January 19, 2016

Stephen Ostroff, M.D., Acting Commissioner U.S. Food and Drug Administration 10903 New Hampshire Avenue Silver Spring, MD 20993

## Dear Dr. Ostroff:

We are physicians and researchers who have expertise in toxicology and/or behavioral problems in children and write to express our concerns about the adverse effects of artificial food dyes on children's behavior, and to urge timely federal action on this important issue.

The first hints that food ingredients can impair children's behavior came in the early 1970s, when Kaiser-Permanente allergist Dr. Ben Feingold publicized his clinical findings. His contentions generated great public concern and spurred scientific research. One of the early studies was funded by the U.S. Food and Drug Administration (FDA).<sup>1</sup>

In 2011, in response to a 2008 citizen petition filed by the Center for Science in the Public Interest, FDA convened a meeting of its Food Advisory Committee (FAC) to consider the evidence linking food dyes and adverse behavior. That evidence included two seminal studies funded by the Food Standards Agency of the British government.<sup>2</sup> The authors concluded after the first study that "We believe that this suggests that benefit would accrue for all children if artificial food colours and benzoate preservatives were removed from their diet." The second study, which replicated the results from the first study and also found effects in older children, concluded that the findings from the two studies "lend strong support for the case that food additives exacerbate hyperactive behaviours (inattention, impulsivity, and overactivity) in children at least up to middle childhood," and that adverse effects are seen "not just in children with extreme hyperactivity (i.e., ADHD) but can also be seen in the general population and across the range of severities of hyperactivity." The British studies led to a warning label in Europe.<sup>3</sup> The 2011 FAC also

<sup>&</sup>lt;sup>1</sup> Weiss B, Williams JH, Margen S et al. Behavioral responses to artificial food colors. *Science* 1980;207(4438):1487-8.

<sup>&</sup>lt;sup>2</sup> McCann D, Barrett A, Cooper A, et al. Food additives and hyperactive behaviour in 3-year-old and 8/9-year-old children in the community: a randomised, double-blinded, placebo-controlled trial. Lancet 2007 Nov 3;370(9598):1560-7. Bateman B, Warner JO, Hutchinson E, et al. The effects of a double blind, placebo controlled, artificial food colourings and benzoate preservative challenge on hyperactivity in a general population sample of preschool children. *Arch Dis Child*. 2004;89(6):506-11.

<sup>&</sup>lt;sup>3</sup> Foods in Europe that contain certain food dyes (those studied by the UK-funded studies cited above) are required to bear a statement that the dyes "may have an adverse effect on activity and attention in children."

reviewed a 2004 meta-analysis that concluded "our results strongly suggest an association between ingestion of [artificial food colorings] and hyperactivity."<sup>4</sup> Several FAC members questioned FDA's estimation of safe levels of dyes based on standard chronic rodent studies and its conclusion that dyes are not neurotoxic, given the lack of adequate data on neurobehavioral toxicity. The committee recommended additional safety studies and an exposure assessment and was closely divided as to whether additional

information (e.g., warnings) should be required on labels.<sup>5</sup>

Since 2011, the relationship between synthetic food dyes and behavioral impacts in children has become even clearer. Several new comprehensive reviews of the evidence, including two meta-analyses, concluded that specifically excluding food dyes, or adopting a restriction diet that eliminates dyed foods as well as certain other foods, reduces adverse behavior in some children. For example:

- One meta-analysis concluded that a restriction diet reduces symptoms of attention-deficit/hyperactivity disorder (ADHD) in one-third of children with ADHD, and estimated that 8 percent of children with ADHD have symptoms related to food dyes. In objective, computerized measures of attention, a significant effect was associated with FDA-approved food dyes, not explainable by publication bias. These findings were deemed by the authors as "too substantial to dismiss."
- Another meta-analysis of six non-drug treatments for ADHD found that excluding artificial food dye from the diet produced the largest effects of the treatments analyzed (often in individuals selected for food sensitivities).<sup>7</sup>
- A recent review on behalf of the European ADHD Guidelines Group compared the three most recent meta-analyses and concluded that elimination of food dyes "is a potentially valuable treatment" for ADHD, although it noted that it was not possible to predict *which* children would benefit.<sup>8</sup>
- Another recent review rated the evidence for different treatments aimed at reducing ADHD symptoms, using guidelines developed by the Oxford Center for Evidence-Based Medicine.<sup>9</sup> It ranked exclusion of food dyes and more restricted diets as

<sup>&</sup>lt;sup>4</sup> Schab DW, Trinh NH. Do artificial food colorings promote hyperactivity in children with hyperactive syndromes? A meta-analysis of double-blind placebo-controlled trials. *J Dev Behav Pediatr*. 2004;25(6):423-34.

<sup>&</sup>lt;sup>5</sup> The question "Should additional information be disclosed on the product label of food containing certified color additives to ensure their safe use" was put to the committee and the vote was 6 (43%) yes, 8 (57%) no. See Quick Minutes, Food Advisory Committee Meeting March 30-31, 2011 at

http://www.fda.gov/AdvisoryCommittees/CommitteesMeetingMaterials/FoodAdvisoryCommittee/ucm250901.htm.

<sup>&</sup>lt;sup>6</sup> Nigg JT, Lewis K, Edinger T, Falk M. Meta-analysis of attention-deficit/hyperactivity disorder or attention-deficit/hyperactivity disorder symptoms, restriction diet, and synthetic food color additives. *J Am Acad Child Adolesc Psychiatry* 2012;51(1): 86-97.e8. doi: 10.1016/j.jaac.2011.10.015.

<sup>&</sup>lt;sup>7</sup> Sonuga-Barke EJ, Brandeis D, Cortese S, et al. Nonpharmacological interventions for ADHD: systematic review and meta-analyses of randomized controlled trials of dietary and psychological treatments. *Am J Psychiatry* 2013;170(3):275–89. doi: 10.1176/appi.ajp.2012.12070991.

<sup>&</sup>lt;sup>8</sup> Stevenson J, Buitelaar J, Cortese S, et al. Research review: The role of diet in the treatment of attention-deficit/hyperactivity disorder—an appraisal of the evidence on efficacy and recommendations on the design of future studies. *J Child Psychol Psychiatry*. 2014;55(5):416-27. doi:10.1111/jcpp.12215.

<sup>&</sup>lt;sup>9</sup> Faraone SV, Antshel KM. Towards an evidence-based taxonomy of nonpharmacologic treatments for ADHD. *Child Adolesc Psychiatr Clin N Am.* 2014; 23(4):965–972. doi: 10.1016/j.chc.2014.06.003.

- treatments supported by the second-highest level of evidence, lower than FDA-approved medications, but much stronger than many other treatments, including psychotherapy or clinic-based social skills training.
- Still other reviews since 2011 have suggested minimizing children's exposure to food dyes, <sup>10</sup> noting that some children improve significantly on a dye-free diet, <sup>11</sup> and recommending an elimination diet for children who react to dyes or other components of the diet. <sup>12</sup>

Sadly, the general public remains unaware of the risks and children suffer unnecessarily, in part due to FDA's misleading public communication about the issue. Despite the evidence, one FDA website promises that dyes are not just safe, but "very safe," and another FDA website and brochure that is published jointly with the food industry's International Food Information Council, poses the question "[d]o additives cause childhood hyperactivity?" and asserts that "results from studies on this issue either have been inconclusive, inconsistent, or difficult to interpret." 14

Such statements contradict FDA's own conclusion in 2011 that "[e]xposure to food and food components, including artificial food colors and preservatives, may be associated with adverse behaviors, not necessarily related to hyperactivity, in certain susceptible children with ADHD and other problem behaviors, and possibly in susceptible children from the general population." <sup>15</sup> It also contrasts with efforts by the British government to help consumers avoid foods using dyes linked to adverse behavior and to urge the food industry to stop using those dyes. <sup>16</sup>

FDA's clear legal responsibility is to ensure that dyes are "safe," a determination that requires "convincing evidence that establishes with reasonable certainty that no harm will

<sup>&</sup>lt;sup>10</sup> Arnold LE, Lofthouse N, Hurt E. Artificial food colors and attention-deficit/hyperactivity symptoms: conclusions to dye for. *Neurotherapeutics* 2012 Jul;9(3):599-609. doi: 10.1007/s13311-012-0133-x.

<sup>&</sup>lt;sup>11</sup> Stevens LJ, Kuczek T, Burgess JR, et al. Dietary sensitivities and ADHD symptoms: thirty-five years of research. *Clin Pediatr (Phila)*. 2011;50(4):279-93. doi: 10.1177/0009922810384728.

<sup>&</sup>lt;sup>12</sup> Arnold LE, Hurt E, Lofthouse N. Attention-deficit/hyperactivity disorder: dietary and nutritional treatments. Child *Adolesc Psychiatr Clin N Am.* 2013; 22(3): 381–402, v. doi: 10.1016/j.chc.2013.03.001.

<sup>&</sup>lt;sup>13</sup> "Color additives are very safe when used properly," says Linda Katz, M.D., M.P.H., Director of the Office of Cosmetics and Colors in FDA's Center for Food Safety and Applied Nutrition." From US Food and Drug Administration, How safe are color additives? at

http://www.fda.gov/ForConsumers/ConsumerUpdates/ucm048951.htm..

<sup>&</sup>lt;sup>14</sup> US Food and Drug Administration. Do additives cause childhood hyperactivity? at

 $<sup>\</sup>underline{http://www.fda.gov/Food/IngredientsPackagingLabeling/FoodAdditivesIngredients/ucm094211.htm\#qahyper}$ 

<sup>&</sup>lt;sup>15</sup> Aungst J. Evaluation of studies on artificial food colors and behavior disorders in children. Food and Drug Administration. <a href="http://www.fda.gov/downloads/AdvisoryCommittees/CommitteesMeetingMaterials/FoodAdvisoryCommittees/CommitteesMeetingMaterials/FoodAdvisoryCommittee/UCM273033.pdf">http://www.fda.gov/downloads/AdvisoryCommittees/CommitteesMeetingMaterials/FoodAdvisoryCommittees/UCM273033.pdf</a> and cited by Cheeseman MA. Artificial food color additives and child behavior. *Environ Health Perspect* 2012; 120(1):A15-16. doi: 10.1289/ehp.1104409.

<sup>&</sup>lt;sup>16</sup> UK Food Standards Agency. Products free from the colours associated with hyperactivity. <a href="http://www.food.gov.uk/policy-advice/additivesbranch/foodcolours/colourfree/#.UIL9gRD0hD4">http://www.food.gov.uk/policy-advice/additivesbranch/foodcolours/colourfree/#.UIL9gRD0hD4</a>; and Agency revises advice on certain artificial colours. Sep 11, 2007. <a href="https://www.food.gov.uk/news/newsarchive/2007/sep/foodcolours">www.food.gov.uk/news/newsarchive/2007/sep/foodcolours</a>.

result from the intended use of the color additive." Based on current scientific evidence, food dyes do not meet that standard.

As one researcher has stated, "there is no cost to health or safety in giving up artificial colors." <sup>17</sup> We urge the FDA to adopt measures that would protect children from the unnecessary harm caused by food dyes, including by taking the following steps:

- Announcing FDA will withdraw approval for the use of dyes that may adversely affect children's behavior and beginning the process of such a withdrawal.
- As an interim measure, requiring warning labels on products containing any certified food dyes.
- Revising the FDA's inaccurate brochure "Food Ingredients and Colors" and other relevant misinformation on FDA's websites and in agency materials.
- Require sensitive developmental neurotoxicity and neurobehavioral testing as well as other appropriate tests for new food additives.

## Sincerely,

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<sup>&</sup>lt;sup>17</sup> Kaplan, BJ. Food additives and behavior: First genetic insights. *Am J Psychiatry* 2010: 167(9):1023-1025.

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