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DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service
Food and Drug Administration

Memorandum

Date: September 1, 2010

Subject: Citizen Petition from the Center for Science in the Public Interest (CSPI) requesting the revocation of the color additive approvals of eight synthetic dyes for use in food –
Interim Toxicology Review Memorandum

Docket No. FDA-2008-P-0349
Correspondence No. 84566

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CSPI has submitted a petition requesting that FDA revoke approvals for eight certified color additives for use in foods: FD&C Blue 1 and 2, FD&C Green 3, Orange B, FD&C Red 3, FD&C Red 40, and FD&C Yellow 5 and 6. In support of this request, CSPI cites findings from a study that was conducted by the University of Southampton on the effect of certain mixtures of color additives in children; this study was published in the *Lancet* in 2007¹. CSPI also references a number of publications, including a 2004 meta-analysis by Schab and Trinh² of previously conducted clinical trials that investigated the proposed relationship between consumption of artificial food colors and behavioral changes in children diagnosed with hyperactivity. This interim review memorandum along with its four attachments presents FDA's detailed in-depth review and analyses of these study publications, and other relevant published information pertaining to color additives and their potential to cause adverse neurobehavior in children. The review was conducted by the Toxicology group of FDA's Center for Food Safety and Applied Nutrition, Office of Food Additive Safety, Division of Petition Review (DPR).

In our evaluation of this petition request FDA has conducted a thorough review of the Southampton Study from the perspective of its design, results and conclusions. The FDA also has reviewed the other publications included in this petition, including the 2004 Schab and Trinh meta-analysis publication. In addition, FDA conducted a comprehensive search, review and analysis of the scientific literature on color additives and their potential relationship to neurobehavioral disorders in children. Both ToxLine and PubMed databases were searched to identify articles related to the effect of consumption of color additives on children's behavior, with a focus on clinical trials. The criteria used for the review and the search terms are detailed

¹ McCann, D. et al. 2007. 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. *The Lancet*, November, 2007, Volume 370, Issue 9598, pg. 1560-15-67.

² Schab, DW and Trinh, NT. 2004. Do artificial food colors promote hyperactivity in children with hyperactive syndrome? A meta-analysis of double-blind placebo-controlled trials. *J. Dev. Behav. Pediatr.* 25(6): 423-34.

in attachment 1. Articles deemed most relevant were selected for in-depth review based on the abstracts retrieved in the search.

Our review reports of the 2007 Southampton study and the 2004 Schab and Trinh meta-analysis are included as attachments to this cover memorandum (attachments 2 and 3). Our review and analysis of other published scientific literature is included as attachment 4, which incorporates the overview report, reviews and critiques of 33 of the most relevant clinical trials identified from the literature search, a tabular summary of these clinical trials, and a bibliography. All of these reviews were conducted by an expert neurotoxicologist through an Interagency Agreement with Oak Ridge National Laboratories (ORNL). The draft ORNL review reports were reviewed by an OFAS toxicologist and have been accepted as final.

In summary, based on the data reviewed in these publications FDA concludes that a causal relationship between exposure to color additives and hyperactivity in children in the general population has not been established. However, for certain susceptible children with ADHD and other problem behaviors, the data suggest that their condition may be exacerbated by exposure to a number of substances in food, including, but not limited to, artificial food colors. 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.

ATTACHMENT 1: Review Criteria and Search Terms Used in ORNL Literature Review

ATTACHMENT 2: Finalized Review of 2007 Southampton Study – ORNL

ATTACHMENT 3: Finalized Review of 2004 Schab and Trinh Publication – ORNL

ATTACHMENT 4: Finalized Review and Analysis of the Literature – ORNL