

February 19, 2019

Office of Environmental Health Hazard Assessment (OEHHA)  
1515 Clay Street, 16<sup>th</sup> floor  
Oakland, California 94612  
*Attention:* Anna Smith, Food Dye Study

Submitted via <http://www.oehha.ca.gov/comments>

**Re: Request for Information on the Neurologic and Neurobehavioral Impacts of Synthetic Food Dyes**

To Whom It May Concern,

Thank you for this opportunity to submit information describing the neurologic and neurobehavioral impacts of synthetic food dyes.

The Center for Science in the Public Interest (CSPI) is a non-profit, independent, science-based organization. More than 60,000 Californians are among its members/subscribers. CSPI has been investigating the effects of synthetic food dyes<sup>1</sup> since the late 1990s.

Our response to OEHHA's request for information is divided into four parts:

- (I) a brief overview of the issue
- (II) key considerations for OEHHA's risk assessment
- (III) a discussion of FDA's 2011 Food Advisory Committee meeting
- (IV) additional important resources to aid OEHHA in conducting its evaluation

***I. Overview: The Evidence of Harm to Susceptible Children from Artificial Dyes is Clear***

In 2016, CSPI published a report ([Seeing Red: Time for Action on Food Dyes](#)<sup>1</sup>) that summarizes the scientific evidence on the effects of food dyes on children's behavior, the growing consensus among researchers and healthcare providers who treat behavioral problems that avoiding food dyes can benefit some children, and FDA's failure to adequately regulate food dyes.

The first controlled studies of behavioral effects of dyes on children with suspected sensitivities were carried out in the late 1970s. More than 30 clinical trials were conducted over the following several decades. Two large government-sponsored and groundbreaking studies done in the United Kingdom and published in 2004 and 2007 concluded that dyes affect the behavior of children in the general population.

As our report explains, since FDA last examined the issue in 2011, eight major independent analyses, including two meta-analyses, have concluded that excluding food dyes, or a diet that

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<sup>1</sup> We use the term "synthetic food dyes" and "food dyes" to refer to the certified color additives listed in the October 22, 2018, OEHHA Request for Information.

eliminates dyed foods and certain other foods and ingredients, reduces adverse behavior in some children.

It is not known how many of California's over eight million children experience adverse behavioral reactions from dyes. Some children experiencing reactions have been diagnosed with attention deficit hyperactivity disorder (ADHD), one of the most common neurodevelopmental disorders of childhood, and a debilitating one, causing problems at school, at home, and with friends. The prevalence of ADHD among children ages 4-17 in families with incomes less than 200% of the federal poverty threshold is significantly higher than that among children in families with higher incomes.<sup>2</sup> The causes of ADHD are not well understood, although genetics plays an important role.<sup>3</sup>

According to one estimate, 8 percent of children with ADHD have symptoms related to food dyes.<sup>4</sup> That would translate into about half a million children nationwide, including more than 52,000 in California.<sup>2</sup> Dyes also affect an unknown percentage of children who have not been diagnosed with ADHD. The harm to children and the costs to society from dyes are needless and preventable.

*Seeing Red* includes examples of some of the more than 2,000 first-hand testimonials CSPI has received. They illustrate the difficulties parents and children report facing in dealing with the adverse reactions triggered by dyes. (These examples are intended to be illustrative; more compelling scientific evidence comes from the systematic studies we discuss below.) Parents recount troubling episodes of hyperactivity, inattention, repetitive motions, aggression, and even violence. Some report that when their child avoided artificial colorings, they saw dramatic improvements in behavior. The reports also convey the difficulties parent face in identifying dyes as the trigger for adverse behavior, and the challenges faced in attempting to eliminate dyes from the diet.

That is not surprising, because food dyes are ubiquitous. A study of food labels in one supermarket found that more than 90 percent of child-oriented candies, fruit-flavored snacks, and drink mixes and powders were artificially colored with synthetic dyes.<sup>5</sup> Recent analyses of the dye content of foods and beverages<sup>6</sup> indicate that many American children are consuming amounts of dyes far higher than the levels demonstrated in many clinical trials to impair the behavior of susceptible children (e.g., many studies used a total of 26-30 mg of a mixture of dyes, in the same proportion as the amounts certified for use in food in the United States). The

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<sup>2</sup> Approximately 9.4% of children ages 2-17 (6.1 million) in the United States had ever been diagnosed with ADHD, according to the CDC, based on parent reports in 2016 (Centers for Disease Control and Prevention. Attention-Deficit/Hyperactivity Disorder (ADHD). Data & Statistics <https://www.cdc.gov/ncbddd/adhd/data.html>), and 7.3 percent of California children ages 4-17 had ever been diagnosed, according to CDC, based on parent reports in 2011, the most recent year reported (Centers for Disease Control and Prevention, State-based Prevalence Data of Parent Reported ADHD Diagnosis by a Health Care Provider, <http://www.cdc.gov/ncbddd/adhd/prevalence.html>). Using U.S. Census data population estimates for California as of July 1, 2018 (39,557,045 people, 22.9% of whom were under 18 years of age, according to <https://www.census.gov/quickfacts/fact/table/ca.US/AGE295217>) and applying the 7.3% estimate from above gives 661,275 California children with ADHD. Multiplying that figure by 8% gives the estimate of 52,902 California children with ADHD who are affected by food dyes.

amount of dyes contained in just a single cupcake or glass of Kool-Aid can be enough to prompt adverse behavioral reactions in certain children.

Dyes confer no health or nutritional benefit. Not only are they completely unnecessary, they are sometimes used to spare companies the expense of using actual fruit or other “real” ingredients, and to trick consumers into thinking that the colors in blueberry muffins, breakfast cereals, fruit snacks, or fruit-flavored beverages derive from real fruits and vegetables, rather than from synthetic chemicals.

In response to the accumulating evidence, the British government and the European Union have taken actions to inform and protect the public from the risks of dyes. Since 2010, warnings have been required on most dyed foods sold in the EU. The British government has encouraged companies to find alternatives, and has issued public advisories to inform families that eliminating certain food dyes might benefit children with hyperactivity or ADHD. FDA has not taken any such action. Most companies reformulated products sold in Europe, eliminating dyes to avoid having to include a warning label on packages. Some of these companies continue to sell the same foods in the United States with artificial food dyes in them, as we discuss below.

## ***II. Key Considerations for OEHHA’s Risk Assessment***

Given the substantial shortcomings in FDA’s and industry’s assessments of the risks of dyes, which are discussed in full below, we look to the OEHHA review and seek a thorough and objective review of the evidence.

Specifically, OEHHA should take into account the considerations listed below.

### Contextual Considerations

- Requirements and precedents under California law require OEHHA to protect the health of children and vulnerable populations.
- Food dyes are used for cosmetic purposes, generally, to make unhealthy foods more appealing. Food dyes often displace and mask the absence of colorful fruits and vegetables and can mislead consumers into thinking that a product contains fruit, vegetables, or other real food ingredients instead of food dyes. Examples:
  - [Tropicana Twister Cherry Berry Blast](#) has no cherries or berries, except those pictured in cartoon form on the label. It contains 10% juice and the ingredients are: Filtered Water, High Fructose Corn Syrup, Apple and Grape Juice Concentrates, Citric Acid, Natural and Artificial Flavors, Ascorbic Acid (Vitamin C), and Red 40.
  - [Kellogg’s Fruity snacks Mixed Berry Flavored](#) contain no berries, and the only fruit is apple puree concentrate, which is the third ingredient after two forms of sugar. It contains artificial and natural flavors, as well as Red 40 and Blue 1.
- All children aged 2 through 5 in the United States are exposed to FD&C Blue 1, FD&C Red 40, FD&C Yellow 5, and FD&C Yellow 6, according to FDA estimates (Doell et al. 2016).

- Synthetic food dyes are required to be listed on food labels by their specific name (e.g., FD&C Red 40 or the abbreviated name, Red 40). But many consumers have no idea that color additives in food are linked to adverse behavioral reactions in some children, and often, their doctors don't either, as described in numerous testimonials CSPI has received from parents.
- Many consumers are interested in avoiding dyes, but avoiding them can be challenging. One industry-funded survey found that 43 percent of consumers report that they are trying to limit or avoid food dyes,<sup>7</sup> and another found that two-thirds of consumers (and 80 percent of millennial moms) say that they are “extremely/very” or “somewhat” concerned about food dyes.<sup>8</sup> However, the presence of synthetic food dyes in products is not always obvious, and is not always associated with brightly colored foods. Dyes also are used in pickles, salad dressing, other condiments, noodles, white foods, and brown foods. For example, Little Debbie Swiss Rolls (which are brown and white) have a combined 32 mg of Yellow 5, Red 40, and Blue 1 per serving, according to data provided in FDA's exposure assessment. In contrast, a similar product, Hostess Ho Hos Snack Cakes, doesn't contain any synthetic food dyes. Again, many parents who have contacted us report that avoiding dyes can be challenging, especially when eating foods away from home. Separately, we are enclosing letters from affected consumers that address this point.
- Lack of access to fresh and healthy (dye-free) food is an economic justice issue. While a growing number of retailers and restaurants have eliminated synthetic food dyes or have pledged to do so,<sup>3</sup> synthetic food dyes are still widely used. Accessing healthy, nutritious, affordable, high-quality food is a challenge for many Californians, particularly those living in low-income neighborhoods, rural areas, and communities of color. While Whole Foods and Trader Joe's have taken steps to ensure that their foods and drinks are free of synthetic dyes, not every family has the means to shop at those establishments. Similarly, organic and private-label products that are free from dyes are often more expensive than similar products that contain dyes.
- Some products that contain synthetic dyes in the United States don't contain synthetic dyes in Europe. For example, Mountain Dew in the [U.S.](#) has Yellow 5, but in [the UK](#) it doesn't. And Betty Crocker Red Velvet Cake Mix in the [U.S.](#) has Red 40, but in the [UK](#) it doesn't (it uses paprika extract and carmine instead). It is clear that exposure to synthetic dyes is unnecessary.

### Considerations re: Exposure

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<sup>3</sup> Including restaurants like Chipotle Mexican Grill, Dunkin' Donuts, Kentucky Fried Chicken, Noodles & Company, Panera Bread, Papa John's, Pizza Hut, Starbucks, Subway, and Taco Bell; manufacturers like Campbell, Frito-Lay (PepsiCo), General Mills, Kraft Heinz, Kellogg, Mars, Nestlé, and Schwan Food Co.; and supermarkets like Aldi's, Trader Joe's, and Whole Foods (others, including Kroger and Ahold-Delhaize, offer private label products that are free from dyes).

- Consumers are exposed to mixtures of dyes, not one dye at a time. Recognizing that, most clinical trials also used mixtures, many in proportion to the amounts certified for use in food. OEHHA's exposure and risk assessments should include mixtures of dyes.
- Consumers are exposed to food dyes primarily from foods and beverages, but also from other sources. OTC drugs, prescription drugs, cosmetics, and dietary supplements also contain both FD&C and D&C dyes. Students at San Diego State University found synthetic food dyes listed in over half of the 151 OTC drugs surveyed that were marketed to children and sold at CVS. One in five contained synthetic dyes not permitted for use in food (i.e., D&C dyes), either as the sole coloring or in addition to FD&C colorings. OEHHA should explicitly factor in non-food exposures as well as exposures from food in its risk assessment.
- Short-term exposures trigger behavioral effects. OEHHA should be sure to include short-term exposures in its risk assessments of behavioral effects. It would not be appropriate to only use FDA's exposure estimates that are derived from 10-14-day food consumption data.
- Some exposures pose concerns because they affect children who have a health condition. For example, products intended for sick infants and children to replace fluids and electrolytes lost during diarrhea and vomiting often contain synthetic food dyes. FDA measured 18.7 mg/kg of Yellow 6 in Babies R Us Pediatric Electrolyte Fruit Flavor and 13.2 mg/kg of Red 40 (3 mg per serving) in Pedialyte Fruit Punch. Dyes are also found in medications intended for sick children. Ironically, two forms of the drug Ritalin, which is often used to treat children with ADHD, contain dyes as the first inactive ingredients.<sup>9</sup> OEHHA's risk assessment should ensure that exposures to vulnerable children are assessed.
- Some children consume large amounts of dyes in a single product, meal, or other short time frame, such as at a birthday party or other celebration. And that could spell trouble if, for example, a cake uses Betty Crocker's Black Decorating Cake Icing. According to FDA's exposure assessment and serving size information, a serving of the icing has 80 mg of a mixture of Blue 1, Blue 2, Red 40, and Yellow 6. And Pillsbury Supreme Collection Red Velvet Mix has 66 mg of Red 40 per serving. FDA didn't measure the dye content of Crayola Color Your Mouth candies, but they are specifically designed to stain kids' tongues bright colors and likely result in high exposures.<sup>4</sup> OEHHA should explicitly take those exposure scenarios into account when conducting its assessment.
- Studies that have been conducted by FDA<sup>10,11</sup> that measure actual amounts of dyes in food, paired with information on serving size or other estimates of short-term intake of foods that contain synthetic dyes, are more accurate than industry estimates based on surveys (discussed in more detail below). OEHHA should utilize FDA measurements in its assessment. OEHHA should also take into account data from independent researchers,<sup>12,13</sup> especially a reanalysis<sup>14</sup> using a method adapted from FDA (Harp et al. (2013), cited above), and data from FDA

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<sup>4</sup> Distributed by Bee International, the gumballs are made with sugar, corn syrup, gum base, unspecified artificial flavors, and Red 3, Red 40, Yellow 5, Yellow 6, and Blue 1. Color Your Mouth hard candies, lollipops, and "dippers" (artificially flavored vanilla dipping sticks meant to be inserted into a packet of dyed candy powder and licked) are also marketed.

[Color Certification Reports](#), which provide poundage of dyes certified for use in food, as well for other uses, in the United States.

- Chemically related “azo” dyes (e.g., Red 40, Yellow 5, and Yellow 6) comprise about 90 percent of the dyes certified for use in food in the United States. Other azo dyes that are not permitted in food are used in drugs and cosmetics (see below). OEHHA should assess the cumulative risk from chemically related azo dyes, as a class, and consider other substances that are chemically or pharmacologically related.

#### Considerations re: Hazards/Outcomes

- Modern, sensitive developmental neurotoxicity and neurobehavioral studies in animals have not been conducted on synthetic food dyes (discussed in more detail below).
- Most food dyes have not been adequately studied for their ability to cross the blood-brain barrier. According to Dr. Charles Voorhees, professor of neuroscience at the Cincinnati Children’s Hospital Medical Center and member of the FDA 2011 Food Advisory Committee, and Dr. Steven Taylor, representing the International Association of Color Manufacturers, the blood brain-barrier is not present in the embryo or fetus and is still developing (incomplete) in infants and children.<sup>15</sup> Blue 1 can cross the blood-brain barrier.<sup>16</sup>
- Measuring behavioral effects of food dyes in children is complex. Attention should be given to:
  - Dose. Children vary in their sensitivity to dyes, and many studies used doses (e.g., 26–30 mg) much smaller than what we now know children routinely consume. The clinical trials by Swanson and Kinsbourne and Rowe and Rowe described below make it clear that dose matters in terms of the number of children affected and the severity of reactions.
  - Timing. Effects must be measured at an appropriate interval following intake of synthetic dyes, but when effects occur may vary depending on the child and other factors (e.g., the type and amount of dye-containing food consumed).
  - How and where measurements are made. Children behave differently in different settings (e.g., at home, in the classroom, in a medical or research center), which can complicate assessment of behavioral reactions to synthetic dyes. Also, assessments by parents, teachers, or researchers may produce different results. Some studies find detrimental effects from food dyes on behavior at home when rated by parents, but no detectable effect on behavior at clinics. The Southampton study (described below) used an aggregate measure combining parent and teacher ratings, observations of children in a preschool setting or classroom, and a computerized test of attention for the 8/9-year old children. Instruments for assessing behavior should also be age-appropriate
  - Adequacy of blinding. In some studies, it is difficult to ascertain the adequacy of blinding. In one of the meta-analyses described below, studies that appeared to have the best blinding were analyzed separately, and the effects of artificial dye exclusion as a treatment for ADHD remained statistically significant (unlike most of the other non-pharmacological treatments examined). Dye exclusion had an even larger effect size under this “best probably blinded” assessment. In the Southampton study,

masked testing showed that two independent panels of 20 young adults couldn't tell the difference between the active and placebo juice drinks.

### Summary

- OEHHA should ensure that its assessment adequately address children at greatest risk to food dyes, whether due to high acute or chronic exposure, increased susceptibility (due to genetic, health, or other reasons), or both.
- OEHHA should assess the cumulative risks from mixtures of food dyes on the behavior of children, since mixtures are consumed in the diet and since most clinical trials that examined the behavioral effects of synthetic food dyes assessed mixtures. In particular, OEHHA should assess the combined risk from chemically related “azo” dyes (e.g., Red 40, Yellow 5, and Yellow 6) that comprise about 90 percent of the dyes used in food in the United States, as well as azo dyes that are not permitted in food but are used in drugs and cosmetics (see below). OEHHA should also consider other substances in the diet that are chemically or pharmacologically related (see below).
- OEHHA should apply appropriate safety/uncertainty factors and/or other methodologies to compensate for data gaps (e.g., lack of developmental neurotoxicity testing).
- OEHHA should take all sources of exposure to synthetic food dyes into account, including non-food sources from drugs, supplements, and cosmetics.

### ***III. FDA's 2011 Food Advisory Committee Meeting and its Failure to Conduct an Adequate Risk Assessment***

FDA last examined food dyes' impact on children's behavior in 2011, when it convened its Food Advisory Committee to review the evidence, in response to a 2008 Citizen Petition filed by CSPI. We highly recommend that OEHHA carefully review the transcript of that meeting, along with the presentations and other information made available.<sup>5</sup>

At the meeting, FDA's background document stated that “Based on our review of the data from published literature, FDA concludes that a causal relationship between exposure to [certified] 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.”

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<sup>5</sup> All of the materials from the meeting can be accessed at <https://wayback.archive-it.org/org-1137/20170405014342/https://www.fda.gov/AdvisoryCommittees/CommitteesMeetingMaterials/FoodAdvisoryCommittee/ucm149740.htm>, including a [Background Document for the Food Advisory Committee: Certified Color Additives in Food and Possible Association with Attention Deficit Hyperactivity Disorder in Children](#) and FDA's [Interim Toxicology Review Memorandum \(Certified Color Additives\)](#), which contains a detailed report by a contractor.

Rather than asking the committee whether dyes therefore violate the relevant federal safety standard for color additives, or whether the committee agreed that exposure to food dyes exacerbated problem behaviors in some children, FDA asked it instead whether the committee agreed that a *causal* relationship between consumption of *certified* color additives in food and adverse behavior in children in the *general* population had not been *established*. The committee agreed, although it conveyed concerns about the evidence. And, as one committee member stated, “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.”<sup>17</sup> Another 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, the problem is taken care of, this shouldn’t be looked at.”<sup>18</sup>

And because FDA limited the question to certified color additives, it made the question even more difficult, since the most robust studies of color additives in the general population are the UK-sponsored studies (discussed below) that studied mixtures of (mostly) azo dyes, including some dyes that are not certified for use in food in the United States.<sup>6</sup>

Further, federal law directs FDA to consider the “cumulative effect” of color additives in the diet, taking into account “chemically or pharmacologically related” substances.<sup>19</sup> Had this part of the law been brought to the committee’s attention and had the legal standard of a “reasonable certainty of no harm” been applied, the committee may well have concluded that dyes fail to meet the federal safety standard for food additives.

Committee members raised serious questions about (1) FDA’s conclusion that the effects on behavior were not due “to any inherent neurotoxic properties” of dyes, (2) the agency’s poorly done estimates of children’s exposure to dyes, and (3) its estimation of safe levels for dyes. The committee recommended that FDA require additional safety testing of dyes and develop a robust intake estimate. In a closely divided vote (6 to 8), the committee ultimately failed to recommend that FDA require a warning notice on the labels of foods that contain dyes.

Meanwhile, eight independent analyses published since that 2011 meeting have confirmed the link between food dyes and adverse behavior. They demonstrate that dyes fail to meet the federal safety standard for color additives.

### ***Exposure Estimates Since 2011 Are Informative but Omit Non-Food Exposures***

In 2016, FDA published its exposure estimate for food dyes, including its analytical data on levels of dyes in specific foods. The results confirm that the dye content of many foods is higher than what was thought when many of the initial clinical trials on dyes and behavior in children were conducted. In other words, to appropriately assess the impact from exposure to dyes in food, higher doses should have been used.

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<sup>6</sup> The UK studies include Red 40 (Allura Red), Yellow 5 (Tartrazine), and Yellow 6 (Sunset Yellow FCF), which account for about 90% of dyes certified for use in food.



For example, according to FDA's results and serving sizes from manufacturers, Little Debbie Swiss Rolls have 32 mg of total synthetic dyes per serving, a 20 oz. bottle of Powerade Orange has 36 mg, and a snack consisting of one serving of Orville Redenbacher's Cheddar Cheese Microwave Popcorn and 8 oz. of Hawaiian Punch Fruit Juicy Red contains 36 mg of dyes. Each exceeds the 26-30 mg of dyes that were frequently used in studies that triggered behavioral reactions in some children, as detailed in our *Seeing Red* report.

Unfortunately, FDA's exposure assessment did not assess cumulative exposure to synthetic food dyes; it only looked at each dye separately. Nevertheless, under a high-exposure scenario, based on NHANES two-day food consumption data, a 90<sup>th</sup> percentile consumer (aged 2 years and older) would consume 53 mg/day, and a child aged 2-5 would consume 38.8 mg/day, of *just Red 40 alone*.

Clearly, many of us consume mixtures of dyes greater than the 26-30 mg that were frequently used in clinical trials.

Other studies confirm that the dye content of individual foods and of combinations of foods that might reasonably be consumed by children in a single meal or a single day is higher than the amount found to trigger adverse effects in many of the studies on dyes and behavior. For example, Purdue researchers concluded that "Depending on choice of beverages, it would be easy for a child to consume large amounts of dyes just from the beverages alone without considering the rest of the diet."<sup>20</sup>

However, necessary data on exposures from supplements, drugs, and cosmetics are lacking from FDA's analysis. FDA subtracted the non-food exposures to produce its estimates presented to the 2011 Advisory Committee, and it did not consider non-food exposures in its exposure assessment published in 2016.

Dyes that are used in food are also permitted in cosmetics, supplements, over-the-counter medications, and prescription drugs, and some of these types of exposures are of particular concern because they specifically affect susceptible children, as previously discussed.

Non-food sources must be included in determining "probable consumption" (short-term or long-term) of a dye under the law.

### ***FDA's Approach to Setting Acceptable Daily Intakes (ADIs)<sup>7</sup> Is Deeply Problematic***

Synthetic food dyes used in the United States were approved between 1966 and 1987 based on studies in animals that had been done even earlier. Those studies were incapable of detecting subtle effects on behavior or the developing brain, including those that have been observed since

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<sup>7</sup> FDA's background document for the 2011 Food Advisory Committee explains that part of the agency's safety determination involves comparing the estimated intake of the dye with an "Acceptable Daily Intake," or ADI, for that dye. If the estimated intake is less than the ADI, that supports a conclusion that the use of the dye at the current levels in food is safe. FDA's ADIs for food dyes were derived from conventional animal toxicology studies. They apply an uncertainty factor, or safety margin, of 100 to the highest level at which adverse effects were not observed in that study (the "No Observed Adverse Effect Level," or NOAEL).

in studies of sensitive children exposed to dyes.<sup>21</sup> More recent human studies indicate that **no** no-effect level has been clearly demonstrated for behavioral effects of dyes. In one study,<sup>22</sup> for example, effects were observed at doses as low as 1 mg for tartrazine (Yellow 5), the lowest dose tested.

The data clearly show that dyes affect the behavior of children at doses far lower than the ADIs. At a minimum, the ADIs should be set with explicit reference to susceptible children, such as those identified in numerous human studies involving dyes.

In materials provided to its Advisory Committee, FDA acknowledged that neurotoxicity is a possible explanation for the documented harms. Yet toxicological studies that the agency used in setting its ADIs fall well short of the tests that are available and are recommended today to assess neurodevelopmental and neurobehavioral toxicity effects, a point emphasized by a neuroscientist member of the committee.<sup>23</sup>

FDA's failure to base its "acceptable" intakes on appropriate tests was a stated concern of the two Advisory Committee experts who have the highest levels of expertise on neurodevelopmental and neurobehavioral toxicity testing.<sup>24</sup> (That failure is also contrary to FDA policy, which requires use of the most sensitive endpoint when setting the ADIs to ensure that they protect against the most sensitive adverse effect.)

#### ***FDA Failed to Consider the Cumulative Effects of Synthetic Dyes in Setting Exposure Limits***

As previously mentioned, in establishing the relevant ADIs, FDA failed to consider, as it was required to by federal law, "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.

While FDA recognizes that dyes are chemically divided into classes (azo, xanthene, triphenylmethane, and indigoid), it has not conducted an analysis of the safety of each class of dyes, including the chemically related azo dyes." However, a number of studies raise questions regarding the cumulative effects of azo dyes as a class, including the Southampton study and the Rowe and Rowe study, discussed below, as well as numerous other studies in which azo dyes represented about 90 percent of the mixture of dyes tested.

Furthermore, even though food dyes fall into distinct chemical classes, they may still behave similarly from a behavioral point of view. Given the complexity of the mixtures to which people are exposed and the lack of sensitivity of existing studies to tease apart the effects of the various dyes, it may make sense to consider these dyes collectively for risk assessment purposes. Unlike some additives, colorings often don't serve as substitutes for one another, but are used in combination in a food to achieve a visual effect.

Additionally, non-food dyes or other chemicals used in food, cosmetics, and medical products may be chemically or pharmacologically related to food dyes, and should be taken into account, as already noted.

### ***FDA Applied Inadequate Safety Factors Given the Risks Dyes Pose to Children***

In establishing its ADIs for individual synthetic food dyes, FDA applied two 10-fold factors, based on no-effect levels in chronic animal studies, to account for intra- and inter-species variability. That approach is inadequate and contrasts with current practice at other federal agencies.

For example, the Environmental Protection Agency applies a 10-fold safety/uncertainty factor in addition to all other safety/uncertainty factors (e.g., for a total of 1,000) whenever its safety database is incomplete, in particular to account for potential toxicity to infants and children. EPA specifically asks, “[w]hat are the resulting uncertainties in the database with regard to children’s risk?” and “[h]ave any uncertainties in developmental exposure been identified?”

FDA did the opposite. An FDA document made available at the Advisory Committee meeting argued that the “unique intolerance” of some children “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>25</sup> Thus, rather than focusing on how best to protect children—including whether its safety factors were appropriate and adequate in light of the variability among children and the lack of adequate neurotoxicity studies—FDA indicated that it should focus on better understanding what makes some people more sensitive.<sup>8</sup>

Given the lack of animal data from appropriately sensitive studies, FDA should either have applied additional safety factors to the animal study results to reflect the considerable data gaps or have applied appropriate safety factors to the human data. That would have been the way to ensure adequate protection of a vulnerable sub-population like children.

Clearly, current approvals for dyes are not well grounded in science. For example, FDA’s ADIs for dyes range from 2.5 mg/kg/day (Red 3, Blue 2, Green 3) to 12 mg/kg/day (Blue 1). For a 30 kg child, that means between 75 mg and 360 mg/day. For Yellow 5, FDA’s ADI translates to 150 mg/day for a 30 kg child. Yet doses as low as 1 mg of Yellow 5 triggered effects in some children in the study by Rowe and Rowe, as discussed below, and many studies found effects at 26-30 mg of a mixture of dyes.

#### ***IV. Additional Important Resources Enclosed for OEHHA’s Review***

In addition to CSPI’s report and the comments above, we provide the following to inform OEHHA’s evaluation, and we explain the significance of these resources below:

- 1) Nine key published reviews of the evidence (notably, eight of them not considered by the FDA in 2011)
- 2) An overview of the most noteworthy of the more than 30 clinical trials that have been conducted on behavioral effects of synthetic food dyes

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<sup>8</sup> Paradoxically, FDA does not make much of an attempt to better understand why some children are more sensitive than others. See section IV.2 for relevant references not examined by FDA that were available in 2011.

- 3) Additional relevant studies not considered by FDA in 2011
- 4) Relevant information pertaining to “azo” dyes, the class of food dyes most frequently used and studied
- 5) Key conclusions and actions by other regulatory authorities
- 6) Support for actions to limit exposure to dye-containing foods
- 7) Industry’s failure to provide adequate data or assessments
- 8) Information to OEHHA from affected families

All publications are hyperlinked in the text. If there are any references for which the links are missing or not working, or if you are unable to access the full text of the article, please let us know.

***1) Nine key published reviews of the evidence (notably, eight of them not considered by FDA in 2011)***

In [Seeing Red](#), we describe nine key analyses of the human data (including both challenge studies and restriction/elimination diet studies that eliminated foods containing dyes as well as other foods and food components from the diet). Eight of these were published since 2011 and thus were not considered by FDA.<sup>9</sup> All relied on essentially the same underlying data, although different meta-analyses used different criteria for selecting what data to include and exclude. All nine, including three important meta-analyses, conclude that excluding food dyes, or a diet that eliminates dyed foods and certain other foods and ingredients, reduces behavior problems in some children:

- 1) A [meta-analysis](#)<sup>26</sup> by Schab and Trinh that was published in 2004 in *the Journal of Developmental and Behavioral Pediatrics* analyzed 15 studies and concluded that the results “strongly suggest an association between ingestion of [synthetic food dyes] and hyperactivity.” It estimated that the magnitude of the effect of dyes is between one-third to one-half of the deterioration in behavior that would occur if medications were withdrawn from children being treated for attention deficit/hyperactivity disorder (ADHD).
- 2) [A meta-analysis](#)<sup>27</sup> by Nigg, et al. (2012) published in the *Journal of the American Academy of Child Adolescent Psychiatry* found that adopting a diet free of food dyes and some other foods and ingredients reduced symptoms of ADHD in approximately a third of children with that condition. The meta-analysis, which received funding from an arm of the food industry, found that synthetic colorings were associated with a slight statistically significant increase in ADHD symptoms as assessed by attention tests or by parents. It estimated that 8 percent of the millions of children with ADHD may suffer symptoms from synthetic food colorings.
- 3) [A meta-analysis](#)<sup>28</sup> by Sonuga-Barke et al. (2013) published in the *American Journal of Psychiatry* by an international team of researchers found that of six non-drug treatments for ADHD, only two produced statistically significant effects on ADHD when using the best probably blinded assessment, including artificial food color exclusion. Artificial food color exclusion produced the largest effects, often in individuals selected for food sensitivities. It differed from the previous two meta-

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<sup>9</sup> One was published in 2011 and is listed in FDA’s Bibliography as “not reviewed by FDA.”

- analyses listed here by only analyzing studies of children who had been formally diagnosed with ADHD. It found that the effect of excluding dyes from the diet on ADHD symptoms was greater but similar in magnitude to what was found in the previous meta-analyses.
- 4) A critical [appraisal of the three meta-analyses](#)<sup>29</sup> described above by an international team of researchers on behalf of the European ADHD Guidelines Group (Stevenson et al. (2014)) concluded that “(t)he results suggest that food colour elimination is a potentially valuable treatment approach for ADHD” that “may be beneficial for children thought to be adverse responders to food colour exposure.” It suggested an average SMD effect size of around 0.30.
  - 5) An [analysis of non-drug treatments for ADHD](#)<sup>30</sup> (Faraone<sup>10</sup> et al. (2014)) used guidelines developed by the Oxford Center for Evidence-Based Medicine. Those guidelines are used to assess the degree to which treatments are supported by scientific evidence. The review gave both exclusion of food dyes and restricted elimination diets (that restrict/eliminate certain foods or additives, including food dyes) its second-highest rating (4 out of 5)—just behind FDA-approved medications (5 out of 5) and stronger than a dozen other non-drug treatments, such as psychotherapy or clinic-based social-skills training (each of which earned a 1 out of 5)—for strength of the evidence in treating ADHD. The reviewers also examined the effectiveness of different treatments for ADHD and rated artificial food dye exclusion as being far more effective at treating ADHD than behavioral parent training or supplementation with omega-3-fatty acids, although less effective than drugs.
  - 6) A [review of dietary and nutritional treatments for ADHD](#) by researchers at Ohio State University (Arnold et al. (2013))<sup>31</sup> examined the quality of evidence for elimination diets and rated it as “good” in children diagnosed with or having symptoms consistent with ADHD and in children without ADHD who exhibit some ADHD symptoms. It recommended an elimination diet for children who are documented to react to dyes or other additives or foods.
  - 7) A [review of food elimination diets](#) by researchers at Oregon State University and American University (Nigg et al. (2014))<sup>32</sup> concluded that “a small but extensively discussed literature yields an emerging consensus that dietary intervention to remove additives (color and perhaps preservatives) likely yields a small aggregate benefit.”
  - 8) A [qualitative review](#) by researchers at Purdue University (Stevens et al. (2011))<sup>33</sup> covering 35 years of research on dietary sensitives and ADHD symptoms concluded that a sub-population of children with ADHD improves significantly on a dye-free diet and experiences ADHD symptoms when challenged with food dyes, and that those children are often sensitive to other foods. The review recommended a trial “elimination” diet for children not responding well to conventional treatment or whose parents wish to pursue a dietary approach.

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<sup>10</sup> Stephen Faraone PhD, Distinguished Professor and Vice Chair for Research at the Department of Psychiatry, SUNY Upstate Medical University, was listed in “The World’s Most Influential Scientific Minds” in 2014 for the fields of psychiatry and psychology, according to Thomson Reuters. The world’s most influential scientific minds: 2014. Accessed at <https://people.engr.ncsu.edu/ytzhu/news/worlds-most-influential-scientific-minds-2014.pdf>

- 9) A [review summarizing the history of the issue and testimony to the 2011 FDA Food Advisory Committee](#) by researchers at Ohio State University (Arnold et al. (2012))<sup>34</sup> concluded that “Recent data suggest a small but significant deleterious effect of AFCs [artificial food colors] on children’s behavior that is not confined to those with diagnosable ADHD.” It stated that artificial food colors “appear to be more of a public health problem than an ADHD problem” (i.e., the dyes affect children in the general population that don’t have ADHD) and suggested “minimizing children’s exposure to artificial food colors.”

2) *An overview of the most noteworthy of the more than 30 clinical trials that have been conducted on behavioral effects of synthetic food dyes*

A list of the clinical trials of dyes is in FDA’s [Bibliography: All references related to overview assessment of artificial food colors/additives and hyperactivity \(ADHD\) and problem behaviors in children](#). More information on the clinical trials is available at CSPI’s [Diet, ADHD & Behavior: A Quarter-Century Review](#).<sup>35</sup>

We would like to direct OEHHA to the most important clinical trials. Five are especially noteworthy:

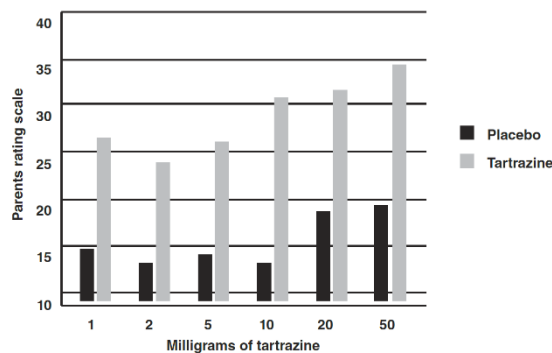
- 1) Two groundbreaking double-blind placebo-controlled clinical trials published in 2004<sup>36</sup> and 2007<sup>37</sup> were sponsored by the British government. The results from the [first study \(in three-year-olds\)](#) were replicated and extended to older children in the second study, known as “the [Southampton study](#).” The replication of findings adds more weight to the conclusions. Unlike earlier studies, these tested the sensitivity of children in the general population (rather than children with behavioral problems or food sensitivities) and were large (each tested nearly 300 children). Mixtures of chemically related azo dyes, including some not used in the United States, and the preservative sodium benzoate were tested. More than 90 percent of food dyes used in the United States are azo dyes (primarily Red 40, Yellow 5, and Yellow 6, which were included in the mixtures tested).

The second study concluded that “[a]rtificial colours or a sodium benzoate preservative [or both] in the diet result in increased hyperactivity in 3-year-old and 8/9-year-old children in the general population.”

The editor of an American Academy of Pediatrics journal commentary, Alison Schonwald MD, FAAP, of Children’s Hospital in Boston, stated, “the overall findings of the study are clear and require that even we skeptics, who have long doubted parental claims of the effects of various foods on the behavior of their children, admit we might have been wrong.”<sup>38</sup>

The Southampton study prompted the British government to inform consumers that “[i]f a child shows signs of hyperactivity or Attention Deficit Hyperactivity Disorder (ADHD) then eliminating the colours used in the Southampton study from their diet might have some beneficial effects” and to urge food makers to discontinue the use of the dyes. The European Parliament voted to require a warning label on products containing the dyes.<sup>39</sup>

- 2) In a [double-blind placebo-controlled clinical trial by Rowe and Rowe](#), researchers tested multiple doses of a single dye (tartrazine, or Yellow 5) and reported a dose-response effect on the behavior of children with suspected hyperactivity.<sup>40</sup> In other words, the more dye that was consumed, the worse the children scored on behavior, as assessed by parents (see figure below). Determination of a dose-response relationship is considered strong evidence for a causal relationship between the exposure and the outcome. The study used a 30-item behavioral rating inventory that assessed irritability/control, sleep disturbance, restlessness, aggression, and attention span. Even very low doses (1 mg or 2 mg) evoked responses. The study identified 24 children as “clear reactors” to dyes.



Source: Stevens et al., 2011; adapted from Rowe and Rowe.

- 3) An [FDA-funded study](#) by Bernard Weiss et al. and published in *Science* in 1980 tested 22 children, ages 2 to 7, who were suspected of reacting to artificial colorings and flavors. None had been diagnosed as hyperkinetic (what we now call hyperactive). For 77 consecutive days, each child drank a beverage that on eight randomly selected days concealed a 35.3 mg mixture of dyes. Two of the children showed clear reactions, according to observations by their parents. The researchers stated, “[t]hese data further strengthen the accumulating evidence from controlled trials, supplemented by laboratory experiments, that modest doses of synthetic colors, and perhaps other agents excluded by elimination diets, can provoke disturbed behavior in children.”<sup>41</sup>
- 4) A [study by Swanson<sup>11</sup> and Kinsbourne](#) published in 1980 in the same issue of *Science* as the FDA-funded study (above) used higher doses of dyes, as well as laboratory tests, rather than assessments by parents or teachers. The researchers challenged 40 children, 20 of whom were considered hyperactive, with doses up to 150 mg of a mixture of dyes thought to represent the 90th percentile intake of artificial colors. For three days the children, ages 5 to 12, were put on a Feingold diet (which eliminates synthetic food dyes and certain other additives and ingredients). The researchers then administered either placebos or a mixture of either 100 mg or 150 mg of dyes. Compared to the placebo, the dyes significantly decreased the attention span of the hyperactive children, and 17 of the 20 hyperactive children suffered significantly impaired performance on a learning test during the second phase. The challenge did not affect children classified as nonhyperactive. The effect of the high dose of food dyes took more than half an hour to

<sup>11</sup> (now at the University of California-Irvine School of Medicine)

become evident, reached its maximum by 1½ hours, and lasted at least 3½ hours, a pattern that “is consistent with the notion that the response to food dye is based on a pharmacologic or toxic mechanism, rather than an immunologic or allergic mechanism,” according to the authors. The authors suggest that the negative results in some previous studies of dyes might have been a result of testing too low a dose.<sup>42</sup>

### 3) *Additional relevant studies not considered by FDA in 2011*

The studies considered by FDA in 2011 are listed in a bibliography made available at the 2011 Food Advisory Committee: [Bibliography: All references related to overview assessment of artificial food colors/additives and hyperactivity \(ADHD\) and problem behaviors in children.](#)

Relevant studies not considered by FDA (some not available in 2011) include the following, which provide insight into possible mechanisms of action (how dyes exert their effects on children) and the variability of response among children (why some children react and others do not):

- Ly V, Bottelier M, Hoikstra PJ, Vasquez AA, Buitelaar JK, Rommelse NN. [Elimination diets efficacy and mechanisms in attention deficit hyperactivity disorder and autism spectrum disorder.](#) *Eur Child Adolesc Psychiatry* 2017; 26(9):1067-1079.
- Stevens L, Kuczek T, Burgess JR, Stochelski MA, Arnold LE, Galland L. [Mechanisms of behavioral, atopic, and other reactions to artificial food colors in children.](#) *Nutr Rev* 2013; 71(5):268-81.
- Stevenson J, Sonuga-Barke E, McCann D, Grimshaw K, Parker K, Rose-Zerilli M, Holloway J, Warner J. [The role of histamine degradation gene polymorphisms in moderating the effects of food additives on children’s ADHD symptoms.](#) *Am J Psychiatry* 2010; 167(9):1108-1115.

The following reviews and commentaries provide further evidence of the growing consensus about dyes:

- Austerman J. [ADHD and behavioral disorders: Assessment, management, and an update from DSM-5.](#) *Cleve Clin Med* 2015; 82(11 Suppl 1):S2-7.  
“Although challenging to accomplish, management of diet, specifically removal of artificial food coloring and sodium benzoate preservatives, has been more efficacious than behavioral management in the long-term reduction of core symptoms of ADHD.” (cites McCann and Schab)
- Buka I, Osornio-Vargas A, Clark B. [Food additives, essential nutrients and neurodevelopmental behavioral disorders in children: A brief review.](#) *Paediatr Child Health* 2011; 16(7):e54-6.  
“Food additives, especially preservatives and artificial colours as well as suboptimal intake of essential nutrients, have been linked to hyperactive behaviors and poor attention in a subgroup of children. ... Clinical and epidemiological evidence supports a potential role of food additives and



essential nutrients in NDBD [neuro-developmental behavioral disorders] in children as modifiable risk factors for certain symptoms and behaviours.” It calls for “reviewing food regulatory processes to better protect children in Canada—similar to the regulations recently undertaken by the British Food Standards Agency.”

- Goodman DW. [Artificial food colour exclusion and free fatty acid supplementation may reduce symptom severity in children with ADHD](#). *Evid Based Ment Health* 2013; 16(3):77.  
A comment on the Sonuga-Barke systematic review. “Artificial food colour exclusion, and to a lesser extent free fatty acid supplementation, significantly reduce symptom severity in ADHD, although the clinical significance of these results has not been determined.”
- Heilskov Rytter MJ, Andersen LB, Houmann T, et al. [Diet in the treatment of ADHD in children—a systematic review of the literature](#). *Nord J Psychiatry* 2014; 64:1-18.  
“Elimination diets and fish oil supplements seem to be the most promising dietary interventions for a reduction in ADHD symptoms in children.”
- Kanarek RB. [Artificial food dyes and attention deficit hyperactivity disorder](#). *Nutr Rev* 2011; 69(7):385-91.  
“... a portion of children respond positively to the removal of synthetic food dyes from the diet. ADHD is a multifaceted disorder, and one treatment will not work for all.”

Recent animal studies of interest:

- Ceyhan BM, Gultekin F, Doguc DK, Kulac E. [Effects of maternally exposed colouring food additives on receptor expressions related to learning and memory in rats](#). *Food Chem Toxicol* 2013; 56:145-8.
- Doguc DK, Aylak F, Ilhan I, Kulac E, Gultekin F. [Are there any remarkable effects of prenatal exposure to food colourings on neurobehavioral and learning processes in rat offspring?](#) *Nutr Neurosci* 2015; 18(1):12-21.
- Doguc DK, Ceyhan BM, Ozturk M, Gultekin F. [Effects of maternally exposed colouring food additives on cognitive performance in rats](#). *Toxicol Ind Health* 2013; 29(7):616-23.
- Erickson ZT, Falkenberg EA, Metz GA. [Lifespan psychomotor behavior profiles of multigenerational prenatal stress and artificial food dye effects in rats](#). *PLoS One* 2014; 9(6):e92132.

Other articles of interest:

- Kirland AE, Holton KF. [Measuring treatment response in pharmacological and lifestyle interventions using electroencephalography in ADHD: A review.](#) *Clinical EEG and Neuroscience* 2019. Jan 9 epub ahead of print.

**4) *Relevant information pertaining to “azo” dyes, the class of food dyes most frequently used and studied***

As previously noted, the groundbreaking UK-sponsored studies described above that led to warning labels in Europe primarily focused on azo dyes, which comprise about 90 percent of dyes certified for use in food, according to FDA certification reports. Generally, azo dyes comprised a similar percentage (i.e., about 90 percent) of the mixtures of dyes tested in clinical trials. (Azo dyes have an -N=N- in their chemical structure.)

Currently approved azo dyes include:

FD&C Red 40 (Allura Red)\*  
 FD&C Yellow 5 (Tartrazine)\*  
 FD&C Yellow 6 (Sunset Yellow FCF)\*  
 Citrus Red 2  
 D&C Orange 4  
 D&C Red 6  
 D&C Red 7  
 D&C Red 34  
 D&C Red 36  
 D&C Red 31  
 D&C Brown 1\*\*  
 D&C Red 17\*\*

\* In Europe, foods containing this dye must bear a warning label.

\*\* diazo dyes.

Ten of the 14 dyes that have been banned by the FDA are azo dyes.

Consumers are exposed to other azo compounds in addition to azo dyes. For example, azodicarbonamide, a food additive used in bread, and pyridium, a drug used to treat the symptoms of urinary tract infections, are azo compounds.

**5) *Key conclusions and actions by other regulatory authorities***

Our [Seeing Red](#) report discusses key reviews and events in Europe and elsewhere. Among them:

- The [UK’s Committee on Toxicology](#) evaluated the Southampton study and concluded that “the results of this study are consistent with, and add weight to, previous published

reports of behavioral changes occurring in children following consumption of particular food additives.”

- [Health Canada](#) said, regarding the Southampton study: “Health Canada scientists reviewed the results of the UK study and agreed with the conclusions of the UK Committee on Toxicology that the results of this study are consistent with, and add weight to, previous published reports of behavioral changes occurring in children following consumption of particular food additives which included a number of azo food colours. Health Canada also noted the inconsistencies in the results between the two mixtures of food colours and between age groups, and the small observed effect relative to the degree of variation in effect between individuals, which suggested that conclusions could not be drawn regarding possible changes that might be observed at the population level. Health Canada has since found information suggesting a mechanism by which the azo food colour component of the tested food additive mixtures could affect the availability of neurotransmitters in the brain and thus influence behavior. The results of the UK study became more consistent when analyzed on the basis of the dose of azo food colours received by the two age groups and with the two food additive mixtures. Due to the multiple factors affecting susceptibility to the effects of azo colours, susceptibility would differ widely with the individual.”
- [EFSA](#) (the European Food Safety Authority) acknowledged but downplayed the evidence as “limited” that the mixture of dyes used in the Southampton study had a statistically significant effect on the activity and attention of children selected from the general population. (EFSA’s panels have been criticized for their industry-oriented opinions and for including members with conflicts of interest.)<sup>43</sup>

The UK [Food Standards Agency](#) (the counterpart of the FDA) informed parents that

“[i]f a child shows signs of hyperactivity or Attention Deficit Hyperactivity Disorder (ADHD) then eliminating the colours used in the Southampton study from their diet might have some beneficial effects.”

FSA based its advice on the effects of the mixtures of dyes rather than insisting that each dye be tested separately.

- FSA produced [guidance](#) to help companies eliminate synthetic food dyes. FSA also maintained a list of dye-free foods for many years, but no longer does so. Many products were in fact reformulated in Europe to eliminate synthetic dyes.<sup>44</sup>

#### **6) Support for actions to limit exposure to dye-containing foods**

- CSPI’s [2008 “Petition to FDA to Ban the Use of Yellow 5 and Other Food Dyes, in the Interim to Require a Warning on the Foods Containing These Dyes, to Correct the Information the Food and Drug Administration Gives to Consumers on the Impact of These Dyes on the Behavior of Some Children, and to Require Neurotoxicity Testing of New Food Additives and Food Colors,”](#) submitted by CSPI

on June 3, 2008. The petition includes CSPI's earlier report, [Diet, ADHD, & Behavior](#)

- A [January 2016 letter from CSPI to FDA](#) includes a brief legal analysis of the deficiencies in the agency's inaction on the risks of synthetic food dyes
- [A 2016 letter to FDA](#) from leading scientists and experts supporting the analysis in CSPI's *Seeing Red* Report
- Letters of support from health organizations and researchers for SB 504, a bill in the U.S. Senate requiring a warning label on dyed foods, were signed by 17 organizations and 25 individuals, 10 of whom are scientists or physicians who have published relevant articles<sup>12</sup> (available upon request)
- Testimony in support of SB 504 by Mark Horton, former director of the California department of Health (available upon request)

### ***7) Industry's failure to provide adequate data or assessments***

After a presentation at the FDA Food Advisory Committee meeting in 2011 by Dr. Steve Taylor, representing the food dyes industry, committee member Dr. Charles Voorhees, a professor of pediatrics in the division of neurology at Cincinnati Children's Hospital with an expertise in neuroscience, stated, "Not one of the studies that you listed among the safety studies is what is commonly referred to as a DNT study, and that's developmental neurotoxicity study. So in fact it

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<sup>12</sup> The 17 organizations included Center for Science in the Public Interest, Children's Advocacy Institute (Sacramento, CA), Association for Comprehensive NeuroTherapy, Berkeley Media Studies Group (Berkeley, CA), Center for Environmental Health (Oakland, CA), Center for Food Safety (Washington, DC, with offices in San Francisco, CA), Consumer Federation of America, Consumers Union (Yonkers, NY, with offices in San Francisco, CA), Environmental Defense Fund (New York, NY, with offices in Sacramento and San Francisco, CA), Feingold Association of the United States, Natural Resources Defense Council (New York, NY, with offices in San Francisco and Santa Monica, CA), Orange County Food Access Coalition (Santa Ana, CA), Prevention Institute (Oakland, CA, and Los Angeles, CA), Public Health Institute (Oakland, CA), Real Food for Kids, Real Food for Kids Montgomery, School Food Focus. The 10 published experts in the field include L. Eugene Arnold, MD, MEd (professor emeritus of psychiatry, Nisonger Center Clinical Trials Program, Ohio State University), Ameena Batada DrPH (associate professor, University of North Carolina at Asheville), Stephen Faraone PhD (distinguished professor of psychiatry and of neurosciences & physiology, SUNY Upstate Medical University), Michael F. Jacobson, PhD (Center for Science in the Public Interest), Joel Nigg, PhD (professor, departments of psychiatry and behavioral neuroscience, School of Medicine, Oregon Health & Science University), David Schab, MD (assistant clinical professor of psychiatry, Columbia University), Laura J. Stevens, MS (research associate, department of foods & nutrition, Purdue University), Jim Stevenson, PhD (emeritus professor of developmental psychopathology, School of Psychology, University of Southampton), James M. Swanson, PhD (professor emeritus of pediatrics, University of California, Irvine), Bernard Weiss, PhD (professor of environmental medicine, School of Medicine and Dentistry, University of Rochester) (now deceased), and 15 other individuals, including Californians Jonathan E. Fielding, MD, MPH, MBA (distinguished professor of health policy and management, and of pediatrics, University of California, Los Angeles), Sanford Newmark, MD (professor, University of California, San Francisco), Tara Scott, MD (family physician, associate program director, Santa Rosa Family Medicine Residency), David Wallinga, MD (senior health officer, NRDC, San Francisco, CA)

isn't clear to me that you have preclinical data that speak to the issue which is the subject of this conference." Dr. Voorhees then asked, "So what would trigger the manufacturers to decide that it would be appropriate to undertake developmental neurotoxicity or neurobehavioral studies ...?" Dr. Taylor clearly stated that "guidance from the FDA" would be needed.<sup>45</sup> Yet, to our knowledge, FDA has not requested such data, nor has industry provided them.

The food industry has published a study assessing the safety of FD&C food color additives and estimating the daily intake in the U.S. population.<sup>46</sup> Funded by members of the International Association of Color Manufacturers (IACM) and written by IACM staff, members, and consultants, the assessment is so riddled with inaccuracies and misleading statements that CSPI sent a [letter to the editor](#) arguing that it should be retracted and disregarded. Every one of its conclusions is incorrect.

As our [letter to the editor](#) documents, the IACM study (1) mischaracterizes the relationship between the study's exposure estimates and actual concentrations measured analytically by FDA, describing them as "consistent" when they are actually much lower, (2) systematically underestimates food dye exposure, primarily by relying on a database that contains only *new* food labels published between January 2011 and February 2015 and not the complete array of labels currently in the marketplace (food companies have more recently taken steps to eliminate synthetic dyes), (3) relies on acceptable daily intake (ADI) estimates that are based on outdated animal studies incapable of detecting the kinds of adverse behavioral effects reported in multiple clinical trials in children, as noted above, while ignoring the nine recent reviews (including three meta-analyses) drawing from over 30 such clinical trials (described in the previous section), and (4) makes misleading statements about the Southampton study, asserting that it tested "above conservative intakes for the US population," when the doses given in the Southampton study (McCann et al. (2007)) were about two orders of magnitude less than amounts equal to each ADI, and within the range of exposures reported by FDA in Doell et al.<sup>13</sup>

### ***8) Information to OEHHA from affected families***

(See separate attachment).

### Endnotes

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<sup>1</sup> Lefferts, L. Seeing Red: Time for Action on Food Dyes. Center for Science in the Public Interest, 2016.

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<sup>13</sup> More specifically, in the Southampton study, three-year-olds were given between 2.5 mg and 7.5 mg of each of four dyes, for a total of 20 mg of dyes in Mix A and 30 mg of dyes in Mix B. FDA (in Doell et al. (2016)) reported that for 2-to-5-year-olds, average consumption of FD&C Red 40 alone ranged from 2.6 mg to 15.3 mg under different exposure scenarios and up to 38.8 mg for 90<sup>th</sup> percentile consumers (using two-day consumption data). For FD&C Yellow 5 and FD&C Yellow 6, consumption was as high as 5.5 mg and 6.2 mg on average, and 12.7 mg and 14.2 mg at the 90<sup>th</sup> percentile, respectively. In contrast, an amount equal to each ADI for a three-year-old child weighing 15 kg would total 330 mg for Mix A and 270 mg for Mix B.

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- <sup>2</sup> Pastor PN, Reuben CA, Duran CR, Hawkins LD. Association between ADHD and selected characteristics among children aged 4-17 years: United States, 2011-2013. National Center for Health Statistics Data Brief No. 201, May 2015. <https://www.cdc.gov/nchs/data/databriefs/db201.pdf>.
- <sup>3</sup> Centers for Disease Control and Prevention. Attention-Deficit/Hyperactivity Disorder (ADHD): Facts about ADHD and Data & statistics. Oct. 9, 2015. <http://www.cdc.gov/ncbddd/adhd/facts.html> and <http://www.cdc.gov/ncbddd/adhd/data.html>.
- <sup>4</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; Jan, 51(1):86-97.
- <sup>5</sup> Batada A, Jacobson MF. Prevalence of artificial food colors in grocery store products marketed to children. *Clin Pediatr* 2016; 55(12):1113-9.
- <sup>6</sup> Doell DL, Folmer DE, Lee HS, Butts KM, Carberry SE. [Exposure estimate for FD&C colour additives for the US population](#). *Food Addit Contam Part A Chem Anal Control Expo Risk Assess* 2016; 33(5):782-797.
- <sup>7</sup> International Food Information Council, *Food Decision 2016: Food & Health Survey*, [https://foodinsight.org/wp-content/uploads/2016/05/2016-Food-and-Health-Survey-Report-FINAL\\_0.pdf](https://foodinsight.org/wp-content/uploads/2016/05/2016-Food-and-Health-Survey-Report-FINAL_0.pdf) (More recent IFIC surveys did not specifically ask about artificial colors).
- <sup>8</sup> Sensient H/W study, 2015, cited in Morris S, "Can natural color help cereal sales?" July 2016, at <http://sensientfoodcolors.com/en-us/market-trends/can-natural-color-help-cereal-sales/>.
- <sup>9</sup> See [https://www.accessdata.fda.gov/drugsatfda\\_docs/label/2015/010187s080.018029s049.021284s027lbl.pdf](https://www.accessdata.fda.gov/drugsatfda_docs/label/2015/010187s080.018029s049.021284s027lbl.pdf)
- <sup>10</sup> Doell DL, Folmer DE, Lee HS, Butts KM, Carberry SE. [Exposure estimate for FD&C colour additives for the US population](#). *Food Addit Contam Part A Chem Anal Control Expo Risk Assess* 2016; 33(5):782-797. Including [Supplemental Data Tables](#) with brand-name specific results.
- <sup>11</sup> Harp BP, Miranda-Bermudez E, Barrows JN. [Determination of seven certified color additives in food products using liquid chromatography](#). *J Agric Food Chem* 2013; 61(5):3726-36.
- <sup>12</sup> Stevens L, Burgess J, Stochelski M, et al. [Amounts of artificial food colors in commonly consumed beverages and potential behavioral implications for consumption in children](#). *Clin Pediatr (Phila)* 2014; 53(2):13340. doi:10.1177/0009922813502849. Epub Sept. 13, 2013.
- <sup>13</sup> Stevens L, Burgess J, Stochelski M, et al. [Amounts of artificial food dyes and added sugars in foods and sweets commonly consumed by children](#). *Clin Pediatr (Phila)* 2015; 54(4):309-21. doi:10.1177/0009922814530803. Epub April 24, 2014.
- <sup>14</sup> Stevens L, Burgess J, Stochelski M, 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 Apr. 14, 2015.
- <sup>15</sup> FDA Food Advisory Committee transcript, March 31, 2011, discussion between neuroscientist Dr. Voorhees and industry representative Dr. Taylor, pp. 66-67.
- <sup>16</sup> FDA Food Advisory Committee transcript, March 31, 2011, discussion between child and adolescent psychiatrist Dr. Castellanos and industry representative Dr. Taylor, pp. 104-105.
- <sup>17</sup> George Gray PhD, professor, department of environmental and occupational health, George Washington University, FDA Food Advisory Committee transcript, March 31, 2011 Food Advisory Committee Meeting p. 242.
- <sup>18</sup> Francisco Xavier Castellanos MD, 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. Transcript, March 31, 2011 Food Advisory Committee Meeting page 251.
- <sup>19</sup> 21 U.S.C. 379e(b)(5)(A).
- <sup>20</sup> Stevens L, Burgess J, Stochelski M, 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 Apr. 14, 2015.
- <sup>21</sup> Charles Vorhees, professor of neuroscience at the Cincinnati Children's Hospital Medical Center and member of the 2011 Food Advisory Committee, stated that these studies "are known to be completely insensitive" for detecting neurobehavioral outcomes. FDA Food Advisory Committee transcript, March 31, 2011 p. 142, available at <https://wayback.archive-it.org/org-1137/20170406211705/https://www.fda.gov/downloads/AdvisoryCommittees/CommitteesMeetingMaterials/FoodAdvisoryCommittee/UCM255119.pdf>.

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- <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.
- <sup>23</sup> For example, Charles Vorhees PhD, professor of neuroscience at the Cincinnati Children's Hospital Medical Center, one of two members appointed to the committee for this meeting because of their specialized expertise, noted, "So if you're relying on 30-year-old data, I would suggest that that's not an adequate basis to make a determination that the preclinical studies have ruled out the possibility that these might have developmental neurotoxicity." FDA Food Advisory Committee transcript, March 31, 2011, p. 141.
- <sup>24</sup> Charles Vorhees PhD, op. cit., asked FDA's Jason Aungst, "Did any of those studies [used to establish the ADIs] include neurobehavioral outcomes?" Aungst replied, "Not specific neurobehavioral testing, but clinical observations of ... behaviors in the normal cage setting." Vorhees retorted, "Which are known to be completely insensitive." He concluded, "I do not believe that the tests done, including the two-year rodent bioassays, provide a sufficient basis for determining a NOAEL ... 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." FDA Transcript, March 31, 2011, FAC Meeting, p. 142, and pp. 214-216. Penny Fenner-Crisp PhD, a retired EPA senior toxicologist, stated, "the 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." FDA Transcript, March 31, 2011, p. 143.
- <sup>25</sup> U.S. Food and Drug Administration. Interim Toxicology Memorandum. September 1, 2010. Attachment 4, p. 44. <https://wayback.archive-it.org/org-1137/20170113062757/http://www.fda.gov/AdvisoryCommittees/CommitteesMeetingMaterials/FoodAdvisoryCommittee/ucm248008.htm>.
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