Background Document for the
Food Advisory Committee:
Certified Color Additives in Food and Possible Association with
Attention Deficit Hyperactivity Disorder in Children
March 30-31, 2011

I. Introduction/History of Issue

Certified ("synthetic") color additives have been a source of controversy in the U.S. since the 1970s, when pediatrician Dr. Benjamin Feingold first claimed a link between children's behavior and consumption of the additives. The Food and Drug Administration (FDA or the Agency) reviewed literature available at the time and concluded that the data *suggested* that some children may be adversely affected by synthetic colors but that more research was needed for the Agency to make any final determination with regard to the effects of color additives.

In 1982, a Consensus Development Panel of the National Institutes of Health concluded that, while a controlled diet may have benefits in the treatment of childhood hyperactivity, further research was needed. The Panel identified a number of critical data gaps that needed to be filled in the investigation of the dietary management of hyperactivity, including a lack of standardized diagnostic criteria, studies on genetic, developmental, and environmental factors, and longitudinal prospective studies.

In 1986, FDA's Ad Hoc Advisory Committee on Hypersensitivity to Food Constituents reviewed and evaluated available information and data relevant to adverse reactions in humans associated with the use of food ingredients, including FD&C Yellow No. 5. The committee did not report any evidence of behavioral disorders associated with food ingredients evaluated.

In 2007, synthetic color additives again came under scrutiny following publication of a study conducted by the University of Southampton (Southampton study) in the United Kingdom (U.K.) and published in *The Lancet*. This six-week study was commissioned by the U.K. Food Standards Agency (FSA). The study was intended to investigate whether certain color additive mixtures and the preservative, sodium benzoate, when consumed in a beverage, cause hyperactivity in three-year-old and eight and nine- year-old children[1].

The following additives were evaluated in the Southampton study:

- **Quinoline Yellow**: In the U.S., this color (primarily monosulfonated quinoline yellow) is certifiable as D&C Yellow No. 10 and is approved for use in coloring drugs, cosmetics, and contact lenses, but not food.

- **Ponceau 4R**: This color additive has not been approved by FDA for any use.

[1] FDA notes that three of the individual color additives used in the Southampton study are not approved for food use in the U.S. The others are approved only if batch certified. Batch certification ensures the purity of the color additive prior to use in a FDA-regulated product.

- **Allura Red**: In the U.S., this color is certifiable as FD&C Red No. 40 and is approved for use in coloring food, drugs, and cosmetics.

- **Azorubine (carmoisine**): This color was listed in 1939 as Ext. D&C Red No. 10 for use in externally applied drugs and cosmetics and provisionally listed for these uses in 1960, but was delisted in 1963 because no party was interested in supporting the studies needed to establish safety. This color additive has never been approved by FDA for use in food.

- **Tartrazine**: In the U.S., this color is certifiable as FD&C Yellow No. 5 and is approved for use in coloring food, drugs, and cosmetics. This color additive is known to cause allergic-type reactions (e.g., hives) in a small subset of the population and, as a condition of use, must be declared as an ingredient when used to color food.

- **Sunset Yellow**: In the U.S., this color is certifiable as FD&C Yellow No. 6 and is approved for use in coloring food, drugs, and cosmetics.

- **Sodium benzoate,** a preservative**,** was included with the color additive mixtures. In the U.S., sodium benzoate is affirmed as generally recognized as safe (GRAS) for use as an antimicrobial agent at a level not to exceed 0.1 percent in food. Adding sodium benzoate to foods inhibits growth of bacteria, yeasts, and molds.

Following completion of the study, the Committee on Toxicity (COT), an independent group of scientists that advises FSA, issued its evaluation of the study. The COT concluded that the study provides supporting evidence of a possible link between the test mixtures and hyperactivity in children. However, because of study limitations, results could not be extrapolated to the general population, and further testing was recommended.

In March 2008, the European Food Safety Authority (EFSA) completed an assessment of the Southampton study and concluded that the study provided only limited evidence that the additives had a small effect on the activity and attention of some children; however, the significance of the effects was unclear. For example, it was not known if the small alterations in attention and activity noted in the study would interfere with schoolwork or other intellectual functioning. Further, because mixtures were tested, rather than individual ingredients, the observed effects could not be attributed to any individual additive. EFSA also noted that the effects observed were not consistent for the two age groups or for the two mixtures tested in the study. In 2009, EFSA re-evaluated the safety of the six color additives used in the Southampton study and concluded that the available scientific evidence does not substantiate a link between the color additives and behavioral effects.

In 2008, the Center for Science in the Public Interest (CSPI) petitioned FDA to ban eight of the nine certified color additives currently regulated for use in foods in the U.S.[2] CSPI contends that these additives cause hyperactivity and behavior problems in some children. In support of

[2] The only certified food color that CSPI has not requested that FDA ban is Citrus Red No. 2, which is approved for use only in coloring the skins of oranges that are not intended for or used in processing.

its argument, CSPI references a number of studies, including the Southampton study and a 2004 meta-analysis of 21 double-blind studies on artificial colors and children's behavior.[3] CSPI also requests that, until FDA makes a final decision regarding CSPI's request to ban these color additives, FDA require warning labels on foods containing these color additives, stating that they cause hyperactivity and behavioral problems in some children.

In July 2010 the European Union (EU) began requiring warning labels on foods that contain any of the color additives tested in the Southampton study.[4] The U.S has expressed concerns to the World Trade Organization that the warning label is not based on adequate scientific evidence. In the U.S, any food containing color additives that FDA certifies for food use, such as FD&C Red No. 40 and FD&C Yellow No. 5 (two of the color additives tested in the Southampton study), must be declared by name as ingredients on the food label.

Results from the Southampton study, the CSPI petition, and recent actions by the EU, have once again raised questions regarding a possible association between consumption of synthetic color additives in food and effects on children's behavior.

II. FDA Regulation of Certified Color Additives in food

A color additive, as defined by regulation, is any dye, pigment, or other substance that imparts color to a food, drug, cosmetic or to the human body. Color additives are required to be approved by FDA and listed in the U.S. Code of Federal Regulations (CFR) before they may be used in products marketed in the U.S. Under the Federal Food, Drug, and Cosmetic Act (FFDCA or the Act), a color additive is not to be listed unless data establish that the proposed use of the color additive is safe (sec. 721(b)(4) of the Act [21 U.S.C § 379e(b)(4)]). Under 21 CFR 70.3(i), an additive is "safe" only if there is "convincing evidence that establishes with reasonable certainty that no harm will result from the intended use of the color additive."

a. Color Additive Certification

For regulatory and labeling purposes, FDA differentiates between color additives based on whether they are subject to batch certification or exempt from certification. Color additives subject to batch certification are mostly synthetic organic dyes, lakes, or pigments. Those for food use are chemically classified as azo, xanthene, triphenylmethane, and indigoid dyes. Although certifiable color additives have been called coal-tar colors because of their traditional origins, today they are synthesized mainly from raw materials obtained from petroleum.

Color additives exempt from certification generally include those derived from plant or mineral sources. One, cochineal extract (and its lake, carmine) is derived from an insect.

[3] Schab D, Trinh N. Do Artificial Food Colors Promote Hyperactivity in Children with Hyperactive Syndromes? A Meta-analysis of Double-Blind Placebo-Controlled Trials. J Dev Behav Pediatr. 2004;25:423-434.

[4] Manufacturers must include the statement, "name or E number of the colour(s): may have an adverse effect on activity and attention in children" on food products containing one or more of the six colors tested in the Southampton study

Color additive certification is the process by which FDA determines whether newly manufactured batches of color additives meet the identity and specification requirements of their listing regulations. The decision on the need for batch certification is made during the Agency's review of a petition requesting a listing of a color additive. The decision to require batch certification is usually made based on the nature of the impurities and variability in the manufacturing process. Color additives that typically require batch certification contain impurities of toxicological concern, such as constituents shown to be carcinogenic in animal studies.

Under the certification process, a sample from each manufactured batch of a certifiable color additive must be sent to FDA's Color Certification Laboratory. Upon receipt of the sample, FDA personnel evaluate its physical appearance and chemically analyze it. The results are reviewed for compliance with the identity and specifications described in the listing regulation for the color additive. If the sample is found to meet these requirements, FDA issues a certificate for the batch that identifies the color additive, the batch weight, the uses for which the color additive is certified, the name and address of the owner, and other information as required. FDA also assigns a unique lot number for the batch and the name of the batch changes. For example, a batch of "tartrazine," once certified, becomes "FD&C Yellow No. 5."

b. Historical Perspectives: The Basis of the Current Regulations

Federal oversight of color additives began in the 1880s. By 1900, many foods, drugs, and cosmetics available in the U.S. contained some sort of coloring agent. However, not all of the coloring agents were harmless and some were being used to hide inferior or defective foods.

In 1906, Congress passed the Pure Food and Drug Act, which prohibited the use of poisonous or deleterious colors in confectionery and the coloring or staining of food to conceal damage or inferiority. The U.S. Department of Agriculture had initial enforcement authority for this act. In 1927, responsibility for enforcing the Pure Food and Drug Act was given to the newly established FDA. By 1931, 15 straight colors (i.e., color additives that are not mixed or chemically reacted with any other substance) were approved for use in food, including six of the nine in use today: FD&C Blue No. 1 (Brilliant Blue FCF), FD&C Blue No. 2 (Indigotine), FD&C Green No. 3 (Fast Green FCF), FD&C Red No. 3 (Erythrosine), FD&C Yellow No. 5 (Tartrazine), and FD&C Yellow No. 6 (Sunset Yellow).

The FFDCA which was passed by Congress in 1938, mandated the certification of “coal tar colors” and required label declaration of artificial coloring used in food. In fall 1950, many children became ill from eating an orange Halloween candy containing FD&C Orange No. 1, a color additive approved at that time for use in food. That same year, U.S. House Representative James Delaney began holding hearings on the possible carcinogenicity of pesticide residues and food additives. These events prompted FDA to reevaluate the safety of color additives. In the next few years, FDA found that several caused serious adverse effects and proceeded to terminate their listings.

The Color Additive Amendments of 1960 amended the FFDCA to establish the current framework under which color additives are regulated. The 1960 amendments defined "color additive" and required that only color additives determined to be "suitable and safe" for a given

use could be used in food, drugs, cosmetics, and medical devices. The 1960 amendments also prescribed the factors that FDA must consider in determining whether a proposed use of a color additive is safe, as well as the specific conditions for safe use that must be included in the listing regulation. FDA revised the procedural regulations for the petition process in response to these amendments. Under these amendments, the approximately 200 color additives that were in commercial use at the time were provisionally listed in FDA regulations and could be used on an interim basis until they were either permanently listed or terminated due to safety concerns or lack of commercial interest. Permanently listing a color additive for a proposed use is prohibited unless scientific data established its safety.

The 1960 amendments also contained the anti-cancer "Delaney Clause" that prohibited the listing of a color additive shown to be a carcinogen. The Delaney Clause states that "A color additive shall be deemed unsafe. . . if the additive is found. . . to induce cancer when ingested by man or animal, or . . . after other relevant exposure of man or animal to such additive" (see section 721(b)(5)(B) of the Act [21 U.S.C § 379e(b)(5)(B)]).

c. Petition Review Process

In accordance with section 721(b)(5)(A) of the Act [21 U.S.C. § 379e(b)(5)(A)], the following factors that are to be considered when evaluating the safety of a new color additive or a new use for a listed color additive are probable consumption or exposure from its use, cumulative effect in the diet, safety factors appropriate for extrapolation of animal experimentation data, and the availability of analytical methods for determining its purity and quantity from the proposed use. Further, under section 721(b)(6) of the Act [21 U.S.C. § 379e(6)] a color additive is not to be listed for a proposed use if the data show that such proposed use would promote deception of the consumer in violation of the FFDCA or would otherwise result in misbranding or adulteration within the meaning of the FFDCA .

Any interested person may petition FDA for the use of a new color additive or to amend the listing of a color additive for a new use. Under 21 CFR 71.1, the petitioner must provide information on the following:

- Identity of the proposed color additive
- Physical, chemical, and biological properties
- Chemical specifications
- Manufacturing process description
- Stability data
- Intended uses and restrictions
- Labeling
- Tolerances and limitations
- Analytical methods for enforcing chemical specifications
- Analytical methods for determination of the color additive in products
- Identification and determination of any substance formed in or on products because of the use of the color additive
- Safety studies
- Estimate of probable exposure

- Proposed regulation
- Proposed exemption from batch certification
- An environmental assessment or claim for categorical exclusion

III. Safety Determination of Currently Approved Certified Color Additives

Under 721(b)(4) of the Act [21 U.S.C. § 379e(b)(4)], the so-called "general safety clause" for color additives, a color additive is not to be listed for a particular use unless the data presented to FDA establish that the color is safe for that use. Although what is meant by "safe" is not explained in the general safety clause, the legislative history makes clear that this word is to have the same meaning for color additives as for food additives. (See e.g., H. Rept. No. 1761. "Color Additive Amendments of 1960." Committee on Interstate and Foreign Commerce, 86th Cong., 2d Sess. 11 (1960).) The Senate report on the Food Additives Amendment of 1958 states:

> The concept of safety used in this legislation involves the question of whether a substance is hazardous to the health of man or animal. Safety requires proof of a reasonable certainty that no harm will result from the proposed use of an additive. It does not—and cannot—require proof beyond any possible doubt that no harm will result under any conceivable circumstances.
>
> This was emphasized particularly by the scientific panel which testified before the subcommittee. The scientists pointed out that it is impossible in the present state of scientific knowledge to establish with complete certainty the absolute harmlessness of any chemical substance.
>
> S. Rept. No. 2422, "Food Additives Amendment of 1958." Committee on Labor and Public Welfare, 85th Cong., 2d Sess. 6 (1958).

FDA has incorporated this concept of safety into its color additive regulations. Under 21 CFR 70.3(i), a color additive is "safe" if there is "convincing evidence that establishes with reasonable certainty that no harm will result from the intended use of the color additive." Therefore, the general safety clause prohibits the listing of a color additive unless it is safe, as defined in 21 CFR 70.3(i).

To establish with reasonable certainty that an additive is not harmful under its intended conditions of use, FDA considers the projected human dietary intake of the additive, the additive's toxicological data, and other relevant information (such as published literature) available to the Agency.

The following table lists the acceptable daily intakes (ADIs), where available, that have been established for the eight certified colors that are the subject of the CSPI petition. It also includes the pivotal safety study(ies) on which determination of the ADI was based and the dose level on which the ADI was based.

The ADI for these color additives was calculated using the test concentration that produced the No Observed Effect Level (NOEL) in the test animals divided by a 100-fold safety factor (10 for inter-species variability times 10 for intra-human variability).

Certified Color	Year Approved	ADI (mg/kg bw/day[5])	Pivotal Study(ies) (ADI basis)	ADI Dose Level (pivotal study)
FD&C Blue No. 1	1969	12.0	2-year plus bioassays in Charles River albino rats (*in utero* exposure) and CD-1 mice	Rat – 2.0% of diet (20,000 parts per million (ppm)) Mouse – 5.0% of diet (50,000 ppm)
FD&C Blue No. 2	1987	2.5	2-year plus bioassay in Charles River albino rats (CD) (*in utero* exposure)	Rat – 0.5% of diet (5,000 ppm)
FD&C Green No. 3	1982	2.5	2-year plus bioassays in Charles River CD-1 mice and albino (CD) rats (*in utero* exposure)	Rat – 5.0% of diet (50,000 ppm) Mouse – 5.0% of diet (50,000 ppm)
Orange B*	1966	None established	N/A	N/A
FD&C Red No. 3	1969	2.5	2-year study in rats (strain not noted), supported by 2-year study in dogs (beagle)	Rat – 0.5% of diet (5,000 ppm) Dog – 2.0% of diet (20,000 ppm)
FD&C Red No. 40	1971	7.0	21 month study in Charles River CD-1 rats	Rat – 1.39% of diet (13,900 ppm)
FD&C Yellow No. 5	1969	5.0	2-year bioassays in Charles River CD-1 mice and albino rats (CD) (*in utero* exposure); 2-year bioassay in dogs (beagle)	Dog – 2.0% of diet (20,000 ppm)
FD&C Yellow No. 6	1986	3.75	2-year bioassays in Charles River CD-1 mice and albino (CD) rats (2 long-term studies with *in utero* exposure)	Rat – 0.75% of diet (7,500 ppm)

*approved for use only in casings or surfaces of frankfurters and sausages at levels not to exceed 150 ppm by weight of food.

FDA compares an individual's estimated daily intake (EDI) of the additive from all food sources to the ADI established by toxicological data as part of the review of the information relied on to support the proposed use of a color additive. Typically, the EDI is determined by combining the amount of the color additive proposed for use in particular foods with the consumption of those foods, summed over all foods containing the color additive. When such data are not available, FDA can use "disappearance" poundage data to calculate an EDI. This is the amount of a substance sold to the food industry that "disappears" into food as an additive or ingredient and, typically, overestimates mean consumption.

[5] Milligrams per kilogram bodyweight (mg/kg bw).

FDA has calculated per capita intakes of the certified color additives using the total pounds of the color additive batch-certified by FDA in 2010 and U.S. census data from the 2010 census. The estimates were further adjusted to account for the portion of the colors certified that go into food in the U.S. According to one source, 95% to 97% of the total amount of certified colors are used to manufacture U.S. products (e.g., food, pharmaceuticals, and cosmetics), with the remaining 3% to 5% being exported. Of the 95% to 97%, of the certified colors used in U.S. products, 10% are used in pharmaceuticals, 3% are used in cosmetics and about 73% are used in human food.[6] These poundage data may overestimate consumption because of food loss through waste and spoilage in the home and market.

The following formula was used to estimate intakes:

(Pounds (lbs) color certified/1 year) x (0.73) x (453.6 grams (g)/1 lb) x (1 year/365 days) x (1/U.S. population for that year) x (1000 milligrams (mg)/1 g) = intake of the certified color for the U.S. population in mg per person per day (mg/p/d)

For example, for 2010, the per capita intake of FD&C Blue No. 1 was calculated to be:

(587,430.97 lbs/year) x (0.73) x (453.6 g/1 lb) x (1 year/365 days) x (1/308,745,538) x (1000 mg/1 g) = 1.72 mg/p/d

The per capita intakes of the certified color additives for the U.S. population (EDI; mg/p/d) calculated in this manner are summarized in the table below. This table also includes the ADIs, determined from toxicological data, for comparison. With regard to the ADI, FDA typically presumes an average body weight of 60 kilograms (kg) for the U.S. population and 30 kg for children.

Color Additive	U.S. Population Per Capita EDI (mg/p/d)	ADI (mg/p/d)	
		U.S. Population (60 kg person)	Children (30 kg child)
FD&C Blue No. 1	1.72	720	360
FD&C Blue No. 2	1.95	150	75
FD&C Green No. 3	0.038	150	75
FD&C Red No. 3	0.61	150	75
FD&C Red No. 40	17.91	420	210
FD&C Yellow No. 5	12.06	300	150
FD&C Yellow No. 6	10.74	225	113

As shown in the table, per capita EDIs for the certified colors are below the ADIs established by toxicology studies.

[6] Specialty Chemicals Update Program. 2005. SRI Consulting.

The EDIs calculated on a per capita basis assume an even distribution of consumption of the additives for the entire population. A more conservative approach is to assume that 10% of the population consumes all certified color additives used in human food. A similar approach has been used by the Joint Food and Agriculture Organization/World Health Organization Expert Committee on Food Additives (JECFA) to estimate exposure to flavors for the high consumer. As shown below, using this revised approach, the levels are still below the ADIs for both adults and children.

Color Additive	U.S. Per Capita EDI for high consumer (mg/p/d)*	ADI (mg/p/d)	
		U.S. Population (60 kg person)	Children (30 kg child)
FD&C Blue No. 1	17.2	720	360
FD&C Blue No. 2	19.5	150	75
FD&C Green No. 3	0.38	150	75
FD&C Red No. 3	6.1	150	75
FD&C Red No. 40	179.1	420	210
FD&C Yellow No. 5	120.6	300	150
FD&C Yellow No. 6	107.4	225	113

*Assumes 10% of population consumes all certified color used in human food.

IV. FDA's Evaluation of Relevant Literature

FDA has conducted a thorough review of the published literature on color additives and behavioral effects in children, including the studies cited by CSPI's citizen petition currently under review.

a. Rationale for Selecting Studies

The FDA submitted a work assignment through an Interagency Agreement with Oak Ridge National Laboratories (ORNL) to conduct a literature search for peer-reviewed articles on the possible association of food ingredients and neurobehavioral issues in children. The FDA also requested an in-depth review and analysis of all selected publications. Specifically, the work assignment requested that:

- ORNL conduct a thorough search of the literature from 1982 to the present for peer-reviewed publications dealing with consumption of additives in food and their possible correlation with hyperactivity and behavioral changes. The search included both animal

and human studies. TOXLINE and PUBMED were searched for the years 1982 through 2008[7] using the following terms:

Food additives hyperactivity, Food additives autistic, Food additives psychomotor, Food additives attention deficit, Food additives neurotoxic, Food additives behavior neurologic*[8], Food coloring hyperactivity, Food coloring autistic, Food coloring psychomotor, Food dyes hyperactivity, Food dyes autistic, Food dyes psychomotor, Food dyes attention deficit, Food dyes neurotoxic, Food dyes neurologic*, Food dyes behavior.

- All references and abstracts identified from the literature search were submitted to an expert neurotoxicologist contracted by ORNL. The neurotoxicologist reviewed each abstract to determine the relevancy of each article. If the reviewer determined an article as not relevant, he wrote a brief statement giving reasons for rejecting the article. Those articles determined to be relevant were thoroughly reviewed by assessing the overall quality of the study and whether the study results supported a correlation between food and color additives and behavioral and/or hyperkinetic changes. In addition, the reviewer noted any deficiencies in the studies reviewed and made recommendations as to how these deficiencies could be addressed in future studies. The review included all relevant publications submitted in citizen petitions under review at FDA.

b. Criteria for Evaluating Studies

In the review and assessment of each clinical trial, FDA deemed it important to identify both positive and negative study findings, and to consider any relevant experimental factors, particularly limitations, and inconsistencies or uncertainties in the data that may affect the credibility, reliability, or interpretability of the reported study findings. In the interpretation of results, efforts were made to distinguish between statistically significant and clinically relevant findings, because some outcome measures may reveal statistical differences between treatment and control that may be within normally accepted standards. To this end, the general criteria used for assessing the trials and interpreting the findings included consideration of the following:

- homogeneity of sample
- randomization to treatment
- crossover designs with subjects serving as own control
- counterbalanced treatment/challenge order
- double-blind/placebo-controlled challenges
- placebo and challenge indistinguishable
- *verification of effectiveness of blinding particularly for behavioral raters
- appropriate control outcome measurements

[7] The original literature search was completed in September 2008. FDA conducted a second literature search for relevant studies published from October 2008 to early March 2011. Two articles from the second search were identified and are provided in the Committee briefing materials; however, FDA has not conducted a comprehensive review of these publications.

[8] * represents a wildcard for searching.

- age-appropriate outcome measures
- use validated measures (i.e. detect behavior differences/sensitive to treatment)
- *confirmatory sources of outcome data (parents, teachers, testing, etc.)

∗These two factors were considered to be particularly important in the evaluation and assessment of the study findings.

The importance of the factor *confirmatory sources of outcome data* was related to assessing reliability of study findings. That is, is a positive effect based on one source of data sufficient to conclude a reliable finding. Out of 33 clinical trials, 11 used only a single source of outcome data to assess treatment-related effects on behavior and 8 of those showed positive effects; no other source of data was included in those studies to provide any confirmation of the positive findings. In determining weighting and level of confidence, FDA adopted a conservative approach and, in most cases, considered any findings that were based solely on one data source to be suggestive, but not adequate conclusive evidence, of a treatment effect. Less confidence was given to the reliability of a single source finding when other sources of assessing behavioral change were used in the same study and provided data showing no confirmation or supportive evidence of any treatment-related effects.

Many of the trials (14/33) reviewed reported treatment-related effects based only on a parental rating outcome measure (either as the only source outcome measure used or the only outcome measure to detect a treatment effect with no confirmation by other behavioral measures). Consequently, since only a single source outcome measure detected an effect, a lowered weighting/level of confidence was generally assigned to these study findings. This lower weighting/less confidence was not selectively directed at the use of parental ratings but at the use of a single source outcome measure of behavioral change. The main issue in assigning the weightings/confidence levels in this review was confirmation of a treatment-related finding across outcome measures within the same study.

The importance of *verifying the effectiveness of the blind* stems from the widely acknowledged tenet that in any clinical therapeutic study the use of appropriate blinding procedures is essential to preclude placebo effects and observer bias from influencing the study results. In non-blinded studies the participants are typically aware of the subjects' treatment conditions and, consequently, the possible influence of placebo effects and observer bias lessens confidence in the reliability of those study findings. Double-blind studies, however, are considered more reliable, since various efforts are made to prevent (blind) the researchers, observers, and subjects from knowing when the active or placebo treatments are administered**.** Even in double-blind studies, it is possible that the blinding procedures used in a particular study may not be completely adequate or effective; therefore, it is important that the effectiveness of the blinding procedures be assessed in each study. Without such assurance of the effectiveness of the blinding, the reliability of the study's findings may be considered questionable.

V. Food Labeling - Applicable Legal Principles

Labels provide a variety of information about a food, including its name, ingredients, and nutritional profile. For example, the labeling of any food containing color additives that FDA certifies for food use, such as FD&C Red No. 40 and FD&C Yellow No. 5, must declare those additives by name as ingredients.[9] Labeling is a means of informing consumers who may want to avoid certain substances for health or other reasons of their presence in food.

Section 403 of the Act sets forth various conditions under which a food is deemed to be misbranded. Under section 403(a)(1) of the Act [21 U.S.C. § 343(a)(1)], a food is misbranded if its labeling is false or misleading in any particular. Section 201(n) of the Act [21 U.S.C. § 321(n)] provides additional information on how labeling can be misleading. It states that labeling is misleading if it fails to reveal facts that are (1) material in light of representations made or suggested in the labeling, or (2) material with respect to consequences that may result from the use of the food to which the labeling relates under the conditions of use prescribed in the labeling, or under such conditions of use as are customary or usual.

Under sections 403(a)(1) and 201(n) of the Act, then, FDA has the authority to impose a food labeling requirement, such as a required warning statement, to prevent labeling from being misleading only if the information required to be included on the label is material in light of representations made in the labeling or with respect to the consequences that may result from the customary use of the article to which the labeling relates. Although FDA's authority to require labeling is subject to the constraints of the Act, producers and manufacturers may, on their own initiative, include additional information in the labeling of their products, provided that the information is truthful and not misleading. A manufacturer or producer must also be able to substantiate that such information is truthful and not misleading.

In the past, FDA has required labeling under section 201(n) of the Act to provide material information about the food itself in situations where the absence of such information may (1) mislead the consumer in light of other statements made on the label (e.g., the requirement that labeling include quantitative nutrient information when certain nutrient content claims are made about a product[10]), or (2) lead a consumer to assume that a food, because of its similarity to another food, has nutritional, organoleptic (e.g., taste, smell, or texture), or functional (e.g., storage) characteristics of the food it resembles, when in fact it does not (e.g., reduced fat margarine not suitable for frying[11]).

FDA also has required labeling under section 201(n) of the Act to convey information that is material about the consequences that may result from the consumption of a given food. For example, FDA requires that a warning statement appear in the labeling of unpasteurized juice to provide information to consumers about the possible consequences (serious illness from harmful

[9] 21 CFR. 101.22(k).
[10] See, e.g., 21 CFR 101.13(h) (requiring that, if a food bearing a nutrient content claim contains more than a certain level of fat, saturated fat, cholesterol, or sodium, the labeling of that food bear a disclosure statement regarding the level of that nutrient); 58 Fed. Reg. 2302, 2307 (Jan. 6, 1993).
[11] 21 CFR 130.10(c); see also 58 Fed. Reg. 2431, 2436-37 (Jan. 6, 1993).

bacteria) of consuming the product because it has concluded that information is material.[12] FDA also has determined, however, that not all effects from customary or usual consumption are material with respect to the consequences of use. For example, FDA concluded in 2003 that a previously required label statement regarding the possible gastrointestinal effects of olestra was no longer necessary to prevent olestra-containing products from being misbranded because of widespread consumer awareness about possible effects and because the potential effects were relatively insignificant.[13]

Under current law, FDA does not have the authority to require labeling based on consumer interest alone.[14] Although FDA may consider consumer opinion in determining whether a label is required to disclose a material fact, consumer opinion may not be considered in determining whether a fact is material in the first instance. For example, FDA determined that it did not have the authority to require additional labeling of all foods derived from genetically-engineered (GE) organisms based on its conclusion that, in general, genetic engineering does not materially alter foods, even though there was significant consumer interest in requiring such labeling.[15] Similarly, although there was consumer demand for additional labeling of milk from cows treated with recombinant Bovine Somatotropin (rBST), a synthetic growth hormone that increases milk production in dairy cows, because FDA found that there was no material difference between milk from rBST-treated cows and non-rBST-treated cows, FDA did not have the authority to require any additional labeling.[16].

VI. Conclusion

Based on our review of the data from published literature, FDA concludes that a causal relationship between exposure to color additives and hyperactivity in children in the general population has not been established. For certain susceptible children with Attention Deficit/Hyperactivity Disorder and other problem behaviors, however, the data suggest that their condition may be exacerbated by exposure to a number of substances in food, including, but not limited to, synthetic color additives. Findings from relevant clinical trials indicate that the effects on their behavior appear to be due to a unique intolerance to these substances and not to any inherent neurotoxic properties.

The task before this Food Advisory Committee is to consider available relevant data on the possible association between consumption of synthetic color additives in food and hyperactivity in children, and to advise FDA as to what action, if any, is warranted to ensure consumer safety.

[12] 63 Fed. Reg. 37030, 37043-44 (July 8, 1998); see also, e.g., 49 Fed. Reg. 13679 (April 6, 1984) (establishing a warning statement required in the labeling of protein products used in very low calorie diets).
[13] 68 Fed. Reg. 46364, 46387 (Aug. 5, 2003).
[14] See, e.g., International Dairy Foods Ass'n v. Amestoy, 92 F.3d 67, 73 (2d Cir. 1996) (holding that consumer interest alone is not a sufficient government interest on which to compel labeling); Alliance for Bio-Integrity v. Shalala, 116 F. Supp. 2d 166, 179 (D.D.C. 2000) ("[O]nly once materiality has been established may the FDA consider consumer opinion to determine whether a label is required to disclose material fact."); Stauber v. Shalala, 895 F. Supp. 1178, 1193 (W.D. Wisc. 1995).
[15] Alliance for Bio-Integrity, 116 F. Supp. 2d at 178-79.
[16] Stauber, 895 F. Supp. at 1193.