A Research Model for Investigating the Effects of Artificial Food Colorings on Children With ADHD

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**ABBREVIATIONS**

AFC—artificial food coloring
ADHD—attention-deficit/hyperactivity disorder
DSM—Diagnostic and Statistical Manual
MTA—Multimodal Treatment Study of Children With ADHD

The United Kingdom and European Union recently restricted the use of artificial food colorings (AFCs) to improve the health of children. These decisions provide an interesting case study of the role of scientific evidence in the assessment of food additives and risk to children’s health and formulation of food policy. Although there continues to be uncertainty concerning the link between AFCs and attention-deficit/hyperactivity disorder (ADHD), policy decisions have been made that have far-reaching implications. In addition, publicity surrounding the policy changes may shape public perceptions concerning effective management of ADHD. We believe that the balance of existing evidence neither refutes nor supports the link between AFCs and ADHD, which highlights the need for carefully designed studies to further investigate the link between AFCs and ADHD. In this article we describe a model for such studies. In developing our model, we drew from current investigative standards in ADHD research, such as those used in the landmark Multimodal Treatment Study of Children With ADHD. These standards encompass methodologic considerations including sample selection, outcome assessment, and data analyses. It is our hope that this model research methodology may prove valuable in addressing design considerations in future studies of AFCs and ADHD with the goal of producing reliable data that will enable policy-makers to better formulate effective, evidence-based food-policy decisions. *Pediatrics* 2011;127: e1575–e1584

In recent years, debates concerning the safety to human health of ingredients and technologies used by the food industry have become increasingly common. Examples include controversies surrounding the role of irradiation in food-processing, health risks associated with plastics in drink and food containers, use of antibiotics and hormones by the meat industry, and development of genetically modified foods. Policy discussions related to these issues often center on defining acceptable risk and its determinants, a process in which science plays a crucial role. The place of objective scientific evidence is especially important when one considers the tendency for stigmas about products or technologies to arise from popular perceptions of risk, which are often driven by fears or misinformation.

The ongoing debate concerning the link between artificial food coloring (AFC) and attention-deficit/hyperactivity disorder (ADHD) provides a useful case study of the role of scientific evidence in the assessment of food additives and risk to children’s health and formulation of food policy. There is disagreement on the question of whether an association exists and, if it does, how strong such an association may be. A
recent meta-analysis of existing studies concluded that the link between ADHD and AFCs was supported by better-designed studies. Furthermore, findings from a recent large and carefully designed study conducted in the United Kingdom by researchers at the University of Southampton have revealed a link between consumption of AFCs and/or preservatives and increased symptoms of ADHD among children in the general population.27 These results and findings from an earlier study by the same group28 prompted changes in food regulations in the United Kingdom and European Union and proposed federal and state legislation in the United States.29–34 The UK Food Standards Agency has called for voluntary bans on 6 AFCs.31 In addition, the European Parliament has called for warnings on products that contain AFCs.35 However, findings from the Southampton study, which focused on a general population sample, still do not shed light on the question of whether AFCs may contribute to ADHD as a clinical syndrome. In addition, the study was not designed to separately assess the potential effects of individual compounds in the test mixture, which contained both AFCs and sodium benzoate, a point that illustrates just one of the intricacies involved in investigations in this area. New regulations in the United Kingdom and the European Union reflect the judgment that AFCs and ADHD should be the subject of further investigation. If AFCs do increase the risk of developing ADHD in a subgroup of children, it is important to identify the risk group that may benefit from a modified diet, as is done for phenylketonuria and other diseases. Thus, there is a need for more studies that focus on possible associations between AFCs and ADHD to build on results from existing studies.

Current food-policy developments in the United Kingdom, European Union, and United States, with respect to the link between AFCs and ADHD, support the need for a model research methodology to inform food-policy decisions. In this article we present such a model. Our results represent the consensus opinion of a group of experts convened by the University of Massachusetts (UMass) Amherst Food Science Strategic Policy Alliance, a public-and industry-sponsored policy institute located at UMass Amherst. The opinions and positions taken in this consensus report are scientifically based and not influenced by the UMass Amherst Food Science Strategic Policy Alliance or its members. We take no position on the effects of AFCs on ADHD but recognize that there is a need for more well-designed research to examine the link between AFCs and the clinical syndrome of ADHD.

OVERVIEW OF EXISTING RESEARCH ON FOOD ADDITIVES AND ADHD

To establish a context for our recommendations, we conducted a review of the existing literature on food additives and ADHD through 2009 by using several biomedical and psychological databases (Ovid Medline, PsycINFO, Google Scholar, and PubMed). In addition, we searched the bibliographies of key articles.

Our literature search identified 25 blinded, controlled human studies published from 1970 through April 200934–62 and 2 meta-analyses of human studies.22,24 All studies reviewed were controlled, double-blind trials, many of which involved a crossover design. Several important conclusions can be drawn on the basis of our review of the existing literature on AFCs and ADHD. First, there is a relatively small body of controlled human research in this area, and most studies were relatively small. With the majority of studies conducted before 1990, diagnostic criteria used for sample selection were largely outdated, which raises concerns about the generalizability of results to an ADHD population.38–62 The outcome assessment methodology used in the majority of studies lacks consistency with current standards for ADHD assessment, which require measuring change in both symptoms of the disorder and functional impairments associated with the disorder and ensuring that measurements are made in multiple settings with multiple informants and different methodologies.63 These discrepancies raise questions concerning the reliability of the conclusions drawn in these studies. Because the majority of studies involved small samples, insufficient power may have affected results from studies that failed to detect differences between groups.
ADVANCES IN OUR UNDERSTANDING OF ADHD

Because most extant research on the link between AFCs and ADHD predates 1990, it is important to be aware of key developments that have taken place regarding ADHD since this research appeared. Since its first appearance in the Diagnostic and Statistical Manual of Mental Disorders (DSM), ADHD has become the most common cognitive, behavioral, and emotional disorder treated in children.63 ADHD was first included in the DSM in 1968 as “hyperkinetic disorder of childhood.” During the 1970s, the symptoms of inattention, impulsivity, and hyperactivity began to be recognized as core symptoms and integral to the disorder. However, not until 1980 was the disorder recategorized (DSM-III) as attention-deficit disorder with or without hyperactivity. With the DSM-III-R in 1987, criteria for diagnosis of the disorder required the presence of 8 of 14 symptoms related to the 3 core symptom clusters (inattention, impulsivity, hyperactivity) and onset before the age of 7 years.64 Currently, according to DSM-IV-TR criteria, a diagnosis of ADHD is made on the basis of developmentally inappropriate symptoms of inattention and/or hyperactivity-impulsivity. Three ADHD subtypes are recognized, including inattentive, hyperactive/impulsive, and a combined subtype. For a valid diagnosis of ADHD, there must be evidence of symptoms early in life (before the age of 7 years), symptoms must be pervasive across different settings, they must be persistent over time, and they must lead to clinically significant impairment in social, academic, or occupational functioning.65 Although not used in isolation to diagnose ADHD, rating scales have become useful for documenting symptoms and measuring responses to treatment. These scales have evolved along with our understanding of the disorder and changes in diagnostic requirements.66 Although there have been advances in the management of ADHD since the 1960s, no treatment study has had more impact than the landmark Multimodal Treatment Study of Children With ADHD (MTA).67–70 The MTA has evaluated the relative efficacy of the stimulant medication methylphenidate, behavioral treatment, and community-based care in the treatment of ADHD in children, which led the way in establishing methodologic standards in ADHD research. Many of the research standards established in the MTA are reflected in the model that we describe here.

PROPOSED MODEL RESEARCH METHODOLOGY

The objective of our model research methodology is to identify and address key considerations in the design of research projects that examine associations between AFCs and ADHD. It is our hope that results from such projects will inform food-policy decisions that affect children with ADHD.

Specifying the Research Question

Our research model is intended to address specific questions that concern the relationship between AFCs and ADHD. The primary research question for our model is whether consumption of dietary AFCs is associated with changes in ADHD symptoms and functioning in children with ADHD. An important secondary question is whether consumption of AFCs is associated with the occurrence of ADHD symptoms in typically developing control subjects.

Study Funding

In any research project, it is important to ensure freedom from real or perceived biases.71 Therefore, all funding sources must be clearly identified, and assurances that the study design and methods are appropriate for addressing the research question(s) in an unbiased manner must be made.

Experimental Design

A carefully designed and sufficiently powered randomized controlled trial (RCT) was considered the best means of investigating the potential effects of AFCs on ADHD. Our main phase III RCT will be preceded by a preliminary, small phase II study (Fig 1) designed to establish proof of concept and examine issues of dosing and timing. We determined that before proceeding to a large, expensive phase III RCT study, it would be prudent to have at least some evidence of causality in the link between consumption of AFCs and symptoms of ADHD.

Our phase II study will be conducted in 2 stages: stage 1, in a laboratory (classroom) setting, which will allow for structured assessments; and stage 2, in the home setting (free-living). Each phase will last for 1 week. Providing our phase II study establishes at least limited evidence of causality, it will be followed by a large-scale, short-term (6-week), phase III, double-blind, randomized, controlled, parallel-group study designed to measure the acute effects of AFCs on ADHD symptoms in subjects with ADHD (Fig 2). This study will also have an extension phase (6 months) for assessing maintenance. During this extension, study interventions will remain the same, and periodic assessments will be made. For both the phase II and III studies, we propose using a control group of children without ADHD to assess the secondary question of whether AFCs are associated with the occurrence of ADHD symptoms in the general population.

Treatment/Intervention

Although it may be possible to structure a naturalistic intervention in which subjects are randomly assigned to receive blinded, specially prepared
meals that are similar in appearance but contain either AFCs or natural colorings as a means of determining the effects of AFCs on ADHD symptoms, we believe that considerations of logistics and cost make this type of intervention unfeasible. Therefore, we propose an intervention in which participants will be randomly assigned to a range of double-blind treatment arms with AFC-free meals plus opaque capsules that contain different concentrations of AFCs above and below the amounts found in typical meals. We propose testing AFC concentrations that range from AFC-free (0%) to twice the normal or typical AFC concentration (200%) to obtain results that represent a wide range of dietary exposures. An average level of AFCs per meal (breakfast, lunch, dinner, drinks, and snacks) will be determined on the basis of analysis of a representative sample of meals.

The phase II study is designed to provide proof of concept and to guide treatment selection and assessment timing for the larger phase III study. It is also designed to test specific AFCs alone and in combination at different concentrations to determine if an effect is associated with an individual AFC or a combination of them. Participants in the phase II study, subjects with ADHD and those without ADHD, will be randomly assigned to 1 of 5 groups; groups will receive capsules that contain 0%, 50%, 100%, 150%, or 200% concentrations of a mixture of AFCs (Fig 1). If an effect is seen with the AFC mixture at 1 or more dosage levels, then the study will be repeated, and individual colorings will be withdrawn in a staged manner to determine if the effect results from 1 or a combination of the colorings.

In the larger phase III study, subjects with ADHD and those without ADHD will be randomly assigned to the same 5 treatment arms as in the phase II study (assuming that all 4 active doses produce a result, and fewer will be used if no effects are seen at a given dose or doses) to test the AFC or AFC mixture as determined in the phase II study at concentrations including 0%, 50%, 100%,
150%, and 200% (Fig 2). AFC capsules will be administered with AFC-free meals at breakfast, lunch, and dinner, and AFC-free snacks and beverages will also provided.

**Study Sample**

The selection of subjects for any research project depends on the population to which results will be generalized. Our proposed study will be conducted in a sample of children with ADHD. However, within this general group there are some important considerations in terms of further defining the study sample. For instance, using a school-based population will result in a sample with a more severe presentation of disease. Another consideration in sample selection is whether the study should focus on 1 or more ADHD subtypes. We propose using ADHD combined type only for our sample rather than including all 3 subtypes. Combined type is the ADHD subtype that is most common in clinical practice and has been studied most widely. It is associated with the greatest clinical impairment. Also, previous studies have primarily linked AFCs with hyperactivity, not inattention, and there is some controversy in the ADHD field as to whether ADHD inattentive type is actually a separate disorder involving different brain structures than those involved in ADHD combined type. Inclusion of subjects with other comorbid psychiatric diagnoses in addition to ADHD, including other externalizing (eg, conduct disorder, oppositional defiant disorder) and internalizing (eg, anxiety disorders, depression) disorders will allow us to determine if AFC effects are specific to ADHD.

Age is a critical variable in the selection of our study sample. Because inclusion of preschool-aged children poses certain challenges (ie, difficulty in establishing accurate diagnosis), we propose using a school-based sample that consists of boys and girls aged 6 to 12 years.

Inclusion criteria are based on current

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*Refs 24, 27, 28, 42, 46, 51, 56, and 59.
diagnostic criteria for ADHD. Participants must meet dimensional criteria for ADHD based on parent and teacher rating scale scores that exceed specified criteria (eg, beyond the 93rd percentile for child’s age and gender) and full research diagnostic criteria for ADHD, combined type, on the basis of a structured diagnostic interview with the parent(s). Exclusion criteria are current hospitalization, participation in another treatment study, having no telephone, low IQ (<80), major neurologic or medical illness, or ongoing or previously undisclosed child abuse. For study entry, we propose using a multiple gating procedure (4 phases) similar to that used in the MTA study (Table 1).22

The use of a control group of children without ADHD will allow our study to address the question of whether AFC contributes to ADHD symptoms among typically developing subjects. This control group will be subject to the same intervention and assessment plan as subjects with ADHD in the primary study. Control-group participants will not meet criteria for any DSM-IV-TR diagnosis on the basis of parent interview and will be matched by age and gender with the participants with ADHD.

**TABLE 1** Study Entry: Multiple Gating Procedure (4-Phase)

<table>
<thead>
<tr>
<th>Phase</th>
<th>Procedure</th>
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</thead>
<tbody>
<tr>
<td>A</td>
<td>Telephone intake: initial inclusion and exclusion criteria</td>
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<tr>
<td>B</td>
<td>Mailed rating scales Parent, teacher: Conners’ Rating Scales; ADHD Rating Scale-IV</td>
</tr>
<tr>
<td>C</td>
<td>In-person assessment Parent: Diagnostic Interview Schedule for Children; Columbia Impairment Scale Child: mental status examination, Wechsler Intelligence Scale for Children-II, physical examination Child: mental status examination, Wechsler Intelligence Scale for Children-II, physical examination</td>
</tr>
<tr>
<td>D</td>
<td>Full baseline assessment</td>
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**Measurements**

Because most existing controlled studies of AFCs and ADHD were conducted in the 1970s and 1980s, outcomes are not consistent with the current standards required of research on ADHD. To ensure valid results, any study that investigates the link between AFCs and ADHD must adopt a measurement strategy that incorporates psychometrically sound outcome measures that focus on symptom change as well as functional impairment. Outcome assessment must encompass multiple functional domains (school, peer relationships, family functioning), and changes in ADHD symptoms must be associated with concomitant changes in functional impairments. In addition, there must be measures in multiple settings from multiple informants that use different methodologies (ratings, direct tests, observations, measures of academic and social functioning).

Study measures for our proposed studies are listed in Table 2. Full assessments for the phase III study, both for subjects with ADHD and control subjects without ADHD, will be made at screening, at baseline, and at the close of the study, and selected assessments will be made at specific time points during the study. The timing of these assessments will depend on timing of response as determined during the preliminary phase II study. In the laboratory stage (stage 1), assessments will be made at baseline and daily. During stage 2 (free-living), assessments will be made daily.

In addition to direct measurements of the effect of the proposed intervention, we will also assess potential moderators and mediators of outcomes, which include adherence/compliance to treatment/intervention, food intake apart from the intervention (assessed by using food diaries), consumer satisfaction with the intervention, comorbidity of disorder, parental psychopathology, and demographic characteristics. Steps should be taken to ensure consistency of assessments, including central preparation of assessment and data forms and consistency in training across study sites and personnel.

**Sample-Size Issues**

Instead of adopting an effect size of 0.4, such as in the MTA study, we propose using a lower effect threshold of 0.28 for our primary outcome (change in ADHD symptoms) and as the basis for power calculations for our phase III study. This threshold is based on the findings at a recent meta-analysis of 15 trials from which a positive association between AFCs and increased symptoms of ADHD was reported (effect size: 0.28 [95% confidence interval: 0.079 – 0.488]). In the most recent Southampton study, McCann et al (2007) found similarly modest effect sizes among a general population of children. Smaller effect sizes are also appropriate when seen in the context of exposures that may have significant public health consequences. Although larger effect sizes may be appropriate for trials of medications, such as is the case with the MTA, more modest effects may be seen as critical when investigating widespread exposures such as food additives or colorings.

For our phase II study, our design objective is to detect a clinically important change in subjects (>=50%) in parent- and teacher-rated symptoms and behaviors/attention observed in a structured setting. To achieve this goal, we will recruit 200 participants: 100 subjects with ADHD and 100 control subjects without ADHD, which will provide 20 subjects with ADHD and 20 control subjects for each of the 5 AFC treatment groups (0%, 50%, 100%, 150%, 200%). The threshold of response for a dose in proceeding to the phase III study is somewhat arbitrary.
but should be chosen in advance. If we accept that the threshold for proceeding to the phase III study should be a majority (>50%) with a clinically significant response, then a response in ≥14 of 20 subjects would occur by chance only 5.8% of the time if the true rate of impact is 50%. Thus, we choose as our decision rule for proceeding to the phase III study ≥14 of 20 subjects with a ≥30% change on the symptom scale as a level sufficient to show that this is more than might be expected by pure chance because of measurement error. If one judged that a response in 12 of 20 subjects was sufficient for moving forward rather than ≥14 of 20, then either the sample size would need to increase or we would need to accept a lower limit of the threshold for what proportion responses would warrant continuing to the phase III study. For example, if one were willing to proceed to the phase III study if only 10 of 20 subjects responded, then the threshold value for this decision would be ≥35% of subjects experiencing a significant (>30%) change in symptoms. That is, when 10 of 20 subjects respond, the probability of it happening by chance is only 0.053 when the true response rate is 35%; thus, the response rate is more likely to be higher than 35%, a value sufficient to warrant a large and expensive phase III study. This within-dose selection rule would be used to determine if any effective dose should be tested further. If ≥2 doses are chosen, then those levels would be used in a subsequent design bolstered by more analyses on the basis of the continuous responses of changes in the symptom scale, analyzed by using regression and analysis-of-variance techniques (discussed below) and multiple comparisons against a control as well as dose-response analyses.

For the phase III study, the primary objective is to detect a clinically important change in ADHD symptoms on the basis of a minimal effect size of 0.28 in subjects with ADHD. The secondary objective is to detect a change in behaviors in control subjects without ADHD with the same minimal effect size. A sample size of 270 subjects in each group at the time of analysis will have 90% power to detect an effect size of 0.28 using a 2-group t test with a type I error of 0.05 (2-sided). This sample size does not account for dropouts and crossovers or the possibility of more than 1 effective dose found from phase II. Assuming a dropout rate of 10% and a crossover or noncompliance rate of 10%, 420 subjects per group, for both the ADHD and control groups, would need to be randomly assigned. If >2 groups are used, adjustments would be made for multiple comparisons and the expected differences among the individual groups, estimated from the phase II results.

### Data Analysis

Existing ADHD treatment studies such as the MTA investigation provide a model for data analysis.\(^6\) The objective is to predict outcomes on the basis of measurement of continuous variables. Analysis of combined metrics should be avoided. For our phase III study, data analysis will be conducted on the intent-to-treat population. The main analytic approach will be mixed-effects repeated-measures regression modeling, a method that allows for inclusion of subjects with incomplete data across time and accounts for within-subject correlations between repeated observations. Analyses should report effects separately for each measure and setting with appropriate statistical controls for experiment-wise type I error. Our primary intent-to-treat analysis will focus on change in ADHD symptoms as determined by outcome measures across multiple domains (Table 2). We use multiple outcome variables rather than a single outcome in anticipation of our intervention having a differential impact across various areas of functioning. Regression modeling will allow us to adjust for multiple covariates in determining the effect of individual variables. Outcomes will be assessed at baseline and during and after the active intervention period.

### Publishing and Related Issues

Trial registration is an important means of achieving full transparency and public confidence and should be required of any study that investigates nutritional exposures and ADHD.\(^7\) Registration also provides a mechanism for addressing publication bias.\(^8\)

### DISCUSSION AND CONCLUSIONS

The model research methodology we have proposed here is an attempt to outline the essential features of a study that investigates the role of AFCs.
in contributing to symptoms of ADHD. ADHD has a high prevalence\textsuperscript{76,77} and is associated with a variety of negative outcomes if not managed effectively.\textsuperscript{78–81} Therefore, making available effective management strategies, including elimination of harmful nutritional exposures as evidence warrants, is a national public health priority.

Food-policy decisions that affect child health should be based on the best possible scientific evidence. Examples abound of instances in which policy decisions in a given area that lacked a solid evidential foundation have been followed by unintended negative consequences. In the 1970s, industries in the eastern United States adopted the use of tall smokestacks to better disperse factory emissions. The unintended consequence was the transport of sulfur pollution higher in the airshed, where it mixed with water vapor and was dispersed to a wider geographic area, which resulted in acid-rain destruction in northeastern and Canadian forests.\textsuperscript{82} In the area of nutrition, dietary recommendations in the 1970s and 1980s emphasizing the importance of lowering dietary fat intake resulted in the introduction of numerous fat-free and low-fat food products, many of which contained high amounts of sugar and refined carbohydrates.\textsuperscript{83,84} Although the low-fat campaign decreased dietary fat intake in the United States, during the same period there was an increase in the prevalence of diabetes and obesity. It is now increasingly recognized by experts in nutrition that there was little scientific evidence supporting the low-fat campaign and that it may have led to unintended negative health consequences.\textsuperscript{85}

In developing our model research methodology, we have drawn from current standards in ADHD research and have included what we view to be essential design features. It is our hope that this model methodology may inform the design of future studies of the effects of AFCs on children with ADHD and enable policy-makers to formulate effective, evidence-based food-policy decisions.

**ACKNOWLEDGMENTS**

This article was prepared at a meeting convened by the University of Massachusetts (UMass) Amherst Food Science Strategic Policy Alliance on April 1–3, 2009, to address the issue of the current state of research in food policy and ADHD and was supported by the UMass Amherst Food Science Strategic Policy Alliance and its members, including the Massachusetts Department of Agricultural Resources (grant) and UMass Amherst. The meeting gathered thought leaders in the areas of food science and policy and clinical psychology with emphasis on the design and conduct of clinical trials that assess the effects of pharmacotherapeutic and behavioral interventions for ADHD, pediatric nutrition with emphasis on assessing the bioavailability and metabolism of nutritional exposures, and biostatistics and the design and conduct of clinical trials and research projects. Participants were selected on the basis of large-scale screening and in-depth personal interviews. Moderators were selected to facilitate discussion, and a writer with expertise in medical publications was chosen to work with panel members to develop a consensus report based on expert panel recommendations. The UMass Amherst Food Science Strategic Policy Alliance is a policy program based at UMass Amherst with members from industry, government (including the US Food and Drug Administration and US Department of Agriculture), and university faculty and students. The opinions and positions taken in this consensus report are scientifically based and not influenced by the UMass Amherst Food Science Strategic Policy Alliance or its members. Editorial assistance for this project was provided by BioScience Communications with financial support from the UMass Amherst Food Science Strategic Policy Alliance.

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Pediatrics; originally published online May 16, 2011;
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