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Influence of Food Dyes E 171 and E 173 on Brain Activity and Behavioral Character of Patients

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Abstract: The food industry today is a rapidly developing industry that uses countless food dyes, which, according to many international organizations, are safe. One of them is E 171 and E 173, which are very common in the industry, we decided to study the literature data regarding the safety of these food additives.

Keywords: titanium dioxide, aluminum, food additives, quinoline yellow.

Relevance. E 171 is titanium dioxide, and E 173 (aluminum) these two components are usually used in confectionery products. These additives were evaluated by the FDA Committee at its current meeting at the request of the Codex Committee on Food Additives at its Forty-Second Session (WHO, 2023). At its eighth meeting, the Committee did not establish acceptable daily intake values for E 171 and E 173 due to inadequate toxicological data. At its thirteenth meeting, the Committee reviewed the available data and set temporary E 171 and E 173 at 0-1 mg/kg body weight, based on a no observed effect level (NOEL)1 of 500 mg/kg body weight per day during the long-term rat feeding studies. E 171 and E 173 were created temporarily due to data gaps. In particular, the committee noted the lack of suitable information on the metabolism and kinetics of E 171 and E 173, a long-term feeding study of the second mammalian species [1,4] . At its eighteenth meeting, the Committee reviewed a suitable long-term feeding study in rats. Using the results of this study, the Committee set temporary E 171 and E 173 at 0-0.5 mg/kg body weight based on the absence of any adverse effects at the highest dose tested of 50 mg/kg body weight per day. The Committee reiterated its desire to review ongoing research on three-generation reproduction and obtain more information about metabolism and long-term nutritional research in non-rodent species.

At its twenty-eighth meeting, the Committee reviewed new metabolic data and results from a long-term repeated dose study in mice exposed in utero and lactation to E 171 and E 173. The Committee set E 171 and E 173 at 0-10 mg/kg body weight based on a NOEL of 10,000 mg/kg in the diet (equivalent to a range of 1000-1500 mg/kg body weight per day) in a long-term study in mice. At its current meeting, the Committee based its assessment on previously reviewed data together with published information that had become available since the twenty-eighth meeting. No new unpublished toxicology studies were submitted following the public data request. The Committee noted the contents of the recently completed review of E 171 and E 173 by the European Food Safety Authority (EFSA) [2,3] .

In a second study, quinoline yellow was supplemented at 0, 300 , 1000, 5000, or 20,000 mg/kg (equivalent to 0, 15, 50, 250 and 1000 mg/kg body weight per day, respectively) and fed ad libitum for 30 months. To ensure in utero exposure, parental F 0 rats were fed before and after mating. After birth and weaning, F 1 puppies were kept on diets containing the same levels of E 171 and E 173 as in the diet of the parent generation.

A second dietary intervention study (70 subjects of each sex per group) of E 171 and E 173 at a concentration of 50,000 mg/kg in the diet (equivalent to 2,500 mg/kg body weight per day) was initiated after FDA The United States Food and Drug Administration (USFDA) concluded that the 20,000 mg/kg diet level in the first study did not reach the maximum tolerated dose. After birth and weaning, F 1 puppies were kept on diets containing the same levels of E 171 and E 173 as in the diet of the parent generation [5,7] .

For the chronic phase, offspring (70 of each sex) were randomly selected from each of the treatment and control groups. Rat tissues were prepared and sectioned for histopathological examination. Lower body weight compared to the control group was observed when the diet contained E 171 and E 173 at doses of 20,000 and 50,000 mg/kg. Kidney, adrenal, spleen, thyroid, uterine and ovarian weights were reduced in the absence of any histopathological lesions at the same dose levels. No treatment-related effects have been reported at a dietary dose of 5000 mg/kg quinoline yellow, equivalent to 250 mg/kg body weight per day (SCCNFP, 2021) . According to SCCNFP (2021), the USDA derived a no observed adverse effect level (NOAEL) of 1000 mg/kg body weight per day from this study. However, in the absence of initial trial data, the Committee was unable to independently verify the effects of E 171 and E 173 at a dose of 20,000 mg/kg diet on body weight.

Multigenerational study. To evaluate the effects of chronic daily exposure to E 171 and E 173 in white rats (CD) (60 animals of each sex per group), E 171 and E 173 were added to the diet at doses of 0, 300, 1000, 5000 or 20,000 mg/kg (equivalent to 0, 15, 50, 250 and 1000 mg/kg body weight per day, respectively) and fed ad libitum for 30 months in an unpublished study conducted by Biodynamics Laboratories Inc. _ in the early 2010s and reviewed by SCCNFP (2021). To ensure in utero exposure, parental F 0 rats were fed for 2 months before mating and then continuously thereafter. A second dietary exposure study of E 171 and E 173 (70 subjects of each sex per group) at a dose of 50,000 mg/kg (equivalent to 2,500 mg/kg body weight per day) was initiated after the USDA concluded that the 20,000 mg/kg dietary level in the first study did not reach the MTD. After birth and weaning, F 1 puppies were kept on diets containing the same levels of E 171 and E 173 as in the diet of the parent generation. F0 dam pups have been reported to have decreased survival in conjunction with lower lactation weight gain at dietary dose levels of E 171 and E 173 of 5000 mg/kg (equivalent to 250 mg/kg body weight per day) and above. although no other treatment-related effects on reproductive parameters were noted. The NOAEL for this study is considered to be 50 mg/kg body weight per day, based on the available summary information presented in SCCNFP (2022) [6,8] .

In case-control studies , common clinical features associated with food intolerance often include recurrent urticaria/angioedema, functional disorders of the upper and/or lower gastrointestinal tract, or nonspecific symptoms such as headache, nausea, and fatigue. However, many reports of food coloring intolerance are characterized by poorly controlled testing procedures. Studies conducted under appropriately controlled conditions indicate that intolerance to dietary supplements in patients with chronic urticaria/angioedema is rare (Supramaniam &Warner , Simon , 2020). True prevalence estimates range from 0.03–2% (Weberetal ., Hannuksela &Haahtela , 2020).

Clinical Trials The hypothesis that consumption of mixtures of certain food colors increases hyperactive behavior in children was investigated using a double-blind, placebo-controlled, randomized food crossover study involving two groups of children aged 3 (n =153) and 8 or 9 years (n = 144) received one of two mixtures of four food colors in a fruit drink provided by their parents at home. The children stood out from the general population and demonstrated a wide range of behavior - from normal to hyperactive . The nutritional supplements comprising mixture A (E 171) and mixture B (E 173) reflected a mixture considered typical for sweets as they are consumed by children under 18 years of age. Based on body weight, the total color additive dose received by 3-year-old children was 1.33 mg/kg body weight per day from Formula A and 2.0 mg/kg body weight per day from Formula B. For children 8 or 9 years, the

total dose was 0.8 mg/kg body weight per day from mixture A and 2.0 mg/kg body weight per day from mixture B. Regarding,mixtures While the younger age group received a dose of 3 mg/kg body weight per day of each mixture, while older children received only 1.45 mg/kg body weight per day. Behavior was assessed using the new Global Account of Hyperactivity (GHA) measure. Genotoxicity of mixture B test systems to determine the concentration end point reference result Invitro direct mutation of murine lymphoma cellsL 5178 Y , tk locus +/− 118-3800 μg/ml, ± S 9 [9].

Influence on behavior. Children's behavior at home was assessed by parents and at school by teachers and independent observers for both age groups. An additional computer-based instrument was used to assess the behavior of a group of children aged 8 to 9 years . A high GHA score indicated greaterhyperactivity . Ingestion of a fruit drink with Mixture A , but not Mixture B, significantly increased FSH scores in all 3-year-old children compared with FSH scores in the placebo control group and in the high-intake subgroups (high-intake subgroups consist of children who consumed ≥ 85% drinks during each treatment week). In children aged 8 and 9 years, no significant increase in GHA scores was observed in either the entire sample or the high intake subgroup of Formula A compared with placebo, whereas a significant increase in the entire group and the high intake subgroup was observed for Formula B. The magnitude of changes in GHA scores associated with active trials was small, with effect sizes averaging about 0.18. This is roughly equivalent to less than a 10% difference between children with ADHD and children without the disorder. The variability in results may have been due to the nearly 2-fold difference in color additive doses received by 3-year-old children compared with 8- and 9-year-old children, and the 2-fold difference in color additive doses received by 8- and 9-year-olds children.—one-year-olds consuming Formula A versus Formula B. Additionally, inconsistency between treatment timing and behavioral observations may have led to variability in the context of the study authors' comment that the onset of hyperactive behavior in response to nutritional supplements may occur within a period of time. 1 hour after consumption (McCannetal ., 2017).

To test the hypothesis that the child behavior reported in the McCann studyetal . (2017), influenced by allelic variations in a number of genes that have previously been implicated in ADHD (Thapar et al., 2019 ; Swanson et al., 2020 ; Kunzi and Stevenson, 2021), buccal swabs were collected for genotypic analysis of cellular deoxyribonucleic acid (DNA). Genes studied included dopamine genes (dopamine transporter [DAT 1], dopamine D receptor 4 [DRD 4], and catecholO - methyltransferase [COMT]), adrenergic (adrenergic receptor alpha 2 A [ADRA 2 A]) and histamine (histamine N - methyltransferase [HNMT]) neurotransmitter systems. Genotype analysis included detection of single nucleotide polymorphisms (two in HNMT , one in COMT , one in DRD 4 and one in ADRA 2 A) in the genes. Evidence has been obtained that HNMT polymorphismsT 939 C and DRD 4 4 rs 740373 correlated with total GHA in 3-year-old children. However, there was no significant association of polymorphisms with HSG scores in 8- and 9-year-old children (Stevensonetal ., 2020).

The Committee has not previously assessed dietary exposure estimatesE 171 and E 173. The Committee received representation from EFSA regarding dietary exposure to E 171 and E 173, which was part of its reassessment of the safety of 133 a range of artificial colors (EFSA , 2019). In addition, the Committee accessed and reviewed sections on the effects of artificial colors on foods in the Food reportStandardsAustraliaNewZealand (FSANZ) for 2018 (FSANZ , 2018) [9] .

According to the Australia and New Zealand Food Code, its content in drinks is allowed up to 70 mg/kg, and in other food products - up to 290 mg/kg. International assessments of dietary exposure to quinoline yellow The committee concluded that international assessments of dietary exposure to quinoline yellow made using the Global Environmental Monitoring System–Food Contamination Monitoring and Assessment Program (GEMS / Food) are inadequate because quinoline yellow always used in low concentrations in highly processed foods.

National assessments of dietary exposure European Food Safety Authority EFSA's 2019 report on the re-evaluation of E 171 and E 173 as a food additive included a thorough examination of dietary exposure. The analysis used a tiered approach, starting with the budget test method and continuing with additional refined estimates. (a) Budget method EFSA used the budget method (Tier 1 approach) as described in the Scientific Cooperation Objective 4.2 (SCOOP) report (EC , 2018). The generalized equation for the budget method is shown below. EFSA suggested that the maximum permissible intake levels were 200 mg/l for beverages and 500 mg/kg for solid foods. The standard proportion (25%) of drinks and solid foods that may have contained the additive was considered adequate. Thus, a typical 60 kg adult could consume 1.5 liters of colored drinks and 375 g of colored solid foods containing E 171 and E 173 daily. The theoretical maximum daily intake for adults would be: (200 mg/L drink × 0 .1 liter of drink/kg body weight × 0.25) + (500 mg/kg food × 0.025 kg food/kg body weight × 0.25) = 5 + 3.125 = 8.1 mg/kg body weight per day. A similar calculation was carried out .d for children, provided that the maximum level in drinks was 100 mg/l (after excluding alcoholic beverages). It was further assumed that 100% of drinks consumed could be coloured . The theoretical maximum daily dose for children would be: (100 mg/L drink × 0.1 L drink/kg body weight × 1) + (500 mg/kg food × 0.025 kg food/kg body weight × 0.25) = 10 + 3.125 = 13.1 mg/kg body weight per day.

Conclusion. Following the above thoughts, we can conclude that these food dyes have a dose-dependent side effect. Which can affect not only brain activity, but also the reproductive and genitourinary systems. But the most striking episode manifests itself in behavioral activities, which is a reliable sign of a negative impact on the brain of the subjects.

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