



Food Advisory Committee

Certified Color Additives and Childhood Hyperactivity

Mitchell Cheeseman, Ph.D.

**Acting Director
Office of Food Additive Safety
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Brief Statutory History

1938 - Federal Food, Drug and Cosmetic Act was passed, revising the 1906 Pure Food and Drug Act.

- **Mandated the certification of coal tar colors**
- **Forbids the use of uncertified coal tar colors in food, drugs, and cosmetics other than hair dyes**
- **Authorizes fees to certify coal tar colors**
- **Requires label declaration of artificial coloring, flavoring, and chemical preservatives in food**

1960 – Color Additive Amendments

- **Defined “color additive” and “unsafe color additive”**
- **Established a provisional list of color additives in use at that time**
- **Established a petition process for permanently listing color additives**





Color Additive Definition

201(t) of the Act

A “color additive” means a material which

- Is a dye, pigment, or other substance made by a process of synthesis ... or extracted, isolated, or otherwise derived...from a vegetable, animal, mineral, or other source, and
- When added or applied to a food, drug, or cosmetic, or to the human body or any part thereof, is capable (alone or through the reaction with other substance) of imparting color thereto.
- Includes black, white, and shades of gray





Adulteration Provisions

- **§ 721(a) – A color additive is unsafe for use in food unless there is an authorizing regulation or exemption**
- **§ 402(c) - A food containing an unsafe color additive is adulterated**





Why Use Color Additives In Food?

- **To offset color loss due to exposure to light, air, temperature, moisture, and storage conditions**
- **To correct natural variations in color**
- **To enhance colors that occur naturally but at levels weaker than those usually associated with a given food**
- **To provide a colorful identity to foods that would otherwise be colorless**





How does FDA regulate color additives for use in food?





Petition Process

- **§ 71.1(a) - Any interested person may propose the listing of a color additive for use in or on any food, drug, or cosmetic or for coloring the human body. Such proposal shall be made in a petition in the form prescribed in paragraph (c) of § 71.1.**
- **Burden is on the petitioner to demonstrate safety and suitability**
- **Successful petition results in new listing or amendment of existing regulation**





Color Additive Petition: Required Information: §71.1(c)

- **Identity**
- **Physical, chemical, and biological properties**
- **Manufacturing process description**
- **Stability data**
- **Information on use level and color effect**
- **Proposed tolerances or other limitations, if needed**
- **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**
- **Labeling**
- **Full reports of safety studies**
- **Estimate of probable exposure**
- **Rationale for exemption from batch certification**
- **Appropriate filing fee**
- **An environmental assessment or claim or categorical exclusion**





Batch Certification

Decision on need for batch certification is part of the petition review based on:

- **Variation in the manufactured color additive**
- **Relevance to safety of any variation in the composition of the color additive**





Safety Decision

- **Standard of Review**
 - **Fair Evaluation of the Data**

From the legislative history, "... should not be based on isolated evidence in the record, which evidence in and of itself may be considered substantial without taking account of the contradictory evidence of equal or even greater substance ..."



Safety Decision

- **Safety Standard**
 - **Reasonable Certainty of No Harm**

From the legislative history:

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 circumstance."



Safety Decision

- Decision addresses questions of a probative nature
- Decision does not weigh benefits
- Decision is always made under some level of uncertainty and cannot ensure safety with absolute certainty
- Decision is temporal...made at one point in time
- Decision can and should be reconsidered based on new information which raises serious questions related to the intended use



Elements of Review

- Manufacturing process, identity, purity and specifications
- Estimated Daily Intake to color additive and impurities
- Consideration of adequacy of methods needed to ensure safety of color additive
- Identification of any controls, specifications, or other limitations that are necessary to ensure safety



Elements of Review

- Review of safety studies presented to identify relevant studies
- Review of all other available data to identify relevant studies
- Evaluation of relevant safety studies to determine adequacy of the data set to support estimated exposure
 - Identification of any additional questions raised by data
 - Determination of a safe exposure level (ADI)



Elements of Review

- Review is iterative and FDA places the burden on the submitter to address safety questions until all are resolved
 - Additional data or analysis
 - Additional limitations
- FDA guidance documents and specific guidance on a proposed submission are a starting point
 - Guidance is not binding on industry or FDA to the exclusion of better or more appropriate methods
- FDA must issue a regulation permitting the use before such use is legal





Two Critical Aspects of Review

Estimating consumer exposure

Determining what consumer exposure may be safe





Exposure Evaluation Methods

- 1st Tier – Simplest
 - Budget methods
 - “Worst-case” scenarios
- 2nd Tier – Some refinement
 - Model diets (default food consumption with substance concentration data)
 - Poundage data (validation and central tendency)
 - ▣ No/Limited ability to describe distribution
- 3rd Tier – Common premarket review model
 - Survey food consumption data with probable (or max) substance concentration
- 4th Tier – Probabilistic methods
 - Comprehensive, expensive, extensive



Setting a Safe Level of Exposure

- **Using guidance as a reference to assess whether the safety database is adequate to address predicted levels of exposure**
- **Analyzing the safety dataset to determine a point of departure (NOEL, BMDL)**
- **Safety factors - To account for uncertainties in data and for differences between animals and humans and differences in sensitivity among humans (10-2000)**
- **Establishing an Acceptable Daily Intake (ADI) or an acceptable margin of exposure.**





Listing of Color Additives

- **Part 73 - Color additives exempt from certification**
- **Part 74 - Color additives subject to certification**
- **Part 81- Provisionally listed lakes of certified colors**
- **Regulation addresses identity, limitations on conditions of use, specifications, and labelling requirements**



Color Additives Approved for Food Use subject to batch certification

21 CFR Section	Straight Color	Year Approved	Uses and Restrictions
74.101	FD&C Blue No. 1 *	1969	Foods generally
74.102	FD&C Blue No. 2 *	1987	Foods generally
74.203	FD&C Green No. 3*	1982	Foods generally
74.250	Orange B	1966	Casings or surfaces of frankfurters and sausages; Not to exceed 150 ppm
74.302	Citrus Red No. 2	1963	Skins of oranges not intended or used for processing; Not to exceed 2.0 ppm
74.303	FD&C Red No. 3	1969	Foods generally
74.340	FD&C Red No 40 *	1971	Foods generally
74.705	FD&C Yellow No. 5 *	1969	Foods generally
74.706	FD&C Yellow No. 6*	1986	Foods generally

*Lake also is permitted. (A lake is a straight color made insoluble by extending it on a substratum)





Regulatory Status of a Color Additive

- **Must conform to listing regulation in all aspects**
 - **Batch Certification**
 - **Identity**
 - **Specifications**
 - **Use Limitations**





Amounts Certified in 2010

Color Additive	Pounds Certified
FD&C Red No. 40	6,094,445
FD&C Yellow No. 5	4,105,501
FD&C Yellow No. 6	3,656,010
FD&C Blue No. 2	664,328
FD&C Blue No. 1	587,431
FD&C Red No. 3	208,876
FD&C Green No. 3	13,051
Orange B	0
Citrus Red No. 2	0
Total	15,329,642





2010 Per Capita Exposure vs ADI

Color Additive	Per Capita Exposure mg/p/d	ADI _{60 kg adult} mg/p/d	ADI _{30 kg child} mg/p/d
FD&C Blue 1	1.72	720	360
FD&C Blue 2	1.95	150	75
FD&C Green 3	0.038	150	75
FD&C Red 3	0.61	150	75
FD&C Red 40	17.91	420	210
FD&C Yellow 5	12.06	300	150
FD&C Yellow 6	10.74	225	113



High Consumer EDI* vs ADI

Color Additive	Per Capita Exposure mg/p/d	ADI _{60 kg adult} mg/p/d	ADI _{30 kg child} mg/p/d
FD&C Blue 1	17.2	720	360
FD&C Blue 2	19.5	150	75
FD&C Green 3	0.38	150	75
FD&C Red 3	6.1	150	75
FD&C Red 40	179.1	420	210
FD&C Yellow 5	120.6	300	150
FD&C Yellow 6	107.4	225	113

*Assumes 10% of population consumes 100% of color additives in food





FAC Charge

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





Questions

- **Question 1:** In the review of published research presented in the “Overview and Evaluation of *Proposed Association Between Artificial Food Colors and Attention Deficit Hyperactivity Disorders (ADHD) and Problem Behaviors in Children*,” studies were evaluated based on the criteria described in Part III of the review. Were these review criteria appropriate in the evaluation of these studies? Should the criteria be modified in any specific way, and if so, what is the basis for the committee’s recommendation? Are there other criteria or other studies that should be considered, and if so, what is the basis for the committee’s recommendation?
- **Question 2:** Do the current relevant data support FDA’s conclusion, as set forth in the September 1, 2010 Interim Toxicology Review Memorandum, that a causal relationship between consumption of certified color additives in food and hyperactivity in children in the general population has not been established?





Questions (cont.)

- **Question 3:** National Institutes of Health's 1982 Consensus Development Panel on Defined Diets and Childhood Hyperactivity concluded that for some children with both attention deficit hyperactivity disorder and a confirmed food allergy, dietary modification has produced some improvement in behavior. The panel recommended that elimination diets should not be used universally to treat childhood hyperactivity (with or without the presence of food allergies), since there is no scientific evidence to predict which children may benefit. The panel, however, also recognized that initiation of a trial of dietary treatment or continuation of a diet in patients whose families and physicians perceive benefits may be warranted. Are these conclusions and recommendations still relevant today in light of subsequently published studies, especially as those conclusions and recommendations apply to certified color additives?



Questions (cont.)

- **Question 4:** Under current FDA regulations, the label of any food to which a certified color additive has been added must declare the color additive as an ingredient by its certified name (e.g., FD&C Yellow No. 5). In light of the scientific evidence presented to the Committee concerning the consumption of certified color additives in food and hyperactivity in children, what additional information, if any, should be disclosed on the product label of foods containing certified color additives to ensure their safe use in food?
- **Question 5:** Regarding the possible association between consumption of certified color additives and hyperactivity in children, are additional studies necessary to address any questions that have been raised as to whether, and under what conditions, the continued use of these certified color additives is safe? If so, what type of studies?



Questions?

