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Via electronic submission

Office of Environmental Health Hazard Assessment
1515 Clay Street, 16th Floor
Oakland, CA 94612
Attention: Anna Smith, Food Dye Study

RE: Comments in Response to OEHHA Request for Information on the Neurologic and Neurobehavioral Impacts of Synthetic Food Dyes (October 22, 2018)

Dear Ms. Smith:

On behalf of the International Association of Color Manufacturers (IACM), we appreciate the opportunity to submit comments in response to the California Office of Environmental Health Hazard Assessment (OEHHA) information request on the neurologic and neurobehavioral impacts of synthetic food dyes.

IACM is the trade association that represents the global color industry, comprised of manufacturers and end-users of coloring substances that are used in foods, including certified and exempt from certification colors. IACM members create and use colors for a wide variety of food and beverage products. Color additives play an important role in food, and they do so without posing a health risk to consumers.

I. Executive Summary

We understand that OEHHA is conducting a risk assessment of the potential impacts of synthetic food dyes on children, particularly for neurobehavioral and neurologic effects, at the request of the California Legislature.

OEHHA has advised that it plans to include the nine batch certified colors currently authorized for use in the United States in its assessment: FD&C Blue No. 1, FD&C Blue No. 2, FD&C Green No. 3, Orange B, Citrus Red No. 2, FD&C Red No. 3, FD&C Red No. 40, FD&C Yellow No. 5 and FD&C Yellow No. 6. In conducting the risk assessment, OEHHA has shared that it plans to evaluate their toxicology, epidemiology, and exposure literature and databases. We note that only seven of these nine food colors are FD&C food colors approved by the US Food and Drug Administration (US FDA) for ingestion. The other two colors (Orange B, Citrus Red No. 2) are approved by the US FDA only for limited use as external colorants and are not part of the discussion that follows.

IACM is pleased to provide information responsive to OEHHA's request. The following key points highlight information provided in this letter:

- There are many studies in humans of food colors and neurobehavioral endpoints. All the relevant studies of the food colors of interest to OEHHA must be carefully evaluated for strengths and weaknesses, including bias (e.g., selection, performance, detection), methods for blinding, control for confounders and the number of subjects. The studies purporting an association between consumption of food color additives and adverse behavior all suffer from protocol limitations and all the purported associations are extremely weak.

- Many of the studies, including the Southampton studies, evaluated mixtures that included colors not approved in the United States. Studies of mixtures of food colors are not appropriate for hazard identification as they do not allow the identification of specific food colors that might pose a hazard if such a hazard exists. Therefore, these studies are not appropriate for hazard identification or risk assessment in the US.

- The diagnosis of attention-deficit/hyperactivity disorder (ADHD) is complex, and there are no consistent diagnostic criteria. In many studies, the diagnosis of ADHD is tenuous because it is based on a diagnosis often made by parents or teachers, without the use of objective criteria. Without valid and objective measures of ADHD, epidemiological studies using ADHD as the outcome are subject to response misclassification and no conclusions on associations can be drawn.

- Neurobehavioral effects in animal studies have been reviewed by expert organizations who concluded they did not provide evidence that warranted the revision of the respective acceptable daily intakes (ADIs). Rodent models of ADHD have been recently developed, but animal models can only evaluate proxy endpoints or certain aspects of the complex symptomatology ascribed as ADHD and at best provide feasible hypotheses regarding the underlying causes of specific aspects of ADHD behavior.

- In the US, the US FDA regulates all color additives, including evaluating safety based on scientific evidence and regulating labeling. All nine food colors of interest to OEHHA have been reviewed and approved as safe by the US FDA. Additionally, due to the US FDA's regulations, all color additives are required to be specifically listed by name on a product's ingredient label. This labeling requirement allows consumers to know which products contain FD&C certified colors.

- The US FDA, the European Food Safety Authority (EFSA), and the Joint FAO/WHO Expert Committee on Food Additives (JECFA) all have found that there is not sufficient evidence to link ADHD to any of the nine food colors of interest to OEHHA – or any other food color. Without establishing a neurobehavioral hazard for food colors, it is not possible to conduct a risk assessment for food colors based on neurobehavioral impacts. The authors of systematic reviews and meta-analyses who have reviewed the clinical studies evaluating food color additive intake and behavioral effects agree that neither a strong nor consistent association has been demonstrated for food color additive consumption and adverse behavioral effects in children.

- Detailed risk assessments for seven of the nine food colors of interest to OEHHA have been recently conducted by EFSA or JECFA or both. ADIs were developed by conducting risk assessment on each color based on a relevant endpoint of toxicity other than neurobehavioral effects. None of these expert agencies concluded that the available data on neurobehavioral effects provided sufficient evidence upon which to base a risk assessment for neurobehavioral effects in children. Both JECFA and EFSA have concluded that all of the color additives are safe for their intended use in foods and for all users, including children. The only two colors not recently studied (Orange B, Citrus Red No. 2) have very limited uses as external colorants only and have negligible sales and use.

- High exposure children in the US receive markedly less exposure to food colors than the doses utilized in UK studies. In addition, US children's exposure to food colors is dramatically below recently affirmed evidence-based ADIs adopted by international expert panels.

- OEHHA should exercise caution in identifying a link between food colors and ADHD in the absence of convincing evidence. A rush to judgment on food colors and ADHD could have unintended consequences and could stymie or detract broader research on the possible causes of ADHD.

II. Human Studies

Challenges of conducting and interpreting human studies to evaluate food colors and ADHD

There are numerous clinical studies of food colors and childhood neurobehavioral effects, including ADHD. According to the American Academy of Child & Adolescent Psychiatry (AACAP), the exact causes of ADHD are currently unknown, but are likely to be multifactorial involving genetic and environmental factors (AACAP,

2018).[1] Clinical studies generally are a useful way to evaluate the potential for an association between a treatment or exposure and an effect on health, but they cannot ascribe *cause* and effect. Randomized Control Trials (RCTs) are currently viewed as the gold standard method for assessing questions concerning treatment or exposure resulting in a health outcome (Jepsen *et al.,* 2004). But, studies of food colors and ADHD have particular challenges, and it is important to assess the strengths and limitations of each of these studies. Some common challenges of conducting and interpreting human studies of food colors and ADHD are described below.

Challenges in the Diagnosis of ADHD

The clinical diagnosis of ADHD can be challenging. Selective and sensitive biomarkers pointing to an ADHD diagnosis have not been established (Hamed *et al.,* 2015). Additionally, numerous other health-related issues not related to ADHD can present with similar symptoms as ADHD, including: hearing problems, learning or cognitive disabilities, sleep problems, depression or anxiety, and substance abuse (McCarthy, 2018).

In a nationwide survey focusing on lifestyle factors and a diagnosis of ADHD in children in the US, Lingineni *et al.* (2012) demonstrated that in addition to known factors associated with an ADHD diagnosis such as anxiety and depression, not participating in sports and watching television for 1 hour or more a day were associated with an ADHD diagnosis. Because other conditions or lifestyle behaviors can mimic ADHD symptoms, addressing such conditions and/or adopting lifestyle changes associated with better health may be impactful on the expression of ADHD and ADHD-like symptoms in children and are difficult to control for in epidemiological studies.

Holton and Nigg (2016) evaluated lifestyle habits of children with and without an ADHD diagnosis. They demonstrated that children with an ADHD diagnosis had a greater propensity to have lifestyle habits thought to be associated with a less healthy lifestyle than children without an ADHD diagnosis. While it is not possible to conclude whether a causative relationship exists between lifestyle and ADHD (nor what the direction of that causation is), or whether poor lifestyle habits are misinterpreted as symptoms of ADHD, Holton and Nigg (2016) concluded that improving lifestyle habits of children with an ADHD diagnosis may be impactful to the management of behavior in children.

The ability to determine the ADHD status of a child can also be complicated by differential scoring of the child's abilities in the evaluations used for diagnosis of ADHD as put forth in the *Diagnostic and Statistical Manual* (DSM) of mental disorders. Fair *et al.* (2012) evaluated the response ranges from DSM specified tests for children with and without an ADHD diagnosis and reported that the heterogeneity in the scoring of

[1] Approximately 10.6% of children aged 5-17 years in the US are diagnosed with ADHD and understanding the cause(s) of behaviors in children is an active topic of scientific and medical research (CDC NCHS, 2017).

individuals with ADHD in the different tests fell within the range of individuals without an ADHD diagnosis on one or more specific test.

Overdiagnosis of ADHD

The overdiagnosis or misdiagnosis of ADHD in developed countries, including the US, has been documented in the literature and is a serious concern for specialists and advocates of children's health (Merten *et al*., 2017; Evans *et al.,* 2010; Elder, 2010; Ford-Jones, 2015; Bruchmüller *et al.,* 2012; Layton *et al.*, 2018). ADHD is the most commonly diagnosed behavioral disorder for children in the US, with at least 4.5 million diagnoses among children under age 18, according to the Centers for Disease Control and Prevention. The absence of objective and consistent criteria for diagnosis calls ADHD studies into question since it compromises the validity of the response by introducing response misclassification of responders. For example, concerns have been raised regarding overdiagnosis of ADHD in response to a recent study reporting suspiciously high prevalence rates up to 20% (Merten *et al.*, 2017).

According to recent publications, about one million children may be over or mis-diagnosed for ADHD because their evaluation fails to address other factors that may explain their behavior. There are compelling data showing that the age of the child relative to the age group against which the behavior is measured leads to misdiagnosis, and that boys are more than twice as likely to be diagnosed than girls (Merten *et al.*, 2017; Evans *et al*., 2010; Elder, 2010; Layton *et al*., 2018). Younger children are significantly more likely than their older peers in the same school grade to be diagnosed with ADHD and be prescribed stimulants such as Ritalin.

Drawing conclusions from RCTs is complicated by the underlying psychiatric diagnoses relying heavily on reported behavior by parents and teachers. Intentional overdiagnosis intended to ensure medical help for children with unclear or borderline symptoms has been noted as a concern (Merten *et al.*, 2017). The trend of over-prescription and the expansion of the diagnostic criteria that match no other disorder listed in DSM-5 (comments by Patrick Landman and Christopher Lane; book by Alan Schwarz) also are expected to play a role in over-diagnosis.[2] The criticisms of over-prescription point to the observation that *"the sharp rise in Ritalin prescriptions directly parallels ADHD's dramatic ascent in diagnostic rates", … "doubling every six years since the early 1970s"* while in the late 1990s, prescriptions increased by "a stupefying 400 percent in just five years," after a brief period of low prescription rates between 1987-1990, which has been attributed to several well-publicized lawsuits about lax prescribing. Annual diagnoses more than doubled between 1990 and 1993, from 900,000 to 2,000,000 and they kept rising since (Schwarz, 2016). There is a wealth of

[2] Patrick Landman: https://stop-dsm.com/en/why-should-we-contest-adhd/
Christopher Lane: https://www.psychologytoday.com/us/blog/side-effects/201710/adhd-is-now-widely-overdiagnosed-and-multiple-reasons
Alan Schwarz: ADHD Nation: Children, Doctors, Big Pharma, and the Making of an American Epidemic (2016). Scriber Publisher. ISBN-13:978-1501105913.

literature on ADHD over/mis-diagnosis and drug prescriptions and a complete review is beyond the scope of the comments provided here.

Multiple Unknown Etiologies

Experts agree that ADHD is a term that covers a range of conditions with multiple and complex etiologies. However, little has been done to investigate the contributing factors systematically and thoroughly. Although AACAP states "most research points to genes inherited from parents as the leading contributor to ADHD," (AACAP, 2018) none of the human studies to date have controlled for this variable. [Subject to confirmation and discussion]. Multiple possible known and unknown etiologies and the possible role of genetics prevent one from effectively controlling for confounders in human studies.

Bias

Findings from RCTs, because of their complexity, lack of objective and standardized criteria to diagnose ADHD, or selection of participants differing from the rest of the population of interest, can be limited in informing hazard assessment or risk assessment (Boyko, 2013). RCTs are designed to include specific and strict criteria to produce valid conclusions that must be interpreted carefully within the context and scale of the study. The limitations of even well-conducted RCTs may not be fully understood and results may be misinterpreted by the public and some researchers if taken out of context (Deaton and Cartwright, 2018). RCTs are known to produce results that are limited to the study population but cannot be generalized and may produce biased results when the trials neglect consideration of alternative factors potentially contributing to the main reported outcome, among many other issues (Krauss, 2018). While the RCTs are considered the gold standard to obtain data on causes of health outcomes, there are limitations on what outcomes they are most effective in assessing. Therefore, ascribing cause and effect relationships to associations deemed statistically significant in clinical studies, including RCTs must be done very cautiously.

Accurate interpretation of RCTs requires the proper control of and/or acknowledgment of potential bias (Hartling *et al.,* 2009). There are four main categories of bias in RCTs: 1) selection, 2) performance, 3) detection, and 4) attrition (Hartling *et al.,* 2009). These four categories of bias can be evident in different phases of RCTs and can begin with the recruitment of study subjects that may not represent the broader population through self-selection of participation (Clay, 2010) and become evident again when subjective judgement is required for interpretation of effects (Hartling *et al.,* 2009). Defined, objective measures of behavioral responses, especially with ADHD, are critical. Emser *et al.* (2018) concluded that objective measures provide better prevention of bias from an evaluator in the detection of a response and of other errors associated with subjective measures for ADHD.

Systematic Review is a methodical procedure to systematically evaluate multiple RCTs covering the same topic (Cochrane Consumer Network, 2019). However, the

ability of a systematic review to be valuable may be affected by bias inherent to the design, conduct, analysis, or reporting in the studies that it evaluates (Jørgensen *et al.,* 2016). In the conduct of a systematic review, the extent to which biases have impacted study results may be difficult to know (Higgins *et al.,* 2011).

The University of Massachusetts (UMass) Amherst Food Science Strategic Policy Alliance convened a meeting of experts in April 2009 to develop a model and methodology to assess potential links between color additives and ADHD in children (Kleinman *et al.,* 2011). The UMass expert panel included individuals with expertise in food science, policy, the design and conduct of clinical psychological studies assessing the effects of pharmacotherapeutic and behavioral interventions for ADHD, pediatric nutrition, and biostatistics. Based on a recent literature review, we have been unable to confirm that any RCT has utilized the methodology recommended by these experts. Even if a new study were conducted according to the model proposed by Kleinman *et al.*, optimized to address the limitations of other studies, the challenge of potential response misclassification introduced by the lack of objective or consistent diagnostic criteria remains unresolved.

In summary, it is critical for OEHHA to consider the details of the experimental design and to evaluate the strengths and weaknesses of each clinical study that investigated food colors and potential neurobehavioral impacts.

III. Individual human studies

A large number of publications reporting on epidemiological studies on diet and ADHD have appeared in the literature over the past forty-plus years. Beginning with the work of Feingold (Feingold, 1975), numerous publications from clinical studies have reported on dietary intake patterns and ADHD, and these studies are referenced in recent meta-analyses (e.g. Sonuga-Barke *et al.,* 2013; Stevenson *et al.,* 2014; and Pelsser *et al.,* 2017).

The Southampton Studies

Much of the recent research activity on the topic of food additives, including color additives, and childhood behavior has been driven by research published by Bateman *et al.* (2004) and McCann *et al.* (2007), which are commonly referred to as the Southampton studies because they were conducted by investigators at Southampton General Hospital in the UK. The two Southampton studies utilized mixtures of four food color additives and sodium benzoate as test articles.

The Bateman *et al.* (2004) study included sunset yellow (FD&C Yellow No. 6), tartrazine (FD&C Yellow No. 5), carmoisine (a.k.a. azorubine; not approved for use in food in the US), and ponceau 4R (also not approved for use in food in the US). The McCann *et al.* (2007) study utilized the same color combination as Bateman *et al*. (2004) in Mix A, and used sunset yellow (FD&C Yellow No. 6), carmoisine, quinoline yellow (not approved for use in food in the US), and allura red (FD&C Red No. 40) in

Mix B. Of the six colors utilized in the Southampton studies, three are subject to the OEHHA information request (i.e. FD&C Yellow No. 6, FD&C Yellow No. 5, and FD&C Red No. 40).

In both studies, the test article was administered via a juice drink. The results of Bateman *et al.* (2004) revealed increases in children hyperactivity only when subjectively reported by the parents (who were not blinded to the test articles) but not when children were more objectively evaluated by professional psychological examinations. The medical community understands that parents are less objective judges of ADHD than teachers and both are less objective than professionals in identifying ADHD as they do not have the benefit of a large enough reference group for comparison (Ougrin *et al.,* 2010) and may have an interest in ascribing a cause (confirmation bias). There were no significant differences detected based on objective testing in the clinic by a tester blind to the dietary status.

McCann *et al.* (2007) utilized a double-blinded test article protocol. However, the induction of hyperactivity was reported mostly by parents and to a much smaller degree by teachers. The magnitude of the effect size (i.e., standardized mean difference), of worsening of hyperactivity for color additives reported and acknowledged by McCann *et al.* (2007) was miniscule. Additionally, the reported symptoms by parents as compared to teachers in the Southampton studies were less consistent (reflecting a higher degree of subjectivity) compared to reported symptoms by parents and teachers when effective interventions are tested (e.g. pharmacological treatment) (Schachter *et al.,* 2001). While teachers may benefit from a larger comparator dataset than parents for the identification of children with ADHD, they, as well as medical general practitioners, are not equipped to make an accurate diagnosis of ADHD, unlike professionals with specialized training (Ougrin *et al.,* 2010).

The McCann *et al*. (2007) study was evaluated by the EFSA Panel on Food Additives, Flavourings, Processing Aids, and Food Contact Materials (EFSA, 2008) shortly after it was published. According to the EFSA Panel, the main limitations of the study include: the study investigated mixtures not individual colors, unverified validity of the novel behavioral scoring, small sample size, absence of information regarding a dose-response relationship, and the absence of a possible biological mechanism to explain behavioral changes. ESFA also noted that McCann *et al.* (2007) used an unconventional and inadequately justified statistical model.

EFSA re-analyzed the original data using a more appropriate and conventional statistical model. Using this model, where each subject served as its own reference, EFSA disagreed with two conclusions drawn by McCann *et al.* (2007) and the statistical significance of the findings. Overall, EFSA concluded: (1) the McCann *et al.* (2007) study provided limited evidence that the two mixtures of color additives and sodium benzoate had a small but statistically significant effect on behavior in a small number of children, (2) those reported effects were not observed for all children in both age groups studied and were not consistent for the two mixtures of color additives, (3) that the study

findings could not be extrapolated into an assessment of the these additives' impact on behavioral changes in the general population, and (4) it was not possible to determine a potential sensitivity to individual additives.

Lok et al. (2013)

Lok *et al.* (2013) used a randomized double blind placebo controlled protocol to assess the findings reported for UK children by McCann *et al.* in eight to nine year-old children in Hong Kong. The authors stated that this study "*does not attempt to negate or contest the findings of the Southampton study but to build on this study in a sample of Chinese children because food safety in China is a major public health issue*", hence the study adhered to a protocol very similar to that used by McCann *et al.* (2007). Lok *et al*. (2013) used higher doses of the same color additives used in McCann *et al*. (2007) in Mix A (FD&C Yellow No. 6, FD&C Yellow No. 5, carmoisine, and ponceau 4R). In contrast to McCann *et al.* (2007), Lok *et al.* (2013) did not detect an association between color additive intake and behavior, even though evaluation was also based on parent and teacher assessments and were unable to reproduce the findings of McCann *et al.* (2007), despite using higher doses of the same color additives and a very similar study protocol. Considering the different geographic location and population, and that the instruments for evaluation "validated with local norms in Hong Kong" it is plausible that sensitivity of the outcome to response misclassification was different in this study compared to the McCann *et al.* study.

New Clinical Studies

A search of Clinicaltrials.gov and the Cochrane Library on February 5, 2019 retrieved one possibly new study, "Food Additives Effects on Children With ADHD", reported to be conducted at American University by Kathleen Holton.[3] The last update entered into the Clinicaltrials.gov website for this study on January 11, 2018, reported that the study is in the recruitment phase. From the Clinicaltrials.gov listing, the purpose of this study is to address the unanswered question of whether certain food additives cause behavioral changes in children with ADHD. The study design appears to provide blinding with the use of a matrix, chocolate cookie, in which the added food color additives may not be discernable.

The study at American University proposes to have the participants refrain from ADHD treatment on the day of evaluation and the day after evaluation following exposures to the test article for three days prior to clinical evaluation. The information on the protocol, as listed on the Clinicaltrials.gov, includes: 60 participants, randomized placebo controlled crossover design, mixture of food color additives in a chocolate cookie as study article, six administrations of test article, and two clinic evaluation sessions following exposures to test articles.

[3] Dr. Holton is the last author of *Restriction and Elimination Diets in ADHD Treatment* (Nigg and Holton 2014).

The limited description of the above study provides evidence that several limitations highlighted in the previous studies that attempted to evaluate food color additives association with children behavior are unfortunately repeated, including: small size (expected n=60), the use of high doses (much higher than dietary estimates) of *mixtures* of food color additives, short duration (six days of test article administration and two evaluations), and reliance on the parents for ensuring that the dietary requirements for study participation are met, as the study is based on a "free-living" design. Another important factor that may prove to be an uncontrolled confounder is that the parents are to be educated and encouraged to make changes to their child's diet. Such dietary changes may have a confounding impact on the study outcome, especially the evaluation of behavior by parents and teachers. Overall health improvements, including proper nutrition and adequate sleep are advised for children diagnosed with ADHD and are believed to have a positive impact on a child's behavior (Holton and Nigg 2016; McCarthy, 2018).

IV. Meta-analyses and reviews

Numerous reviews and meta-analyses have been conducted on human studies on color additives and behavior (Table 1).

Table 1: Summary of meta-analyses and systematic reviews of human studies on color additives and behavior

	# of studies included in meta-analysis	# of meta-analyses included in review
Catalá-López *et al.* (2017)	Up to 2*	
Pelsser *et al.* (2017)		2
Heilskov Rytter *et al.* (2015)	8	
Stevenson *et al.* (2014)		3
Sonuga-Barke *et al.* (2013)	8	
Nigg *et al.* (2012)	24^	
Schab and Trinh (2004)	15	

*Two "dietary therapy" trials were included in the Network meta-analysis for efficacy (Table 1), however, details of these two "dietary therapy" trials were not reported.
^Only 11 studies evaluated hyperactive children (Pelsser *et al.* 2017).

Schab and Trinh (2004)

Schab and Trinh (2004) reviewed the available studies (n=15) published from 1976 to September 2002 testing the hypothesis that children with an ADHD diagnosis reacted differently following the consumption of food color additives than children without an ADHD diagnosis. The authors concluded that studies reporting an association between consumption of food color additives and increased behavioral impact in children with an ADHD diagnosis suffered from publication bias and methodology limitations. The authors also reported that there was a reliable effect

linking synthetic colors to ADHD symptoms only in parent ratings, but not in teacher or observer ratings and that the effect was greater when individuals enrolled in studies were previously screened to be responsive to either challenge or restriction diets. Clinical recommendations were not warranted.

Nigg, et al. (2012)

Nigg *et al.* (2012) performed a meta-analysis and identified 24 studies published from 1976 through February 2011 directly evaluating behavioral effects (relevant to inattention and hyperactivity) and color additives. As noted in Table 1, only 11 studies evaluated hyperactive children. Nigg *et al*. (2012) included the McCann *et al.* (2007) study. The authors noted a wide variation in responders between studies. The authors also reported that some children in the reviewed studies saw reduced symptoms of ADHD on restriction diets. However, consistent with Schab and Trinh (2004), this finding was based solely on parental observations and was not representative for studies that evaluated food color additives alone as the test article.

The authors noted that the parental ratings that were related to the greatest effects on behavior were from outside of the US and included food color additives not approved for use in the foods in the US. These investigators also stated that ratings in the studies published after the evaluation by Schab and Trinh (2004) for objective observers and teachers did not change the overall conclusions put forth by Schab and Trinh (2004). As with Schab and Trinh (2004), the authors noted that the small number of available studies that evaluated color additives only likely indicated publication bias and that the studies suffered from methodological limitations, such as low numbers of participants, variations in the baseline behavioral state of the participants, and a range of response effects reported. Based on methodological limitations and efficacy levels demonstrated, the authors reported mixed results based on parental versus objective observer/teacher ratings and indicated that the findings of the studies evaluated cannot be used for clinical or policy recommendations.

Sonuga-Barke, et al. (2013)

In a paper published on behalf of the EUNETHYDIS[4] European ADHD Guidelines Group, using largely the same dataset as Nigg *et al*. (2012), Sonuga-Barke *et al.* (2013) reported similar statistically significant but small (and probably clinically insignificant) effects on symptoms of ADHD from ingestion of color additives, but drew slightly different conclusions than Nigg *et al.* (2012). The authors identified eight papers that evaluated food color additives which met the authors' criteria for inclusion. The meta-analysis revealed a statistically significant, but weak, association between

[4] EUNETHYDIS, the European Network for Hyperkinetic Disorder, is a network of scientists and clinicians dedicated to the study and treatment of children with Attention-Deficit/Hyperactivity Disorder (ADHD) or Hyperkinesis. The EUNETHYDIS European ADHD Guidelines Group has published papers evaluating the data associating color additive intake and ADHD.

restriction of food color additives and improved behavior. However, when the analysis was limited to: (1) four papers that utilized a protocol with low or no pharmacological interventions (because allowing subjects to continue with taking medication to treat ADHD may reduce the ability to detect a potential effect due to food colors) and (2) protocols that were likely blinded, the association between food color additives and behavioral effects was further reduced and ceased to be statistically significant.

The authors concluded:

> "Free fatty acid supplementation and artificial food color exclusions appear to have beneficial effects on ADHD symptoms, although the effects of the former are small and those of *the latter may be limited to ADHD patients with food sensitivities*. *Evidence for the value of behavioral interventions is limited to unblinded ratings made by individuals likely to have an investment in treatment success.* While the most proximal assessment data on neurofeedback, cognitive training, and restrictive elimination diets were potentially more positive, evidence of efficacy from blinded assessments is required before they are likely to be supported as ADHD treatments. The challenge for the future is to improve the efficacy of nonpharmacological interventions on the basis of a growing understanding of ADHD pathophysiology and to better integrate these interventions with pharmacological approaches. Properly powered, randomized controlled trials with blinded, ecologically valid outcome measures are urgently needed, especially in the psychological treatment domain. Future trials should focus across a broader range of child-, parent-, and family-related functional outcomes. *It is important that implementation of adequately blinded designs in future studies does not compromise the quality of the treatment being evaluated."* [emphasis added]

Stevenson, et al. (2014)

In a second publication on behalf of the EUNETHYDIS European ADHD Guidelines Group, Stevenson *et al.* (2014) focusing only on dietary treatments for ADHD, reviewed three meta-analyses related to ADHD and the purported efficacy of the artificial food color elimination diet treatment (i.e. Schab *et al.*, 2004; Nigg *et al*., 2012; Sonuga-Barke *et al*., 2013). They concluded that the effect size was too small to be of value and that the patient population for which color additive elimination diet would benefit remains uncertain. Consistent with previous evaluations, the authors ultimately came to the same conclusions that the methodology used in most of the trials on which the meta-analyses are based were weak, limiting their ability to demonstrate an efficacious treatment for ADHD.

Heilskov-Rytter, et al. (2015)

In a systematic review of the literature, Heilskov-Rytter, *et al.* (2015) identified six diet studies (four were randomized double-blinded crossover design) evaluating the effects of food color additive restriction diets on ADHD, and four challenge studies evaluating whether children's symptoms worsened when exposed to artificial food colors. Because two of the challenge studies were also included as two of the diet studies, a total of eight studies were reviewed. The authors noted the *same protocol limitations and lack of consistent ratings for effects across objective evaluations and parents' evaluations*. Heilskov-Rytter, *et al.* (2015) noted that all the studies evaluated were decades old and that *the children included in those studies likely did not meet the criteria in place in 2015 for an ADHD diagnosis.* [emphasis added]

The authors came to similar conclusions as others before - that the data do not support dietary restriction, including the elimination of food color additives, as an efficacious treatment for ADHD and that more thorough investigations will be necessary to decide whether elimination diets should be recommended as part of treatment of ADHD symptoms.

Pelsser, et al. (2017)

Pelsser *et al.* (2017) performed a critical analysis of two meta-analyses that evaluated the evidence associated with elimination diets for food color additives and ADHD (i.e. Schab, *et al.*, 2004; Nigg, *et al*., 2012). All the studies included in this evaluation have been included in the previously discussed meta-analyses and systematic reviews. From the same data set, yet another set of authors' conclusions mirrored those of previous publications stating that the results of the analysis of the published literature do not support restriction of food color additives for the treatment of ADHD.

Catalá-López, et al. (2017)

In the latest systematic review of pharmacological and non-pharmacological treatments of ADHD up to April 7, 2016, Catalá-López *et al.* (2017) also reported that dietary therapy, which included a color additive restriction diet, lacked evidence as an effective treatment for ADHD. The authors used a Bayesian random-effects model of analysis which had the benefits of allowing for individual effects and evaluating the effects as a range. The use of Bayesian statistical evaluation is gaining greater acceptance in psychological studies for its significant advantages over the frequency-based approaches to better represent the data as a range of behaviors (van de Schoot *et al.,* 2014). Using a different statistical tool designed to better evaluate the uncertainties associated with psychological datasets, the authors came to the same conclusions as observed in previous reviews: that dietary therapy did not have any beneficial effect compared to placebo and cannot be recommended as evidence-based intervention for global functioning and core ADHD symptoms.

Summary

Reviews of the clinical trial literature associated with ADHD and the consumption of color additives have produced neither consistent nor strong association between color additive intake and undesired neurobehavioral symptoms, including ADHD. Furthermore, removal of color additives has not been demonstrated to be an efficacious treatment of ADHD. Interesting and unexplained is the exclusion of and lack of reference to Lok *et al.* (2013) from all the meta-analyses and systematic reviews published after 2013. Lok *et al.* (2013) used essentially the same protocol with higher doses of food color additives as McCann *et al.* 2007 but the findings were not reproducible. None of the studies conducted has succeeded in providing the evidence that would support the conclusion reached by several meta-analyses that an association exists. Moreover, all the studies evaluated in systematic reviews and meta-analysis are methodologically flawed and the validity of any weak evidence that is detected is inconsistent and likely the product of non-objective diagnostic criteria. Consistent with the findings of the meta-analyses described above, an earlier meta-analysis by Kavale and Forness (1983) of studies that evaluated several elimination diets, including the Feingold diet, and challenge trials with color additives found no statistically significant association between color additives and hyperactivity in children. Considering all the above, the null hypothesis has not been rejected by any of the studies conducted to date.

V. Animal Studies

Animal studies in mice and rats designed to detect neurobehavioral effects have been conducted for several food color additives, including the US certified food colors FD&C Red No. 40, FD&C Red No. 3, FD&C Yellow No. 5, FD&C Yellow No. 6, FD&C Blue No. 1, and FD&C Blue No. 2 (Ceyhan *et al.*, 2013; Dalal and Poddar 2009; Dalal and Poddar 2010; Doguc *et al.*, 2013; Doguc *et al*., 2015; Gao *et al.*, 2011; Mohamed *et al*., 2015; Tanaka, 1994; Tanaka, 2001; Tanaka, 2006; Tanaka *et al*., 2008; Tanaka *et al*., 2012; Vorhees *et al*., 1983). Non-US colors, including ponceau 4R, amaranth, azorubine and other were also examined. These studies have been reviewed by both JECFA and EFSA in their respective evaluations of these colors and both expert bodies drew similar conclusions. Animal studies in rats and mice have generally examined proxy endpoints of functional and behavioral neurodevelopment, such as locomotor activity, open-field rearing activity, running-wheel activity, surface righting, negative geotaxis, cliff avoidance, swimming behavior, olfactory orientation, exploratory behavior measured by movement analyzing system, water maze, spatial learning and memory. In these studies, doses ranged from levels below the respective ADIs to levels up to 10% in the diet (Vorhees *et al.*, 1983), or up to 2520 mg/kg bw/day (Tanaka, 1994). Some studies examined molecular effects in brain tissue, such as binding to receptors (Ceyhan *et al.*, 2013), or changes in neurotransmitter levels (Mohamed *et al*., 2015), or biomarkers of oxidative stress in brain homogenates (Gao *et al.*, 2011).

While some of these studies were well-designed and methods were generally fully described (Tanaka 2006; 2008), several limitations were identified and described in detailed discussions. None of the animal studies were considered to provide robust evidence of behavioral effects and could not be used in the risk assessments of either JECFA or EFSA. Both expert bodies concluded that the results did not demonstrate any adverse effects on neurobehavioral development and that revision of the ADIs based on these data was not warranted. The expert reviewers included observations such as the study tested mixtures, effects were not dose related, effects were not consistent, were not considered adverse (e.g. improved cognition, or accelerated achievement of developmental milestones), or the study had other design limitations (e.g. small numbers of animals per dose group) that overall concluded that these studies were of no significance for safety evaluation and precluded them from use in risk assessment.

VI. Exposure to Food Colors

The most accurate current assessment of color additive intake, including intake for children of two age groups, was published by Bastaki *et al*. (2017). This publication demonstrated that the estimated daily intakes (EDIs) for all seven FD&C color additives are a) well below the respective ADI levels established by JECFA for all age groups and b) well below the doses that have been tested in children in clinical trials, for individual colors and combinations of colors.

Table 2: Estimated Intake of FD&C Color Additives – Comparison of EDI to ADI in Children 2-5 years of age - Bastaki *et al.* (2017)

	Max use level EDI, 95th% (mg/kg bw/day)[1,2]	ADI (mg/kg bw/day)	EDI (95th)/ ADI (%)	ADI Reference
FD&C Blue No. 1 Brilliant Blue	0.0476	6	<1%	JECFA, 2017
FD&C Blue No. 2 Indigo carmine	0.0369	5	<1%	JECFA, 2018
FD&C Green No. 3 Fast Green	0.0002	25	<0.01%	JECFA, 2017
FD&C Red No. 3 Erythrosine	0.0114	0.1	11%	JECFA, 2018
FD&C Red No. 40 Allura red	0.217	7	3%	JECFA, 2016
FD&C Yellow No. 5 Tartrazine	0.101	10	1%	JECFA, 2016
FD&C Yellow No. 6 Sunset yellow	0.205	4	5%	JECFA, 2011

[1] Maximum use level, 95th percentile (see Tables 3-9 of published article)

[2] The EDIs are shown in units of mg/kg bw/day for direct comparison with the respective ADI values;

these EDI values correspond to the dark green bars in Figure 1, expressed in units of μg/kg bw/day (1 mg = 1000 μg).

Bastaki *et al*. improved on prior intake estimates by using data from finished product labels between January 2011 and February 2015 to identify the proportion of packaged food products that contain each food color, rather than simply assuming all products in a particular category contain food coloring. Thus, while still employing conservative assumptions that tend to overstate consumption, the Bastaki *et al*. work offers a more accurate, less exaggerated picture of consumption.

Table 2 presents the estimated intake of seven food colors, under the most conservative exposure scenario of the upper percentile (95th %) of food consumption of products containing colors at the maximum use level (Bastaki *et al*., 2017), for children 2-5 years of age, as well as the ADI established by JECFA (JECFA, 2011, 2016, 2017, 2018). The estimated intakes of the seven food colors at the highest exposure scenario were all well below their respective ADIs. For context of the exposure scale, the highest exposure scenario is represented by the dark green bars in Figure 1 for children ages 2-5 and 6-12 years. Bastaki *et al*. also estimated the intake of each of these food colors for other age groups: adolescents, 13-18 years; adults, 19+ years. The estimated intakes for these other age groups were substantially less that the estimated intake for the children 2-5 years of age for all seven food colors on a body weight basis.

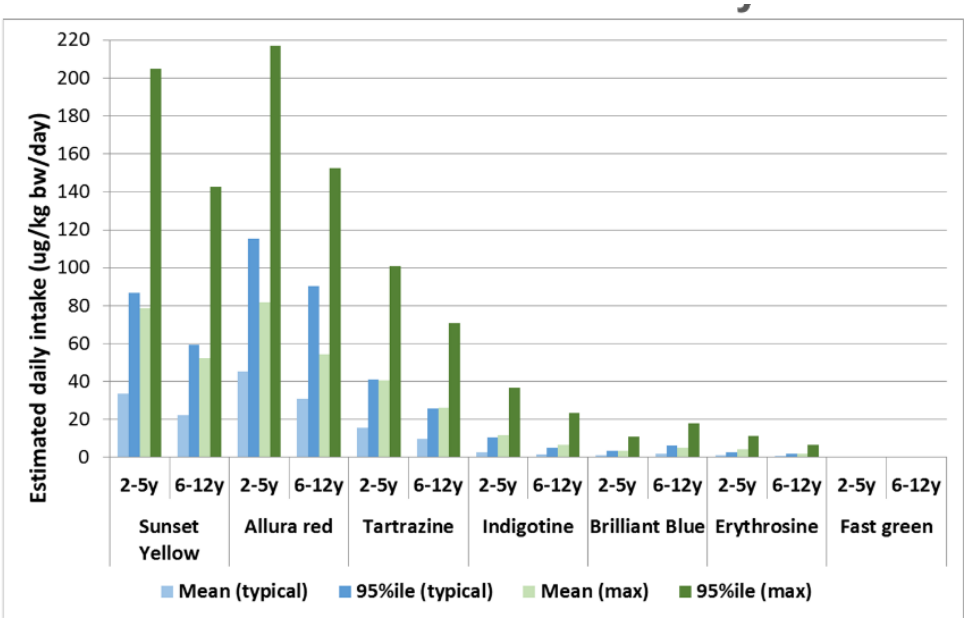
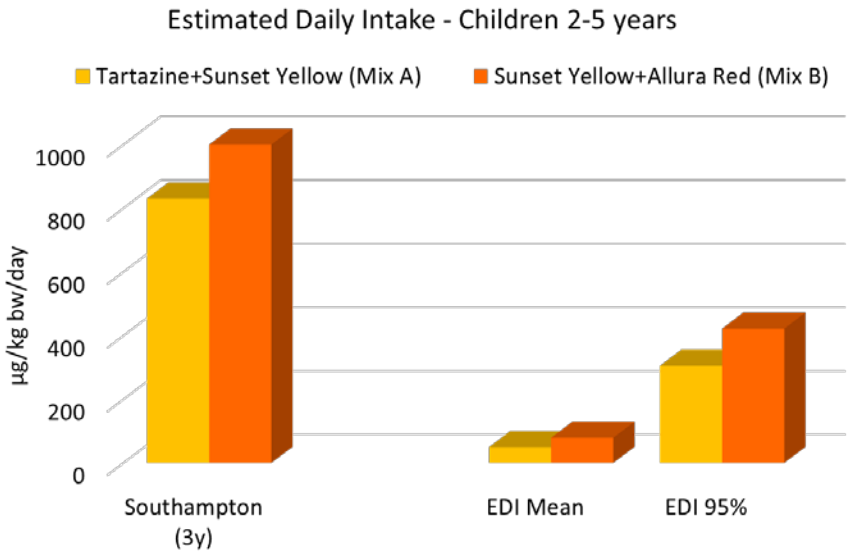


Figure 1 Cumulative Estimated Daily Intake (EDI) of FD&C colors, expressed in micrograms per kg of body weight per day (μg/kg bw/day) for US children ages 2-5 and 6-12 years under four intake scenarios: for average and high consumer, and for typical and maximum use levels of color additive. Mean (typical): intake based on the mean food consumption at typical use levels of color; 95%ile (typical): intake based on the 95% food consumption at typical use levels of color; Mean (max): intake based on the mean food consumption at maximum use levels of color; 95%ile (max): intake based on the 95% food consumption at maximum use levels of color.

More pertinent to the context of the studies conducted with the purpose of detecting an association of color intake with ADHD, the results of Bastaki *et al.*, exposure assessment demonstrate that in the McCann *et al*. study, children were given a combined dose of colors at daily amounts adding up to levels of intake well above the high end (95%) of the estimated range in that age group. First, only two of the four colors in each mix given to children are US FDA certified colors. Therefore, children in the US are not exposed to the full mix of colors given to children in the McCann *et al.* study. Second, the combined doses of the relevant combinations that children may ingest were calculated for the age groups 2-5 years and 6-12 years. The relevant combinations are tartrazine and sunset yellow (included in mix A of the McCann *et al.* study) and sunset yellow and allura red (included in mix B of the McCann *et al.* study). Figure 2 illustrates the scale of McCann *et al*. study administered doses relative to the estimated intakes for the same color combinations reported by Bastaki *et al.*



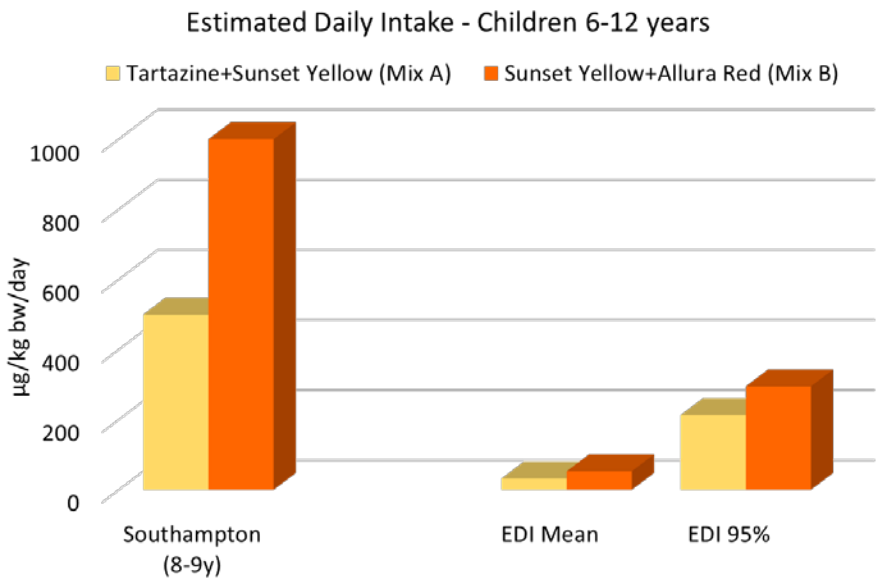


Figure 2 Doses of FD&C colors tested in children by McCann et al., 2007 (Southampton) as part of Mix A (yellow bars) and Mix B (orange bars) relative to the sum of the EDIs (Mean, and 95%) for the respective combinations of these colors as reported by Bastaki et al., (2017). Upper Panel: doses in children 3 years old (McCann et al.) and EDIs in US children 2-5 years; Lower Panel: doses in children 8-9 years old (McCann et al.) and EDIs in US children 6-12 years. Note: unit conversion of daily doses (mg/person/day) used by McCann et al. study to doses per unit of body weight (mg/kg bw/day) is based on default child body weight of 15 kg. The units shown here are micrograms/kg bw/day (µg/kg w/day), (1 mg=1000 µg).

The age groups in the Bastaki *et al.* study overlap with the age groups in the McCann *et al.* study. The combined mean intake of tartrazine and sunset yellow is 49.3 µg/kg bw/day and 32 µg/kg bw/day for children 2-5 years and 6-12 years, respectively. Compared to these intakes, the combined intake of tartrazine and sunset yellow given together in Mix A in the McCann *et al.* study was 16.8 and 15.6 times higher, respectively (830 µg/kg bw/day and 500 µg/kg bw/day, in 3-year-old and 8-9-year-old children, respectively). Compared to the high (95%) estimated exposure for the same color combinations (305 µg/kg bw/day and 213 µg/kg bw/day, respectively for these age groups), the McCann *et al.* study doses were still 2.7 and 2.3 times higher. It is worth noting that adding up 95% values further overestimates intake; therefore, these figures are exceptionally conservative.

The combined mean intake of sunset yellow and allura red is 79 µg/kg bw/day and 53 µg/kg bw/day for children 2-5 years and 6-12 years, respectively. Compared to these intakes, the combined intake of allura red and sunset yellow given together in Mix B in the McCann study were 12.7 and 18.9 times higher, respectively (1000 µg/kg bw/day for both age groups). Compared to the high (95%) estimated exposure for the same color combination (422 µg/kg bw/day and 295 µg/kg bw/day, respectively for these age groups), the Southampton Study doses are still 2.4 and 3.4 times higher.

Therefore, the doses given to children in the McCann *et al.* study are significantly higher (2-3 times greater) than the most conservative exposure estimate which is based

on the assumptions that a) foods contain colors at maximum levels, b) consumption of food quantities are at the higher end (95%) of the dietary range for the respective age group, and c) consumption at this pattern occurs every day.

Prior to Bastaki *et al*., the US FDA analyzed 44 foods and beverages to determine the concentrations of certified food colors (Harp *et al*., 2013). The color concentrations in food products that were measured analytically and reported by Harp *et al.* were comparable to the use levels reported by the industry and used in the Bastaki *et al.* exposure assessment. An exposure assessment based on the analyses by Harp *et al.* was subsequently published by the US FDA (Doell *et al*., 2016). However, the exposure estimates by Doell *et al*. are less accurate than the estimates by Bastaki *et al*. because Doell *et al*. assumed that each color is always present in every product within a food category.

In comparison, Bastaki *et al*. used actual data to incorporate the frequency of color presence in foods. As expected, the more popular colors have a higher frequency of use. However, even for the more popular colors, the frequency of color presence barely exceeds 60% of all packaged products combined, indicating that the assumption by Doell *et al*. that color is present in 100% of the products is unrealistic and overly conservative. We note that the McCann *et al.* study dose levels also exceed the more conservative Doell *et al*. estimated mean and 95% exposure levels under the "Average Exposure Scenario" of the Doell *et al.*, 2016 study (data not shown here).

VII. Risk Assessments of Food Colors by Regulatory Bodies

In order to conduct a risk assessment of food colors, a critical step is to identify any potential hazards. Risk assessments of food colors have been conducted by the US FDA, EFSA, and JECFA; however, these risk assessments are based on endpoints of toxicity other than neurobehavioral effects. Even though these regulatory agencies have reviewed all the available studies on neurobehavioral effects, none of these regulatory agencies have concluded that the evidence that food colors cause neurobehavioral effects. Hazard evaluation for neurobehavioral effects has been determined insufficient to be included in the risk assessment or to warrant consideration in derivation of the ADIs.

OEHHA cannot and should not perform a risk assessment of food colors and childhood neurobehavioral effects, such as ADHD, as the evidence does not support a conclusion that food colors cause neurobehavioral effects in children. In fact, there is no consistent evidence that there is even an association between food colors and neurobehavioral effects, much less a causal relationship. No regulatory agency in the US or EU has drawn any such conclusion. Without clear evidence that food colors cause neurobehavioral effects in children, a risk assessment of food colors may be performed, but it should be based on other endpoints of toxicity, which have been demonstrated in animals or humans to be indeed caused by food colors.

Many of the relevant studies of food colors and neurobehavioral effects in children are studies of mixtures, and in some cases the mixtures contain food colors that are not on the market in the US. The problem with studies of mixtures of food colors is that they do not allow the identification of specific food colors that might pose a hazard, if such hazard exists.

Synthetic color additives have been extensively studied in a wide variety of toxicology studies, including subchronic and chronic toxicity and carcinogenicity, reproductive toxicity, developmental toxicity, metabolism and pharmacokinetics, and genetic toxicology assays. Much of the data on the safety of color additives have been published and are therefore available to the public. The relatively small number of color additives used globally permits more attention to be given to the safety assessment of individual materials.

In the US, color additives are subject to the US FDA's extensive safety assessment procedures as described in the US FDA Redbook. Global standard setting bodies, such as Codex Alimentarius and its international expert scientific committee, JECFA, and regional regulatory agencies such as EFSA, have re-evaluated the full breadth of available synthetic colors to determine if there is any health risk and whether the ADI required adjusting based on the latest toxicological data.

The ADI represents a conservative upper daily intake that is not expected to result in *any* adverse effect in the most sensitive individuals with respect to general and organ-specific toxicity, including reproductive, developmental, neurotoxicity, genotoxicity and other forms of toxicity. The ADI is typically set with the top 10% of most sensitive individuals in mind and, in addition, assumes that humans are 10 times more sensitive than test species, therefore incorporating conservative assumptions. Animal studies examining the potential effects of food colors on neurobehavioral endpoints were included in these regulatory safety reviews. However, none of those studies presented evidence of adverse effects at daily intake that would warrant revision of the established ADIs.

VIII. US Food and Drug Administration

In the US, the nine color additives of interest to OEHHA are approved for use in foods. The US FDA has established regulations for color additives in Title 21 of the Code of Federal Regulations (CFR), parts 70-82. These color additive regulations identify each listed color additive, provide chemical specifications, define uses and restrictions, labeling requirements and applicable certification requirements. The regulations in 21 CFR part 71 describe the premarket approval process for new color additives or new uses for listed color additives. Color manufacturers routinely carry out quality assurance testing on the products they sell to ensure that they meet the specifications laid out in the CFR.

The US FDA defines a color additive in FD&C Act Section 201(t) as a material which is a dye, pigment, or other substance…and when added or applied to a food,

drug, or cosmetic, or to the human body or any part thereof, is capable (alone or through reaction with another substance) of imparting color thereto. A color additive is unsafe if not used in accord with a promulgated color additive regulation, and there is no generally recognized as safe (GRAS) exemption for colors.

The color additives of interest to OEHHA are primarily those color additives subject to US FDA batch certification (21 CFR 74). These are synthetic organic dyes, lakes, or pigments. Batch certification means that every batch of synthetic colors produced in the US must be certified to meet the standards set by the 1938 FDA Food, Drug, and Cosmetics (FD&C) Act, and a sample of each batch of a certified color is submitted to the US FDA for testing to ensure that the color meets the strict specifications set by the US FDA before a manufacturer can legally place the color into intra- and inter-state commerce (FDA, 2018d).

Records are available for each batch of color additive certified by the US FDA (FDA, 2018a). From 2016 through 2018, no batches of Orange B and only one batch of Citrus Red No. 2 were certified. The fact that Orange B and Citrus Red No. 2 have narrow allowances for use combined with a lack of certification by the FDA in the past three years indicates that these two color additives have limited use in the food supply of the US. In fact, Orange B and Citrus Red No. 2 were not included in the US FDA study published in 2016 that estimated intake of FD&C color additives in the US population (Doell *et al.*, 2016).

All certified color additives, including the nine colors in question, are required to be listed by name on the product label in such a way as to allow consumers to make informed choices. Color additives provide an excellent example of the US FDA's efforts associated with ongoing post-market surveillance of food additives, including those color additives included in OEHHA's request for data. The US FDA's policy is to continuously monitor and evaluate any new information and data relevant to the safety of all food ingredients that have been granted approval. Over the last forty years, the US FDA has continued to stay up to date on the latest research on color additives.

Beginning with the promotion of and publication of epidemiological studies in the 1970's investigating potential links between consumption of color additives and behavioral effects in children, the US FDA has initiated formal reviews and communications on color additives. A Food Advisory Committee (FAC) meeting was convened in March 2011 to "…consider available relevant data on the possible association between consumption of certified color additives in food and hyperactivity in children, and to advise the US FDA as to what action, if any, is warranted to ensure consumer safety" (FDA, 2018b). The US FDA FAC determined that "…relevant scientific data did not support a causal link between consumption of certified color additives in food and hyperactivity and other problematic behaviors in children." The FAC also voted against recommending additional information to be disclosed on the product label of food containing certified color additives to ensure their safe use (FDA, 2011b).

In preparation for the 2011 FAC Meeting, the US FDA prepared a comprehensive review and evaluation of the published science associated with color additives and ADHD and other behaviors in children up to August 23, 2010 (FDA, 2010). Thirty-three clinical trials, non-clinical studies, and possible biological mechanisms were evaluated in the review. Following an evaluation of the totality of the evidence included in the review, the US FDA FAC concluded that undesired behaviors observed in children are not a result of intrinsic neurotoxic properties by any of the color additives included in the review. The US FDA hypothesized that any behavioral response observed in children would likely be the result of a predisposition to a "unique food intolerance" in an individual child. The US FDA goes on to state that the cause of the "unique food intolerance" is unknown but may be associated with genetic or epigenetic modes of action.

Additionally, Dr. Mitchell Cheeseman, PhD, then Acting Director of the Office of Food Additive Safety (OFAS) of the Center for Food Safety and Applied Nutrition (CFSAN) at the US FDA, when asked during the FAC's discussion on March 31, 2011 on the need for more testing on color additives, stated that "…if there were a reason to take action to protect consumers, we certainly wouldn't wait on studies to address questions" (FDA, 2011a). It is duly anticipated and expected that the same amount of diligence in reviewing new science on color additives and acting swiftly to protect consumer safety remains to be held by those charged with the safety of color additives at the US FDA. As described earlier, the evidence demonstrating safety of the nine color additives of interest to OEHHA for their intended use in foods has been thoroughly evaluated by the US FDA.

If the US FDA were concerned that its reasonable certainty of no harm safety standard was not being met, it would act accordingly. The US FDA has been challenged on its perceived lack of actions and decisions concerning the color additives in question, such as described in commentary by Bernard Weiss (Weiss, 2012). In a correspondence addressing Bernard Weiss's 2012 commentary, the US FDA responded that it was thoroughly evaluating all evidence and the conclusions provided by the 2011 FDA FAC and would decide how best to move forward to protect public health (Cheeseman, 2012). As no action has been taken to date, it is reasonable to conclude that the US FDA supports the safety of approved color additives for use in the US food supply.

IX. European Food Safety Authority (EFSA)

EFSA has also recently evaluated the available literature, similarly concluding that the studies do not provide compelling evidence to cause concern about potential impacts to ADHD from consumption of food colors. Based on the conclusions of the EFSA Panel on Food Additives, Flavourings, Processing Aids, and Food Contact Materials described earlier and the fact that the clinical significance of the observations reported was unclear, EFSA concluded that the findings reported by McCann *et al.* (2007) did not affect the ADI of the six food color additives in the two mixtures evaluated

by these investigators and thus were not considered to be relevant to the safety of the studied color additives for the general population and public health (EFSA, 2008). EFSA concluded that the evidence currently available did not substantiate a causal link between the individual colors and possible behavioral effects.

Between 2009 and 2014, EFSA has conducted detailed evaluations of six of the nine food colors of interest to OEHHA. None of these six EFSA risk assessments relied on a neurobehavioral effect to revise the ADI for the food color because EFSA has stated there is not sufficient evidence for it to conclude that there is a causal link between any food color and neurobehavioral effects in children. In no case was a neurobehavioral effect, including ADHD, considered to be a sufficiently and convincingly demonstrated hazard to warrant establishing an ADI on that basis. In every case, EFSA established the ADI on the basis of a conventional toxicology study in laboratory animals or a clinical trial in human volunteers.

In fact, some of the six EFSA risk assessments specifically addressed the McCann *et al.* (2007) study. For example, the EFSA risk assessment for FD&C Red No. 40 (i.e., allura red) stated:

- the McCann *et al.* study provides limited evidence that the two different mixtures of synthetic colours and sodium benzoate tested had a small and statistically significant effect on activity and attention in children selected from the general population, excluding children medicated for Attention Deficit Hypersensitivity Disorder, despite the effects not being statistically significant for the two mixtures in both age groups;
- since mixtures and not individual additives were tested in the study by McCann *et al*., it is not possible to ascribe the observed effects to any of the individual compounds, and;
- in the context of the overall weight of evidence and in view of the considerable uncertainties, such as the lack of consistency and relative weaknesses of the effect, and the absence of information on the clinical significance of the behavioural changes observed, the findings cannot be used as a basis for altering the ADI of the respective food colours or sodium benzoate."

Additionally, the UK and EU provide good case studies to evaluate whether risk management interventions like warning labeling or prohibitions have positive outcomes on the neurobiological or neurobehavioral health of European children. In Europe, all food additives are given labeling codes commonly referred to as "E-numbers," e.g., FD&C Red No. 40 is labeled as E129. Without an encyclopedic knowledge of the labeling code system, a consumer may not understand whether a given food product in Europe contains the specific color of interest. Since 2010, the EU has also required a specific warning label for the Southampton study colors, saying that they may have effects on activity and attention in children. It is important to note that while the EU has required a warning label for the colors included in the McCann *et al*. study, this

requirement was not based on adequate scientific evidence or on the opinion of EFSA,[5] but instead on a political decision taken by members of the European Parliament. The UK also called for a voluntary ban on the colors included in the Southampton studies. OEHHA should consider carefully whether there is documented evidence that these interventions have had any impact on neurobehavioral effects in children, including ADHD. To the best of our knowledge, there is no reliable evidence that these risk management practices have reduced the prevalence of ADHD in the UK or EU.

X. Joint FAO/WHO Expert Panel on Food Additives (JECFA)

JECFA re-reviewed a series of food colors and determined they are safe for their intended use and for all users, including children. These reviews were conducted by the JECFA Expert Committee, which consists of an international panel of highly-respected scientific experts in toxicology, epidemiology, nutrition and other fields that meet annually. JECFA re-evaluated food colors include all seven FD&C food colors approved for ingestion in the US and of interest to OEHHA:

- FD&C Blue No. 1 (Brilliant Blue FCF, E133),
- FD&C Blue No. 2 (Indigo Carmine / Indigotine, E132),
- FD&C Green No. 3 (Fast Green FCF)
- FD&C Red No. 3 (Erythrosine, E127),
- FD&C Red No. 40 (Allura Red AC, E129),
- FD&C Yellow No. 5 (Tartrazine, E102), and
- FD&C Yellow No. 6 (Sunset Yellow FCF, E110).

Like EFSA, JECFA has maintained or increased ADIs for these food colors (see ADIs in Table 2), and JECFA did not consider the evidence of neurobehavioral effects in children to be sufficient for revising the ADI. All these JECFA risk assessments were based on endpoints other than neurobehavioral effects.

FD&C Blue No. 1

FD&C Blue No. 1 (Brilliant Blue FCF) was re-reviewed at the 84th meeting of the JECFA Expert Committee in June 2017.[6] The JECFA Expert Committee found "no concerns re carcinogenicity or genotoxicity." Their report identified a one-generation

[5] EFSA AFC (European Food Safety Authority and Additives, Flavourings, Processing Aids and Contact Material). (2008). Assessment of the results of the study by McCann *et al*. (2007) on the effect of some colours and sodium benzoate on children's behavior. *EFSA Journal*. 660:1-54. https://efsa.onlinelibrary.wiley.com/doi/pdf/10.2903/j.efsa.2008.660.

[6] JECFA (2017) Eighty-fourth meeting of the Joint FAO/WHO Expert Committee on Food Additives" (June 2017). WHO Technical Report Series 1007 https://apps.who.int/iris/bitstream/handle/10665/259483/9789241210164-eng.pdf;jsessionid=182D278C306128EA9CFA661D4C2C94C4?sequence=1

reproductive toxicity study that evaluated neurobehavioral development in mice, but the JECFA Expert Committee concluded that the "findings were not robust enough" for purposes of risk assessment.

FD&C Blue No. 2

FD&C Blue No. 2 (Indigo carmine; Indigotine) was re-reviewed at the 86th meeting of the JECFA Expert Committee in June 2018.[7] The JECFA Expert Committee concluded that "dietary exposure to indigotine for all age groups does not present a health concern." JECFA also reviewed of animal neurobehavioral studies which were taken into account in this JECFA conclusion.

FD&C Green No. 3

FD&C Green No. 3 (Fast Green FCF) was re-evaluated at the 84th meeting of the JECFA Expert Committee in June 2017.[8] The JECFA Expert Committee found "no concern" with respect to genotoxicity or developmental toxicity, and it concluded "dietary exposures to Fast Green FCF for adolescents and all other age groups do not present a health concern."

FD&C Red No. 3

FD&C Red No. 3 (Erythrosine) was re-evaluated at the 86th meeting of the JECFA Expert Committee in June 2018.[9] According to their report, "The evidence newly available at this meeting indicates that there are no concerns with respect to genotoxicity and reproductive and developmental toxicity of erythrosine." The JECFA Expert Committee concluded that studies by Tanaka (2001) at the Tokyo Metropolitan Research Laboratory of Public Health and Dalal and Poddar (2009, 2010) at the University of Calcutta "did not provide robust evidence" of behavioral effects and could not be used for purposes in the risk assessment.

[7] JECFA (2018) Eighty-sixth meeting of the Joint FAO/WHO Expert Committee on Food Additives" (June 2018) WHO Technical Report Series 1014
https://apps.who.int/iris/bitstream/handle/10665/279832/9789241210232-eng.pdf?ua=1

[8] JECFA (2017) Eighty-fourth meeting of the Joint FAO/WHO Expert Committee on Food Additives" (June 2017). WHO Technical Report Series 1007
https://apps.who.int/iris/bitstream/handle/10665/259483/9789241210164-eng.pdf;jsessionid=182D278C306128EA9CFA661D4C2C94C4?sequence=1

[9] JECFA (2018) Eighty-sixth meeting of the Joint FAO/WHO Expert Committee on Food Additives" (June 2018) WHO Technical Report Series 1014
https://apps.who.int/iris/bitstream/handle/10665/279832/9789241210232-eng.pdf?ua=1

FD&C Red No. 40

FD&C Red No. 40 (Allura Red AC) was re-reviewed at the 82nd meeting of the JECFA Expert Committee in June 2016.[10] The JECFA Expert Committee addressed the McCann *et al.* (2007) study in its evaluation of FD&C Red No. 40:

> "The Committee noted that it had previously considered a study that investigated the possibility of a relationship between hyperactivity in children and the consumption of beverages containing a mixture of food colours, including Allura Red AC, and a preservative, sodium benzoate [50]. As concluded previously by the Committee (Annex 1, reference 206), this study was of limited value because of inconsistencies in the findings and the use of mixtures of food colours."

The JECFA Expert Committee concluded: "dietary exposure to Allura Red AC for children and all other age groups does not present a health concern." Reviews of animal neurobehavioral studies were also taken into account in this JECFA conclusion but were not considered sufficient or robust enough to be included in the risk assessment.

FD&C Yellow No. 5

FD&C Yellow No. 5 (Tartrazine) was also re-reviewed at the 82nd meeting of the JECFA Expert Committee in June 2016.[11] As in the case of FD&C Red No. 40, the JECFA Expert Committee concluded the McCann *et al.* (2007) was of limited value for its evaluation of FD&C Yellow No. 5. As above, the JECFA Expert Committee concluded the McCann *et al.* (2007) was of limited value for its evaluation of FD&C Yellow No 5 and animal neurobehavioral studies were not considered sufficient or robust enough to be included in the risk assessment.

FD&C Yellow No. 6

FD&C Yellow No. 6 (Sunset Yellow FCF) was re-reviewed at the 74th meeting of the JECFA Expert Committee in June 2011.[12] The JECFA Expert Committee concluded that "dietary exposure of children to Sunset Yellow FCF does not present a health concern." As above, the JECFA Expert Committee concluded the McCann *et al.* (2007) was of limited value for its evaluation of FD&C Yellow No 6 and animal

[10] JECFA (2016) Eighty-second meeting of the Joint FAO/WHO Expert Committee on Food Additives" (June 2016) WHO Technical Report Series 1000 https://apps.who.int/iris/bitstream/handle/10665/250277/9789241210003-eng.pdf?sequence=1

[11] Id.

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neurobehavioral studies were not considered sufficient or robust enough to be included in the risk assessment.

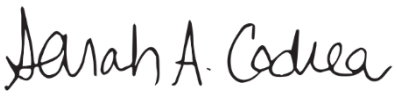
XI. Conclusions

The US FDA and international expert scientific bodies evaluating food safety such as JECFA and EFSA have re-reviewed all safety information available, including clinical studies, for commonly used and approved color additives and have concluded that all these color additives are safe for their intended use in foods and for all users, including children.

Beginning with EFSA (2008), numerous reviews, including work by the US FDA (2011), and numerous groups of authors have specifically evaluated the clinical evidence purportedly linking consumption of color additives to neurobehavioral effects in children with ADHD and in the general population, all concluding no relationship. The results of McCann *et al.* (2007) were the impetus for a renewed interest in the potential for food color additives to negatively affect behavior in children. As regulatory agencies worldwide had dismissed and discounted the findings from McCann *et al.* (2007), Lok *et al.* (2013) likewise examined the findings in McCann *et al.* (2007) in a different population using a very similar protocol and larger doses of the food color additives but was unable to reproduce the results.

The potential effectiveness of dietary interventions, including color additive exclusion diets, as treatment for ADHD has not been demonstrated. The meta-analyses and systematic reviews published in the last 5-7 years coalesce around a common theme – that the current evidence for dietary methods, both restrictive (including color restricting) and pro-nutrient diets, does not support an association between food colors and neurobehavioral endpoints. Additionally, as noted by others, existing studies contain significant methodological limitations. Studies have been and will continue, even with improved study designs, to be limited by the complex etiology of ADHD with no consistent diagnostic criteria, rendering interpretation of findings extremely challenging and making any causal conclusion impossible.

Sincerely,



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XII. References

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