Comments on "Health Effects Assessment: Potential Neurobehavioral Effects of Synthetic Food Dyes in Children" PUBLIC REVIEW DRAFT August 2020

This is a wide ranging and meticulously conducted set of systematic reviews on synthetic food dyes and their impact on children.

My expertise is on the epidemiology and long-term outcome of behaviour problems in pre-school children, including in conducting studies on the roles that food additives and genetics play in behaviour problems, particularly hyperactivity. Therefore, I have focused my comment primarily on the material in Chapters 2 and 5. However I think it important to note that the animal toxicology literature summarised on p.283 concludes:

"Nonetheless, many animal studies conducted in a number of laboratories have found evidence of changes in behavior. Thus, the animal studies provide evidence that the synthetic food dyes may contribute to adverse behavioral effects in children."

The coverage of the material in Chapter 2 is a very impressive and comprehensive review of the studies undertaken to date. Reference is made to the Stevenson et al. (2010) study identifying polymorphisms in the histamine N-methyl transferase (HNMT) gene which moderated the impact of food dyes on behaviour. This is a potentially important indicator of possible pathways via which food dyes can influence behaviour. The report correctly suggests that this finding has not been replicated. However, as far as I know, no-one has attempted to replicate it using a RCT challenge of food dyes in children. It should be noted that there is accumulating evidence of the role of HNMT in brain functions (Yoshikawa et al. (2019). Histamine N-transferase in the brain. International Journal of Molecular Sciences, 20, (3): **DOI:** 10.3390/ijms20030737).

I agree with and wish to underscore the statements in Chapter 5 Hazard Identification that ADHD is considered to exist on a spectrum of neurobehavioral symptoms and severity. The evidence from the Bateman et al. (2004) and McCann et al (2007) studies is that the presence of dyes in the diet increases the population mean on measures of hyperactivity by about one fifth of a standard deviations (effect size = 0.20). This is very similar to the effect size reported for high quality studies in the Nigg et al. (2012) meta-analysis (effect size = 0.23).

This 0.20 effect size needs to placed in a public health context. It is very close the effect of environmental lead on children's IQ. Grosse et al. (2002) [Environmental Health Perspectives, 110, 563-569] concluded that ""These calculations imply that, because of falling Blood Lead Levels, U.S. preschool-aged children in the late 1990s had IQs that were, on average, 2.2–4.7 points higher than they would have been if they had the blood lead distribution observed among U.S. preschool-aged children in the late 1970s ". Taking a mid-point effect of 3.5 IQ points and given the standard deviation of IQ is 15, this produced an effect size of the gain from the reduction of lead of 3.5/15 = 0.23. This suggests that the gains for children's behaviour from the removal of dyes would be equivalent to the benefit obtain for IQ of the reduction of lead exposure.

It is important to recognise that this 0.20 is only an average figure – some children's hyperactivity scores will increase more than this, other less so. A feature of this variation in the response to dyes is that it is normally distributed. Below are appended unpublished graphs showing these distributions from the McCann et al (2007) study. There is no evidence of a sub-group that are much more severely affected than others. This makes it dubious to attempt to identify the number of children affect by dyes because this is not an all or none effect. It is a question of degree. When we examined factors that might influence the degree of change in Bateman et al. (2004) we found no effects on the degree of behaviour change under dye exposure of initial hyperactivity level or the presence of

atopy (allergic sensitivity). In McCann et al. (2007) we found no effect on the degree of change of gender, pretrial diet, mothers education or social class. The only factors influencing vulnerability that we were able to identify were the HNMT polymorphisms reported in Stevenson et al. (2010). There is then no readily available method of identifying which children are most affected.

Exposures to food dyes can be seen as shifting more children towards more severe symptoms. The effect of this shift is enhanced at the high end of the distribution, thereby increasing the numbers of those who meet the criteria for the clinical diagnosis of ADHD, resulting in large costs for society.

I fully support the conclusions in the final paragraph of section "8.1 Summary of human studies." This summary is balanced and gives due appreciation of the challenges in conducting research on human subjects. It also rightly emphasises the paramount value of findings from well-conducted randomised control trials on this topic.

On p.286 it is recognised that "Research is generally a long-term proposition." This is true. Adequately powered RCTs on children from the general population are time consuming and expensive. Their complexity is markedly increased if they are designed to test the effects of combinations of dyes in mixtures. Whatever further RCTs on the topic are commissioned, it must be acknowledged that there is already evidence that "neurobehavioral effects of synthetic food dyes" are found in children. Harm can be prevented by reduction in exposure to food dyes before further studies are completed. The harm includes not only the immediate symptoms but also later educational difficulties and antisocial behaviour, which can have lifetime consequences - as is shown by the following finding: "There were strong linear relationships between early hyperactivity and later adverse outcomes. Adjustment for other childhood variables suggested that early hyperactivity was associated with continuing school difficulties, problems with attention and poor reading in adolescence." (McGee et al. (2002) Journal of Child Psychology and Psychiatry, 43, 1004-1017).

The following final conclusion/recommendation is entirely justified:

"At a minimum, in the short-term, the neurobehavioral effects of synthetic food dyes in children should be acknowledged and steps taken to reduce exposure to these dyes in children."

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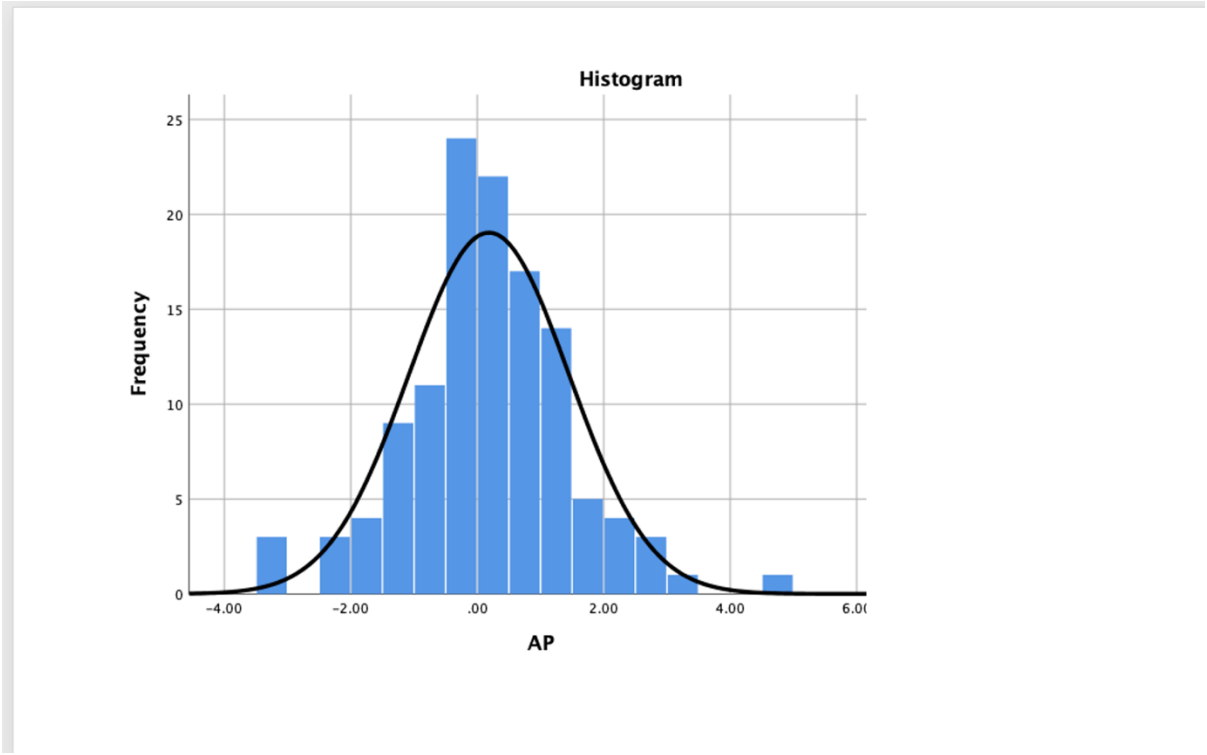
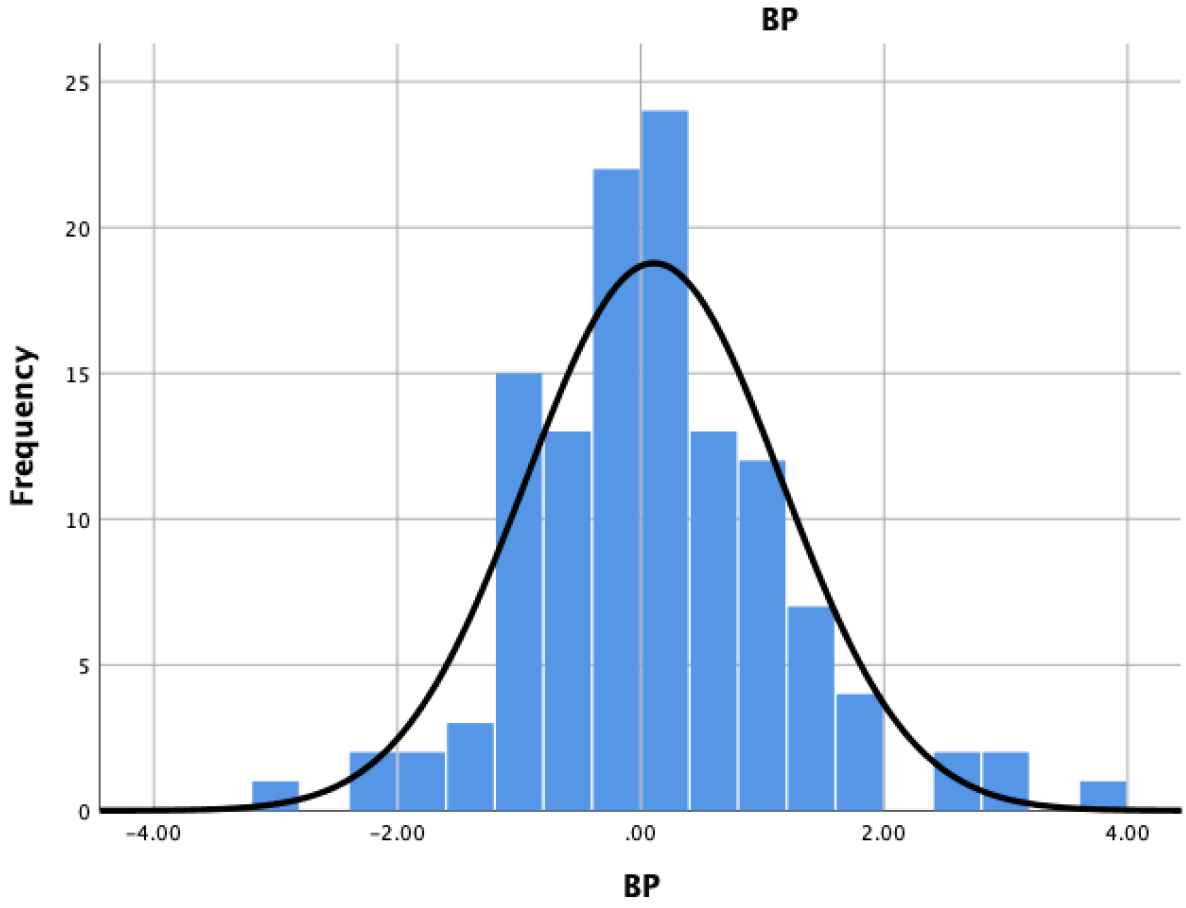
18 September 2020

Appendix of unpublished graphs showing the distributions of the response to dyes from the McCann et al (2007) study

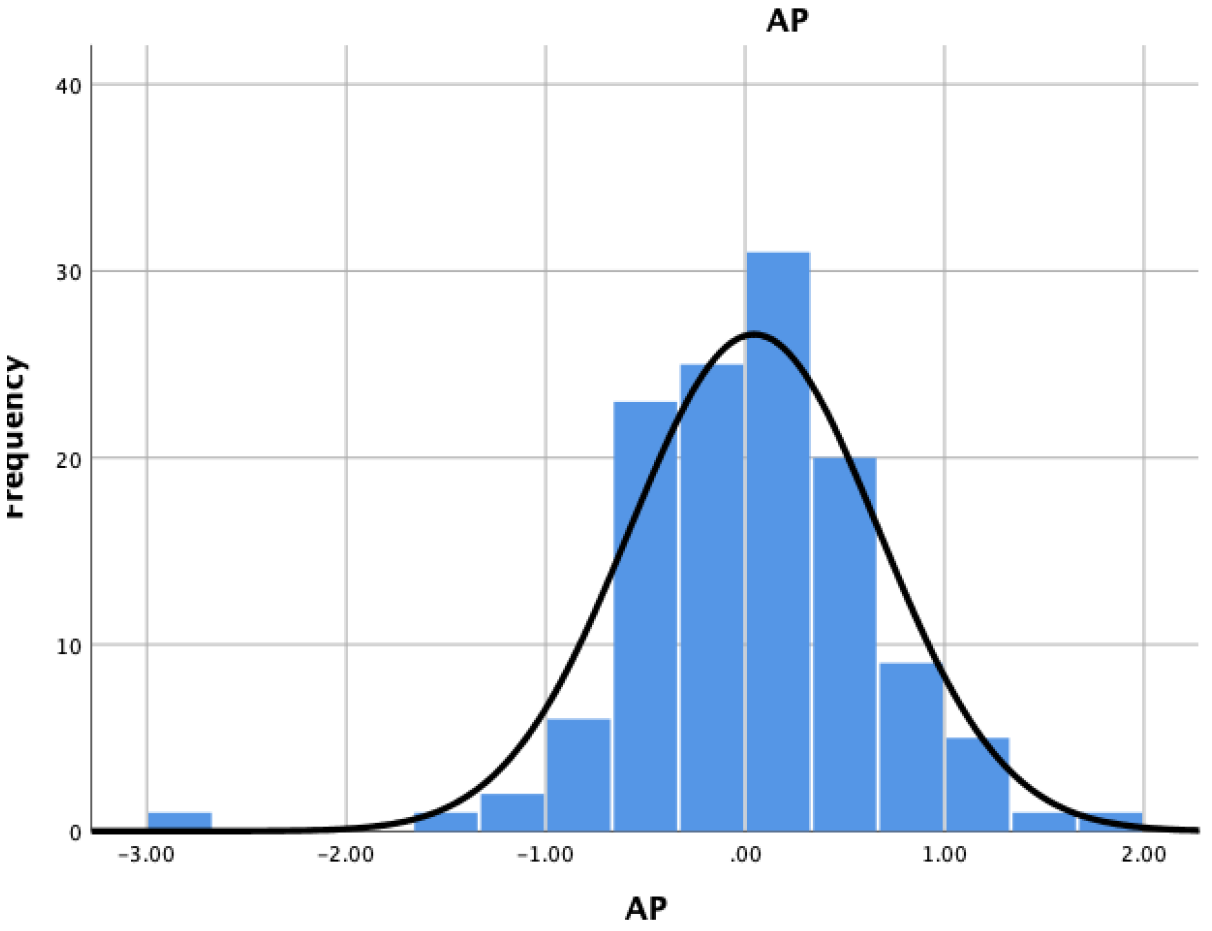
The distribution of the difference between Global Hyperactivity Aggregate (GHA) scores on Mix A and on Placebo. Positive score indicates higher GHA on food dye for 3 year olds



The distribution of the differences between Global Hyperactivity Aggregate (GHA) scores on Mix B and on Placebo. Positive score indicates higher GHA on food dye for 3 year olds



The distribution of the differences between Global Hyperactivity Aggregate (GHA) scores on Mix A and on Placebo. Positive score indicates higher GHA on food dye for 8 year olds



The distribution of the differences between Global Hyperactivity Aggregate (GHA) scores on Mix B and on Placebo. Positive score indicates higher GHA on food dye for 8 year olds