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The Consumer Healthcare Products Association (CHPA)¹ appreciates this opportunity to comment on the Office of Environmental Health Hazard Assessment (OEHHA) Public Review Draft report entitled “Health Effects Assessment: Potential Neurobehavioral Effects of Synthetic Food Dyes in Children.” CHPA member companies marketing over-the-counter (OTC) medicines and dietary supplements containing approved, batch-certified FD&C colors have an interest and expertise in this area.

We note that the current draft of the report contains inaccuracies in estimated color additive exposure values for cough/cold/allergy syrup products indicated for children. Once the correct calculations are applied, these estimated values will be well below Acceptable Daily Intake (ADI) limits established and repeatedly confirmed as safe by expert regulatory bodies such as FDA and the Joint FAO/WHO Expert Committee on Food Additives (JECFA).

While we include a more detailed assessment of this issue below, we ask that OEHHA ensure that a corrected draft report is issued containing these updated values with a corresponding opportunity to comment.

Prior to their use in food, drugs, or cosmetics, the Food and Drug Administration (FDA) must approve color additives. FDA also maintains and regularly monitors postmarket surveillance databases to which consumers, health professionals and industry can submit adverse events believed to be related to color additives (as well as other products).² Color additives have been safely used in a wide variety of consumer products for decades and given the well-established

¹ The Consumer Healthcare Products Association (CHPA), founded in 1881, is the national trade association representing the leading manufacturers and marketers of over-the-counter (OTC) medicines, dietary supplements, and consumer medical devices. Every dollar spent by consumers on OTC medicines saves the U.S. healthcare system more than \$7, contributing a total of \$146 billion in savings each year. CHPA is committed to empowering consumer self-care by preserving and expanding choice and availability of consumer healthcare products.

² The CFSAN Adverse Event Reporting System (CAERS) database collects reports submitted by consumers, health professionals, industry, and others about adverse health events and product complaints related to CFSAN-regulated products. It includes voluntary reports involving conventional foods, including food additives and color additives, and cosmetics, and both mandatory and voluntary reports with respect to adverse events involving dietary supplements. The FDA Adverse Event Reporting System (FAERS) is a database that contains information on adverse event and medication error reports submitted to FDA. The database is designed to support the FDA's post-marketing safety surveillance program for drug and therapeutic biologic products.

role of FDA in regulating these color additives, consideration must be given to the potential for consumer confusion should OEHHA suggest additional regulatory action.

The OEHHA report analyzes the available data on the possible effects of synthetic food dyes (*i.e.*, color additives) on neurobehavior in children, including epidemiologic and animal studies. However, a weight of evidence analysis reveals that a causal association between exposure to food dyes and adverse neurobehavioral effects has not been demonstrated. FDA and other scientific expert bodies have been examining this issue since 1982 and have yet to find strong, consistent evidence linking color additive intake with adverse neurobehavioral effects including Attention Deficit Hyperactivity Disorder (ADHD). A series of robust reviews of the available scientific evidence have routinely found that a causal relationship between color additive intake and adverse neurobehavioral effects does not exist.

Following the initial OEHHA call for data (October 2018) regarding a risk assessment of the potential impacts of synthetic food dyes³ on children, CHPA commented as part of a coalition led by the International Association of Color Manufacturers (IACM). The comments noted the following:

Color additives are safe

- FDA regulates the use of color additives *in food* (and dietary supplements), drugs, cosmetics, and medical devices. Most color additives (including all of the colors examined by OEHHA in their 2020 Report) are subject by law to approval by the FDA and can only be used in compliance with approved uses, specifications, and restrictions following an FDA data review to ensure that a color additive is safe for its intended purposes.
- FDA convened a Food Advisory Committee Meeting (March 2011) to consider available data on a possible association between consumption of certified color additives and hyperactivity. The committee found 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.*” and voted against additional information being added to product labeling.
- Additional authoritative experts, including the European Food Safety Authority (EFSA) and the Joint FAO/WHO Expert Committee on Food Additives -JECFA) have reviewed the potential neurobehavioral effects of food dyes and concluded that the available evidence does not demonstrate a consistent association between intake and adverse behavioral effects.

³ The nine currently approved certified colors noted in the OEHHA report are 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.

Colors do not cause adverse neurobehavioral effects, including ADHD

- Studies used to support an association between intake of color additives and adverse neurobehavioral effects suffer from a series of limitations including examination of mixtures of colors, unverified validity of behavior scores, small sample size and lack of a dose-response relationship.

Consumers can easily identify color additives on product labels and thus avoid exposure should they choose

- Current FDA labeling requires that all color additives added to foods (including dietary supplements) and medicines be specifically listed on the product's ingredient label, allowing consumers to easily assess their presence.
- A recent study⁴ found that estimated daily intakes for all seven FD&C color additives are well below respective ADI levels (all age groups).

CHPA continues to believe that the available evidence does not support an association and does not warrant additional label information warning of potential adverse neurobehavioral effects. Below we briefly cover previous expert regulatory body reviews which have affirmed the safety of color additives, as well as our observations on several sections within the OEHHA report.

⁴ Bastaki M, Farrell T, Bhusari S, Bi X and Scrafford C 2017 Estimated daily intake and safety of FD&C food-colour additives in the US population *Food Addit Contam Part A Chem Anal Control Expo Risk Assess* 34(6):891-904.

Previous regulatory reviews of food dyes

European Food Safety Authority (EFSA)

In 2008, the EFSA Panel on Food Additives, Flavourings, Processing Aids, and Food Contact Materials reviewed a study⁵ examining a possible association between intake of food colors and a preservative (sodium benzoate) on hyperactivity in children. EFSA concluded that there was limited evidence that the colors studied had a statistically significant effect on behavior; the reported effects were not consistent for the two mixtures of color additives; the study findings could not be extrapolated to the general population; and it was not possible to determine sensitivity to individual color additives.⁶ Limitations identified by EFSA included investigation of color mixtures (not individual colors); unverified validity of the behavioral score; lack of information on a dose-response relationship; the absence of a possible biological mechanism underlying the behavioral changes; and use of an unconventional/inadequately justified statistical model.

Between 2009 and 2016 EFSA conducted additional reviews of food colors (including Red No. 40)^{7,8} and found no evidence to support a causal link between intake of these colors and adverse neurobehavioral effects.⁹

Joint FAO/WHO Expert Committee on Food Additives (JECFA)

The Joint FAO/WHO Expert Panel on Food Additives (JECFA) has also recently reviewed the safety of food colors, including all noted in the OEHHA report, and confirmed their safety for all users.^{10,11} These reviews considered available data on possible adverse neurobehavioral effects of certain dyes and found that results were not consistent.

Food and Drug Administration (2011)

Prior to a Food Advisory Committee (FAC) meeting in March 2011, FDA reviewed available published literature on color additives and behavioral effects in children. Their conclusion was that a causal relationship between exposure to color additives and hyperactivity in children had not been established.¹² FDA also noted that there was “...*no definitive evidence of a biological mechanism for effects on behavior.*” The FAC came to the same conclusion.

⁵ McCann D, Barrett A, Cooper A, Crumpler D, Dalen L, Grimshaw K, Kitchin E, Lok K, Porteous L, Prince E, Sonuga-Barke E, Warner JO and Stevenson J2007 Food additives and hyperactive behaviour in 3-year-old and 8/9-year-old children in the community: a randomised, double-blinded, placebo-controlled trial *Lancet* 370(9598):1560-1567.

⁶ 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>

⁷ EFSA Panel on Food Additives and Nutrient Sources added to Food (ANS) Scientific Opinion on the re-evaluation of Allura Red AC (E 129) as a food additive, 2009 EFSA J 7(11):1327.

⁸ EFSA 2015 Refined exposure assessment for Allura Red AC (E 129) EFSA J 13(2):4007.

⁹ <https://www.efsa.europa.eu/en/topics/topic/food-colours>

¹⁰ Joint FAO/WHO Expert Committee on Food Additives, 2016 Evaluation of certain food additives WHO Technical Report Series, 1000.

¹¹ Joint FAO/WHO Expert Committee on Food Additives, 2017 Safety evaluation of certain food additives

¹² Background Document for the Food Advisory Committee: Certified Color Additives in Food and Possible Association with Attention Deficit Hyperactivity Disorder in Children March 30-31, 2011.

Subsequent to this meeting FDA published an exposure assessment for FD&C colors in 600 representative foods.¹³ Their results showed that estimated daily intake of food colors were well below acceptable daily intake values.

Since that meeting there have been a number of reports published examining a possible relationship between ingestion of color additives and ADHD, including two meta analyses,^{14,15} a double-blind placebo-controlled trial¹⁶ and a systematic review.¹⁷ While FDA recently noted¹⁸ that they are aware of these studies, no update of their previous position has been issued based on these findings.

- Nigg et al., 2012 - a meta-analysis of 24 studies assessing color additive restrictions effects on behavior
- Sonuga-Barke et al., 2013 - included 8 trials; participants in food color exclusion trials were often preselected before entering the controlled phase of the trial
- Lok et al., 2013 – 6-week randomized, double-blind, placebo-controlled trial in 130 children; no significant associations observed between food colors and children’s behavior (8-9 y/o)
- Pelsser et al., 2017 – a systematic review of meta-analyses; authors note that restricting color additive intake “should not be advised as general ADHD treatment”

The conclusion from FDA after reviewing this recent evidence published since the 2011 FAC meeting was that “...findings did not support the use of artificial food color exclusions as an efficacious dietary intervention in the nonpharmacological treatment of children with ADHD and related problem behaviors.”¹⁹ A recent review also notes that “[t]here is no clear evidence that supports dietary interventions for the treatment of ADHD”²⁰

¹³ Doell DL, Folmer DE, Lee HS, Butts KM and Carberry SE 2016 Exposure estimate for FD&C colour additives for the US population *Food Addit. Contam Part A Chem Anal Control Expo Risk Assess* 33(5):782-797.

¹⁴ Nigg JT, Lewis K, Edinger T and Falk M 2012 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 Psych* 51(1):86-97.

¹⁵ Sonuga-Barke EJ *et al.*, 2013 Nonpharmacological interventions for ADHD: systematic review and meta-analyses of randomized controlled trials of dietary and psychological treatments. *Am J Psych* 170(3):275-289.

¹⁶ Lok KYW, Chan RS, Lee VW, Leung PW, Leung C, Leung J and Woo J 2013 Food Additives and Behavior in 8- to 9-Year-Old Children in Hong Kong: A Randomized, Double-blind, Placebo-Controlled Trial, *J Dev Behav Pediatr* 34(9):642-650.

¹⁷ Pelsler LM, Frankena K, Toorman J, Rodrigues RP 2017 Diet and ADHD, Reviewing the Evidence: A Systematic Review of Meta-Analyses of Double-Blind Placebo-Controlled Trials Evaluating the Efficacy of Diet Interventions on the Behavior of Children with ADHD *PLoS One* 12(1): e0169277.

¹⁸ In an October 7, 2019 Advisory Committee Meeting of the Science Board to the FDA, Dr. Scott Thurmond, Ph.D., Review Toxicologist, (CFSAN FDA) noted that FDA performed a literature search in “early or mid-2019”

¹⁹ Quote from Dr. T. Scott Thurmond, Ph.D.

²⁰ Cagigal C, Silva T, Jesus M and Silva C 2019 Does Diet Affect the Symptoms of ADHD? *Curr Pharm Biotechnol* 20(2):130-136.

Comments on the “Epidemiologic Studies of Synthetic Food Dyes and Neurobehavioral Outcomes in Children”

Diagnosing ADHD is a complex process and the criteria underlying this diagnosis have continued to evolve, making any comparison of studies difficult. The studies contained in OEHHA’s Health Effects Assessment: Potential Neurobehavioral Effects of Synthetic Food Dyes in Children, do not fully support a conclusion that consumption of synthetic food dyes is associated with adverse neurobehavioral outcomes in children.

Results from a 2012 meta-analysis,²¹ which covered largely the same studies contained in the OEHHA report, suggested that only a weak conclusion could be drawn due to the extent of heterogeneity in study results. The review by OEHHA includes all 24 studies in Nigg et al plus 4 additional studies (2 that were pilot studies and 2 other studies with samples sizes of less than 3). These additional studies would not likely have changed the assessment reported by Nigg et al. (2012).

Nigg et al. stratified their analyses by who conducted the neurobehavioral assessment (parent or teacher/observer) because this was a known source of heterogeneity. The combined estimate when parents did the testing was 0.18 (95% CI 0.08–0.29), a moderate and statistically significant association. OEHHA also noted that assessments by parents were more likely to report a statistically significant effect. The combined estimate when a teacher (or observer) did the testing was 0.07 (95% CI -0.03–0.18), a much smaller, nonsignificant association.

Nigg et al also prespecified other subgroup analyses of interest, all stratified by assessor. A subset of studies examined only FDA-approved colors. The combined estimated for parent assessed studies for FDA approved colors was .13 (95% CI -0.04–0.30), which was small and not statistically significant. The corresponding combined estimate for teacher/observer assessors was .12 (95% CI -0.01–0.35), another nonsignificant result.

Another source of variability was whether the outcome measure was validated, which is considered to be of higher quality and more reproducible. When the analysis was confined to studies with a validated outcome, the parent assessed result was 0.13 (95% CI 0.00–0.25), which is small and of borderline significance. For teacher/observer assessors, the result was small and not statistically significant (0.10; 95% CI: -0.01–0.21).

The combined effect estimate in studies including only hyperactive children as assessed by a parent was .21 (95% CI -0.02–0.43), which is where one might expect the largest effect. No corresponding analysis was available for teacher/observer assessors.

Many of the reviewed studies (as presented in Table 2.1 in the OEHHA report) had small sample sizes (nearly 60% of the studies included 20 or fewer children), inadequate definition of the effect size, gaps in the description of the cohort selection/recruitment process, and/or a lack of effect in the measured outcome. Indeed, OEHHA notes in their report that studies with larger numbers of participants and studies involving higher doses showed “*weak and inconsistent*” results. The smallest sample in the Nigg et al review was 4 and the largest was 277.

²¹ Nigg JT, Lewis K, Edinger T, Falk M 2012 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 Psych* 51(1):86-97.

A dose-response relationship was identified in one of three studies²² in which this information was available, but the effect was weak. Further, the authors noted that reactors were not well-defined and that the dose-response was not consistent in the non-reactors. Nigg et al. also assessed dose response in a meta regression analysis separately for parents and teacher/observers. For both analyses the association was essentially zero.

The study conducted by Bateman et al. (2004)²³ is one of the few reported clinical trials that seems to support a possible effect of color additives on behavior, having a large sample size and showing statistically significant effects for both the improvement of hyperactivity while on the elimination diet and the reappearance of hyperactivity upon re-challenge. However, increases in hyperactivity were only observed upon parental evaluation not following evaluation by professional psychological examinations.

In summary, while the data come from randomized clinical trials, results suggest any associations between color additive intake and adverse neurobehavioral effects are inconsistent and weak at best. The studies do not provide strong, reliable evidence that consumption of color additives is associated with adverse neurobehavioral outcomes in children.

Comments on the “Exposure Assessment” (Exposures to FD&C food dyes from over-the-counter medications, prenatal vitamins)

In their report, OEHHA presents exposure assessments for certain OTC medications indicated for children (pain reliever/fever reducer syrups; cold, cough and allergy syrups as well as dietary supplements). The methodology employed to measure color additive levels in these products is described in greater detail in a recent publication.²⁴ Based on results presented in the report,²⁵ OEHHA notes that exposures above the ADI (for FD&C Red No. 40) would occur with certain brands of children’s pain reliever/fever reducer syrups or cold, cough and allergy syrups if the maximum labeled daily dose were to be taken. These values were noted to be greater than 10-40 times higher compared to estimated intakes from food (based on data from NHANES).²⁶

In a recent discussion²⁷ held between CHPA members, OEHHA and UC Davis regarding the methodology described in the Lehmkuhler et al., 2020 paper and referenced in the OEHHA report²⁸, an error was identified in the calculations used to estimate color additive exposures from children’s cough/cold and allergy syrups. This error led to erroneous values being reported

²² Rowe KS and Rowe KJ 1994, Synthetic food coloring and behavior: A dose response effect in a double-blind, placebo-controlled, repeated-measures study. *J Pediatr* 125:691-698.

²³ Bateman B, Warner JO, Hutchinson E, Dean T, Rowlandson P, Gant C, Grundy J, Fitzgerald C and Stevenson J 2004 The effects of a double blind, placebo controlled, artificial food colourings and benzoate preservative challenge on hyperactivity in a general population sample of preschool children *Arch Dis Child* 89(6):506-511.

²⁴ Lehmkuhler AL, Miller MD, Bradman A, Castroina R and Mitchell AE 2020, Certified food dyes in over the counter medicines and supplements marketed for children and pregnant women. *Food and Chemical Toxicology* 143: 111499 doi.org/10.1016/j.fct.2020.111499

²⁵ As depicted in Tables 6.17 (Brand 2) and 6.18 (Brands 4 and 5)

²⁶ Data from Table 6.10

²⁷ Telephone conference held between members of CHPA, OEHHA and UC Davis on November 3, 2020

²⁸ ‘Health Effects Assessment: Potential Neurobehavioral Effects of Synthetic Food Dyes in Children’ (August 2020).

for the children’s pain reliever/fever reducer syrups and cold, cough and allergy syrups noted in both the Lehmkuhler et al. paper as well as the OEHHA report.

CHPA asks that OEHHA issue a revised report, with a corresponding request for comments, providing corrected estimated exposure values as well as additional detail of the methodology utilized to measure FD&C colors in OTC medicines, dietary supplements and foods as well as corrections to the following:

- Erroneous values noted for estimated exposure (in mg/kg/day) to FD&C Red No. 40 and Blue No. 1 (off by a factor of 100)²⁹
- Statements regarding hazard indices (margins by which estimated exposures exceed an ADI)
- Incorrect statements in the report related to exposures for FD&C Red No. 40 being above the Acceptable Daily Intake (ADI).³⁰
- We also note that OTC medications studied in this report are not indicated for chronic use.³¹

Comments on “High-throughput screening assays”

OEHHA’s review of the data available from high throughput screening assays (ToxCast) measuring events possibly involved in neurodevelopment noted a relatively high number of active assay hits compared to a very low number of hits observed in a recent publication.³² As described in the Chappell et al. 2020 paper, of critical importance is obtaining and accounting for information on chemical purity and stability as well as issues, such as cytotoxicity, which can potentially interfere with assay results. Indeed, OEHHA excluded a number of high throughput screening assays based on a lack of chemical quality information or issues associated with analytical results in their 2019 report ‘Evidence on the Carcinogenicity of Acetaminophen’.³³

Importantly, OEHHA did recognize the limitations associated with these results, noting that “...activity for the food dyes ranged widely making it difficult to make strong correlations between what was observed, and adverse effects or mechanisms that have been reported in the literature”. Currently, regulatory agencies such as the Environmental Protection Agency and the Center for Computational Toxicology and Exposure do not use high throughput screening assays for either hazard or risk assessment owing to a disconnect between what is measured in a high throughput screening assay and the outcome of concern.³⁴

²⁹ e.g., see page 269 of the report

³⁰ As depicted in Tables 6.17 and 6.18

³¹ OEHHA notes in several instances (pp. 269,279,285) that “children with allergies or other health conditions may receive such medication chronically” without providing support for this assertion.

³² Chappell GA, Britt JK and Borghoff SJ 2020 Systematic assessment of mechanistic data for FDA-certified food colors and neurodevelopmental processes *Food Chem Toxicol* 140: 111310.

³³ <https://oehha.ca.gov/media/downloads/crn/acetaminophenhid092019.pdf>;

³⁴ Villeneuve DL, Coady K, Escher BI, Mihaich E, Murphy CA, Schlekot T and Garcia-Reyero N 2019 High Throughput Screening and Environmental Risk Assessment – State of the Science and Emerging Applications, *Environ Toxicol Chem* 38(1):12-26.

Comments on “Animal Neurotoxicology”

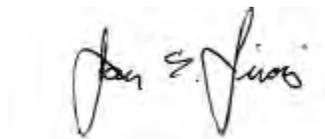
OEHHA reviewed a number of animal studies of potential relevance to the current assessment, concluding that “...effects on activity, and learning and memory were reported in both young and adult animals.” However, OEHHA did not evaluate these animal studies for quality or reliability using any type of published method. In addition, for several studies the purity of the test substance was not reported, as such one cannot determine if the observed effect was due to the color additive or to an impurity. Much of this evidence has previously been evaluated (*e.g.*, by FDA, JECFA and EFSA). The lack of a robust, predictable animal model for assessing the effects of color additives on behavior has been noted.³⁵

Conclusion

When viewed in its entirety, the available evidence informing a possible link between color additive intake from a number of different sources (*e.g.* foods, drugs, cosmetics) and adverse neurobehavioral effects does not demonstrate a causal effect. Each source of evidence that OEHHA has identified in the current report (human epidemiology, animal studies, in vitro high throughput screening assays and estimates of exposure) suffers from limitations and inconsistencies in individual study results. Although some results suggest that certain sensitive populations may exist, color additives are required to be listed on product labels and as such, consumers can easily avoid products containing them.

Thank you again for the opportunity to submit these comments.

Sincerely,



Jay E. Sirois, Ph.D.
Senior Director, Regulatory and Scientific Affairs
Consumer Healthcare Products Association

³⁵ Quote from Dr. T. Scott Thurmond, Ph.D., FDA Review Toxicologist - “...as far as I know the animal models are not the best choice for those types [assessment of hyperactivity] of studies.”; at an October 7, 2019 Science Board to the FDA meeting Expert Panel meeting, transcript available at <https://www.fda.gov/media/135001/download>