**Specific Care Question**
In children, does Red Dye 40 versus no Red Dye 40 cause behavioral changes?

**Question Originator: Scott Rodgers, D.O.**

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**Significance and importance of the question:**

Families ask if Red Dye 40 has recently been "banned" by the European Union due to the relation to the risk of food dyes and ADHD are food dyes safe to consume. Specifically parents ask area health care practioners will Red Dye 40 make my child's ADHD symptoms worse. This is a summary of the Southhampton study and EU documents. They are summarized here to inform decision-making.

In 1973, Benjamin Feingold, MD proposed that food additives caused learning disabilities and hyperactivity in children. He reported major improvements when dye was removed from a child's diet. In fact ~ 75% of children who had the offending substances removed from their diets ahd improved behavior. He never published research; rather he wrote a signed editorial in *Hospital Practice* 1973 and a commentary in *American Journal of Nursing* 1975. Plus he wrote a bestselling book, *Why Your Child Is Hyperactive*.

Much research was conducted on this question in the ensuing years. However, a relationship was difficult to identify as most studies were underpowered and follow up of subjects was poorly reported. In a meta-analysis Schab (2004) reported a significant effect of artificial food colors and additives. Three studies have been published since the Schab 2004 meta-analysis (Bateman 2004, McCann 2007 & Stevenson 2010) "aka the Southampton studies". These studies bring the food coloring and ADHD question into the 21st century.

Based in these studies, the European Union adopted a new set of regulations on food additives (Regulation 1133/2008) that consolidates all previous regulations under one set of directives. The regulation went into effect January 2010. The regulation states foods that contain the "Southampton 6" colors have to be labeled with the following: "name or E number (E number similar to FD&C designation) of the color may have an adverse effect on activity and attention in children." It does not ban artificial or synthetic colors. Of note, of the Southampton 6, only 3 colors are allowed in foods in the US. FD&C Yellow 6. FD&C Red 40 and FD&C Yellow 5. D&C Yellow 10 is allowed in drugs and cosmetics, but not food.

The Southampton Six

| Color | Effect | FD&C designation (USA) | E number European Union | US Usual amt | EU ADI (Adequate Daily Intake |
|---|---|---|---|---|---|
| Sunset yellow FCF | Orange shade | Yellow 6 | E110 | The US does not give amounts, but refers to GMP or "'Good Manufacturing Practice" | 1 mg/kg/d |
| Quinoline yellow | Yellow shade | D&C yellow 10 (not a food additive | E104 | | 0.5 mg/kg/d |
| Carmoisine | Red shade | Unapproved in the USA | E122 | | 4 mg/kg/d |
| Allura red | Red shade | Red 40 | E129 | | 7 mg/kg/d |
| Tartrazine | Orange shade | Yellow 5 | E102 | | 7.5 mg/kg/d |
| Ponceau 4R | Red shade | Unapproved in the USA | E124 | | 0.7 mg/kg/d |

Of note, the European Food Safety Authority (EFSA) did not change the acceptable daily intake (ADI) for Red 40, Yellow 5 or Carmoisine (It lowered the ADI for (Yellow 10, Yellow 6, and Ponceau 4R (A systematic review carried out by the ANS Panel ((Panel on Food Additives and Nutrient Additives Added to Food) not published) concluded the "research did not substantiate a causal link between individual colors and possible behavioral effects." The colors are not "banned", they are just more tightly regulated and the food industry responded by voluntarily removing them from foods and marketing this fact.

**Search Strategy and Results**:
Medline Search
"Food Coloring Agents/adverse effects"[Mesh] AND ("Neurologic Manifestations/etiology"[Mesh] OR "Mental Disorders Diagnosed in Childhood/chemically induced"[Mesh]) AND ("infant"[MeSH Terms] OR "child"[MeSH Terms] OR "adolescent"[MeSH Terms])) NOT AND ((Editorial[ptyp] OR Letter[ptyp] OR Case Reports[ptyp] OR News[ptyp])

39 articles returned. Ten studies have been published since 1990. Most studies published prior to 1990 were excluded.

*Exclusions:*

Pollock 1990 – high attrition only 19/39 completed the study
No Author (2003) it is a side bar in the journal
Silfverdal 2008 is in Swedish.
No Author 2009 is a narrative review
Eigenmann 2007 – letter to the editor
Stevenson 2005- response to Eigenmann

*Included:*

Bateman 2004
McCann 2007
Rowe1988
Schab 2004
Stevenson 2010

**Method Used for Appraisal and Synthesis**:
Review Manager (RevMan 5.1) was used to synthesize Bateman. 2004 Other included studies were analyzed using the Critically Appraised Topic (CAT) worksheet.

**Summary:**
A recommendation cannot be made due to the poor quality of the studies. However, family values play a strong role in this clinical question. Avoiding food additives is a difficult task, but it may not be an all or nothing situation. Most food additives are in highly processed foods. Supporting healthy food choices and avoiding highly processed foods is judicious.

- The included studies use dye mixtures with or without sodium benzoate, not single dyes. It is impossible to sort out the effects of FD&C Red 40.
- The Rowe 1988 study is included because it is an example of the inherent difficulties encountered in doing a study of this type. Major problems include, only parents reported on behavior, more objective reports were not gathered. Only 2 of the 14 children in the crossover study responded to the diet with food color + sodium benzoate. The low number of responders makes the findings imprecise. The results section reads more like a two case studies.
- The Schab (2004) meta-analysis analyzed 15 trials with 219 subjects. The major limitation of the review is the quality of the studies included. Most studies were cross over design. Thirty-three percent did not use a wash out period between diets. The included studies use dye mixtures with or without sodium benzoate, not single dyes. It is impossible to sort out the effects of a specific additive like FD&C Red 40. Publication bias is apparent because small studies with a negative estimate of effect have not been published.

- McCann (2007) – See critically appraised topic (CAT). The methods of this study are strong. However, because dyes and additives were added as mixtures, not as separate entities, it is difficult to state which compound is the causative agent.

- Bateman 2004 reported differences in behavior were only apparent in observations made by parents (but not significantly), not in assessments performed in clinic. Atopy did not appear to play a role in reactivity to the dyes that included

- Stevenson (2010) - is an RCT that included children from the McCann (2007) study. Children from both the 3 year old group (n=137) and from the 8/9 year old group (n= 130). The children underwent a buccal swab for DNA genotyping during the study. Data showed a relationship between the overall level of hyperactivity and the HMNTT939C and DRD4rs740373 (Histamine risk alleles) polymorphisms in the 3 year old group. Children with polymorphisms in these genes may have more response to color than children without the polymorphisms. No effects were seen in the 8/9 year old group. This study the first of its type to be published, so it difficult to put into context.

- It is difficult to conclude FD&C Red Dye 40 plays a role in either causing or amplifying hyperactivity in children. The Southhampton studies did not look at individual dyes, but mixtures of dyes.

- However, parents are finding information like this on reputable web pages- http://www.fda.gov/downloads/AdvisoryCommittees/CommitteesMeetingMaterials/FoodAdvisoryCommittee/UCM272299.ppt.

**References**

Bateman, B.; Warner, J.O.; Hutchinson, E.; Dean, T.; Rowlandson, P.; Gant, C.; Grundy, J.; Fitzgerald, C.; Stevenson, J.. The effects of a double blind, placebo controlled artificial food colorings and benzoate preservative challenge on hyperactivity in a general population sample of preschool children. Archives of Disease in Childhood 2004; 89:506-511.

Edelkind, S. (2011). Food Dye and Behavior. [Presentation to the FDA Hearing on Food Dyes]. By The Feingold Association of the United States. www.fiengold.org. Retrieved from: http://www.fda.gov/downloads/AdvisoryCommittees/CommitteesMeetingMaterials/FoodAdvisoryCommittee/UCM272299.ppt.

McCann, D., Barrett, A., Cooper, A., Crumpler, D., Dalen, L., Grimshaw, K., Kitchin, E., Lok, K. Porteous, L., Prince, E., Sonuga-Barke, E., Warner, J.O., & Stevenson, J.. Food additives and hyperactive behaviour in 3-year-old and 8/9-year-old children in the community: a randomized, double-blinded, placebo-controlled trial. Lancet 2007; 370:1560-1567.

Regulation (EC) No 1333/2008 of the European Parliament and of the Council of 16 December 2008 on food additives (Text with EEA relevance). Retrieved from http://eur-lex.europa.eu/LexUriServ/LexUriServ.do?uri=CONSLEG:2008R1333:20100720:EN:PDF

Schab, D. w. & Trinh, N. (2004). Do artificial food colors promote hyperactivity in children with hyperactive syndromes? A meta-analysis of double- blind placebo-controlled trials. Developmental and Behavioral Pediatrics, 25, 6, 423-434.

Stevenson, J., Sonuga-Barke, E., Mcann, D., Grimshaw, K., Parker, K.M., Rose-Zerilli, M.J., Holloway, J.W., Warner, J.O. The Role of Histamine Degradation Gene Polymorphisms in Moderating the Effects of Food Additives on Children's ADHD Symptoms. Am J Psychiatry 2010;167:1108-1115.

**Updated: October 2011, November 2011**

**Bateman 2004**

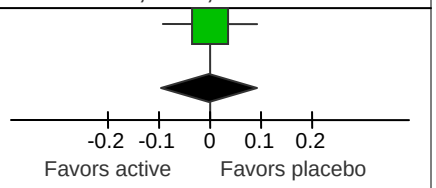
| | |
|---|---|
| **Methods** | Cross-over RCT |
| **Participants** | 277 3-year-old children evenly stratified by presence of hyperactivity, absence of hyperactivity, presence of atopy, and absence of atopy. |
| **Interventions** | All received the same treatments in cross over fashion.<br>Treatment phase included received 20 mg of artificial coloring and 45 mg sodium benzoate daily as a diet supplement during the 2nd and 4th weeks of a 4 week period.<br>Control groups received a placebo mixture daily as a diet supplement during the 2nd and 4th weeks of a 4 week period. |
| **Outcomes** | Clinically-assessed aggregated hyperactivity (ATH) and parent-assessed aggregated hyperactivity (APHR). |
| **Notes** | |

| **Bias** | **Scholars' judgment** | **Support for judgment** |
|---|---|---|
| Random sequence generation (selection bias) | Low risk | Random number table was used. |
| Allocation concealment (selection bias) | Low risk | A dietician prepared the drinks and did not follow the subjects thereafter |
| Blinding of participants and personnel (performance bias) | Low risk | All the study team and the personnel were blinded. |
| Blinding of outcome assessment (detection bias) | Low risk | All the study team and the personnel were blind. |
| Incomplete outcome data (attrition bias) | High risk | Attrition occurred (30% or 120 out of 397 selected for final phase). A per protocol analysis was used. ~ 50% of the withdrawals were due to behavioral reasons. Missing data was imputed. |
| Selective reporting (reporting bias) | Low risk | All primary outcomes were reported. |
| Other bias | Unclear risk | |

## Comparison 1. Food coloring/preservative vs. placebo, Outcome: Hyperactivity tests performed in clinic

| Study or Subgroup | Post-active Mean | SD | Total | Post-placebo Mean | SD | Total | Weight | Mean Difference IV, Fixed, 95% CI |
|---|---|---|---|---|---|---|---|---|
| Bateman 2004 | -0.03 | 0.55 | 277 | -0.03 | 0.56 | 277 | 100.0% | 0.00 [-0.09, 0.09] |
| **Total (95% CI)** | | | **277** | | | **277** | **100.0%** | **0.00 [-0.09, 0.09]** |

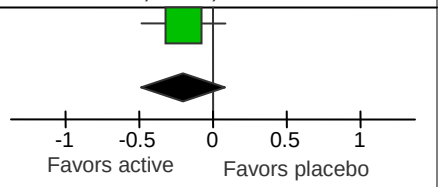
Heterogeneity: Not applicable
Test for overall effect: Z = 0.00 (P = 1.00)




## Comparison 2 Food coloring vs. placebo, Outcome: Hyperactivity ratings performed by parents

| Study or Subgroup | Post-active Mean | SD | Total | Post-placebo Mean | SD | Total | Weight | Mean Difference IV, Fixed, 95% CI |
|---|---|---|---|---|---|---|---|---|
| Bateman 2004 | -0.06 | 1.61 | 277 | 0.14 | 1.8 | 277 | 100.0% | -0.20 [-0.48, 0.08] |
| **Total (95% CI)** | | | **277** | | | **277** | **100.0%** | **-0.20 [-0.48, 0.08]** |

Heterogeneity: Not applicable
Test for overall effect: Z = 1.38 (P = 0.17)




## Critically Appraised Topic-

| Author, date, country, and industry of funding | Patient Group | Level of Evidence (Oxford) / | Research design | Significant results | Limitations |
|---|---|---|---|---|---|
| McCann, D., Barrett, A., Cooper, A., Crumpler, D., Dalen, L., Grimshaw, K., Kitchin, E., Lok, K. Porteous, L., Prince, E., Sonuga-Barke, E., Warner, J.O., & Stevenson, J.. Food additives and hyperactive behaviour in 3-year-old and 8/9- | Children<br>3 year olds N= 153 (16 did not complete the study)<br>8/9 year olds n=144 (14 did not complete the study) | 1 b<br>Individual RCT with narrow confidence intervals | Randomized, double blinded, placebo controlled cross over<br>Two active mixes | Outcomes: T tests for differences between Mix A and Placebo and Mix B and placebo were not significantly different. However when the Global Hyperactivity score was estimated in linear mixed models the following was reported:<br><u>3 year olds-</u><br>Mix A had adverse effects on GHA for the (a) entire sample and the sub group (b) those that consumed > 85% of the supplements containing the dyes and (c) | Cannot tell the specific compounds in each mix that caused the effect.<br><br><u>Mix A:</u> 20 mg of artificial food colorings (5 mg sunset yellow [E110], 2·5 mg carmoisine [E122], 7·5 mg tartrazine [E102], and 5 mg ponceau 4R [E124, Forrester Wood, Oldham, UK]) and 45 mg of sodium benzoate [E211, Sigma Aldridge, Gillingham, UK] |

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|---|---|---|---|---|---|
| year-old children in the community: a randomized, double-blinded, placebo-controlled trial. Lancet 2007; 370:1560-1567. | | | of additives<br>Mix A and Mix B and Placebo | those for which complete study data was available.<br>Mix B had no effect<br><br><u>8/9 year olds</u><br>Mix A had adverse effects on GHA for the ( (a)those that contained > 85% of the supplements and (b) those for which complete study data was available Mix A did not have adverse effects on GHA for the entire sample<br>Mix B had adverse effect on (a) the entire sample,(b) those that consumed > 85% of the supplements containing the dyes and (c) those for which complete study data was available. | <u>Mix B</u>**:** 30 mg of artifi cial food colourings (7·5 mg sunset yellow, 7·5 mg carmoisine, 7·5 mg quinoline yellow [E110], and 7·5 mg allura red AC [E129]) and 45 mg of sodium benzoate.<br><br>The amount of either Mix A or Mix B given to 8/9 year old children was increased by 1.25% to account to the increased amount of food consumed by this age group. |
| Rowe, K. S. (1988). Synthetic food colourings and 'hyperactivity': a double-blind crossover study. Australian Paediatric Journal, 24, 143-147. | Open study 55 children<br>Double blind crossover study 14 children | RCT-crossover | Open study was observational<br>Crossover was double blinded | Open study: 14/55 children claimed adverse reaction to the reintroduction of the synthetic additives. The claimants were spread between those with primary, secondary, mixed attention disorders and normal children. Children with mental retardation (5 children) psychiatric disorders (2 children) did not respond to the reintroduction of dyes.<br>Double blind crossover study- the 14 responders from above were enrolled. Only 2/14 demonstrated significant response. | Only parents' reports collected. Teachers were asked to complete behavior scales, but did not feel able to complete the task and did not submit useable data forms.<br>Although this is a cross over, and they used good blinding techniques, it is reported as two case studies. Descriptions only, not data. |
| Schab, D. w. & Trinh, N. (2004). Do artificial food colors promote hyperactivity in children with hyperactive syndromes? A meta-analysis of double- blind placebo- controlled trials. Developmental and Behavioral | 15 trials (219 subjects) met inclusion criteria of RCT<br>Consumption of food color and behavioral change in children<br>< 18 years of age<br>Included both | 1 b<br>Meta analysis poor quality studies. | Meta-analysis | To answer the question are artificial colors harmful, the estimate of the effect was 0.283 (95% CI, 0.079, 0.488). This is a significant difference between no artificial color and presence of artificial color.<br>The results were split by results given by health care provider, teachers and parents only. The parents survey responses were significantly different for days the subjects consumed food dye.<br>Health care provider estimate of effect 0.107 (95% CCI -1.128 to 0.343)<br>Teacher estimate of effect 0.0810, (95% | 5/15 trials had washout periods between treatments. (2-5 days).<br>An insufficient data from 5 of 15 trials to compute correlation coefficient, but it was imputed by the MA writers.<br>Heterogeneity in the treatments- some used a single dye (tartrazine) some used dye mixtures.<br>Only 2 trials were scored as highly valid by the MA writers<br>One study did not randomize<br>One study did not blind treatments or placebos well. |

<table>
<tr>
<td>Pediatrics, 25, 6, 423-434.</td>
<td>trials that looked at additives in children with hyperactivity syndromes and those without such syndromes.</td>
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<td>CI, 1.173 to 0.235)<br>Parents estimate of effect 0.441,( 95% CI, 0.161 to 0.721)<br>IN the secondary analysis, the estimate of the effect was not significant 0.117(95% CI -0.113 to 0.347).<br>However in the secondary analysis, when subjects who were responders were evaluated, those who were responders had a statistically significant ES of 0.316 (95% CI, 0.157 to 0.175)</td>
<td>Most did not discuss allocation concealment<br>A secondary analysis was performed on 8 crossover studies that included 132 participants. “Two of these studies were included in the primary analysis as well. 84(62%) of the subjects were assessed as responsive to artificial colors before entry into the specific study. Three trials employed unorthodox outcome measures-<br>Indication of publication bias against small studies with negative estimate of effect is apparent.</td>
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<td>Stevenson, J., Sonuga-Barke, E., Mcann, D., Grimshaw, K., Parker, K.M., Rose-Zerilli, M.J., Holloway, J.W., Warner, J.O. The Role of Histamine Degradation Gene Polymorphisms in Moderating the Effects of Food Additives on Children's ADHD Symptoms. Am J Psychiatry 2010;167:1108-1115.</td>
<td>Using the subjects from McCann 2007, buccal swabs were obtained to determine polymorphisms in</td>
<td></td>
<td>RCT</td>
<td>Looking at 6 genes that control histamine degradation, presence of increased hyperactivity with specific mixes was seen in children the
<table>
<tr><td>Significant Effect Seen (p<0.05)</td><td colspan="2">3 year olds</td><td colspan="2">8 year olds</td></tr>
<tr><td>MIX→<br>Gene↓</td><td>A</td><td>B</td><td>A</td><td>B</td></tr>
<tr><td>HTMTTHR105Ile</td><td>+</td><td></td><td></td><td>+</td></tr>
<tr><td>HNMTT939C</td><td>+</td><td></td><td>+</td><td>+</td></tr>
<tr><td>COMTVal108Met</td><td></td><td></td><td></td><td></td></tr>
<tr><td>ADRA2AC1291G</td><td></td><td></td><td></td><td></td></tr>
<tr><td>DAT1</td><td></td><td></td><td></td><td>+</td></tr>
<tr><td>DRD4rs740373</td><td></td><td></td><td></td><td></td></tr>
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polymorphisms identified above.</td>
<td>This is the first study of its kind. The length of exposure was short. Does chronic exposure habituate the subject to either increased or decreased behavior change when the substances are introduced?</td>
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