



January 19, 2016

Dr. Stephen Ostroff, M.D., Acting Commissioner  
Food and Drug Administration (FDA)  
10903 New Hampshire Avenue  
Silver Spring, MD 20993

**Re: Docket No. 2008-P-0349: A new report regarding the evidence on the failure of current color additive approvals to meet the legal standard for safety**

Dear Acting Commissioner Ostroff:

In 2008, the Center for Science in the Public Interest (CSPI) filed a citizen petition asking for FDA to withdraw approvals for eight certified color additives, for warning labels on foods containing such dyes as an interim step, and for corrections to the agency's website and public materials regarding the risks posed by dyes.<sup>1</sup> We submit the enclosed report, *Seeing Red: Time for Action on Food Dyes*, a letter from leading physicians and researchers, including many experts and recognized authorities on the link between dyes and adverse behavior, and this letter as a comment to that docket. Below, we provide a brief legal analysis of the deficiencies in the agency's inaction on the risks of dyes. Both the enclosed report and letter from scientists summarize two meta-analyses and other relevant reviews and studies completed since 2011 that further clarify the link between food dyes and adverse behavior. Alongside the scientists, we urge FDA to take steps to protect children from the completely unnecessary harm being caused by synthetic food dyes.

*Current FDA Approvals of Synthetic Colors Violate Federal Law*

Under the law, FDA is charged with a clear and ongoing duty to assess the safety of substances in the diet.<sup>2</sup> Color additives, in particular, must meet a stringent legal standard for safety and require specific approval from FDA under the law.

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<sup>1</sup> Citizen Petition from CSPI requesting the revocation of the color additive approvals of eight synthetic dyes for use in food—Interim Toxicology Review Memorandum. CSPI Petition to Ban the Use of Yellow 5 and Other Food Dyes. Docket No. FDA-2008-P-0349, June 3, 2008. See <https://www.cspinet.org/new/pdf/petition-food-dyes.pdf>.

<sup>2</sup> See Tentative Determination Regarding Partially Hydrogenated Oils; Request for Comments and for Scientific Data and Information. 78 Fed. Reg. 67169, at 67170 (Nov. 8, 2013). This obligation is reinforced by the legislative history relevant to food and color additives. See Comments Regarding Substances Generally Recognized as Safe, FDA-1997-N-0020, from Center for Science in the Public Interest, Consumers Union, Environmental Working Group (EWG), and Natural Resources Defense Council (NRDC), Feb. 2015, <http://cspinet.org/new/pdf/GRAS%20Comment%20FINAL.pdf>.

Dyes provide no nutritional, health-related, or other essential value. Congress thus held them to a high standard for safety, and subjected them to a certification process distinct from all other additives.<sup>3</sup> Moreover, color additives may not be determined “generally recognized as safe,” but instead require FDA’s approval through a formal petition process. FDA’s present leniency with regard to the safety of food dyes is at odds with clear direction from Congress to require data establishing safety.

The Color Additives Amendments of 1960 creates the current legal framework for color additives, requiring that color additives must be “safe and suitable” for a given use, and barring use of a color additive in food unless FDA finds that “the data...establish that such use...will be safe.”<sup>4</sup> The law states that “the term ‘safe,’ refers to “the health of man or animal.”<sup>5</sup> FDA’s regulations define safe as requiring “convincing evidence that establishes with reasonable certainty that no harm will result from the intended use of the color additive.”<sup>6</sup>

Three of the factors considered when evaluating the safety of a color additive include:

- (i)** the probable consumption of, or other relevant exposure from, the additive and of any substance formed in or on food, drugs or devices, or cosmetics because of the use of the additive;
- (ii)** the cumulative effect, if any, of such additive in the diet of man or animals, taking into account the same or any chemically or pharmacologically related substance or substances in such diet; and
- (iii)** safety factors which, in the opinion of experts qualified by scientific training and experience to evaluate the safety of color additives for the use or uses for which the additive is proposed to be listed, are generally recognized as appropriate for the use of animal experimentation data.<sup>7</sup>

Approval of a color is not a permanent status. The law authorizes “amendment or repeal”<sup>8</sup> of any food color regulation “based upon a fair evaluation of the entire record.”<sup>9</sup> The analysis on which FDA is apparently grounding its present inaction regarding the safety of dyes—as documented in the questions presented to the 2011 Food Advisory Committee

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<sup>3</sup> O’Reilly, J.T. (2007). *The Food and Drug Administration*. 3rd ed. Eagan, MN: Thomson/West. Commenting on the 1960 Color Additives Amendment, James T. O’Reilly, an adjunct professor at University of Cincinnati College of Law, noted that “Congress felt that ... colors deserved greater regulation because of their lesser net benefit to society than such items as food preservatives and common spices.”

<sup>4</sup> 21 U.S.C. 379e(b)(4).

<sup>5</sup> 21 U.S.C. 321(u).

<sup>6</sup> 21 C.F.R. 70.3(i). While the safety standard is not absolute, as no scientific evaluation is perfect, the bar for determining safety is high under the law and relevant regulations.

<sup>7</sup> 21 U.S.C. 379e (b)(5)(A).

<sup>8</sup> 21 USC 721(b)(5)(C)(i).

<sup>9</sup> Sections 721(d)(4) and 409(g)(2) of the FFDCA, 21 U.S.C. 379e(d)(4) and 21 U.S.C. 348(g)(2).

(FAC) and background materials prepared for that meeting—is seriously flawed under the law.<sup>10</sup>

In 2011, as officials explicitly acknowledged, FDA failed to ask the FAC whether the current use of dyes, given the weight of the evidence linking dyes and adverse effects on behavior, satisfies the legal standard for safety.<sup>11</sup> Thus FDA failed to ask the FAC to answer the critical question under the law. Instead, the FDA directed the FAC to focus on a different question: whether a “causal” relationship had been established between consumption of dyes and hyperactivity or other adverse effects on behavior in children in the general population. Establishing a cause–effect relationship between food dyes and hyperactivity or other adverse behavioral effects is far more difficult than establishing whether food dyes meet the legal definition for safety considering the evidence on behavioral effects, and has no legal relevance.<sup>12</sup>

Regardless of FDA’s framing of the question for the FAC, the legal safety standard and its requirements apply equally to “susceptible” children—harm to them is still harm under the law—and FDA concedes that susceptible children may be harmed by dyes.<sup>13</sup> A fair

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<sup>10</sup> We note that the law further provides that in deciding whether to approve a color for all uses the FDA should “take into account...(subject to the paramount criterion of safety)...the availability, if any, of other color additives suitable and safe for one or more of the uses proposed.” Section 721(b)(8) of the FFDCFA. As discussed in the enclosed report, dyes can easily be replaced by natural food colors or other ingredients.

<sup>11</sup> FDA Transcript. Food Advisory Committee (FAC) Meeting. March 31, 2011. p. 212. Dr. Cheeseman (in response to changing the charge of the FAC to be consistent with the legal safety standard) stated: “I think the last suggested change is problematic because you're only looking at a portion of the information that we would consider in making that ultimate determination. A lot of the discussion today has been around the rigor, for example, of the exposure assessment, and you in fact have not been offered a rigorous exposure assessment. Any safety assessment going forward would require that. And so I don't think you have adequate information to in fact address that charge. And so that was not the charge that we gave you for that very reason.” (Statement of Dr. Mitchell Cheeseman, Ph.D.) This also suggests that FDA could not assure that the legal standard of safety was met at that time since it lacked a rigorous exposure assessment.

<sup>12</sup> FDA Transcript. FAC Meeting. p. 242. For example, Dr. George Gray noted that: “This charge question, to me, asks a very hard question when it asks for us to decide whether there is a causal relationship. It’s very different, in fact, even than the legal standard....Reasonable certainty of no harm is different than believing that there is a causal relationship.” (Statement of George Gray, Ph.D., Professor, Department of Environmental and Occupational Health at George Washington University.) And on p. 251 of the transcript, Dr. F. Xavier Castellanos stated: “As I’ve mentioned, causality is a distant aspiration, but certainly these data don’t give us any confidence that we can say there’s nothing to worry about here, this problem is taken care of, this shouldn’t be looked at.” Statement of F. Xavier Castellanos, M.D., Brooke and Daniel Neidich Professor of Child and Adolescent Psychiatry, Director of the Phyllis Green and Randolph Cowen Institute for Pediatric Neuroscience, and Director of Research, NYU Child Study Center, NYU Langone School of Medicine.

<sup>13</sup> FDA. Background Document for FAC: Certified Color Additives in Food and Possible Association with Attention Deficit Hyperactivity Disorder in Children. March 30–31, 2011. “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.” *See also* FDA Interim Toxicology Review Memorandum. September 1, 2010. Attachment 4. FDA/CFSAN March 30-31, 2011. “Consequently, a parsimonious assessment of the available information concludes that small subpopulations of susceptible children with ADHD or other problem

evaluation of all the scientific evidence, considerably strengthened since FDA's 2011 analysis, would show that instead of "convincing evidence" that dyes cause "no harm," there is "convincing evidence" that the dyes *do* cause harm to children, as amply documented in the enclosed report.

Because the FAC was directed to answer the wrong question, its answers are not responsive to resolving FDA's duties under the law or to the CSPI petition. In lieu of further delay, and on the basis of its conclusion that dyes may be harming children, FDA should withdraw approval of certified dyes. If a petitioner can show that they are safe as required by law, they can be approved.

Indeed, current approvals for certified dyes are legally deficient in at least four additional major areas.

First, FDA lacks relevant information regarding "the probable consumption of, or other relevant exposure from, the additive and of any substance formed in or on food, drugs or devices, or cosmetics." Prior to 2011, FDA estimated dye consumption on the amounts of dyes certified, an approach criticized by the FAC as an "embarrassment" that was called "not rigorous" by an FDA official.<sup>14</sup>

Since 2011, FDA conducted an analysis of dye levels in foods, but has only partially disclosed the results.<sup>15</sup> In 2014, FDA released its initial exposure estimates and in 2015 the agency released updated estimates as posters at the American Chemical Society's annual meetings.<sup>16</sup> The results of these studies indicate that the dye content of many foods is

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behaviors and, possibly, certain susceptible children from the general population may be predisposed to a unique intolerance to a variety of foods and food ingredients, not limited to artificial food colors and preservatives, that may be associated with adverse behavioral responses, including nonhyperactive behaviors such as irritability, restlessness and sleep disturbances, and physical responses."

<sup>14</sup> FDA Transcript. FAC Meeting. March 31, 2011. p. 212. Dr. Cheeseman indicated that: "A lot of the discussion today has been around the rigor, for example, of the exposure assessment, and you in fact have not been offered a rigorous exposure assessment. Any safety assessment going forward would require that." And Dr. Gray noted, pp. 318-9, that: "I think that a real problem that I learned about in these last couple days and in reading this material is that the exposure assessment here is an embarrassment to FDA, I think. FDA has a lot of knowledge, a lot of talent, a lot of ability to do exposure assessment in a very serious way, and this idea of taking the total number of pounds that are produced and dividing it by 300 million or something like that is not a helpful thing, especially—and Dr. Voorhees brought this up several times—when it appears, using that method, that you could in fact be getting close to levels of concern, getting close to ADIs, especially as production increases. I just think that a much better assessment of exposure has to be done—something that looks at the exposures by populations helps us get a better understanding of the range of exposures in different age groups—in order to be confident that we, in fact, are using these color additives in a safe way. So I think the exposure assessment has to be addressed in a very serious way."

<sup>15</sup> CSPI received partial responses from FDA with testing results, and filed a Freedom of Information Act request for the remainder. FDA recently denied CSPI's request; we have appealed that decision.

<sup>16</sup> Doell D, Folmer D, Lee H, *et al.* Exposure estimate for FD&C colors for the U.S. population, at <http://www.fda.gov/downloads/AdvisoryCommittees/CommitteesMeetingMaterials/FoodAdvisoryCommitt>

higher than what was thought when many of the initial studies on dyes and behavior were conducted, as explained in the enclosed report.

For example, according to FDA's results, two tablespoons of Pillsbury Confetti Funfetti Chocolate Fudge Frosting contains 41.5 mg of dyes, which is more than the amount of dyes that triggered adverse reactions in some children in double-blind studies, many of which used doses as low as 26 mg (or even lower). Similarly, a child who drinks a cup of Hawaiian Punch (14.1 mg) and eats 4 pieces of Twizzlers (15.4 mg) or a Red, White and Blue Popsicle (21.6 mg) would exceed the amount of dyes used in studies that triggered behavioral reactions in some children, as detailed in the report. Other studies analyzing the dye content of foods confirm that the dye content of individual foods and of combinations of foods that might reasonably be expected to be consumed by children in a single meal or a single day are higher than the amount used in many of the studies on dyes and behavior and found to trigger adverse effects on behavior.<sup>17</sup>

In addition, key aspects of the agency's assessment are flawed. FDA's second estimate, in 2015, applied the wrong yard-stick by measuring exposure to dyes over 10 to 14 days, when it is clear from the research that short-term exposures cause adverse behavioral reactions. The amounts of dyes that a child might consume in one sitting or in one day, which is higher than an amount averaged over a longer period, should be the focus of an exposure assessment.

Compounding these problems, necessary data on exposures related to drugs, devices and cosmetics are lacking from the analysis, as FDA concedes it subtracted the non-food exposures to produce its estimates presented to the FAC<sup>18</sup> ; and it did not consider non-

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[ee/UCM411983.pdf](#); and Doell D, Folmer D, Lee H, *et al.* Updated exposure estimate for FD&C color additives for the U.S. population, at <http://www.iacmcolor.org/color-info/fda-updated-exposure-assessment-on-fdc-colors/>.

<sup>17</sup> Laura Stevens and her colleagues at Purdue University published the first studies of the dye content of brand-name beverages consumed by children. Because of criticisms of those researchers' methods, the researchers reanalyzed the data on beverages, using a method adapted from FDA. Those studies found that in some cases *a single serving* of a beverage contained more dyes than the doses used in the early studies—and an amount that other research shows is sufficient to produce behavioral responses in some children. That research found, for instance, that a cup of Kool-Aid Burst Cherry contains 50 mg of dyes—almost twice as much as the dose that caused behavioral reactions in some children. *See Stevens, et. al.* Amounts of Artificial Food Colors in Commonly Consumed Beverages and Potential Behavioral Implications for Consumption in Children: Revisited. *Clin Pediatr (Phila)*. 2015; 54(12):1228-30. doi: 10.1177/0009922815581348. Epub April 14, 2015.

<sup>18</sup> In the background document for the FAC meeting, FDA indicates that it “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. These poundage

food exposures in its 2014 or 2015 exposures assessments.<sup>19</sup> Dyes used in food are also permitted in cosmetics, supplements, over-the-counter medications, and prescription drugs, and these sources must be included in determining “probable consumption” (short-term or long-term) of a dye under the law. Some of these types of exposures are of concern because they would specifically impact susceptible children. For example, synthetic dyes top the list of inactive ingredients in two versions of Ritalin, a drug frequently prescribed for children with ADHD.<sup>20</sup> Additionally, non-food dyes, or other chemicals used in food, cosmetics, and medical products may be chemically or pharmacologically related to food dyes.<sup>21</sup>

Second, the basis for FDA’s present determinations regarding safety are inappropriate. Human studies indicate that *no* no-effect level has been found for dyes—effects have been observed at doses as low as 1 mg for tartrazine (Yellow 5),<sup>22</sup> for example—dividing this exposure by FDA’s standard safety factors makes clear that dyes are unsafe under the law. Instead, and mistakenly, FDA’s assessment bases the acceptable daily intakes (ADIs) for each dye on chronic studies in animals done decades ago—studies that were incapable of detecting subtle effects on behavior or the developing brain, such as those observed in studies of sensitive children exposed to dyes.

Those toxicological studies fall well short of the tests available and recommended today to assess neurodevelopmental and neurobehavioral toxicity effects. FDA’s failure to base its “acceptable” intakes on appropriate tests was a stated concern of the two FAC experts with

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data may overestimate consumption because of food loss through waste and spoilage in the home and market.” FDA/CFSAN Meeting Materials. Background document for the FAC: certified color additives in food and possible association with attention deficit hyperactivity disorder in children. March 30–31, 2011. (*Emphasis added. Citations omitted.*) Notably, FDA’s own guidance documents calls for assessments to estimate 100-percent migration of color additives from non-food sources.

<http://www.fda.gov/ForIndustry/ColorAdditives/GuidanceComplianceRegulatoryInformation/ucm171631.htm>

<sup>19</sup> Doell D., *op. cit.*

<sup>20</sup> Ritalin tablets contain D&C Yellow No. 10 (5- and 20-mg tablets), FD&C Green No. 3 (10-mg tablets). See [http://www.accessdata.fda.gov/drugsatfda\\_docs/label/2015/010187s080,018029s049,021284s027lbl.pdf](http://www.accessdata.fda.gov/drugsatfda_docs/label/2015/010187s080,018029s049,021284s027lbl.pdf).

<sup>21</sup> D&C Red 33 and D&C Orange 4 are two examples of non-food dyes which belong to the azo class of dyes, as do the FD&C dyes Red 40, Yellow 5, and Yellow 6. The Southampton study tested azo dyes and found they caused adverse effects on behavior in children selected from the general population. Moreover, non-dye food chemicals are also a concern with regard to their potential for pharmacologically similar effects. As Maffini explains, “ethoxyquin, FD&C Red No. 3 and heptyl paraben individually cause adverse effects in the thyroid system in animals, and disrupt thyroid hormone function by blocking its binding to the thyroid receptor in cell-based studies. By either mechanism, thyroid hormone function is disrupted, potentially damaging the developing brain and causing severe health problems.” Maffini, Maricel. “Overloaded: approaches to assess cumulative effects of food additives on brain development,” NRDC Switchboard, July 2, 2014, [http://switchboard.nrdc.org/blogs/mmaffini/overloaded\\_approaches\\_to\\_asses.html](http://switchboard.nrdc.org/blogs/mmaffini/overloaded_approaches_to_asses.html).

<sup>22</sup> Rowe, KS, Rowe, KJ. Synthetic food coloring and behavior: a dose response effect in a double-blind, placebo-controlled, repeated-measures study. *J Pediatr.* 1994 (Nov);125(5 Pt 1): 691-8.

the most expertise on neurodevelopmental and neurobehavioral toxicity testing.<sup>23</sup> It is also contrary to agency policy, which requires use of the most sensitive endpoint when setting the ADIs, to ensure that the ADIs protect against the most sensitive adverse effect.<sup>24</sup> The data clearly show that dyes affect the behavior of children at doses far lower than the ADIs.<sup>25</sup> Other agencies have developed and implemented requirements for such testing, and FDA's failure to require them in this instance is out-of-step with both science and law.<sup>26</sup>

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<sup>23</sup> For example, Dr. Charles Vorhees, professor of neuroscience at the Cincinnati Children's Hospital Medical Center, one of two FAC members appointed for this meeting due to his specialized expertise, had this exchange with FDA's Jason Aungst: "Vorhees: Did any of those studies [used to establish the ADIs] include neurobehavioral outcomes? Aungst: Not specific neurobehavioral testing, but clinical observations of...behaviors in the normal cage setting. Vorhees: Which are known to be completely insensitive." Vorhees also noted, "...You don't have data that speaks directly to the issue of whether or not there's developmental neurotoxicity," concluding "there is a significant risk that the ADIs are set too high... there could be significant risk that the ADIs are erroneous, [that] they're incorrect...we're talking here about the developmental effects of these compounds on brain development and behavior. I do not believe that the tests done, including the two-year rodent bioassays, provide a sufficient basis for determining a NOAEL [no observed adverse effect level, critical for estimating the ADIs]...Since the FDA bases ADIs on NOAELs from two-year rodent bioassays, there is a significant risk that the ADIs are set too high...there could be significant risk that the ADIs are erroneous, they're incorrect." Another FAC member, Dr. Penny Fenner-Crisp, Ph.D., a retired EPA Senior Toxicologist and former Director of the Health Effects Division of EPA's Office of Pesticide Programs stated: "[T]he value of the chronic bioassays that were the basis of the ADIs would have no value in assessing any kind of neurological responses. As you point out, the kinds of cage-side observations that are done as a quick screen in those studies don't tell you anything." See FDA Transcript. FAC Meeting. March 31, 2011. pp. 142-3.

<sup>24</sup> FDA. Redbook 2000: Chapter IV.C.10. Neurotoxicity Studies. "Toxicological principles for the safety assessment of food ingredients. p. 11: "Agency scientists determine the most sensitive treatment-related toxic endpoint (adverse effect) from the data submitted in support of the petition. This endpoint is the adverse or toxic effect that occurs in test animals at the lowest exposure to the test substance. The highest exposure that does not produce this adverse effect is called the no-observed-effect level (NOEL) or the no-observed-adverse-effect level (NOAEL)..." And on p. 12, FDA notes that: "Because the ADI is calculated to protect against the most sensitive adverse effect, it also protects against other adverse effects occurring at higher exposures to the ingredient."

<sup>25</sup> For example, FDA's ADIs for FD&C Yellow 5, established in 1969, is 5 mg/kg-bw/day, or 100 mg for a 20 kg child. Most studies showing adverse reactions of dyes used doses of 26-30 mg, and lower doses of tartrazine (Yellow 5) provoked adverse behavior in Rowe, KS, Rowe, KJ. Synthetic food coloring and behavior: a dose response effect in a double-blind, placebo-controlled, repeated-measures study. J Pediatr. 1994 (Nov);125(5 Pt 1): 691-8.

<sup>26</sup> The Select Committee on GRAS Substances (SCOGS) long ago identified this gap, and other agencies have moved forward to address it. As Maffini writes: "In 1982, SCOGS said "[m]uch effort is needed in the development of animal tests of relative simplicity that may provide quantifiable and reproducible information on behavioral effects in animals at the levels of intake relevant to human exposure." It stated that to answer whether "foods and food ingredients" may cause or aggravate some behavioral disorders, the development of such tests "should command a far more aggressive attack than it has up to now," concluding that "a firm foundation can then be achieved within the next decade or two...During the 1980s, EPA promulgated regulations describing how to conduct behavioral and developmental neurotoxicity testing, respectively, and adopted specific behavioral tests for learning and memory. In the late 1990s, EPA updated its toxicology data requirements for pesticides used on food (40 CFR Subpart F 158.500). It established screening tests that rely on a semi-quantitative evaluation of a functional observational test. It includes evident behavior endpoints and requires developmental neurotoxicity tests. Similarly, the Organization for Economic Co-operation and Development (OECD) has published a guidance document for neurotoxicity

It is indefensible for FDA to conclude (as it did in materials provided to the FAC) that neurotoxicity is one of two possible explanations for the documented harms, and then take no action to protect children from those possible neurotoxic effects, including a ban or warning, and is patently insufficient following questions raised by the FAC pointing out that the agency lacks the data it would need to rule out neurotoxicity or other relevant sensitive end-points as an explanation for the documented harms.

At a minimum, FDA should have required testing by companies to determine whether, as the agency proposes, dyes are neurotoxic.<sup>27</sup> Yet FDA has not publicly announced any plans to require or obtain results from sensitive tests to assess neurodevelopmental and neurobehavioral toxicity risks. Thus, FDA is failing to assess the all of the “cumulative

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testing (OECD 2004) as well as guidelines (OECD 1997, 2007) to be used in chemical testing programs. For OECD, behavioral testing and endpoints provide “one of the most sensitive strategies to reveal subtle functional deficits,” adding that “behavioral endpoints can uncover alterations in neural or extraneural substrates for which no compensatory alternate behavioral response is available.” Its guideline (OECD 2007) provides details of study design, frequency of observations, and endpoints, including a section on learning and memory tests...In summary, FDA has not aggressively pursued the development of test methodologies for behavioral impacts. It has not incorporated into its Redbook methods that EPA and OECD adopted years ago.” See Maffini M, *et. al.* Looking back to look forward: a review of FDA’s food additives safety assessment and recommendations for modernizing its program. Comprehensive Reviews in Food Science and Food Safety. The Pew Charitable Trust. Vol. 12, 2013. <http://onlinelibrary.wiley.com/doi/10.1111/1541-4337.12020/epdf>

<sup>27</sup> See FDA Interim Toxicology Review Memorandum. p. 37: “For example, are the colors acting through some toxic, physiologic, allergic or other immunologic process?...Are these color effects associated with some factor(s) that predispose children to ADHD or other types of behavioral pathology, or could the color effects be associated with some predisposing factor(s) not necessarily related to behavioral disorders? Although many investigators have speculated about these various issues, most of these basic questions still remain largely unanswered.” And on p. 44: “As a general observation, there seem to be two possible basic scenarios that could be operative whereby food additive/environmental chemicals would be associated with triggering adverse behaviors such as those related to ADHD or other behavioral disorders of childhood, or even in the general population. One “traditional toxicology” scenario is that certain chemicals may have inherent neurobehavioral toxicity properties which may directly or indirectly (*e.g.*, endocrine or immunologic pathways) affect nervous system function resulting in behavioral deficits. This scenario may be addressed with reliable toxicological testing including adequate neurobehavioral toxicological evaluations as a routine component of the process of chemical safety assessment.” We note that no “traditional toxicology” scenario has been addressed, since there is not “reliable toxicological testing including adequate neurobehavioral toxicological evaluations” in the records before the agency. FDA’s alternative explanation for the harms also remains speculative, and fails to satisfy the safety standard under the law. FDA notes that “[t]he other “non-traditional toxicology” scenario is that the elicitation of problem behaviors by various common foods and food related chemicals may be due not to an inherent neurobehavioral toxic property of these food items and food related chemicals but to some unique hypersensitivity or intolerance in certain children stemming from some genetic/epigenetic/polymorphic related predisposition.” This is a *non-sequitur*: given biological variability among humans, it is completely typical that a variety of factors, including genetic, epigenetic, and polymorphic factors influence the response of an individual to a substance. That variability, by itself, says nothing about whether dyes exhibit neurobehavioral toxicity. Moreover, the mere fact that other substances might trigger similar responses has no bearing on the safety of dyes and does not demonstrate that dyes are safe.

effect[s]” of exposure to “such additive” as required by the second factor in its safety determination.<sup>28</sup> Indeed, an entire category of known hazards—behavioral harms—is excluded from FDA’s calculation of the ADIs. At a minimum, the ADIs should be set with explicit reference to susceptible children, as have been identified in numerous human studies involving dyes.

Third, in establishing the ADIs, FDA failed to consider “the cumulative effect, if any, of such additive in the diet of man or animals, taking into account the same or any chemically or pharmacologically related substance or substances in such diet” with regard to adverse effects on behavior when it established what exposure is safe. The agency should assess the cumulative effect of multiple dyes in combination—as they are in the diet—on the behavior of children in establishing acceptable intakes.<sup>29</sup>

This failure substantially impairs FDA’s safety analysis. FDA should move beyond a single-chemical assessment approach that runs contrary to its statute and conduct a cumulative risk assessment, for example, on the mixtures of dyes used in many studies of children, or at the very least on the chemically related azo dyes (Red 40, Yellow 5, and Yellow 6), which currently account for about 90 percent of dyes used in food certified in the United States. While FDA recognizes that dyes are chemically classified into classes (azo, xanthene, triphenylmethane, and indigoid),<sup>30</sup> it has not conducted an analysis of the safety of each class of dyes, including azo dyes, that are “chemically related” under the law.<sup>31</sup> Yet the Southampton study, which replicated the results of the Isle of Wight study on azo dyes, and numerous other studies, including those in which azo dyes represented 90% of the mixture of dyes tested and those testing the azo dye Yellow 5, raise questions regarding the cumulative effects of azo dyes as a class.<sup>32</sup> FDA must conduct further safety assessments by

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<sup>28</sup> In the statute, “cumulative effect” refers to both the full effects measured across different endpoints of a particular substance as well as the effect of exposures to that substance and other, related substances. *See, e.g.,* “The Food Additives Amendment of 1958 requires that FDA consider the cumulative effect of an additive in the diet over a lifetime, together with any chemically or pharmacologically related substances in such diet (21 U.S.C. § 348(c)(5)).” Alger H *et al.* Perspectives on how FDA assesses exposure to food additives when evaluating their safety: workshop proceedings. Comprehensive Reviews in Food Science and Food Safety. The Pew Charitable Trusts. Vol. 12, 2013. p. 102.

<sup>29</sup> The ADIs that FDA developed, taken together, add up to an amount for a 35-pound child that is more than 15 times greater than the amount that in a 1980, FDA-funded study triggered adverse reactions in some children. Lefferts L., *Seeing Red: Time for Action on Food Dyes*. CSPI. Jan. 2016.

<sup>30</sup> FDA. Background Document for FAC. Certified Color Additives in Food and Possible Association with Attention Deficit Hyperactivity Disorder in Children. March 30-31, 2011. p. 3.

<sup>31</sup> 21 CFR §70.11. Related substances. “(a) Different color additives may cause similar or related pharmacological or biological effects, and, in the absence of evidence to the contrary, those that do so will be considered to have additive toxic effects. (b) Food additives may also cause pharmacological or biological effects similar or related to such effects caused by color additives, and, in the absence of evidence to the contrary, those that do so will be considered as having additive toxic effects.”

<sup>32</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 randomized, double-blinded, placebo-controlled trial. *Lancet*. 2007 Nov. 3; 370:1560–7. *See also* Bateman B, Warner JO, Hutchinson E, *et al.* The effects of a double blind, placebo

known chemical class, or read across from these results to ascertain the effects of azo dyes as a class, which it has not done.<sup>33</sup>

Also, because mixtures of dyes produce similar behavioral effects across many studies, FDA must determine whether all or most dyes are “pharmacologically related” under the law,<sup>34</sup> and thus considered as a class for risk assessment purposes.<sup>35</sup> Unlike some additives, colorings are often not serving as substitutes for one another, but are used in combination in the diet to achieve a visual effect.

Fourth, the law requires consideration of relevant and appropriate safety factors when assessing the safety of a color additive. Clearly, the law intended that the safety factors used be adequate to ensure safety of the color additive. The agency applied two 10-fold factors, based on no-effect levels in animal studies, to account for intra- and inter-species variability.<sup>36</sup> That approach is inadequate to address the differences between laboratory animals and people (inter-species variability) with regard to possible behavioral effects, and with regard to the differences in human response to dyes (intra-species or intra-human variability). As a result, FDA’s approach fails to adequately protect children who are sensitive to the adverse behavioral effects of dyes.<sup>37</sup>

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controlled, artificial food colourings and benzoate preservative challenge on hyperactivity in a general population sample of preschool children. *Arch Dis Child*, 2004; 89:506-11. See also *Seeing Red*, *op. cit.*, for discussion of the full body of research on mixtures containing azo dyes.

<sup>33</sup> FDA’s recent final rule on three perfluoroalkyl ethyl-containing food contact substances relied on a showing that long-chain perfluorinated compounds (PFCs) may be determined to be unsafe based on their structural similarity to other compounds known to be unsafe, in the absence of contradictory data, and on a legal conclusion that gaps in the safety data on particular chemicals can be filled using appropriate data from chemically related compounds. Department of Health and Human Services. Food and Drug Administration. Final Rule. Modifying 21 CFR Part 176, 81 FR 5, 7 (noting that “FDA has confirmed our 2010 determination that data demonstrating reproductive and developmental toxicity for long-chain perfluorocarboxylic acids and fluorotelomer alcohols are applicable to long-chain PFCs on a general basis. FDA’s updated review noted that there are no available toxicological studies conducted with the three FCSs that address the endpoints of reproductive or developmental toxicity. As all three FCSs are long-chain PFCs, and in the absence of data specific to the three FCSs to address these endpoints, FDA utilized the available data demonstrating reproductive and developmental toxicity for long-chain perfluorocarboxylic acids and fluorotelomer alcohols to assess the safety of the approved food-contact use of the FCSs.”)

<sup>34</sup> 21 CFR § 70.11.

<sup>35</sup> FDA clearly stated in 1959 that: “[f]ood additives that cause similar or related pharmacological effects will be regarded as a class, and in the absence of evidence to the contrary, as having additive toxic effects and will be considered as related food additives.” (21 CFR §170.18(a)) (*Emphasis added.*) This is also consistent with contemporary mainstream science. In 2008, at the request of EPA, the NRC (the working arm of the U.S. National Academy of Sciences) released its guidance for assessing cumulative risk assessment. The report recognized the need for a broader approach to grouping chemicals with similar effects by focusing on “health outcomes and not...the pathways that lead to them.” Committee on the Health Risks of Phthalates, National Research Council of the National Academies. *Phthalates and Cumulative Risk Assessment: The Task Ahead*. The National Academies Press. 2008. p. 4. See <http://www.nap.edu/catalog/12528.html>.

<sup>36</sup> FDA. Background Doc. for FAC. p. 6.

<sup>37</sup> The 1997 Presidential Executive Order 13045, “Protection of Children from Environmental Health Risks and Safety Risks,” directs all federal agencies, including FDA, to make it a high priority to identify and assess

FDA's method for assessing and assuring the safety of dyes (and other food ingredients) must be updated to be aligned with current expert opinion, as required by law,<sup>38</sup> including mechanisms to adequately address both variability and uncertainty and to provide adequate protection for sensitive subpopulations, such as children, known to be sensitive to dyes.<sup>39</sup> For example, EPA uses an additional 10-fold uncertainty factor whenever its safety database is incomplete, in particular to account for potential toxicity to infants and children. EPA specifically asks "What are the resulting uncertainties in the database with regard to children's risk?" and "Have any uncertainties in developmental exposure been identified?"<sup>40</sup>

FDA did the opposite—arguing that the fact that some children are unusually sensitive to dyes was a reason to *dismiss* safety concerns—rather than considering whether its safety factors were appropriate and adequate to account for such variability.<sup>41</sup> The FDA's approach is counter to law because, obviously, the purpose of applying safety factors is to ensure safety. Moreover, a central use of dyes in the food supply is to make foods more appealing to children and their use is widespread in products marketed to and consumed by children. Thus, FDA should have considered whether this particular "condition of use" for dyes meets the standard for safety. Given the lack of animal data from appropriately sensitive studies, at a minimum FDA should have applied additional safety factors to the results from animal studies to reflect the considerable data gaps and ensure adequate protection of children, a vulnerable sub-population, when determining safety.<sup>42</sup>

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health and safety risks that may disproportionately affect children and to ensure that their policies, programs, activities, and standards address those risks. See Executive Order 13045. Protection of Children from Environmental Health Risks and Safety Risks. 62 FR 19885 (April 23, 1997).

<sup>38</sup> 21 U.S.C. 379e (b)(5)(A).

<sup>39</sup> FDA should also have been guided by the recommendations of the National Academy of Sciences (NAS) in its 2009 report on modernizing methods for risk assessment. A key recommendation was for risk assessments to better identify and address both uncertainty and variability in human exposure and vulnerability, so that all people are better protected. NAS also emphasized that special attention should be paid to vulnerable individuals and populations that may be particularly susceptible or more highly exposed. Science and Decisions, Advancing Risk Assessment. National Research Council of the National Academies. 2009.

<sup>40</sup> Environmental Protection Agency (EPA). A framework for assessing health risks of environmental exposures to children. EPA/600/R-05/093F. September 2006.

<sup>41</sup> FDA. Interim Toxicology Review Memorandum. September 1, 2010. Attachment 4. FDA/CFSAN. March 30-31, 2011. FAC Meeting Materials. p. 44: "The other 'non-traditional toxicology' scenario is that the elicitation of problem behaviors by various common foods and food related chemicals may be due not to an inherent neurobehavioral toxic property of these food items and food related chemicals but to some unique hypersensitivity or intolerance in certain children stemming from some genetic/epigenetic/polymorphic related predisposition. This latter scenario of unique hypersensitivity can best be addressed by continuing efforts to understand the biomolecular factors that may predispose an organism to this type of unique disruptive behavioral response to otherwise non-neurotoxic chemical substances."

<sup>42</sup> Such evidence more than justifies additional factors under 21 CFR 170.22, as "evidence...which justifies use of a different safety factor."

Instead, it both ignored this gap in its existing data and, unaccountably, failed to even factor in the data on effects on children from the human studies, which should have been the focus of its safety analysis. Applying appropriate safety factors to the human studies, as the agency should have done under the law, would yield the clear result that current approvals for dyes lack a basis in the available evidence.

On all of these grounds, FDA's current approvals for certified dyes are deficient, and FDA should withdraw approvals of all currently permitted dyes. As an interim matter, at a minimum, it must require a warning on foods and drinks containing certified dyes. Authority for a label is specifically provided in law: "to assure the safety of the use" of a color additive the FDA "shall...prescribe the conditions under which such additive may be safely employed for such use or uses (including, but not limited to...labeling...for such additive)."<sup>43</sup>

Moreover, "the Secretary shall not list a color additive ... for a proposed use if the data before him show that such proposed use would promote deception of the consumer in violation of this Act or would otherwise result in misbranding ...within the meaning of this Act."<sup>44</sup> Whether a food is misbranded can be based on omission of a material fact related to that food.<sup>45</sup> The omitted fact that dyes cause behavioral problems in some children is certainly a "material" fact. Therefore, FDA should consider misbranded any food containing dyes unless the label includes a warning that the dyes may adversely affect behavior. The label should state "WARNING: This food contains synthetic food colorings that may impair the behavior of some children" or similar wording.<sup>46</sup>

An FDA document made available at the FAC meeting argued that instead of conducting reliable neurobehavioral testing, that this unique intolerance "can best be addressed by continuing efforts to understand the biomolecular factors that may predispose an organism to this type of unique disruptive behavioral response to otherwise non-neurotoxic chemical substances." This second explanation for the results, if proven to be true, warrants a legal requirement for a warning, to ensure that children and their families do not continue to suffer these behavioral effects without being alerted of a potential cause for these

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<sup>43</sup> Section 721(b)(3) of the FFDCFA.

<sup>44</sup> Section 721(b)(6) of the FFDCFA.

<sup>45</sup> Section 502 of the Federal Food, Drug and Cosmetic Act (FFDCA) contains provisions on misbranding including some that relate to false or misleading labeling: "In determining whether the labeling...is misleading there shall be taken into account (among other things) not only representations made or suggested by statement, word, design, device, or any combination thereof, but also the extent to which the labeling...fails to reveal facts material in the light of such representations or material with respect to consequences which may result from the use of the article to which the labeling...relates under the conditions of use prescribed in the labeling...thereof or under such conditions of use as are customary or usual."

<sup>46</sup> We requested such warning labels in our 2008 Citizen Petition. CSPI also filed a petition in 2012 asking the agency to require front-of-package disclosure of color additives. See Petition to Require Front of Package Disclosure of Food Color Additives, Docket No. FDA-2011-P-0886. June 6, 2012.

unfortunate and troubling effects. We estimate, given available evidence, that more than half a million children in the United States suffer adverse behavioral reactions after ingesting food dyes, with an estimated cost for just those children with identified symptoms of attention-deficit/hyperactivity disorder of between \$3.5 billion and more than \$5 billion dollars.<sup>47</sup>

Either explanation of the documented harms that was offered by FDA—*i.e.*, that either dyes are neurotoxic or that they pose a hazard only for sensitive individuals—requires some legal and definitive response from the agency, since both the evidence the agency reviewed in 2011 and subsequent studies clearly show harm from dyes to some children. Even if FDA does secure a sufficient basis to conclude—based on convincing evidence from comprehensive and sensitive developmental neurobehavioral testing and appropriate exposure assessments—that behavioral effects linked to dyes are not due to neurotoxicity, it still must require a warning label stating that dyes may impact children sensitive to them, to alert consumers of this known potential harm. FDA cannot, consistent with its legal requirements, acknowledge the evidence regarding the harmfulness of dyes and yet continue to do nothing.<sup>48</sup>

Indeed, continued inaction is the only course that remains utterly unjustified by ethics, science or law. If the British navy had waited until doctors understood how eating citrus fruit on long journeys prevented scurvy before providing sailors with that “medicine,” countless lives would have been lost. The FDA’s job is to protect the public—not to wait until the mechanism of action of a problem is completely understood.

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<sup>47</sup> See the analysis of costs and prevalence in *Seeing Red* (citing ADHD data from CDC as of July 8, 2015. <http://www.cdc.gov/ncbddd/adhd/data.html>; and Pelham WE, Foster EM, Robb JA. The economic impact of attention-deficit/hyperactivity disorder in children and adolescents. *Ambul Pediatr.* 2007; 7(1 Suppl):121-31.).

<sup>48</sup> Comments by FDA officials acknowledge that harm to subpopulations can be considered harm under the law and that labeling may be an appropriate response. From FDA Transcript. FAC Meeting. March 30, 2011. Dr. Cheeseman noted: “Well, no harm is generally applied to the overall population. If there are specific subgroups that require protection, then there are a number of regulatory options that FDA has to address that issue, that range from labeling to not approving or revoking an existing code, an existing regulation. So I think you would need to address it within the constraints of the general population as a starting point, but you have discretion, I think, under the questions to apply other recommendations to FDA for specific subpopulations, if that is in fact, something that the committee consensus suggests should be recommended.” As above, however, we also dispute that the agency is on solid legal ground in treating harm to subpopulations as distinct. Taken as a whole, the law reflects deep concern for vulnerable populations, and does not allow the agency to disregard evidence of harm because only a subpopulation may be impacted.

In sum, FDA should:

- Immediately require warning labels on foods that contain dyes to alert parents and affected individuals of FDA's conclusion that dyes may adversely affect behavior of some children.
- Update FDA's website to make this conclusion clear to the public.
- Ban synthetic dyes in foods and beverages, since they do not meet the legal safety standard. Companies that wish to use a synthetic dye in food must submit convincing evidence showing that the dye is safe and does *not* cause adverse behavior, using sensitive studies. FDA must have adequate data on these endpoints, and take sensitive subpopulations, such as children, into account when determining whether a dye is safe. Withdrawal of FDA approvals are appropriate for all dyes, and particularly urgent for the chemically-related azo dyes Red 40, Yellow 5, and Yellow 6, and for Blue 1, which raised concerns for the FAC because has been shown to cross the blood-brain barrier.<sup>49</sup>
- Require companies to re-petition the agency to permit continued use of certified dyes, and to require as a condition of approval that companies conduct sensitive testing for neuro-developmental and neurotoxicity endpoints relevant to the observed effects on behavior in children;
- Revise its safety assessment and ADIs to take into account:
  - The requirements of Executive Order 13045 for sensitive measures that protect the health of children;
  - Studies documenting behavioral effects in children at particular levels of exposure in an appropriate time-frame for observations as well as other adequate data on sensitive endpoints, including behavioral effects;
  - In measuring exposure, the missing data on non-food sources of dyes, including drugs, supplements, and cosmetics, as required by law, as well as the results of recent studies by the agency and others regarding daily dietary exposures in foods marketed to vulnerable populations and other relevant industry data;
  - The cumulative effects of both chemically and pharmacologically related substances. In particular, FDA should assess the chemically related azo dyes (Red 40, Yellow 5, and Yellow 6) that comprise 90 percent of the dyes used in food in the U.S., determine whether all or most dyes are pharmacologically related given the similarity of their effects in studies, and identify other substances in the diet that may be pharmacologically related given the results of human or animal studies; and

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<sup>49</sup> FDA Transcript. Food Advisory Committee Meeting. March 31, 2011. p. 323. Comments by Dr. F. Xavier Castellanos, M.D., and Dr. Jeanne Freeland-Graves, Head of the Division of Nutritional Sciences at the University of Texas.

- Appropriate safety factors should be applied to address both risks to vulnerable populations and data gaps, in recognition of the absence of sensitive, modern developmental neurotoxicity and neurobehavioral tests, or other appropriate tests, and of the variability amongst children in response to dyes.

Sincerely,

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