions
*if username/password is requested, use "**private/papers**"*

1. **BHATT 2018:** (Yellow 5 metabolite sulfanilic acid passes BBB)
2. **BMJ 1996**: (stress increases BBB permeability to dyes)
3. **FRIEDMAN 1996**: (BBB of Israeli soldiers in Gulf War)
4. **GOLDENRING 1982:** (Sulfanilic acid passes BBB)
5. **HAJILUIAN 2017:** (junk food and BBB)
6. **HANIN 1996:** (BBB and Gulf War)
7. **KIRALY 2007:** (BBB damage in traumatic brain injury)
8. **SHARMA 1988:** (stress & increased serotonin related to BBB permeability)
9. **TOMKINS 2001:** (BBB under stress and excitotoxins)
10. **WINKLER 1995:** (BBB permeability with serotonin increase)
11. **YANG 2018:** (BBB damage in stroke)

POSSIBLE MEDICAL BENEFITS

As more is learned about their effect on sodium channels, receptors etc., medical uses for dyes are emerging:

1. **ANGARITA 2019: Blue 1 -** Measuring intestinal integrity in sepsis
2. **APOLLONI 2014: Blue 1 -** Spinal cord pathology
3. **BARTLETT 2018: Blue 1 -** Amyotrophic Lateral Sclerosis
4. **CARMO 2014: Blue 1 -** Parkinson's Disease
5. **De FREITAS 2019: Red 3 -** To kill diseased cells by phototoxicity
6. **FERRAZOLI 2017: Blue 1 -** Parkinson's Disease
7. **FERREIRA 2016: Blue 1 -** Spinal cord injury, prion illnesses, traumatic brain injury, Duchenne Muscular Dystrophy, Amyotrophic Lateral Sclerosis
8. **GARAPATI 2015: Red 3 -** Sinusitis
9. **IRWIN 2013: Blue 1 & Red 3 -** Alzheimer's Disease
10. **JO 2011: Blue 1 -** Pain, Epilepsy, Bipolar
11. **LEE 2016: Red 3 -** Alzheimer's Disease
12. **LI 2018: Red 3 -** Dengue Fever, Zika Virus, Yellow Fever, Japanese Encephalitis, West Nile Fever
13. **PENG 2009: Blue 1 -** Spinal cord injury
14. **ROMAO 2018: Red 3 -** Fights tooth decay with dental light
15. **RYBERG 2018: Red 3 -** Solar water purification
16. **WONG 2011: Blue 1 -** Alzheimer's Disease
17. **WONG 2011: Red 3 -** Alzheimer's Disease
18. **WONG 2013: Red 3 -** Alzheimer's Disease

Should substances with medical uses be permitted in food for cosmetic reasons?

STUDIES & POST-1998 REVIEWS
RELATED TO NEUROLOGICAL OR BEHAVIORAL
REACTIONS TO SYNTHETIC FOOD DYES
Username/Password = "Private/Papers"

1. **ADAMS 1981: (FDA) (Study) Lack of Behavioral Effects from Feingold Diet Violations.** *Perceptual and Motor Skills.* 52: 307-313.

   a. **Note:** *The Conners' scores for the children when they were ON the diet were not given, but it is assumed the children had actually responded to the diet before being tested on "violations" of the diet.*

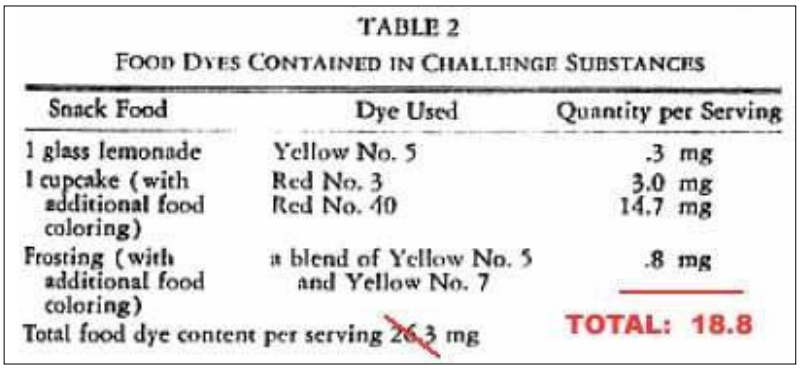


TABLE 2

FOOD DYES CONTAINED IN CHALLENGE SUBSTANCES

Snack Food	Dye Used	Quantity per Serving
1 glass lemonade	Yellow No. 5	.3 mg
1 cupcake (with additional food coloring)	Red No. 3 Red No. 40	3.0 mg 14.7 mg
Frosting (with additional food coloring)	a blend of Yellow No. 5 and Yellow No. 7	.8 mg
Total food dye content per serving 26.3 mg		TOTAL: 18.8

   b. **Note:** *Math error in Table 2: The food dye amounts actually total **18.8** mg-- not **26.3** mg as claimed.*

   c. The placebo cupcakes had vanilla frosting. The "challenge" cupcakes had vanilla frosting with an amount of food dye so small that it **DID NOT CHANGE THE COLOR** of the frosting.

   d. **9 of the 14 variables tested "showed a tendency toward deterioration for the artificial snack."** But significance could not be reached -- the study was too small.

   e. **Note:** *Adams concluded the diet didn't work. But this was not a test of the diet – it was a test of a small **challenge.** Possibly, the diet worked **so well** that the small challenge had no effect. Or perhaps it was the wrong challenge … the diet excludes thousands of additives, not just food dyes.*

2. **AL-SHABIB 2017: (*) (Lab) Unveiling the Stimulatory Effects of Tartrazine on Human and Bovine Serum Albumin Fibrillogenesis: Spectroscopic and Microscopic Study.** *Spectrochimica Acta Part A: Molecular and Biomolecular Spectroscopy.* 15(191): 116-124.

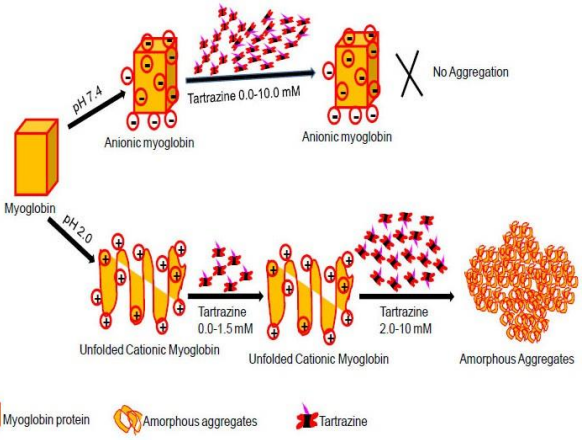
   a. Tartrazine (Yellow 5) interacts with both human and bovine albumins to form amyloid fibrils such as those found in some neurodegenerative diseases such as Alzheimer's.

3. **AL-SHABIB 2017: (*) (Lab) Synthetic Food Additive Dye "Tartrazine" Triggers Amorphous Aggregation in Cationic Myoglobin.** *International Journal of Biological Macromolecules.* 98: 277-286.

   a. This study investigated the interaction of Yellow 5 with the muscle protein myoglobin.

   b. The dye interacts with myoglobin protein to form amorphous aggregates at a pH of 2.0 but not at a pH of 7.4, at which point the myoglobin charge changes and they repel each other.

   c. Supportive testing suggests that Yellow 5 can cause aggregation in any protein that is cationic (positively charged).



4. **AL-SHABIB 2019: (*) (Lab) Allura Red Rapidly Induces Amyloid-Like Fibril Formation in Hen Egg White Lysozyme at Physiological pH.** *International Journal of Biological Macromolecules.* 127: 297-305.

   a. Red 40, with hen egg white lysozyme (HEWL), forms amyloid-like aggregates. (*A lysozyme is an enzyme in tears and egg white.*)

   b. The amyloid fibril formation can be observed by an electron microscope, is very quickly formed, and needs very little Red 40.

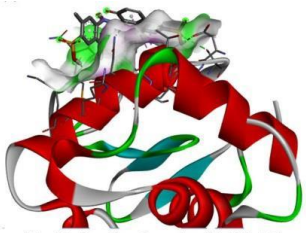


Fig. 5A. Docking Complex (HEWL-AR)

   c. Amyloid fibrils are involved with most neurodegenerative disorders such as Alzheimer's and Parkinson's.

5. **AMCHOVA 2015: (*) (Review) Health Safety Issues of Synthetic Food Colorants.** *Regulatory Toxicology and Pharmacology.* 73(3):914-22

   a. This is a review of food dye toxicity per official EFSA reports and other studies since 2008. See also Appendix A.

   b. Amchova wrote that prenatal exposure to dye mixtures can damage spatial working memory, and may affect brain signaling, but whether dyes increase asthma is unclear and studies have been contradictory.

6. **ANDERSON 1983: (*) (Lab) Relative Refractory Period as a Measure of Peripheral Nerve Neurotoxicity.** *Toxicology and Applied Pharmacology.* 71: 391-397.

   a. The relative refractory period is consistent in specific animal nerves, so small alterations due to neurotoxin exposure would be easily detected. On the other hand, when behavioral deficits are observed but the refractory period doesn't change, it means the toxin is acting on the nerve endings and not the axon.

   b. Using the relative refractory period as an index can help in determining the mechanism of action of neurotoxic agents.

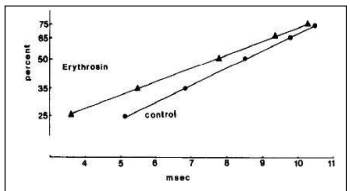


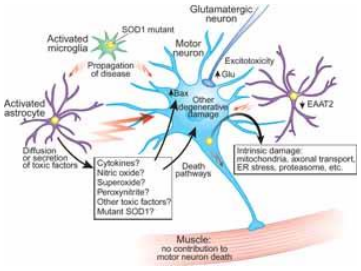
FIG. 4. Effect of erythrosin B on the sciatic nerve relative refractory period. Untreated sciatic nerves were placed in an isolated nerve chamber and the control relative refractory period (circles) recorded. The nerves were then exposed to erythrosin B and the relative refractory period was again recorded (triangles). Data are plotted as a function of the percentage of action potential recovery at each interstimulus interval.

   c. **Note**: *This was not actually a study of Red 3 – rather, Red 3 as a **known excitatory neurotoxin**, was used to help develop the testing method.*

7. **APOLLONI 2014: (*) (Lab) (Medical) Spinal Cord Pathology is Ameliorated by P2X7 Antagonism in a SOD1-Mutant Mouse Model of Amyotrophic Lateral Sclerosis.** *Disease Models and Mechanisms.* 7(9): 1101-1109.

   a. This paper describes a neurological effect of Blue 1 that may be of medical benefit in treating spinal cord pathology in amyotrophic lateral sclerosis (ALS).

   b. The receptor P2X7 is involved in the central nervous system and immune system. In ALS, this receptor is upregulated (excessively "turned on") in the spinal cord.



   c. Blue 1 interferes with this P2X7 receptor, lowering its activity and thereby lowering the neuroinflammatory component of ALS. Thus Blue 1 shows promise as a treatment for ALS.

   d. **Note**: *The P2X7 receptor is important in the immune system of all people. Should we be interfering with it by adding Blue 1 to food? See more about P2X7 in a review article by Wiley (2011).*

8. **ARNOLD 1999: (FDA) (Review) Treatment Alternatives for Attention-Deficit Hyperactivity Disorder (ADHD).** *Journal of Attention Disorders.* 3 (1): 30-48.

   a. 23 non-drug treatments for ADHD were evaluated. The oligoantigenic *(few foods)* diet "has convincing double-blind evidence of efficacy in multiple trials for a properly selected subgroup."

   b. **Note:** *Oligoantigenic diets always exclude synthetic food dyes.*

9. **ARNOLD 2013: (*) (Review) Attention-Deficit/Hyperactivity Disorder: Dietary and Nutritional Treatments.** *Child & Adolescent Psychiatric Clinics of North America.* 22 (2013): 381–402.

    a. Some treatments for ADHD may have inconclusive evidence but are safe, easy, cheap, and sensible (SECS) enough to be tried while awaiting better research.

    b. Quote: "Many complementary/alternative treatments for ADHD are not specific treatments of ADHD but instead sensible health measures."

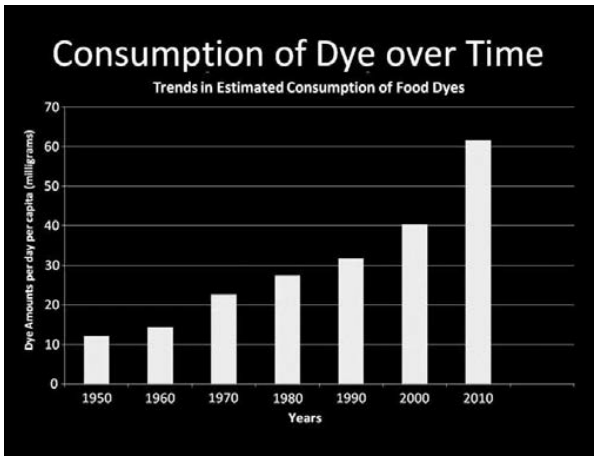
    c. Note: *He includes the eliminating of food dyes as a SECS treatment.*

10. **ARNOLD 2012: (*) (Review) Artificial Food Colors and Attention-Deficit/Hyperactivity Symptoms: Conclusions to Dye for.** *Neurotherapeutics.* 9(3): 599-609.

    a. This is a history of artificial food color (AFC) research and testimony at the 2011 FDA Food Advisory Committee.

    b. Quote: "ADHD is a quantitative diagnosis, like hypertension, and some individuals near the threshold may be pushed over it by a small symptom increment."

    c. Quote: "AFCs appear to be more of a public health problem than an ADHD problem."



11. **ASSOCIATE PARLIAMENTARY FOOD AND HEALTH FORUM 2008: (*) (Review) The Links Between Diet and Behaviour: The Influence of Nutrition on Mental Health.** *Report of an inquiry held by the Associate Parliamentary Food and Health Forum.* January 2008.

    a. They reviewed studies on food dyes (pages 21-23) and recommended regulations to "**prohibit all artificial colours and non-essential preservatives in food products and soft drinks**."

12. **AUGUSTINE 1980: (*) (Lab) Neurotransmitter Release from a Vertebrate Neuromuscular Synapse Affected by a Food Dye.** *Science*. 207(4438): 1489-90.

    a. Red 3 was applied to nerve synapses in the frog, producing an irreversible, dose-dependent increase in neurotransmitter release.

    b. The author suggested this may be useful for studying neurotransmitters, but that the use of Red 3 as a food additive should be reexamined.

13. **AUGUSTINE 1983 (*) (Lab) Neurotransmitter Release and Nerve Terminal Morphology at the Frog Neuromuscular Junction Affected by the Dye Erythrosin B.** *The Journal of Physiology.* 334:47-63.

    a. This is a study on frog nerves exposed to Red 3 and the results on the frog's nerve terminals, including miniature end-plate potential (m.e.p.p.) frequency which increased exponentially during exposure to the dye.

    b. Presynaptic effects were irreversible and the mitochondria were swollen.

14. **AUGUSTINE 1983: (*) (Lab) Presynaptic Effect of Erythrosin B at the Frog Neuromuscular Junction: Ion and Photon Sensitivity.** *The Journal of Physiology.* 334:65-77.

    a. Calcium, sodium, potassium and light were experimentally increased or decreased to determine interactions with Red 3.

    b. The dye showed evidence of competing with calcium at a common site, while the enhancement of its effect in elevated external calcium suggests that the dye may also increase the permeability of the nerve terminal to calcium ions.

15. **AUSTERMAN 2015: (*) (Review) ADHD and Behavioral Disorders: Assessment, Management, and an Update from DSM-5.** *Cleveland Clinic Journal of Medicine.* 82 (Suppl.1): S2-S7.

    a. The author concluded that removal of artificial food coloring and sodium benzoate from the diet is "challenging," but "has been more efficacious than behavioral management in the long-term reduction of core symptoms of ADHD."

16. **AZADBAKHT 2012: (*) (Study) Dietary Patterns and Attention Deficit Hyperactivity Disorder Among Iranian Children.** *Nutrition.* 28: 242-249.

    a. The sweet and fast-food dietary patterns are significantly associated with ADHD.

    b. **Note**: *In this study the "Western" diet is not associated with ADHD, perhaps because they considered the "Western" components of the diet separately from the "sweet" and "fast food" components of the diet.*

17. **BAMFORTH 1993: (*) (Lab) Common Food Additives are Potent Inhibitors of Human Liver 17α-Ethinyloestradiol and Dopamine Sulphotransferases.** *Biochemical Pharmacology.* 46(10): 1713-1720.

    a. Detoxification enzymes provide the means for inactivation, transport and excretion of the xenobiotics including food dyes. Sulfate conjugation is one of the important methods of handling these compounds.

    b. Not only are the synthetic food dyes and other xenobiotics managed via sulfation, but so are some of the neurotransmitters, such as steroid hormones and monoamine neurotransmitters. The required enzymes are called phenolsulfotransferases (PST) and – more recently – SULT1A.

    c. Bamforth wrote that the observed inhibition of M-PST enzyme activity by food additives suggests a possible mechanism for behavioral side effects associated with exposure to these food additives.

Compound	% Inhibition of Sulphotransferase Activity: Dopamine	Oestrone
(±)-Catechin	84 ± 5	67
(+)-Catechin	85	75
4-Chlorobenzoic acid	9 ± 9	41
Aspartame	52 ± 6	27
Benzoic acid	53 ± 10	12
Erythrosin B	18 ± 22	16
Gallic acid	54 ± 15	18
Octyl gallate	68 ± 12	20
p-Hydroxybenzoic acid	47 ± 14	54
Propyl gallate	59 ± 26	20
Protocatechuic acid	56 ± 14	40
Saccharin	44 ± 7	—
Tannic acid	54 ± 16	61
Tartrazine	94 ± 3	60
Vanillin	100 ± 0	85

This table is extracted from Table 1: Inhibition of human liver STs by food additives. Dopamine is a neurotransmitter. Oestrone is an estrogen hormone.

    d. In the table at right, you can see that Red 3 and Yellow 5 (highlighted) inhibit sulfotransferase activity. Other additives in the list are also potent inhibitors and it is interesting that most of them are eliminated on the Feingold diet.

18. **BANERJEE 2007: (FDA) (Review) Environmental Risk Factors for Attention-Deficit Hyperactivity Disorder.** *Acta Paediatr.* 96(9):1269-1274.

    a. Bannerjee wrote, "It is notable that many of the environmental risk factors for ADHD occur early in development, which is consistent with the idea that ADHD is a neurodevelopmental condition."

    b. However, he specifically excluded food additives from possible environmental risk factors, saying systematic reviews had shown the Feingold diet was not effective, and citing the Conners (1980) study for support of this opinion.

    c. **Note:** *Conners (1980) was not a systematic review, but a study of 9 children published 27 years earlier. In that study, Conners himself had speculated that the 15 mg of food dye he used as a challenge may have been too small a "dose" to justify his conclusions.*

19. **BARRETT 2007: (*) (Review) Hyperactive Ingredients?** *Environmental Health Perspective.* 115(12): A578.

    a. The author says research does not support any but "small effects" of food additives on hyperactivity.

    b. She downplays the McCann (2007) study by saying the researchers do not show that the food additives "cause clinically defined ADHD" but that effects are "modest."

    c. **Note**: *McCann used children from the general population. See reply by Weiss (2007).*

20. **BARTLETT 2018: (*) (Lab) (Medical) P2X7 Antagonism Using Brilliant Blue G Reduces Body Weight Loss and Prolongs Survival in Female SOD1G93A Amyotrophic Lateral Sclerosis Mice.** *PeerJ.* 5: e3064

    a. This paper describes a neurological effect of Blue 1 that may be of medical benefit in treating spinal cord pathology in amyotrophic lateral sclerosis (ALS).

    b. The P2X7 receptor channel is involved with ALS, and Blue 1 is an antagonist of P2X7. In this study, mice with ALS were injected 3 times a week with 45.5 mg/kg Blue 1. Although they lost less weight and did live longer, they still developed ALS, indicating that more than the single kind of receptor is involved.

21. **BATEMAN 2004: (FDA) (Study) The Effects of a Double Blind, Placebo Controlled, Artificial Food Colourings and Benzoate Preservative Challenge on Hyperactivity in a General Population Sample of Preschool Children.** *Archives of Disease in Childhood.* 89(6):506-511.

    a. This is the first of the two studies referred to as the "Southampton studies." Bateman concluded, "There is a general adverse effect of artificial food colouring and benzoate preservatives on the behavior of 3 year old children."

    b. Quote: **"We believe that this suggests that benefit would accrue for all children if artificial food colours and benzoate preservatives were removed from their diet**."

    c. **Note:** *Only 20 mg and 30 mg of dye were used – but for very young children this "dose" is larger than it would be for teens. If benzoate enhances the effect is not yet known, but many products contain both coloring and benzoate together.*

    d. **Note**: *Apparently, the benzoate preservative was chosen rather than the BHA, BHT, and TBHQ so prevalent in American foods because those are already banned in England.*

    e. See also: Eigenmann's comment (2004) and Bateman's answer and an erratum (2005)

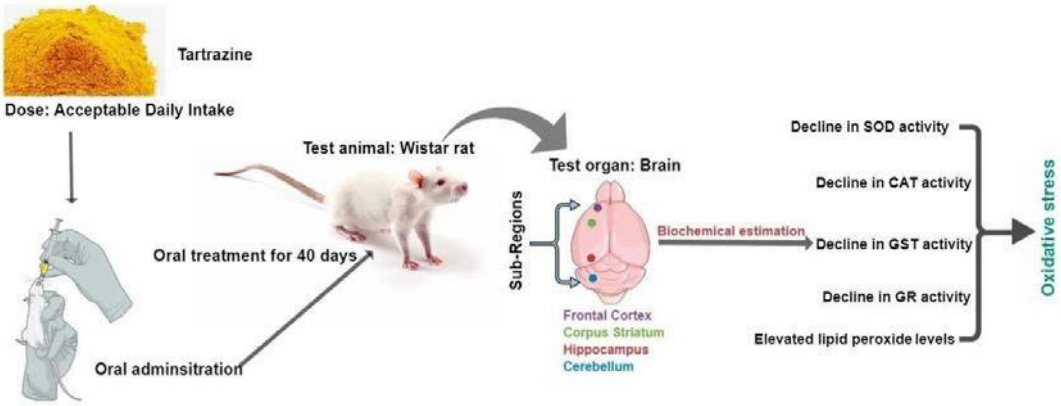
22. **BELLISLE 2004: (*) (Review) Effects of Diet on Behaviour and Cognition in Children.** *British Journal of Nutrition.* 92(sup.2) S227-S232)

    a. Bellisle reviewed the Swanson (1980) and Weiss (1980) studies, while ignoring those from the 1990s. She said that 100 mg of food dyes (in the Swanson study) was higher than children would experience in the "real world," but "some effect can appear in particularly sensitive individuals."

    b. Bellisle also says that food additives have changed enormously in the food supply since Feingold's original hypothesis and the "potential contribution of dietary substances to the problem deserves vigilant consideration." Moreover, she said, poor nutritional status can alter mental and behavioural functions but can be corrected, to a certain extent, by dietary measures

    c. **Note**: *Bellisle is connected to ILSI, a descendant of the Nutrition Foundation which was a food industry organization.*

23. **BHATT 2018: (*) (Lab) Tartrazine Induced Neurobiochemical Alterations in Rat Brain Sub-Regions.** *Food and Chemical Toxicology.* 113:322-327.



    a. Rats were given the ADI amount of Yellow 5.
    b. Their body weight was lower.
    c. The brain protein levels in all brain sub-regions decreased.
    d. Lipid peroxide levels in all brain sub-regions increased.
    e. Glutathione-S-transferase activity in all brain sub-regions decreased.
    f. Glutathione reductase activity in some areas of the brain decreased.
    g. Glutathione peroxidase activity in all brain sub-regions increased.
    h. MDA levels in all brain sub-regions increased, indicating damage.
    i. Sulfanilic acid (a breakdown product of Yellow 5) can cross the blood-brain-barrier.
    j. Severe oxidative stress conditions were induced by Yellow 5.
    k. Authors conclude that **ADI levels are not safe levels, causing oxidative stress.**

24. **BORIS 1994: (FDA) (Study) Foods and Additives are Common Causes of the Attention Deficit Hyperactive Disorder in Children.** *Annals of Allergy*. 72(5):462-8.

a. 73% of 26 children with ADHD responded favorably to a diet eliminating reactive foods and artificial colors. 16 of the improved children were given a double blind challenge with 100 mg mixed food dyes or a food chosen by the parents.

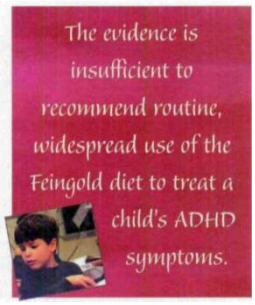
b. ALL of them reacted to the challenge, and a placebo effect was ruled out. **Note:** *Although only 4 of the children were challenged by food dye, all of the children had eliminated the dye from their diet in this study. It is not known whether ALL of the children would have been sensitive to a challenge with the dyes alone, or just the four whose parents decided to use it for a challenge.*

Table 2. Challenge Agents in Study Group

Subject	Age, yr	Sex	Agent
1	9	Male	Corn
2	8	Female	Wheat
3	8	Female	Milk
4	5	Female	Milk
5	5	Male	Soy
6	5	Male	Colors
7	4	Male	Milk
8	8	Male	Colors
9	10	Female	Wheat
10	9	Male	Corn
11	5	Male	Oranges
12	3	Male	Milk
13	8	Male	Colors
14	6	Female	Milk
15	11	Male	Corn
16	6	Male	Colors

c. Quote: "Dietary factors may play a significant role in the etiology of the majority of children with ADHD."

25. **BRAGANZA 2006: (*) (Review) Nutritional Interventions: Part Two. When Parents Ask About Diet Therapy for ADHD.** *Contemporary Pediatrics.* 23(5): 47-49.



a. This paper's stated purpose was to advise doctors on how to respond to parents asking about diet therapy for ADHD – in particular, the Feingold diet. To support her advice, she cites (*and misquotes*) a study and a review more than 20 years old.

b. Braganza cites the Weiss (1980) study, claiming it "demonstrated no change in behavior when a child was on the Feingold diet." **Note:** *This was a study on 22 children who were **not ADHD**. 100% of them (by definition) had already **benefitted** from the diet, and Weiss wanted to see if they would react to a small dye challenge. Two of them (10%) did.*

c. Braganza then writes that only 1% of children "exhibited a consistent improvement of symptoms while on the diet," citing Wender (1986). **Note:** *Wender was writing about a series of small studies of children who had already improved on the diet and she claimed only about 1% of them had reacted to a small dye challenge "in the expected direction." Her wording was exceedingly unclear, however, and Braganza apparently misunderstood. This is a case of confusing **reaction to challenge** with **response to diet.***

d. Braganza also wrote that Feingold had banned aspartame, referring to it as a "salicylate-containing compound." **Note:** *(1) Aspartame is not a salicylate. And (2) Feingold did not ban it, anyway, since it was not introduced into the US market until 1981, the year before his death. The Feingold Association did officially ban it years later because of its reported effects on members and relevant research, but it was never considered a "salicylate."*

26. **BREAKEY 1991: (*) (Study) A Report on a Trial of the Low Additive, Low Salicylate Diet in the Treatment of Behaviour and Learning Problems in Children.** *Australian Journal of Nutrition and Dietetics.* 48(3): 89-94.

    a. 516 children in a psychiatry service were put on a low-additive diet. **79.5%** of them improved.

        - For **54.5**% - the diet brought their behavior into the normal range.
        - For **25%** - the diet helped but was not sufficient as a stand-alone treatment.

    b. Quote: "… outcome was not affected by a belief that food affected the child."

    c. Quote: "Additives and salicylates are better thought of as aggravating the underlying predisposition in susceptible children, rather than as causative agents."

27. **BRENNER 1977: (*) (Case) A Study of the Efficacy of the Feingold Diet on Hyperkinetic Children. Some Favorable Personal Observations.** *Clinical Pediatrics.* 16(7):652-6.

    a. Brenner writes that he had actually intended to disprove the Feingold diet via this study.

    b. Of 32 children in the study, 11 were "markedly improved" on the diet, and 8 others were "somewhat improved." Of these 8, two were actually very improved but older – and Brenner thought they could have possibly "outgrown" their ADHD. Two others still needed medication, but less than before. The other 4 had better behavior but continued poor school performance. Of the 13 children who did not respond at all to the diet, three had had meningitis in childhood, two may have had neonatal hypoxia, and two were of "borderline intelligence."

    c. Brenner wrote that a placebo effect could not definitely be ruled out, but that "the startling changes seen in patients who had been followed for years with other forms of therapy suggest strongly that this improvement was genuine."

28. **BRENNER 1979: (*) (Study) (Extra) Trace Mineral Levels in Hyperactive Children Responding to the Feingold Diet.** *The Journal of Pediatrics.* 94(6):944-5.

    a. Since children who do or don't respond to the Feingold diet are not eating differently, Brenner wanted to see if there might be a biochemical difference between them.

    b. Two groups of children were compared – both groups had tried the Feingold diet, but one group had responded well, and the other group did not in spite of their best efforts.

    c. Brenner found an elevation of serum copper concentration – which may directly influence neurotransmitter systems – in children responding to the Feingold diet. **Note:** *If copper is elevated, zinc is usually deficient. Ward (1990; 1997) found that children with ADHD lost zinc through urine more quickly than others when eating Yellow 5 or Yellow 6.*

29. **BUKA 2011: (*) (Review) Food Additives, Essential Nutrients and Neurodevelopmental Behavioural Disorders in Children: A Brief Review.** *Paediatrics & Child Health.* 16(7):e54-56.

    a. The authors wrote that there is enough evidence "to consider dietary influences as a modifiable risk factor" and that "improving the diets of children with respect to essential nutrients and non-essential food additives needs to be addressed, and very soon, by society as a whole."

    b. While this could be left to the parents, they wrote, it "would, ultimately, be **more effective if regulated nationally**."

30. **BURLTON-BENNET 1987: (*) (Case) A Single Subject Evaluation of the K-P Diet for Hyperkinesis.** *Journal of Learning Disabilities.* 20(6). 331-5. 346.

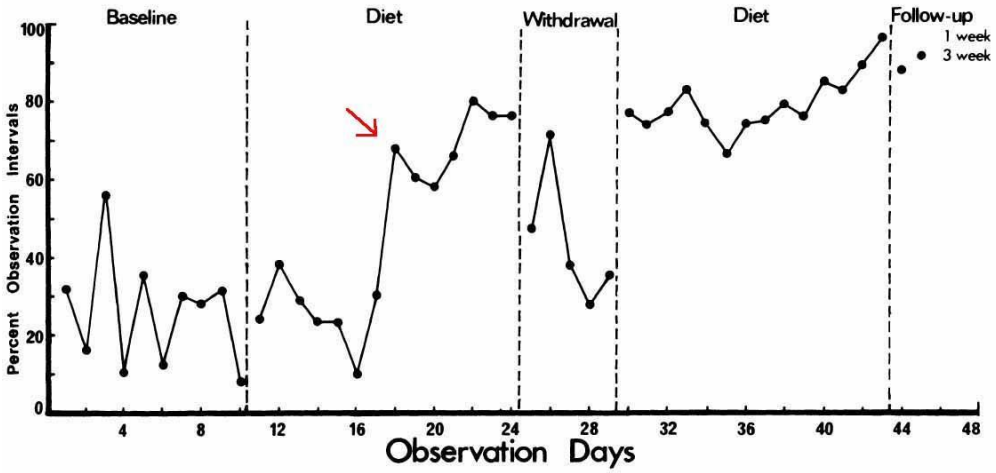


Figure 1. Percentage of attending-to-task behavior across phases

    a. A single subject ABAB design was used to test the effectiveness of the Feingold (K-P) diet in the treatment of a 6-year-old boy who seemed diet-responsive. His behavior was measured by classroom observations and by teacher and foster-mother reports.

    b. It was concluded that the K-P diet was effective in controlling his hyperkinesis.

    c. **Note:** *It took a week for the behavioral change to begin to become apparent (see red arrow).*

31. **CARMO 2014: (*) (Lab) (Medical) The P2X7 Receptor Antagonist Brilliant Blue G Attenuates Contralateral Rotations in a Rat Model of Parkinsonism Through a Combined Control of Synaptotoxicity, Neurotoxicity and Gliosis.** *Neuropharmacology.* 81: 142-152.

    a. As an antagonist to the P2X7R receptors which are overactive in Parkinson's disease (PD), Blue 1 improved short term memory and prevented the synapse dysfunction in the rat model of PD. This highlights the possible therapeutic potential of Blue 1 in PD.

    b. **Note:** *This may be good for those with Parkinson's, but is it a good idea to randomly block the P2X7R in children via blue candy/cereal?*

32. **CARTER 1993: (FDA) (Study) Effects of a Few Food Diet in Attention Deficit Disorder.** *Archives of Disease in Childhood.* 69(5):564-568.

    a. 59 of 78 hyperactive children **(75.6%)** improved on an open trial of an oligoantigenic (*few foods*) diet. 19 of them were studied in a placebo-controlled double-blind challenge protocol.

    b. Challenges included provoking foods and food dyes as determined on open trials. Multiple challenge materials were used at the same time to mimic the real world. 26 mg (or less) of food dye mixture was included in the challenges.

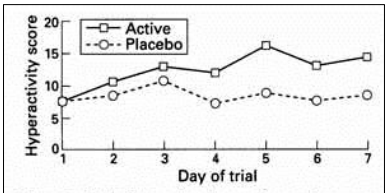


Figure 2 Daily Conners' scale scores (parents' hyperactivity ratings). The mean scores, on the hyperactivity factor of the Conners' behaviour rating scale, are separately shown for the placebo period and the period during which a potentially active food was given.

    c. Quote: "Clinicians should give weight to the accounts of parents and consider this treatment in selected children with a suggestive medical history."

33. **CEMEK 2014: (*) (Lab) Effects of Food Color Additives on Antioxidant Functions and Bioelement Contents of Liver, Kidney and Brain Tissues in Rats.** *Journal of Food and Nutrition Research.* 2(10): 686-691.

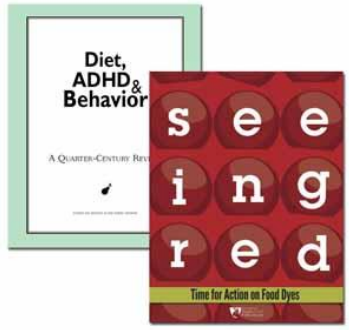
    a. Tartrazine (Yellow 5) and carmoisine (*not used in the US*) were given to rats by gavage (*orally*) for 15 days to study their effect on trace elements.

    b. The dosages of the Yellow 5 were 3 mg/kg and 15 mg/kg. The low dose was only about half the ADI (for the US). The control group received no dye.

    c. Results: Iron and zinc levels changed in the rats' liver, kidney and brain tissues. Copper was elevated in the kidney, and some trace elements were reduced in the brain by both the high and low doses of Tartrazine.

    d. Cemek wrote these trace elements are needed for antioxidant defense and their depletion "may result (in) some disruptions in crucial pathways."

34. Center for Science in the Public Interest. (FDA) (Review) **Diet, ADHD & Behavior/A Quarter-Century Review: 2009 Update on Food Dyes and Behavior.** *Center for Science in the Public Interest.* Washington, DC 20009.

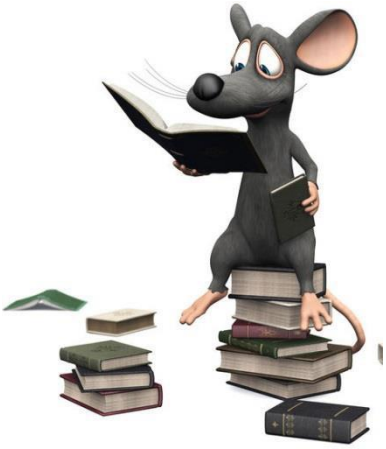


   a. This is a comprehensive review of studies first printed in 1999 with a 2009 update.

   b. The CSPI recommends several approaches for future research on Page 16.

   c. It is updated by their 2016 report, **Seeing Red.**

35. CEYHAN 2013: (*) (Lab) **Effects of Maternally Exposed Coloring Food Additives on Receptor Expressions Related to Learning and Memory in Rats.** *Food and Chemical Toxicology.* 56:145-8.



   a. This is the first study on the effects of food dyes on specific receptors involved in the learning and memory process.

   b. One ml of a mixture of food dyes at the ADI levels (or water) was given by gavage to female rats daily before and during pregnancy. The food dyes used in this study (and which are also used in the US) were Red 3, Red 40, Yellow 6, Yellow 5, Red 2, Blue 1, and Blue 2.

   c. No abnormal symptoms were observed for 3 months after birth, at which time 12 males and 12 females from each group were sacrificed for examination.

   d. Some receptors involved in learning, memory, and/or excitotoxicity had increased, and others were decreased – with gender-related differences. The authors suggest repeating the same study using each color additive separately.

36. CHUNG 2015: (*) (Review) Extra) **Azo Dyes and Human Health: AReview.** *Journal of Environmental Science & Health.* 34(4): 233-261

   a. This is a review of the current knowledge regarding azo dyes. They account for more than 50% of the dyes produced in the world for use in foods, textiles, fuel, etc. When released into the environment, even when decolorized, their residues and degradation products **damage water quality and aquatic organisms,** often rendering the water unfit for use.

   b. Chung recommends that if we can restrict the use of these dyes and control their polluting of our environment, we would be able to drastically reduce the incidence of cancer and other relevant human diseases.

37. **COLLINS-WILLIAMS 1983: (*) (Study) Intolerance to Additives.** *Annals of Allergy.* 51: 315-316.

    a. Working at the same hospital as Swanson, and "extending" the Swanson (1980) study, Collins-Williams concluded that the ADHD effects of food dyes are not related to IgE allergy.

38. **CONNERS 1976: (FDA) (Study) Food Additives and Hyperkinesis: A Controlled Double-Blind Experiment.** *Pediatrics.* 58(2): 154-166.

    a. This is a double blind study using the K-P (Feingold) diet and a "control" diet.

    b. Conners reported, "Both parents and teachers reported fewer hyperkinetic symptoms on the K-P diet."

39. **CONNERS 1980: (FDA) (Study) Dose-Time Effect of Artificial Colors**. *Journal of Learning Disabilities.* 13 (9): 48-52.

    a. Nine children on the Feingold diet were challenged with 15 mg of food dye in two chocolate cookies. A lack of any consistent effect was reported, and attributed to one or more of the following:

        - Chocolate or other problem ingredient in the cookies
        - Dose of dyes might be too low
        - Significance is statistically more difficult to reach in group studies using few subjects

    b. **Note:** *Results appear to be combined which may mask any individual reactions to the challenges.*

40. **COOK 1976: (*) (Case) The Feingold Dietary Treatment of the Hyperkinetic Syndrome.** *Medical Journal of Australia.* 2(3):85-88, 90. *(abstract only)*

    a. In Australia, 15 children were given the Feingold diet. Parents of 13 of them **(87%)** reported improvement in their children's behavior and a relapse upon eating off-diet items.

    b. **Note:** *There have been claims that the only "science" supporting the Feingold diet involves case studies. Actually, most studies were not case studies, but certainly there were some, such as this one.*

41. **CORMIER 2007: (FDA) (Review) Diet and Child Behavior Problems: Fact or Fiction?** *Pediatric Nursing.* 33(2):138-143.

    a. This review was intended for nurses, to help them deal with parents who want to try a diet such as the Feingold diet, oligoantigenic (few foods) diet, or gluten-free, casein-free (GFCF) diet for their children.

    b. The nurses were advised to listen sympathetically to provide "empirically sound literature," and to provide referrals to nutritionists if needed.

    c. **Note:** *The literature the nurse was instructed to give is not specified, but neither the Feingold Association nor any GFCF resources seem to be suggested, which makes it unsurprising that the author expected parents to find such diets very difficult.*

42. **CRUCHET 2016: (*) (Review) Truths, Myths, and Needs of Special Diets: Attention-Deficit/ Hyperactivity Disorder, Autism, Non-Celiac Gluten Sensitivity, and Vegetarianism.** *Annals of Nutrition & Metabolism.* 68(suppl.1): 43-50.

    a. Cruchet recommended restriction of sugar, sweeteners, colorants and preservatives to improve behavior and attention for children with ADHD.

    b. **Note:** *There are a few minor errors on Page 44 which have been marked.*

43. **CRUZ 2006: (FDA) (Review) Do Food or Additives Cause Behavior Disorders?** *Pediatric Annals.* 35(10): 744-5, 748-754.

    a. This was written as advice to doctors.

    b. The doctor was not counseled to recommend any dietary changes, but to accommodate a parent who insisted on it.

44. **DALAL 2009: (*) (Lab) Short-Term Erythrosine B-Induced Inhibition of the Brain Regional Serotonergic Activity Suppresses Motor Activity (Exploratory Behavior) of Young Adult Mammals.** *Pharmacology, Biochemistry, and Behavior*. 92(2009): 574-582.

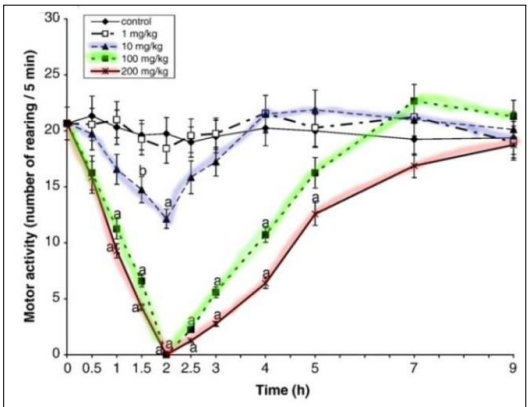


Fig. 1. Effect of single administration of erythrosine (1, 10, 100 or 200 mg/kg, p.o.) on motor activity of rats at different time intervals. Each point represents mean ± SEM of 8–12 separate observations (each observation was made from a single rat). Vertical line represents ± SEM. *X* axis indicates time (h) after administration of erythrosine. No significant change was observed between the control values corresponding to time of erythrosine exposure. Significantly different from corresponding control $^{a}p<0.01$ and $^{b}p<0.05$.

a. Long-term administration of Red 3 increased movement in a dose-dependent manner, but Dalal wanted to test a single large dose *in vivo*.

b. Dalal said Red 3 is known to increase calcium permeability in the neural membrane, and to effect the release of neurotransmitters like dopamine, GABA, serotonin, acetylcholine, norepinephrine, etc. It also inhibits brain magnesium, sodium, potassium and other ions.

c. The single high dose of Red 3 in this study elicited a significant reduction in vertical motor activity in young adult rats (rearing), with a maximum effect after 2 hours, and slow return to the baseline.

d. Dalal explained that this reflected a decrease in regional serotonergic activity in the brain, in a time-dependent manner, affecting not only the hypothalamic serotonergic system but also the medulla-pons region.

45. **DALAL 2010: (*) (Lab) Involvement of High Plasma Corticosterone Status and Activation of Brain Regional Serotonin Metabolism in Long-Term Erythrosine-Induced Rearing Motor Hyper Activity in Young Adult Male Rats.** *Toxicology Mechanisms & Methods.* 20(6):287- 297.

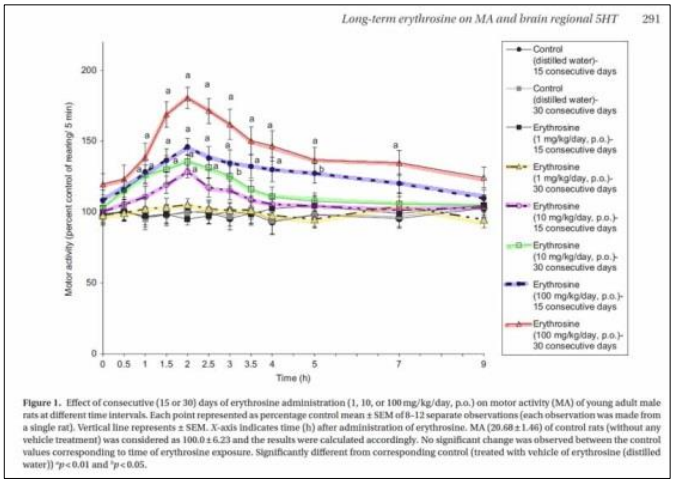


Figure 1. Effect of consecutive (15 or 30) days of erythrosine administration (1, 10, or 100 mg/kg/day, p.o.) on motor activity (MA) of young adult male rats at different time intervals. Each point represented as percentage control mean ± SEM of 8–12 separate observations (each observation was made from a single rat). Vertical line represents ± SEM. *X*-axis indicates time (h) after administration of erythrosine. MA (20.68 ± 1.46) of control rats (without any vehicle treatment) was considered as 100.0 ± 6.23 and the results were calculated accordingly. No significant change was observed between the control values corresponding to time of erythrosine exposure. Significantly different from corresponding control (treated with vehicle of erythrosine (distilled water)) $^{a}p<0.01$ and $^{b}p<0.05$.

a. This study investigated a long-term trial of Red 3 administration.

b. 10 – 100 mg/kg/day of Red 3 increased plasma corticosterone levels after several days of administration, similar to pargyline, an MAO inhibitor.

c. Serotonin was increased, but MAO-A activity decreased.

d. The higher doses of Red 3 also produced hyperactivity in a dose-dependent manner.

46. **DAVID 1987**: **(FDA) (Study) Reactions to Dietary Tartrazine.** *Archives of Disease in Childhood.* 62:119-122.

    a. 24 children who were on a diet that avoided additives and any other foods under suspicion, with a clear history from the parents that any lapse caused an obvious adverse behavioral reaction within two hours, were selected for the study. Some of the parents had come to Dr. David for assistance with implementing and/or understanding the diet.

    b. David proposed to challenge them with 250 mg of Yellow 5 and benzoic acid (separately), some as outpatients and others in the hospital setting.

    c. The vehicle drinks used for challenge and placebo vehicle drinks were orange juice and Ribena. **Note:** *Both drinks are problematic as a vehicle, because: (1) Both contain salicylate, and (2) David said the Ribena contained (at that time)benzoate and sodium metabisulfite. How can he test benzoic acid with this vehicle?*

    d. No changes in behavior were noted either by the parents or nursing staff after administration of placebo or active substance. No specific scoring system was employed.

    e. Of the 24 children, 18 were described by nursing staff as behaving normally throughout the time of observation, with no detectable change in behavior with or after placebo or active challenges. The other six children, all of whom were studied as inpatients, displayed abnormal behavior (e.g., frequent tantrums, aggressive behavior, or pronounced overactivity.)

    f. In one case, the child's temper tantrums "were so gross, prolonged and frequent that it was initially unclear whether she could be contained on the ward." When she was no better after four days, David administered the challenge anyway, without any alteration in the tantrums with either placebo or active challenge. **Note:** *What could he have been expecting? A bigger tantrum?*

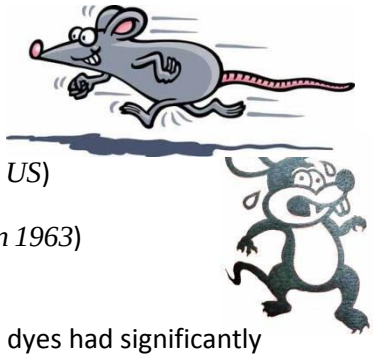
    g. In the other five, the behavioral abnormalities (as observed by the nursing staff and parents) were unrelated in time to the administration of either placebo or active challenges.

    h. David acknowledged that a drawback of the study was that it was performed in a hospital, and that it is well known and recognized by the DSM-III criteria for attention deficit with hyperactivity that signs of the disorder may be absent when the child is in a new or "one-to-one situation." Thus, the failure of the challenges to elicit a change in behavior may be attributed to unfamiliarity of the ward environment where all (not just the inpatients) went for testing.

    i. The parents of 4 children decided – at the end of the first day -- that as they had not reacted to either placebo or food dye, there was no need to return for further testing. **Note:** *It is not explained how David managed both the placebo and active tests on the same day.*

47. **DOGUC 2013: (*) (Lab) Effects of Maternally Exposed Colouring Food Additives on Cognitive Performance in Rats.** *Toxicology and Industrial Health.* 29(7): 616-23.

    a. Doguc gave pregnant rats the ADI amounts of food dyes by mouth, continuing after the babies were born so the pups were exposed both prenatally and through their mothers' milk. Control rats received an equal amount (1 ml) water. The dyes included were:



- Erythrosine (Red 3)
- Ponceau (E124, *a red color not used in the US*)
- Allura Red (Red 40)
- Sunset Yellow (Yellow 6)
- Tartrazine (Yellow 5)
- Amaranth (Red 2, *used only on orange skins in US*)
- Brilliant Blue (Blue 1)
- Azorubine (E122, D&C Red 10, *delisted in US in 1963*)
- Indigotine (Blue 2)

    b. When the rat pups were tested, those exposed to the dyes had significantly **increased activity, as well as increased exploration and anxiety**, but not spatial learning difficulty.

48. **DOGUC 2015: (*) (Lab) Are There Any Remarkable Effects of Prenatal Exposure to Food Colourings on Neurobehaviour and Learning Process in Rat Offspring?** *Nutritional Neuroscience*. 18(1); 12-21.

    a. No adverse effects were seen on spatial working memory in the rats, but there was **increased motility and anxiety, and decreased motivation** with gender differences.

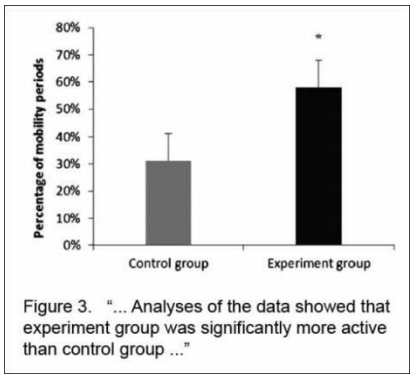


Figure 3. "... Analyses of the data showed that experiment group was significantly more active than control group ..."

    b. Doguc writes that the gender differences suggested an effect on different hormones and/or neurotransmitter pathways.

    c. Doguc suggests that future studies should look at which specific dyes are responsible for the effect or whether it may be an interaction of two or more of them.

49. **D'SOUZA 1987: (*) (Lab) Aspirin, Indomethacin, and Tartrazine Increase Carotid-Sinus-Nerve Activity and Arterial Blood Pressure in Guinea Pigs.** *Pharmacology.* 34: 96-103.

    a. 0.1 - 2.0 mg/kg of Yellow 5 given intravenously to guinea pigs caused dose-dependent **increases in activity of the carotid- sinus nerve and increased blood pressure.**

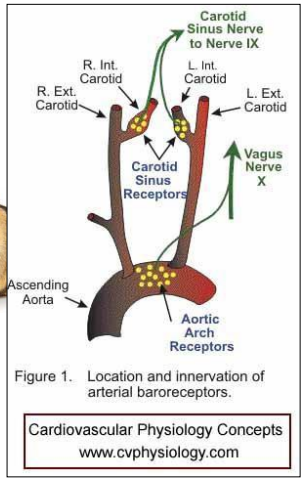


Figure 1. Location and innervation of arterial baroreceptors.

    b. The dye acts directly on the carotid baroreceptors to increase their activity. (Baroreceptors are receptors located in the carotid sinus that detect pressure changes.)

50. **DUMBRELL 1978: (*) (Study) Is the Australian Version of the Feingold Diet Safe?** *Medical Journal of Australia.* 2(12): 569-70. *(abstract only)*

    a. The before-and-after diets of 16 children put on the Feingold diet were compared.

    b. While their previous diets had been good, Dumbrell found that the nutritional quality of the Feingold diet was superior.

51. **EAGLE 2012: (*) (Review) (Extra) Toxicological Effects of Red Wine, Orange Juice, and Other Dietary SULT1A Inhibitors via Excess Catecholamines.** *Food and Chemical Toxicology.* 40: 2243-2249.

    a. This is an overview of how certain compounds affect the enzymes called phenolsulfotransferase (also called PST or SULT1A), and how enzyme inhibition enzyme causes problems such as migraines, heart arrhythmias, or increased blood pressure. Genetic variations are involved in how susceptible a particular person may be. Table 1 contains a list of common inhibitors, and you can see Yellow 5 is considered a "strong inhibitor."

(Extracted from Table 1)

Table 1
SULT1A inhibitors, extent of inhibition, and common sources.

Substance	SULT1A1 inhibition	SULT1A3 inhibition	Common sources
Quercetin[a]	Complete	Partial	Chocolate, onion, blueberry
Octyl gallate[c]		Strong	Antioxidant E311
Tartrazine[c]		Strong	FD&C Yellow 5
Eriodictyol[b]	Extr potent	Extr potent	Lemon
Carmoisine[g]	100%		Synthetic colorant E122

    b. **Note:** *Because this same enzyme is needed for food dye and neurotransmitter metabolism, this background information may help in understanding the variation in responses to food dye.*

52. **EAGLE 2012: (*) (Review) (Extra) SULT1A Inhibition and How a Migraine Stops.** *Headache.* 52(8): 1321.

    a. This paper describes how SULT1A enzymes affect dopamine, a neurotransmitter. Yellow 5 is one of the items that can inhibit SULT1A (**Note:** *called PST in some studies*).

    b. Elevated dopamine is generally blamed for a migraine, but something must elevate it. A mechanism connecting a list of ingested "triggers" to dopamine is described: The usual "triggers" contain phenols and polyphenols that have been shown in vitro to inhibit the SULT1A1 and SULT1A3 enzymes needed to keep the dopamine within the normal range.

    c. Inhibition of these enzymes prevents them from deactivating catecholamines (such as dopamine) which would then build up.

    d. Migraines often appear to follow stress; what happens is that stress releases the catecholamines (including dopamine) which should then be deactivated …. But since the enzymes are inhibited and can't deactivate it, the dopamine then builds up and causes the migraine. Therefore, even though the immediate trigger appears to be stress, the real trigger, or root cause, is the inability of the body to deactivate the dopamine.

    e. **Note**: *Many people with ADHD — and many parents of children with ADHD — also suffer from migraines. There are several dopamine pathways in the brain, one of which plays a major role in the motivational component of behavior.*

53. **EAGLE 2014: (*) (Lab) (Review) ADHD Impacted by Sulfotransferase (SULT1A) Inhibition from Artificial Food Colors and Plant-Based Foods.** *Physiology & Behavior.* 135: 174-179.

a. This study re-examined 50 previous studies on food dye and ADHD that had ended with inconclusive results. Eagle evaluated the placebo items for SULT1A inhibitors which can exhibit an inverted-U response.

b. SULT1A inhibitors in foods, including natural substances and artificial food colors, have a role in ADHD that can both worsen or improve symptoms. SULT1A inhibition can influence brain catecholamines through the intermediary of plasma tyrosine levels, which are influenced by dopamine inhibition of intestinal tyrosine hydroxylase.

c. Indeed, SULT1A inhibitors were found in both placebo and delivery vehicles. In eight studies, Eagle found evidence of ADHD symptoms caused by SULT1A inhibitors in "inactive" materials; in ten other studies, additional SULT1A inhibitors reduced symptoms of some of the subjects.

d. **Note**: *SULT1A is an enzyme also known as PST (phenol sulfotransferase). This is a complicated study for those without an organic chemistry background, but it basically gives a clue why some children appear to get worse when first put on the Feingold diet, as noticed by Egger (1985) and many Feingold parents.*

54. **EGGER 1985: (FDA) (Study) Controlled trial of oligoantigenic treatment in the hyperkinetic syndrome.** *Lancet.* 1(8428): 540-5.

a. 62 of 76 overactive children **(81.6%)** improved by at least one grade level on an oligoantigenic (few foods) diet. Benzoic acid and Tartrazine (Yellow 5) were the most common problems, but all children had other sensitivities as well.

TABLE IV -- CHANGE IN SEVERITY OF SYMPTOMS WITH DIET

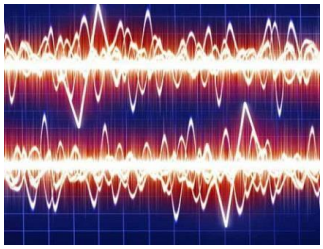
	Total	No Improvement	Improved	Recovered
Mild	6	1 (17%)	0 (0%)	5 (83%)
Moderate	31	5 (16%)	16 (52%)	10 (32%)
Severe	39	8 (21%)	25 (64%)	6 (15%)

No improvement = grade unchanged
Improved = 1 or 2 grades less severe
Recovered = requires normal management only

b. Other symptoms that also improved: headaches, abdominal pain, seizures.

c. **Note:** *Egger noticed something commonly reported by Feingold Association members -- the behavior of some of the children deteriorated for the first few weeks on the diet before improving.*

55. **EGGER 1989: (*) (Study) Oligoanatigenic Diet Treatment of Children with Epilepsy and Migraine.** *The Journal of Pediatrics.* 114(1):51-8.



a. Of 63 children with epilepsy, 45 also had migraine, hyperkinesis, or both, while 18 had epilepsy alone.

- Of the 18 with epilepsy alone, none improved on the oligoantigenic diet.
- Of the 45 with a combination of symptoms, 25 ceased to have seizures and 11 had fewer seizures during diet therapy.

b. Quote: "Headaches, abdominal pains, and hyperkinetic behavior ceased in all those whose seizures ceased, and in some of those whose seizures did not cease."

c. 12 children were tested with Tartrazine (*Yellow 5*) and benzoic acid; 25% of them had a return of seizures and 58% of them had other symptoms such as headache, GI symptoms and behavior problems.

d. **Note:** *Other food dyes were not tested, but all additives (including the dyes) are always removed on an oligoantigenic diet.*

56. **EGGER 1992: (*) (Study) Effect of Diet Treatment on Enuresis in Children with Migraine or Hyperkinetic Behavior.** *Clinical Pediatrics.* 31(5):302-7.

a. 21 children, who had been successfully treated by an oligoantigenic (*few* foods) diet for migraine and/or hyperkinetic behavior, had also been diagnosed with enuresis (*bedwetting*).

b. For 12 of them, the enuresis stopped while on the diet, and for another 4 of them it improved.

c. 9 of the children were given a placebo-controlled double-blind trial. 6 of them relapsed during the challenge with suspected foods, and none of them reacted to the placebo.

d. Specifically, **36%** of them reacted to the benzoic acid and Tartrazine (Yellow 5) challenge.

57. **ERICKSON 2014: (*) (Lab) Lifespan Psychomotor Behaviour Profiles of Multigenera- tional Prenatal Stress and Artificial Food Dye Effects in Rats.** *PLoSOne.* 9(6):e92132.

a. Prenatal stress can result in hyperactivity, so Erickson wanted to look for any synergistic effect or whether vulnerability to food dyes may be modified by prenatal stress. Food dyes were given in the rats' water from postnatal days 22 to 50 to resemble juvenile and adolescent dietary exposure, and rats had been stressed prenatally for 4 generations.

b. Food dye consumption resulted in hyperactivity only during the time of exposure, subsiding after they stopped giving it.

c. Prenatal stress, however, resulted in hyperactivity in early life and again in later life (13 months) with normal activity at the reproductive age.

d. Both promoted risk-taking behavior in the young adult rats (3 months) but interactions were not seen.

58. **FARAONE 2005: (FDA) (Review) Molecular Genetics of Attention Deficit Hyperactivity Disorder.** *Biological Psychiatry.* 57(11): 1313-1323.

a. In studies of mice, certain genes appear to mediate susceptibility to neurotoxins having an affinity for the dopamine transporter.

b. **Note:** *Although reviewed by the 2011 FDA Advisory Committee, this paper does not mention food dyes at all, but it is possible to extrapolate from hints such as the above that certain genes might possibly make a person more (or less) susceptible to "side effects" of food dyes or other additives.*

59. **FARAONE 2014: (*) (Review) Towards an Evidence-Based Taxonomy of Nonpharmacologic Treatments for ADHD.** *Child & Adolescent Psychiatric Clinica of North America.* 23(4): 965-72

a. This paper reviews an evidence-based approach to help doctors explain to parents the relative benefits of nonpharmacologic treatments for ADHD.

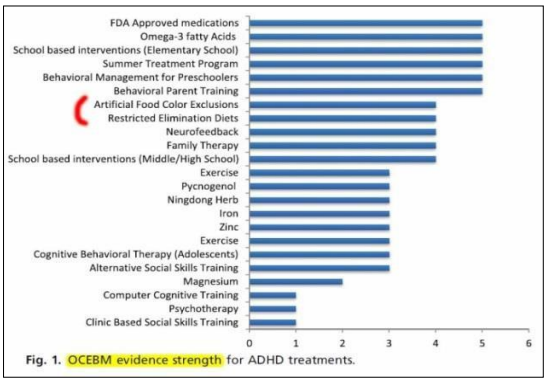


Fig. 1. OCEBM evidence strength for ADHD treatments.

b. Food dye exclusion is given a "4" in their listing of treatment effect size (see picture) – meaning these treatments have had a randomized trial or observational study with clear effect. It is suggested that diet – and other nonpharmacological treatments – can be used also as adjunct treatments. There is an explanation of the difference between broad-band and narrow-band treatments.

60. **FEINGOLD 1973**: **(FDA) Hearings on Food Additives and Hyperactivity in Children.** *Congressional Record, U.S. Senate*. October 30, 1973.

   a. **Note:** *This paper was included in the original Bibliography prepared for the 2011 FDA Hearings of the Advisory Committee but was removed from the version available to the public.*

   b. **Note:** *The correct name of this paper is "Food Additives and Hyperactivity in Children" but the FDA had listed it as above.*

   c. This discussion and comments about Dr. Feingold's clinical findings were read into the Congressional Record, with a request to support further research on the subject.

   d. The source of the salicylates list, and three case studies are described.

   e. The similarity to the inherited enzyme deficiency G6PH (also called G6PD) is discussed, postulating that there is some similar deficiency on the X chromosome related to ADHD and its habit of not manifesting any problem until exposed to environmental/dietary chemicals that impact it.

61. **FEINGOLD 1973 (*) (Extra) (Allergy) Introduction to Clinical Allergy.** *Charles C. Thomas, Publisher.* (pages 10 & 157-160)

   a. For background, this is Feingold's description of haptens, the way they "work," and why allergy testing is not useful.

62. **FEINGOLD 1975**: **(FDA) Hyperkinesis and Learning Disabilities Linked to Artificial Food Flavors and Colors.** *American Journal of Nursing*, 75:797.

   a. Feingold described the history of hyperactivity and the understanding of possible causes from 400 BC through his day. **Note:** *"H-LD" and "hyperkinesis" are two of several outdated references to "ADHD."*

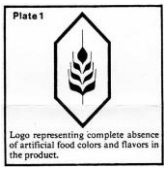
   b. Feingold described the recognition in the 1960s that hyperkinesis "does not necessarily indicate organic brain damage" and the substitution of the term "minimal brain dysfunction" as the umbrella term to replace "brain damage," and other alarming diagnoses then in use.

   c. He singled out the synthetic colors and flavors as nonessential and used merely for cosmetic or esthetic effects. "The risks in their use," he wrote, "outweigh the benefits." He explained that "**both drugs and food chemicals are low molecular compounds**" and that "drugs can influence the behavior of animals and men. Accordingly, it is reasonable to expect food chemicals to cause behavioral modifications."

   d. Because this was a paper for nurse practitioners, Feingold discussed ways for them to work with a family, and the types of response to diet to expect in different age groups. He also told them that when stopping drug treatment, it may take **up to 40 days** on the diet before a response is observed. (**Note:** *Please keep this in mind; it is often ignored in other studies.)*

63. **FEINGOLD 1975: (*) Commentary: Food Additives in Clinical Medicine.** ***International Journal of Dermatology*****. Vol. 14. 112-114.**

a. Discussing the diet itself and the difficulties (back in the 1970s) of "careful shopping" for an elimination diet, he introduced the idea of a special symbol to be carried on acceptable products. It was never adopted, but there is good background information in this paper.



64. **FEINGOLD 1977: (*) Hyperkinesis and Learning Disabilities Linked to the Ingestion of Artificial Food Colors and Flavors.** *Speech to American Academy of Pediatrics, NY.* Nov. 8, 1977.

a. Quote: "Recognizing that any compound under the appropriate conditions can induce adverse reactions, including behavioral disturbances, it becomes necessary to evaluate each compound or class of compounds on the basis of benefit compared with risk. … colors and flavors have no nutritional value whatsoever. If they were removed from our food supply, nothing nutritionally would be lost. Therefore, on balance, the risk outweighs the benefit."

65. **FEINGOLD 1977: (*) Food Additives in Dentistry.** *Journal of the American Society for Preventive Dentistry.* 7(1): 13-15.

a. Feingold wrote: "The presence of food additives in products used in dental procedures may have serious consequences for many patients. Hyperactivity and learning disabilities as well as buccal, gingival and oral cankers have occurred following the use of diagnostic aids. Furthermore, hyperkinetic patients, whose symptoms have been controlled by withdrawal of all artificial colors and flavors from their diets, have suffered relapses following a dental visit."

b. He urged dentists to recognize these problems because "only by the concerted efforts of professionals in the field will diagnostic aids free of artificial color and flavor become available."

66. **FEINGOLD 1979: (*) Dietary Management of Juvenile Delinquency.** *International Journal of Offender Therapy and Comparative Criminology.* 23(1): 73-84.

a. Feingold wrote that the Ford Foundation in 1977 wanted to investigate the role of nutrition and biochemical factors in delinquency, because the rehabilitation techniques then in use were not working. This is a paper reprinted from the *International Journal of Offender Therapy and Comparative Criminology.*

b. Quote: "We have now managed approximately 600 children with the diet. Initially, our successes for control of observed behavior ranged between 30 and 50 percent; however, since we are emphasizing the elimination of BHT (butylated hydroxytoluene) and BHA (butylated hydroxyanisole) our successes for control of behavior average between 60 to 70 percent of our samples."

67. **FEINGOLD 1982: (*) The Role of Diet in Behavior.** *Ecology of Disease.* 1(2-3): 153-165.

a. Feingold said, "The increase in behavioural disorders accompanied by a persistent drop in scholastic performance coupled with the continuing rise in the prevalence of delinquency is undoubtedly one of the most important expressions of the disruption of nature by the rising concentration of pollutants in the ecosystem."

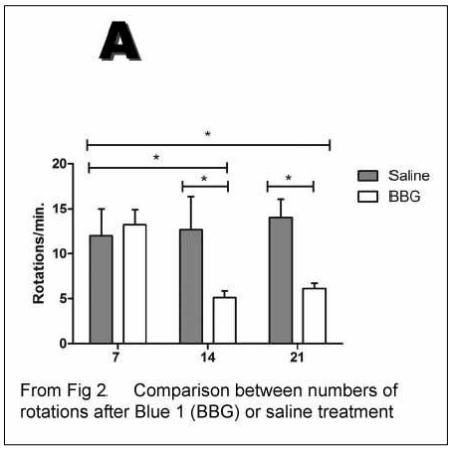

Ben F. Feingold, MD
1899 - 1982

b. In what may sound like prophesy, Feingold warned, "Public recognition and participation in the problem are mandatory to correct the insidious downgrading of the human race, which is already evident."

c. **Note:** *Feingold finalized this paper a few days before his death. He had not had time to list his references, and the editors decided to publish it without them.*

68. **FERRAZOLI 2017: (*) (Lab) (Medical) Brilliant Blue G, But Not Fenofibrate, Treatment Reverts Hemiparkinsonian Behavior and Restores Dopamine Levels in an Animal Model of Parkinson's Disease.** *Cell Transplantation.* 26: 669-677.

a. This paper describes an effect of Blue 1 of potential medical benefit in Parkinson's disease.



From Fig 2 Comparison between numbers of rotations after Blue 1 (BBG) or saline treatment

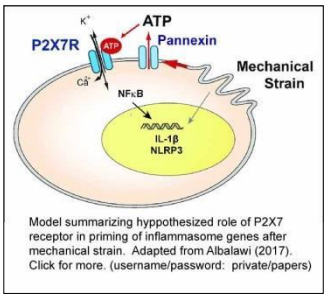
b. Purinergic signaling activates ATP and influences various functions including neurotrans-mission. However, with too much release of ATP and sustained P2X7 receptor activation, cell death is induced, resulting in Parkinson's disease. Thus, the P2X7 receptor is one "target" for drugs to suppress it. Another target is a protein called PGC-1α, involved in energy metabolism.

c. Using a rat model of Parkinson's disease, the P2X7R antagonist Brilliant Blue G (a Blue 1 analog) and the PGC-1α agonist Fenofibrate were used. Blue 1 (but not Fenofibrate) was helpful.

69. **FERREIRA 2016: (*) (Review) (Medical) Brilliant Blue Dyes in Daily Food: How Could Purinergic System be Affected?** *International Journal of Food Science.* 2016:7548498

a. Ferreira reviewed what was known about the medical uses of Blue 1.

b. The purinergic system is widespread throughout the brain, nervous system and every other system in the body. Because Blue 1 and the related BBG are antagonists of purinergic receptors such as P2X7R, they may one day be used as treatment of a number of illnesses that currently have no good treatments -- **Alzheimer's, spinal cord injury, prion illnesses, traumatic brain injury, Duchenne muscular dystrophy, Amyotrophic lateral sclerosis, and others.**



Model summarizing hyppothesized role of P2X7 receptor in priming of inflammasome genes after mechanical strain. Adapted from Albalawi (2017). Click for more. (username/password: private/papers)

c. Blue 1 inhibits mitochondrial respiration *in vitro.* In eye surgery, it may help relieve inflamed tissues that have P2X7R hyperactivity. Ferreira reviewed a number of other possible medical benefits of Blue 1, but warns consumers that **Blue 1 in food and toiletries can approach the amount used medically**, especially since it can also be absorbed through shaven skin, mucosal membranes (e.g., the tongue), and even the gut when permeability is increased (e.g., by NSAID pain meds, kidney failure, bowel disease, etc.) Thus, Blue 1 can be useful where the receptor P2X7R has been upregulated by disease and needs to be suppressed – but may be problematic at other times.

70. **GALLOWAY 1986: (FDA) (Lab) Behavioral effects of erythrosine following light exposure.** *Neurobehavioral Toxicology & Teratology.* 8(5):493-7.

a. This is a study on the effect of light and Red 3 on the activity level of mice in a figure 8 maze, running in the dark (*the active time for mice*).

b. The activity of the mice was not affected by IP doses of 1.25 mg/ kg (*half the US ADI*).

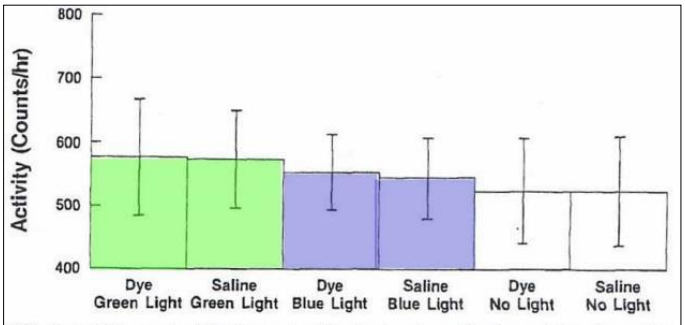


FIG. 5. Activity counts following each of the treatment combinations of Experiment III. Means and SEMs are shown for each treatment condition. N=18.

c. Pre-exposure to blue or green light before running the mice in the dark maze consistently produced increased activity levels, with or without the dye.

71. **GAMAGE 2006: (*) (Extra) Human Sulfotransferases and Their Role in Chemical Metabolism.** *Toxicological Sciences.* 90(1), 5–22

    a. This is information about the phenolsulfotransferase (PST or SULT1A) enzymes, and how they are related to neurological effects. Elsewhere are studies on how food dyes affect this enzyme.

72. **GANESAN 2011: (*) (Lab) The Food Colorant Erythrosine is a Promiscuous Protein- Protein Interaction Inhibitor.** *Biochemical Pharmacology.* 81: 810-818.

    a. After observing that Red 3 is a relatively potent inhibitor of one particular protein-protein interaction, the authors investigated whether it had similar activity in other interactions.

    b. They found that Red 3 can inhibit a number of protein-protein interactions and it only takes a little bit – less than 100 micrograms.

    c. It inhibits dopamine uptake, acetylcholine release, and reduces serotonergic activity in rodents. At 50 micrograms, it can stimulate IgE while inhibiting IgG and IgM.

    d. Because Red 3 can pass through the blood-brain-barrier, it may possibly accumulate to toxic levels even with its low ADI of 0.1 mg/kg (this was suggested, not proven).

    e. **Note:** *0.1 mg/kg is the Japanese ADI – the US ADI is 2.5 mg/kg – more than 20 times higher.*

73. **GAO 2011: (*) (Lab) Effect of Food Azo Dye Tartrazine on Learning and Memory Functions in Mice and Rats, and the Possible Mechanisms Involved.** *Journal of Food Science.* 76(6): T125-T129.

    a. Middle and high Tartrazine (Yellow 5) doses produced learning and memory deficits.

    b. Doses are equivalent to 40 and 80 mg/kg for humans, which is far above the ADI.

    c. **Note:** *It may be a typo, but the ADI level that they list for Tartrazine* ***is 75 mg/kg****, while the dosages they gave the animals corresponds, they say, to 80 mg/kg and 40 mg/kg. But the Japanese ADI is 7.5 mg/kg – not 75 -- so the question is: Did they just miss the decimal? Did they mean 8.0 mg/kg and 4.0 mg/kg?*

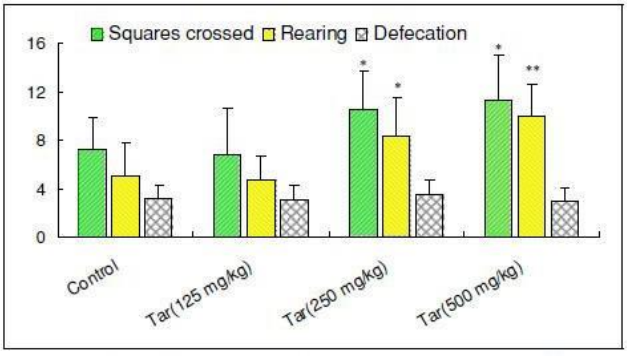


Figure 3–Effects of tartrazine on locomotor activity in rats. Each column represents the mean ± S.E.M. of 10 animals. Rearings = exploratory activity; squares crossed = motor activity; defecation = fear score. Tar = Tartrazine. $^{*}P < 0.05$, $^{**}P < 0.01$ compared with Control.

74. **GHUMAN 2011: (*) (Review) Restricted Elimination Diet for ADHD: The INCA Study.** *The Lancet.* 377: 446-448.

a. Ghuman commented that the Pelsser (2011) study was well-designed and carefully done, and showed the benefit of a supervised elimination diet.

75. **GIBB 1987: (*) (Lab)** ***In Vitro*** **Inhibition of Phenolsulphotransferase** *(PST)* **by Food and Drink Constituents.** *Biochemical Pharmacology*, 36(14): 2325-2330.

a. Several additives and foods were tested *in vitro* for their ability to inhibit enzymes known to affect behavior.

b. PST is important to neurotransmission. **See more.** It is an enzyme involved in handling exogenous and endogenous phenols, so if inhibition were to occur *in vivo*¸ potentially toxic concentrations of some of these phenols could occur.

c. Gibb writes the effect of coloring on children may be related to inhibiting the PST enzymes, resulting in an increase of circulating free phenols. He says two juices tested were potent inhibitors – grape juice and apple juice.

d. **Note:** *How interesting that both of these juices are on the Feingold "salicylate" list and are some of the least well tolerated juices for children on the Feingold diet, even at Stage 2 (testing the salicylates for tolerance)*

.

e. **Note**: *Other studies show that children with ADHD or autism often have low levels of PST-P. If a child starts out with a low level of this enzyme, it may magnify the effect of ingesting enzyme-inhibiting food dyes.*

76. **GOLDENRING 1980: (*) (Lab) Effects of Continuous Gastric Infusion of Food Dyes on Developing Rat Pups**, *Life Sciences.* 27(20):1897-904.

a. Rat pups receiving food dyes were significantly more active than comparable pups not receiving food dyes at all ages tested – and regardless of the 6-OHDA treatment status.

b. Pups treated with food dyes had impaired avoidance performance in a shuttle box.

c. The pups treated with dyes and those treated with 6-OHDA but no dye displayed "over 100% impairment" in avoidance performance compared to sham-treated pups without food dye.

d. Goldenring wrote that these results suggest **food dyes and or their metabolites exert deleterious effects on rat pup behavioral development.**

77. **GOLDENRING 1981: (FDA) (Lab) Effect of Chronic Erythrosin B Administration on Developing Rats.** *Neurobehavioral Toxicology and Teratology.* 3: 57-58.

a. Rats were given 1 mg/kg/day of Red 3 during their first month after birth.

b. No effect was seen and no indication that it crossed the blood brain barrier.

c. In other studies that did show an effect of mixed dyes, Red 3 was only a small part.

78. **GOLDENRING 1982: (FDA) (Lab) Sulfanilic Acid: Behavioral Change Related to Azo Food Dyes in Developing Rats.** *Neurobehavioral Toxicology & Teratology.* 4(1):43-9.

a. Sulfanilic acid is a metabolite of both Yellow 5 and Yellow 6. It has a slow excretion time in rats and goes through the blood-brain barrier.

b. Daily IP injection of 1 mg/kg/day of sulfanilic acid elicited **hyper-activity and impaired shock escape performance** in rat pups.

c. Sulfanilic acid did not have an effect on pups treated with 6-OHDA. (6-OHDA is a neurotoxic compound used to destroy dopaminergic and noradrenergic neurons in the brain.)

d. The author suggests that **sulfanilic acid may be one of the causative agents in food dye-induced behavioral changes in developing rats**.

79. **GOODMAN 2013: (*) (Review) Artificial Food Colour Exclusion and Free Fatty Acid Supplementation May Reduce Symptom Severity in Children with ADHD.** *Evidence-Based Mental Health.* 16(3):77.

a. This commentary summarizes the extensive review by Sonuga-Barke (2013), noting that it employed a "rigorous selection of high-quality data trials."

b. Goodman describes the conclusion as: "Artificial food colour exclusion, and to a lesser extent free fatty acid supplementation, significantly reduce symptom severity in ADHD, although the clinical significance of these results has not been determined."

80. **GOYETTE 1978. (FDA) (Study) Effects of Artificial Colors on Hyperkinetic Children: A Double-Blind Challenge Study.** *Psychopharmacology Bulletin*. 14 (2): 39-40.

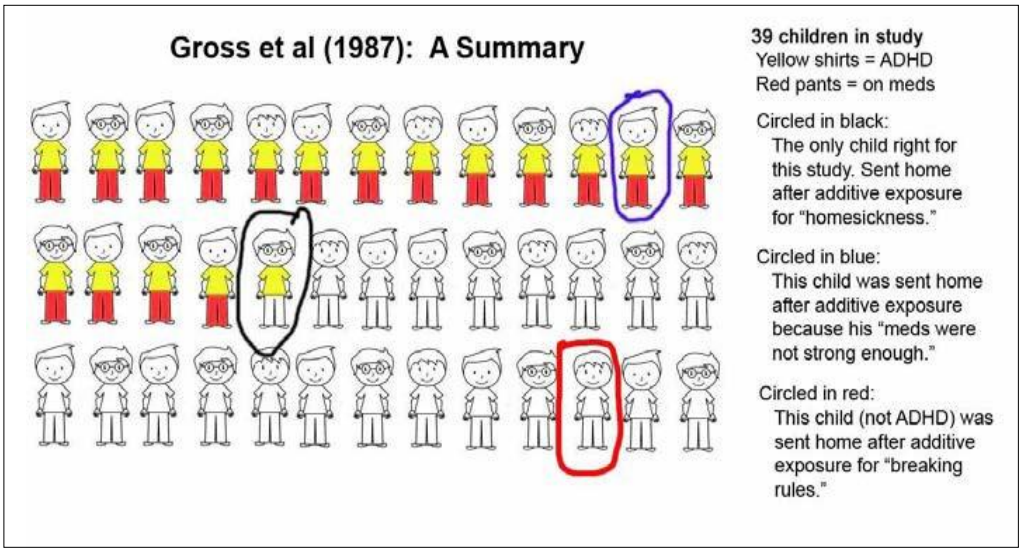
a. Although the 16 children in this study had a **57%** average reduction in behavior problems on the diet at home and a **34%** reduction of problems in school, Goyette reported that symptoms remained low after eating 13 mg of coloring via cookies (eaten after a meal).

b. There was, wrote Goyette, a "**trend towards performance deficits**" after the cookies with dye but no deficits after placebo cookies. **Note:** *It's hard to reach significance with a small number of subjects.*

c. He also said that younger children tended to have a "more pronounced response to the challenge." **Note:** *For younger children, 13 mg is a larger "dose."*

d. His second experiment on 8 younger children with a **45%** reduction in behavior problems on the Feingold diet, showed a clearer "challenge effect" after the 13 mg food dye. There was, he wrote, "**a significant challenge effect p < 0.025), with more problems reported during the active challenge period** as compared to the placebo period."

81. **GROSS 1987: (*) (Study) The Effect of Diets Rich in and Free From Additives on the Behavior of Children with Hyperkinetic and Learning Disorders.** *Journal of the American Academy of Child and Adolescent Psychiatry*. 26(1): 53-55.



a. Gross carried out a diet study in a 2-week summer camp.

b. The children were one week on the "Feingold" diet followed by one week on a diet containing additives. **Note:** *In the best of circumstances, it usually takes more than one week to **begin to see** an improvement on the diet (per the Feingold Association of the US).*

c. Only 18 of the 39 children had been diagnosed with ADHD, and 17 of them were taking medication for it. They continued their (colored) meds during the study. No mention was made about providing natural toothpaste, shampoo, etc. during the "Feingold Diet" week. Behavior was recorded by a teacher operating a video for **4-minutes *during* *each mealtime*** and these videos were rated for misbehavior by three people "blind to the respective diets the children were on."

- **Note:** *Since the raters could obviously see the food and condiments (or lack thereof) on the tables in the video, how could they possibly be "blind to the respective diets?" Even if two of the raters didn't know anything about the study diets, the third one was the senior author of the study himself. He could not possibly have been "blind" to the diet …*

- **Note:** *Since any reaction to the additives eaten would require some hours to take effect, why would videotaping the children during the act of eating be useful?*

- **Note:** *If the medication had been "working" for the children at home on their normal diet, what results could possibly have been expected from giving them additives at camp?*

d. One child on medication was sent home on Week 2 because he became "more boisterous" during this "additive" diet week; his medication was blamed as having become "inadequate."

e. The one ADHD child not on medication was also sent home on Week 2 "for homesickness."

f. A third child (not ADHD) was sent home on Week 2 for "breaking rules."

- **Note:** *Why were none of these behaviors considered a possible reaction to the additives?*

g. The children were not told that they were in a study or that they were on any special diet. The lack of condiments and candy during the "Feingold" week was explained to them as a delivery delay. No additive-free cookies, candy, snacks or desserts were provided. Is it any wonder the children hated the food during this first week?

h. Quote: "The children were not happy with the Feingold Diet.**"** (How *not* surprising.)

i. Quote: "The authors conclude that the Feingold Diet has no beneficial effect on most children with learning disorders, or on hyperkinetic children taking medication."

j. **Note:** *Actually, Dr. Feingold himself warned that the diet was not likely to "work" while a child remained on medication, except that sometimes the medication may become overstimulating as the child needed less of it.*

82. **HAAVIK 1979: (*) (Case) Effects of the Feingold Diet on Seizures and Hyperactivity: A Single-Subject Analysis.** *Journal of Behavioral Medicine.* 2(4): 365-374.

a. This is the first indication that eliminating additives is effective in reducing seizures (from a high of 6 per day to none).

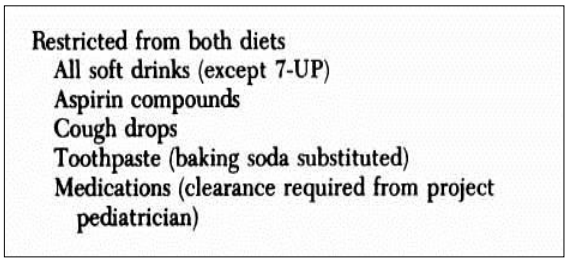
b. By the end of a year, 2 medications had been discontinued and the third reduced from 300 to 50 mg/day.

83. **HARLEY 1978: (FDA) (Study) Hyperkinesis and Food Additives: Testing the Feingold Hypothesis.** *Pediatrics*. 61(6):818-28.

a. Two diets were used – the Feingold diet and a "control" diet that included some 13 mg of food dyes in cookies or candy bars (not enough to "show"). Each diet was maintained for 3 or 4 weeks.

b. Behavior ratings were made weekly, so only 3 or 4 ratings per child were made on each diet. *(***Note***: Few children take less than 2 weeks to improve on a Feingold-type diet.)*

c. **Note:** *Some of the children were reported as worse on the "experimental" (Feingold) diet. Eagle (2014) describes the interaction of additives and the enzyme SULT1A, making some children get worse before they improve. Other researchers have also noticed this occurrence (Egger 1985). This study did not last long enough to see if those who first got worse would later improve.*


Restricted from both diets
All soft drinks (except 7-UP)
Aspirin compounds
Cough drops
Toothpaste (baking soda substituted)
Medications (clearance required from project pediatrician)

d. Harley reported an order effect – most of the children who improved on the Feingold diet had been on the control diet first. He ignored Dr. Feingold's finding that children previously on medication take longer to respond. Also, the "control" diet itself was fairly free of additives, thus giving the children (newly off meds) an extra few weeks of a pretty clean diet to recover from the meds before implementing the Feingold diet phase.

e. In the second study -- on preschoolers -- all 10 mothers said their children improved on the Feingold diet. None had previously been on medication, and there was no order effect.

f. **Note:** *Harley complains about an absence of teacher ratings for preschoolers, which is a bit odd since he obviously knew there would be no teacher reviews when designing the study.*

84. **HARLEY 1978**: **(FDA) (Study) Synthetic Food Colors and Hyperactivity in Children. Double- Blind Challenge Experiment.** *Pediatrics*, 62: 975-983.

a. Harley tested 9 hyperactive boys who had shown a favorable response to the Feingold diet in the previous study.

- **Note:** *His use of hostile quotes around "response" in the abstract is a clue to his apparent hostility to the idea that the diet might actually have been beneficial.*

b. Harley used only 27 mg of food dyes for his challenge materials, based on advice of the industry-supported Nutrition Foundation.

c. There was no difference in color between the placebo and experimental items! The children did not react to these "challenges."

85. **HARNER 1980: (*) (Study) Effect of Feingold's K-P Diet on a Residential, Mentally Handicapped Population.** *Journal of American Dietetic Association.* 76(6): 575-578.

a. In this study, Harner tested the Feingold diet on a mentally handicapped population. Psychoactive and other medications *(most likely containing dye and flavorings)* were continued as usual. Toiletries and toothpaste without dyes were used "wherever possible." **Note:** *Poor planning. If you want to test a diet avoiding coloring, then you have to AVOID it, not just when convenient.*

b. The control diet was the usual diet of the center, with no evaluation of its quality or usual inclusion of additives (if any).

c. Subjects were rates 3 times a week and by different people (morning/afternoon staff). Group scores were averaged, using only 2 data points per child. With only 15 per group, it would be hard to reach statistical significance.

d. Although an unspecified "difference in the raters' perception" of the subjects was reported, the researchers found "no significant differences between the group on the Feingold K-P diet and the group receiving the control diet."

86. **HARPER 1978: (*) (Study) (Extra) Nutrient Intakes of Children on the Hyperkinesis Diet.** *Journal of the American Dietetic Association.* 73(5): 515-519. *(abstract only)*

a. Harper calculated the nutrient intake of 54 children before and on the Feingold diet. Their diet was as good as or better than the Recommended Dietary Allowances (RDA) — in other words, the Feingold diet did not cause any vitamin deficiencies.

87. **HEILSKOV RYTTER 2015: (*) (Review) Diet in the Treatment of ADHD in Children – A Systematic Review of the Literature.** *Nordic Journal of Psychiatry.* 69(1): 1-18.

a. 52 studies were identified that investigated whether ADHD symptoms can improve by avoiding or adding certain food elements.

b. Elimination diets and fish oil supplementation seem to be the most promising dietary interventions for reducing ADHD symptoms. The author recommends studying the long-term effect of both.

88. **HELAL 2000: (*) (Lab) Effect of Some Food Colorants (Synthetic and Natural Products) on Young Albino Rats: I-Liver and Kidney Functions.** *The Egyptian Journal of Hospital Medicine.* 1(1); 103-113.

a. Permitted doses of natural and synthetic food dyes were shown to increase serum AST (*aspartate amino transferase*), ALT (*alanine-amino transferase*) and urea. All colorings except sunset yellow (Yellow 6) significantly increased serum total bilirubin.

b. The rats were in 7 groups of 10 rats each, and received no dye or one of the listed dyes every day for 30 days. At that point, 5 animals in each group were sacrificed while the rest were kept for two more weeks without any additional dye to see if they recovered. During this recovery period, some of the negative effects improved but others did not.

c. Rats receiving the food dyes became **more active, nervous and aggressive.** Skin irritation was noticed after administration of sunset yellow (Yellow 6).

d. **Note**: *Rats in this study were housed 10 to a cage; thus there may have been more opportunity to notice if they were aggressive or irritable than in studies where they are housed in single-rat cages. It was not clarified if the "skin irritation" exhibited by rats receiving Yellow 6 may have been a result of aggressive grooming rather than an allergic-type response.*

89. **HINDLE 1978: (*) (Case) The Management of Hyperkinetic Children: A Trial of Dietary Therapy.** *New Zealand Medical Journal.* 88(606):43-45. *(abstract only)*

a. Ten hyperkinetic children were treated with the additive-free Feingold diet.

b. Five improved dramatically and were able to be off other therapy. Their response to accidental or deliberate challenge supports the hypothesis that the diet was responsible for their improvement.

90. **HOLTON 2016: (*) (Review) The Influence of Diet on ADHD.** *Psychiatric Times.* 33(9)

a. This is a review of the various dietary treatments used for ADHD.

b. A meta-analysis has concluded there is enough evidence to suggest that artificial coloring can be a trigger for some patients.

c. Dietary pattern analyses have been finding that eating wild-caught fish increases omega-3 and also other vitamins and minerals. Similarly, low intake of processed foods and beverages limits additive (and dye) exposure.

d. The best evidence to date indicates that **ADHD symptom severity may be reduced by supplementing with omega-3 and reducing or removing processed foods high in food colors and preservatives.**

e. Sources of food dyes are children's vitamins, children's medications, and juice drinks; the authors suggest substitutions. The oligoantigenic diet can be used when allergies are suspected.

91. **HOWARD 2010: (*) (Study) ADHD is Associated with a "Western" Dietary Pattern in Adolescents.** *Journal of Attention Disorders.* 15(5): 403-411.

a. Eating habits of adolescents in Australia were divided into "Western" and "Healthy" dietary patterns. The "Western" dietary pattern was associated with an ADHD diagnosis, both inattentive and combined.

b. In this case, "Western" included snack foods and foods high in sugars, food dyes and other additives.

c. The author pointed out that it could not be determined if those eating the Western diet were therefore more prone to ADHD, or if children with ADHD were more likely to want to eat that sort of food.

92. **HURT 2011: (*) (Review) Dietary and Nutritional Treatments for Attention- Deficit/Hyperactivity Disorder: Current Research Support and Recommendations for Practitioners.** *Current Psychiatry Reports.* 13(5): 323-332.

a. A diet eliminating food dyes and other additives has some support by controlled studies, and can be included in treatments labeled SECS (Safe, Easy, Cheap, and Sensible).

b. The author says that **removing artificial food dyes may be more applicable to the general pediatric population than to children with diagnosed ADHD**."

93. **INSTITUTE OF FOOD TECHNOLOGISTS 1986: (*) (Extra) Food Colors.** *Food Technology.* 49-56.

a. This is a scientific status summary by the Expert Panel on Food Safety & Nutrition, based on the Survey of Industry on the Use of Food Additives, 1977, by the National Academy of Sciences.

b. The NAS report is large and the print quality poor. See the introduction and the pages relating to food dyes. **Note:** *See the charts I created to make sense of the above pages here*

Table 1—National Academy of Sciences 1977 survey of the amount of certified FD&C colorants consumed[a,b]

Colorant	Average Daily Intake (mg)
FD&C Red No. 3	24
FD&C Blue No. 2	7.8
FD&C Yellow No. 5	43
FD&C Green No. 3	4.3
FD&C Blue No. 1	16
FD&C Red No. 40	100
Orange B	7.8
FD&C Yellow No. 6	37
FD&C Red No. 3 Lake	15
FD&C Blue No. 2 Lake	3.1
FD&C Yellow No. 5 Lake	22
FD&C Blue No. 1 Lake	6.6
FD&C Red No. 40	27
FD&C Yellow No. 6 Lake	14
TOTAL = 327.6 mg/day	

[a]NAS/NRC, 1979.
[b]Data represent the 99th percentile of persons over two years of age, in the "eaters" group (those who consumed one or more foods containing the additive in question during the fourteen-day survey period). Ninety-nine percent of the population sampled was estimated to have intakes equal to or below the value shown. Total sample size was 12,000 persons.

c. **Note:** *The Institute list (above, right) gives the average of the top 1% of "eaters" for each color. The total has been added (by me), giving 327.6 mg/day as a maximum average.*

d. The Expert Panel says the FDA decided the actual food color intake is only 1/5 the amount recorded in the study. No reason is given. After reviewing the 1970s studies, they concluded that "changes in behavior are probably not associated with food hypersensitivity or other immunologic reactions to foods or food additives."

e. Quote**: "At the heart of the debate is the meaning of "safety"."**

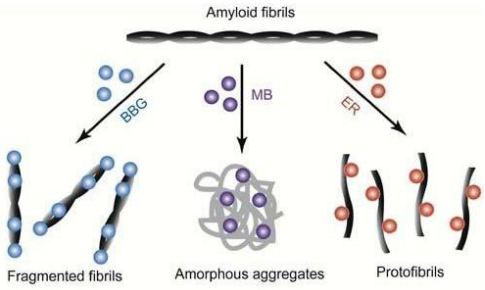
f. The importance of food colors is spelled out: although contributing nothing nutritionally, they are "very important food ingredients. They play a significant role in the **success or failure of a food product** …" *(emphasis added)*.

g. **Note:** *In other words, food dyes are important … to the FOOD INDUSTRY, to increase profit.*

94. **IRWIN 2013: (*) (Lab) (Medical) Different Fates of Alzheimer's Disease Amyloid-beta Fibrils Remodeled by Biocompatible Small Molecules.** *Biomacromolecules.* 14(1): 264- 274.

a. Amyloid fibrils such as those found in Alzheimer's disease are thermodynamically very stable, but there is evidence that small molecules like food dyes can remodel them safely.

b. The authors performed a remodeling trial using methylene blue, brilliant blue G (Blue 1) and erythrosine B (Red 3).



c. Methylene blue perturbed the fibrillary structure leading to amorphous aggregates, Blue 1 fragmented the fibrils into shorter fibrils, and Red 3 separated the fibrils into protofibrils successfully. All three are "promising candidates to remove insoluble amyloid fibrils deposited in the human brain."

95. **JO 2011: (*) (Lab) (Medical) Inhibition of Neuronal Voltage-Gated Sodium Channels by Brilliant Blue G.** *Molecular Pharmacology.* 80: 247-257.

a. BBG, a variant of Brilliant Blue FCF (Blue 1) is a P2X7 receptor antagonist and is shown to also block neuronal sodium channels.

b. It is the most potent agent yet found that interacts with sodium channels. Other sodium channel blockers include lidocaine, lamotrigine (Lamictal), phenytoin (Dilantin), and carbamazepine (Tegretol) – drugs used for treating pain, epilepsy, bipolar disorder, etc.

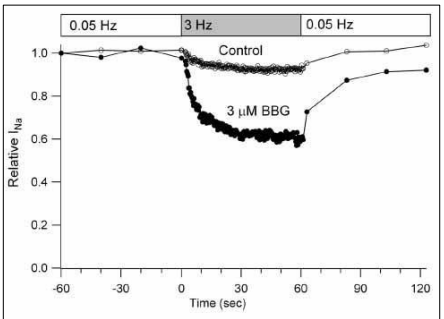


Fig. 2. Use-dependent block by BBG. Sodium current was elicited by 20-ms depolarizations from −80 to 0 mV. After a period of slow stimulation (every 20 s), the frequency was abruptly increased to 3-Hz train. The protocol was run in control conditions and then in 3 μM BBG, which reduced the current elicited by slow stimulation from 3.0 to 1.3 nA. Peak sodium current was normalized with reference to the current with slow stimulation in each condition.

96. **KAMEL 2011: (*) (Lab) The Potential Health Hazard of Tartrazine and Levels of Hyperactivity, Anxiety-Like Symptoms, Depression and Anti-social Behaviour in Rats.** *Journal of American Science.* 7(6): 1211-1218.

a. In a double-blind controlled study, various doses of Yellow 5 were provided in the drinking water of 45 male rats. They were evaluated for behavioral changes.

b. Quote: "This study provides **sufficient scientific evidence that a causal link truly exists between Tartrazine and inflection of hyperactivity, anxiety and depression-like behaviours in rats and points to the hazardous impact of tartrazine on public health."**

Well, this is not what the "forced swim" test really looks like but it's much cuter.

97. **KANAREK 2011: (*) (Review) Artificial Food Dyes and Attention Deficit Hyperactivity Disorder.** *Nutrition Reviews*. 69(7):385-91.

a. Kanarek reviews the old studies from the 1970s and 1980s, as well as a few of the newer papers -- Bateman (2004), McCann (2007), Stevenson (2010), Schab (2004). He goes into some detail about other nutritional factors such as zinc, iron, and omega 3.

b. He warns that an elimination diet can be challenging and that parents may need to be counseled on how to make good choices.

98. **KAPLAN 1989**: **(FDA) (Study) Dietary Replacement in Preschool-Aged Hyperactive Boys.** *Pediatrics*. 83(1): 7-17.

a. 24 preschool hyperactive boys with sleep problems and other physical symptoms were entered into a 10-week study.

b. The control (placebo) diet provided by the researchers matched the baseline diet day-by-day of each child.

c. The experimental diet eliminated food dyes, artificial flavorings, preservatives, MSG, chocolate, and caffeine, and anything else (such as milk or salicylates) suspected by parents. If an item (e.g., carrots) was reported as a problem or an allergy, it was excluded from all diets, since this was not a test of allergy.

d. More than half exhibited a reliable improvement in behavior with negligible placebo effects.

e. Nonbehavioral variables that also improved: halitosis and sleep.

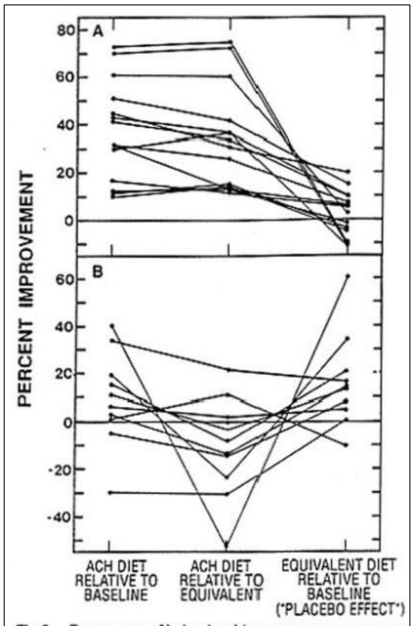


Fig 3. Percentage of behavioral improvement on parent Abbreviated Symptom Questionnaire, part 1, for each child. A, Data for ten responders and four mild responders, for whom hospital (ACH) diet improved behavior and there was little placebo effect. B, Nonresponders, for whom no pattern of change was discernible.

99. **KAPLAN 2010**: **(*) (Review) Food Additives and Behavior: First Genetic Insights (Editorial).** *American Journal of Psychiatry.* 167: 9.

a. Kaplan agrees with Stevenson (2010), in that the behavioral effects of the Southampton study (McCann 2007) "were likely moderated by histamine degradation gene polymorphisms…"

b. Kaplan says histamine has been neglected up to this point in ADHD genetic studies, and that histamine H3 receptors should be studied because they affect hyperactivity in animal models and also influence frontal cortex dopamine release.

c. Quote: "… the cumulative evidence is sufficient for society to demand adherence to the precautionary principle and to **begin to restrict the use of artificial dyes, at least in foods that target children**."

100. **KHIRALLA 2015: (*) (Lab) Effect of Natural and Synthetic Food Coloring Agents on the Balance of Some Hormones in Rats.** *International Journal of Food Science and Nutrition Engineering.* 5(2): 88-95.

    a. Groups:
        - Control
        - Beet extract & Curcumin extract groups
        - Red 3 – ADI and "Overdose" groups
        - Yellow 6 – ADI and "Overdose" groups

    b. Beet and curcumin extracts – rats had normal brain & hormone levels.

    c. ADI of Yellow 6 and Red 3 induced hyperactivity, dopamine and noradrenaline imbalance, and brain alterations.

    d. Overdoses of Yellow 6 and Red 3 induced hyperactivity, hormone imbalance – increased dopamine and noradrenaline, but decreased interstitial cell-stimulating hormone and testosterone – as well as severe changes in various brain areas.

101. **KIDD 2000: (*) (Review) Attention Deficit/Hyperactivity Disorder (ADHD) in Children: Rationale for its Integrative Management.** *Alternative Medicine Review.* 5(5): 402-28.

    a. In this review, Kidd says that while the exact etiology of ADHD is unknown, many things are involved: Genetics, food additives, and food intolerances, as well as sensitivity to environmental chemicals, molds, fungi, and toxins such as heavy metals and pesticide pollutants.

    b. For some, thyroid hypofunction may link toxic insults with ADHD symptoms; other possibilities are abnormality of brain function and hypofunctioning of the dopaminergic pathways, as well as possible nutrient deficiencies. **Note:** *Interesting, since in Khiralla (2015) above, we see that the dyes affect dopamine and brain function.*

102. **KIDD 2002: (FDA) (Review) Autism, an Extreme Challenge to Integrative Medicine. Part 2: Medical Management.** *Alternative Medicine Review.* 7(6): 472-99.

    a. Kidd describes the problems that food additives can cause for children dealing with autism, and the ways that avoiding them can be of benefit.

    b. He discusses metabolic problems such as sulfation inadequacies, dietary restrictions, including removal of milk and other casein-containing dairy products, gluten, sugar, chocolate, preservatives, and **food coloring, the removal of which he says are prerequisite to benefit from other interventions.**

103. **KIM 2018: (*) (Study) Associations between Attention-Deficit/Hyperactivity Disorder Symptoms and Dietary Habits in Elementary School Children.** ***Appetite.*** 127: 274-279.

a. More than 16,000 parents in Korea responded to the Korean version of the ADHD rating scale and also to a food questionnaire.

b. The study found that ADHD symptoms are positively associated with higher consumption of fast food, soft drinks, and instant noodles.

c. The author discussed the deficits in those foods, which include their probable high content of sugar, salt, and food additives.

104. **KIRKLAND 2019: (*) (Review) Measuring Treatment Response in Pharmacological and Lifestyle Interventions Using Electroencephalography in ADHD: A Review.** *Clinical EEG and Neuroscience* 2019. Jan 9 epub ahead of print.

a. Kirkland reviews the only two studies on EEG and food colorings -- Salamy (1982) and Uhlig (1997) in the section named *Dietary Intervention.*

b. Kirkland says that the Salamy study was the first to report changes in the alpha band during exposure to food dye, while the Uhlig study was the first to report changes in more than one frequency band in children with food-induced ADHD given food dyes or other foods the individual reacts to.

105. **KOBYLEWSKI 2012: (*) (Review) Toxicology of food dyes.** *International Journal of Occupational and Environmental Health*. 18(3): 220-246.

a. This review of the toxicology of food dyes finds that all nine of the currently approved dyes in the US have health concerns, including cancer, contamination with benzidine or other carcinogens, hyperactivity and hypersensitivity reactions.

b. Kobylewski believes that since the dyes do not improve the safety or nutritional quality of foods, **they should all be removed from the food supply and replaced if at all) by safer colorings.**

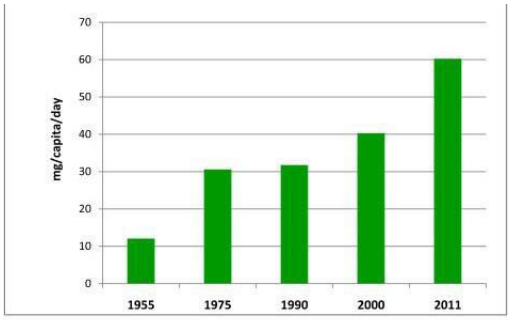


Figure 1: Food dyes marketed per capita per day (mg)

106. **KONIKOWSKA 2012: (*) (Review) The Influence of Components of Diet on the Symptoms of ADHD in Children**. *Roczniki Panstwowego Zakladu Higieny*. 63(2): 127-34.

a. After a review of ADHD treatments, Konikowska discusses environmental factors known to increase the risk of ADHD during and after pregnancy — pollution, pesticides, smoking, and toxins. She reviews papers on nutritional factors such as synthetic food dyes, preservatives, refined sugars, and deficiencies of magnesium, zinc, iron, B6, iodine, omega-3, etc.

b. Quote: "Results of research suggest that food additives and salicylates may aggravate hyperactive behavior [in] children."

c. She writes that even though only some children will respond to an elimination diet, it may be worth considering, and would have fewer side effects than stimulant medications.

107. **KREGIEL 2015: (*) (Review) Health Safety of Soft Drinks: Contents, Containers, and Microorganisms.** *BioMed Research International.* Article ID 128697. 15 pgs.

a. In the Ingredients section, page 4, is a short review of the current use of food dyes in soft drinks.

108. **KUMAR 2011: (*) (Lab) Genotoxic Effects of Two Commonly Used Food Additives of Boric Acid and Sunset Yellow in Root Meristems of Trigonella Foenum-Graecum.** *Iranian Journal of Environmental Health Science & Engineering.* 8(4): 361-366.

a. The plant *Trigonella foenum-graecum* (Fenugreek) was exposed to Yellow 6 for three hours. It's growing tips reacted with precocious movement, disorientation, and scattering.

b. **Note**: *This must be as close as a plant can get to being hyperactive.*

109. **LAFFERMAN 1979: (FDA) (Lab) Erythrosine B Inhibits Dopamine Transport in Rat Caudate Synaptosomes**. *Science.* 205: 410-412.

a. Erythrosin B (Red 3) given to rats prevents the uptake of dopamine -- the "feel good" neurotransmitter -- by nerve cells in the brain called the caudate synaptosomes.

b. The author says this is consistent with the hypothesis that Red 3 **"can act as a central excitatory agent able to induce hyperkinetic** *[hyperactive]* **behavior."**

110. **LAMPORT 2016: (*) (Study) Concord Grape Juice, Cognitive Function, and Driving Performance: A 12-wk, Placebo-Controlled, Randomized Crossover Trial in Mothers of Preteen Children.** *American Journal of Clinical Nutrition.* 103: 775-783.

a. The intent of this study, funded by Welch Foods, was to show that grape juice improves driving ability in stressed people (moms of teens). The authors concluded that the flavonoid-rich grape juice has cognitive benefits.

b. No baseline test of their driving after drinking plain water was performed.

c. **Note:** *The "placebo" drink ingredients were not specified. I contacted the researchers and was told that it was supplied by Welch, wasn't Kool-Aid, and looked/tasted like grape juice but ingredients were unknown. One can only assume it must have contained artificial coloring and flavoring.*

d. **Note:** *Having no baseline, and having a possibly "active" placebo containing artificial dyes and flavors means it is not really known if the grape juice made the moms drive better … or if the artificially-colored/flavored "placebo" made them drive worse.*

111. **LANGE 2017: (*) (Review) Dietary Factors in the Etiology and Therapy of Attention Deficit/ Hyperactivity Disorder.** *Current Opinion in Clinical Nutrition and Metabolic Care.* 20(6): 464-469.

a. This is a review of papers published from January 2016 to January 2017 covering gut microbiota, prenatal diet, fish oil, vitamin deficiency and food additives.

b. While Lange says the few foods diet may have "some efficacy" but needs further study, he says that artificial food color elimination does not provide convincing evidence of therapeutic efficacy.

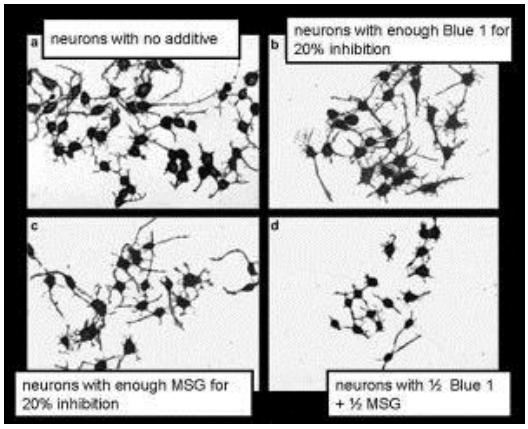
c. **Note:** *I suppose these are the kind of results one would get limiting the literature search effort to a single year on a subject that has been of interest to science for more than half a century.*

112. **LAU 2006: (FDA) (Lab) Synergistic Interactions Between Commonly Used Food Additives in a Developmental Neurotoxicity Test.** *Toxicological Sciences.* 90(1):178-87.

a. This is one of the few studies comparing the neurotoxic activity of food additives alone and in combination.

b. After determining how much of each additive reduces neurite development by 20%, Lau combined pairs of the additives — half of each, so that one would expect the same result.

c. However, in combination these additives are far more toxic than each alone.

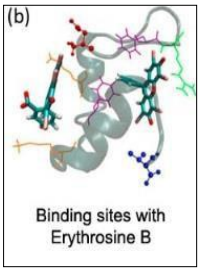


d. Quote: "**Inhibition of neurite outgrowth was found at concentrations of additives theoretically achievable in plasma by ingestion of a typical snack and drink**. . ."

113. **LEE 2016: (*) (Lab) (Medical) Investigation of the Effect of Erythrosine B on Amyloid Beta Peptide Using Molecular Modeling.** *Journal of Molecular Modeling.* 22(4): 92.

a. This paper describes the study of a neurological effect of Red 3 that may be of medical benefit in Alzheimer's disease.

b. Red 3 inhibits formation of amyloid fibrils and plaques in vitro. In this study, the method of action was demonstrated. It appears that Red 3 interacts with certain side chains, destabilizing the inter-chain stacking of Aß40 and disturbing its conformational transition. Details are described. **Note:** *This may become a treatment for people with Alzheimer's, but is it good for the rest of us?*



114. **LEO 2018: (*) (Lab) Occurrence of Azo Food Dyes and their Effects on Cellular Inflammatory Responses.** *Nutrition*. 46:36-40

a. This study found that 11.54% of 1,681 items examined in a supermarket in Singapore contained at least one food dye; Yellow 5, Yellow 6, and Red 40 were the most prevalent.

b. Examining human blood neutrophils, the researchers found that all the dyes tested increased the synthesis of leukotriene B4 and F2-isoprostanes – in other words, they said, these **dyes promote inflammation and suggest a potential health risk**.

c. Quote: "This finding is significant as oxidative damage has been implicated in the pathogenesis of atherosclerosis and stroke."

115. **LEVITAN 1977: (*) (Lab) Food, Drug, and Cosmetic Dyes: Biological Effects Related to Lipid Solubility.** *Proceedings of the National Academy of Sciences of the US.* 74(7): 2914-8.

a. In a study on mollusks, the authors wanted to see if certain dyes are biologically active compounds and what they do. Indeed, application of food dyes increased the resting membrane potential and neuron conductance by increasing potassium permeability of the membrane of the mollusk neurons.

b. The effects were dose-dependent, and provided a basis for estimating the toxicity and brain uptake of the dyes in vertebrates, as well as predicting the effects of the dyes on blood clotting and metabolism. This sort of study was hoped to help select "relatively innocuous dyes" and to establish safe levels of consumption.

116. **LEVITAN 1984: (*) (Lab) Brain Uptake of a Food Dye, Erythrosin B, Prevented by Plasma Protein Binding.** *Brain Research.* 322: 131-134.

a. Putting radioactive Red 3 into the circulation of adult rats, Levitan determined it was more than 99% bound to proteins in the blood and mostly did not get past the blood brain barrier into the brain.

b. He suggested that some people may have altered binding capacity, through age or disease.

c. **Note**: *Other drugs are also highly bound. Warfarin, for example, is 97% bound to plasma proteins. Two drugs can interact if one binds more strongly than the other, while blood brain barrier permeability can also change with illness or stress.*

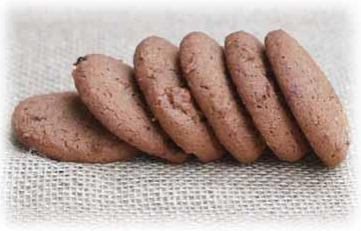
d. See also Skultetyova (1998) on MSG and the blood brain barrier.

117. **LEVITAN 1985: (FDA) (Lab) Brain Uptake of the Food Dye Erythrosine B.** *International Research Communications System/Medical Science.* 13(1): 64.65.

a. In no region did the brain uptake of Red 3 exceed that of sucrose, used as an indicator. However, Levitan says that this does not mean Red 3 cannot influence neuronal function. "In young animals, or in pathological states, significant brain uptake may occur through an immature or defective blood-brain barrier." Moreover, there are non-barrier regions of the brain that could be entered.

b. Neuronal or hormonal interconnections between the open regions and the protected regions may lead to effects on the brain or the peripheral nervous system.

118. **LEVY 1978: (FDA) (Study) Hyperkinesis and Diet: A Double-Blind Crossover Trial with a Tartrazine Challenge.** *Medical Journal of Australia*. 1(2): 61-64.



a. In this paper, Levy describes a series of small experiments in which he put children on the Feingold diet, and then challenged them with 5 cookies per day, each containing ONE (**1) mg** of Yellow 5, for two weeks. Then the children were tested a DAY AFTER the last of these "challenge" cookies … In the first batch of cookies, the placebo and colored cookies matched; the second batch didn't match, so on the third batch, they added cocoa *(without testing for sensitivity to cocoa, apparently)*

b. **Note:** *It would be hard to design a study less likely to show any positive results.*

c. While his description is hard to follow, it seems that most of the mothers in each of his series of studies felt their children were doing better on the diet, and their Conners' scores had improved. They did not show an increase of problem behavior during the challenge period, however, except that a "subgroup of mothers" reported a significant challenge effect of symptoms during the 24 hours after the last cookie but before testing.

119. **LEVY 1978: (FDA) (Study) Hyperkinesis and Diet: A Replication Study.** *American Journal of Psychiatry*. 135: 1559-1560.

a. There were only 7 children left after one dropped out, so this was a very small study. The "challenges" were 4 cookies, each containing ONE (1) mg of Yellow 5.

b. The mothers' reports were on average 2.6 points lower on the Conners' test for their children when given placebo than when given food-dye containing cookies. Although the author says this represents an *average* of 13.8% improvement, it just misses significance, probably due to the small number of children in the study.

120. **LOGAN 1979: (*) (Lab) Erythrosin B Inhibition of Neurotransmitter Accumulation by Rat Brain Homogenate.** *Science.* 206(4416):363-4.

a. A mixture of food dyes inhibited 8 neurotransmitters.

b. Red 3 inhibited dopamine accumulation.

c. Logan wrote the inhibition behavior of Red 3 may be nonspecific and secondary to general membrane alteration.

121. **LOK 2006: (*) (Study) Is an Azo-Free Diet Nutritionally Superior than One Containing Azo-Dyes?** *British Dietetic Association Abstracts, Journal Human Nutr Diet.* 19.458-477.

a. Evaluating the diet of the children involved in the Bateman (2004) study, Lok determined that while there was no difference in the energy, protein or fat intake between the baseline diet and the azo-dye free diet, there was a reduction in two micronutrients: potassium and magnesium, as well as a reduction in carbohydrate. These were all below the levels recommended for their age by the Department of Health in 1991.

b. Lok concluded that "elimination diets may have a detrimental effect on nutritional intake, even when the food that is eliminated is perceived as unhealthy."

c. **Note:** *Previous studies – Dumbrell (1978) and Harper (1978) -- had found that the additive-free Feingold diet was actually an improvement, in which all RDA levels were met or exceeded. A child who refuses acceptable fruits or vegetables, of course, can always be given an appropriate vitamin – but simply increasing the consumption of fruits a bit to replace artificially-colored snacks would surely have taken care of both lack of carbohydrate as well as lack of minerals. This is what the Feingold diet book recommends for new members, as well. It is not, after all, the azo dyes that were providing magnesium and potassium – and the actual carbohydrate loss was most likely sugar-related. Some nice mashed potatoes or even some natural candy could take care of that.*

122. **LOK 2013: (*) (Study) Food Additives and Behavior in 8- to 9-Year-Old Children in Hong Kong: A Randomized, Double-Blind, Placebo-Controlled Trial.** *Journal of Developmental & Behavioral Pediatrics.* 34(9): 642-650.

a. Lok found "no significant associations between AFCs (*artificial food colors*) and a preservative on Chinese children's behavior"

b. Nevertheless, 3 months later, **62.4%** of the parents were still using the additive-free diet; **43.4%** believed additives affected their child's behavior, temper, mood, etc.

c. It seems the removal of additives did reduce problematic behaviors, but reintroducing SOME of them didn't bring all the problems back to "baseline."

d. Like in the McCann (2007) study, these children were from the general population. Nevertheless, this was not really a replication of the McCann (2007) study. The differences may be significant:

- Lok excluded kids with ADHD, learning disabilities, or diabetes; McCann did not.
- Lok used pills; McCann used drinks (contact of dye with mouth/esophagus).
- Lok tested the dyes and sodium benzoate separately; McCann tested them together.
- McCann included Red 40; Lok did not.
- Lok dropped any children who had "allergy after taking the capsule"

123. **LUCOVA 2013: (*) (Lab) Absorption of Triphenylmethane Dyes Brilliant Blue and Patent Blue Through Intact Skin, Shaven Skin and Lingual Mucosa from Daily Life Products.** *Food and Chemical Toxicology.* 52: 19-27.

a. Lucova says there is evidence of health risks from these blue dyes after systemic absorption, so they wanted to investigate the fate of both colors when applied to intact and shaven skin, from cosmetics under normal use conditions.

b. Both the Brilliant Blue (Blue 1) and Patent Blue showed no measurable passage through intact skin but significantly passed through shaven skin. The dye was also absorbed via the surface of the tongue (i.e., lollipop licking).

c. The authors say these findings "**are troubling, particularly with regard to the frequent use of after-shave products by the male population and repeated lollipops licking by children.**"

d. Letter from the International Association of Color Manufacturers, and Lucova's reply.

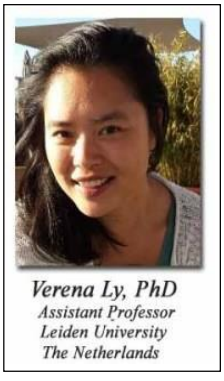
124. **LV 2017: (*) (Lab) (Extra) A Novel Preparation Method of Two Polymer Dyes with Low Cytotoxicity.** *Materials.* 10(219): 1-11.

a. The author writes that Yellow 6 and Red 40 have genetic toxicity and cause DNA damage, while Red 40 has behavioral effects; therefore, China (*a supplier of food dyes to the US and other markets*) is developing water soluble, stable polymeric dyes by grafting the Yellow 6 and Red 40 to OMCS.

b. It is believed that the resultant dyes will be less able to pass the gut wall and be less toxic, but their color will compare well with the original synthetic dyes. In a study on human liver cell lines, the polymer dyes are apparently less cytotoxic than the original azo dyes.

c. **Note***: I hope these will not be substituted for the current dyes China exports to the US without some proper neurotoxicity testing. Just because they bear the same name doesn't mean they are the same or better; they could be worse*.

125. **LY 2017: (*) (Review) Elimination Diets' Efficacy and Mechanisms in Attention Deficit Hyperactivity Disorder and Autism Spectrum Disorder.** *European Child & Adolescent Psychiatry.* 26(9):1067-1079.



a. Ly discusses the interaction of the metabolic, immune, endocrine, and neural systems related to food additives.

b. Quote: "… given the positive, albeit small effects of this intervention in children with ADHD as well as in children from the general population, and the fact that food additives do not provide any health benefits, it is **recommended that children preventatively minimize consumption of processed food products with these ingredients.**

126. **MADZHIDOVA 2019: (*) (Review) The Use of Dietary Interventions in Pediatric Patients.** *Pharmacy.* 7(1). 13 pgs

a. Madzhidova reviewed a number of CAM treatments and recommends how pharmacists can help.

b. For people on an elimination diet for ADHD, for example, pharmacists can help them find medications without food dyes and flavorings. Pharmacists are warned, however, that dyes present in binding agents may not be listed in the package insert, and the author suggests that they can contact the manufacturer directly.

127. **MAILMAN 1980: (FDA) (Lab) Erythrosine (Red No. 3) and Its Nonspecific Biochemical Actions: What Relation to Behavioral Changes?** *Science.* 207: 535-557.

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a. Mailman says Red 3 had no effect on locomotor activity of rats when injected.

Treatment	Drug	Locomotor activity: Before drug (counts per 60 minutes)	Locomotor activity: After drug (counts per 20 minutes)
None	Erythrosine	376 ± 73	375 ± 97
None	None (saline)	265 ± 67	190 ± 50
6-OHDA	Erythrosine	438 ± 136	298 ± 92
6-OHDA	None (saline)	302 ± 74	409 ± 139

b. **Note:** *Table 1 (at right) has two columns – one for "Before" and the other for "After" treatment. But the "Before" column heading is "**counts per 60 minutes**" and the "After" column heading is "**counts per 20 minutes**." The numbers of the group in the top are similar in both columns … but if the "After" column is really for 20 minutes, doesn't that indicate a dramatic increase of activity? Or, just a typo?*

c. Mailman also tested rats in a conflict paradigm and found that the dye attenuated the effects of punishment – i.e., under the effect of Red 3, the rats received many more shocks.

d. **Note:** *Would you call that a learning disability?*

128. **MASONE 2015: (*) (Lab) Study on the Interaction of Artificial and Natural Food Colorants with Human Serum Albumin: A Computational Point of View.** *Computational Biology and Chemistry.* 56(2015): 152-158.

a. Five artificial food dyes were compared to their "natural equivalents" in ability to bind to human serum albumin (HSA). **Note:** *In the case of binding to HSA, less is better.*

b. The picture at right is extracted from Figure 4, comparing Yellow 5 to the natural dye curcumin (turmeric).

c. The dye binds stronger to HSA than the curcumin, as you can see in the picture. **This supports the hypothesis that the artificial food dye is of potential risk to human health.**

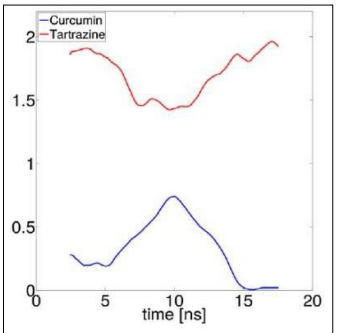


Fig. 4. (Curcumin - Tartrazine Comparison) Comparison of H-bond formation during restrained molecular dynamics as measured by collective variable H.

129. **MATTES 1978**: **(FDA) (Study) A Crossover Study of Artificial Food Colorings in a Hyperkinetic Child.** *American Journal of Psychiatry.* 135 (8): 987-988.

a. The child had been on the Feingold diet 13 months. **Note:** *This means he was likely able to tolerate an occasional minor food dye or salicylate intake without trouble, according to the Feingold Association.*

b. Mattes used cookies containing only 5 mg of dye per cookie, which he considered "1/5 the average intake" …. Since a first trial of 6 cookies elicited irritability in the child, he decided to use only 3 cookies for the study. Even so, the mother did notice some irritability apparently triggered by the "challenge" cookies.

c. **Note**: *Why would one test anything by giving only 1/5 the dosage? Moreover, once you find a "dosage" that gives results, why cut it in half?*

d. *All 6 cookies would only have contained 30 mg dye … not much when kids can get 300 mg/day.*

e. *One reason many of these studies used so little food dye is that they had to make sure the "active" cookie was the same color as the "placebo" cookie …. so they used only enough of the food dye **not to change the color**. Do not mistake this with the cookies you might buy at the supermarket (like the picture).*

130. **MATTES 1981: (FDA) (Study) Effects of Artificial Food Colorings In Children With Hyperactive Symptoms: A Critical Review and Results of a Controlled Study.** *Archives of General Psychiatry.* 38:714-718.

a. In an effort to maximize the effects of food dyes, Mattes (1) studied children already on the Feingold diet; (2) tried to exclude placebo responders; and (3) administered high dosages of coloring. He reported "no evidence of a food coloring effect."

Letter written to the Feingold Association from a mom whose child was in the Mattes 1981 study

My daughter, Christine, was one of the children in the study.

Points I remember:

1. Took a long time to do the study, because each time Chrissy got a "toxic" cookie she not only got hyper, but also got severe ear infections and sick. Her school work regressed, as much as it can in kindergarten. After school she was in a dance class the school sponsored, and after her "after school snack cookie" got so bad they called me to pick her up early.
2. I also remember getting a phone call after it was completed, telling me that 5 out of 6 of the children reacted to the "toxic" cookies and that Chrissy was definitely one of those children.

   The next day he published in Newsday that there was no significant proof. Even her teachers laughed.
3. In the report he states some of the children did not eat all six cookies. That is correct! After 2 cookies, Chrissy was nuts; after 4 my family was ready to drive me off a ships plank for agreeing to this mess; also Chrissy was ready to kill me.
4. As far as getting a cookie 1.5 hr before seeing him, only once did that occur. I couldn't control her and drive the Long Island Expressway for 1.5 hours with her in a reaction.

b. **Note:** *Cookies provided by the Nutrition Foundation with 13 mg dye usually were chocolate – thus the placebo is problematic since chocolate itself can be an active substance for many children; indeed, two children were dropped during placebo trial because they were sensitive to the placebo cookie – thus assuring that **the most sensitive children were gone**.*

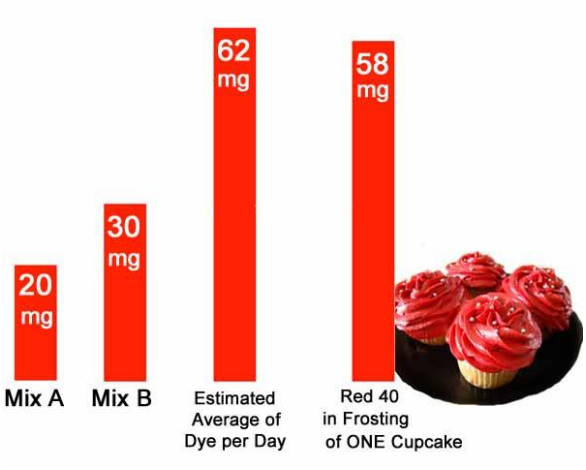
c. **Note:** *The "high dose" of coloring did not even change the color of the cookies. To reach the 78 mg coloring per day, 6 cookies with 13 mg dye each were required. According to parents involved in the study, some children could not eat so many rather large cookies. There is some controversy about the study results according to a letter from one parent which you can see here. (or click on the picture)*

d. **Note:** *Even though there were only 11 children in this study, results appear to be averaged. That is a good way to miss individual responders, and it is hard to reach significance in a small study.*

131. **McCANN 2007**: **(FDA) (Study) Food Additives and Hyperactive Behaviour in 3-year-old and 8/9-year-old Children in the Community: A Randomised, Double-Blinded, Placebo-Controlled Trial.** *The Lancet.* 370(9598): 1560-1567.

a. As a follow-up to the earlier Bateman (2004) study, the authors tested 153 toddlers and 144 elementary school children from the general population. They were briefly put on an additive-free diet and then tested with sodium benzoate mixed with a modest amount of food dyes (20 mg and 30 mg for the younger group; 25 mg and 62.4 mg for the older group).

b. These children were not hyperactive, nor were they screened for sensitivity to the dyes or any other additives. Nevertheless, they showed more hyperactive-type behaviors when consuming the combination of food dyes and preservative.



c. Conclusion: **"Artificial colours or a sodium benzoate preservative (or both) in the diet result in increased hyperactivity in 3-year-old and 8/9-year-old children in the general population."**

d. **Note:** *If you are wondering why the UK studies tend to use the preservative sodium benzoate instead of testing the BHT, BHA and TBHQ so prevalent in the US, it appears to be because they have already banned those in the UK and thus have no need to test them.*

132. **MILLICHAP 2012**: **(*) (Review) The Diet Factor in Attention-Deficit/Hyperactivity Disorder.** *Pediatrics.* 129(2): 330-337.


J. Gordon Millichap
Division of Neurology
Children's Memorial Hospital
Chicago, IL

a. Twice in his abstract, Millichap promises a comprehensive overview "with emphasis on recent controlled studies."

b. However, he reviews mainly the old studies from the 1970s, claiming that there were only 2 studies from 1990 through 2010 – which, he says, shows that interest in additives in relation to ADHD has waned.

c. **Note:** *Funny, I did a quick search of MedLine for the same two decades, and I found almost 40 studies on diet and ADHD, not 2. But then much of this review, including a delightful misrepresentation of the Feingold diet, appears to be more than 30 years out of date, with numerous errors.*

133. **MOHAMED 2015: (*) (Lab) (Extra) Comparative Protective Effects of Royal Jelly and Cod Liver Oil against Neurotoxic Impact of Tartrazine on Male Rat Pups Brain.** *Acta Histochemica.* 117(7):649-658.

a. For 30 days, groups of rat pups were fed water (control), royal jelly, cod liver oil, Tartrazine, Tartrazine with royal jelly, or Tartrazine with cod liver oil. Then their brain neurotransmitters, GABA, dopamine, serotonin, and some oxidative stress biomarkers were measured and compared.

b. The group receiving only Tartrazine (Yellow 5) suffered serious brain damage including a decrease in neurotransmitters, an increase in malondialdehyde *(a marker for oxidative stress)*, and numerous dead brain cells. Those groups receiving royal jelly or cod liver oil with the Yellow 5, however, were almost as good as the control.

134. **MORRIS 1982: (*) (Lab) Erythrosin B (US FD&C Red 3) Inhibits Calcium Transport and ATPase activity of Muscle Sarcoplasmic Reticulum.** *Biochemical and Biophysical Research Communications.* 104(4): 1306-1311.

a. Calcium release and reuptake by the sarcoplasmic reticulum controls muscle contraction and relaxation. The way it works is described, as well as the effects of low concentrations of Red 3 which inhibit both calcium transport and ATPase activities.

b. While the brain may be protected, muscle cells are more accessible to Red 3 and similar chemicals circulating in the blood. This may explain the tendency for poor performance of Red-3 treated animals in a "punished behavior" (aversive stimuli) situation.

135. **MORRIS 1982 (*) (Lab) Toxic Effects of Ouabain and Food and Cosmetic Dyes on Nerve Growth Factor-Promoted Differentiation of Neurites in Culture.** *Journal of Neuroscience Research.* 7: 331-339.

a. Ouabain is a poison from the Acokanthera schimperia and Strophantus gratus (pictured) plants used to tip poison arrows in Africa for thousands of years. It is also a cardiac glycoside used to treat heart failure in some countries.

b. Both Red 3 and ouabain added to cultures of neurites (nerve tips) **reduced the neurite growth**. In addition, the dyes used also caused those neurites that had already formed to be retracted, and inhibited fibroblast migration.

c. Moreover, the Red 3 also **inhibited a number of enzymes important to cell function repair,** and the authors suggested a possible interaction *in vivo* between use of this dye and exposure to strong light.

136. **NIGG 2012: (*) (Review) Meta-Analysis of Attention-Deficit/Hyperactivity Disorder or Attention-Deficit/ Hyperactivity Disorder Symptoms, Restriction Diet, and Synthetic Food Color Additives.** *Journal of the American Academy of Child and Adolescent Psychiatry.* 51(1): 86-97.

Joel T. Nigg
Director, Division of Psychology
Oregon Health & Science Univ.

a. This meta-analysis of 24 published studies on food colors, plus 10 more on dietary restriction, concluded that a restriction diet (e.g., the Feingold or oligoantigenic diet) affects some children.

b. He concluded that "**renewed investigation of diet and ADHD is warranted**."

137. **NIGG 2014: (*) (Review) Restriction and Elimination Diets in ADHD Treatment.** *Child Adolescent Psychiatric Clinics of North America.* 23(4): 937-953.

a. Today, says Nigg, ADHD is seen as an "epigenetic condition triggered, in susceptible individuals, by varying environmental amplifiers."

b. After an extensive overview of studies and other reviews, Nigg suggests that "**dietary intervention for ADHD was abandoned too quickly in North America**" and that "for some children such intervention can be quite effective."

c. **Note:** *He complains about the small data base, so it is unfortunate that he must have missed the Schoenthaler (1986) study of 803 New York City schools which included more than a million children.*

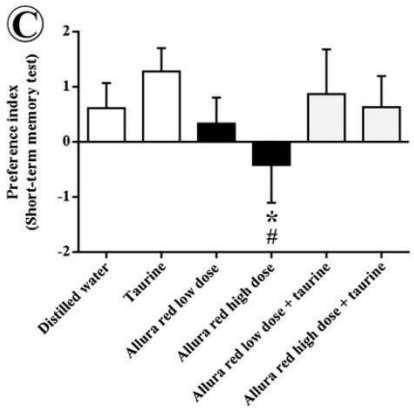
138. **NIH: National Institutes of Health 1983: (FDA) Defined Diets and Childhood Hyperactivity: NIH Consensus Statement.** *American Journal of Clinical Nutrition.* 37(1): 161-165.

a. This is a report of the 1982 Consensus Development Conference. The NIH panel examined the research from the late 1970s through 1981 and concluded that inadequacies in the design of the controlled studies made analysis difficult, but there was indication of an association between the diet and a decrease in hyperactivity.

b. The Panel recommended changes in the law to require listing all ingredients on labels, including substances that may migrate from wrappers and containers that come into contact with foods.

c. They also recommended more and better designed research be done.

139. **NOORAFSHAN 2018: (*) (Lab) High Dose Allura Red, Rather Than the ADI Dose, Induces Structural and Behavioral Changes in the Medial Prefrontal Cortex of Rats and Taurine Can Protect It.** *Acta Histochemica.* 120(6): 586-694.



a. Red 40, at the ADI level and at the higher level, damages memory and learning, as well as brain and neuron structure. The higher dose did a lot more damage – reducing cortex volume, numbers of neurons and glial cells, etc., while the low dose "only" reduced the number of glial cells (*the brain cells supporting and insulating the neurons*).

b. Taurine – a neuroprotectant – prevented this damage when given at the same time.

140. **NOVEMBRE 1992: (*) (Case) Unusual Reactions to Food Additives.** *Pediatria Medica e Chirurgica.* 14(1): 39-42. *(abstract only – article in Italian)*

a. The author describes two cases of reactions to the food additives Tartrazine (*Yellow 5*) and benzoates involving mainly the central nervous system (headache, migraine, overactivity, concentration and learning difficulties, depression) and joints (arthralgias), confirmed with diet and double blind challenge.

b. The possible pathogenetic mechanisms are discussed *(in the Italian full text).*

141. **OPLATOWSKA-STACHOWIAK 2015: (*) (Review) Food Colours: Existing and Emerging Food Safety Concerns.** *Critical Reviews in Food Science and Nutrition.* 57(3): 524-548.

a. This is a review of the status of the concerns about color additives in food. They are:
   - Lack of uniform regulation concerning legal colors worldwide;
   - Possible link to hyperactive behavior;
   - Replacement with natural colors;
   - Presence of harmful illegal dyes – both those known and those emerging;

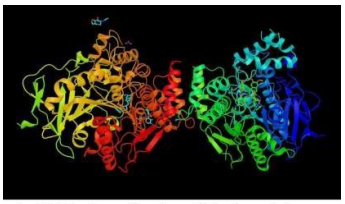
b. Detection methods are also reviewed.

142. **OSMAN 2002: (*) (Lab) Synthetic Organic Hard Capsule Colouring Agents: *in vitro* Effect on Human True and Pseudo-Cholinesterases.** *British Journal of Biomedical Science.* 59(4): 212-217.

a. Yellow 6, Yellow 10, and Red 3 are strong inhibitors of cholinesterase, a group of enzymes important to neurotransmission. The inhibition is dose-dependent.

b. The authors **recommend using natural colors both for food and in manufacture of medication capsules.**

143. **OSMAN 2004: (*) (Lab) Synthetic Organic Food Colouring Agents and Their Degraded Products: Effects on Human and Rat Cholinesterases.** *British Journal of Biomedical Science.* 61(3): 128-132.



Acetylcholinesterase, the primary cholinesterase in the body. It's a primary target of inhibition by organophosphorus compounds such as nerve agents and pesticides

a. Yellow 6 and its metabolite sulfanilic acid are both potent inhibitors of both kinds of cholinesterase (AChE and BChE) in human blood (*in vitro*) and in rats (*in vivo*).

b. **Note:** *Cholinesterase breaks apart the neurotransmitter acetylcholine, which is necessary for transmission of nerve impulses.*

c. Osman reports that during production, nearly all artificial food dyes are treated with sulfuric acid or nitric acid, and both are often contaminated with arsenic.

d. Osman recommends that **products containing food dyes should be stored away from heat and light**, in order to avoid the toxic effects of their by-products (e.g., sulfanilic acid).

e. Quote: "Furthermore, as an alternative to azo dyes, **the use of natural colours as food additives is supported.**

144. **PARK 2008: (*) (Study) (Allergy) Dermatologic Adverse Reactions to 7 Common Food Additives in Patients with Allergic Diseases: A Double-Blind, Placebo-Controlled Study.** *Journal of Allergy & Clinical Immunology.* 121(4): 1059-1062.

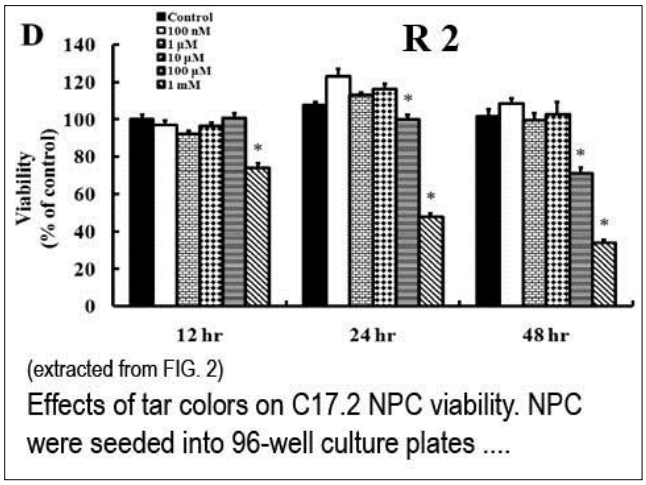
a. Testing 54 patients known to react to a number of food dyes and other items, skin prick and patch testing did not predict positive oral challenge. In fact, 81.5% of them didn't react to either test, and some had reacted to the placebo only.

b. The authors redid the test using combinations to address possible synergistic effects in real life. They discontinued medication before testing – but pretested them to avoid false positives related to withholding medication. Nevertheless, their results indicated that skin prick and patch tests are "limited" as far as identifying what additives are causing adverse skin reactions.

145. **PARK 2009: (*) (Lab) Risk Assessment for the Combinational Effects of Food Color Additives: Neural Progenitor Cells and Hippocampal Neurogenesis.** *Journal of Toxicology and Environmental Health, Part A* . 72: 1412-1423 .

a. This testing was an attempt to determine how combinations of the food dyes used in Korea affect food safety. Red 2, Red 40, Yellow 5, Yellow 6, and Blue 1 were tested for neuron toxicity at both the developmental and adult stages.

b. The combination of high doses of Yellow 5 + Blue 1 suggest **synergistic effects on neurogenesis.**



(extracted from FIG. 2)
Effects of tar colors on C17.2 NPC viability. NPC were seeded into 96-well culture plates ....

c. The authors concluded that based on their results, c**hronic exposure to combined food dyes may adversely affect developmental and adult hippocampal neurogenesis**. They also expressed concern about exposure during **critical windows of development and the possible connection with later development of ADHD** or other disorders.

146. **PARK 2012 (*) (Study) Association Between Dietary Behaviors and Attention-Deficit/Hyperactivity Disorder and Learning Disabilities in School-Aged Children.** *Psychiatry Research.* 198(3):468-476.

a. Quote: "After adjusting for potential confounders, a high intake of sweetened desserts, fried food, and salt is associated with more learning, attention, and behavioral problems…"

b. **Note:** *This is not surprising, considering food dyes and flavorings are usually added to sweetened desserts, and MSG, salt & flavorings are added to salty fried foods.*

147. **PEACOCK 2011: (*) (Study) Childhood Diet and Behavioural Problems: Results From the ALSPAC Cohort.** *European Journal of Clinical Nutrition.* 65(6): 720-6.

a. The records of almost 13,000 children were reviewed to see if there was a correlation between a "junk food" diet at age 81 months (6.75 years) and a diagnosis of behavioral problems at 97 months (8 years).

b. At first there seemed to be a correlation, until they "adjusted" for those who already had behavioral problems at 81 months, excluding them in order to identify new cases.

c. **Note:** *This makes an interesting follow-up to this group's earlier study -- Wiles (2009) -- which showed a correlation between a junk food diet at 4 ½ years and ADHD at 7 years.*

148. **PELLOW 2011: (*) (Review) Complementary and Alternative Medical Therapies for Children with Attention-Deficit/Hyperactivity Disorder (ADHD).** *Alternative Medicine Review.* 16(4): 323-337.

a. This review covers a number of treatments, and briefly mentions that a relationship between food additives such as food dyes and behavior is concluded to be "clinically relevant for individual children, particularly those with a tendency toward hyperactivity."

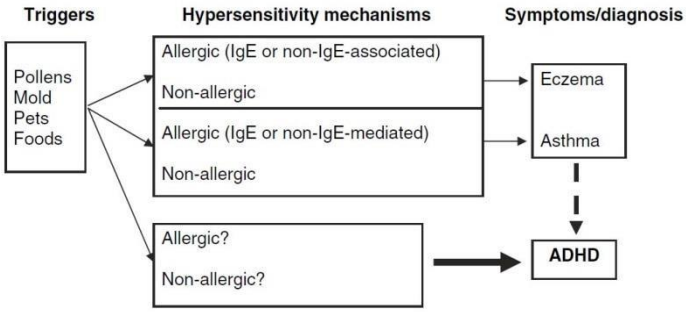
149. **PELSSER 2002: (*) (Case) Favourable Effect of a Standard Elimination Diet on the Behavior of Young Children with Attention Deficit Hyperactivity Disorder (ADHD): A Pilot Study.** *Nederlandsch Tijdschrift Voor Geneeskunde.* 146(52): 2543-7. (*abstract only – article in Dutch)*

a. 40 children with ADHD were put on an oligoantigenic *(few foods)* diet for two weeks. **62%** of them – or, actually, **80.6%** of the 31 who completed the study – showed an improvement of at least 50%.

b. Pelsser concluded that in **"**young children with ADHD an elimination diet can lead to a statistically significant decrease in symptoms."

150. **PELSSER 2008: (*) (Review) ADHD as a (non) Allergic Hypersensitivity Disorder: A Hypothesis.** *Pediatric Allergy & Immunology.* 20(2): 107-12.

a. Pelsser presents the suggestion that effects of food additives or foods may be independent of any allergic condition but yet may involve a non-IgE-dependent histamine release from mast cells.



b. She points out that combinations of food additives have been shown to inhibit neuronal cell differentiation, and suggests considering ADHD as two different entities: hypersensitive and non-hypersensitive ADHD just as there are currently hypersensitive and non-hypersensitive eczema diagnoses.

c. If triggers can be determined, she says, it may reduce the use of medication to control the problem, but agrees that genetic, immunological, IgE and IgG research will be needed, as well as the development of immunotherapeutic treatments.

151. **PELSSER 2008: (*) (Study) A Randomised Controlled Trial into the Effects of Food on ADHD.** *European Child & Adolescent Psychiatry.* 18(1): 12-9.

a. 27 children were assigned to an elimination diet or a "waiting list" control group for 5 weeks, after a 2-week "baseline" diet during which they ate their normal diet and parents in both groups kept a careful diet diary.

b. The oligoantigenic diet consisted of rice, turkey, lamb, vegetables, fruits, margarine, vegetable oil, tea, pear juice and water. As always, it excluded all the additives.

c. **73%** of parent ratings and **70%** of teacher ratings reported behavioral improvement of 50% or more in symptoms of ADHD and ODD in the intervention group, while none of the parents or teachers reported any improvement in the control group.

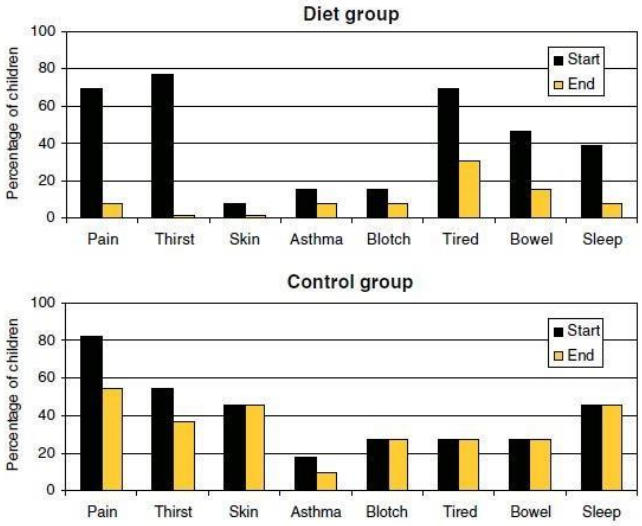
d. **Note**: *Using the few-foods diet might also have addressed allergies or intolerance to milk, wheat, eggs, etc., as well as additives. Otherwise, the diet is basically an extreme version of the standard Feingold diet or additive-free diet.*

e. **Note***: It is regrettable that they used a waiting list as the control group, rather than some sort of sham intervention. Nevertheless, **73% vs 0%** is a pretty steep difference.*

152. **PELSSER 2010: (*) (Study) Effects of Food on Physical and Sleep Complaints in Children with ADHD: A Randomised Controlled Pilot Study.** *European Journal of Pediatrics.* 169(9): 1129-38.

a. The 27 children in the Pelsser (2008) study above were also evaluated for the effect of their diet condition on physical complaints such as headaches, bellyaches, unusual thirst, unusual perspiration, and problems sleeping.

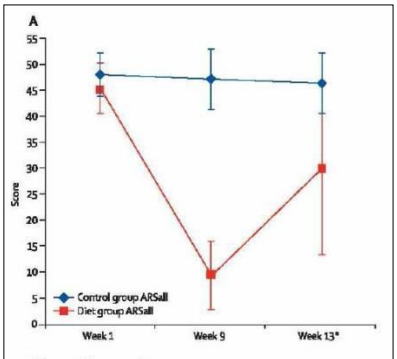
b. All problems were significantly decreased in the diet group but not in the control group.



153. **PELSSER 2011: (*) (Study) Effects of a Restricted Elimination Diet on the Behaviour of Children with Attention-Deficit Hyperactivity Disorder (INCA Study): A Randomised Controlled Trial.** *The Lancet.* 377(9764): 494-503.

a. This is a study of children diagnosed with ADHD but not selected on expectation of a dietary effect. Parents of the control group children were given the Dutch Nutrition Center "healthy diet" advice.

b. 32 **(78%)** of the 41 children in the experimental diet group improved. Parent, teachers, and psychiatrist scores were all better for the diet group than the control group. The additive-free diet group was almost **12 points better** than the control group on the Abbreviated Conners' Scale scores and **23.7 points better** on the ADHD Rating Scale. Scores in the "healthy diet" control group did not improve.



From Figure 3.
Behaviour scores of ARS for attention comparisons between weeks 1, 9, & 13.

ARS = ADHD Rating Scale

Weeks 1-9: Diet or "healthy diet advice"
Week 13: End of challenge part of study

c. Then, 30 of the responders from the experimental diet group began a 4-week double-blind food challenge phase. The children were challenged with various foods based on results of their IgG blood test. Although the children did react to many of the challenges, it seemed to have nothing to do with their IgG scores.

d. Pelsser concluded tha**t dietary intervention should be considered in all children with ADHD, and those children who respond favorably should be diagnosed with food-induced ADHD.**

154. **PELSSER 2017: (*) (Review) Diet and ADHD, Reviewing the Evidence: A Systematic Review of Meta-Analyses of Double-Blind Placebo-Controlled Trials Evaluating the Efficacy of Diet Interventions on the Behavior of Children with ADHD.** *PLOS One.* 12(1): e0169277

a. This paper is a review of other reviews of (1) food dye, (2) few foods diet, (3) PUFA supplements, discussing effect sizes.

b. Conclusion: More research is needed.

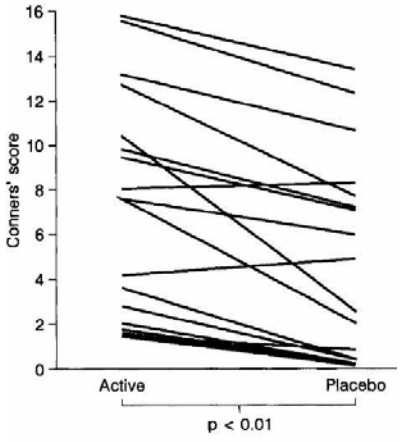
155. **PENG 2009: (*) (Lab) (Medical) Systemic Administration of an Antagonist of the ATP- Sensitive Receptor P2X7 Improves Recovery After Spinal Cord Injury.** *Proceedings of National Academy of Sciences USA.* 106(30): 12489-93.

a. This paper describes a neurological effect of Blue 1 that may be of medical benefit in treating spinal cord injury.

b. After a spinal injury, the injured tissue releases excessive ATP, followed by activation of the P2X7 receptors leading to swelling and a secondary injury causing paralysis. No treatment exists yet to prevent the activation of the P2X7 receptors.

c. Brilliant Blue G, which is basically Blue 1, is a P2X7 antagonist …. More simply, it is toxic enough to the receptor that it stops the process of activation. Since it also crosses the blood brain barrier, it can go where it is needed to prevent spinal cord swelling and paralysis.

156. **POLLOCK 1990: (FDA) (Study) Effects of Artificial Food Colours on Childhood Behaviour.** *Archives of Disease in Childhood.* 65(1):74-77.



a. Pollock did a double-blind placebo-controlled challenge study on 19 children who were doing well on an additive-free diet. He gave them 125 mg food dyes or a placebo by capsule every morning.

b. The food dyes had an adverse effect on the children based on the Conners' Scale that the parents filled out every day (see chart at right).

c. Pollock reported "most parents could not detect these changes" which appears odd since they were the same parents who had filled out the Conners' Scale indicating significant change.

d. Reading the text carefully, however, one understands that they had to guess about the challenge or placebo once a week, and they had to be right *every* week, and most were not. All but two of the children were not in the Conner's Scale hyperactivity range, which may have made the parents' weekly guesses more difficult.

e. **Note:** *Another possibility worth considering for this and other studies: Can it be that the opaque capsules do not dissolve as well as expected? Certainly the dyes are not absorbed through the tongue or mouth as they would be in a real life exposure.*

157. **POLLOCK 1991**: **(FDA) (Review) Hyperactivity and Food Additives.** *Bibl Nutr Dieta*. (48):81-89.

a. Pollock reviewed some of the diagnostic problems of hyperactivity, noting that psychologists believe the rate is 1% while teachers assume it is 20%.

b. Pollock believed that no child should be on any elimination diet unless as part of a research protocol. He cited possible nutritional inadequacies, the use of "diet" as punishment, and even Munchhausen by proxy possibilities. Some suggestions are given on how a clinician can convince a family to abandon an additive-free diet.

c. **Note:** *He apparently had not seen the Dumbrell (1978) study of children on the Feingold diet in which their food intake was found to be nutritionally sound and better than the "regular" diet.*

158. **POULSEN 1991: (*) (Extra) Safety Evaluation of Substances Consumed as Technical Ingredients (Food Additives),** *Food Additives & Contaminants.* 8(2): 125-133.

a. This is a discussion of how the ADI levels of various food additives were determined.

159. **POULSEN 1993: (*)(Extra) Case Study: Erythrosine.** *Food Additives & Contaminants.* 10(3): 315-323.

a. This is a review of studies used to show how the ADI for Red 3 was ascertained.

160. **PRESCRIRE International 2009: (*) (Review) Artificial Food Colouring and Hyperactivity Symptoms in Children.** Prescrire International. 18(103): 215 (no author listed) *(abstract only)*

a. In a health assessment of artificial food dyes, *Prescrire International*, a non-profit organization providing information and continuing education for healthcare professionals, considers the hypothesis that artificial food dyes worsen hyperactivity symptoms in children:

b. After reviewing several studies and a meta-analysis, they conclude: "In practice, even though the mechanism underlying this phenomenon has not been elucidated, these data suggest that it is best to **avoid exposing children to artificial food coloring.**"

161. **PRICE 1990: (*) (Study) Associations of Excessive Irritability with Common Illnesses and Food Intolerance.** *Paediatric and Perinatal Epidemiology.* 4: 156-160.

a. Surveying families of more than 8,000 children in England and Scotland, irritability was associated with food intolerance, even after adjusting their analysis for asthma, wheeze, cough, eczema, hives, age of mother, etc.

b. Since they couldn't rule out the connection, but are very sure it can't be due to food additives (*they assure us the prevalence of that is "very low" and don't even SAY the words "food dyes/colours"),* they suggest further population studies and more double blind challenges.

162. **PTACEK 2014: (*) (Study) Disruptive Patterns of Eating Behaviors and Associated Lifestyles in Males with ADHD.** *Medical Science Monitor: International Medical Journal of Experimental & Clinical Research.* 20: 608-613.

a. The authors are concerned that almost half the daily fluid intake of ADHD children consists of "sweetened beverages."

b. **Note**: *They are concerned about obesity, but do not mention that these beverages generally contain significant amounts of food dyes. Correlations, of course, do not prove causation, but at the very least, these dyes are not going to be therapeutic.*

163. **PTACEK 2016: (*) (Review) Attenton Deficit Hyperactivity Disorder and Disordered Eating Behaviors: links, Risks, and Challenges Faced.** *Neuropsychiatric Disease & Treatment.* 12: 571-579.

a. In this review, Ptacek posits that ADHD has many comorbidities including a number of eating disorders. What brings this to our attention for this list is that one of the noticeable eating habits mentioned is an abnormal consumption of "junk food." Such a diet would be high in food additives, particularly the artificial food dyes.

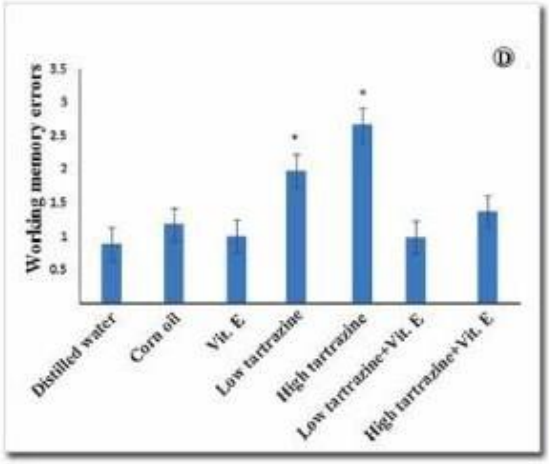
b. It is not known, of course, whether the eating of such food elicits, triggers, or worsens symptoms of ADHD, or whether children who have these symptoms prefer this sort of diet.

c. **Note**: *Removing the food dyes from the junk food might give researchers a clue. If it is an addictive situation created by the additives themselves, removing them may "cure" the problem, at least in part. That may sound less strange when you look again at the study Mehedi (2013) in which the higher the amount of dye in the water, the more the mice drank.*

164. **RAFATI 2017: (*) (Lab) Using Vitamin E to Prevent the Impairment in Behavioral Test, Cell Loss and Dendrite Changes in Medial Prefrontal Cortex Induced by Tartrazine in Rats**. *Acta Histochemica.* 119(2): 172-180.

a. The authors used a rat model to answer the following questions:

1. Does Tartrazine *(Yellow 5)* influence the rats' memory and learning?
2. Does Tartrazine exposure have any effect on the volume of the various brain areas called mPFC?
3. Does Tartrazine affect neurons and glial cells in the mPFC? *(neurons are the nerve cells; glial cells surround and support them)*
4. Does Tartrazine change the shape and length of dendrites *(spikes)* on the neurons?



5. Can vitamin E prevent any (or all) the above?

b. **The answers they got to all questions was "yes."**

c. The low dose of Tartrazine was 5 mg/kg/day (the ADI for people in the US). The high dose was 50 mg/kg/day because "individuals' exact intakes during the day and in different dietary habits are hard to record."

d. **Note**: *5 mg/kg/day (the ADI) equals 150 mg Yellow 5 for a 30 kg (66 lb) child. Not impossible considering that one bowl of Cap'n Crunch Oops All Berries cereal contains 41.3 mg of coloring (Stevens 2015). Husain (2006) found that children in Kuwait were getting **4 to 8 times the ADI** of Yellow 5. How much vitamin E would they need?*

e. Conclusion: "The **low dose of Tartrazine could induce impairments in spatial memory and dendrites structure**. On the other hand, the high dose of Tartrazine defected the visual memory and the structure of the mPFC as well as the spatial memory and caused dendritic changes. However, **vitamin E could prevent the behavioral and structural changes.**"

165. **RANGAN 2009: (*) (Review) Food Additives and Sensitivities.** *Chemical Contamination and Additives. In Disease-a-Month Series.* 55(5): 292-311.

a. This is a review of food additives. Table 1 lists the banned food additives with the reasons for having banned each.

b. The authors say 10% of children with asthma may be sensitive to food additives. Several additives are reviewed, including the food dyes.

166. **RAPOSA 2016: (*) (Lab) Food Additives: Sodium Benzoate, Potassium Sorbate, Azorubine, and Tartrazine Modify the Expression of NFkB, GADD45α, and MAPK8 Genes.** *Physiology International*. 103(3): 334-343.

a. This study concludes that Yellow 5 (and some other food additives) contribute to activation of inflammatory pathways and may induce oxidative stress.

b. The two dyes tested separately and together had similar results, but the two preservatives tested together had 4 or 5 times the effect of each alone. **Note:** *For a study of a combination of a dye plus other additives see Lau (2006).*

c. Raposa recommends that the **human intake of preservatives and artificial dyes should be reduced.**

167. **RAPP 1978: (*) (Study) Does Diet Affect Hyperactivity?** *Journal of Learning Disabilities*, 11(6):383-9.

a. Children identified as sensitive to food dyes and/or foods were put on an individually designed diet and most of them showed moderate to marked improvement within a week.

b. Behavior improved, as well as other chronic symptoms such as gastrointestinal discomfort, headaches, nasal symptoms, and muscle aches.

c. These improvements persisted for at least the 12 weeks of the study; 8 of 15 children using Ritalin or other drugs were able to discontinue them within 6 weeks on the diet.

168. **RASTOGI 2015: (*) (Lab) Simultaneous Determination of Acetaminophen and Synthetic Color(s) by Derivative Spectroscopy in Syrup Formulations and Validation by HPLC: Exposure Risk of Colors to Children.** *AAPS PharmSciTech.* 16(3): 505-517.

a. This was a study of syrups given to children. The authors calculated the amount of coloring per dose of syrup.

b. Based on the number of doses (3 or 4) per day, they determined that Sunset Yellow (Yellow 6) and Erythrosine (Red 3) in the syrups would – by themselves – "saturate more than 50% of the ADI" when given according to instructions.

c. The authors feel this is **alarming and modifications should be required.**

169. **REISEN 1986: (*) (Lab) Brief Communication: Effect of Certified Artificial Food Coloring on Learning and Activity Level in Rats.** *Neurobehavioral Toxicology and Teratology.* 8(3): 317-320.

a. Neither dose of the mixed dyes had any effect on rat activity.

b. The ADI amounts for all the dyes together would be 36.25 mg/kg/day, but the "high dose" Reisen used is 5 mg/kg/day (14% of the ADI) and the "low dose" Reisen used is 2 mg/kg/day (only 5.5% of the ADI). **Note:** *Not only were they getting a low dose of coloring, but the rats were also eating high fiber chow, which may be protective; see Ershoff (1977).*

170. **REYES 1996: (*) (Lab) (Extra) Effect of Organic Synthetic Food Colours on Mitochondrial Respiration.** *Food Additives and Contaminants.* 13(1): 5-11.

a. In this lab study, 11 artificial food dyes were tested on the mitochondria of rat liver and kidney. **Note**: *Mitochondria are important in cell metabolism – they are the "energy factories" of a cell.*

b. Most dyes are metabolized in the liver and kidney, which is why Reyes chose to investigate the effect of the dyes on oxygen uptake in mitochondria from those organs.

c. **All the dyes inhibited mitochondrial respiration,** although the inhibition varied widely, e.g., from 16% to 100%. The effect was dose related, but the same in both liver and kidney cells.

171. **RIOS-HERNANDEZ 2017: (*) (Study) The Mediterranean Diet and ADHD in Children and Adolescents.** *Pediatrics.* 139(2): e20162027.

a. In Spain, 60 children with ADHD and 60 controls without ADHD were studied.

b. Those with ADHD had lower adherence to the Mediterranean diet, and ate more candy, fast food, cola beverages, and noncola soft drinks.

c. **Note:** *Most of these items would be loaded with food dyes and other additives. Also, don't forget this study was done in Spain, where the Mediterranean diet is still the norm – not in the US where it may be considered "special."*

d. The authors do not suspect causality, but suggest that those with ADHD are eating an unhealthy diet and this should be improved for their overall health.

172. **RIPPERE 1981: (*) (Extra) Placebo-Controlled Tests of Chemical Food Additives: Are They Valid?** *Medical Hypotheses.* 7: 819-823.

a. Methodological problems with some placebo-controlled studies of food dyes:
   - The active item may be inadequately specified.
   - The placebo may be inadequately specified.
   - There may be an inappropriate choice of placebo (e.g., an allergen) such as chocolate in the Conners' studies.

b. Comparing an active allergen with a pharmacologically active substance may be taken to support the unwarranted conclusion that the allergen is effectively inert.

c. **Note:** *As old as this paper may be, the same problems crop up in today's studies, it seems.*

173. **RODRIGUEZ 2016: (*) (Study) (Medical) Multimodal Randomized Functional MR Imaging of the Effects of Methylene Blue in the Human Brain.** *Radiology.* 281(2): 516-526.

a. This is a double-blind study showing that oral use of Methylene Blue improves memory. It appears to enhance mitochondrial respiration.

b. Blue 2 is used as the placebo.

c. **Note:** *Considering that Blue 2 has been shown to harm mitochondrial respiration – see Reyes (1996) – it makes me wonder about this choice of placebo.*

174. **ROGERS 1981: (*) (Study) Dietary Treatment of Children with Problematic Activity Level.** *Psychological Reports.* 48: 487-494.

a. 10 children were placed on either the Feingold K-P diet or a low-sugar diet for 9 weeks. Those on the K-P diet were less active, using an actometer *(instrument for measuring movement in three directions).*

b. The diet logs confirmed substantial sugars in the non-K-P diet group even though they were supposed to restrict refined sugar foods. The K-P diet group successfully restricted both additives and salicylates.

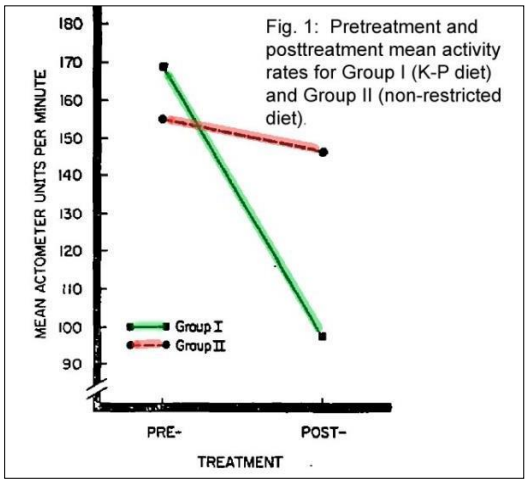


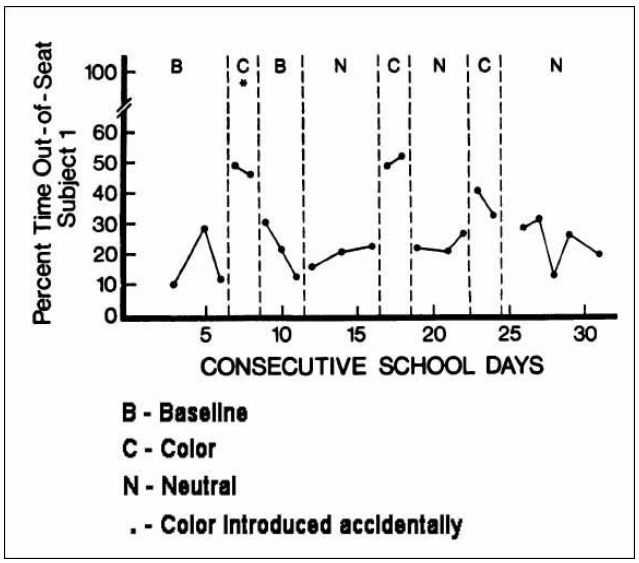
Fig. 1: Pretreatment and posttreatment mean activity rates for Group I (K-P diet) and Group II (non-restricted diet).

175. **ROSE 1978**: **(FDA) (Study) The Functional Relationship Between Artificial Food Colors and Hyperactivity.** *Journal of Applied Behavior Analysis*. 115(4): 439-446.

a. Two girls who had been on the Feingold diet for almost a year were challenged with one cookie per day with only 1.2 mg of Yellow 5 in it.

b. The oatmeal cookies were the same color with or without the dye.

c. Trained observers recorded an increase in the duration and frequency of target behaviors, as well as an absence of a placebo effect.



d. **Note:** *Either the observers were very perceptive, or the children were very sensitive since this study used a really really small amount of "challenge" dye.*

176. **ROWE 1984: (*) (Study) Food Additives.** *Australian Paediatric Journal.* 20(3): 171-3.

a. Rowe reviewed the research to 1984, and noted that a "subgroup of reacting children may be overlooked in an unresponsive majority."

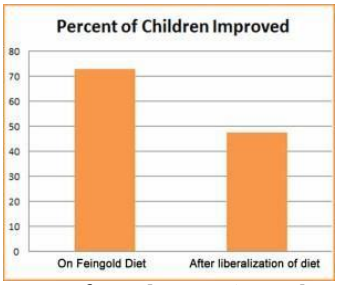
b. Because Rowe found that parental observation is a better predictor of behavioral changes than that obtained via the Conners' Rating Scale, he developed a questionnaire including parent observations of irritability and sleep disturbances.

c. This questionnaire was used in his later studies.

177. **ROWE 1988**: **(FDA) (Study) Synthetic Food Colourings and 'Hyperactivity': A Double-Blind Crossover Study**. *Australian Paediatric Journal.* 24(2):143-7.

a. Of 220 children referred for suspected hyperactivity, 55 were put on a 6-week trial of the Feingold Diet. They were a "heterogeneous group," including some children who did not appear hyperactive at the clinic but whose parents said they sometimes were.

b. 40 of them — **72.7%** — exhibited improved behavior, and 26 of those — **47.3%** — remained improved following "liberalization" of the diet over a 3-6 month period. Rowe suggested that this may indicate a placebo effect.



c. **Note:** *"Liberalization" apparently involved reintroducing the eliminated foods or additives one at a time, which is the way the usual Feingold diet works upon entering Stage Two (testing for tolerance). With no Feingold Association in Australia, more than 20% of the families either overly-"liberalized" or abandoned their diet, no longer showing improvement.*

d. A second double-blind study was done on 8 of the children in the original group, to test their reaction to 50 mg of Yellow 5 or carmoisine (a red color not used in the US). They were given capsules containing either the coloring or a placebo inside an outer capsule containing lactose. Two of the children (25%) were dramatic reactors to the dyes – one boy, in particular, reacted to the coloring with extreme and dangerous behavior, and it was weeks before his behavior returned to normal, while the female reactor returned to normal within a few days.

e. **Note**: *When a child improves on a diet that eliminates thousands of additives, and then a single one is chosen as a challenge …if nothing happens, that does not mean the diet doesn't work, but only that the challenge doesn't work. You may have chosen the wrong item, too low an amount, or it may need to be ingested at the same time as something else.*

178. **ROWE 1994**: **(FDA) (Study) Synthetic Food Coloring and Behavior: A Dose Response Effect in a Double-Blind, Placebo-Controlled, Repeated-Measures Study.** *Journal of Pediatrics.* 125 (5 Pt 1):691-698.

a. 150 of 200 children **[75%]** improved on an open trial of a diet free of synthetic food coloring, and deteriorated upon introduction of foods containing synthetic colorings.

b. 34 other "clear" or "suspected" reactors plus 20 controls were studied in a separate double blind study. **82.5%** of "suspected reactors," **27%** of "uncertain reactors," and **10%** of controls reacted to a challenge of Tartrazine (Yellow #5). The kind of reaction and length of time the children were affected was **dose-dependent**.

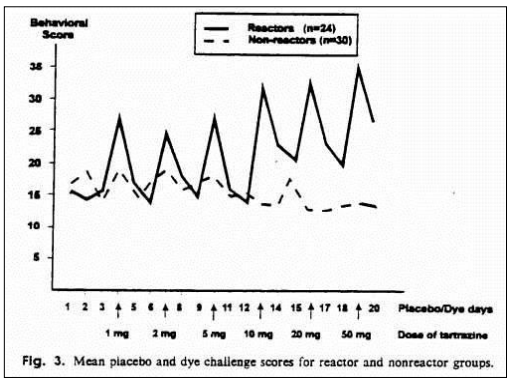


Fig. 3. Mean placebo and dye challenge scores for reactor and nonreactor groups.

c. Parents reported that beyond hyperactivity or other core ADHD symptoms, Tartrazine increased irritability, restlessness, and sleep disturbance.

d. **Note:** *Notice on the chart that this dose effect was obtained by using 1, 2, 5, 10, 20, and 50 mg food dye — the Rowe questionnaire must be far more sensitive than the older Conners' questionnaire for monitoring reactions.*

e. **Note:** *10% of the controls reacted to the Yellow 5 challenge — and the controls were not diagnosed with any disorder and not expected to react to food dye.*

179. **SALAMY 1982: (FDA) (Study) Physiological Changes in Hyperactive Children Following the Ingestion of Food Additives.** *Int J Neurosci*. 16(3-4):241-246.

a. This was a small study of 8 children – 4 with ADHD and 4 without. EEG and heart rate were obtained before and after the ingestion of drinks containing Red 40 or placebo.

b. The magnitude of physiological changes in the hyperactive children was greater in response to ingestion of the additives than to placebo.

180. **SALTMARSH 2014: (*) (Review) Recent Trends in the Use of Food Additives in the United Kingdom.** *Journal of the Science of Food and Agriculture*. 95(4): 649-652.

a. This is a review of the history of the E-numbers and how they are used today.

b. The authors say that the food colors involved in the Southampton study have already mostly been replaced by natural colorings in Europe.

181. **SALZMAN 1976: (*) Case) Allergy Testing, Psychological Assessment and Dietary Treatment of the Hyperactive Child Syndrome.** *Medical J. of Australia.* 2(7): 248-251.

a. 15 children who were positive on allergy tests were given the Australian version of the Feingold diet. **93%** improved in the areas of overactivity, distractibility, impulsiveness and excitability. Sleep and bedwetting problems were also resolved partially or fully.

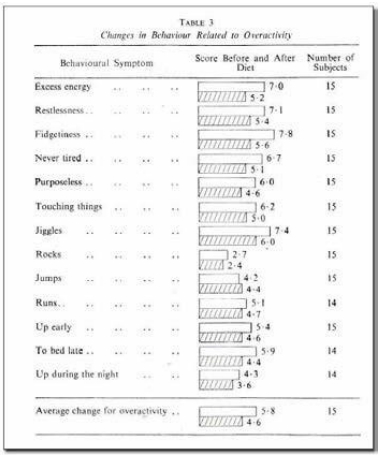


TABLE 3

Changes in Behaviour Related to Overactivity

Behavioural Symptom	Score Before and After Diet	Number of Subjects
Excess energy	7·0 / 5·2	15
Restlessness	7·1 / 5·4	15
Fidgetiness	7·8 / 5·6	15
Never tired	6·7 / 5·1	15
Purposeless	6·0 / 4·6	15
Touching things	6·2 / 5·0	15
Jiggles	7·4 / 6·0	15
Rocks	2·7 / 2·4	15
Jumps	4·2 / 4·4	15
Runs	5·1 / 4·7	14
Up early	5·4 / 4·6	15
To bed late	5·9 / 4·4	14
Up during the night	4·3 / 3·6	14
Average change for overactivity	5·8 / 4·6	15

b. Salzman reported that the most frequently occurring indication of a positive response was a fall in systolic blood pressure accompanied by an increased pulse rate.

c. Quote: "This study demonstrates that the afore-mentioned elimination diet significantly affects behaviour."

d. **Note**: *Sensitivity to additives is not usually an allergy, so being positive on an allergy test is not a pre-requisite for avoiding additives, and those other children who were not positive on the allergy tests may have benefitted as well.*

182. **SAN MAURO MARTIN 2017: (*) (Study) Nutritional and Environmental Factors in Attention-Deficit Hyperactivity Disorder (ADHD): A Cross-Sectional Study.** *Nutritional Neuroscience.* 21(9): 641-647.

a. Lower adherence to the Mediterranean diet was associated with ADHD *(this study was done in Spain where the Mediterranean diet is the norm).*

b. The author points out that junk foods are high in fat, sugar, additives, artificial food colorings and preservatives, which may all affect ADHD symptoms.

183. **SARANTINOS 1990: (FDA) (Study) Synthetic Food Colouring and Behavioral Change In Children With Attention Deficit Disorder: A Double-Blind,Placebo Controlled Repeated Measures (Challenge Study).** *Proceedings of the Nutrition Society of Australia.* 233.

a. Sarantinos studied 13 children on a diet free of synthetic food dyes as part of their treatment for ADHD. Nine of them **(69%)** had improved on the diet.

b. The challenge used was 10 mg of food dye -- less than 7% of the amount consumed by the bottom 50% (see chart below). Only 2 of the children reacted to this challenge.

National Research Council of the National Academy of Sciences:
Average Dye intake of 12,000 people over a period of 2 weeks
1979

	EATERS ONLY: Those eating some food dyes				
2 years +	Mean	50%	90%	95%	99%
Orange B	2.2	1.7	4.5	5.5	7.8
Blue 1	4.1	3.3	8.6	11.0	15.0
Red 3	7.8	6.8	15.0	18.0	24.0
Red 40	29.0	24.0	57.0	70.0	100.0
Yellow 5	14.0	12.0	26.0	31.0	43.0
Green 3	1.0	0.8	2.2	2.8	4.3
Yellow 6	11.0	9.3	21.0	26.0	37.0
Blue 2	1.1	0.5	2.7	3.8	7.8
Blue 1 Lake	0.9	0.4	2.1	3.3	6.6
Red 3 Lake	2.5	1.6	5.9	8.1	15.0
Red 40 Al Lake	4.1	2.4	9.1	13.0	27.0
Red 40 Ca Lake	2.5	1.9	2.4	6.4	8.0
Yellow 5 Al Lake	3.3	1.8	7.6	11.0	22.0
Yellow 5 Ca Lake	0.1	0.1	0.2	0.3	0.6
Yellow 6 Al Lake	1.9	0.9	5.2	8.1	14.0
Blue 2 Lake	0.5	0.2	1.3	1.7	3.1
TOTALS	85.9	67.6	170.8	220.0	335.2

c. Sarantinos concluded that a dye-free diet may be of benefit for "a small number of children" with ADHD.

d. **Note*: Here's another case of confusing reaction to challenge with response to diet.*** *Rippere (1981) would say the challenge was inappropriate as it was too small, and the placebo was equally inappropriate, being an active substance (orange juice) which some of the children reacted to.*

184. **SCHAB 2004: (FDA) (Review) Do Artificial Food Colors Promote Hyperactivity in Children with Hyperactive Syndromes? A Meta-Analysis of Double-Blind Placebo- Controlled Trials.** *Journal of Developmental & Behavioral Pediatrics.* 25(6):423-434.

David W. Schab, MD
Columbia Univ. Dept. of Psychiatry
New York State Psychiatric Institute

a. Schab concluded that his meta analysis of the studies supports the hypothesis that food dyes "promote hyperactivity in hyperactive children, as measured on behavioral rating scales."

b. Schab recommends that assessment behavioral toxicity studies should be a part of food additive evaluation, and that people should think about "whether the aesthetic and commercial rationale for the use of AFCs is justified."

c. Explaining why his results are not consistent with the Kavale (1983) meta-analysis, Schab says that his analysis includes two trials Kavale & Forness had overlooked and two that were published later; three of these were large, which increased the power of his meta-analysis.

185. **SCHMIDT 1997: (FDA) (Study) Does oligoantigenic diet influence hyperactive/conduct- disordered children - a controlled trial.** *European Child & Adolescent Psychiatry,* 6, 1997: 88-95.

Table 1 Distribution of diagnoses: Attention Deficit Hyperactivity Disorder (ADHD) and Conduct Disorder (CD): three grades of severity

CD	ADHD				Total
	no	mild	moderate	severe	
no	–	1	4	3	8
mild	1	3	6	4	14
moderate	–	5	1	1	7
severe	–	3	5	12	20
total	1	12	16	20	49

a. 49 hyperactive, disruptive children were put on an oligoantigenic (*few foods*) diet or a "control" diet. The "control" diet was also limited, but it contained 10 mg each of three dyes not used in the US and 20 mg of Yellow 5.

b. **Note:** *With so few additives in the control diet, it is not surprising that the children's scores were better on the control diet than at baseline, although Schmidt attributed that to a placebo effect.*

c. Combined scores were significantly lower on the few foods diet. The breakdown was like this:

- **45%** of the children did better in the **test situation**.
- **43%** of the children did better in the **play situation**.
- **24%** of the children did better in **both situations** –mostly improving more than 1 standard deviation over control diet scores *(already better than baseline scores).*
- **4%** of the children got worse on the diet. **Note:** *This happens sometimes, where they get worse before they get better – see Eagle (2014).*

d. Comparing the effectiveness of the diet with Ritalin, **44%** responded to Ritalin while the **24%** who had responded best on the diet did equally well.

e. Conclusion: "dietary treatment cannot be neglected as a possible access to treating hyperactive/disruptive children."

186. **SCHNOLL 2003: (FDA) (Review) Nutrition in the Treatment of Attention-Deficit Hyperactivity Disorder: A Neglected But Important Aspect.** *Applied Psychophysiological Biofeedback. 28(1):63-75.*

Roseanne Schnoll
Associate Professor
Health & Nutrition Sciences
Brooklyn College

a. Schnoll reviewed the research on food additives, refined sugar, food allergies, and fatty acid metabolism as it relates to ADHD.

b. Quote: "In general, diet modification plays a major role in the management of ADHD and should be considered as part of the treatment protocol."

187. **SCHOENTHALER 1983: (*)(Study) The Northern California Diet-Behavior Program: An Empirical Examination of 3,000 Incarcerated Juveniles in Stanislaus County Juvenile Hall.** *International Journal of Biosocial Research.* 5(2): 99-106 *(abstract only)*

a. *See slightly different abstracts at APA PsycNET and National Criminal Justice Reference Service*

b. In 1982, in a quasi-experimental design, the young inmates were no longer allowed junk foods brought in by family or as rewards for good behavior. Instead, the facility's staff started preparing nutritious snacks without much sucrose or food additives. These snacks included popcorn, fruit, nuts, and unsweetened orange juice instead of candy bars and soft drinks.

c. The only changes made were in the between-meal snacks; daily meals were not changed. Behavioral records were examined for incidents of formal disciplinary action for the preceding 12 months and compared to records for the 12 months after the change. For the males, serious antisocial behaviors declined 21%. Disruptions and "horseplay" declined 25%, and there were slight reductions in suicide attempts, verbal threats, and disobedience.

d. Most of the 573 female inmates were there only for a short time, and less than 19% of them had been involved in antisocial behavior, so no meaningful data on females was acquired.

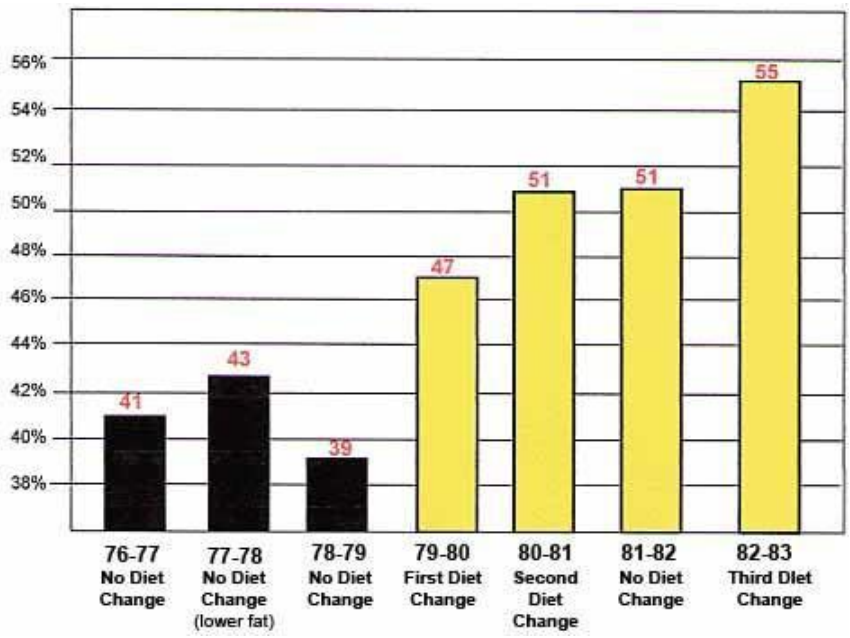
e. The author suggested results could have been related to any combination of (1) decreased sugar, (2) decreased food additives, or (3) increase in nutritious foods.

f. His recommendation is that because the implementation of sound nutrition was inexpensive and easy, and because it benefitted personal health, it should be implemented whenever possible.

188. **SCHOENTHALER 1986: (*) (Study) The Impact of a Low Food Additive and Sucrose Diet on Academic Performance in 803 New York City Public Schools.** *International Journal for Biosocial Research.* 8(2): 185-195.

a. Over 4 years, 803 New York City schools changed their breakfast and lunch programs. They lowered sucrose, and eliminated synthetic food colors/flavors, and two preservatives (BHA and BHT). For each change, there was an improvement (and no improvement for the year without any change) until they had increased **15.7% in mean academic percentile ranking** above the rest of the nation's schools who used the same standardized tests.

Table 1: National Rankings of 803 New York City Public Schools Before and After Diet Changes



b. Prior beginning this change, the standard deviation of the annual change in national percentile ratings had been less than 1% — except for the year 1977-78 in which they tried lowering fat levels which also removed many processed foods from their menu.

c. Before this change, the more students in a school who ate the school breakfast and lunch, the worse that school's scores; after the changes, the more students who ate at school, the better that school's scores.

d. The above chart is an average of over a MILLION children. This is a very big study.

e. Not all the children improved in the same way; in fact, before the diet change, 12.4% of the students were 2 or more years behind their grade level, but by the end of the study, only 4.9% of students were 2 years below grade level.

189. **SCHOENTHALER 1986: (*) (Study) The Testing of Various Hypotheses as Explanations for the Gains in National Standardized Academic Test Scores in the 1978-1983 New York City Nutrition Policy Modification Project.** *International Journal of Biosocial Research.* 8(2): 196-203.

a. Because the above study was not double-blind, an extensive search for explanations was made in accordance with the rules for interrupted quasi-experimental time-series designs. Examined as possible alternative explanations were:

- Possible placebo effects
- Student-to-teacher ratios
- Nutrition education program introduction
- Increased breakfast consumption
- Reduction in malnutrition

b. Several other possible explanations were considered and rejected for various reasons. The only hypothesis capable of explaining all the data with one variable is that reducing foods with fat, sugar, food dyes, flavors, BHT, and BHA resulted in an increase of more nutritious, less processed foods.

c. Thus, he concludes that until such time as a rival theory can be generated to explain the gain in national academic rank from the 39th to the 55th percentile, the conclusion must stand that the primary cause of the academic gains was the dietary changes.

d. While removal of food dyes are only a part of the dietary change in this study, their removal was first and preceded the first year's gains.

190. **SCHWEIGGERT 2018: (*) (Review) Perspective on the Ongoing Replacement of Artificial and Animal-Based Dyes with Alternative Natural Pigments in Foods and Beverages.** *Journal of Agricultural and Food Chemistry.* 66: 3074-3081.

a. The author reviews some history on food coloring and updates on the food industry's "enormous efforts" to replace the artificial food dyes with more acceptable ones.

b. **Note:** *This paper is sprinkled with negative-sounding references to the "so-called Southampton study" and the "so-called Feingold diet" but possibly this is a language artifact, as the author works in Switzerland and Germany, and he also refers to "so-called 'enrichment factors'" and "so-called azo-dyes."*

191. **SEARIGHT 2012: (*) (Review) Complementary and Alternative Therapies for Pediatric Attention Deficit Hyperactivity Disorder: A Descriptive Review.** *International Scholarly Research Network.* Vol. 2012, Article ID 804127.

a. This paper is a review of various CAM treatments including the Feingold, oligoantigenic, and low-sugar diets. **Note**: *What all these diets have in common is* ***the elimination of food dyes.***

192. **SHAYWITZ 1978: (*) (Lab) The Effects of Chronic Administration of Food Colorings on Activity Levels and Cognitive Performance in Normal and Hyperactive Developing Rat Pups.** *Annals of Neurology.* 4(2): 196

a. Shaywitz treated rat pups with 6-OHDA to reduce dopamine and a create a clinical disorder similar to ADHD (here called MBD for "minimal brain dysfunction").

b. Four groups of rat pups were used – 6-OHDA pups with and without food dyes, and untreated pups with and without food dyes. Shaywitz used 0.5, 1, and 2 mg/kg of mixed food dyes.

c. 6-OHDA pups were hyper even without any dye, but were more so with it. Normal pups treated with food dyes also had elevated activity levels.

d. Performance of the normal pups fed the food dyes was "markedly impaired" in both the T-maze and the shuttle box. The 6-OHDA pups' performance was also impaired, but the same with or without the food dyes.

e. Shaywitz wrote that these results "suggest that the administration of **food colorings may affect normal development, and they mandate a more critical evaluation of the effects of food colorings in both animals and children."**

193. **SHAYWITZ 1979: (*) (Lab) Effects of Chronic Administration of Food Colorings on Activity Levels and Cognitive Performance in Developing Rat Pups Treated with 6-Hydroxydopamine.** *Neurobehavioral Toxicology,* 1(1):41-47.

This paper apparently refers to the same study as Shaywitz (1978) above (or a similar one). The following additional items were noted:

a. At every age the highest dose of food dye (2.0 mg/kg) produced the greatest activity.

b. This dose also resulted in significant effects on habituation of activity … reducing activity in a new environment by only 7.25% in the same time period that normal pups decreased their activity by 32%.

c. **Note**: *2.0 mg/kg is about 60 mg for a 66 pound (30 kg) child. At a little over 1 mg/g of Red 40 in frosting ... or 1 mg/drop if using liquid food dye to make your own ... that is about what the child would get in a red-frosted cupcake with 3 Tb of frosting.*

194. **SILBERGELD 1981: (*) (Lab) Erythrosin B is a Specific Inhibitor of High Affinity 3H- Ouabain Binding and Ion Transport in Rat Brain.** *Neuropharmacology.* 20(1): 87-90.

a. Red 3 was studied in rat brain membranes. It is a "potent inhibitor of 3H-ouabain binding and ion flux in synaptosomes."

b. **Note:** *Ouabain is from the Acokanthera schimperia and Strophantus gratus plants. It is used medically as a cardiac glycoside and used historically to prepare poison-tipped arrows.*

195. **SINN 2008: (*) (Review) Nutritional and Dietary Influences on Attention Deficit Hyperactivity Disorder.** *Nutrition Reviews.* 66(10): 558-568.

a. Sinn says current evidence supports a dietary connection to ADHD, including nutrients, foods, essential fatty acids, and food additives.

b. She discusses metabolic wastage of zinc when a person is under chemical stress (e.g., having encountered food dye), and suggests some reactions to food dyes may be related to the lead, mercury and arsenic present in them.

196. **SKYPALA 2015: (*) (Review) Sensitivity to Food Additives, Vaso-Active Amines and Salicylates: A Review of the Evidence.** *Clinical and Translational Allergy.* 5:34.

a. Although this is a review of elimination diets, there is only a single brief reference to any study eliminating food dyes – the McCann 2007 study. Otherwise, she discusses "food chemicals" but specifies them as "benzoate, sulphite, monosodium glutamate, vasoactive or biogenic amines and salicylate."

197. **SOBOTKA 1977: (FDA) (Lab) Tartrazine and the developing nervous system of rats.** *Journal of Toxicology & Environmental Health*, 2: 1211-1220.

a. Sobotka fed groups of pregnant rats with 0%, 1% or 2% Yellow 5, continuing the diet through lactation and for 3 months after weaning. The "high" level was the "no-effect" level according to Davis et al (1964). The only effect noticed in postnatal CNS development was a small transient improvement in female "clinging" ability. Brain weights were normal.

b. The only signs of general toxicity noticed were reduced body weight, elevated red blood cells and hemoglobin, and a reduction in weight of the thymus gland.

c. **Note:** *Is it possible that the laboratory procedures for measuring complex neurological and metabolic changes were less developed in the 1970s than today*.

198. **SOBOTKA 2010: (FDA) (Review) Overview and Evaluation of Proposed Association Between Artificial Food Colors and Attention Deficit Hyperactivity Disorders (ADHD) and Problem Behaviors in Children.** *Interim Toxicology Review Memorandum for 2011 Food Advisory Committee.*

   a. **Note:** *This paper was prepared specifically for the 2011 Food Advisory Committee.*

   b. Sobotka includes an interesting discussion of the Mattes (1978) study in which they "individualized" doses of the challenge dye. Their efforts maxed out at 18 mg and only the parents could detect any behavioral change but not the teachers.

   c. **Note:** *They must have been trying to determine a dose not likely to create results … and the result was "no credible support" -- a favorite claim, used 7 times in this paper.*

199. **SOBOTKA 2010: (*) (Review) Reviews and Critiques; 33 Clinical Trials Related to Artificial Food Colors and ADHD in Childhood and Related Problem Behaviors.** *Interim Toxicology Review Memorandum for 2011 Food Advisory Committee.*

   a. **Note:** *This paper, also, was prepared specifically for the 2011 Food Advisory Committee.*

   b. Reviews of several food dye trials are presented:
      - 9 papers from the 1970s;
      - 14 papers from the 1980s;
      - 8 papers from the 1990s;
      - Only 2 papers more recent than 2000.

   c. **Note:** *In the assessment of the Bateman study, a peculiar accusation was made – since half the parents correctly guessed the order of control or challenge treatments, Sobotka claimed that half the parents "may not have been completely blind to treatment conditions." Is it not more reasonable that half the parents could tell when their kids were irritable?*

   d. **Note:** *For the McCann study, again, their evaluation was negative, claiming it "does not provide credible evidence" etc. They pointed out that there were different reactions to Mix A and Mix B as though this negated their validity. But the two mixes contained different food dyes! Is it not possible that some children may react to one combination of food dyes more than to a different one?*

200. **SONUGA-BARKE 2013: (*) (Review) Nonpharmacological Interventions for ADHD: Systematic Review and Meta-Analyses of Randomized Controlled Trials of Dietary and Psychological Treatments.** *American Journal of Psychiatry.* 170(3): 275-8.

Edmund Sonuga-Barke
Developmental Brain-Behavior Lab, Dept of Psychology University of Southampton, UK

   a. After a comprehensive review, the author concluded that artificial food color exclusion produced effects that were significant even when the "best probably blinded assessment" was employed.

201. **SPRING 1981**: **(FDA) (Study) Case Studies of Effects of Artificial Food Colors on Hyperactivity.** *The Journal of Special Education.* 15 (3): 361-372.

a. This was a double-blind, double-crossover challenge study of 6 boys on the Feingold diet. The boys ate a chocolate cookie with (or without) 13 mg food dye before school and another after school. Mostly, no effect was detected. Spring mentioned the possibility of the boys being sensitive to some other component of the diet not being tested, but decided it was more likely that any benefit of the diet would be a placebo effect.

b. **Note:** *Teachers never saw any impact of the after-school cookie, while parents didn't see any impact of the before-school cookie, each of which contained food dye amounts more than 10 times lower than those published by the National Academy of Science in 1979.*

202. **STEFANIDOU 2003**: **(*) (Lab) Controversies in Toxicology: Assessing Food Additive Toxicity Using a Cell Model.** *Veterinary and Human Toxicology.* 45(2): 103-105.

a. Tartrazine (Yellow 5) was one of the four food additives studied using protozoa.

b. They all caused a stimulating effect on the DNA – increasing mitosis of the protozoa compared to control.

c. **Note:** *Would that be a hyperactive protozoan?*

Tetrahymena pyriformis

203. **STEVENS 2011**: **(FDA) (Review) Dietary Sensitivities and ADHD Symptoms: Thirty-Five Years of Research.** *Clinical Pediatrics*. 50(4):279-93.

a. In her review of the past 35 years of research, Stevens writes that evidence suggests that some children with ADHD show significant improve-ment on a dye-free diet and react with ADHD-type symptoms on challenge with dyes.

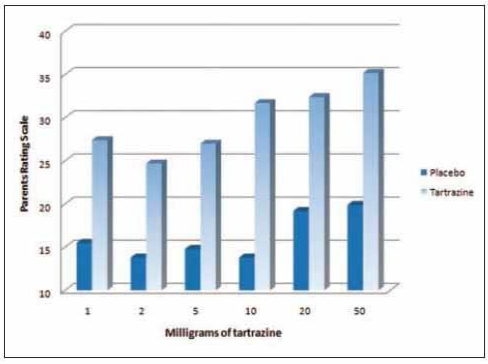


Figure 1. Dose–response effect of tartrazine on parent rating scales (adapted from Rowe and Rowe[26])

b. Oligoantigenic diet studies suggest that in addition to being sensitive to dyes, some are also sensitive to common foods such as milk, chocolate, soy, eggs, wheat, corn, or legumes, as well as salicylate-containing grapes, tomatoes, etc. Some studies found co-sensitivity to be more the rule than the exception.

c. In the most recent decade reviewed, two large studies demonstrated behavioral sensitivity to food dyes and benzoate in children both with and without ADHD.

d. Stevens concluded that a trial of an elimination diet is appropriate for children who have not responded to conventional treatment or whose parents wish to pursue a dietary approach.

204. **STEVENS 2011: (*) (Review) Solving the Puzzle of Attention Deficit Hyperactivity Disorder.** *Nutrition Reviews.* 69(7): 383-384.

a. This editorial is actually a short review of some of the research on nutrition and ADHD.

b. Quote: "If parents, doctors, and nutritionists don't look for the dietary pieces of a child's ADHD puzzle, the pieces will not be found, and the complete puzzle will remain unsolved."

205. **STEVENS 2013: (*) (Review) Mechanisms of behavioral, atopic, and other reactions to artificial food colors in children.** *Nutrition Reviews.* 71(5):268-81.

Laura Stevens
Research Associate at Purdue University, Department of Nutrition Science, Indiana

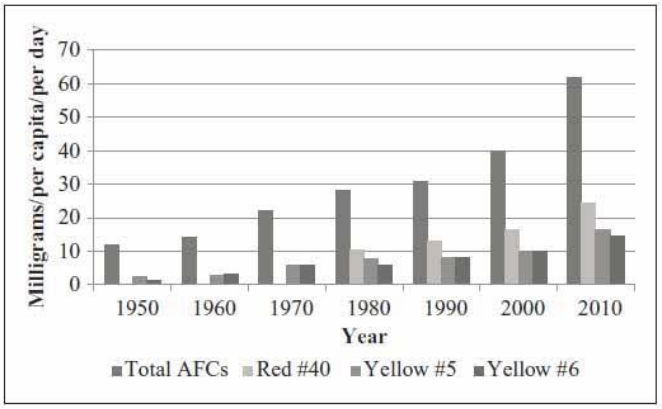
a. Reviewing the research, Stevens finds a subgroup of children who (with or without ADHD) react adversely to challenges with food dyes, and that more of them react in studies using at least 50 mg of the dyes.

b. Three types of potential mechanisms are explored: Toxicological, anti-nutritional, and hypersensitivity. Suggestions for future studies in animals and/or children include dose studies as well as studies to determine the effects of food dyes on the immune system, the intestinal mucosa, and nutrient absorption.

206. **STEVENS 2014: (*) (Lab) Amounts of Artificial Food Colors in Commonly Consumed Beverages and Potential Behavioral Implications for Consumption in Children.** *Clinical Pediatrics.* 53(2):133-40

a. The amount of food dyes certified over the years has increased more than 5-fold since 1950 (from 12 mg to 68 mg per capita per day.

b. Studies that used 50 mg or more of food dyes showed a more negative effect on more children than those which used less.



c. The aim of this study was to quantify the amounts of food dyes in beverages commonly consumed by children in the United States.

d. Her conclusions were that most sweetened and artificially sweetened beverages contain either caramel color or food dyes in widely varying amounts. Many of them are consumed daily by children and knowing the average intake in the diet would benefit the design of challenge studies.

207. **STEVENS 2015: (*) (Lab) Amounts of Artificial Food Dyes and Added Sugars in Foods and Sweets Commonly Consumed by Children.** *Clinical Pediatrics.* 54(4):309-21.

a. Food dyes were measured in foods and candies purchased from local stores. Below are some samples of the "high dose winners" in the junk food category:

Item Measured	Food Dye in 1 Serving
Strawberry Wafers	24.2 mg
Betty Crocker Red Cupcake	34.7 mg
M&Ms	29.5 mg
Skittles Original	33.3 mg

b. Ordinary food items also often contain significant amounts of food dyes per serving, such as the samples below:

Item Measured	Food Dye in 1 Serving
Trix	36.4 mg
Fuity Cheerios	31.8 mg
Cap'n Crunch Oops All Berries	41.3 mg
Keebler Cheese & Peanut Butter Crackers	14.4 mg
Kraft Creamy French Salad Dressing	5.0 mg
Kraft Macaroni & Cheese, 1 cup prepared	17.6 mg

c. Quote: "Artificial food colors (AFCs) are used to color many beverages, foods, and sweets in the United States and throughout the world. … Amounts of AFCs reported here along with the beverage data show that many children could be consuming far more dyes than previously thought. "

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208. **STEVENS 2015: (*) (Lab) Amounts of Artificial Food Colors in Commonly Consumed Beverages and Potential Behavioral Implications for Consumption in Children: Revisited.** *Clinical Pediatrics.* 54(12): 1228-1230.

a. In response to industry criticisms of high numbers in the previous study, Stevens re-measured the dyes using the method approved by Harp et al (2013) as requested, and correcting for any overlap. The largest difference is less than 5 mg.

b. Some of the "winners" for beverages with high amounts of food dye per single 8-oz (240 ml) serving of beverage are:

- Powerade Orange -- **18 mg**
- Faygo Redpop -- **30 mg**
- Kool-Aid Burst Cherry -- **50 mg**
- Full Throttle Red Berry -- **15.0 mg**

209. **STEVENSON 2006: (FDA) (Review) Dietary Influences on Cognitive Development and Behaviour in Children.** *Proc Nutr Soc. 65(4):361-5.*

a. Stevenson reviewed the Bateman (2004) study and a similar study underway at that time in Southampton - McCann (2007) - as well as a number of other studies.

b. In spite of the children in these studies being from the general population (not diagnosed as clinically hyperactive or ADHD as a prerequisite for inclusion) and having been put on the elimination diet for only a single week before beginning to test them for reactions to food dyes, "reductions in hyperactivity were observed during the introduction of the elimination diet" and an increase in hyperactivity was found during the active challenges.

c. **Note:** *As in other studies, and as Feingold himself had observed, younger children respond to an elimination diet faster and are more likely to react even to the relatively low dose of food dyes used in the challenges.*

d. Quote: "there is therefore concerted evidence that **dietary manipulations to remove artificial food colourings and flavourings can beneficially improve the behaviour of children with hyperactivity."**

210. **STEVENSON 2007: (FDA) (Study) Chronic and Acute Effects of Artificial Colourings and Preservatives on Children's Behaviour.** *Study Report: School of Psychology, U. of Southampton (England). 2007 (b)*

a. This is a detailed description of the McCann (2007) study on 3 year olds and 8/9 year olds, commissioned by the Food Stardards Agency.

b. Annexes 1 and 2 contain the details of the design, sampling, measurement and data analytic methods.

211. **STEVENSON 2009: (*) (Review) Food Additives and Children's Behaviour: Evidence-Based Policy at the Margins of Certainty.** *Journal of Children's Services,* Vol. 4(2)

a. Stevenson concluded the findings are consistent with a causal effect of food dye mixtures on hyperactivity. Since these colors have no nutritional value, "even the small overall benefit of removing them from children's diets would come at no cost or risk to the child." Removing food dyes can also be regulated easier than trying to address related genetic factors that may make some children more vulnerable than others.

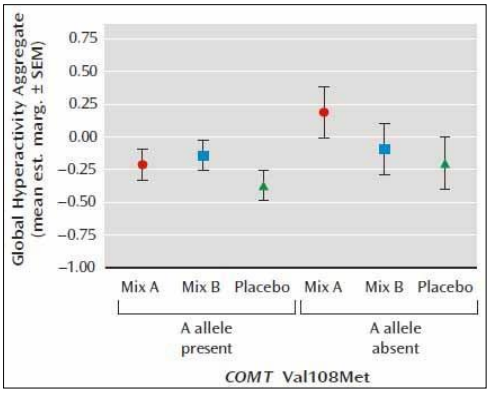
b. Stevenson wrote, "The EU Parliament decided that the findings from the Southampton Study did warrant a legislative change. In July 2008, it decided that it would require manufactures to label foods containing the six colours with the following warning: "**may have an adverse effect on activity and attention in children.**"

c. However, he suggested, putting a ban on the food dyes is better than giving parents the job of inspecting products for warning labels. In short, when faced with uncertain risks, **the precautionary principle should be invoked.**

212. **STEVENSON 2010: (FDA) (Study) The Role of Histamine Degradation Gene Polymorphisms in Moderating the Effects of Food Additives on Children's ADHD Symptoms.** *American Journal of Psychiatry*. 167(9):1108-15

a. Hypothesis: Genetic polymorphisms affecting histamine degradation would explain the diversity of responses to food additives, such that ADHD symptoms are exacerbated in some children more than others.

b. During the McCann (2007) study, DNA swabs were taken in order to determine whether particular gene polymorphisms were related to the child's response to food dyes. It was determined that polymorphisms in the HNMT gene moderated behavioral responses to the food dyes. Stevenson writes that the histamine risk alleles identified can make a child more vulnerable to the behavioral effects of food additives in the diet.



c. See the picture at right – it is extracted from Figure 1 and it rather clearly shows how children with or without this particular "A" allele (gene type) will react differently to the two different dye challenges. Note that they will also fall somewhat differently on the hyperactivity scale even without any food dye exposure.

213. **STEVENSON 2013: (*) (Review) Correspondence: Food Colors and Behavior.** *Current Opinion in Pediatrics.* 25(4): 549-550.

a. Letter to the Editor: In rebuttal of a comment by Bader and Adesman on the McCann (2007) study, followed by their response.

214. **STEVENSON 2014: (*) (Review) Research Review: The Role of Diet in the Treatment of Attention-Deficit/Hyperactivity Disorder – an Appraisal of the Evidence on Efficacy and Recommendations on the Design of Future Studies.** *Journal of Child Psychology and Psychiatry.* 55(5):416-27.

a. Stevenson wrote that all the studies in the Sonuga-Barke (2013) meta analysis have positive standardized mean differences.

b. Because of methodological concerns with some of the studies, however, it is hard to estimate the overall effect accurately.

c. The chart at right shows a summary of meta-analysis effect sizes.

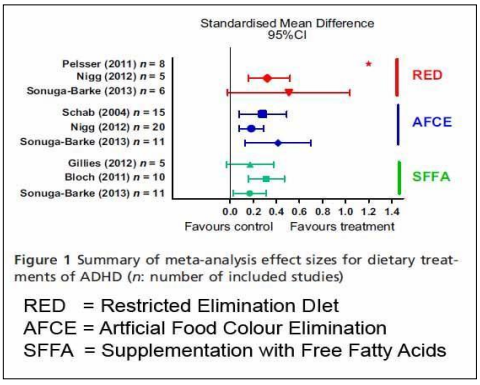


Figure 1 Summary of meta-analysis effect sizes for dietary treatments of ADHD (*n*: number of included studies)

RED = Restricted Elimination DIet
AFCE = Artficial Food Colour Elimination
SFFA = Supplementation with Free Fatty Acids

215. **SULEKOVA 2016 (*) (Lab) The Determination of Food Dyes in Vitamins by RP-HPLC.** *Molecules.* 21: 1368.

Very pretty ... but how much dye is in there? And how many can I safely eat?

a. Vitamin producers usually declare the presence of food dyes in their vitamins, but not the amount. Amounts were measured in a number of vitamin supplements and were determined to be very low, with the author remarking that one would have to consume several hundred capsules to reach the ADI.

b. **Note:** *The author doesn't mention that the amount of dye is actually not declared on the label of* ***anything****, not just vitamins.*

c. **Note:** *Even items like Jell-O, in which the dye is a major ingredient, have no indication of amount, and if you call the company they will not tell you – it's proprietary information.*

216. **SWANSON (1980): (FDA) (Study) Food Dyes Impair Performance of Hyperactive Children on a Laboratory Learning Test.** *Science*. 207: 1485-1487.

a. Swanson used challenge doses of food dye of 100 mg and 150 mg based on an FDA memo in 1976, estimating food dye consumption for the top 90th percentile.

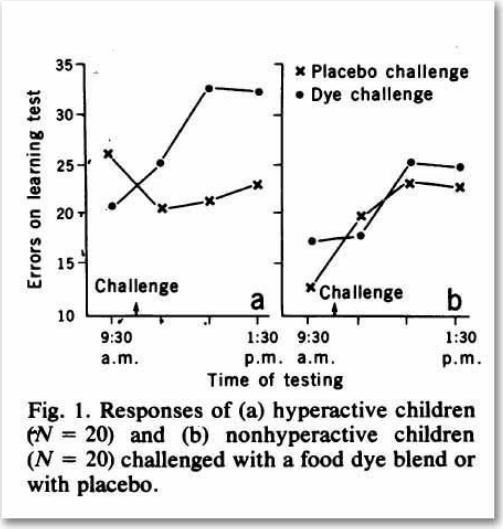


Fig. 1. Responses of (a) hyperactive children (N = 20) and (b) nonhyperactive children (N = 20) challenged with a food dye blend or with placebo.

b. **Note:** *When the FDA actually published their report in 1979, the 90th percentile average consumption was listed at 170.8 mg for "eaters" and 165.8 mg for "eaters and non-eaters" combined. (NAS 1979 charts; NAS intro, and original pages).*

c. In this double-blind study, children stopped their medication the day before the study began, and began an additive-free diet provided by hospital personnel for a whole 3 days.

d. **Note:** *They didn't show any particular behavioral change on the diet – three days is simply not long enough for an observable behavioral change except maybe in very young children or babies.*

e. The dye challenge elicited a measurable adverse response on a paired-associate learning task in 17 of the 20 children who were hyperactive, but not in the control (normal) children.

217. **TABARA 2012: (*) (Lab) (Extra) Low-Calorie Bread Baked with Charred Cellulose Granules and Wheat Flour to Eliminate Toxic Xanthene Food Dye in the Alimentary Canal.** *Bioscience, Biotechnology, & Biochemistry.* 76(12): 2173-2180.

a. The charred cellulose granules baked into this bread were shown to be able to adsorb "toxic xanthene food dyes" so that any food dyes eaten were excreted in the feces with the non-digestible cellulose granules. The bread would also be lower in calories because of the cellulose.

b. **Note:** *That one would even think of making a bread as an "antidote" to colored foods is mind-blowing.*

218. **TANAKA 1992: (FDA) (Lab) Effects of Amaranth on F_1 Generation Mice.** *Toxicology Letters.* 60(3):315-24.

a. This is a study of Red 2. There was an adverse effect on survival of pups in the highest level group; groups receiving the dye gained weight more slowly, and several developmental parameters – in particular olfactory orientation and swimming direction - were significantly reduced in the treatment groups.

b. Tanaka concluded that the dose levels used did influence reproductive, developmental and behavioral parameters in mice.

219. **TANAKA 1994: (FDA) (Lab) Reproductive and Neurobehavioral Effects of Allura Red AC Administered to Mice in the Diet.** *Toxicology.* 92(1-3):169-77.

a. This is a study of Red 40. The male:female birth ratio was reduced in the low dose group, and body weights were increased. There were a "few adverse effects on reproductive and neurobehavioral parameters" compared to controls.

b. Tanaka says these results "suggest that Allura Red AC will not produce adverse effects on reproduction and behavior at typical human intake levels."

220. **TANAKA 1996: (*) (Lab) Reproductive and Neurobehavioral Effects of Sunset Yellow FCF Administered to Mice in the Diet.** *Toxicology & Industrial Health.* 12(1):69-79.

a. This is a study of Yellow 6. Swimming direction, surface righting, negative geotaxis, and swimming head angle were significantly affected in a dose-related manner.

b. Tanaka says that although these dose levels did product some adverse effects, the actual dietary intake is "**presumed to be much lower**" in Japan, so the level of actual dietary intake "should have only a limited effect in humans."

221. **TANAKA 1997: (FDA) Reproductive and neurobehavioural effects of lac dye administered in the diet to mice.** *Food Additives & Contaminants.* 14(4):373-80.
This paper was provided to the FDA Food Advisory Committee in 2011 but it is not relevant to a discussion of food dyes.

a. Lac is a natural dye made from an insect and used in some countries as a wood finish or textile dye. According to Srivastava et al (2013) lac dye it is a potential replacement for synthetic red food dyes

b. Under the effect of this dye, a number of differences were noted in development and behavior: Surface righting, Cliff avoidance (dose related); Swimming (dose related); Olfactory orientation (dose related); Exploratory behavior; Number of movements (dose related); Water T-maze errors.

222. **TANAKA 2001: (FDA) (Lab) Reproductive and Neurobehavioural Toxicity Study of Erythrosine Administered to Mice in the Diet.** *Food & Chemical Toxicology.* 39(5):447-454.

a. This is a study of Red 3. Reviewing previous studies, Tanaka writes that Red 3 had already been shown to cause caecal distention *(a bowel problem)*, a decrease of spleen weight, a potential toxic effect on spermatogenesis in mice, and increased "punished responding" in rats.

b. In this study the following effects are reported:
- Turning was increased (dose related – indicative of emotionality);
- Number of movements and average distance increased (dose related);
- Movement time and average speed increased in the high dose group;
- Exploratory behavior increased (dose-related).

c. Tanaka says that the amounts of dye used were in excess of the ADI, and that actual dietary intake is "**presumed to be much lower**."

223. **TANAKA 2006: (FDA) (Lab) Reproductive and Neurobehavioural Toxicity Study of Tartrazine Administered to Mice in the Diet**. *Food & Chemical Toxicology*. 44(2):179-187.

a. This is a study of Yellow 5. Effects seen were:
- Surface righting was accelerated (dose-related);
- Cliff avoidance was accelerated (middle dose);
- Negative geotaxis was delayed (high dose, female);
- Movement was affected in males.

b. Tanaka says the high dosage used in the study was in excess of the ADI of Tartrazine. The actual dietary intake, he concludes, is "**presumed to be much lower**."

224. **TANAKA 2008: (*) (Lab) Effects of Tartrazine on Exploratory Behavior in aThree- Generation Toxicity Study in Mice.** *Reproductive Toxicology.* 26(2008), 156-163.

a. This is a study of Yellow 5. In the first generation born to mice given Tartrazine, the swimming, surface righting and exploratory behavior were affected at 3 weeks of age.

b. In the next generation, swimming, olfactory orientation and exploratory behavior were affected.

c. However, Tanaka said, the actual dietary intake is "**presumed to be much lower**" in Japan and therefore the dye is "unlikely to produce any adverse effects in humans."

225. **THORLEY 1984: (FDA) (Study) Pilot Study to Assess Behavioural and Cognitive Effects of Artificial Food Colours in a Group of Retarded Children.** *Developmental Medicine & Child Neurology.* 26(1):56-61.

a. Ten retarded children in residential care were put on a diet without dyes, flavorings or preservatives – but only for 14 days.

b. No effort was made to remove salicylates or allergenic foods, and they were given cocoa each day since that was to be the vehicle drink, in spite of its known allergenic potential.

c. 91.8 mg dye was used – but it was a mix of 16 colors, including *titanium dioxide*, *annatto*, *beta carotene*, *and iron oxides. (***Note:** *These dyes had never been considered problematic by Feingold.*)

d. Thorley's mix also included several dyes not used in the US. The dyes used in the largest amount were "chocolate brown" (19.24 mg), titanium dioxide (28.34 mg), and Yellow 5 (Tartrazine, 13.38 mg).

e. **Note:** *Today, titanium dioxide is used in nanoparticle form which has been shown to cause multiple problems, but back in 1984 this was not an issue.*

f. The children were compared as a group, not as their own control, and results did not reach significance.

226. **TRASANDE 2018: (*) (Review) Food Additives and Child Health.** *Pediatrics.* 142(2).

Leonardo Trasande, MD, MPP
Professor, Dept. of Pediatrics
Dept. of Environmental Medicine
School of Medicine, NYU, New York

a. This is a policy statement and technical report to highlight health concerns related to deliberate additives as well as additives added by contact with wrapping materials.

b. In the past two decades, studies have been documenting endocrine disruption and other adverse health effects of these additives. The "generally recognized as safe" (GRAS) label is now generally recognized as insufficient protection against conflicts of interest.

c. Children may be more affected because not only are they more vulnerable, but their dietary intake per pound results in a higher exposure, and artificial food dyes are specified as being associated with exacerbation of ADHD symptoms.

d. Trasande says a more comprehensive FDA authority to reconsider and retest additives using more modern methods is required, and meanwhile suggestions are given to doctors on how to guide patients in avoiding such additives, with concern that many will be unable to afford better quality foods.

227. **UHLIG 1997: (FDA) (Study) Topographic Mapping of Brain Electrical Activity in Children with Food-Induced Attention Deficit Hyperkinetic Disorder.** *European Journal of Pediatrics.* 156(7): 557-561.

a. Uhlig carried out EEG brain mapping on 15 children with food-induced ADHD, both when they were on their diet and when they had been given provoking foods.

b. Consuming the provoking foods caused a significant increase in betal activity in the fronto-temporal areas of the brain.

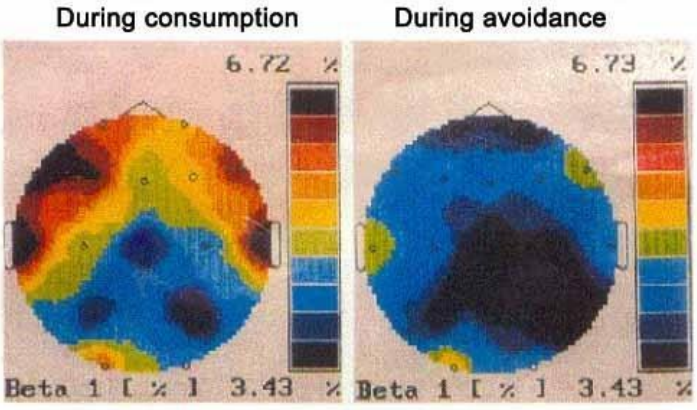


Fig. 4 Patient during avoidance and consumption of provoking foods

c. Uhlig concluded, "These data support the hypothesis that **in a** subgroup of children with attention deficit hyperactivity disorder **certain foods may not only influence clinical symptoms but may also alter brain electrical activity.**"

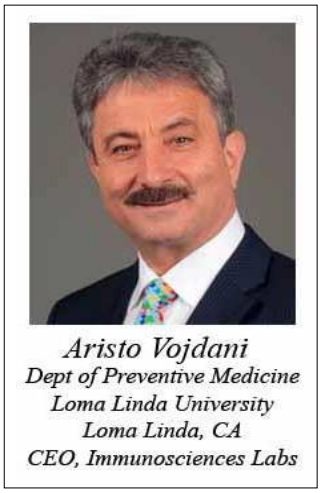
228. **VERLAET 2014: (*) (Review) Nutrition, Immunological Mechanisms and Dietary Immunomodulation in ADHD.** *European Child & Adolescent Psychiatry.* 23(7):519-529.

a. Verlaet discusses the common causes of GI problems, asthma, eczema, ear infections, and ADHD – involving genes, immunity, and inflammation.

b. Food dyes, she says, may involve pharmacological mechanisms causing chronic inflammation and oxidative stress which can lead to ADHD symptoms.

c. Quote: **"**If immune pathways contribute to ADHD, both its diagnosis and treatment should be reconsidered. Modulation of immune system activity might have potential in ADHD treatment, for example by nutritional approaches providing safe and low-cost ADHD therapy …"

229. **VOJDANI 2015: (*) (Review) Immune Reactivity to Food Coloring.** *Alternative Therapies in Health and Medicine.* 21. Suppl. 1: 52-62.



a. Vojdani reviews the history of food dyes and their impact on the human immune system, color by color.

b. He writes that during the past 50 years, the amount of synthetic dye used in food has increased by 500%. At the same time, there has been an alarming rise in behavioral problems such as aggression and ADHD.

c. Vojdani says the molecules of synthetic colorants are small, and the immune system finds it difficult to defend the body against them. He describes the ways that they get into the blood and their interactions with human proteins.

d. Quote: "This consumption can **activate the inflammatory cascade**, can result in the induction of intestinal permeability to large antigenic molecules, and could lead to cross-reactivities, autoimmunities, and even neurobehavioral disorders."

230. **VORHEES 1983: (FDA) (Lab) Developmental Toxicity and Psychotoxicity of FD and C Red Dye No. 40 (Allura Red AC) in Rats.** *Toxicology.* 28(3):207-17.

a. Groups were fed 0%, 2.5%, 5%, or 10% of Red 40. Hydroxyurea *(a chemotherapy medication)* was injected in one group as a "positive control."

b. Results:
   - Impaired reproductive success in all dye groups
   - Offspring mortality was increased in the 10% group after weaning
   - Weight reduction was present in all groups.
   - Tests affected significantly:
     - Swimming
     - Open-field activity *(post-weaning, increased ambulation)*
     - Vaginal patency *(delayed in all groups)*
     - Passive avoidance
     - Running wheel *(decrease, dose-dependent)*
     - Rearing activity *(increase in 5% and 10% groups, dose-dependent)*
     - Brain cerebellum weights (*reduced in all dye groups)*

c. Quote: "The consistent behavioral effects, taken together with the other measures of toxicity, indicate that R40 at the doses used here is both **physically and behaviorally toxic, and that the manifestation of the behavioral toxicity was most evident on measures of activity."**

231. **VORHEES 1983: (FDA) (Lab) A Developmental Toxicity and Psychotoxicity Evaluation of FD and C Red Dye #3 (Erythrosine) in Rats.** *Archives of Toxicology*. 53(4):253-64.

a. Groups were fed 0%, .25%, .5%, or 1% of Red 3. Hydroxyurea *(a chemotherapy medication)* was injected in one group as a "positive control."

b. There were delays or accelerations of the following abilities, but since they were either not consistent or not dose dependent, they were not considered toxicologically significant.
   - Swimming angle development;
   - Swimming direction development;
   - Increased activity but not consistently;
   - Increased food consumption without weight change (parent groups);
   - Increased food consumption without extra weight change (low-dose pups);
   - Increased defecation in 0.5 group;
   - Hyperactivity on wheel running, but not consistently;
   - Inconsistent differences in cerebellar brain weights.

c. Vorhees concluded there is no evidence that Red 3 is a developmental psychotoxin in rats at doses up to 1% of the diet.

d. **Note**: *Vorhees does not explain why Red 3 was used* ***at one-tenth the amount*** *of Red 40 (see previous study). Red 40 ADI is 7.0 mg/kg in both US and Japan, but the Red 3 ADI is about 1/3 of that in the US while it is 1/70 of that in Japan.*

232. **WARD 1990: (*) (Study) The Influence of the Chemical Additive Tartrazine on the Zinc Status of Hyperactive Children: A Double-Blind Placebo-Controlled Study.** *Journal of Nutritional Medicine.* 1(1). 51-57.

a. Ward first studied the zinc status in blood, hair, saliva, etc. in 20 hyperactive boys compared to 20 non-hyperactive boys. Then, in a double-blind placebo-controlled study of 10 hyperactive boys matched with 10 non-hyperactive boys, he determined that Tartrazine (Yellow 5) causes a loss of zinc (by increasing it in the urine) **"with a corresponding deterioration in behaviour/emotional responses of the hyperactive children but not the controls."**

b. **Note**: *Ward is a chemist, not a psychologist or psychiatrist. He analyzed the zinc levels in serum, saliva, urine, etc. The children's behavior was monitored by a pediatric neurologist.*

c. **Note**: *The amount of Yellow 5 used in this study was miniscule — 520 µg is only HALF of a single milligram. The study has been criticized by some because his results were not dramatic. I am astonished he had any results at all.*

233. **WARD 1997: (*) (Study) Assessment of Chemical Factors in Relation to Child Hyperactivity.** *Journal of Nutritional & Environmental Medicine.* 7: 333-342.

a. Using questionnaires for 486 hyperactive children and 172 sex-matched and age-matched control children, it appeared that more than 60% of the hyperactive children (but only 12% of the controls) reported increased problems in relation to exposure to synthetic coloring, flavoring, preservatives, milk, or perfumes.

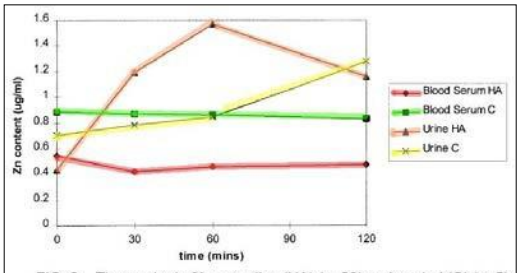


FIG. 2: Zinc content of hyperactive (HA) (n=23) and control (C) (n=5) children following a dose (50 mg) of tartrazine (E102)

b. Hyperactive children also tended to have low zinc and iron, and in some cases elevated aluminum, cadmium and/or lead.

c. In a second trial, 47 hyperactive children and sex-matched and age-matched controls were given 50 mg of Yellow 5, Yellow 6 or Red 2, and their zinc levels and behavior were monitored for two hours. Although the Red 2 had no effect on zinc levels, both the yellow dyes elicited a significant reduction in blood serum zinc with an increase in zinc output through urine, as well as a number of moderate or severe behavior and/or physical changes. In the 23 children who got 50 mg of Yellow 6, the following behavioral changes were noticed:

- Overactivity (18)
- Aggressive activity (16)
- Violent activity (4)
- Poor speech (2)
- Poor coordination (12)
- Asthma and/or eczema (8)

d. The control children showed no such effect.

234. **WARING 1982: (*) (Study) (Extra) Polymorphic Sulphoxidation of S-Carboxymethyl-L- Cysteine in Man.** *Biochemical Pharmacology.* 31(19): 3151-3154.

a. Waring investigates the possibility of a polymorphic distribution of sulfoxidation capacity. She created a sulfoxidation index (SI) which was reproducible on repeat trials.

b. In her population of 181 adults, 11.6% of them showed sulfoxidation impairment, indicating a polymorphism in the population.

c. **Note:** *This may be clinically important since some drugs and additives (including food dyes) either contain sulfur or are metabolized to sulfoxides.*

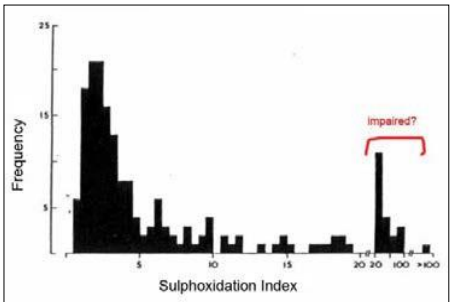


Figure 2. Frequency distribution of 'sulphoxidation index' in 181 unrelated British white volunteers.

235. **WARING 2000: (*) (Review) Sulphur Metabolism in Autism.** *Journal of Nutritional & Environmental Medicine.* 10: 25-32.

a. Previous studies had shown that children with autism may have reduced levels of plasma sulfate. This study showed that autistic children excrete higher levels of sulfate, sulfite and thiosulfate, but reduced levels of thiocyanate.

b. The significance of these findings is discussed, including a gene for slow S-oxidation being an autosomal recessive gene whose phenotype is associated with autoimmune dysfunction and with a number of diseases which are common in families of autistic children.

c. Waring explains why it is common for children with autism to have a family background of migraine, and their behavior may improve by eliminating a number of problematic foods such as chocolate and bananas – and "**food colourants such as Tartrazine**."

236. **WATSON 2008: (FDA) (Review) European Agency Rejects Links Between Hyperactivity and Food Additives.** *BMJ.* 336(7646):687.

a. The EFSA rejected the Bateman (2004) and McCann (2007) studies on the effect of food dyes on the general population of children.

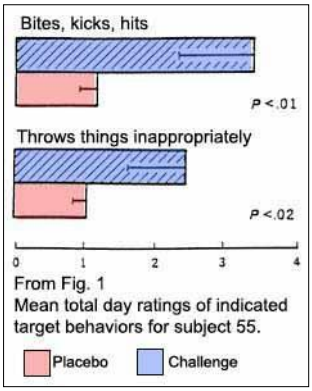
b. Watson said the effect of the study was unclear because it was not known if the small changes seen would **actually interfere with schoolwork.**

c. **Note:** *The EFSA has been accused of conflicts of interest, as well as incomplete declaration of outside interests (Corporate Europe Observatory, 2011)*

237. **WEBER 2007: (*) (Review) Complementary and Alternative Medical Therapies for Attention-Deficit/Hyperactivity Disorder and Autism.** *Pediatric Clinics of North America.* 54(6): 983-1000.

a. This is a review of various "CAM" treatments. In a description of the Feingold diet, she defers to the Wender (1986) review and ignores all the studies done in this field in the 1990s and 2000s, except for a brief description without comment of the McCann (2007) study.

238. **WEISS 1980: (FDA) (Study) Behavioral Responses to Artificial Food Colors**. *Science*, 207: 1487-1489.



a. The 22 children in this study were not diagnosed as hyperkinetic (ADHD). They had other "problem behaviors" that had improved on the Feingold diet.

b. The challenge was a low dose of blended colors; no other additives were tested.

c. Two children reacted to the challenge, and a very young child had the strongest reaction.

d. **Note:** *As with any pharmacological agent when the same amount is given to children of various ages, it would be a higher "dose" for a smaller child.*

e. See Wender's Letter to the Editor and Weiss's response.

239. **WEISS 2000: (*) (Review) Vulnerability of Children and the Developing Brain to Neurotoxic Hazards.** *Environmental Health Perspectives.* 108(suppl 3): 375-381.

a. Here Weiss discussed the vulnerability of babies and children to environmental chemicals. He said adult responses are an inadequate guide to responses of the developing brain, relating a little of the history of lead and mercury and how they were not recognized as toxicants in children for a long time. He reviewed several subjects – not just food dyes.

b. Weiss said the discipline of teratology is largely a result of Thalidomide sold by a company that kept its risk of birth defects – which they knew about – a secret as long as they could.

c. Weiss gives the example of Fetal Alcohol Syndrome, and the FDA's history of discounting neurobehavioral toxicity in children, in particular in their dismissal of food dyes.

d. Weiss warned that although the prevailing practice is to estimate each risk in isolation, multiple risks can affect each other.

e. About neurobehavioral toxicity testing for food additives, Weiss said, **"The doses eliciting behavioral responses in children are many times lower than the ADI, which is not based on neurobehavioral testing."**

240. **WEISS 2000: (*) (Review) (Extra) The Developing Brain and the Environment: An Introduction.** *Environmental Health Perspectives.* 108(suppl.3): 373-374.

a. This paper is not specifically about food additives but describes the effort to begin studying the environmental impact of low level toxicity on children.

241. **WEISS 2007: (*) (Review) Food Additives and Hyperactivity.** *Environmental Health Perspectives.* 116(6): 240-241 *Reply to Barrett (2007) above*

a. In this letter to the editor, Weiss responds to Barrett who quoted an FDA official that the agency sees "… no reason at this time to change our conclusions …" about food dyes, Weiss says that his own study was funded by the FDA and its results, along with others "definitively demonstrated adverse behavioral effects of synthetic food colors."

b. The FDA, he says, has remained "blindly obstinate," and apparently believes that adverse behavioral effects are not an expression of toxicity.

c. Weiss quotes Philip Handler about balancing risks, advising to accept "no hazard at all when the benefit seems relatively trivial."

242. **WEISS 2012: (*) (Review) Synthetic Food Colors and Neurobehavioral Hazards: The View from Environmental Health Research.** *Environmental Health Perspectives.* 120(1): 1-5.

Bernard Weiss
Professor Emeritus of Environmental Medicine and Developmental and Behavioral Pediatrics
University of Rochester, NY
1926 - 2018

a. Weiss examines the basis of the FDA's position on food dyes, the decision of the Food Advisory Committee (in 2011), and the reasons that this is an environmental health issue.

b. He points out that the Committee limited itself to considering the effect of food dyes only on those children with diagnosed hyperactivity, **and never asked the environmental question of behavioral effects in the general population.** He says that they failed to recognize the significance of vulnerable subpopulations and misinterpreted the meaning of effect size as a criterion of risk.

c. Mitchell Cheeseman, on behalf of the FDA, replies more or less that Weiss has "misconstrued" the FDA safety assessment processes, that he has not made clear what behaviors are normal and what are "adverse," has cited results from studies the FDA considers flawed, and that some of his statements are out of context. See text of Cheeseman's reply here.

243. **WILES 2009: (*) (Study) "Junk Food" Diet and Childhood Behavioural Problems: Results from the ALSPAC Cohort.** *European Journal of Clinical Nutrition.* 63(4):491-8

a. Using a birth cohort of about 4,000 children from 1991/1992, the authors determined that a one standard deviation increase in eating "junk food" at the age of 4 ½ years was associated with increased hyperactivity at age 7. In particular, they are more likely to be in the top 33% of the hyperactivity sub-scale by then.

b. This may reflect a long-term nutritional imbalance or different parenting style, so more research is needed. Meanwhile, it is known that a diet high in junk food is likely to be lower in essential fatty acids but high in fat and/or sugar, additives, food colorings and preservatives. The authors adjusted for sugar intake, but that did not change the observed association.

244. **WILLIAMS (1978): (FDA) (Study) Relative Effects of Drugs and Diet on Hyperactive Behaviors: An Experimental Study.** *Pediatrics.* 61, 1978: 811-817.

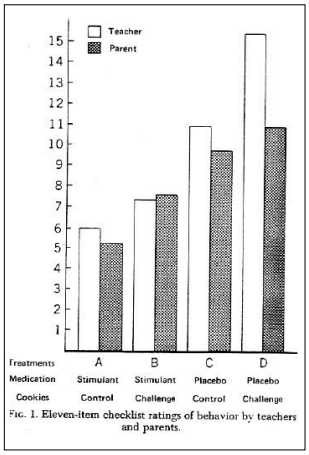


FIG. 1. Eleven-item checklist ratings of behavior by teachers and parents.

a. Williams used a "modified" Feingold diet in which salicylates were not eliminated. When the children were receiving the placebo capsules, "their hyperactive behaviors in the classroom were greater when eating cookies with artificial colors than when eating cookies without artificial colors."

b. Conclusion: "drugs plus diet provided better results than drugs alone." The worst combination, he reported, was food dyes + 'placebo' meds.

245. **WILSON 1989: (FDA) (Study) A Double-Blind Assessment of Additive Intolerance in Children Using a 12 Day Challenge Period at Home.** *Clinical and Experimental Allergy*. 19: 261-268

a. The challenge and placebo drinks were:
   - Lucozade plus carotene (placebo)
   - Lucozade plus 8.5 mg Yellow 5 and Yellow 6, each.
   - Lucozade plus sodium metabisulphite and sodium benzoate.

b. **Note:** *Lucozade is a popular British* ***energy drink*** *containing lots of sugar (glucose), as well as flavorings and caffeine. This would make it a mild stimulant – perhaps not the best choice for this sort of study? Depending on the flavor, ingredients today may also include artificial food dyes such as Yellow 6, any of several preservatives, and aspartame.*

c. The children were allowed to consume the drink "at any time of day." **Note**: *If a child consumed it at night, might he not sleep through a reaction? This is not addressed in the study.*

d. In only 3 of the 19 children was there any "consistent deterioration" from the challenge drinks. **Note:** *Considering the study's defects, even three is remarkable.*

246. **WINKLER 1995: (*) (Lab) (Extra) Impairment of Blood-Brain Barrier Function by Serotonin Induces Desynchronization of Spontaneous Cerebral Cortical Activity: Experimental Observations in the Anaesthetized Rat.** *Neuroscience.* 68(4): 1097-1104.

a. Increasing the circulating serotonin changes the BBB so that dyes can pass.

247. **WOLRAICH 1994: (FDA) (Study) Effects of diets high in sucrose or aspartame on the behavior and cognitive performance of children.** *New England Journal of Medicine,* 330 (No. 5), 1994: 301-307.

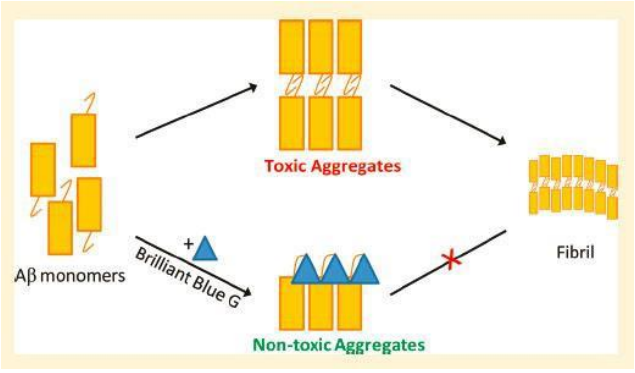
a. This study compared sucrose (table sugar) to aspartame, and is not relevant to a discussion of food dyes, except as follows:

- Both of the diets used in this study (one with sugar and the other with aspartame) were free of additives, food dyes, and preservatives.
- Wolraich wrote, "It could be argued that all three sweeteners had adverse effects. **This possibility seems unlikely because behavior ratings and test scores generally improved during the dietary periods, as compared with the base-line values**."
- **Note:** *He may have accidentally done a study showing that an additive-free diet improves behavior.*

b. Letters to the editor by Schoenthaler, Samuels, Crook, Brenner, Furukawa & Mahan, Wolraich (reply), and Kinsbourne.

248. **WONG 2011: (*) (Lab) (Medical) A Safe, Blood-Brain Barrier Permeable Triphenylmethane Dye Inhibits Amyloid-ß Neurotoxicity by Generating Nontoxic Aggregates.** *ACS Chemical Neuroscience.* 2(11): 645-657.

a. This paper describes a neurological effect of Blue 1 that may be of medical benefit in treating Alzheimer's Disease.



b. Amyloid-ß (Aß) oligomers have a direct connection to the onset of Alzheimer's disease, but Brilliant Blue G (basically Blue 1) is an effective Aß modulator, crossing the blood-brain barrier, and forming nontoxic aggregates which reduce Aß cytotoxicity.

249. **WONG 2011: (*) (Lab) (Medical) Xanthene Food Dye, as a Modulator of Alzheimer's Disease Amyloid-beta Peptide Aggregation and the Associated Impaired Neuronal Cell Function.** *PLoS One.* 6(10): e25752

a. This paper describes a neurological effect of Red 3 that may be of medical benefit in treating Alzheimer's Disease.

b. Red 3 seems to be a good candidate as a treatment of Alzheimer's Disease because it passes through the blood-brain barrier and binds to the N-terminus of Aß and inhibits amyloid fibril formation. Its effect is dose-dependent.

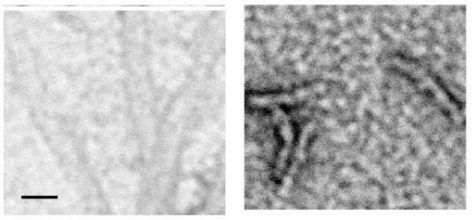


Figure 5. TEM images of Aβ aggregates after three day incubation. Aβ monomers were incubated for three days
Left picture is with no Red 3 and right picture is with 10 x Red 3

250. **WONG 2013: (*) (Lab) (Medical) Halogenation Generates Effective Modulators of Amyloid-Beta Aggregation and Neurotoxicity.** *PLos One.* 8(2): e57288

a. This paper describes a neurological effect of Red 3 that may be of medical benefit in treating Alzheimer's Disease.

b. The authors say they have conclusively established that Red 3 and two of its analogs effectively reduce Aß-associated neurotoxicity. The Red 3 molecule is halogenated and the authors say this is "the first report demonstrating the heavy halogen atoms added to multiple aromatic rings can confer inhibitory capacities on Aß-associated cytotoxicity."

251. **WOO 2014: (*) (Study) Dietary Patterns in Children with Attention Deficit/Hyperactivity Disorder (ADHD)** *Nutrients.* 5: 1539-1553.

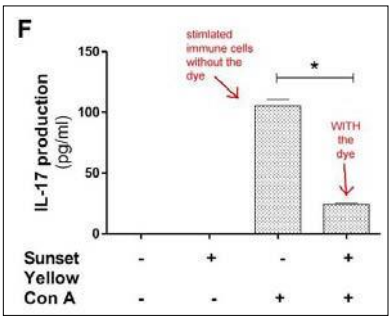
a. 4 dietary patterns in Korea were analyzed for their relationship to ADHD.

b. Although food dyes were not quantified, they were ingested least in the "Traditional-Healthy" pattern, which was also least associated with ADHD.

c. Besides low levels of copper, iron, zinc, magnesium, and omega-3, higher sugar, artificial food dyes, and preservatives are all associated with an increased risk of ADHD.

252. **YADAV 2013: (*) (Lab) Sunset Yellow FCF, a Permitted Food Dye, Alters Functional Responses of Splenocytes at Non-Cytotoxic Dose.** *Toxicology Letters.* 217(3):197-204.

a. Yadav tested Sunset Yellow (Yellow 6) at a level that was not cytotoxic, and found it suppressed the function of the T cells and B cells of the immune system, leading to a decline in cytokine production.



b. Concanavalin A (Con A) is a carbohydrate binding protein from the legume lectin family. As a plant mitogen, it is used in laboratories to stimulate mouse T cells.

c. Yadav used Con A to stimulate the T cells and used Con A together with Yellow 6 to see if that would change the T-cell stimulation. It did. They were suppressed (see chart at right). Yadav did a number of variations on this type of experiment, and determined that **children getting this dye near to the ADI level are likely to develop impaired resistance against infectious disease.**

d. The authors concluded from their experiments, moreover, that the results they observed support the McCann (2007) conclusions that several food additives (including Yellow 6) can cause hyperactive behavior in children.

253. **YAN 2018: (*) (Study) Dietary Patterns Are Associated with Attention-Deficit/Hyperactivity Disorder (ADHD) Symptoms Among Preschoolers in Mainland China.** *European Journal of Clinical Nutrition.* 72(11):1517-1523.

a. Quote: "… the prevalence of having ADHD symptoms was positively associated with the higher tertiles of "processed," "snack," and "beverage" dietary patterns."

254. **ZAGORECKA 2003: (*) (Study) Subjective Perception of Hypersensitivity to Selected Additives-containing Foods in Children and Adolescents from Schools in Bialystok.** *Pol Merkur Lekarski.* 15(87): 217-221. *(abstract only – article in Polish)*

a. In a survey of parents of over 5,000 children, 9.8% complained of symptoms such as abdominal pain, rash, cough, runny/stuffy nose (rhinitis), and headache after eating additive-containing foods.

b. The most incriminated foods were those containing synthetic colorings as well as sugars.

255. **ZHOU 2016: (*) (Study) Dietary, Nutrient Patterns and Blood Essential Elements in Chinese Children with ADHD.** *Nutrients.* 8: 352.

a. Unhealthy snack-heavy dietary patterns were significantly related to ADHD, in the same manner as other studies:

b. Zhou cites Howard (2011), Azadbakht (2012), and Woo (2014)

Please continue with
Appendix A

Appendix A

ADDITIONAL ARTICLES RELEVANT TO
ALLERGY, ASTHMA AND THE
GENERAL TOXICITY OF SYNTHETIC FOOD DYES
Username/Password = "Private/Papers"

1. **ABO-EL-SOOUD 2018: (*) (Lab) Assessment of Hepato-Renal Damage and Genotoxicity Induced by Long-Term Exposure to Five Permitted Food Additives in Rats.** *Environmental Science and Pollution Research.* 25(26):26341-26350

   a. Tartrazine (Yellow 5) was fed to rats at 10 times the ADI for 60 days.

   b. The author confirmed destructive and degenerative changes to liver and kidney, and recommended finding natural substitutes.

2. **ABOEL-ZAHAB 1997: (*) (Lab) Physiological Effects of Some Synthetic Food Colouring Additives on Rats.** *Bollettino chimico farmaceutico.* 136(10): 615-27. *(abstract only)*

   a. Groups of rats were fed "chocolate" color mixes of Yellow 5, Yellow 6, Blue 1 and carmoisine.

   b. Lipids, cholesterol, triglycerides, and various markers of liver and kidney damage were increased, while red blood cell counts decreased. Hemorrhages and congested blood vessels were seen in liver and kidneys. The brain and nervous system were not analyzed in this study.

3. **AL-SEENI 2018: (*) (Lab) (Extra) Nigella Sativa Oil Protects Against Tartrazine Toxicity in Male Rats.** *Toxicology Reports.* 5: 146-155.

   a. This was not a test of Tartrazine (Yellow 5) – they already knew it would be toxic. Rats in the "positive control" group (given Yellow 5) had elevated liver enzymes, cholesterol and triglycerides, as well as pathological changes in the liver, kidney, testes and stomach.

   b. The authors were testing *Nigella sativa oil* as protection against Yellow 5. It worked, and was recommended as protection against the dye's toxicity.

   c. **Note:** *Nigella sativa is also called black caraway, black seed, black cumin, fennel flower, nigella, nutmeg flower, Roman coriander, and kalonji. It's used as a spice in Indian, Middle Eastern and Polish cuisine.*

4. **AL-SHINNAWY 2009: (*) (Lab) Physiological Effect of a Food Additive on Some Haematological and Biochemical Parameters of Male Albino Rats.** *Egypt. Acad. J. Biological Sciences.* 2(1): 143-151.

   a. For 30 days, the authors fed Amaranth (Red 2) to rats.
   b. The rats in the high dose group had a marked decrease in red blood cell counts and hemoglobin, but an increase in several markers of liver and kidney damage such as AST and ALP, as well as glucose.
   c. The measurements improved after a 30 day recovery period, especially in the low-dose group.

5. **ALSOLAIMAN 2003: (*) (Case) FD&C Blue Dye No. 1 and Blue Nail Discoloration: Case Report.** *Nutrition.* 19-395-396.

   a. A patient was given 40 to 80 mg/day of Blue 1 in her tube feedings. All her nails turned blue.
   b. The doctor remembered that absorption of blue dye can be fatal so they stopped using it.
   c. She died a month later, but without an autopsy they say they don't know if her death was connected to the dye.

6. **AMCHOVA 2015: (*) (Review) Health Safety Issues of Synthetic Food Colorants.** *Regulatory Toxicology and Pharmacology.* 73(3):914-22

   a. This is a review of food dye toxicity per official EFSA reports and other studies since 2008. See also Page 4.
      - **Allura Red (Red 40)** may cause urticaria/asthma when mixed with other colorings.
      - **Brilliant Blue (Blue 1)** may cause hypersensitivity reactions even at low doses. It can be absorbed into the blood via shaven skin and oral mucosa. When used in eye surgery, it has sometimes caused foveal thinning and hyperpigmentation.
      - **Erythrosine (Red 3)** is iodine-based and may induce thyroid gland damage, causing release of TSH.
      - **Indigo Carmine (Blue 2):** Three case reports of adverse events are discussed, but each is different. It can be absorbed into the blood via shaven skin and oral mucosa.
      - **Tartrazine (Yellow 5)** can activate estrogen receptors (xenoestrogens), increasing the risk of primary biliary cirrhosis in postmenopausal women. At high doses, it can cause learning/ memory deficits in mice and rats.
      - **Sunset Yellow (Yellow 6)** can reduce testes size and distort the lipid profile at low doses.

7. **AMIN 2010: (*) (Lab) Effect of Food Azo Dyes Tartrazine and Carmoisine on Biochemical Parameters Related to Renal, Hepatic Function and Oxidative Stress biomarkers in Young Male Rats.** *Food and Chemical Toxicology.* 48(2010): 2994-2999.

    a. The two dyes were given in low (15 mg/kg) and high (500 mg/kg) doses for 30 days.

    b. Both doses adversely changed biochemical markers in liver and kidney (ALT, ASP, ALP, urea, creatinine, total protein, albumin, glucose, etc.).

8. **ANGARITA 2019: (*) (Study) (Medical) Quantitative Measure of Intestinal Permeability Using Blue Food Coloring.** *Journal of Surgical Research.* 233: 20-25.

    a. Blue 1 can be used to measure the intestinal barrier integrity because the gut becomes permeable in sepsis and multiple organ failure.

    b. After being given by mouth, it can be measured in the blood if the gut barrier is impaired.

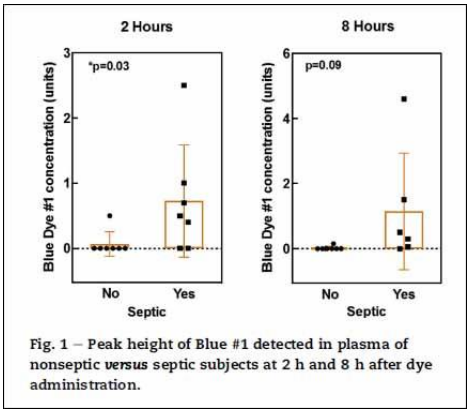


Fig. 1 – Peak height of Blue #1 detected in plasma of nonseptic *versus* septic subjects at 2 h and 8 h after dye administration.

9. **AREFIN 2017: (*) (Lab) Tartrazine Induced Changes in Physiological and Biochemical Parameters in Swiss Albino Mice, *Mus musculus.*** *Marmara Pharmaceutical Journal.* 21(3): 564-569.

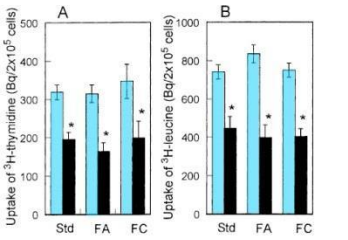
    a. For 25 days, mice were fed a diet with Yellow 5. Those given the dye gained less weight. Their heart and kidney size increased, while their liver size decreased. Triglyceride, creatinine and bilirubin levels were significantly increased.

    b. The authors concluded that s**ince consumption above the ADI has been reported in some countries, such exposure to excessive amounts of Yellow 5 may pose a health risk.**

10. **ASHIDA 2000: (*) (Lab) Synergistic Effects of Food Colors on the Toxicity of 3-Amino-1, 4-dimethyl-5H-pyrido[4, 3-b]indole (Trp-P-1) in Primary Cultured Rat Hepatocytes.** *Journal of Nutritional Science and Vitaminology (Tokyo).* 46(3): 130-136.

    a. When a very weak mix of 6 food dyes was added *in vitro* to hepatocytes removed from rats fed a normal diet, the food dyes reduced cell viability without membrane damage. When Trp-P-1 (a carcinogen) was added after 12 hours, its expected effect was increased by the food dyes, inducing cell membrane damage and cell death.

    b. On the other hand, the hepatocytes from food-color-fed rats were more sensitive to Trp-P-1, suggesting that the daily intake of artificial food colors may impair hepatic functions such as gluconeogenesis and ureogenesis, when liver cells are also exposed to dietary carcinogens.

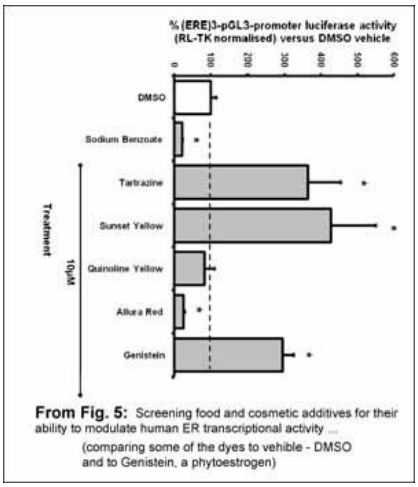


From Figure 4.
Std - rats fed standard diet
FA - rats fed food additives
FC - rats fed food colors
* - significance
A - DNA syntheses in hepatocytes
B - Protein syntheses in hepatocytes
Blue bars - cells treated with DMSO (vehicle)
Black bars - cells treated with Trp-P-1

11. **AXON 2012: (*) (Lab) Tartrazine and Sunset Yellow are Xenoestrogens in a New Screening Assay to Identify Modulators of Human Oestrogen Receptor Transcriptional Activity.** *Toxicology.* 298(1-3):40-51.

    a. Yellow 5 and Yellow 6 were identified as human estrogen activators. Both dyes are water soluble and not absorbed via the gut or skin; absorption can be increased by cosmetic agents such as alcohol.

    b. The author calculated that such absorption may be sufficient for an estrogenic effect over time sufficient to contribute to the development of the liver disease *primary biliary cirrhosis* which occurs most frequently in post-menopausal women.



From Fig. 5: Screening food and cosmetic additives for their ability to modulate human ER transcriptional activity ...
(comparing some of the dyes to vehible - DMSO and to Genistein, a phytoestrogen)

12. **BASAK 2014: (*) (Lab) Effects of Maternally Exposed Food Coloring Additives on Laryngeal Histology in Rats.** *Journal of Environmental Pathology, Toxicology, and Oncology.* 33(2): 123-130.

    a. Pregnant rats were given the "no observable adverse effect" level of mixed food dyes. When the pups became adults, they were killed and their larynx *(voice box)* examined.

    b. The maternally-exposed rats had fewer of some cells such as the cilia (*tiny "hair" cells that move mucus*), and reduced villin (*a special kind of protein)*. Increased Ki67 index and p53 activity predicted future cancerous lesions.

13. **BASAK 2016: (*) (Lab) Does Maternal Exposure to Artificial Food Coloring Additives Increase Oxidative Stress in the Skin of Rats?** *Human and Experimental Toxicology.* 36(10);1023-1030.

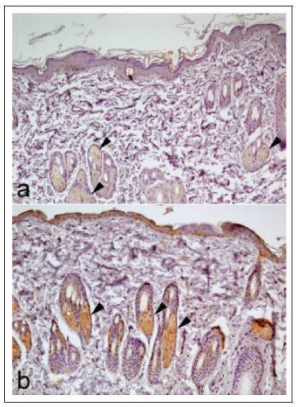


Figure 2. Immunohistochemical expression of GSTM in the control group (a) and the study group (b).

   a. A mix of food dyes at the "no observable adverse effects" level were given to the mother rats from one week before pregnancy until birth.

   b. There were clear differences in how maternal exposure to food dyes affects the expression of a number of genes in the skin, sebaceous gland, subcutaneous striated muscle, dermal fibroblasts, vascular endothelia, epidermal keratinocytes and vascular endothelia.

14. **BASTAKI 2017a: (*) (Lab) Lack of Genotoxicity *in vivo* for Food Color Additive Allura Red AC.** *Food and Chemical Toxicology.* 105: 308-314.

   a. Red 3 was given to mice by gavage (*orally*) – for 3 days, once each day – and it was concluded that Red 40 is not genotoxic.

   b. Funding: **International Association of Color Manufacturers.**

   c. Authors:

      - **M. Bastaki:** Scientific Director, International Association of Color Manufacturers, advertising they "advance the interests of manufacturers, producers, and users in the color industry."
      - **T. Farrell:** Director at Colorcon Inc., making products for the pharmaceutical industry.
      - **S. Bhusari:** Manager of Ingredient Safety at Coca-Cola.
      - **K. Pant** & **R. Kulkarni** work for Sigma-Aldrich Corp, a biotechnology company owned by Merck.

   d. **Note:** *The funding and affiliation of the authors suggest that careful reading of this study is required.*

15. **BASTAKI 2017b: (*) (Lab) Lack of Genotoxicity *in vivo* for Food Color Additive Tartrazine.** *Food and Chemical Toxicology.* 105: 278-284.

   a. Yellow 5 was given to mice by gavage (*orally*) – once a day, for 3 **days – and it was concluded that Yellow 5 is not genotoxic.**

   b. Funding: **International Association of Color Manufacturers.**

   c. Authors: Same as Bastaki (2017a).

16. **BASU 2016: (*) (Lab) Multispectroscopic and Calorimetric Studies on the Binding of the Food Colorant Tartrazine with Human Hemoglobin.** *Journal of Hazardous Materials.* 318:468-476.

    a. The binding mechanism of Tartrazine (Yellow 5) to hemoglobin was studied. Unless you have a degree in chemistry, skip to the "Conclusions" where it says, "Toxicity of pollutants like azo dyes which are introduced into the blood stream as a consequence of environmental exposure is a **serious health concern for the humans**."

    b. The author further says that since the dye can bind strongly to hemoglobin, it can pose a risk of toxicity to the normal function of the hemoglobin.

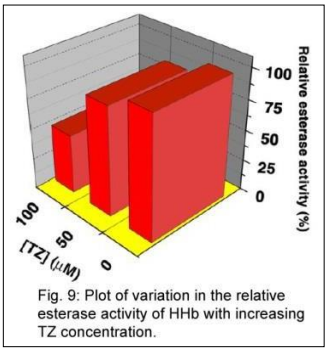
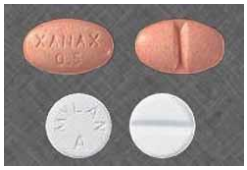


Fig. 9: Plot of variation in the relative esterase activity of HHb with increasing TZ concentration.

17. **BHATIA 1996: (*) (Case) (Allergy) Allergy to Tartrazine in Alprazolam.** *Indian Journal of Medical Sciences.* 50(8): 285-286.

    a. 20 out of 960 patients prescribed alprazolam (*Xanax)* with Tartrazine (Yellow 5) had reactions – mostly rash or urticaria. All of them had no problem (afterwards) taking the same drug in a dye-free form.

    b. The authors say that an apparent allergic reaction to this drug may actually be a reaction to the Yellow 5 in it. **Note:** *Today, this drug appears to contain Yellow 10, Yellow 6, or Blue 1, depending on dose and manuracturer.*



18. **BHATIA 2000: (*) (Case) (Allergy) Allergy to Tartrazine in Psychotropic Drugs.** *Journal of Clinical Psychiatry*. 61(7): 473-476. *(abstract only)*

    a. 83 out of 2,210 patients **(3.8%)** prescribed psychotropic drugs seemed to be allergic, but were not allergic to other brands of the same drug without the dye.

    b. A person who appears allergic to a drug may be simply allergic to the dye in it, so a brand without that dye can be tried instead of stopping treatment with the drug. **Note:** *Assuming an undyed brand can be found*.

19. **BOUTILIER 2000: (*) (Case) Green Colon: An Unusual Appearance at Autopsy.** *Archives of Pathology & Laboratory Medicine.* 124(9): 1397-1398.

    a. Except to report the staining of the colon and adjacent tissues at autopsy, and the appearance of green or blue skin and diarrhea (before death), this author was unaware of any damage to internal organs or to the patient from this practice.

    b. **Note:** *Until recently, Blue 1 food dye was routinely added to enteral feeding tubes.*

20. **CARPENITO 2002: (*) (Case) Green Urine in a Critically Ill Patient.** *American Journal of Kidney Diseases.* 39(4): E20

Fig 2. Patient's urine.

a. A 39 year old man with normal kidney function was given Blue 1 in tube feedings while in the hospital for sepsis. Three days later, his urine turned dark green.

b. This was unexpected since Blue 1 had been studied only in healthy animals and people and was not supposed to be in the urine at all.

c. The author wrote that Blue 1 had been estimated by the National Academy of Science in 1977 to have an average daily intake of 16 mg. The patient had been given 180 to 240 mg per day via tube feedings.

d. Carpenito reviewed the research on Blue 1, as well as its apparent inhibition of mitochondrial oxidative phosphorylation. He hoped that increased awareness by nephrologists may lead to increased research regarding the potential toxicity of Blue 1 when absorbed by the gut.

21. **CEMEK 2014: (*) (Lab) Effects of Food Color Additives on Antioxidant Functions and Bioelement Contents of Liver, Kidney and Brain Tissues in Rats.** *Journal of Food and Nutrition Research,* 2(10): 686-691.

a. Tartrazine (Yellow 5) and Carmoisine (not used in the US) were given to rats by gavage (orally) for 15 days to study their effect on trace elements.

b. The dosages of the Yellow 5 were 3 mg/kg and 15 mg/kg. The low dose was only about half the ADI (for the US). The control group received no dye.

c. Results: Iron and zinc levels changed in the rats' liver, kidney and brain tissues. Copper was elevated in the kidney, and some trace elements were reduced in the brain by both the high and low dose Tartrazine.

d. Cemek wrote these trace elements are needed for antioxidant defense and their depletion "**may result (in) some disruptions in crucial pathways."**

22. **CESERANI 1978: (*) (Lab) (Allergy) Tartrazine and Prostaglandin System.** *Prostaglandins and Medicine.* 1: 499-505.

a. Guinea pig lungs were treated with 3 different levels of Tartrazine (Yellow 5) or indomethacin, using a procedure that usually gives stable responses in less than two hours.

b. The Tartrazine (Yellow 5) inhibits prostaglandins and TXA_2 like indomethacin, but much less – about 200 times less for the first and 300 times less for the second. In other words, the asthmatic who reacts to 5 mg of indomethacin should be expected to have a similar reaction to 100 mg of Tartrazine. As of 1978, according to the author, no more than 25 mg of Tartrazine had been used to test asthmatics.

c. Ceserani commented that since daily small doses of aspirin or indomethacin attenuates the reactivity to it in asthmatics, he had successfully used 1 mg Tartrazine per day for 2 weeks to reduce a patient's reactivity to aspirin.

23. **CHEN 2018: (*) (Lab) Characterizing the Noncovalent Binding Behavior of Tartrazine to Lysozyme: A Combined Spectroscopic and Computational Analysis.** *Journal of Biochemical and Molecular Toxicology.* Oct 28: e22258.

a. Lysozyme is an antimicrobial enzyme produced by animals in tears, saliva, human milk, and mucus. It is also found in white blood cells and egg white. It forms part of the innate immune system of animals; it digests bacteria, inhibits the growth of germs, and can be used commercially as a preservative.

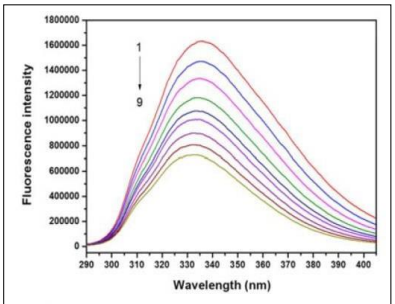


FIGURE 1 Fluorescence spectra of lysozyme in the presence of different concentrations of tartrazine; conditions: tartrazine ($\times 10^{-5}$ mol·L^{-1}) 1-9: 0, 0.5, 1.0, 1.5, 2.0, 2.5, 3.0, 3.5, 4.0; lysozyme: 2×10^{-6} mol·L^{-1}; buffer: NaH_2PO_4/Na_2HPO_4, pH7.4; T = 293 K

b. Tartrazine (Yellow 5) reacts with lysozyme, binding with it at two docking sites, and causing it to act abnormally. Some studies have found that abnormal lysozyme levels are related to bronchopulmonary dysplasia, diarrhea, conjunctivitis, and kidney damage.

c. This study provides insight into the molecular binding of Tartrazine to lysozyme *in vivo*.

24. **CHEQUER 2012: (*) (Lab) Genotoxic and Mutagenic Effects of Erythrosine B, a Xanthene Food Dye, on HepG2 Cells.** *Food and Chemical Toxicology.* 50(10):3447-5.

a. To analyze the genotoxicity of Red 3, the authors chose HepG2 cells which can mimic *in vivo* metabolism. Treating the cells with 7 concentrations of Red 3 up to 70 µg/ml resulted in genotoxicity at the two highest concentrations and mutagenicity at 6 of them.

b. Chequer suggests that although Red 3 is approved for use in food, cosmetics and drugs, it must be "**used carefully because it damages the DNA structure."**

c. **Note:** *Used carefully??*

25. **CHEQUER 2017: (*) (Lab) Erythrosine B and Quinoline Yellow Dyes Regulate DNA Repair Gene Expression in Human HepG2 Cells.** *Toxicology and Industrial Health.* 33(10): 765-774.

    a. This study on the expression of repair genes under the influence of food dyes showed that Quinoline Yellow (D&C Yellow 10) and Erythrosine B (Red 3) decrease expression of some genes, downregulate others and increase apoptosis *(cell death)*.

    b. These effects would involve genes related to the DNA repair system and cell cycle.

26. **CHUNG 1978: (*) (Lab) Reduction of Azo Dyes by Intestinal Anaerobes.** *Applied and Environmental Microbiology.* 35(3): 558-562.

    a. This is a study of the reduction of azo food dyes into carcinogenic metabolites by anaerobic bacteria in the intestine. In reduction, their N=N (azo links) are broken.

    b. All the anaerobes tested reduce more than one azo dye, and some can reduce most of them. The colon is the most suitable environment and Chung says it is probably the primary site for the reduction of azo dyes. To see more on this, see also Chung 1981 and Chung 1983

27. **COLLINS 1992: (*) (Lab) Study of the Teratogenic Potential of FD&C Yellow No. 5 When Given in Drinking Water.** *Food & Chemical Toxicology.* 30(4): 263-268.

    a. Various doses of Yellow 5 in drinking water were given to pregnant rats up until gestation day 20 *(rats usually give birth between days 20-23).*

    b. The rats were killed and fetuses examined. No problems were found except for some delayed ossification *(bone formation)* that was not considered dose-related. Nine litters of pups were completely resorbed – none in the control group, but some in each of the dye groups. This occurrence was not (quite) dose related, so it was not considered important.

    c. **Note:** *No neurological or behavioral observations were described.*

28. **COLLINS 1993: (*) (Lab) Teratogenic Potential of FD&C Red No. 3 When Given in Drinking Water.** *Food and Chemical Toxicology.* 31(3): 161-167.

    a. Various doses of Red 3 in drinking water were given to pregnant rats up until gestation day 20.

    b. The rats were killed and fetuses examined. No problems were found. Four of the females died because they wouldn't drink the water.

    c. **Note:** *No neurological or behavioral observations were described.*

29. **COLLINS 1993: (*) (Lab) Teratogenic Potential of FD&C Red No. 3 When Given by Gavage.** *Toxicology and Industrial Health.* 9(4): 605-616.

    a. Various doses of Red 3 in water were given to pregnant rats by gavage up until gestation day 20.

    b. The rats were killed and fetuses examined. No problems were found.

    c. **Note:** *No neurological or behavioral observations were described.*

30. **CORDER 1995: (*) (Study) Allergy) Aspirin, Salicylate, Sulfite and Tartrazine Induced Broncho-constriction. Safe Doses and Case Definition in Epidemiological Studies.** *Journal of Clinical Epidemiology*. 48(10): 1269-75.

    a. Corder estimated safe doses to use for epidemiological studies by studying reactions of patients in an allergy clinic. She said that reactions to the four compounds listed in the table are common, and may cause symptoms that appear to be allergy even though no IgE is involved. She said a chronic exposure can cause a chronic inflammation that mimics infection.

Doses to Which Susceptible People Respond

Compound	The most sensitive 5% of responders	The other 95% of responders
Metabisulfite	4.6 mg	255.8 mg
Tartrazine	3.4 mg	885.6 mg
Aspirin	0.8 mg	332.3 mg
Salicylate	2.6 mg	89.9 mg

    b. Corder defined a 15% decrease in the amount of air expired in one second as a positive airway response, and did not discuss behavioral issues. She identified doses to which the most sensitive (5%) and practically all (95%) of susceptible persons might respond. Corder said doses within these ranges *(see table)* can be used in epidemiological studies.

    c. **Note:** *In most studies, far lower doses have been used – indeed, I have never found any study using anything close to 800 mg Tartrazine (Yellow 5) on a human being, and the only ADHD study of aspirin I have found (Fitzsimon 1978) used only 40 mg (half a baby aspirin) – and astonishingly, he got results.*

31. **CZOP 2002: (*) (Case) Green Skin Discoloration Associated with Multiple Organ Failure.** *Critical Care Medicine.* 30(3): 598-601.

    a. The patient was in the hospital for treatment of a heart condition which had multiple complications involving her lungs and liver. She was tube fed from post-operative day 3 through postoperative day 16, receiving Blue 1 at about 10 mg/hour. Her urine became green the day after tube feeding began. The last few days her skin was pea-green.

    b. While the authors don't believe the dye contributed to her death, they warn that patients with multiple organ failure may be at risk of "unusual pigmentation effects" from tube feeding dyes because of increased absorption from the gut and failure of the usual excretion routes.

32. De FREITAS 2019: (*) (Lab) (Medical) **PEG-Coated Vesicles from Pluronic/Lipid Mixtures for the Carrying of Photoactive Erythrosine Derivatives.** *Colloids and Surfaces B: Biointerfaces.* 175: 530- 544.

    a. Lipid nanoparticles can deliver drugs to internal tumors.

    b. The authors wanted to use Red 3 as a photosensitizer which, when applied to the unhealthy tissue, will produce "singlet" oxygen. To be used properly, they are developing a way to encapsulate them in modified liposomes, so that the dye molecules can exert their phototoxic effect once inside the target cells.

33. DESMOND 1981: (*) (Case) (Allergy) **Tartrazine (FD&C Yellow #5) Anaphylaxis: A Case Report.** *Annals of Allergy.* 46(2): 81-82. *(abstract only)*

    a. This paper is a description of a case of anaphylaxis after repeated occult exposures to Yellow 5 in a person not aspirin-sensitive.

34. DOEGLAS 1975: (*) (Study) (Allergy) **Reactions to Aspirin and Food Additives in Patients with Chronic Urticaria, Including the Physical Urticarias.** *British J. of Dermatology.* 93, 135.

    a. Aspirin-sensitive patients were tested with Tartrazine, benzoates, salicylates and several drugs. 2 mg, 5 mg and 10 mg Tartrazine (Yellow 5) were used in the tests performed on patients who had improved on an additive-free diet. Antihistamines and corticosteroids were discontinued for at least a week before testing.

    b. Seven of the 23 patients **(30.4%)** reacted to this small Tartrazine challenge.

35. DWIVEDI 2015: (*) (Lab) **Genetic Damage Induced by a Food Coloring Dye (Sunset Yellow) on Meristematic Cells of *Brassica campestris L.*** *Journal of Environmental and Public Health.* Vol. 2015 (319727).

    a. Meristematic cells are the fast-growing stem or root tip cells, and Brassica are in the mustard family of plants including cabbage, turnips, etc. Exposure to the various amounts of Yellow 6 dye induced several kinds of dose-dependent DNA damage such as stickiness of chromosomes and partial genome elimination.

    b. Quote: "**The present study suggests that extensive use of synthetic dye should be forbidden due to genotoxic and cytotoxic impacts on living cells.**"

Brassica is the mustard family and includes cabbage, mustard, broccoli, cauliflower, rutabaga, turnip, etc.

36. **EGGER 1983: (*) (Study) Is Migraine Food Allergy? A Double-Blind Controlled Trial of Oligoantigenic Diet Treatment**. *Lancet.* 2(8355): 865-9.

a. **93%** of 88 children with severe frequent migraine recovered on an oligoantigenic (*few foods*) diet. Other symptoms that improved were abdominal pain, behavior disorders, fits, asthma, and eczema, and even those with known provocations such as flashing lights, were no longer affected while on the diet.

b. In 12 of the patients, challenge with Tartrazine (Yellow 5) caused symptoms.

c. **Note:** *While other food dyes were apparently not tested, all of them would have been removed on this sort of diet.*

37. **EHLERS 1998: (*) (Study) (Allergy) Role of Nonallergic Hypersensitivity Reactions in Children with Chronic Urticaria.** *Allergy.* 53: 1074-1077.

a. The role of nonallergic (*pseudoallergen-induced*) hypersensitivity to food was investigated in all 16 children seen in their clinic for chronic urticaria over 2 years.

b. In 81%, all symptoms were gone after a 3-week low-allergen diet, and no medications were needed. One had no more problems after being treated for Helicobacter pylori, so the effect of diet may have been indirect. In the others (75%) reacted to provoking foods.

c. A double-blind placebo-controlled trial identified the most provocative agents as food dyes and preservatives. MSG and saccharin caused problems for some.

d. **Note:** *In provocation tests, 50 mg Yellow 5 but only 5 mg of each of the other dyes were used.*

38. **EHRENBERG 2019: (*) (Lab) (Extra) Dyeing but not Dying: Colourful Dyes as a Non-Lethal Method of Food Labelling for *in vitro*-reared Honey Bee (*Apis mellifera*) Larvae.** *Journal of Insect Physiology*. 113: (26 pages).

a. In order to determine food sources and other environmental factors involving honey bees, larvae and adult worker bees were fed honey colored with Red 40 and Blue 1 food dyes.

b. Larvae survived without “significant differences” until the “late pupal stage.” From that time on, larvae fed Blue 1 had a higher mortality, especially in the pupal stages. Possible reasons for their deaths are discussed.

39. **ELBANNA 2017: (*) (Lab) Microbiological, Histological, and Biochemical Evidence for the Adverse Effects of Food Azo Dyes on Rats.** *Journal of Food and Drug Analysis.* 25(3):667-680.

a. Both certain lactic acid bacterial strains and bacterial intestinal isolates can degrade Yellow 5. But the degradation products of the intestinal bacteria are similar to toxic aromatic amines.

b. For 90 days, rats were treated with either the dye or its degradation products, then allowed to recover for 30 more days before being dissected.

c. The rats treated with either the dye or the toxic degradation products had significant changes in red blood cell count, hemoglobin, hematocrit, and more. Also, there were several markers of damage to the liver and kidney, as well as visible tissue damage to the liver, kidney, spleen, and small intestine.

d. Those rats given lactic acid bacteria at the same time as the food dye fared much better. **Note:** *The picture comes from an ad suggesting you add it to your beer to make it taste more sour. Other uses seem to be as skin peels. I guess protection against Yellow 5 hasn't caught on yet.*

40. **EL-DESOKY 2017: (*) (Lab) (Extra) Curcumin Protects Against Tartrazine-Mediated Oxidative Stress and Hepatotoxicity in Male Rats.** *European Review for Medical & Pharmacological Sciences.* (21): 635-645.

a. Curcumin was studied to see if it could protect against the kidney and liver damage expected from the ADI of Yellow 5 given in the diet.

b. The Yellow 5 caused significant oxidative stress and decreased antioxidant enzymes, while elevating markers for kidney/liver damage, and causing liver changes including hemorrhage and vacuolization.

c. Giving 2 or 4 g/kg curcumin with the dye almost completely prevented or reversed these effects, but giving only 1 g/kg didn't help. The author recommends using curcumin to "moderate potential effects of these artificial dyes" but stresses that decreasing or removing the dyes "**is an essential step for the amelioration of human health status and decreasing risk of onset or progression of degenerative diseases**."

41. **EL-WAHAB 2012: (*) (Lab) Toxic Effects of Some Synthetic Food Colorants and/or Flavor Additives on Male Rats.** *Toxicology and Industrial Health.* 29(2):224-32.

a. Ten groups of 10 rats were fed plain chow (control), or chow plus a color, a flavoring, or a color plus one flavoring for 42 days. **Note:** *The amounts of the three dyes used seem to be at least 10 times the ADI, but they are listed as* ***mg/kg diet*** *rather than* ***mg/kg/wt*** *so this is unclear.*

b. All 3 food colors with or without the flavorings induced the following significant changes:

- Decreased body weight
- Decreased hemoglobin
- Decreased red blood cell count
- Decreased reduced glutathione
- Decreased glutathione-S-transferase activity in blood and liver
- Decreased superoxide dismutase activity in blood and liver
- Increased serum alanine aminotransferase
- Increased aspartate aminotransferase
- Increased alkaline phosphatase activity
- Increased Bilirubin
- Increased urea
- Increased creatinine
- Increased total protein and albumin

c. The author noted the decreased growth rate of all the rats exposed to colorants, even though they ate more than the control rats. El-Wahab suggested that the food dyes may bind to the bacterial cell surface in the rat's intestine, preventing absorption of nutrients.

d. The **author advised limiting the use of the listed food color** and flavor additives, "especially those used by children."

e. **Note:** *There are a few errors in this study which may simply be typos or related to language difficulty (incorrectly named dyes for example), so it should be read with care.*

42. **ENGLUND-OGGE 2012: (*) (Study) (Extra) Association Between Intake of Artificially Sweetened and Sugar-Sweetened Beverages and Preterm Delivery: A Large Prospective Cohort Study.** *American Journal of Clinical Nutrition.* 96(3): 552-559.

a. 60,761 pregnant women in Norway were compared for high intake of sugar-sweetened and artificially-sweetened beverages. Both kinds of beverage were associated with increased risk of preterm delivery.

b. **Note:** *Both kinds of beverages also usually contain artificial food colorings which could have been a confound in this study – in other words, it may just as easily have been the food dyes they ingested that led to increased risk. Or maybe the sodium benzoate? Or maybe both together?*

43. **ERDEMLI 2017**: **(*) (Lab) (Extra) The Protective Role of Crocin in Tartrazine Induced Nephrotoxicity in Wistar Rats.** *Biomedicine & Pharmacotherapy.* 96 (2017): 930-935.

a. Apparently, Tartrazine (Yellow 5) metabolites were already known to cause oxidative stress as well as kidney damage, but the author wanted to find out if giving crocin could prevent the expected damage.

b. **Note:** *Crocin is a carotenoid chemical compound found in the flowers of crocus and gardenia plants, and it is the chemical primarily responsible for the color of saffron.*

c. Erdemli concluded that crocin could be a "**new type of anti-Tartrazine toxicity agent.**"

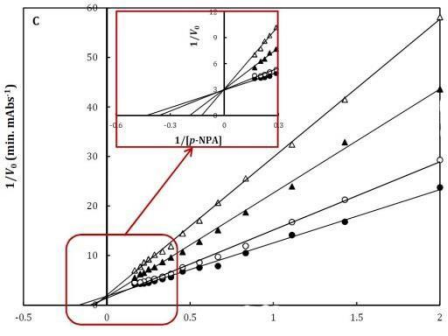
44. **ERSHOFF 1977: (*) (Lab) Effects of Diet on Growth and Survival of Rats Fed Toxic Levels of Tartrazine (FD&C Yellow No. 5) and Sunset Yellow FCF (FD&C Yellow No. 6)** *The Journal of Nutrition.* 107(5): 822-888.

a. In a series of experiments, rats were fed Yellow 5 at several different levels in their usual diet, without any observable effect. All lived for the 14 days, although those at the highest intake level had significant growth retardation.

b. However, when they were fed the same amounts of dye with a low-fiber "purified diet," those getting the higher (5%) dose had growth retardation, matted fur infiltrated with the dye itself, and most of them died before the end of the 14 days of the experiment.

c. When the same experiment was performed with Yellow 6, there were similar results. With Blue 1 and Red 40, however, the rats all lived to the end of the experiment and -- except for some growth retardation -- they seemed okay.

45. **ESMAEILI 2016: (*) (Lab) Degradation Products of the Artificial Azo Dye, Allura Red, Inhibit Esterase Activity of Carbonic Anhydrase II: A Basic *in vitro* Study on the Food Safety of the Colorant in Terms of Enzyme Inhibition.** *Food Chemistry.* 213:494-504.



a. Only 0.1% of Red 40 is excreted unchanged in urine and only 29% of it is excreted unchanged in feces. The rest is excreted as degradation products (DP) after having been broken down by gut flora.

b. DPs are smaller than the original Red 40 compound; they can cross cell membranes and can be more toxic than the original dye. Esmaeili study investigated the effects of the DP on carbonic anhydrase (CA), which is involved in numerous body functions such as respiration, pH balance, calcification, etc.

c. Red 40 and its DPs are **inhibitors of CA esterase activity, which the authors consider a safety risk.**

46. **FDA 2003: (*) Public Health Advisory: Reports of Blue Discoloration and Death in Patients Receiving Enteral Feedings Tinted with the Dye, FD&C Blue No. 1.**

a. This letter was sent to doctors to notify them of the 20 deaths that had been already reported. The letter says that the safety of using Blue 1 in tube feedings never was verified but that other blue dyes may be worse.

b. Doctors are not actually advised to stop using the blue dye, but to report any deaths from it that they may encounter.

c. Below is a collection of papers about blue or green colons / urine. They are discussed alphabetically as well, but here you can see them together.

Alsolaiman 2003	Friedrichsdorf 2003	Maloney 2000
Boutilier 2000	Gaur 2003	Maloney 2002
Carpenito 2002	Granville 2001	Zillich 2000
Czop 2002	Lucarelli 2004	

Van Way 2004 – editorial "The Blue Dye Blues"

d. See Angarita 2019 for the potential medical benefit of using low dose of Blue 1 to measure GI integrity in cases of suspected sepsis and other serious problems.

e. **Note:** *Below, from Maloney (2002), is a list of conditions with increased gut permeability:*

- Sepsis
- Severe burns
- Trauma
- Hemorrhagic shock
- Cardiac bypass
- Major vascular surgery
- Abdominal aortic aneurysm repair
- NSAIDs use (e.g., aspirin, Tylenol (**Note:** *Aleve is blue!*)
- Renal failure
- Celiac sprue
- Inflammatory bowel disease
- Cystic fibrosis

47. **FEKETEA 2017: (*) (Review) (Allergy) Common Food Colorants and Allergic Reactions in Children: Myth or Reality?** *Food Chemistry*. 230:578-588.

a. A number of food dyes are reviewed in this paper, as well as several of the natural colorings.

b. The authors reported that skin testing is unreliable for the synthetic dyes but an additive free diet may be helpful for diagnosis.

c. Feketea warned that for oral challenges there are no standardized protocols – but appears to have accepted the protocol of testing for reactions involving urticaria or asthma by giving small challenges while remaining on preventive medications.

d. The authors called for **full labeling information**, to avoid exceeding ADI levels unknowingly .

48. **FLORIANO 2018: (*) (Lab) Is Tartrazine Really Safe? In Silico and Ex Vivo Toxicological Studies in Human Leukocytes: A Question of Dose.** *Toxicology Research.* 7(6): 1128-1134.

a. Floriano et al tested Yellow 5 via computer simulations, to "predict its toxicity," acknowledging its wide use in spite of the known carcinogenicity of its aromatic amine and sulfanilic acid metabolites.

b. They also created leukocyte (white blood cell) cultures treated with various concentrations of Yellow 5 and performed DNA and chromosomal tests.

c. Significant DNA damage was induced by Yellow 5 at 70 µg/mL concentration, and confirmed by the computerized evaluation, which also suggested that the dye interferes with hydrogen bonds in the DNA, causing damage.

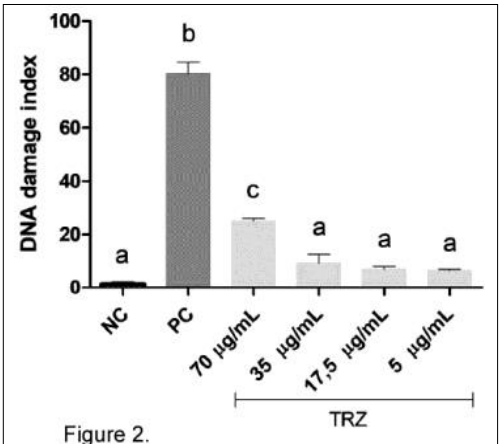


Figure 2.
TRZ - tartrazine, Yellow 5
NC - negative control
PC - positive control

d. The authors wrote that a blood concentration of 70 µg/mL of Yellow 5 is plausible because of the various food, medical and cosmetic products containing it.

e. Floriano referred to the findings in other studies corroborating their own findings as "alarming" -- especially for Yellow 5's possible effect on children's health and its bioaccumulation, leading to several diseases.

49. **FRIEDRICHSDORF 2003: (*) (Case) Green Urine. A Case Report and Review of the Literature.** *Urologe.* 42(1): 80-81. *(abstract only – article in German)*

a. The author described a case of green urine caused by blue food dye during tube feeding.

b. The abstract also refers to a list of more than 20 drugs, chemical agents, and microorganisms which have been associated with green urine.

50. **FUGLSANG 1993: (*) (Study) (Allergy) Prevalence of Intolerance to Food Additives Among Danish School Children.** *Pediatric Allergy and Immunology.* 4: 123-129.

a. 271 children from the population were surveyed for sensitivity to food dyes. 173 were put on an additive-free diet for two weeks before testing.

b. Only 17 were positive on the open challenge. 12 of them went through a double blind challenge which was positive in only 6 cases. Based on this study, the rate of intolerance to food additives in school children is estimated at 1% – 2%

	HIGH DOSE	LOW DOSE
Tartrazine	18.0 mg	1.8 mg
Quinoline Yellow	2.5 mg	0.25 mg
Patent Blue	2.0 mg	0.2 mg
Sunset Yellow	2.5 mg	0.25 mg

Note the amount of food dyes used in their "open challenge."

It is far from surprising that few of the children reacted to this drink.

c. **Note:** *Look at the dose levels in the chart above –at such low levels, it's a wonder anybody had any reactions at all.*

d. Fuglsang said that in the open challenge with lemonade, the additives were in contact with the child's mouth, while the double-blind challenge used capsules so that the additives were not in touch with any membranes or skin. He felt such contact may have been important and would have led to a higher number of reactions.

e. Another possibility he suggested was a synergistic effect between additives when they were all together in the drink used in the open challenge.

f. **Note:** *He didn't suggest trying a higher dosage.*

51. **FUGLSANG 1994: (*) (Study) (Allergy) Adverse Reactions to Food Additives in Children with Atopic Symptoms.** *Allergy.* 49: 31-37.

a. 335 children were put on an additive-free diet for 2 weeks and then given an open challenge in fizzy lemonade using a low dose of additives (see chart in Fuglsang 1993 above). If there was no reaction after 3 hours, they were given another open challenge with the "high doses" as seen in the chart above.

b. 23 children had positive reactions and 16 of them underwent a double-blind challenge contained in gelatin capsules. Only 6 children showed a reaction to any additives in the double-blind challenges, leading to a 2% incidence rate (6/335). This is more than the 1% in their earlier study but Fuglsang said that is because these children all had skin symptoms.

c. **Note:** *Children with asthma were allowed to use ß2-agonist medication as needed, and it is surprising that these tiny "high doses" could overcome such medication in any of the children at all, let alone as many as 2%.*

52. **FURUMIYA 2008: (*) (Lab) Inhibition of Human CYP3A4, UGT1A6, and P-glycoprotein with Halogenated Xanthene Food Dyes and Prevention by Superoxide Dismutase.** *Journal of Toxicology and Environmental Health, Part A,* 71: 1307-1313.

a. Superoxide anions, originating from dyes via light irradiation, may attack drug-metabolizing enzymes.

b. In this way, Red 40 in cosmetics may react with proteins in the skin and lead to skin damage.

c. **Note:** *Furumiya didn't talk about the other red dyes in cosmetics. There are, however, some studies on these dyes, used not in food but in cosmetics and (some) in toothpastes.*

- Shen (2015) – Red 28
- Compound Summary – Red 30
- Wenzel (2010) – Red 181 aka Red 30 (I think)
- Drugs.com – Red 30 Lake
- Field (2003) – Yellow 10, efforts to deal with in sludge

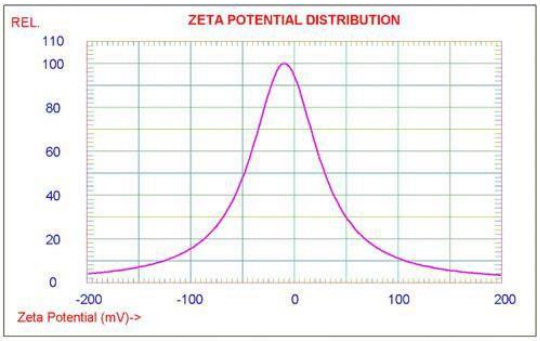
d. **Note:** *There must be more, but it doesn't appear to be in PubMed. We appear to be using these dyes based on approval by the FDA, and nothing else. Perhaps you would like to question their safety after finishing with those found in food?*

53. **GARAPATI 2015: (*) (Lab) (Medical) Development and Characterization of Erythrosine Nanoparticles with Potential for Treating Sinusitis Using Photodynamic Therapy.** *Photodiagnosis and Photodynamic Therapy*. 12(1):9-18.

a. This paper describes an effect of Red 3 that may be of medical benefit.

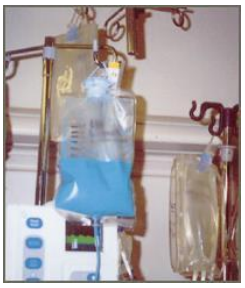
b. Red 3 was loaded into nanoparticles, which released them over 120 hours during which they entered *S aureus* cells, killing them.

c. As a photosensitizer, Red 3 could be used to eliminate bacteria without using antibiotic, without inducing antibiotic resistance and without daily dosing.



54. **GAUR 2003: (*) (Case) Systemic Absorption of FD&C Blue Dye Associated with Patient Mortality.** *Postgraduate Medical Journal.* 79(936): 602-603.

a. Gaus reported that while the addition of Blue 1 to feeding tubes in hospital was a common practice, its safety in critically ill patients had not been studied.



b. The case of a 56 year old woman is described. She was improving on intravenous antibiotics and enteral nutrition (tube feeding) without any color added. When blue dye was added to her feed, her skin, mucous membranes and urine turned greenish blue. Blisters with green fluid were seen on her abdomen and legs. She died 6 days later, and at autopsy all her internal organs were greenish blue.

c. Two other cases are described – in each, the patient was improving until blue dye was added to their feed, whereupon they died of refractory hypotension and acidosis. It is suggested that the dye inhibits the ATP translocator in the inner mitochondrial membrane – Gaus said this would explain the refractory acidosis in all three patients.

d. Gaur suggested using glucose oxidase reagent strips as a safer and more sensitive alternative to blue dye. See Potts (1993) for a comparison.

55. **GOMES 2013: (*) (Lab) Citotoxicity of Food Dyes Sunset Yellow (E-110), Bordeaux Red (E-123), and Tatrazine Yellow (E-102) on Allium cepa L. Root Meristematic Cells.** *Food Science and Technology.* 33(1): 218-223.

a. All three dyes were toxic to fast-growing root-tip cells of onions at all doses tested.

56. **GRANVILLE: 2001: (*) (Case) Blue Colon at Autopsy.** *Archives of Pathology and Laboratory Medicine.* 125(5):599.

a. The patient was a 50 years old diabetic woman in intensive care after surgery. She was receiving enteral feeding including 0.5 ml blue food dye per 250 ml of food. The entire length of her colon turned bright blue.

b. The patient had only one kidney but no evidence of renal insufficiency.

c. Granville pointed out that the FDA had approved the safety of Blue 1 via experiments performed on healthy animals, but there was no research on the absorbability of Blue 1 in critically ill patients.

57. **GULTEKIN 2013: (*) (Review) (Allergy) Allergic and Immunologic Reactions to Food Additives.** *Clinical Reviews in Allergy and Immunology*. 45(1):6-29.

    a. The authors reviewed several classes of food additives, to examine their relationship to allergic reactions.

    b. Both immune and non-immune (intolerance) reactions to food dyes are "supposed to be very rare in the population with the prevalence of 0.14% to around 2%."

    c. Several colorings are reviewed, and those used in the US are highlighted in Table 2.

58. **GRZELEWSKA-RZYMOWSKA 1986: (*) (Case) (Allergy) Sensitivity and Tolerance to Tartrazine in Aspirin-Sensitive Asthmatics.** *Allergologia et immunopathologia*. 14(1): 31-36. *(abstract only)*

    a. 16 of 51 (**31%**) aspirin-sensitive patients with asthma were also sensitive to Tartrazine (Yellow 5). Symptoms were similar and tolerance to both was achieved in some patients.

    b. Authors believe Tartrazine & aspirin have a similar pathogenetic background.

59. **HAGIWARA 2006: (*) (Lab) Assessment of Genotoxicity of 14 Chemical Agents Used in Dental Practice: Ability to Induce Chromosome Aberrations in Syrian Hamster Embryo Cells.** *Mutation Research* 603: 111-120.

    a. Red 3 is used in the mouth for disclosing dental plaque, so it was one of the 14 dental chemicals tested on hamsters in this study. The others are not mentioned here because they either were not dyes or not used in the US.

    b. Red 3 was one of several chemicals that induced statistically significant increases in the levels of chromosome aberrations. However, the study used levels not related to real world use -- a dentist uses a 4% solution of Red 3, which is actually almost 135 times higher than the 330 µM amount used in this study.

    c. **Note:** *No reason was given for using such a significantly smaller dose in the study than what a dentist would actually use. Meanwhile, dental disclosure tablets like the ones pictured are available at pharmacies and grocery stores. They don't appear to contain Red 3, but do contain D&C Red 28 – as a "medicinal ingredient" -- and Blue 1.*

    d. **Note:** *I haven't seen any studies showing that Red 28 is not absorbed from the mouth and/or is safe; but there are studies showing that Blue 1 is absorbed from the mouth and is not safe. How much is actually in these tablets is unknown since it is "proprietary information" of the company.*

60. **HASHEM 2010: (*) (Lab) Immunological Studies on Amaranth, Sunset Yellow and Curcumin as Food Colouring Agents in Albino Rats.** *Food and Chemical Toxicology.* 48: 1581-1586.

a. At doses up to 10 times the ADI, Yellow 6, Red 2, and curcumin (a natural coloring) all depressed the cellular, but not the humoral, immune response.

61. **HASHEM 2011: (*) (Lab) Toxicological Impact of Amaranth, Sunset Yellow and Curcumin as Food Coloring Agents in Albino Rats.** *Journal of Pakistan Medical Students.* 1(2): 43-51.

a. Female rats given ADI doses of Red 2 and Yellow 6 showed no effect on the liver and kidney glutathione and lipid peroxide levels, but at doses 10 times the ADI, levels became abnormally elevated. Red 2 at 10 times the ADI also caused skeletal abnormalities in 25% of pups.

b. Curcumin was tested the same way, but all doses showed liver improvement, not damage.

c. Conclusion: High doses of these colors (47 mg/kg) can damage the liver, and Red 2 should not be used while pregnant. (**Note:** *Luckily, it is now not used much in the US*).

62. **HASSAN 2009: (*) (Lab) Effects of Some Synthetic Coloring Additives on DNA Damage and Chromosomal Aberrations of Rats.** *Arab Journal of Biotechnology.* 13(1): 13-24.

a. Groups of rats were treated for 7 weeks as follows:

   1. Control (untreated)
   2. 7.5 mg/kg (the ADI) of Yellow 5
   3. 15 mg/kg of Yellow 5.
   4. 0.15 mg/kg Chocolate Brown
   5. 0.3 mg/kg Chocolate Brown.

b. The authors referred to the Chocolate Brown as E102 – but that is the European designation for Tartrazine (Yellow 5). Maybe a typo?

c. Thus, it is not clear what Groups 4 and 5 were actually given, but there is a commercial food dye called "Chocolate Brown" in the US that contains Sugar, Red 40, Red 3, Blue 1, Blue 2, Sodium Benzoate and Potassium Sorbate. There may be further ingredients that are not visible in available label pictures.

d. Yellow 5 and Chocolate Brown both caused liver and kidney damage detected by comet assay. Bone marrow cells showed damage, and there was evidence that the dyes could cause a **slow long-term destructive effect on organ function**.

63. **HEDMAN 1981: (*) (Lab) (Allergy) Effects of Tartrazine of Different Contractile Stimuli in Guinea Pig Tracheal Muscle.** *Acta Pharmacol Toxicol.* 48(2): 101-107. *(abstract only)*

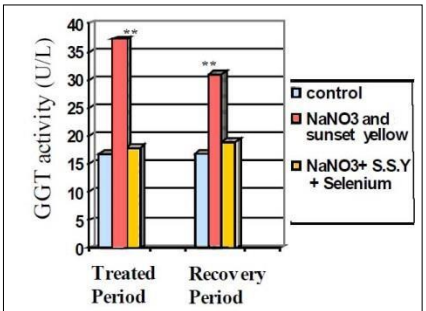
a. Contractions in tracheal muscles elicited by micromolar concentrations of both Yellow 5 and indomethacin were abolished by an enzyme that inactivates SRS-A (an inflammatory agent released by mast cells and called Slow Reacting Substance of Anaphylaxis).

b. It was thus determined experimentally that SRS-A is important to sensitivity reactions of both Yellow 5 and indomethacin.

64. **HELAL 2000: (*) (Lab) Effect of Some Food Colorants (Synthetic and Natural Products) on Young Albino Rats: 1-Liver and Kidney Functions.** *The Egyptian Journal of Hospital Medicine.* 1(1): 103-113. ***(See Page 36, #88)***

65. **HELAL 2001: (*) (Lab) Progressive Effects of the Interaction of Sodium Nitrite and Sunset Yellow on Different Physiological Parameters in Albino Rats.** *The Egyptian Journal of Hospital Medicine.* (2): 23-46.

a. Helal tested the preservative sodium nitrite and the dye Sunset Yellow (Yellow 6) together because that is the way children often ingest them. Giving the ADI of both together proved lethal to the rats, so the rats were given 1/10th the ADIs daily for 30 days. Ten rats were the controls, ten were given the combination, and another ten were given the combination plus selenium to see if an antioxidant might prevent any adverse effects of the dye and preservative mix.



From Figure 6. Notice there is (slight) improvement after the recovery period, but when given selenium, it's almost as good as the control.

b. In addition to changes of liver and heart function markers, the dye/nitrite mix caused a significant increase in serum thyroid hormones T3 and T4 as well as a gradual but significant **increase in blood sugar** levels accompanied by a deficiency of insulin.

c. In almost all aspects, the group receiving the dye/nitrite/selenium mix remained normal. Selenium, it appears, is protective against the dye/nitrite-induced toxicity.

d. Helal **recommends avoiding the use of food additives** as much as possible, especially in foods for infants and children.

66. **HELAL 2005: (*) (Lab) (Extra) Effect of Food Preservative and Food Coloring Agent on Some Physiological and Hematological Parameters in Albino Rats and the Protective Role of Garlic.** *The Egyptian Journal of Hospital Medicine.* (18): 116-123.

a. This study is similar to the Helal (2001) study except that garlic was given to the third group instead of selenium as an antioxidant. Garlic itself contains selenium.

b. The rats receiving nitrite/Yellow 6 had a decrease in body weight, as well as decreased red blood and white blood cell counts and other effects as reported in the 2001 study, while those also receiving garlic were spared these problems so that their group was no different from the controls.

c. Helal **recommends adding garlic to the diet** to protect against possible damage caused by a variety of food additives.

67. **HIMRI 2011: (*) (Lab) A 90-Day Oral Toxicity Study of Tartrazine, a Synthetic Food Dye, in Wistar Rats.** *International Journal of Pharmacy and Pharmaceutical Sciences.* 3(sup. 3): 159-169.

a. After ingestion, Tartrazine (Yellow 5) undergoes metabolic reduction by intestinal bacteria, producing sulfanilic acid and aminopyrazolone (which goes on to yield a second sulfanilic acid molecule).

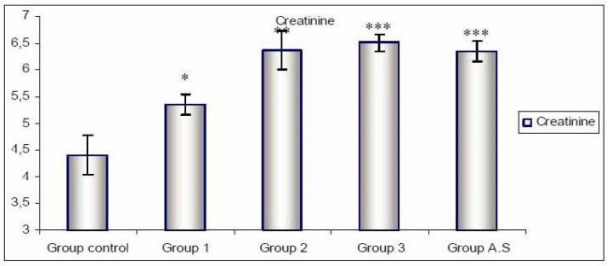


Fig. 6: Effect of Tartrazine on plasma Creatinine.

b. For 90 days, five groups of rats were treated daily by gavage with:

- no dye (control)
- 5 mg/kg Tartrazine (the ADI in the US)
- 7.5 mg/kg Tartrazine (the ADI in Japan)
- 10 mg/kg Tartrazine
- 3.5 mg/kg sulfanilic acid – the metabolite of Tartrazine.

c. All the treated rats showed significant changes from controls in a number of parameters, including:

- Increased echinocytes (red blood cells with abnormal membrane; burr cells)
- Increased glucose
- Increased creatinine (kidney damage)
- Increased cholesterol
- Increased triglycerides

d. Himri says people should be made aware of the "**hazardous effects of consuming Tartrazine.**"

68. **HONMA 2015: (*) (Lab) Evaluation of the *in vivo* Genotoxicity of Allura Red AC (Food Red No. 40).** *Food and Chemical Toxicology.* 84: 270-275.

a. Although large doses of Red 40 were given to the mice, there was no evidence of *in vivo* genotoxicity.

b. **Note:** *The dyes were given only twice, and colon tissue -- which had indicated DNA damage in Tsuda (2001) -- was not examined.*

c. **Note:** *I notice that some of the tests were conducted by the Safety Research Institute for Chemical Compounds – a company supporting drug development. This was not listed as a conflict of interest, however.*

69.

70. **HUANG 1998: (*) (Case) (Allergy) Study of Skin Rashes after Antibiotic Use in Young Children.** *Clinical Pediatrics.* 37: 601-608.

a. 86 children were referred to an allergy clinic because they got a rash after having received antibiotics for a bacterial upper respiratory infection, ear infection, etc. None of them had a history of systemic reactions or food allergy.

b. When given the same antibiotic at a time they were not sick, none of them got a rash. The next time they were sick, most of them chose to use the same antibiotic as before but in a dye-free suspension, and only 8 of them had any rash -- and it was mild and "managed successfully."

c. The authors concluded that a rash does not necessarily mean the antibiotic itself is at fault, and the **same medication can often be used in a dye-free form.**

d. A transient glutathione deficiency during infection was discussed as a possible reason for the reaction to the dye during illness. Although 61% of the 28 patients screened for this had levels two standard deviations below adult levels, a problem with diagnosis is that (in 1998) there was no official "normal value" of glutathione for children.

e. **Note:** *Would children who are sick be more likely to have a reaction to food dyes in a food they might be eating, which would not have bothered them when they were well? I have found no research on this question.*

71. **IBERO 1982: (*) (Case) (Allergy) Dyes, Preservatives and Salicylates in the Induction of Food Intolerance and/or Hypersensitivity in Children.** *Allergol Immunopathol*. 10(4): 263-268. *(abstract only)*

a. After unsuccessfully giving all the standard diagnostic allergy tests to 25 patients, the authors put them on a diet excluding dyes, preservatives and salicylates for 48 hours and then gave them oral provocation tests.

b. Approximately **58%** of them tested positive for dyes, **34%** of them for benzoates and **8%** of them for acetyl-salicylic acid. **32%** of them had crossed intolerance, which the author said was a low incidence.

c. The authors suggest that their results – which are different from other studies – may be related to the age of the patients (1 ½ to 12 years old) or the different regional diets.

d. **Note:** *Apparently, these were patients who had not already been put on suppressive medication, so they weren't being tested while on the medications, as other studies (with low results) do.*

72. **IBRAHIM 2008: (*) (Lab) (Extra) The Role of Ginger or Green Tea in Counteracting the Deleterious Effects of Benzene Sulfonic Acid in Weanling Male Rats.** *Egyptian Journal of Natural Toxins.* 5(1, 2): 56-99.

a. Upon exposure to sunlight or high temperature, the ascorbic acid or citric acid with Sunset Yellow (Yellow 6) in bottled beverages degrades to a benzene sulfonic acid sodium salt (BSA) and ammonia.

b. Rats treated with BSA had tissue damage in the liver, including hepatocytes with abnormal nuclei, dilated portal veins, inflammatory cells, swollen hepatocytes with edematous vacuolated cytoplasm, etc. Those given BSA with ginger or green tea, however, had "limited lesions" and their hepatocytes had a more normal appearance.

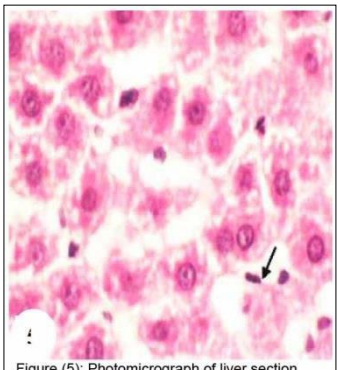


Figure (5): Photomicrograph of liver section from a rat treated with BSA showing swollen hepatocytes with vacuolated cytoplasm and distinct Kupffer cells (arrow)

c. Ibrahim recommends that "**synthetic coloring agents and food additives should be excluded from foods which may be consumed by young children**." However, he also suggests that antioxidant consumption (such as green tea or ginger) could prevent damage for people who can't help consuming items with food coloring.

73. **INOMATA 2006: (*) (Case) Multiple Chemical Sensitivities Following Intolerance to Azo Dye in Sweets in a 5-Year-Old Girl.** *Allergology International.* 55(2): 203-5.

a. This is a case report about a 5-year-old girl in Japan with multiple recurrent problems: Urticaria *(hives)*, angioedema *(swelling)*, headaches, dyspnea *(shortness of breath)*, loss of consciousness, and abdominal pain. Her symptoms were made worse by antihistamines and corticosteroids.

b. Her diet diary revealed that symptoms occurred after eating colorful sweets such as candies and jellybeans..... but skin prick allergy tests were negative for everything.

c. Because all the allergy tests were negative, but the challenge tests (exposures) were positive for coloring, aspirin and acetaminophen (Tylenol), she was diagnosed with intolerance to dyes and NSAID medications.

d. After avoiding the dyes, aspirin and Tylenol, she still had reactions to fragrances and chemical odors, so she was diagnosed further with severe multiple chemical sensitivity (MCS).

e. Inomata concluded that these results "suggest that in pediatric MCS, food and drug additives containing azo dyes might play important roles as elicitors."

f. **Note:** *Members of the Feingold Association will recognize this child. Her reaction to fragrances is not "severe MCS" separate from her reaction to jelly beans, but the normal reaction of a child sensitive to the abnormal petrochemicals throughout our modern environment. Both the azo dyes and most fragrances are made from petroleum. Since the girl also reacted to aspirin, she probably would do best on the Stage One (low-salicylate) Feingold Diet.*

74. **ISHIHARA 1979: (*) (Lab) (Allergy) Experimental Investigation on the Pathogenesis of Tartrazine-Induced Asthma.** *Tohoku J. of Experimental Medicine.* 129(3): 303-9.

a. In this study on guinea pigs, the researchers showed that Yellow 5 potentiates asthmatic reactions to other bronchoconstrictors. In other words, the dye may not cause an asthma attack all by itself, but if any other asthma-related allergen is around, ***the dye will make the reaction to it worse***.

b. Ishihara postulates that this effect might be from a change in cell membrane permeability to Ca++ in the guinea pig tracheal smooth muscle cells.

75. **ISMAIL 2003: (*) (Lab) Microscopic Studies of the Effect of Some Food Additives on the Kidney of Albino Rat.** *The Egyptian Journal of Hospital Medicine.* 12: 12-27.

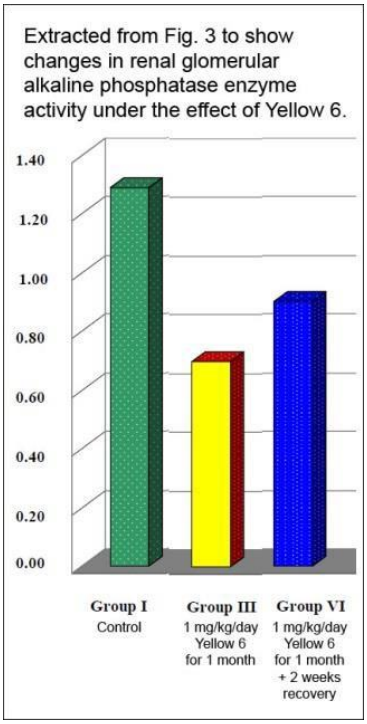
a. Most studies on food dyes use a lot, often 1% – 5% of the diet. This study evaluated effects of a much lower level of sodium nitrate and Yellow 6 on the kidneys of albino rats.

b. Rats were given 1 mg/kg/day of sodium nitrate or Yellow 6 (or both) for a month.

c. Another 3 groups were given the same items plus a 2-week recovery time with no treatment before examination.

d. Of interest here would be Groups 3 and 6 which were treated only with the dye. The picture at right was extracted from Figure 1 to show those groups.

e. Alkaline phosphatase enzyme activity was significantly decreased. There was cellular infiltration and an increase in the inflammatory response leading to glomerulonephritis and interstitial nephritis.



76. **JIMENEZ-ARANDA 1996: (*) (Study) (Allergy) Prevalence of Chronic Urticaria Following the Ingestion of Food Additives in a Third Tier Hospital.** *Revista Alergia Mexico.* 43(6):156. *(abstract only – article in Spanish)*

a. 40 patients with chronic urticaria, and 4 controls, were orally challenged with a variety of food additives.

b. Yellow 5 caused the most reactivity.

77. **JO 2013: (*) (Case) (Extra) Profound Hypotension After an Intradermal Injection of Indigo Carmine for Sentinel Node Mapping.** *Journal of Breast Cancer.* 16(1): 127-128.

a. Indigo carmine (Blue 2) is routinely used for intradermal injections during breast surgery, and is considered safe.

b. Two patients, however, had serious loss of blood pressure after this treatment, so the author wants to warn doctors to be aware that it can happen even with an intradermal injection, and to be prepared.

78. **JOSHI 2017: (*) (Lab) Developmental Toxicity Assay for Food Additive Tartrazine Using Zebrafish (Danio rerio) Embryo Cultures.** *International Journal of Toxicology.* 37(1):38-44

a. A concentration of up to 10 mM of Yellow 5 in their water was not lethal to zebrafish embryos nor did it induce any noticeable deformities.

b. Higher doses produced lots of deformities and death.


Zebrafish larvae are often used in cancer research

79. **JOSHI 2018: (*) (Lab) Food Colorant Sunset Yellow (E110) Intervenes Developmental Profile of Zebrafish (*Danio rerio*).** *Journal of Applied Toxicology.* Nov. 13, 2018 epub ahead of print.

a. In a series of experiments, the food dye had no noticeable effects at 0.1 mM (the lowest exposure tested), but at the 1-5 mM range effects were apparent.

b. Exposure of zebrafish embryos to Yellow 6 causes pericardial edema, indicating interference in the water permeability barrier. The embryos also suffered decreased heart rate, and cell death in the cardiac region, as well as spinal curvature..

c. This study confirms that Yellow 6 has developmental toxicity in zebrafish embryos and the author **cautions against its frequent consumption by pregnant women.**

80. **JUHLIN 1981: (*) (Study) (Allergy) Recurrent Urticaria: Clinical Investigation of 330 Patients.** *British Journal of Dermatology.* 104, 369.

a. 330 patients with urticaria were put on a salicylate-free, dye-free diet for at least 4 or 5 days before testing with food additives including Yellow 5 and Yellow 6. Antihistamines were not given.

b. Provocation tests with several additives had positive results in one-third of the patients.

c. Doses of azo dye were only 0.1 mg, 1 mg and 10 mg, but in spite of the small amounts used, there were 18 positive **(10%)** and 14 uncertain **(7.8%)** results out of 179 patients tested (see Table 12)

81. **KALINKE 1999: (*) (Case) Purpura Pigmentosa Progressiva in Type III Cryoglobulinemia and Tartrazine Intolerance. A Follow-up Over 20 Years.** *Hautarzt.* 50(1): 45-51 *(abstract only – article in German)*

a. A case is described in which Yellow 5 had been triggering flares of purpura in a patient with IgG-IgM cryoglobulinemia for 20 years.

82. **KASHANIAN 2011: (*) (Lab) DNA Binding Studies of Tartrazine Food Additive.** *DNA Cell Biology.* 30(7):499-505.

a. Tartrazine (Yellow 5) interaction with calf thymus DNA was studied. The dye induced oxidative stress and DNA damage, and Kashanian said it "has a toxic potential to CT-DNA *in vitro* and it seems that it binds directly to DNA."

b. Quote: "Combining our result and that of other researchers, we conclude that more attention should be paid to **prevent our children from eating or drinking large amounts of food containing this colorant**."

83. **KAUR 2010: (*) (Lab) Evaluation of Mutagenic Potential of Food Dye (Apple Green).** *Indian Journal of Science and Technology.* 3(12): 1208-1209.

a. Apple Green is a blend of sodium chloride, Yellow 5, and Blue 1.

b. The dye caused a dose dependent increase in the salmonella colonies per plate; it was "moderately mutagenic" and responsible for "base pair substitution type of mutations."

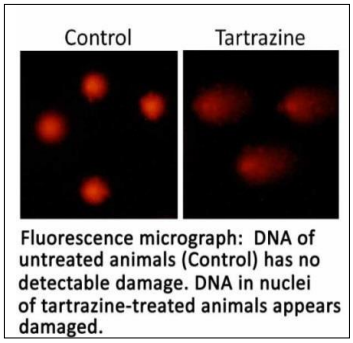
c. While this mutagenic potential was not significantly high, it indicated that prolonged consumption "can **pose a potential risk to human health**."

84. **KHAYYAT 2017: (*) (Lab) Tartrazine Induces Structural and Functional Aberrations and Genotoxic Effects *in vivo.*** *PeerJ.* 2017 Feb 23;5:e3041

a. This is a study on rats given Yellow 5 in their water in the amount of 7.5 mg/kg, which is the EU acceptable daily intake level (in the US, the ADI is 5.0 mg/kg).

b. The group of rats receiving dye had increased levels of a number of liver and kidney markers, as well as decreased antioxidants.

c. The kidney and liver tissues as well as white blood cells of the rats receiving dye were damaged.



Fluorescence micrograph: DNA of untreated animals (Control) has no detectable damage. DNA in nuclei of tartrazine-treated animals appears damaged.

85. **KHAYYAT 2018: (*) (Lab) Sunset Yellow and Allura Red Modulate Bcl2 and COX2 Expression Levels and Confer Oxidative Stress-Mediated Renal and Hepatic Toxicity in Male Rats.** *PeerJ.* Sep. 28, 6: e5689.

a. 3 groups of rats were orally given water (control), 2.5 mg/kg Yellow 6 or 7 mg/kg Red 40 (the Japanese ADI levels) for 4 weeks. Both were toxic to the liver and kidney of rats.

- Liver and kidney function were damaged.
- MDA (a marker of oxidative stress) increased
- Antioxidant levels decreased.
- Both dyes down-regulated Bcl2 and up-regulated COX2 expression.

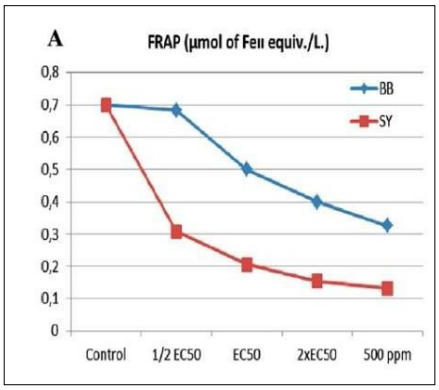
86. **KLUWE 1983: (FDA) (Study) (Extra) Encephalopathy in Rats and Nephropathy in Rats and Mice after Subchronic Oral Exposure to Benzaldehyde**. *Food and Chemical Toxicology,* 21(3): 245-250.

    a. Benzaldehyde is used in the preparation of dyes, perfumes, flavorings, and pharmaceuticals.

    b. This study was an effort to determine the upper level rats and mice can consume benzaldehyde without it killing them.

87. **KOBYLEWSKI 2012**: (*) (Review) Toxicology of food dyes. *International Journal of Occupational and Environmental Health.* 18(3): 220-246. ***(see Page 42, #105)***

88. **KOÇ 2017: (*) (Lab) All Aspect of Toxic Effect of Brilliant Blue and Sunset Yellow in *Allium cepa* Roots.** *Cytotechnology.* 70(1): 449-463.



    a. Blue 1 and Yellow 6 were tested for toxicity to the growing root cells of onions.

    b. ALL concentrations of both dyes inhibited root growth.

    c. EC50 values were determined by an *inhibition test* (i.e., growing roots for 3 days with different dilutions of dye to determine which levels inhibited growth by 50%). The EC50 were determined as 50 ppm (Yellow 6) and 200 ppm (Blue 1). After that, a number of tests were performed using the EC50, half the EC50 and twice the EC50 for each color.

89. **KOUTSOGEORGOPOULOU 1998: (*) (Lab) Immunological Aspects of the Common Food Colorants, Amaranth and Tartrazine.** *Veterinary and Human Toxicology.* 40(1): 1-4. *(abstract only)*

    a. Authors describe a reproducible method using human peripheral blood lymphocytes to determine cytotoxic and immunosuppressive effects of food dyes.

    b. They tested it on Red 2 and Yellow 5, showing "**clear immunosuppressive effects**."

90. **KUMAR 2011: (*) (Lab) Genotoxic Effects of Two Commonly Used Food Additives of Boric Acid and Sunset Yellow in Root Meristems of Trigonella Foenum-Graecum.** *Iranian Journal of Environmental Health Science & Engineering.* 8(4): 361-366. ***(see Page 43, #108)***

91. **LI 2018: (*) (Lab) (Medical) Erythrosin B is a Potent and Broad-Spectrum Orthosteric Inhibitor of the Flavivirus NS2B-NS3 Protease.** *Antiviral Research.* 150: 217-225.

a. Red 3 has been identified as a potent inhibitor for flavivirus protease – this makes it a promising medication to treat Zika Fever, Dengue Fever, and several other nasty diseases that currently don't have good treatments.

b. Red 3 inhibited the Dengue virus type 2 (DENV2) protease non-competitively.

c. Red 3 can significantly reduce titers of several flaviviruses, including the DENV2 *(Dengue Fever),* ZIKV *(Zika Virus)*, YFV *(Yellow Fever)*, JEV *(Japanese Encephalitis Virus)*, and WNV *(West Nile Virus).* The authors say the Red 3 did its work with "micromolar potency and with excellent cytoxicity profile." They say the Red 3 should be safe enough even to give to pregnant women.

d. **Note:** *This paper is quite technical but their excitement at finding a treatment right "under their nose" that promises to be safe, cheap and effective is palpable.*

92. **LINDEMAYR 1979: (*) (Study) (Allergy) Intolerance to Acetyl Salicylic Acid and Food Additives in Patients Suffering from Recurrent Urticaria.** *Wien Klin Wochenschr.* 91(24): 817-22. *(abstract only – article in German)*

a. 26 patients in whom acetyl salicylic acid provoked urticaria and 18 in whom it did not were tested with various food additives. Six of them reacted to Tartrazine (Yellow 5) and three to indigo carmine (Blue 2).

b. With a diet avoiding salicylates, benzoates, and food dyes, **20%** of the patients recovered completely and a further **55%** showed marked improvement.

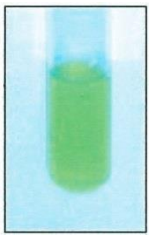
93. **LOCKEY 1975: (*) (Case) Reactions to Hidden Agents in Foods and Drugs Can Be Serious.** *Annals of Allergy.* 35(4): 239-242. *(abstract only)*

a. Lockey presents three case reports in which medications used to treat allergy contained additives that themselves produced allergic or toxic reactions and cross-reacted with aspirin, etc.

94. **LOCKEY 1977: (*) (Lab) Hypersensitivity to Tartrazine (FD&C Yellow No. 5) and Other Dyes and Additives Present in Foods and Pharmaceutical Products.** *Annals of Allergy.* 38(3): 206-210. *(abstract only)*

a. Lockey describes a battery of tests he had developed for determining relevance of food dyes to urticaria and asthma symptoms.

95. **LUCARELLI 2004: (*) (Case) Toxicity of Food Drug and Cosmetic Blue No. 1 Dye in Critically Ill Patients.** *Chest.* 125(2): 793-795.



a. Two cases of patients who died of refractory shock and metabolic acidosis caused by the Blue 1 in their tube feedings are discussed.

b. Blue 1 toxicity is discussed, and the authors question the routine use of it in enteral feedings, suggesting some alternative approaches to gastric aspiration detection.

96. **LUCOVA 2013: (*) (Lab) Absorption of Triphenylmethane Dyes Brilliant Blue and Patent Blue Through Intact Skin, Shaven Skin and Lingual Mucosa from Daily Life Products.** *Food and Chemical Toxicology.* 52: 19-27. ***(see Page 49, #123)***

97. **LV 2017: (*) (Lab) (Extra) A Novel Preparation Method of Two Polymer Dyes with Low Cytotoxicity.** *Materials.* 10(219): 1-11. ***(see Page 49, #124)***

98. **MAGERL 2010: (*) (Study) (Allergy) Effects of a Pseudoallergen-Free Diet on Chronic Spontaneous Urticaria: A Prospective Trial.** *Allergy.* 65: 78-83.

a. Subjects who had not responded adequately to the usual treatments for urticaria were put on a "pseudoallergen-free diet" for 3 weeks, excluding artificial preservatives and dyes.

b. The diet benefited one third of 140 patients. 9 others were able to reduce medication while on the diet without getting worse.

c. Since it was found that many patients could later eat normally, Magerl says the diet actually *cured* their urticaria rather than simply suppressing symptoms.

99. **MAHMOUD 2006: (*) (Lab) Toxic Effects of the Synthetic Food Dye Brilliant Blue on Liver, Kidney and Testes Functions in Rats.** *J. Egypt. Soc. Toxicology.* Vol. 34: 77-84.

a. Rats were fed Brilliant Blue (Blue 1) in their diet for 15, 30, and 45 days.

b. In general, the dye caused an increase of ALT, AST, ALP, bilirubin, urea and creatinine, and a decrease in serum acid phosphatase activity and testosterone. The testes were abnormal and most of the sperm appeared to be dead.

c. The effects on liver, kidney and testes were dose-dependent.

100. **MALONEY 2000: (*) (Case) Systemic Absorption of Food Dye in Patients with Sepsis.** *New England Journal of Medicine.* 343(14):1047-1048.

a. During sepsis, gastrointestinal permeability increases and substances not expected to be absorbable may be absorbed. Maloney reports two deaths associated with the systemic absorption of the dye Blue 1 used in enteral (*tube*) feedings.

b. Although both patients had been very ill, they were improving before they received the dye and turned color – and then died from refractory hypotension and metabolic acidosis, which are "known biochemical effects of this dye."

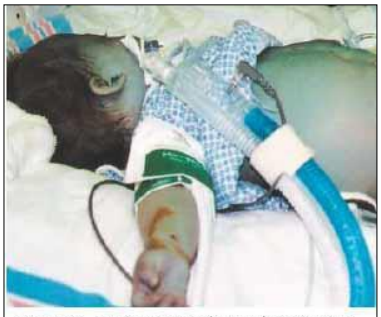


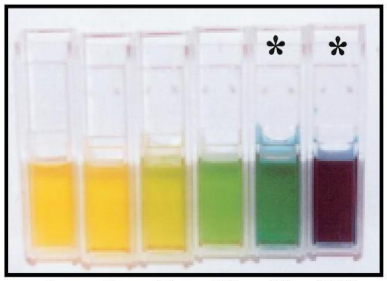
Figure 1. Blue discoloration of the skin in a 12-month-old boy who had received enteral feedings tinted with FD&C Blue Dye No. 1

101. **MALONEY 2002: (*) (Case) Food Dye Use in Enteral Feedings: A Review and a Call for a Moratorium.** *Enteral Food Dye.* 17(3): 169-181

a. Maloney wrote that Blue 1 was popular in spite of evidence that it is only 15% sensitive for detection of aspiration in enteral feeding (which is what it is used for) -- and in spite of deaths attributed to it.

b. According to a survey in 1999, 86% of intensive care nurses and 91% of dietitians in the ICU routinely used it for tube-fed patients. How much? As much as they wanted; there were no rules.

c. Blue 1 is supposed to be non-absorbable through the gut, but that was never tested in sick people. Its mitochondrial toxicity had also not been well publicized.



From Fig. 6. Appearance of increasing Blue 1 in human serum. Those marked with an asterisk will inhibit mitochondrial respiration. So a patient with blue serum is more likely to have dye-related toxicity than a patient whose serum is only green.

d. Maloney called for this method to be abandoned and replaced by better methods of preventing aspiration in enteral feeding.

e. The following conditions are known to have increased gut permeability:

- Sepsis
- Severe burns
- Trauma
- Hemorrhagic shock
- Cardiac bypass
- Major vascular surgery
- Abdominal aortic aneurysm repair
- NSAIDs use (e.g., aspirin, Tylenol (**Note:** *Aleve is blue!*)
- Renal failure
- Celiac sprue
- Inflammatory bowel disease
- Cystic fibrosis

f. **Note:** *Due to the efforts of Maloney and others to bring attention to this problem, in 2003 the FDA sent a Public Health Advisory to doctors to stop using the Blue 1 in enteral feedings. Might it also be a kindness to inform people with any of the above disorders not to eat or drink much in the way of blue colored items?*

102. **MASONE 2015: (*) (Lab) Study on the Interaction of Artificial and Natural Food Colorants with Human Serum Albumin: A Computational Point of View.** *Computational Biology and Chemistry*. 56(2015): 152-158. ***(see Page 50, #128)***

103. **MEHEDI 2009: (*) (Lab) Reproductive Toxicology of Tartrazine (FD and C Yellow No. 5) in Swiss Albino Mice.** *American Journal of Pharmacology and Toxicology.* 4(4): 128-133.

a. Male mice were given 0.1%, 1% and 2.5% of Yellow 5 in drinking water for 13 weeks. **Note:** *This is actually lower than many studies on rats or mice.*

b. Sperm count was decreased and sperm abnormalities increased in the high dose group. Sperm motility and testes changes were observed in both the middle and high groups.

c. Authors concluded **excessive Yellow 5 consumption can have adverse effects on the male reproductive system**.

104. **MEHEDI 2013: (*) (Lab) A Thirteen Week *ad libitum* Administration Toxicity Study of Tartrazine in Swiss Mice.** *African Journal of Biotechnology.* 12(28): 4519-4529.

a. Mice were given Yellow 5 in their drinking water at various "subchronic" doses for 13 weeks.

b. The more dye in the water, the more water the mice drank – it seemed to the authors that the dye stimulated consumption. On the other hand, their blood changes indicated the mice were dehydrated.

c. There were several other changes observed, indicating that the dye affected the bone marrow, and that excessive intake may cause **liver, brain, and kidney damage**.

105. **MEKKAWY 2000: (*) (Lab) Mutagenic Effects of the Food Colour Erythrosine in Rats.** *Problems of Forensic Sciences.* Vol. XLIII. 184-191.

a. Red 3 induced several chromosomal aberrations.

b. The lower dose increased the mitotic index (*number of dividing cells/1000*) but the higher one inhibited it. There was a dose-dependent increase in protein in the liver and brain, similar to that found by others using insecticide or chloramphenicol in rats.

106. **MEYER 2017: (*) (Lab) Hepatic Effects of Tartrazine (E102) After Systemic Exposure are Independent of Oestrogen Receptor Interactions in the Mouse.** *Toxicology Letters.* 273: 55-68.

a. The ability of Yellow 5 to affect liver function may be related to its ability to inhibit bile acid sulfation and not be related to estrogen receptors.

b. In mice and rats, sulfation of bile acids is a minor metabolic route; therefore, an inhibition of such sulfation by Yellow 5 may be less toxic to mice than humans, so the histopathological effects observed in mice could underestimate the potential hepatic effects in man.

c. Also, because there are polymorphisms in human SULT2A1, some people may have increased sensitivity to this dye, as it may have more potential to alter bile homeostasis in some people.

107. **MICHEL 1984: (*) (Case) Decreased Sensitivity to Tartrazine After Aspirin Desensitization in an Asthmatic Patient Intolerant to Both Aspirin and Tartrazine.** *Annals of Allergy.* 52(5): 368-70 *(abstract only)*

a. A patient sensitive to both aspirin and Yellow 5 was desensitized to aspirin via daily doses. He was then observed to be less sensitive also to the dye.

108. **MIKKELSEN 1978: (*) (Study) Hypersensitivity Reactions to Food Colours with Special Reference to the Natural Colour Annatto Extract (butter colour).** *Archives of Toxicology.* (1): 141-143.

a. Testing both natural and artificial food coloring on 61 patients, the authors found the following:

- 26% reacted to Annatto
- 17% reacted to Sunset Yellow (Yellow 6)
- 9% reacted to Amaranth (Red 2)
- 12% reacted to Erythrosine (Red 3)
- 11% reacted to Tartrazine (Yellow 5)
- 16% reacted to Food Red (Red 40)
- 15% reacted to Ponceau
- 14% reacted to Brilliant Blue (Blue 1)

b. The authors said natural colors may induce hypersensitivity reactions as often as synthetic ones.

109. **MIZUTANI 2009: (*) (Review) Toxicity of Xanthene Food Dyes by Inhibition of Human Drug-Metabolizing Enzymes in a Noncompetitive Manner.** *Journal of Environmental and Public Health.* Vol. 2009, 953952.

a. Mizutani reviewed several food dyes, including Red 2, Red 3, Red 40, Yellow 5, Yellow 6, Blue 1, and Blue 2.

b. Chemical pathways are described by which the red dyes inhibit glucuronidation, and denature drug-metabolizing enzymes in human microsomes.

110. **MONERET-VAUTRIN 1979: (*) (Lab) (Allergy) Induction of Reaginic Hypersensitivity to Tartrazine in the Rabbit Immunization by Ingestion of the Covalent Conjugate Tartrazine-Human Serum Albumin.** *Annales d'Immunologie* 130C(3): 419-430. *(abstract only – article in French)*

a. Sensitizing with small molecular items acting as haptens was (then) still a new field of science. Feingold had written about it in his textbook, so if you need a refresher, those pages are here

b. Attempts were made to sensitize rabbits by giving them either tartrazine alone, or with adjuvant, or with human serum albumin (HSA), or conjugated with the HSA. It didn't work, but then they did succeed in sensitizing the rabbits using covalent conjugate tartrazine-HSA mixed with adjuvant. It worked even better when they first irritated the rabbit's intestinal mucous membrane with acetylsalicylic acid.

111. **MOUTINHO 2007: (*) (Lab) (Allergy) Prolonged Use of the Food Dye Tartrazine (FD&C Yellow No. 5) and its Effects on the Gastric Mucosa of Wistar Rats.** *Brazilian Journal of Biology.* 67(1):141-5.

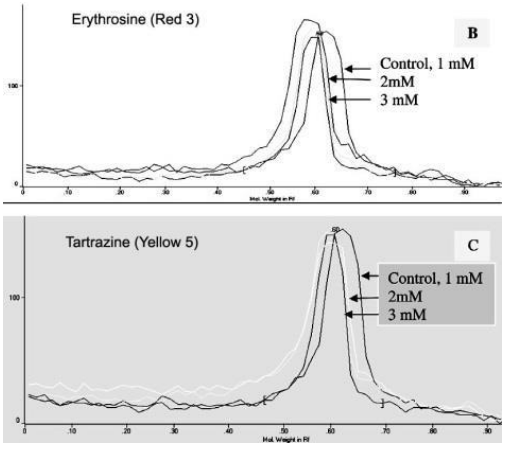
a. Yellow 5 is a nitrous derivative known to cause allergic reactions such as asthma and urticaria. It has also been the focus of studies on mutagenesis and carcinogenesis because it transforms into sulfanilic acid when metabolized by intestinal microflora.

b. Two groups of rats were given 7.5 mg/kg/day (the human ADI outside the US) in their water after weaning until they were 12 months old. There was a significant increase in the number of lymphocytes and eosinophils in the gastric mucosa, but no carcinogenetic changes.

112. **MPOUNTOUKAS 2010: (*) (Lab) Cytogenetic Evaluation and DNA Interaction Studies of the Food Colorants Amaranth, Erythrosine and Tartrazine.** *Food and Chemical Toxicology.* 48: 2934-2944.

a. This is an *in vitro* study of Amaranth (Red 2), Erythrosine (Red 3) and Tartrazine (Yellow 5).

b. Quote: "Results indicate that these food colorants had a toxic potential to human lymphocytes *in vitro* and it seems that they bind directly to DNA."



113. **NEUMAN 1978: (*) (Study) (Allergy) The Danger of "Yellow Dyes" (Tartrazine) to Allergic Subjects.** *Clinical Allergy.* 8(1): 65-8.

a. Neuman tested 50 mg of Tartrazine (Yellow 5) on 122 allergic and non-allergic patients. First, they were put on a one-week additive-free diet, and allergy medication was stopped for 24 hours. They were then given either the dye or sugar in identical capsules. Symptoms were evaluated before and after by blood tests, X-rays, pulmonary function tests, etc.

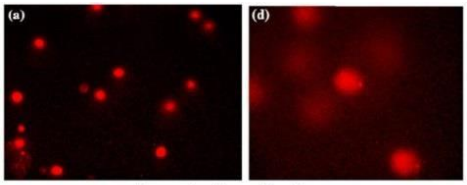
b. The researchers found that about **a third of the allergic patients were clinically affected by the dye**, and **26%** had positive reactions within 15 minutes. Symptoms included weakness, blurred vision, runny nose, palpitations, a "feeling of suffocation," itching, and/ or hives.

c. Another finding was that the patients' **immunoglobulins showed a drop in IgA and IgM** , and their **bleeding time increased**, although within normal limits.

d. **Note**: *Might Yellow 5 or any other food dye be a problem for hemophiliacs? Although MedLine lists 25,728 studies on hemophilia, not one paper comes up in a search for it in combination with Tartrazine, food dye, food color, etc.*

114. **PANDIR 2016: (*) (Lab) DNA Damage in Human Germ Cell Exposed to the Some Food Additives in Vitro.** *Cytotechnology.* 68: 725-733.

a. The food dyes Blue 1 and Yellow 6 were found to damage human sperm cells more, and at lower doses, than citric acid or benzoic acid.



Excerpted from Fig. 4.
DNA damaging activity of sunset yellow (Yellow 6) in isolated human sperm cells.
(a) control group. (d) 200 µg/mL dye

115. **PESTANA 2010: (*) (Study) Safety of Ingestion of Yellow Tartrazine by Double-Blind Placebo Controlled Challenge in 26 Atopic Adults.** *Allergologie et Immunopathologia (Madrid).* 38 (3): 142-6.

a. In this study, calling itself a "gold standard" design, 26 adults with atopy (skin or asthma allergy) were tested for Tartrazine (Yellow 5) sensitivity.

b. They were not on a dye-free diet except for the ***day of the challenge*** each week when they were given three "dye-free" meals and a "challenge" pill of 35 mg Yellow 5 – divided into three doses beginning an hour after the first meal.

c. They maintained their regular medication. **Note:** *Since 35 mg of Yellow 5 is well within the expected usual exposure per day, their medication could be reasonably expected to block any reaction.*

d. The authors concluded that in a group of allergic subjects, 35 mg of Tartrazine did not cause any symptoms compared to placebo.

e. **Note**: *A better conclusion for this study might be: "Adults carefully maintaining their allergy medications can safely include a small to moderate amount of Tartrazine in their usual diet."*

116. **POLLOCK 1989: (*) (Lab) Survey of Colourings and Preservatives in Drugs.** *British Medical Journal.* 299: 679-651.

a. The authors analyzed 2204 drug formulations supplied by UK drug manufacturers. 930 of the formulations contained at least one of 52 colorings or preservatives implicated in adverse reactions. Tartrazine was present in 124 of them.

b. Pollock says that data were not obtained on the actual amounts of particular additives in each drug, but that the data available suggests that some tablets contain up to 2.7 mg of Tartrazine. Pollock suggested labeling drugs with their additives so that people can avoid them if needed.

c. The authors provide a listing of some of drugs available (in the UK) without those dyes or preservatives that are implicated in adverse reactions.

d. **Note:** *Even with labeling, people would have trouble finding dye-free drugs unless there are also dye-free formulations of the needed drug available.*

117. **RAJAMANICKAM 2014: (*) (Lab) (Extra) Photocatalytic Mineralization of a Water Pollutant, Sunset Yellow Dye by an Advanced Oxidation Process Using a Modified Catalyst.** *Toxicological and Environmental Chemistry.* 95(9): 1484-1498.

a. Dyes in wastewater are “decolorized,” forming degradation products that may be more toxic than the original (but have no color).

b. The authors say that ZnS-TiO2 is a catalyst with high photocatalytic activity to degrade Yellow 6, and would be effective for water treatment plants.

c. **Note:** *The more dyes in the food, the more goes into the water treatment plants, perhaps?*

118. **RAWAT 2016: (*) (Review) (Extra) Detoxification of Azo Dyes in the Context of Environmental Processes.** *Chemosphere.* 155: 591-605.

a. This review discusses methods of dealing with the disposal of the 4 million tons of dyes per year which may create a serious ecological problem.

119. **REYES 1996: (*) (Lab) Effect of Organic Synthetic Food Colours on Mitochondrial Respiration.** *Food Additives and Contaminants.* 13(1): 5-11. ***(see Page 66, #170)***

120. **ROMAO 2018: (*) (Lab) (Medical) Effect of Combining Erythrosine with a High-Power Dental Curing Light Appliance on the Viability of a Planktonic Culture of *Streptococcus mutans.*** *Photomedicine and Laser Surgery.* Epub ahead of print.

    a. This is a study to evaluate Red 3 used as a photosensitizer with a high-intensity dental light source, comparing it to the effect of a chlorhexidine solution in killing Strep germs which are involved in tooth decay and tooth surface demineralization.

    b. The authors compared treatment with the dye + light, treatment with light alone, dye alone, neither (control), and chlorhexidine (positive control, a current treatment).

    c. Combined with the high-intensity light, Red 3 was as effective as 0.12% chlorhexidine, killing S. mutans in a short time.

121. **ROS 1976: (*) (Case) (Allergy) A Follow-Up Study of Patients with Recurrent Urticaria and Hypersensitivity to Aspirin, Benzoates and Azo Dyes.** *British Journal of Dermatology.* 95(1): 19-24.

    a. 75 patients with urticaria and angioedema for more than 4 months tested positive to aspirin, azo dyes and/or benzoates, with cross-reactions common. They were all put on a dye-free low-salicylate diet.

    b. On follow-up after 6 to 24 months, **24%** were free of symptoms and **57%** considered themselves "much better." **19%** were unchanged or "slightly better."

    c. Many of those who became symptom-free were able to go off the diet, while those were "much better" usually had to stay on it to prevent symptoms.

    d. The importance of proper labeling of foods and drugs to help such patients maintain their diet is discussed.

122. **RUDZKI 1980: (*) (Study) (Allergy) Detection of Urticaria with Food Additives Intolerance by Means of Diet.** *Dermatologica.* 161: 57-62.

    a. 158 patients with chronic urticaria were put on a diet free of salicylates, benzoates and azo dyes. If they improved, they were then allowed to eat as usual and see what happened. Then they repeated the diet.

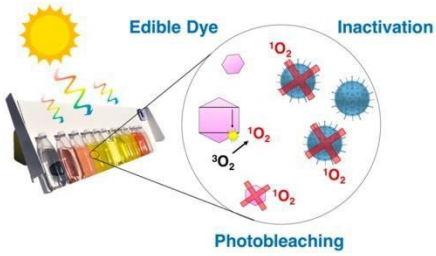
    b. 50 of them were successfully diagnosed as having urticaria triggered by the food additives; only 6 of them had previously suspected any sensitivity.

123. **RUS 2010: (*) (Lab) Comparative Toxicity of Food Dyes on Liver and Kidney in Guinea Pigs: A Histopathological Study.** *Annals of RSCB.* Vol. XV(1):161-165.

a. The authors fed guinea pigs Carmoisine or Tartrazine (Yellow 5) for three weeks and then examined their kidneys and liver.

b. In both, they observed edema, congestion, and a **variety of damages, directly proportional to the amount of dye given.**

124. **RYBERG 2018: (*) (Extra) (Medical) Edible Dye-Enhanced Solar Disinfection with Safety Indication.** *Environmental Science & Technology.* 52(22):13361-13369



a. Red 3 is being considered for water purification use in rural areas of developing countries – it kills viruses by acting as a photosensitizer, working with sunlight, and indicates when water is disinfected by losing its color.

b. **Note:** *This sounds very effective, but it also will involve increased consumption of the Red 3 in a decolorized state. Can one assume it to be safe just because it is an "edible food dye?"*

125. **SAFFORD 1984: (*) (Lab) (Allergy) The Effect of Tartrazine on Histamine Release from Rat Peritoneal Mast Cells.** *International Journal of Immunopharmacology.* 6(3): 233-240.

a. A specific IgE for Tartrazine (Yellow 5) was not found, so a pharmacological nature such as releasing histamine is suspected.

b. NSAIDs inhibit histamine release from rat mast cells, but increase it in humans. This paper describes an investigation of the effect of Tartrazine on histamine release in response to various releasing substances.

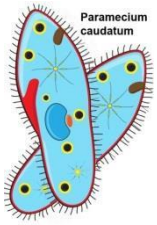
c. **Note:** *it is interesting that to make rats sensitive to egg albumin, the researchers gave a single pertussis vaccine injection plus some micrograms of egg albumin.*

126. **SAFFORD 1985: (*) (Lab) (Allergy) Immunological Studies on Tartrazine and its Metabolites: I. Animal Studies.** *International Archives of Allergy and Applied Immunology.* 77(3):331-336.

a. Tartrazine conjugated to protein can induce antibodies in rabbits and Tartrazine-specific IgD can be found.

b. This study on guinea pigs attempted to discover details of the interaction with Tartrazine.

127. **SAKO 1977: (*) (Lab) Effects of Food Dyes on Paramecium caudatum: Toxicity and Inhibitory Effects on Leucine Aminopeptidase and Acid Phosphatase Activity.** *Toxicology and Applied Pharmacology.* 39: 111-117.



a. 14 food dyes were studied. Xanthene dyes were the most toxic.

b. Instead of rats or other animals, Paramecium caudatum was used.

128. **SALTMARSH 2014: (*) (Review) Recent Trends in the Use of Food Additives in the United Kingdom.** *Journal of the Science of Food and Agriculture.* 95(4): 649-652.

a. This is a review of the history of the E-numbers and how they are used today.

b. The food colors involved in the Southampton study have already mostly been replaced by natural colorings in Europe.

129. **SARHAN 2014: (*) (Lab) (Extra) Biochemical and Molecular Studies on the Possible Influence of the *Brassica oleracea* and *Beta vulgaris* Extracts to Mitigate the Effect of Food Preservatives and Food Chemical Colorants on Albino Rats.** *Saudi Journal of Biological Sciences.* 21: 342-354.

a. Yellow 5 is toxic to rats, causing injury to kidneys, liver and brain, as well as increasing cholesterol, etc.

b. Plants contain hundreds of compounds that act as natural antioxidants. Sarhan tested broccoli and beet extracts on rats given Yellow 6 alone and with Sodium Nitrite. Both the beet and broccoli extracts protected the rats from injury.

130. **SASAKI 2002: (*) (Lab) The Comet Assay with 8 Mouse Organs: Results with 39 Currently Used Food Additives.** *Mutation Research.* 519: 103-119

a. Various organs were studied after a one-time oral administration of a dose of a food additives. Of all the additives tested, dyes were the most genotoxic. Red 2, Red 40, Yellow 5, Red 3, and three other dyes not used in the US induced dose-related DNA damage in the glandular stomach, colon, and/or bladder.

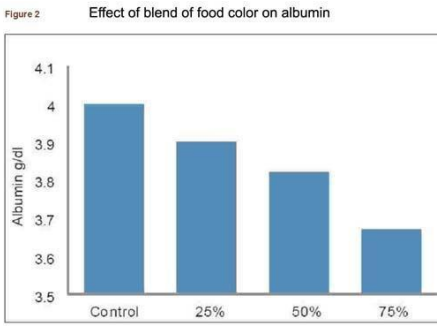
b. All 7 dyes induced DNA damage in the gastrointestinal organs at a low dose (10 mg/kg or 100 mg/kg), with Red 2, Red 40 and Yellow 5 inducing DNA damage in the colon at close to their acceptable daily intakes (ADI).

131. **SAXENA 2014: (*) (Lab) Serological Changes Induced by Blend of Sunset Yellow, Metanil Yellow and Tartrazine in Swiss Albino Rat, *Rattus Norvegicus.*** *Toxicology International.* 21(1):65-68.

a. Giving rats a blend of colors (by gavage) was more toxic than giving them each dye individually.

b. Their total protein and albumin decreased, while alkaline phosphatase, SGPT and total bilirubin increased.

c. The authors concluded that **prolonged consumption of such dyes may adversely affect human health**.



132. **SAXENA 2015: (*) (Lab) Food Color Induced Hepatotoxicity in Swiss Albino Rats, *Rattus norvegicus.*** *Toxicology International.* 22(1): 152-157.

a. This study was done to see if the food colors Tartrazine (Yellow 5), Metanil Yellow (*a non-permitted color but often used illegally*) and Sunset Yellow (Yellow 6) play a part in liver disease.

b. Four groups of 6 rats were fed no dyes (the control) or a mix of the three colors at 25 mg/kg, 50 mg/kg or 75 mg/kg for a month. Several tests were then done to see if their livers had been damaged. They were.

c. Not only did the tests show liver damage, but this damage included dead liver cells, vacuolation (*liquid-filled holes or blisters in the cells*), and a "drastic alteration" in the antioxidant defense system.

133. **SETTIPANE 1975: (*) (Study) (Allergy) Aspirin Intolerance. III. Subtypes, Familial Occurrence, and Cross-Reactivity with Tartrazine.** *Journal of Allergy and Clinical Immunology.* 56(3): 215-21.

a. This was a double-blind study to determine how often a cross-reaction between aspirin and Tartrazine (Yellow 5) sensitivity happens. They found that **15%** of 40 aspirin-intolerant subjects reacted to Tartrazine, while none of the controls did. Symptoms produced by Tartrazine were similar to those produced by aspirin, although their molecular structures are quite different.

b. **Note**: *Using 1971 information, Settipane had estimated the "maximum ingested dose per capita" of Yellow 5 at **16.3 mg** per day. Nevertheless, in this study only **0.22 to 0.44 mg** was used. In other words, they used less than **1/40th** the amount they thought may be actually encountered by real people.*

134. **SETTIPANE 1976: (*) (Study) (Allergy) Significance of Tartrazine Sensitivity in Chronic Urticaria of Unknown Etiology.** *Journal of Allergy and Clinical Immunology.* 57(6): 541-6.

a. 38 patients with chronic urticaria of unknown origin were put on a dye-free diet. Ten were known to be sensitive to aspirin, but avoiding aspirin compounds had not helped them.

b. Only 4 were taking cortisone and none were on steroids during this study.

c. 13 of the patients **(34%)** improved on the diet without food dyes. They were challenged orally in double-blind fashion with 0.22 mg Tartrazine (Yellow 5) – again, a *very tiny amount* –and 3 of them got worse within three hours.

135. **SIMON 2003: (*) (Review) Adverse Reactions to Food Additives.** *Clinical Allergy and Asthma Reports.* 3(1): 62-66.

a. Simon complained that most of the studies showing that people with asthma or urticaria are affected by food dyes are "characterized by poorly controlled challenge procedures."

b. He cited several studies he felt were well done – all had the patients continue their medications as they were tested with a very small amount of a dye.

c. **Note:** *Unsurprisingly, all these studies concluded that dye is not a problem.*

d. Simon said, "Recent studies … imply that sensitivity to food additives in patients with chronic urticaria/angioedema is very uncommon."

e. **Note:** *Translated, this means that for most people 0.22 mg of Yellow 5 is not enough to overcome their medications.*

f. **Note:** *Compare the amounts of Yellow 5 used in research*

- *Nutrition Foundation ……..* ***7.27*** *mg*
- *National Research Council….* ***12*** *mg -- low eaters*
  …….. ***43*** *mg -- top 99%*
- *Settipane, Simon, etc.……..* ***0.22*** *mg*

136. **STEFANIDOU 2003: (*) (Lab) Controversies in Toxicology: Assessing Food Additive Toxicity Using a Cell Model.** *Veterinary and Human Toxicology.* 45(2): 103-105. ***(see Page 79, #202)***

137. **STENIUS 1976: (*) (Study) (Allergy) Hypersensitivity to Acetylsalicylic Acid (ASA) and Tartrazine in Patients with Asthma.** *Clinical Allergy.* 6(2): 119-29.

a. Patients were put on a salicylate-free, dye-free diet for 48 hours before testing, but they continued taking their medications, so the dyes tested had to overcome the medication effect to be "positive."

b. Only 10 mg Yellow 5 and 100 mg aspirin (a little more than a baby aspirin) were used as the test doses. Nevertheless, a significant number of patients reacted to them. Stenius recommended that tests for sensitivity to analgesics and food additives be a routine measure in asthmatics, and sensitive patients should be given information on suitable medication and dietary control.

c. **Note:** *Instead of limiting the test to 10 mg, why not just give them a nice piece of some cake like this one … more yummy and lots more milligrams. (Green color is a mix of Yellow 5 and Blue 1.) You may find more patients than expected react to it.*

d. Quote: *[on trying to design an additive-free diet for their patients]* "The best solution would obviously be to establish an international agreement on compulsory and complete declaration of contents, and a general restriction on the use of azo-dyes."

138. **STEVENSON 1992: (*) (Study) (Allergy) Pulmonary Reactions to Tartrazine.** *Pediatric Allergy and Immunology.* 3(4): 222-227.

a. Stevenson (of Scripps Clinic, US) reviewed numerous studies of asthma, and discussed the pros and cons of giving a dye challenge at the same time (or after) the patient takes his bronchodilator medication.

b. Over several decades, 194 aspirin-sensitive patients and more than 40 who were not sensitive to aspirin were tested for reactions to Tartrazine and – except for two – all were nonreactors. Generally, medications including theophylline and corticosteroids were continued during the testing, and patients were not first put on any additive-free or dye-free diet.

c. Quote: "It is likely that much, if not all of the available literature which reports tartrazine induced asthmatic reactions, in reality reported unstable airways, often in patients deprived of their morning bronchodilators."

139. **SWEENEY 1994: (*) (Lab) Evidence for Direct-Acting Oxidative Genotoxicity by Reduction Products of Azo Dyes.** *Environmental Health Perspectives.* Oct;102 Suppl 6:119-22.

a. Sweeney tested Yellow 6, Carmoisine and Red 2 for genotoxicity after bacterial reduction of the dyes. The Yellow 6 and Red 2 were both found to be genotoxic – inducing DNA damage in E. coli, and specifically through a mechanism involving oxygen radicals.

b. The authors conclude, "The identification of this type of DNA damage hitherto not detected by many conventional genotoxicity assays may have important **implications regarding the continued use of azo dyes in foodstuffs**."

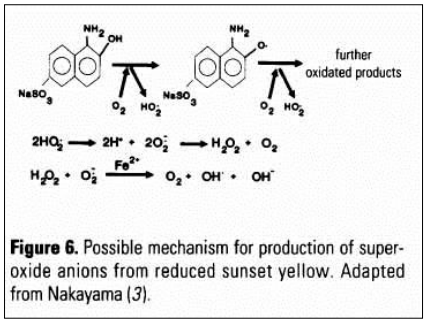


Figure 6. Possible mechanism for production of superoxide anions from reduced sunset yellow. Adapted from Nakayama (*3*).

140. **TATTERSALL 2016: (*) (Case) Fixed Drug Eruption Due to Achiote Dye.** *Case Reports in Dermatology.* 8: 14-18.

a. An immigrant child developed a reaction called a "fixed drug eruption" traced to the change in brand of achiote dye (annatto) her family used for making yellow rice – the new brand contained Yellow 5.

141. **TITOVA 2011: (*) (Lab) Use of the Granulocytic Myeloperoxidase Release Reaction to Diagnose Food Additive Allergies.** *Klinicheskaia Laboratornaia Diagnostika.* 3: 42-44. *(abstract only – article in Russian)*

a. Using a blood test called the granulocytic myeloperoxidase release reaction, 83 patients with suspected food additive sensitivity were diagnosed, correlated with history of each patient and found to be accurate.

b. Leukocyte hypersensitivity to the food dyes used in the US were found as follows:
- Yellow 5 -- 10.8%
- Yellow 6 -- 4.8%
- Blue 2 – 8.4%

142. **TSUDA 2001: (*) (Lab) DNA Damage by Red Food Dyes Orally Administered to Pregnant and Male Mice.** *Toxicological Sciences.* 61: 92-99.

a. Tsuda used the comet assay to measure DNA damage in Red 2, Red 40 and Acid Red *(not used in the US)*. Results were positive in the colon after 3 hours and in the lung after 6 hours.

b. Tsuda wrote, "Because the 3 azo additives we examined induced colon DNA damage at a very low dose, more extensive assessment of azo additives is warranted."

143. **VAN WAY III 2004: (*) (Review) The Blue Dye Blues.** *Journal of Parenteral and Enteral Nutrition.* 28(1): 62.

a. This is an editorial on blue dye used in enteral feedings. It had become generally accepted in clinical practice without any studies on safety or even on efficacy.

b. Van Way wrote not only was it neither sensitive nor specific, and of little practical use, but it was used on the grounds that "it couldn't hurt, and it might help." "Well," said Van Way, "we now know that it **could** hurt and that it **doesn't** help."

c. Van Way posed the question of what else is out there, routinely used without evidence that it helps … and without knowing that it hurts?

144. **VARGAFTIG 1980: (*) (Study) (Allergy) Is Tartrazine-Induced Asthma Related to Inhibition of Prostaglandin Biosynthesis?** *Respiration.* 39: 276-282.

a. 20 aspirin-intolerant patients were tested with Tartrazine. Although the patients stopped bronchodilator medications 24 hours before testing, they were apparently not asked to avoid the dye itself. Then they were tested with small doses –1 to 25 mg.

b. In another study, normal males (not sensitive to Tartrazine) were challenged with rather large doses of Tartrazine (200 mg and 500 mg), while the only patient known to be sensitive to both aspirin and Tartrazine was challenged with only 5 mg.

c. The authors concluded that Tartrazine doesn't block prostaglandin biosynthesis, but might yet potentiate the activity of thromboxane A2 (not tested) which would result in similar bronchoconstriction.

145. **VIRCHOW 1988: (*) (Study) (Allergy) Intolerance to Tartrazine in Aspirin-Induced Asthma: Results of a Multicenter Study.** *Respiration.* 53: 20-23.

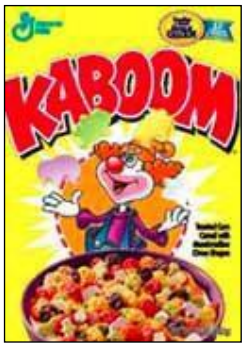
a. 156 patients with aspirin-induced asthma were challenged with Yellow 5 after having not taken medications for at least 8 hours. Some of those using chronic bronchodilators, however, needed to take their routine morning bronchodilator medication before the tests.

b. Apparently, they were not asked to avoid the dye for any period before being tested with increasing doses of it (with a maximum of 25 mg). Very few reacted to it.

c. Two, however, were so sensitive that they reacted to 0.3 mg and 1.0 mg of Tartrazine in the double-blind challenge.

d. Virchow concluded that cross-sensitivity between aspirin and Tartrazine is unlikely to be based on the inhibition of cyclooxygenase by the Tartrazine.

146. **VOUGHT 1972: (*) (Lab) (Extra) Erythrosine: An Adventitious Source of Iodine.** *Journal of Clinical Endocrinology and Metabolism.* 34(4): 747-752.



a. Iodine content of pharmaceuticals and foods colored with Red 3 were analyzed.

b. It was determined that 1/4 to 1/3 of the Red 3 iodine is converted to iodide and a single serving of cereal with Red 3 could increase the daily intake of available iodine by about 400 µg in addition to that ingested from bread, other colored foods, and iodized salt. The author raises the question of whether this may enhance the incidence of iodide goiter.

c. **Note:** *The Red 3-containing cereal they used (Kaboom) was discontinued by General Mills in 2010, almost 40 years later.*

147. **WANG 2015: (*) (Review) Chapter 23: Adverse Reactions to Food and Drug Additives.** *Mount Sinai Expert Guides: Allergy and Clinical Immunology, First Edition.*

a. **Note:** *This paper is taken from Chapter 23 of a textbook of Icahn School of Medicine at Mount Sinai, NY, so it is presumably what doctors are currently being taught.*

b. Yellow 5, Yellow 6, and Blue 1 are "associated with various symptoms" but there is "no compelling evidence."

c. For asthma or urticaria, challenges with an additive can produce a false positive if patients are taken off antihistamines, and a false negative if they are kept on them.

d. While the only treatment offered those who experience adverse reactions is avoidance, doctors are warned not to routinely advise patients to avoid sulfites or additives for treatment of asthma, urticaria, or ADHD.

148. **WEBER 1979: (*) (Study) (Allergy) Incidence of Bronchoconstriction Due to Aspirin, Azo Dyes, non-Azo Dyes, and Preservatives in a Population of Perennial Asthmatics.** *Journal of Allergy and Clinical Immunology.* 64(1):32-7.

a. Patients with asthma were first tested openly with dye and preservative mixes – a maximum of 20 mg for the Yellow 5 and 20 mg for each of the dye mixes – and then tested double-blind on each item.

b. Patients were instructed to avoid artificial coloring and preservatives for 1 to 2 days prior to the challenge. Medications were not taken before the "open" challenges, but were taken before the blind challenges. Testing was usually completed within 5 hours of having used their bronchodilators.

c. **Note:** *Considering the amounts of dye were what may be encountered in normal food, presumably controlled by medication, it would have been surprising had they actually had any reactions to these tests.*

d. The author concluded that "clinically important intolerance to dyes and preservatives is uncommon in patients with moderately severe perennial bronchial asthma."

149. **WELIKY 1979: (*) (Study) (Allergy) Correlation of Tartrazine Hypersensitivity with Specific Serum IgD Levels.** *Immunological Communications.* 8(1): 65-71. *(abstract only)*

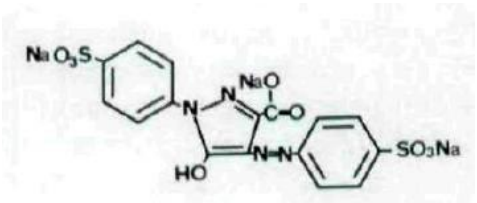
    a. While IgE tests are of little use for diagnosing food dye sensitivity, hypersensitivity to Yellow 5 in 16 subjects correlated with Tartrazine-specific IgD antibodies.

150. **WELTMAN 1978: (*) (Study) (Allergy) An Analysis of the Role of IgE in Intolerance to Aspirin and Tartrazine.** *Allergy.* 34: 273-281.

    a. Quote: "Intolerance to aspirin and to Tartrazine does not appear to be associated with specific antibodies of the IgE class."

151. **WILLIAMS 1989: (*) (Lab) (Allergy) Aspirin-Like Effects of Selected Food Additives and Industrial Sensitizing Agents.** *Clinical and Experimental Allergy.* 19:533-537.

    a. This was a study of several chemicals including Tartrazine (Yellow 5). All inhibited the second phase of aggregation when added in **higher concentrations than aspirin** and contained either **sulphonate** (SO_3H) groups or **carboxyl** (COOH) groups which characterize the largest class of NSAIDs.



    b. Tartrazine IUPAC Name = trisodium;5-oxo-1-(4-**sulfonat**ophenyl)-4-[(4-**sulfonato**phenyl)diazenyl]-4~{H}-pyrazole-3-**carboxylate**

    c. Williams said that Yellow 5 "may induce intolerance in the same way as aspirin, possibly by inhibiting prostaglandin production."

152. **WILSON 2005: (*) (Review) Adverse Reactions to Food Additives.** *Annals of Allergy, Asthma & Immunology.* 95: 499-507.

    a. Reactions to additives can be suspected when symptoms involve multiple unrelated foods or a food only when commercially prepared.

    b. The management is avoidance.

153. **WRIGHT 1986: (*) (Case) (Allergy) Food Allergy or Intolerance in Severe Recurrent Aphthous Ulceration of the Mouth.** *British Medical Journal.* 292: 1237-1238.

    a. Several patients suffering for years from painful mouth ulcers were treated by several diets in an on-and-off fashion to discover causation.

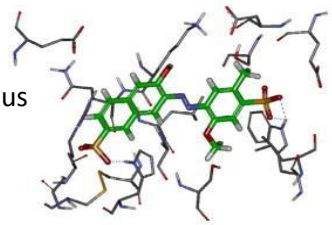
    b. 4 of them were dramatically cured by a dye-free diet in a week - one had suffered for 23 years.

154. **WROBLEWSKA 2009: (*) (Review) Influence of Food Additives and Contaminants (Nickel** and Chromium) on Hypersensitivity and Other Adverse Health Reactions – A Review. *Polish Journal of Food and Nutrition Sciences.* 59(4): 287-294.

a. This paper reviews several of the natural colorings and each of the usual artificial colors individually. Other items briefly reviewed are sweeteners, antioxidants, and flavor enhancers.

b. Conclusion: "If there are any doubts, we should discard such products since this is the only safe way to avoid allergens." **Note:** *In other words, when in doubt, throw it out.*

155. **WU 2015: (*) (Lab) Characterization of Interaction Between Food Colourant Allura Red AC and Human Serum Albumin: Multispectroscopic Analyses and Docking Simulations.** *Food Chemistry.* 170: 423–429.



a. Human serum albumin is the most abundant protein in the circulatory system, and is important for transport of endogenous and exogenous compounds.

b. Red 40 binds to it strongly, forming a complex.

c. Red 40 shares a binding site *(Site 1)* with warfarin, so it becomes unbound in the presence of warfarin *(a medical blood thinner)* but not in the presence of ibuprofen.

156. **WUTHRICH 1981: (*) (Study) (Allergy) Acetylsalicylic Acid and Food Additive Intolerance in Urticaria, Bronchial Asthma and Rhinopathy.** *Schweizerische medizinische Wochenschrift.* 111(39): 1445-50. *(abstract only – article in German)*

a. Wuthrich wrote that adverse reactions to aspirin, additives such as Tartrazine (*Yellow 5*) and the preservative benzoate are seen all over the world. It is described as an intolerance or pseudo-allergy possibly related to an imbalance of prostaglandin synthesis.

b. Testing 620 patients with urticaria *(hives)*, bronchial asthma or chronic rhinitis (*runny nose)*, Wuthrich found that 26.5% of them were intolerant to aspirin and/or some of the additives.

c. Quote: **"…azo-dyes must no longer be used for colouring of drugs."** Unfortunately, more than 30 years later, his warning is still being ignored. In fact, looking at the picture, you can see the ingredients of this children's allergy medicine contains 3 dyes – 2 of which aren't even allowed in food!!

157. **WUTHRICH 1993: (*) (Case) (Allergy) Adverse Reactions to Food Additives.** *Annals of Allergy.* 71(4): 379-384. *(abstract only)*

a. This is a review and two case reports. The case reports involve adverse reactions to Tartrazine (Yellow 5), sulfite preservatives and benzoates. He says a prevalence of 0.03% to 0.23% is estimated.

b. **Note:** *A lot of the tests for prevalence were undertaken with subjects on allergy medication or bronchodilators (or both), and using very small amounts of the dye or other additive, making this estimate hard to swallow for those who have seen far more than 3 out of 1,000 patients get better by avoiding the additives.*.

158. **ZILLICH 2000: (*) (Case) Skin Discoloration with Blue Food Coloring.** *The Annals of Pharmacotherapy.* 34: 868-870.

a. A child being given blue-tinted tube feedings looked cyanotic. Luckily for her, they realized she had been given a very large amount of the dye and stopped using it after the first 12 hours.

b. They decided not to let the nurses pour unknown amounts into the feeding bags any more but to use standardized units of no more than 363 mg/d.

c. **Note:** *This was 3 years before the FDA advisory letter on the subject.*

Please continue on next page

Appendix B

OLD REVIEWS ON FOOD DYES
Through 1998
Username/Password = "Private/Papers"

1. **ANASTOPOULOS 1988: (*) (Review) Biological Factors in Attention Deficit-Hyperactivity Disorder.** *The Behavior Therapist.* 11: 47-53.

    a. The hypothesis that food dyes or diet may cause ADHD is mentioned, with the assurance that "most investigators agree" that they affect only a "small percentage of children diagnosed as ADHD."

2. **BARNES 1998: (*) (Review) (Allergy) Difficult Asthma.** *The European Respiratory Journal.* 12(5): 1209-1218.

    a. In this paper, Barnes mentioned that Tartrazine (Yellow 5) "may cause wheezing and should be avoided."

3. **BELLISLE 1998: (*) (Review) Functional Food Science and Behaviour and Psychological Functions.** *British Journal of Nutrition.* 80(suppl1) S173-S193.

    a. This author is apparently connected to the International Life Sciences Institute (ILSI), a descendant of the Nutrition Foundation which was a food industry organization. Several authors of this paper are connected to Nestle, Kellogg and Mars.

    b. In their short review of "Hyperactivity and food additives" on page 186, only two studies are reviewed: the Swanson (1980) study, and the Weiss (1980) study, both published 18 years earlier.

    c. Bellisle claims that the Swanson study is not appropriate for evaluating the food dyes in a "normal diet," and that only two out of the 22 children showed worsening behavior in the Weiss study which used a much smaller amount of food dye as the "challenge."

    d. **Note:** *Not mentioned is that those 22 children in the Weiss study were not hyperactive to begin with. Weiss himself was known to say that if half the children are sensitive to salicylate, and half are sensitive to preservatives, testing them with a little coloring won't "prove" anything, and they may still respond to the Feingold diet. (per Hersey, personal communication, January 29, 2019)*

4. **BING 1950: (*) (Review) (Extra) Chemicals Introduced in the Processing of Foods.** *Presented before the Food and Nutrition Section of the American Public Health Association at the 77th Annual Meeting in NY, NY. Oct. 25, 1949.*

    a. **Note:** *This paper has nothing to do with food dyes, but is an interesting and easy-to-read short history of chemicals added to foods and the early efforts to deal with them.*

    b. Also historically interesting:
        - Bing 1955: **Chemicals Introduced in Foods**
        - Bing 1956: **Statement on Chemical Additives**

5. **BISHOP 1983: (FDA) (Review) Attention deficit disorder and the Feingold diet.** *The Canadian Journal of Hospital Pharmacy.* 36(3):71-74.

    a. Bishop provides a detailed history of the Feingold Diet and a review of the early studies.

    b. Bishop says that since most of the children did not react to a small dye challenge in double blind studies, their success on the diet must be due to "something else."

    c. **Note:** *Like most researchers at that time, Bishop assumed the "something else" must be psychological or related to family dynamics rather than some other component of the diet which had, after all, automatically eliminated thousands of chemicals.*

6. **BREAKEY 1997: (*) (Review) The Role of Diet and Behaviour in Childhood.** *Journal of Paediatrics and Child Health.* 33(3): 190-4.

    a. The author summarized and discussed the research from the 1970s through the 1990s. She emphasized that studies often only can deal with a single item but in reality multiple types of items may affect a sensitive person, causing changes in mood, behavior, and health. She said that nonfood items such as fragrances are also important.

    b. Quote: "While the connection cannot be said to be simple or neat, these studies have definitely demonstrated a role for diet in behaviour in some children."

7. **BRENNER 1986: (FDA) (Review) Food Additives and Behavior**. *Maryland Medical Journal.* 35(5):344-5.

    a. A short review of the Feingold diet and early studies. Brenner recommends that a "physician's open attitude and encouragement are helpful for patient compliance."

8. **BROOKES 2006: (FDA) A common haplotype of the dopamine transporter gene associated with attention-deficit/hyperactivity disorder and interacting with maternal use of alcohol.** *Archives of General Psychiatry.* 2006, 63: 74-81. **This paper was provided to the FDA Food Advisory Committee in 2011, but is not relevant to a discussion of food dyes.** It's about alcohol in pregnancy

9. **COLLINS-WILLIAMS 1985: (*) (Review) Clinical Spectrum of Adverse Reactions to Tartrazine.** *Journal of Asthma.* 22(3): 139-143.

    a. This is a review of studies on the connection of Tartrazine (Yellow 5) and its effects relating to urticaria, angioedema, asthma, hyperkinesis (ADHD), purpura, and contact dermatitis.

    b. Treatment for suspected sensitivity would be a Tartrazine-free diet, but the author says his patients benefit from an additive-free diet that excludes all the artificial dyes as well as sulfur dioxide, sodium benzoate, aspirin and salicylates. If this diet doesn't help a patient, then it "is obvious that a cause for his complaints must be sought elsewhere."

10. **CONNERS 1970: (FDA) Symptom patterns in hyperkinetic, neurotic, and normal children.** *Child Development.* 41:667-682. **This paper was provided to the FDA Food Advisory Committee in 2011, but it is not relevant to a discussion of food dyes.** Conners says children with ADHD have more symptoms than normal children – especially those to appear at the clinic.

11. **CONNERS 1980: (FDA) (Review) (Study) Artificial Colors in the Diet and Disruptive Behavior: Current Status of Research.** In R Knights and D Bakker (Eds.) *Treatment of Hyperactive and Learning Disordered Children: Current Research.* Baltimore, University Park Press 113-120.

    a. In the review section, an "order effect" in some diet studies was described in that most children who did better on the Feingold diet were those who had been given the control diet first. For the younger children in the Harley (1978) study that Conners reviewed, just after saying that 10 of 10 mothers and 7 of 10 fathers "could still note improved behavior" on the Feingold diet over the control diet, Conners wrote that it is "clear" that the dietary treatment is much less dramatic than was suggested by Feingold, and that only a small subsample of the children account for the improvement.

    b. **Note:** *How did 100% of the younger children become a "small subsample?" His careful wording sounds like an insinuation that the parents broke the blind, but an insinuation has no place in a scientific study (in my opinion).*

    c. **Note:** The "c*ontrol" diets used very little coloring (nothing visible), usually about 26 mg to 27 mg of food dye. Thus, those getting the control diet first had a longer period on a pretty good diet.*

d. **Note:** *Most children need several weeks to respond to the Feingold diet, especially if they were on medications previously, (Why Your Child is Hyperactive, pg. 176; Feingold Cookbook for Hyperactive Children, page 9). Since this time issue was described by Dr. Feingold in various papers in the mid-1970s, as well as the two books listed here, Conners should have been aware of it.*

e. To support his use of dye alone to test the Feingold diet, Conners says, "Feingold had suggested that the salicylate part of the diet could probably be eliminated."

f. **Note:** ***This is false. Dr. Feingold never wrote, said, or even hinted at any such thing.*** *(Personal communication, January 29, 2019, Jane Hersey, Feingold Assn of the US)*

g. Almost half the patients dropped out of the first challenge study described because of reactions to the chocolate in both placebo and challenge cookies. Thus, the more sensitive children were dropped from the study before it began.

h. There was little effect of the challenge on behavior (reported at the end of each day), but a marked effect on visual tracking one hour after ingestion of the cookie. Conners said this may be a transient pharmacological effect.

12. **DICKERSON 1980: (*) (Review) Diet and Hyperactivity.** *Journal of Human Nutrition.* 34(3): 167-74. *(abstract only)*

    a. This is a review of the nature of hyperactivity and the effectiveness of the Feingold diet, based on studies before 1980.

13. **DIPALMA 1990: (*) (Review) Tartrazine Sensitivity.** *American Family Physician.* 42(5): 1347-50. *(abstract only)*

    a. This is a description of sensitivity to Yellow 5; symptoms may include vasculitis, purpura, contact dermatitis, urticaria, or asthma. The solution suggested is avoidance.

14. **EDWARDS 1995: (FDA) Food-Allergic Disease.** *Clinical and Experimental Allergy.* 25 (Suppl. 1): 16-19. **This paper was provided to the FDA Food Advisory Committee in 2011, but it is not relevant to a discussion of food dyes.** Food dyes are not even mentioned - not even when discussing a study or two that tested them.

15. **EGGER 1987: (*) (Review) The Hyperkinetic Syndrome.** In *Food Allergy and Intolerance*, ed. Brostoff & Challacombe, Chapter 38b. p. 674-687.

    a. Egger reviewed the history of hyperkinesis as distinguished from conduct disorder and antisocial behavior. He also reviewed various treatments – drugs, behavioral approaches, and diet. Egger divided diet treatment into Feingold's hypothesis and the food allergy hypothesis, describing each.

16. **EGGER 1992: (FDA) Controlled trial of hyposensitization in children with food-induced hyperkinetic syndrome.** *The Lancet*, 339 (May), 1992: 1150-1153.
This paper was provided to the FDA Advisory Committee in 2011, but it is not relevant to a discussion of food dyes. It is about EPD: Enzyme Potentiated Desensitization

17. **EGGER 1997: (*) (Review) Hyperkinetic Syndrome.** *Journal of Nutritional & Environmental Medicine.* 7: 353-357. Food, Brain and Behavour Conference Proceedings. October 1996.

    a. Egger reviewed a number of studies from the 1980s and 1990s, concluding that "Food intolerance seems to be an important cause of hyperkinetic syndrome and avoidance of provoking foods is the treatment of choice for most patients who have food-induced hyperkinetic syndrome."

    b. While a number of other foods were commonly problems, Egger (1985) found that dyes and preservatives were the most often implicated. Egger suggests that gastrointestinal neurotransmitters may be involved, referring to the significant increase in vasoactive intestinal peptide (VIP) receptor density in duodenal mucosa during avoidance of provoking foods.

18. **FEINGOLD 1979: (*) (Review) Feingold's Regimen for Hyperkinesis.** *The Lancet.* 2(8143): 617-618.

    a. This is a *Lancet* editorial about the Feingold hypothesis and review of some of the early research. Since there is an assumption of a large placebo effect, the editor suggests that children in the UK would benefit from a 6 weeks treatment by a psychologist, while stimulant drugs could be reserved for resistant cases.

    b. **Note:** *This editorial is not written by Feingold, but no name is provided. How the unnamed editor made such a smooth leap from diet to psychotherapy is a remarkable bit of legerdemain.*

19. **FORD 1987: (FDA) Long-Term Toxicity Study of Carmoisine in Rats Using Animals Exposed *in Utero*.** *Food Chem Toxicol.* 1987, Dec; 25(12):919-25.
Carmoisine is not used in the US. Therefore, although this paper was provided to the FDA Food Advisory Committee in 2011, it is not relevant to a discussion of food dyes in the US.

20. **JUHLIN 1980: (*) (Review) Incidence of Intolerance to Food Additives.** *International Journal of Dermatology.* 19: 548-552.

    a. Juhlin wrote that various food additives, including azo dyes, can induce hives in patients with chronic urticaria. Usual symptoms of intolerance are urticaria, angioneurotic edema, asthma, rhinitis, and purpura. Less common reactions include hyperkinesia, contact dermatitis, and other skin rashes.

    b. Juhlin calculates prevalence of these various problems in Sweden.

21. **KAVALE 1983**: **(FDA) (Review) Hyperactivity and Diet Treatment: A Meta-Analysis of the Feingold Hypothesis.** *Journal of Learning Disabilities.* 16(6):324-330.

    a. Kavale and Forness reviewed 23 studies from the 1970s to 1981, some funded by the food additive industry itself through the Nutrition Foundation, They concluded that "diet modification is not an effective intervention for hyperactivity."

    b. Rimland (1983) used some rather strong language (such as GIGO – "garbage in/garbage out) in a rebuttal of this review published in the same journal and immediately following it. You may find it worthwhile reading the two together.

22. **KING 1984: (FDA) (Review) (Allergy) Psychological and Behavioral Effects of Food and Chemical Exposure in Sensitive Individuals.** *Nutrition and Health.* 3(3):137-151. **Although this paper was presented to the FDA Food Advisory Committee in 2011, it really doesn't consider food dyes.** King discusses research on the links between allergy and depression, as well as allergy and hyperactivity. However, King was interested in food items, not food additives.

23. **KRUMMEL 1996**: **(FDA) (Review) Hyperactivity: Is Candy Causal?** *Critical Reviews in Food Science and Nutrition.* 36(1-2): 31-47.

    a. Krummel reviews the diagnostic criteria for ADHD, as well as the criteria for evaluating the effects of dietary substances on behavior.

    b. The "gold standard" is specified as a double-blind, placebo-controlled randomized trial with a washout period. **Note:** *Using an appropriate amount of challenge materials is not mentioned anywhere.*

    c. Krummel's review ignores studies in the 1990s such as those of Rowe, Egger, Boris, or Weiss. She did list the Swanson & Kinsbourne (1980) study but complained there was "no significant effect of challenge on behavior." **Note:** *Well, of course – the children had only been on the diet for 3 days, and that is not enough time for an observable behavioral change; it was a study of cognition, not behavior.*

    d. The author flatly denies that food additives are related to behavioral problems, while admitting the "methodological quality of diet/behavior research has been less than ideal."

    e. The rest of this paper discusses sugar and chocolate which are not related to a discussion of food dyes.

    f. One of the authors listed as affiliated with Hershey Foods Corporation. Probably this should be taken into consideration when evaluating the merits of this review, even though no Conflict of Interest statement is included.

24. **LEVANTINE 1974: (*) (Review) Cutaneous Reactions to Food and Drug Additives.** *British Journal of Dermatology.* 91: 359.

    a. In this short review about skin reactions to food and drugs, Levantine says the incidence of reactions to additives is unknown. Thousands of additives had not (at that time) been officially evaluated, raising "fears of danger to the health of this and subsequent generations."

    b. Levantine says Red 2 is the "most widely used and highly suspect" of the coal tar dyes, but gives more information about Yellow 5 (Tartrazine) which had been implicated in asthma, urticaria and purpura (inflammation and bleeding in the small blood vessels, with small purple spots on the extremities).

25. **LEVINE 1991: (*) (Review) Metabolism of Azo Dyes: Implication for Detoxication and Activation.** *Drug Metabolism Reviews.* 23(3&4): 253-309.

    a. This is an in-depth review of how the azo dyes are metabolized, and what was known (in 1991) about their metabolism, carcinogenesis and mutagenesis.

26. **LIPTON 1977: (*) (Review) Statement Summarizing Research Findings on the Issue of the Relationship Between Food-Additive-Free Diets and Hyperkinesis in Children.** *National Advisory Committee on Hyperkinesis and Food Additives. (abstract only)*

    a. This is a summary of the early research findings (prior to 1977). Lipton concluded that the studies had refuted Feingold's "claim" that food dyes affect the behavior of children with ADHD. He admitted, however, that it is not certain that such additives are "utterly devoid of adverse effects."

    b. **Note**: *Lipton chaired the Nutrition Foundation's investigation into Dr. Feingold's work. The Nutrition Foundation was an industry organization wording on behalf of food, chemical and pharmaceutical companies.*

    c. **Note:** *The National Advisory Committee on Hyperkinesis and Food Additives, who published this paper, is NOT a government-appointed committee; rather, it was set up by the Nutrition Foundation itself to minimize any damage researchers might do to the food additive industry.*

27. **LIPTON 1983: (FDA) (Review) Diet and Hyperkinesis--An Update.** *Journal of the American Dietetic Association.* 83(2):132-134.

    a. In this review of early studies, Lipton, chairman of the Nutrition Foundation's investigation into the Feingold diet, wrote that the food industry organization's Advisory Committee had "immediately recognized the inadequacy of Dr. Feingold's scientific approach to this problem."

    b. Criticizing the Swanson (1980) study, Lipton claimed the "bolus" of 100 mg or 150 mg of food dye used may well have caused the children gastrointestinal upset, which would explain their poor showing on the paired association learning task.

    c. **Note:** *Lipton should have looked at a recipe for Red Velvet Cake which calls for 2 tablespoons of Red 40 -- 592 drops @ 1 mg of dye per drop. At 6 servmgs per cake, your guests would get 99 mg of Red 40 just for dessert. Yet this is probably the most popular cake in the southeastern part of the US, and does not seem to cause GI upset. But ... what if Lipton is right? If this is really a "toxic dose" ... can you tell Southerners to stop eating it? (All is not really lost - Starbucks makes one using beet coloring already.*

    d. Lipton also complained that behavior had not been affected by the dye challenge in Swanson's study;

        - **Note:** *No observable behavioral change was expected in the 3 days the children did not eat additives, so no observable "reaction" to the dyes should be expected; this was a cognition study, not a behavior study.*

    e. Lipton concluded that enough studies had already been done and no more money should be spent on such research.

28. **LUCARELLI 1995**: **(FDA) Food Allergy and Infantile Autism**. *Panminerva Medoca* 37 (3):137-141 **This paper was provided to the FDA Food Advisory Committee in 2011 but it is not relevant to a discussion of food dyes.** It's about a casein-free, gluten-free diet for children with autism. The children improved, but whether food dyes were involved is not mentioned.

29. **MACCARA 1982: (*) (Review) (Allergy) Tartrazine: A Potentially Hazardous Dye in Canadian Drugs.** *Canadian Medical Association Journal.* 126(8): 910-914.

    a. 4% to 14% of people with asthma or allergies and up to 20% of those sensitive to aspirin may react to this dye in medications. Labels on medications did not include dye content.

    b. Symptoms of a reaction are described. MacCara recommends including dye information on medication labels.

30. **MacGIBBON 1983**: **(FDA) (Review) (Allergy) Adverse Reactions to Food Additives**. *The Proceedings of the Nutrition Society*. 42(2): 233-240.

    a. This is a history of the effects of food additives up until 1981, including studies on urticaria and asthmatic reactions to food dyes.

31. **MAHER 1987**: **(FDA) Possible neurologic effects of aspartame, a widely used food additive.** *Environmental Health Perspectives.* 75:53-7. **This paper was provided to the FDA Food Advisory Committee in 2011 but it is not relevant to a discussion of food dye.** It's about aspartame.

32. **MAILMAN 1981: (*) (Review) Food Additives and Developmental Disorders: The Case of Erythrosin (FD&C Red #3), or Guilty Until Proven Innocent?** *Applied Research in Mental Retardation,* Vol. 2, 297-305.

    a. Mailman first describes the history and details of the Feingold diet. **Note:** *Although the details of this diet were freely available in 1981, and were much less elaborate than the later section on DNA chemistry in this paper, he made several errors:*

        - He says the diet eliminates "all common fruits with the exception of grapefruit, lemon, and lime." **Note:** *That does sound harsh – but it's also untrue.*

        - He says condiments and butter are eliminated – **Note:** *No, they are not. Ketchup, of course, contains tomato and is eliminated for the first weeks, but nothing is wrong with mustard and many brands of mayonnaise and (real) butter.*

        - He says pediatric medications and vitamins would be eliminated because they contain aspirin. **Note:** *I am sure that vitamins don't contain aspirin. Of course, those that contain food dyes or flavorings would be eliminated. The same with toothpaste, mouthwash, etc. One simply buys an acceptable brand without the additives.*

    b. **Note:** *Although there may be some valid points in this paper, the severalerrors and omissions in this section (and its age) make it questionable as a reliable resource.*

33. **MAILMAN 1983: (FDA) (Review) Food Additives and Childhood Hyperactivity.** *ASDC Journal of Dentistry for Children.* 50(4):283-286.

    a. Mailman discusses whether animal studies showing increased locomotion after exposure to a toxin could be applicable to humans. He said an acceptable animal model of ADHD would have to improve when treated with stimulant drugs.

    b. Mailman says the reported effect of Red 3 on neurotransmitter uptake *in vitro* is unlikely to affect behavior because it is a result of "nonspecific interactions of Red Dye #3 with biological membranes, rather than a specific central nervous system effect."

34. **MATTES 1983: (FDA) (Review) The Feingold Diet: A Current Reappraisal**. *Journal of Learning Disabilities*. 16(6):319-323.

    a. Mattes opines that improvement on the Feingold diet is "based on anecdotal evidence;" he claims that studies show the diet "is probably not effective, except perhaps in a very small percentage of children."

    b. Mattes supposes that even for children whose parents feel they have been helped greatly by the Feingold diet, "the improvement seems more often a placebo effect" – although Mattes has no evidence and no study supporting any such "placebo effect," he claims it is due to "increased attention."

    c. **Note:** *It's the shopping that gets the attention of a family new to the diet – not the child.*

35. **MAYER 1969: (*) (Review) Food Additives and Nutrition: A Primer.** *Postgraduate Medicine*. 46(6): 195-197.

    a. Mayer writes that Americans are losing faith with the food industry, so doctors must learn about food additives to prevent the public from turning to "food fads and secondary deficiencies."

    b. About food dyes, he says synthetic dye is justified to correct color lost in processing, but color used to create an illusion of real ingredients in a product flavored artificially is not justified.

    c. **Note**: *It looks like that is all the training physicians got on the subject in 1969.*

36. **McFADDEN 1996: (*) (Review) Phenotypic Variation in Xenobiotic Metabolism and Adverse Environmental Response: Focus on Sulfur-Dependent Detoxification Pathways.** *Toxicology*. 222(1-3): 43-65.

    a. Some people don't metabolize drugs or other xenobiotics (foreign items such as food dyes) well. They may have an impairment in sulfation capacity.

    b. The phenol sulfotransferase enzyme system (called either PST or SULT1) is involved, and several studies have connected difficulty with sulfation to autism, ADHD, Parkinson's, rheumatoid arthritis and a number of other degenerative and/or neurological diseases.

    c. McFadden suggests that competition for sulfate substrate between phenolic xenobiotics and "endogenous mediators" (such as neurotransmitters that need the same pathways) may be relevant to conditions such as diet-responsive autism and Feingold-diet-responsive behavior disorders.

    d. **Note:** *In other words, if you have a low ability to sulfate xenobiotics and your capacity is "used up" by the Red 40 and flavorings you are eating in your snacks, there may not be enough left for your neurotransmitter processing.*

37. **MENZIES 1984: (*) (Case) (Review) Disturbed Children: The Role of Food and Chemical Sensitivities.** *Nutrition and Health.* 3(1-2): 39-54.

    a. Menzies reviewed some of the existing literature on "tension-fatigue" syndrome and environmental factors, and presents a number of case studies of children he had treated who had idiosyncratic responses to foods and additives. He described the similarities of 25 of his patients, not only in their behavioral difficulties but in their physical problems. He noticed that before treatment each child had a "most restricted diet" which seemed to consist mostly of junk food.

    b. Quote: "Perhaps not enough attention has been paid to the role of biological and environmental factors in the development of children's problems."

38. **MILLER 1982: (*) (Review) Sensitivity to Tartrazine.** *British Medical Journal.* 285: 1597-1598.

    a. Intolerance to Tartrazine (Yellow 5) was first reported in 1959 and plays a part in intractable urticaria as well as nonthrombocytopenic purpura (rash).

    b. Miller says existing tests (in 1982) are of low predictive value, and recommends that people sensitive to aspirin and allergic to foods should avoid Tartrazine.

39. **MONERET-VAUTRIN 1985: (*) (Review) Mechanisms of Aspirin Intolerance.** *Annales d'otolaryngologie et de chirugie cervico faciale.* 102(5): 357-363. *(abstract only – article in French)*

    a. 42% of people sensitive to aspirin were also sensitive to other chemicals including Tartrazine (Yellow 5).

    b. The author suggests this may be related to an abnormal instability of cell membranes and excessive receptor sensitivity to leukotrienes.

40. **NIH: National Institutes of Health 1998: (FDA) (Review) Diagnosis and Treatment of Attention Deficit Hyperactivity Disorder** *NIH Consensus Statement.* 1998. 16: 1-37. **This paper was provided to the FDA Food Advisory Committee in 2011 but it is not relevant to a discussion of food dyes.** The closest this paper comes to discussing food dyes is the single sentence, **"Some of the dietary elimination strategies showed intriguing results suggesting the need for future research."**

41. **PODELL 1985: (*) (Review) Food, Mind, and Mood: Hyperactivity Revisited.** *Postgraduate Medicine.* 78(2): 119-122, 125.

    a. This is a review of Egger (1985)
    b. Podell does not believe 76 families could have been on the diet with no dropouts.
    c. He claims that 80% improvement "strains credibility" and he would "be more comfortable" if Egger had claimed 60%.

42. **RAPP 1982**: **(FDA) (Review) Food Additives and Hyperactivity : Lette***r. Lancet* 1982, 1(8281) 1128 *(Abstract only)*

    a. In one letter, Rapp suggests that physicians might effectively recommend a simple diet composed solely of fruit, vegetables, and regular meats (no sausage, luncheon meats, etc.) for 1 week, followed by restoring the questionable foods (milk, wheat, egg, sugar, dyes, corn, chocolate) singly (1 each day) during the 2nd week and note the effect of each food.

    b. In the second letter, she proposes a similar approach, noting that hundreds of American physicians have found that most irritable, unhappy, hyperactive children can be helped by a carefully designed trial diet in 5-10 days. Upon noting evidence of a convincing improvement in the child's symptoms lasting for 48 hours, it is felt that problem foods can be identified by having the child eat them again, 1 food a day, over a second 7-10 day period.

    c. **Note:** *Although no mention is made of food additives or food dyes, they are automatically excluded in her diet regimen, and never "added back."*

    d. **Note:** *From personal experience, I think her timing is overly optimistic unless she was working with very young children.*

43. **RIBON 1982: (FDA) (Review) Is There Any Relationship Between Food Additives and Hyperkinesis?** *Annals of Allergy.* 48(5):275-278.

    a. In giving the history of the Feingold diet, he has a few of errors of fact, confusing mint with artificial flavoring, claiming Dr. Feingold had eliminated "seven artificial flavors" (perhaps he meant colors?), and that there were a "few" parents of hyperactive children who supported the diet.

    b. Ribon wrote that the Nutrition Foundation was critical of the Feingold hypothesis (*which they certainly were*) – without identifying them as a food additive industry entity.

    c. Ribon wrote that the results of the Swanson (1980) study using 100 mg and 150 mg food dyes would be a toxic effect rather than an immunological effect.

    d. **Note:** *That may be, but since children in real life do eat that much, should these TOXINS be so widely available they are considered "food?"*

44. **RIMLAND 1983***:* **(FDA) (Review) The Feingold Diet: An Assessment of the Reviews by Mattes, by Kavale and Forness and Others.** *J Learning Disabilities.* 16(6):331-333.

    a. Rimland reviews the papers by those listed above as well as several others who had all concluded that the additive-free diet for ADHD is "at best, of marginal value for a few children." He says this conclusion is "certainly unwarranted, probably incorrect, and very likely damaging."

b. Rimland specifies that if the “incoming data are of no value, no amount of massaging, analysis, or manipulation will increase its value.” He refers to "Gigo" which, he says, stands for "garbage in, garbage out" in computerese. He goes into detail in his discussion of such incoming data, including the dosage and choice of challenges, the general health change of children avoiding junk food, and confounds such as copper levels and fluorescent lighting exposure.

c. Rimland says that despite the anti-Feingold bias so evident in many of the studies and reviews, “all studies, without exception, do concede that some children react to additives and some children do respond to the diet. In view of the weaknesses in the design and conduct of the studies, and the insensitive and subjective behavioral measures typically employed, these findings speak strongly for the robustness of the Feingold effect.”

d. Rimland deplores the way animal and *in vitro* studies have been ignored. He felt such studies should be emphasized, not ignored, because, he says, a lab rat can't "trade a tuna sandwich for a Twinkie" and “neurons and neurotransmitters are the very stuff that brains, and therefore learning and behavior, are made of.”

45. **RIPPERE 1983: (FDA) (Review) Food Additives and Hyperactive Children: A Critique of Conners.,** *British J of Clinical Psychology.* 22 Pt 1:19-32.

a. Rippere claims Conners’ studies “do not constitute a valid test of Feingold’s views” as follows:

- Conners presents no evidence about the effects of flavors, preservatives, or salicylates, but only tests a small component of the diet (food dyes).
- His control conditions are invalid and misleading; his placebos (such as chocolate cookies) are active and not inert as stated.
- The dosage of dyes used is misleading and inadequate, and the dose schedule of dyes is inappropriate.

b. Rippere writes that it is “cavalier to dismiss the observed effects of eliminating these chemicals as due to “placebo effects” since none of the chemicals have been adequately studied in their “many conceivable synergistic interactions.”

46. **RIPPERE 1984: (*) (Review) Some Varieties of Food Intolerance in Psychiatric Patients: An Overview.** *Nutrition & Health.* 3(3): 125-136.

a. While investigators of the Feingold hypothesis have produced generally negative results, those who adopt an individualized approach to a particular child’s hypersensitivities confirm the adverse behavioral effects of food colors in a large proportion of the children they treat.

b. A toxic or pharmacological effect rather than allergic or immunological effect is suggested, but actual allergy is not ruled out.

47. **RIPPERE 1985: (*) (Review) Letters to the Editor: Validity of Alternative Allergy Practices.** *Journal of the Royal Society of Medicine.* 78: 692-693

    a. This letter to the editor attacks David's rejection of "alternative medicine" and his claim that avoidance of chemicals has "failed the double-blind tests."

    b. David's vicious rebuttal is included, likening parents who try elimination diets to child abusers whose children are "unreasonably deprived of food."

    c. **Note**: *See David's own double blind study at* ***David (1987)***

48. **ROBINSON 1992: (FDA) (Review) Food Sensitivity and the Nervous System: Hyperactivity, Addiction and Criminal Behavior .** *Nutrition Research Reviews. 5: 203.*

    a. In his section on food and behavior, Robinson says there are flaws in studies on all sides of this issue, and reviews "often reveal prejudices of the authors for or against an association between food and behavior."

    b. He reviews a number of studies related to food dyes and the Feingold diet and concludes that "there is indeed scientifically sound evidence to support an association between foods and abnormal behavior in children."

49. **SCHAUSS 1984: (FDA) (Review) Nutrition and Behavior: Complex Interdisciplinary Research.** *Nutrition and Health.* 3: 9-37.

    a. In a review pointing out the inadequacies of the early research on food dyes and behavior, Schauss says that although many of the authors consistently minimize or discount findings which might support the Feingold hypothesis, they collectively did show that food dyes have "transient effects upon concentration, learning, and memory."

    b. Schauss cited the study by Prinz (1980) as suggesting a possible synergistic relationship between sucrose consumption and artificial food dyes.

50. **SHAYWITZ 1993: (FDA) Aspartame does not affect behavior and cognitive function in children with Attention-Deficit Disorder (ADD).** 103rd Annual Meeting of the American Pediatric Society and 62nd Annual Meeting of the American Society for Pediatric Research. Washington, D.C. May 3-6, 1993. *Pediatric Research, 1993, 33 (4 Part 2): 17A.* **This paper was provided to the FDA Food Advisory Committee in 2011 but it is not relevant to a discussion of food dyes.**–It is about aspartame..

51. **SILBERGELD 1982: (FDA) (Review) Artificial Food Colors and Childhood Behavior Disorders.** *Bull N Y Acad Med.* 58(3):275-95.

    a. Another early review of studies showing small response to "dye challenges." Silbergeld adds, however, that studies on rodents have shown that "Red 3 produces significant neurochemical and behavioral effects."

52. **SIMON 1986: (*) (Review) Adverse Reactions to Food Additives.** *New England and Regional Allergy Proceedings.* 7(6): 533-542.

    a. Simon complains about all the studies done on the connection of dyes with urticaria and asthma, citing the inadequate amount of dyes used, condition of patients, etc.

    b. He has one small paragraph on hyperactivity, saying "some uncontrolled studies" support the Feingold hypothesis while studies opposing it are "well controlled." None of these are cited; he completes his review of this subject by saying "This subject has been recently fully reviewed" and citing Lipton (1983).

    c. **Note:** *It's interesting that here Simon has no complaint about the inadequate amount of dyes used, or the small number of children in most of the studies.*

53. **SIMON 1996: (*) (Review) Adverse Reactions to Food and Drug Additives.** *Immunology and Allergy Clinics of North America.* 16(1): 137-176.

    a. Simon says research has "failed to confirm" asthmatic reactions from Yellow 5 or other food dyes.

54. **SMITH 1991: (*) (Review) Adverse Reactions to Food and Drug Additives.** *European Journal of Clinical Nutrition.* 45(suppl 1): 17-21.

    a. Smith complains there was no legal requirement (then) to disclose ingredient details in medications, and writes that the dyes are "probably associated with more reports of intolerance or toxicity than other groups of food and drug additives."

    b. Smith concludes that "Food and drug additives can no longer be considered to be inert and non-toxic."

55. **SMITH 1991: (*) (Review) The Role of Food Additives and Intolerance Reactions to Food.** *Bibliotheca nutritio et dieta.* 48: 72-80.

    a. Smith says food additives don't induce reactions but may "provoke or exacerbate" them.

    b. The author calls for informative labels on food and drug products and wants to ensure that food additives are used at "the minimum levels required to achieve their technical function."

56. **SPRING 1976: (*) (Review) Food Additives and Hyperkinesia: A Critical Evaluation of the Evidence.** *Journal of Learning Disabilities,* (9) 9, 560-569.

    a. Spring reviewed the then-available studies and concluded that there was no "epidemic" of hyperactivity.

    b. He agreed with the Nutrition Foundation's statement that the K-P diet "significantly alters the structure and dynamics of the family." Spring claimed the clinical trials available at that time were largely affected by placebo effects, and he recommended a "moratorium on further public advocacy of the Feingold hypothesis."

    c. **Note:** *Families actually using the diet say that most changes are made in the grocery store, not the kitchen, so "family dynamics" is not affected. About the biggest change for the child is that he/she must bring lunch to school. It appears to me that writing off something you don't understand as a "placebo" without a shred of evidence is a little unscientific.*

57. **STARE 1980: (FDA) (Review) Diet and Hyperactivity: is There a Relationship?** *Pediatrics, 66:521.*

    a. Stare describes the "evolution" of the Feingold diet in detail. Although otherwise accurate, he mistakenly claims that the Feingold Cookbook supports the idea that Feingold no longer considered salicylates important – **Note:** *This is an error*.

    b. **Note:** *As a matter of fact, the entire Cookbook is written for the non-salicylate "stage one" part of the diet.*

    c. Stare feels that since most of the children in the studies do not react to the additive "challenge" then "other factors" are the key variables. He targets family dynamics, increased attention, placebo, or even a change in nutritional status. He doesn't consider the possibility that the challenge material chosen may be (1) too low a dose or (2) one the child doesn't happen to be sensitive to among the thousands of chemicals eliminated on the diet.

    d. Stare brings up the problematic concept of communicating to the child via dietary change that his "behavior is controlled by what he or she eats" … **Note:** *He does not appear equally concerned about the child on medication being told his or her behavior is controlled by a pill.*

    e. Stare concludes that "diet plays, at most, a very minor role" in hyperactivity/ADHD.

    f. **Note:** Stare was editor of *Nutrition Reviews*, the journal of the Nutrition Foundation, a food industry organization.

    g. Letters to the Editor by Crook and Campbell (1981) and Stare's responses

58. **STEVENSON 1986: (*) (Review) (Allergy) Adverse Reactions to Tartrazine**, *Journal of Allergy and Clinical Immunology.* 78(1 Pt 2): 182-91.

    a. Stevenson (of the Scripps Clinic) first reviewed studies from 1958 through 1984 on patients who were aspirin-sensitive with possible sensitivity to Tartrazine, triggering either urticaria, asthma, or both. Two studies conducted at the Scripps Clinic were described in this paper and repeated in their 1992 paper

59. **STORY 1998: (FDA) (Review) Diet and Adolescent Behavior: Is There a Relationship?** *Adolesc Med.* 9(2):283-98, vi. *(abstract only)*

    a. This paper is a review of the scientific evidence on the relationship between food and behavioral problems such as hyperactivity, learning disabilities, mental illness, aggression, and juvenile delinquency.

    b. In her paragraph about food additives (page 290), however, she simply repeats the conclusions of Wender (1986) from 12 years previously, ignoring the several studies published in the 1990s. She also ignored all the diet studies carried out at juvenile detention centers by Schoenthaler which one would think important to any discussion of food and juvenile delinquency.

    c. **Note:** *In reading this review, its age and deficiencies should be taken into account.*

60. **STRAIN 1981: (*) (Review) Nutrition, Brain Function and Behavior.** *Psychiatric Clinics of North America.* 4(2): 253-268.

    a. While she concludes that food intake directly affects neurotransmission, she says current research (as of 1981) does not support use of an additive-free diet for hyperactivity.

61. **SUN 1993: (FDA) The Effects of Neonatal Monosodium Glutamate Treatment on Sex-Odor Attractivity and Approach Behavior in Rats**. *Kaohsiung J Med Sci;* 9 (4). 232-242
    This paper was provided to the FDA Food Advisory Committee in 2011, but it is not relevant to a discussion of food dyes. -- It is about MSG.

62. **TARLO 1993: (*) (Review) Asthma and Anaphylactoid Reactions to Food Additives.** *Canadian Family Physician.* 39: 1119-11123.

    a. This is a review of a number of items that cause allergy, including Tartrazine (Yellow 5) which they say is reported to "exacerbate asthma, urticaria, and angioedema." However, they point out that studies show this is rare, so such a "restrictive" diet is unjustified.

    b. **Note**: *They are apparently unaware of the studies where people used a dye-free diet and got better, but only those that challenged people on meds with a tiny amount of one color.*

63. **TAYLOR 1984. (FDA) (Review) Attention Deficit Disorder and Hyperkinesis.** *Indian J Pediatr.* 51(409):193-204.

    a. This is a review of the early studies and a discussion of possible causes of hyperactivity/ brain damage/hyperkinesis.

    b. Taylor concluded that both lead exposure and food dyes are only a minimal problem and do not necessarily cause any real symptoms, but just "placebo reactions."

64. **THORLEY 1983: (FDA)(Review) Childhood Hyperactivity and Food Additives.** *Developmental Medicine and Child Neurology.* 25(4):531-4.

    a. Thorley discussed the concern about whether sensitivity to food dyes might be toxic or allergic in nature, and how the inability to predict which children might be affected is "annoying."

    b. Thorley wrote that although food dyes are regulated by law in most countries, "there is disturbing evidence that existing regulatory powers are not exercised beneficially because basic research on toxicity, even in animals, has not been carried out."

    c. Thorley also complained that over 100 different caramel additives were in use but "not one could be chemically identified and as a consequence those which have been tested cannot be indicators for the others."

    d. **Note:** *This is historically interesting information, but one should keep in mind that it is close to 40 years old now and surely some progress has been made?*

65. **TUORMAA 1994: (*) (Review) The Adverse Effects of Food Additives on Health: A Review of the Literature with Special Emphasis on Childhood Hyperactivity.** *Journal of Orthomolecular Medicine.* 9(4): 225-243.

    a. By 1994, Tuormaa said, the average person was eating at least 8-10 pounds of food additives per year.

    b. Tuormaa discussed each of the food dyes and several other commonly used additives and their possible side effects. Tartrazine, for example, acts as a zinc chelating agent in susceptible individuals, with a corresponding deterioration in their behavior.

66. **VARLEY 1984: (*) (Review) Diet and the Behavior of Children with Attention Deficit Disorder.** *Journal of the American Academy of Child Psychiatry.* 23(2): 182-185.

    a. This is a review of the research from the 1970s and early 1980s. Varley stressed ways for doctors to encourage parents to abandon their efforts at using a diet for ADHD.

67. **WEBER 1993: (FDA) (Review) (Allergy) Food Additives and Allergy**. *Annals of Allergy.* 70(3):183-190.

    a. In this review, Weber agreed studies of additives in asthma should be done while on medications to avoid "false positives"

    b. **Note:** *He gives the same argument dairies gave for adding formaldehyde to milk in the early 1900s -- that without additives, things would be worse.*

    c. An additive-free diet may benefit urticaria, and the behavior of a "small subset of primarily younger children." He summarized the effects of additives by saying: "As with asthma and additives, the problem appears to be much smaller than originally postulated."

    d. Note: *This review predates numerous large studies such as Rowe (1994), while ignoring others already done such as Schoenthaler (1985; 1986)*

68. **WEISS 1979: (*) (Review) Behavioral Epidemiology of Food Additives.** *Neurobehavioral Toxicology.* 1 Suppl 1:149-55.

    a. Weiss wrote that behavioral toxicology can be considered a special branch of epidemiology. Behavioral epidemiology, because it typically relies on complex functional criteria, faces all of the problems of behavior measurement posed by uncontrollable variation, and amplified even further by chemical exposure. Many such issues arose in a study of behavioral responses to artificial food colors in children. Difficulties in employing Applied Behavioral Analysis in such a context run the gamut from selection of retrospective criteria to appropriate statistical models.

    b. Various ways of measuring and understanding appropriate criteria are discussed.

69. **WEISS 1980: (*) (REVIEW) In Rebuttal: Food Additives and Hyperkinesis.** *American Journal of Diseases of Children.* 134(12):1126-8.

    a. Here, Weiss explained the reasons for the choices made in his study (see page 93, #238), in rebuttal to hostile comments by Wender (1980) on Page 172.

    b. He began with a quote by the Director of the National Institute of Environmental Health Sciences: "Suppose that thalidomide, rather than inducing structural deformities, had instead depressed IQ scores by 10%; would we ever have suspected it of adverse effects?"

    c. Weiss concluded that "given the enhanced sensitivity of the fetus and neonate to so many other agents, should not prudent clinicians caution pregnant and nursing women and parents of young children about the conspicuous absence of behavioral data in food-additive safety testing, as well as the balance of risks and benefits?"

70. **WEISS 1982: (*) (Review) Food Additives and Environmental Chemicals as Sources of Childhood Behavior Disorders.** *Journal of the American Academy of Child Psychiatry.* 21(2):144-52.

a. Quote *(re validity of the Feingold diet)*: "Although the literature is too sparse to permit a conclusive review, analysis of all the studies published to date indicates the presence of a real effect."

b. Weiss examined the discrepancies improperly reported in a number of studies of the Feingold diet – when looked at properly, he claimed, these studies are far more supportive of the Feingold hypothesis than previously reported.

c. Weiss further suggested that behavioral toxicity should be a component of standard food additive safety testing, and in fact that its absence is "beginning to seem a curious anomaly."

71. **WEISS 1983: (*) (Review) The Behavioral Toxicity of Food Additives.** *Nutrition Update,* Vol. 1

a. Quote: "Food additive safety evaluation typically excludes behavior as a criterion of toxicity."

b. Weiss discussed the numbers of additives then in use – about 3,000 (Today over 12,000) –and the symptoms of sensitivity, similar to the "early warning systems" of toxicity used in industrial exposure studies. There, safety factors are introduced based on earliest manifestations of toxicity which (if involving the CNS) can be vague and nonspecific.

c. Weiss also discussed a number of other additives such as MSG, and the information is interesting for historical purposes.

72. **WEISS 1984: (*) (Review) Food Additive Safety Evaluation: The Link to Behavioral Disorders in Children**. *From Advances in Clinical Child Psychology, Vol. 7.* Chapter 7.

a. This is a chapter about food additives in general, the development and history of their safety evaluations.

b. On page 223 and 224 where he discusses the history of the Feingold hypothesis, he says, "The evidence is inadequate to yield any estimates of risk or prevalence, but clear enough to show that Feingold had observed a real effect. To me, however, the toxicologic implications of his hypothesis, and the policy issues they illuminate, transcend the possible therapeutic impact of his hypothesis. This (next) chapter approaches the hypothesis from that viewpoint." This is followed by a discussion of the various additives.

c. As Weiss pointed out, carcinogenesis is still the dominant concern of any safety testing, but it may not be the only problem to be concerned about.

73. **WEISS 1986: (FDA)(Review) Food Additives as a Source of Behavioral Disturbances in Children.** *Neurotoxicology.* 7(2):197-208.

a. This paper is a history of the development of the study of food additives and their relationship to behavioral disorders up until then.

b. While admitting that the "data are not extensive, and much of the research was poorly planned, executed, and analyzed," Weiss asserted that the science (in 1986) did contain "enough consistency, however, to allow a clear conclusion: Some children respond with disturbed behavior to some food additives."

c. Weiss pointed out a problem with many of the studies, in that chocolate was used to mask the food dyes used – even though chocolate itself has been linked to intolerance reactions.

d. Weiss also suggested that more adequate tests of food dye toxicity should have used dose levels closer to the allowable daily intakes (ADI) permitted by the FDA, "which are about 50 times greater than those used by most of the investigations."

e. **Note:** *This is especially true today, when several analyses have suggested that consumption by children may be exceeding the ADI in the real world. (Dixit, 2010; Dixit, 2011; Feitosa, 2017; Gajda-Wyrebek, 2016)*

74. **WEISS 1987: (*) (Review) Environmental Contaminants and Behavior Disorders.** *Developmental Pharmacology & Therapeutics.* 10(5): 346-53. *(abstract only)*

a. Toxicity may take the form of subjective complaints that are later followed by overt impairments; the fetus and young child seem to be at special risk for substances such as methylmercury and synthetic food colors, a susceptibility not fully recognized.

b. **Note:** *Weiss is one of the founders of the field of behavioral toxicology.*

75. **WENDER 1977: (*) (Review) Food Additives and Hyperkinesis,** *American Journal of Diseases of Children.* 131(11):1204-6.

a. Wender reviewed some of the early research. She apparently believed that the Feingold diet and food additives had been sufficiently tested and found wanting. **Note:** *Considering how old her conclusions are, and her relationship to the industry-supporting Nutrition Foundation, they might be taken with some salt.*

76. **WENDER 1980: (*) (Review) New Evidence on Food Additives and Hyperkinesis: A Critical Analysis.** *American J of Diseases of Children.* 134(12):1122-5.

a. Wender reviewed two studies recently published (at that time) – Weiss (1980) and Swanson (1980).

b. In her review of the Weiss study, she claimed that the children receiving 35 mg food dye in the Weiss study had received far more than one would get in the "usual infraction" but only one of them was affected. She said the mother must have determined which challenges were active by staining a napkin. **Note:** *Weiss had foreseen this possibility and prevented it by addition of cranberry to both juices. Oh – and it was two children, not one, affected.*

c. In her review of the Swanson study, Wender pointed out that no behavioral change was noted even with food colorings of 100 and 150 mg. **Note:** *She failed to realize, apparently, that no behavioral change can be expected when someone has been on the diet only a couple of days and their behavior has not had any time to improve – this was not a study dealing with behavior but with cognitive function.* Wender described their "turning to" the learning laboratory task as though it were done in desperation or on a whim to prove something.

d. See the rebuttal by Weiss (1980) on page 169, #68.

77. **WENDER 1986: (FDA)(Review) The Food Additive-Free Diet in the Treatment of Behavior Disorders: A Review.** *J Dev Behav Pediatr.* 7(1):35-42.

a. This is a review of studies from the 1950s, 1960, and 1970s, with a few as recent as 1980 and 1981. Based on the studies she has chosen to include, it is not surprising that Wender concluded that studies "generally refute a causal association between food additives and behavioral disturbance in children."

b. It is interesting that she also claimed (Page 36) that "there is no evidence that hyperactivity or learning disability have increased in prevalence."

c. Wender is connected historically to the food industry-supported Nutrition Foundation, and portions of this article are noted to have appeared previously in the "Final Report to the Nutrition Foundation" in 1980.

d. **Note:** *This and all her papers should be read with an understanding of her industry bias.*

78. **WILLIAMS 1978: (*) (Review) Diet in the Management of Hyperkinesis: A Review of the Tests of Feingold's Hypotheses.** *Canadian Psychiatric Association Journal.* 23(4): 241-248. *(abstract only)*

a. This is a review of some of the early studies, including four studies of a Feingold-type diet and one of a modified diet.

b. **Note:** *As many reviewers do, he confuses reactions to a challenge with response to the diet.*

79. **WOLRAICH 1991: (*) (Review)** (book) **Behavioral Pediatrics,** Springer-Verlag New York, Inc.

a. In a short description of the Feingold diet and food dye research on pages 170-171 of this book, Wolraich manages to compress a surprising number of errors into just a few paragraphs:

1) He wrote Feingold was a pediatric allergist. **Note:** *No, Feingold was Chief of Allergy for Kaiser-Permanente, and treated both adults and children.*

2) He wrote Yellow 5 is a salicylate or chemically similar to aspirin. **Note:** *No, it is not.*

3) He wrote foods "in which salicylates occur naturally" are not restricted on the Feingold diet. **Note:** *No, those are the ones that **ARE** restricted in the first weeks, and then tested for tolerance.*

4) He wrote that because some foods with "high salicylate content" are not forbidden while other foods with "low content" are, the diet is "inconsistent." **Note:** *No, the list of salicylates was clinically established in the 1930s to include those items affecting most aspirin-sensitive patients. The **amount** of "salicylate" is irrelevant since there are many **kinds** of related chemicals, with some more "toxic" at lower dose than others. Research has never yet determined which chemical(s) at which dose is in what foods.*

5) He wrote that most children who improve on the diet don't react to a food dye challenge. **Note:** *True, if the challenge is small enough. It means the diet **works so well** that a small challenge with a single item cannot undo it. This does not mean the **diet didn't work**; it means the **challenge didn't work**, but Wolraich doesn't get it.*

6) He claimed the reason for the diet working at all is because of a change in family attitude or family involvement with the child. **Note:** *How wonderful it would be if children could be cured of ADHD by a family attitude adjustment! Unfortunately, there has never been a single study to support this theory. If the diet worked via placebo, it would take effect within a day and last maybe a couple of days … placebos don't last for years. But no; it takes one to six weeks for the diet to take effect, and it continues to "work" for the rest of that child's life. If this is "placebo," it should be patented as the best cure yet, cheap and no side effects.*

b. **Note:** *Judging by the number of errors/false statements in this small section of the book, the entire book should be read with care, or just ignored.*

80. **WOLRAICH 1995: The (FDA) (Review) Effect of Sugar on the Behavior or Cognition of Children: A Meta-Analysis**. *JAMA.* 1995, 274: 1617. **This paper was provided to the FDA Food Advisory Committee in 2011, but it is not relevant to a discussion of food dyes.** – It is about sugar.

81. **YOUNG 1997: (FDA) (Review) (Study) Prevalence of Intolerance to Food Additives.** *Environmental Toxicology and Pharmacology,* 4 (1-2). 111-114.

a. In this review, Young claimed the discrepancy between public perception (i.e., parent perception) and the "true prevalence" of food additive reactions is large, and pointed out that the mechanism "is not immunological and there is no *in* vivo or *in vitro* confirmatory test." **Note:** *There is no test to prove you have a headache either.*

b. Out of the 132 people entered in Young's trial, 65 – almost 50% -- withdrew or were "lost." The rest were put on an additive-free diet for two weeks, followed by trials of "low dose" and "high dose" food additives.

c. Of those food dyes used in the US, the following were tested:

Color	Low Dose (mg)	High Dose (mg)	ADI for 30 kg (66 lb) Child (mg)
Yellow 6	0.5	2.5	112
Yellow 5	0.5	2.5	150
Blue 2	1	2.5	75

d. **Note:** *I have added a column for comparison to the ADI. Is it very surprising that only one child reacted clearly to the food dyes at both low and "high" doses?*

82. **ZEISEL 1986: (*) (Review) Dietary Influences on Neurotransmission.** *Advances in Pediatrics.* 33: 23-47. *(abstract only)*

a. This is a discussion of various ways that diet – and food additives – influence neurotransmission.

Please continue on next page
for Intake Studies

Appendix C

INTAKE STUDIES OF
SYNTHETIC FOOD DYES
BY COUNTRY

Username/Password = "Private/Papers"

BRAZIL:

ANDRADE 2014: Determination of Synthetic Food Dyes in Commercial Soft Drinks by TLC and Ion-Pair HPLC. *Food Chemistry.* 157:193-8

a. Yellow 5, Red 2, Yellow 6 and Blue 1 extracted from soft drinks were compared to the labels.

b. Incorrect labels and sometimes more dye than allowed was found.

FEITOSA 2017: Estimate of the Theoretical Maximum Daily Intake of Sunset Yellow FCF by the Brazilian Population. *Food Additives & Contaminants Part A*. 2017 Feb 20:1-8.

a. This study was able to estimate daily intake of foods containing Sunset Yellow *(Yellow 6)* using the 2008-2009 data collections of food purchases by the Brazilian Institute of Geography and Statistics. In this survey of 55,970 households, individual consumption of food was determined for people age 10 and up. The authors believe that younger children are likely to have even higher intake for their body weights, but that information was not available in the survey.

b. The authors used several methods of determining consumption. According to the FAO/WHO approach to food dyes, or the average intake per capita of foods containing Yellow 6, the average consumption would not exceed the ADI *(Acceptable Daily Intake)*.

- **Note:** *Remember that an "average consumption" averages me - eating no dyes - with my neighbor who may be eating double the "per capita" amount.*

c. However, when using prevalence of food consumption with the current eating habits of parts of the Brazilian population, Feitosa finds that **both adolescents and adults in Brazil are consuming Yellow 6 in excess of the ADI, while seniors are getting 88% of the ADI**.

d. Quote: **"Foods that contribute the most to the excess consumption of SY** *(Sunset Yellow)* **are powder juices, soft drinks and chocolate."**

e. Quote: **"Considering the prevalence of food consumption per capita, one segment of the population of adolescents could be consuming up to 173% of the ADI…"**

CHINA

LI 2018: Inedible Azo Dyes and Their Analytical Methods in Foodstuffs and Beverages. *Journal of AOAC International*, Vol. 101.

c. This guest editorial is not about the food dyes we expect to find on labels — it's about inedible, dangerous food dyes used illegally.

d. **Note:** *Since the US imports many products (including food dyes) from China, it may be relevant.*

e. Quote**:** "In the past decades, the illegal addition of the inedible colorants has become one of the major issues of food safety."

f. The article goes on to describe foods we would not expect to be colored and the various methods by which these dyes can be detected.

LOK 2010: Colour Additives in Snack Foods Consumed by Primary School Children in Hong Kong. *Food Additives and Contaminants: Part B.* 3(3): 148-155.

a. This study is similar to the one below, except here nobody was eating more than the ADI – see Table 5 and compare to Table 3 in the paper below. There are significant differences in the consumption estimate across all the dyes, not just Sunset Yellow (E110 or Yellow 6)

b. In measuring the amount of color in products, the authors report that ingredient labels were not very accurate – sometimes a dye was listed that was not present, and sometimes the dye they found was not listed.

LOK 2011: Synthetic Colourings of Some Snack Foods Consumed by Primary School Children Aged 8-9 Years in Hong Kong. *Food Additives and Contaminants: Part B.* 4(3): 162-167.

a. Examining 87 snack food products often eaten by children in Hong Kong, and using food frequency questionnaires from 142 children, it was determined that most of the dyes were consumed at a level below the ADI. The only one higher than the ADI was Yellow 6 for which the daily average intake was **51% more than the ADI**. This high intake was due to soft drinks and desserts.

b. Table 3 indicates the ADI ranges. In 2009, the ADI of Sunset Yellow (Yellow 6) was lowered to 1 mg/kg. **Note:** *In the US, the ADI for this dye is 3.75 mg/kg.*

c. Look at Table 4 in which the Yellow 6 column has measurements up to a maximum of **3,440 mg/kg** in desserts. A child eating 100 mg (about a half cup) of this dessert would be getting about **34 mg** of that one dye. If the child weighs 30 kg, the ADI would only be **30 mg**, so he has exceeded it just with one dessert.

FRANCE

ELHKIM 2007: New Considerations Regarding the Risk Assessment on Tartrazine: An Update Toxicological Assessment, Intolerance Reactions and Maximum Theoretical Daily Intake in France. *Regulatory Toxicology and Pharmacology.* 47 (2007): 308-316.

a. Quote: " … in France, the estimated maximum theoretical intake of Tartrazine in children is **37.2% of the ADI** at the 97.5th percentile. It may therefore be concluded that from a toxicological point of view, Tartrazine does not represent a risk for the consumer."

b. Elhkim also says that most people affected can read labels, but points out that restaurant food items such as ice cream don't have labels.

GERMANY

DIOUF 2014: German Database on the Occurrence of Food Additives: Application for Intake Estimation of Five Food Colours for Toddlers and Children. *Food Additives & Contaminants.* Part A. 31(2): 197-206.

a. Diouf calculated that high-level consumers in Germany "**heavily exceeded" the ADI** for E110 (Yellow 6), E160 (Annatto), and E124 (Ponceau).

b. Real-use levels were found to be very difficult to obtain. The author complained that industries would give insufficient information or the analyses would be missing altogether. To overcome this problem, they followed the Irish approach and set up a German database.

c. Food additive use was only considered when on the label for specific foods.

d. Using two different approaches, called Tier 2 and Tier 2b, the amount of food dye consumed was either "heavily exceeding" the ADI for all three dyes (Tier 2) or only "exceeding" the ADI for the Ponceau and Annatto (Tier 2b).

INDIA

DIXIT 2008: Benzoate and Synthetic Color Risk Assessment of Fast Food Sauces Served at Street Food Joints of Lucknow, India. *American Journal of Food Technology.* 3(3): 183-191.

a. Tomato and chilli sauces served on the streets in India contained much more food dyes than branded products. Yellow 6 was estimated in **one commodity alone to reach 20% of the ADI.**

b. The author says these street vendors (who cater to the tourist population as well as locals) need assistance to improve this situation.

DIXIT 2010: Usage Pattern and Exposure Assessment of Food Colours in Different Age Groups of Consumers in the State of Uttar Pradesh, India. *Food Additives and Contaminants.* 27(2): 181-189.

a. Although 90% of foods had approved food colors rather than illegal colors, 59% exceeded the maximum allowed limit of dyes with averages of more than 100 mg/kg in most items.

b. The intake of Yellow 6 **exceeded the ADI by 88%** for children and by **39% for adolescents**. Consumption of Yellow 5 ranged from intakes of **27.4% to 90.3% of the ADI**.

c. Dye levels were measured, not calculated from industry information.

DIXIT 2011: Usage Pattern of Synthetic Food Colours in Different States of India and Exposure Assessment Through Commodities Preferentially Consumed by Children. *Food Additives and Contaminants.* 28(8): 996-1005.

a. Only 87.8% of items sampled contained permitted colors rather than illegal colors, and only 48% of those were under the maximum allowed limit of 100 mg/kg. In one sample, Yellow 5 and Yellow 6 were detected at 3,727 mg/kg which is 37 times the allowed limit.

b. Yellow 5 and Yellow 6 were the most popular colors. Exposure assessments showed that consumption **exceeded the ADI** many times over:

c. Red 3: "Average" consumers **exceeded the ADI by 2 to 6 times.**

d. Red 3 & Yellow 6: "High" consumers **exceeded the ADI by 3 to 12 times** in all age groups.

DIXIT 2013: All India survey for analyses of colors in sweets and savories: Exposure risk in Indian population. *Journal of Food Science.* 78(4): T642-7.

a. This is the first national study on food additive use in India, collecting data on "sweets and savories." They were able to separate, identify, and measure each of the permitted color dyes, as well as the non-permitted (illegal) ones.

b. Of the total of 2,409 samples analyzed, 16.4% contained non-permitted food dyes, and **58% contained permitted food dyes at excessively high levels.**

RAO 2004: Exposure Assessment to Synthetic Food Colours of a Selected Population in Hyderabad, India. *Food Additives and Contaminants.* 21(5):415-421.

a. In an exposure assessment of children age 1-5 and 6-18, some of them **exceeded the ADI** for Yellow 5, Yellow 6, and Red 3.

b. The ADI for Red 3 was reduced from 2.5 to 0.1 mg/kg because it produced toxic effects on thyroid function in short-term studies in rats (Larsen 1991).

c. **Note:** *The ADI for Red 3 is still 2.5 mg/kg in the US.*

IRAN

ASADNEJAD 2018: Data on Prevalence of Additive Colors in Local Food and Beverage Products, Tehran, Iran. *Data in Brief*. 19: 2104-2108.

a. 1120 samples were analyzed. Tartrazine was the only non-permitted color.

b. **Note:** *Iranian citizens (as of 2018) believe synthetic colorings are not used in Iran and have long been illegal. Apparently, food dyes do not appear on labels at all. (from personal communications with Iranian citizens)*

MOHAMADI 2015: Study the Effect of Education of Confectionary Workers to Use Synthetic Color in Pastry Cooked in Kermanshah Province, Iran. *International Research Journal of Applied and Basic Sciences.* 9(9): 1636-1638.

a. Bakery products were analyzed. 50 out of 107 samples contained synthetic colors. After a training intervention, 49 out of 107 new samples still contained synthetic colors. The authors concluded that training doesn't help.

b. More than 70% of some products claimed to be "guaranteed to be produced using saffron" contained synthetic colors instead. 8.4% of samples contained illegal colors.

c. The authors concluded that training pastry staff doesn't help and they suggest that
(1) supervising organizations must be stricter and
(2) the media should help put producers under pressure.

d. **Note:** *Public pressure may be difficult to arouse in Iran's political climate.*

MORADI-KHATOONABADI 2014: Synthetic Food Colours in Saffron Solutions, Saffron Rice and Saffron Chicken from Restaurants in Tehran, Iran. *Food Additives & Contaminants: Part B.* 8(1): 12-17.

a. 52% of 573 samples from restaurants in Iran contained synthetic colors instead of saffron in spite of national standards forbidding it. 44% of the dyes were Tartrazine (Yellow 5).

b. Saffron itself is very expensive and may be contaminated with food dye.

IRELAND

CONNOLLY 2010: **Pattern of Intake of Food Additives Associated with Hyperactivity in Irish Children and Teenagers**, *Food Additives and Contaminants.* 27(4): 447-456.

a. According to a complex mathematical analysis, Irish children and teenagers rarely ate the amount of food dyes used in the Southampton (McCann 2007) study, although they did exceed the benzoate level.

b. **Note:** *Considering the year this study was done, food dyes were already being removed from foods and people were more aware of avoiding them, so levels of consumption may well have dropped. On the other hand, consumption of actual additives was not physically measured at any time.*

FOOD SAFETY AUTHORITY OF IRELAND 2005: A Surveillance Study on Levels of Artificial Colours and Sweeteners in Irish Retail Products.

a. Out of 363 foods analyzed, **8.5% were non-compliant** either because they exceeded the maximum levels allowed or they were not declared on the label.

b. Most of the non-compliant items were products aimed at young children, but it was expected that following the survey, more companies were replacing synthetic dyes with natural colors.

KOREA

HA 2013: **Exposure Assessment of Synthetic Colours Approved in Korea.** *Food Additives & Contaminants: Part A.* 30(4): 643-653.

a. Of 704 products chosen for the sample, only 471 (67%) contained food dyes.
b. The estimated daily intake (EDI) for children was higher than adults.
c. The average consumer EDI was not more than 2.5 of the ADI of each color.
d. The "Conservative consumer" (at 95%) was at 37% of the ADI level.
e. The authors measured some of the foods but averaged the color content; there was lots of complicated math in this.

KUWAIT

ALOMIRAH 2010: The Dietary Exposure Assessment to Selected Food Additives and Contaminants for the GCC Countries Population. *5th Saudi Conference for Food and Nutrition, Riyadh, Saudi Arabia.*

a. (Page 16): The average daily intake of Tartrazine (Yellow 5), Sunset Yellow (Yellow 6), Allura Red (Red 40), and Carmoisine (not used in US) were much higher than the ADI for ages 6 – 9.

HUSAIN 2006: Estimates of Dietary Exposure of Children to Artificial Food Colours in Kuwait. *Food Additives & Contaminants.* 23(3): 245-51.

a. Husain evaluated the amount of food dyes consumed by children in 58 schools in Kuwait, and **found that the amounts of four of the colors were 4 to 8 *times* above the acceptable daily limit:**
    - Yellow 5 (Tartrazine, E102)
    - Yellow 6 (Sunset Yellow, E110)
    - Carmoisine (E122, *not used in the USA*)
    - Red 40 (Allura Red, E129)

b. **Note**: *The 24-hour diet recall did not include dyes encountered in toothpaste, medicines, vitamins, or toiletries.*

c. The high intake of colored foods was attributed to "high purchasing power, food consumption patterns and lack of awareness."

d. Disappointingly, the authors didn't recommend using less, but only suggested "further studies."

SAWAYA 2007: Consumption Patterns of Artificially Coloured Foods Among Children in Kuwait. *Nutrition & Food Science.* 37(3): 151-159.

a. The authors surveyed more than 3,000 children in 58 schools. They also bought about 450 items from local supermarkets in Kuwait, grouped them into categories and analyzed them. Posters with pictures of the products were used by the survey teams.

b. Data obtained showed that the average daily intakes of Yellow 5, Yellow 6, carmoisine, and Red 40 – in all age groups – were **more than 100% of the ADI**, with a few exceptions.

c. Reference was made to another study on 100 families in the United Arab Emirates (in Arabic) by Hassan & Marei (1993). In that study, it was found that levels of Yellow 5 and Yellow 6 sometimes exceeded good manufacturing practice which allowed up to 300 mg/kg in snacks. They found intakes between 500 and 2,000 mg/kg for cheese balls and puffed snacks. They also found that consumption by **children under 7 years old exceeded the ADI** level of 2.5 mg/kg, and that a number of children complained of symptoms after eating snacks.

POLAND

GAJDA-WYREBEK 2017: Esposure of Polish Children to Southampton Food Colours. *Food Additives and Contaminants Part A.* 34(1): 1-9

a. This study was undertaken several years after warning labels had been in place and the ADI levels had been adjusted. The author credits these changes with the relatively low levels of exposure, although some individual children did manage to consume up to 58.5% of E122 (carmoisine)

b. Of a total of 197 questionnaires filled out, only 18 of the 3-year-olds and 19 of the 8-9- year-olds consumed anything with food coloring. In determining their average consumption, the authors did not count those who did not consume any, so as to develop a "worst case" level of color intake. Most of the items consumed were candy/confections, sodas, and "other" items.

c. **Note:** Dyes in toiletries such as toothpaste were not considered in any of these studies.

SINGAPORE

LEO 2018: Occurrence of Azo Food Dyes and their Effects on Cellular Inflammatory Responses. *Nutrition*. 46:36-40

a. This study found that 11.54% of 1,681 items examined in a supermarket in Singapore contained at least one food dye

b. Yellow 5, Yellow 6, and Red 40 were the most prevalent.

c. There is more on this study at #114, Page 45.

UNITED STATES

BASTAKI 2017: Estimated Daily Intake and Safety of FD&C Food Colour Additives in the US Population. *Food Additives & Contaminants, Part A, Chemistry, Analysis, Control, Exposure & Risk Assessment*. 2017 March 23.

a. Using complex statistics, not measurements, the daily intake of synthetic food dyes was estimated for the American public. Of all products in a particular category, percentages of those with dye were used so that an estimate for the amount of dye consumed in "chewing gum" – for example – could be obtained.

b. Quote: **"The database captures new products launched … It does not capture existing products …"**

c. **Note:** *Translation: "Old" products such as M&Ms & Twizzlers would not be included. Since many manufacturers are removing food dyes from NEW products, this should vastly underestimate exposure.)*

d. The charts at the end of the paper list expected amount of each food dye per category. See the category "Bakery" for example. **Note:** *How do you define a "typical" bakery item? Can you "average" a slice of 3-layer birthday cake and a Danish?*

e. Quote: **"**In the Southampton study, children were given a combination of four colours and a preservative at daily amounts **equal to each ADI, with totals adding up to very high levels of intake."**

f. Quote: "… for children to reach the intake assumed in the Southampton study, they would have to c**onsume at least 30 times more foods and beverages daily than the high consumers (95%)** and the foods would have to contain four different colours at maximum use levels, a clearly unrealistic scenario."

g. **Note:** *These two quotes are totally untrue, based on a misreading of the Southampton study.*

- In that study, only 20 mg to 62.4 mg were used.
- ADI levels would have been several hundreds of mg.

h. **Note:** *After being confronted with these errors, Bastaki published a (partial) correction which can be seen here. She continued to insist that the children in the Southampton study received "well above the high end of the range estimated in our study." This is technically correct, considering the unrealistically* ***low*** *estimates quoted in her paper.*

i. See Bastaki's charts of cumulative intake levels — in ***micrograms per kg*** *of* body weight per day. Considering that a child can get **14.5 mg — 14,500 micrograms –** of food dye from one single glass of Powerade Fruit Punch (Stevens 2015), does it make any sense to claim that a 20 kg (44 lb) child will have a "maximum" total intake of only **8,580 micrograms (8.6 mg)** for a whole day?

14,500 µg
per cup !!!!

j. **Note:** *See my calculations at right for the "95%" level of her "maximum use" category. Please feel free to check my math against her charts in which I have highlighted the lines included.*

CHILD 6-12 Yrs	Max Use
Yellow 6	21.3
Yellow Lake	121.5
Red 40	63.3
Red 40 Lake	89.1
Yellow 5	26.6
Yellow 5 Lake	44.1
Blue 2	3
Blue 2 Lake	20.6
Blue 1	13.4
Blue 1 Lake	19.4
Red 3	6.5
Green 3	0.2
TOTAL	**429 micrograms/kg**
20 kg child	**8,580 micrograms = 8.6 mg**
25 kg child	**10,725 micrograms = 10.7 mg**

k. Bastaki concludes, "It is concluded that food colour use as currently practiced in the United States is safe and does not result in excessive exposure to the population **…"**

l. **Note:** *You can test this yourself – go to the Stevens (2014) and Stevens (2015) studies (pages 80-81, #206-208) in which Stevens measured how much food coloring is in various items. Choose any you want for your "daily consumption." Add them up and then multiply by 1,000 to convert the milligrams into micrograms and see if you have come in under Bastaki's "maximum total intake" for a day.*

m. Funding: **The International Association of Color Manufacturers (IACM)** advertising they "advance the interests of manufacturers, producers, and users in the color industry."

n. Conflict of Interest Statement: No statement. Just a note thanking the IACM and acknowledging their support.

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o. **Note:** *Author affiliations:*

- **M. Bastaki:** Scientific Director, IACM.
- **T. Farrell:** Director at Colorcon Inc., making products for the pharmaceutical industry.
- **S. Bhusari:** Manager of Ingredient Safety at Coca-Cola.
- **X. Bi and C. Scrafford:** Scientists at Exponent, Inc., advertising they "solve engineering, science, regulatory, and business issues facing our clients."

BATADA 2016: Prevalence of Artificial Food Colors in Grocery Store Products Marketed to Children. *Clinical Pediatrics,* 55(12): 1113-1119.

a. 810 products commonly marketed to children and found in a local U.S. grocery store were evaluated. 43.2% of them contained artificial food colors (AFC), mostly Red 40, Blue 1, Yellow 5, and Yellow 6.

b. The authors say that since about 4 in 10 packaged grocery items have at least one AFC, parents wishing to eliminate them face a challenge. The authors call for clinicians, parents, food companies and the government to **support children's healthy development by reducing the food dyes in their diets.**

DOELL 2016: Exposure Estimate for FD&C Color Additives for the U.S. Population. *Food Additives & Contaminants: Part A.* 33(5):782-797.

a. Numerous products were analyzed for amount of food dyes contained, and two exposure surveys were conducted – a 2-day diet diary and a 10-14 day diet diary.

b. **Note:** *The dyes included in soap, toothpaste, shampoo, mouthwash, lotion, dental dyes (to encourage brushing) etc. were not included in these charts, but keep them in mind, too.*

c. **Note:** *In the charts below, I have added (in purple) the totals for the "low," "average," and "high" food dye exposure for groups aged "over 2 years" and "boys, 13-18 years"*

Based on 2-Day Food Consumption Data

Group	Low Exposure	Low Exposure	Average Exposure	Average Exposure	High Exposure	High Exposure
Age	>2 yrs	13-18 yrs	>2 yrs	13-18 yrs	>2 yrs	13-18 yrs
Blue 1	2.1	2.2	2.9	3.4	4.8	6.3
Blue 2	1.3	1.1	1.6	1.7	3.4	4.0
Green 3	2.6	3.8	2.6	3.8	2.6	3.8
Red 3	3.4	2.3	3.8	2.4	4.2	3.0
Red 40	11.6	14.2	22.5	29.7	53.0	70.2
Yellow 5	6.4	7.6	10.8	13.9	19.3	26.1
Yellow 6	11.3	22.2	15.8	26.4	20.5	34.5
DAILY TOTAL (mg)	38.7	53.4	60.0	81.3	107.8	147.9
Chart	Table 3	Table 5	Table 3	Table 5	Table 3	Table 5

Based on 10-14 Day Food Consumption Data

Group	Low Exposure	Low Exposure	Average Exposure	Average Exposure	High Exposure	High Exposure
Age	>2 yrs	13-18 yrs	>2 yrs	13-18 yrs	>2 yrs	13-18 yrs
Blue 1	1.4	1.6	2.0	2.2	3.0	3.7
Blue 2	0.9	0.8	1.2	1.7	2.1	3.2
Green 3	0.9	1.3	0.9	3.8	0.9	1.3
Red 3	2.1	2.1	3.0	2.4	3.2	2.7
Red 40	6.2	7.8	13.1	29.7	36.6	49.0
Yellow 5	3.4	4.6	5.9	13.9	11.1	14.8
Yellow 6	5.1	8.0	8.2	26.4	11.0	14.7
DAILY TOTAL (mg)	20.0	26.2	34.3	80.1	67.9	89.4
Chart	Table 6	Table 8	Table 6	Table 8	Table 6	Table 8

d. In the 10-14 day survey, if a child ate one item with any coloring on any one day out of the 14, he was called an "eater" and included, so this actually dilutes the averages, resulting in a lower "average" total. Quite possibly, the 2-day survey – as a snapshot of those children actually eating something with food dye on the day of the survey – is more realistic. It is not the child who eats one item a week who will be affected by the dyes, but rather the child who is exposed to the coloring chemicals multiple times per day.

Appendix D

Statement of Interest:

As a retired "volunteer worker," I am building a blog to showcase research I happen to like, and I have been on the HelpLine for the Feingold Association for the past many years. At first, it was simply a desire to "pay forward" the benefit I had received. You can see my son's story here.

Today, it is more. It is the ongoing feedback from members – like the two emails below from a mom named Lisa Robinette. (*Lisa has given me permission to share her emails and name*.) Knowing I can help another child have a chance at a better life makes it worth my while to do all I can. It is thus with pleasure that I have put together this list of research for your review.

Email 1: dated 11/30/2017 10:41:07 PM

Hi Shula and Jane,

I just want to give you all a quick update that my daughter Claire is doing AMAZING!!!

All of a sudden last Wednesday we started to see a noticeable difference, after a hellish previous week full of pee and poop accidents, major nasty tantrums, and manic behavior (withdrawal week...?). Last Wed was the first day in 5 days she did not have a potty accident, and we also started to notice her getting a bit more control of her emotions every day. For the next week, it was like every day she calmed down a bit more, tantrums less frequent and much shorter, occurring mostly at night when she was tired. And for last 2 days, she has had 0 meltdowns or tantrums!!!! That has never happened before in her life.

This is life changing for her and us. Both my husband and I notice a difference in her comprehension and communication, like she can literally think more clearly now. She drew a pretty picture of flowers and grass on her own. She willingly left mamaw's house without a fit or me dragging her out the door screaming. She is letting me brush her hair. She has chosen on her own to go potty without us asking. She has not complained once about the foods she can't have. She is witty and sweet instead of hateful and irrational.

So anyway, this is to thank you for your encouragement to stick to it even as it got worse!! The exciting thing for us is that we don't even know if we've gotten to her new baseline yet, because she is still improving every day!!!

Many thanks,
Lisa

Email 2: dated January 9, 2019

Hi Shula and Jane,

Just wanted to give you a quick update- Claire is doing great!! We've been FG for 14 months and haven't looked back! She has successfully started kindergarten and is doing great - her very experienced teacher questions whether she actually has ADHD! She still received an ADHD diagnosis from a pediatric behavioral psychiatrist in Sept (after waiting 6 months to see him) but figured out she was having a build

up reaction to approved gum she had been chewing! So she clearly showed ADHD tendency on the first appointment, but at her follow up this December, we asked him to retest her and all but one of her scores were totally normal. Huge improvement! Although he is a reputable doctor, he did not put any stock in FG or dietary treatments for ADHD. He didn't discourage it, but just says it's never been proven. …

I may be considering a career change. Working for a chemical company is now a bit of a moral dilemma, and I can't figure out how I can use my chemical engineering degree for good use when it comes to spreading the truth about these food additives! So I'm starting to consider pursuing a masters degree in a field that might put me closer to that goal. Even at age 39 with 2 young kids. A bit of a dream at the moment!!

Thanks so much for any input!

Lisa Robinette

xxx