Statement on the implications of FSA funded study Project code: T07040

Chronic and acute effects of artificial colourings and preservatives on children's behaviour.

Summary

The European Food Standards Authority (EFSA) Panel have published [1] the results of its assessment of the Southampton study of food additives and children's behaviour that appeared in the Lancet in September 2007.[2] This scrutiny, which included an independent re-analysis of the data, supports the project's conclusion that the mixtures of additives had a measurable effect on the activity and attention of some children. The average effects for children as a whole are small, but there is considerable variation with some children responding more and others less. The Panel recognised that the Southampton study was both the largest of its kind and one of the few to be based on children from the general population. Furthermore, the results on 3 year olds replicated the findings of a previous study.[3]

The EFSA Panel concluded that the results of the study could not be used as a basis for changing the recommended levels (Acceptable Daily Intake, ADI) for the food colours or the sodium benzoate preservative. Whilst this study cannot determine whether the effects are produced by the food colours or by the preservative, it is striking that the effects of additives on behaviour in this study were similar to those reported previously for food colours on children with more extreme levels of hyperactivity.[4]

The EFSA Panel describes these effects as small and their significance for children's development and education uncertain. In contrast we suggest that since the colours being tested in this study are of no nutritional value, even the small overall benefit of removing them from children's diets would come at no cost or risk to the child. Under these circumstances a benefit, even a small one, would be worthwhile achieving.

Added weight is given to this conclusion, because other important influences on hyperactivity in children, such as genetic factors,[5] are difficult to address while the risk arising from exposure to food colours can be regulated.

Uncertainties identified by EFSA

The EFSA Panel identified a number of uncertainties that remain in relation to the effects of additives on behaviour.

• the limited consistency of the results with respect to age and gender of the children, the effects of the two mixtures of additives tested and the type of observer (parent, teacher or independent observer);
• the unknown clinical relevance of the novel metric, i.e. the GHA score;
• the unknown relevance of the small effect size (as was also seen in the meta analysis of earlier studies by Schab and Trinh (2004);
• the fact that the study has not been designed to identify the effects of individual additives;
• a lack of information on dose-response;
• the lack of a biologically plausible mechanism for induction of behavioural effects from consumption of food additives.

Of the 6 "uncertainties" they identify, two were never going to be addressed by the Southampton Study - namely **the effects of individual additives** and **dose-response effects**. The study was simply not designed to address these questions. The specification for commissioning the study from the Food Standards Agency stipulated the ingredients for the two mixes used. It should be noted that if dose response effects are required for each individual additive the cost of the research studies would at a first approximation be seven times the £0.75m budget for the Southampton Study.

The other four “uncertainties” need to be further consideration.

The supposed **lack of a plausible biological mechanism** ignores earlier work on histamine release. The EFSA Opinion make no reference to the studies on histamine release [6,7] that we cite in our Technical Reports as indicating a plausible biological mechanism for the effects of food colours on behaviour. It is relevant here that the genetic polymorphisms we have identified as moderators of the effects of additives on hyperactivity are concerned with histamine clearance. We would emphasise that the relevance of these tentative genetic findings is that they are consistent with a histamine release mechanism. We were never advocating their adoption as indicators of risk as suggested in the EFSA Opinion (p.32)

The emphasis in the EFSA Opinion on **inconsistency of the mixture effects** by age puts too much weight on p values rather than effect sizes. The following graph presents the results for the two mixes for 3 and for 8/9 year olds for the whole sample. It can be seen that for both mixes at both ages hyperactivity levels are higher when the children are given the additive mix than on placebo. As we reported the effects do not reach statistical significance for both mixes at both ages. What is clear is that the effects sizes are very similar across mixes and age group. The effects for mix A and mix B are significant for 8/9 year olds when the analysis is restricted to those consuming 85% of the drinks.

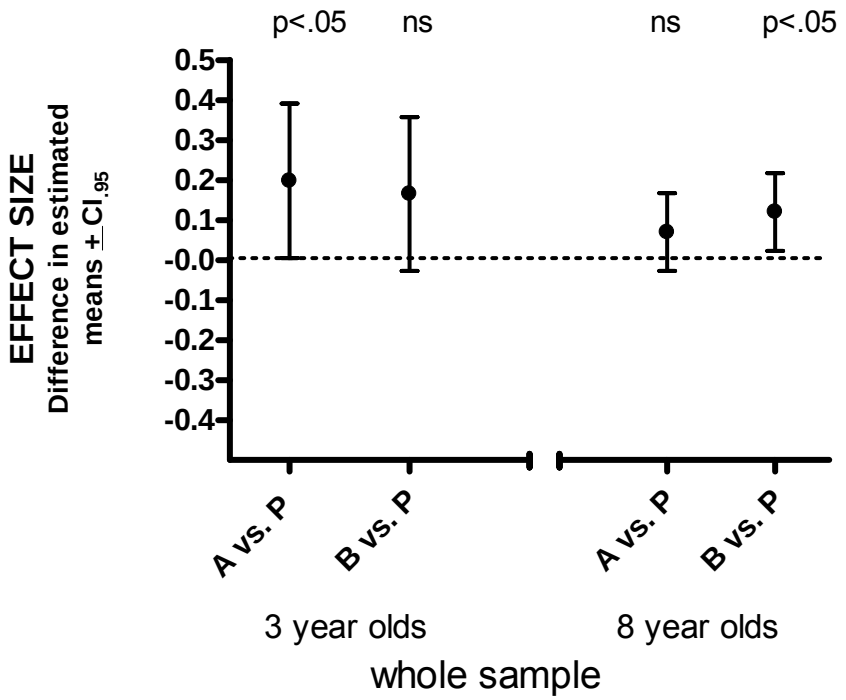

Figure. Effect sizes (+ 95% Confidence Intervals, CI) for Mix A vs. Placebo and Mix B vs. Placebo for 3 and for 8/9 year olds for the whole sample,
NB If 95% CI cut the zero line the effects are not significant at the .05 level.

EFSA have introduced consistency across gender as an issue - that was never a hypothesis the study was designed to test.

The question of consistency across type of observer ignores the situational specificity of hyperactivity (see below).

The suggestion that the **GHA is a novel metric** ignores the fact that this is simply an aggregate of previously validated measures. A key part of the study was the specification in the original protocol of the Global Hyperactivity Aggregate (GHA) as the primary outcome. This followed the requirements for the conduct of clinical trails that outcomes are specified a priori and before data analysis is initiated.

The selection of the measures to comprise the GHA was dictated by the need to measure behaviour at home (Parent ratings) and at school (Teacher ratings). This is necessary as it is known that hyperactivity shows a degree of situational specificity with some children showing a high level at school but not at home and other children the reverse pattern.[8] Indeed there are contextual influences that produce variation in hyperactivity associated with different activities within the school [9] and within the home [10]-settings. In addition we were concerned to

provide evidence of changes in hyperactivity based upon a number of independent sources – classroom observations and the CPT. Full details of the reliability and validity of the components of the GHA are given in the Appendix.

The **small effect size** is deemed to be of unknown relevance. This raises the question of how the magnitude of the effect of the mixes on the mean score population (0.18) should be judged. The EFSA Panel consider them statistically significant but small. There is no attempt by the EFSA to calibrate what benefit a reduction of hyperactivity of 0.18 of a standard deviation would have on the general population. One comparator is the effect of artificial food colour (AFC) removal on children with ADHD. The value of the lowest estimate from the Schab and Trinh meta-analysis was 0.21. So the effect on the general population in our study was comparable with the benefit of AFC removal of clinical cases.

It must be remembered that this effects is on the mean for children as a whole. Some children will experience a bigger benefit (and others less or none). At the extremes these changes will, for a minority of children, be sufficient to bring them below the clinical threshold for a diagnosis of ADHD. From our data we cannot estimate the number of children in this category with precision but he following projection is consistent with our data. If the effects of additives hold across the range of levels of hyperactivity, then we hypothesise that removal of these artificial food colours and sodium benzoate preservative with an effect size of 0.18 may lower the population mean. At the extreme we predict that the percentage of children scoring more than 1.5 SD above the mean (6.6%, a typical population prevalence for ADHD) might be lowered to 4.6%. If this were the case, it would result in a 30% reduction in the prevalence of ADHD in children. We accept this is a conjecture but we would argue a plausible one.

We would argue that although in statistical terms the effects sizes are small the benefits from the removal of AFCs from the diet are not small. Added weight is given to this conclusion, because other important influences on hyperactivity in children, such as genetic factors [5], are difficult to address while the risk arising from exposure to food colours can be regulated.

Placing the Southampton study findings in the context of previous research

A puzzling feature of the EFSA Opinion is that on p. 29 (and repeated on p. 32) equal weight is given to the meta-analyses conducted in 2004 by Schab and Trinh [4] and in 1983 by Kavale and Forness.[12] The weaknesses in the Kavale and Forness meta-analysis were identified by Schab and Trinh as follows.

“In their meta-analysis of the effect of the FD [Feingold Diet] on hyperactivity, Kavale and Forness included trials of hyperactive and nonhyperactive children. They folded together trials of the FD, trials of variant diets eliminating a variety of

foodstuffs, and trials in which subjects were challenged with individual foodstuffs, including AFCs. Their initial analysis included prospective, retrospective, cross-sectional, blind, and nonblind controlled trials that enrolled both hyperactive and nonhyperactive children and employed many categories of outcomes. ……..The breadth of those authors' inclusion criteria, their oversight of several relevant trials, the subsequent publication of additional relevant trials, and other limitations of their study call for focused consideration of whether AFCs promote symptoms of hyperactivity" (Schab and Trinh [4] p.423-424).

As these comments suggest, the Kavale and Forness[12] meta-analysis has been superseded in rigour and sophistication by the work 21 years later by Schab and Trinh [4] and yet the EFSA Opinion gives equal weight both to the former (showing that the FD in general was not effective) and latter (showing specifically that AFCs can effect behaviour).

A crucial aspect of the results of the Southampton study is that they extend the findings reviewed by Schab and Trinh to children studies from the general population. The findings are consistent with a causal effect of the mixtures on hyperactivity. The effects were shown in a randomised controlled trial (the clinical research equivalent of the "experiment" – the touchstone demonstration of causality). Moreover since the study was designed as a within subject cross-over trial there are no between groups artefacts that might confound the attribution of effects to additive exposure. The only likely threat to internal validity of the study is the possibility that some of the measurements were made not blind to mixtures been used week by week. The rigorous control applied in the study will have prevented anyone responsible for measurements being aware of the mixtures being taken by the child at any one time. Moreover repeated tests were made to show that the drinks containing the different mixtures could not be reliably differentiated. This leads us to conclude the effects we identified demonstrate a causal role of food additives on hyperactivity in the general population. However they are just one contributor to a wide range of influences on hyperactivity.

Hazard, exposure and risk

Accepting this causal role the next question is to determine the risk it presents to children. The EFSA Panel assessment confirms that there is low hazard for most children of the mixtures tested i.e. the effects of the additives are small. However in appraising what action is appropriate there is a need to consider hazard, exposure and risk. In terms of exposure these food additives are widely present in foods ingested by children – e.g. confectionery, cakes, biscuits and soft drinks. The food industry itself has recognised the need to reduce exposure and manufacturers have voluntarily been reducing the levels of artificial colours in food products. Nevertheless at present children are still ubiquitously exposed to this hazard.

The hazard is low but the exposure is high, what does that mean for risk? The key here is whether the effects we have identified are of developmental significance to the child. Our own previous research has demonstrated that elevated levels of hyperactivity in young children represent a risk for continuing behaviour problems into later childhood.[13] This is supported by other studies.[14] Moreover studies have established a relationship across the full range of hyperactivity scores with later outcomes, as the following quote indicates:

"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. [15])

It should also be recognised that children with elevated levels of hyperactivity can be disruptive to a family and are sometimes socially isolated because peers find their behaviour unsettling.[16]

Finally the COT Panel concluded - "The mean differences observed, if causal, could be clinically relevant." COT Statement 6 September 2007.[17] We have addressed the question of causality above and suggest that the putative effects of the removal of the additives in the mixtures we investigated would indeed produce changes with real benefit to the average hyperactivity levels of children in the general population.

Need for further research

Some of the uncertainties identified by the EFSA indicate the need for further research on this important question which is of concern to many parents. Most obviously there is a need to clarify the extent to which the effects identified in the Southampton study are attributable to sodium benzoate. A double blind placebo controlled food challenge study of sodium benzoate alone is called for. There also needs to be a more detailed examination of the role of histamine release as a possible biological mechanism. Further investigations of genetic polymorphisms that moderate the effects may also open up new avenues for our understanding of the complex genetics of hyperactivity.

Recommendations on policy

When the FSA first released the result of the Southampton study they changed their advice to parents along the following lines:

"If your child shows signs of hyperactivity or Attention Deficit Hyperactivity Disorder (ADHD), you should try to avoid giving your child the following artificial colours because this might help improve their behaviour.

- sunset yellow (E110)
- quinoline yellow (E104)

- carmoisine (E122)
- allura red (E129)
- tartrazine (E102)
- ponceau 4R (E124)"

There is no commentary in the EFSA Opinion as to whether such guidance is justified by the science. Indeed the only comment the Panel make in relation to regulating exposure is "the Panel concludes that the findings of the study cannot be used as a basis for altering the ADI of the respective food colours or sodium benzoate." [1] (p.33). The Panel entertains the notion that a "sensitive subpopulation" may exist. If that is the case, no guidance is given to parents of this putative subgroup as to how they should regulate their child's exposure or even on whether avoidance is indicated.

We recognise that the Southampton Study was not designed to identify the effects of specific additives. Despite not being able to differentiate the effects of AFCs from those of sodium benzoate, we suggest that the similarities between the present findings and previous studies of effects of AFCs are striking. The significance of later educational difficulties and antisocial behaviour has recently been emphasised by the Government (http://www.dcsf.gov.uk/pns/DisplayPN.cgi?pn_id=2008_0054)

It is a Government policy priority to reduce the level of disruptive behaviour by young people. We suggest that our findings indicate that the removal of food colours might be a small, indirect contribution to such a goal. The role of sodium benzoate needs further investigation.

This view is echoed in the final conclusion of the meta-analysis review on artificial food colours by Schab and Trinh:

"as long as we remain uncertain about the early and long-term effects of these exposures [to AFCs], society should engage in a broader discussion about whether the aesthetic and commercial rationale for the use of AFCs is justified." Schab & Trinh [4].

The analogy with lead

The position in relation to AFCs is analogous to the state of knowledge about lead and IQ in children that was being evaluated in the early 1980s. Needleman found the difference in IQ between high and low lead groups of children was 4.5 IQ points (106.6 vs 102.1) [18]. Using a standard deviation of 15 this gives an effect size of 0.3. Later Needleman [19] (p.241) reports that this difference falls by 2 points when confounding social differences were taken into account. This produced an effect size of 0.17. This is very close to the effects sizes obtained in our study of food additives.

In response to these findings Rutter concluded:
"…. A marked reduction in the level of environmental lead is likely to make an important difference to some children. Moreover it is important to recognise that a small change in mean IQ or average behaviour of the population as a whole will have a much greater effect at the extremes of the distribution …. Accordingly actions to cut down the amount of lead pollution of the environment should be worthwhile; there is sufficient justification for action now" [20](p.364).

We would argue that the findings from our own study and the previous research overviewed by the EFSA would lead to the same conclusion as was reached by Professor Sir Michael Rutter in relation to lead in 1983. Namely that for food colours there is "justification for action now".

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References

1. Scientific Opinion of the Panel on Food Additives, Flavourings, Processing Aids and Food Contact Materials (AFC) on a request from the Commission on the results of the study by McCann *et al.* (2007) on the effect of some colours and sodium benzoate on children's behaviour. *The EFSA Journal* (200x) 660, 1-53.
2. McCann D. Barrett A, Cooper A, Crumpler D, Dalen L, Grimshaw K, Kitchen E, Lok K, Porteous L, Prince E, Sonuga-Barke E, Warner JO & Stevenson J (2007). 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, 1560-1567.
3 Bateman B, Warner JO, Hutchinson E, Dean T, Rowlandson P, Gant C, Grundy J, Fitzgerald C, 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. Archives of Disease in Childhood, 89, 506-511.
4. Schab, D.W. & Trinh, N.T. (2004). Do artificial food colours promote hyperactivity in children with hyperactive syndromes? A meta-analysis of double-blind placebo-controlled trials. Journal of Developmental and Behavioral Pediatrics, 25, 423–34.
5. Thapar, A. Langley, K., Owen, M.J., O'Donovan, M.C. "(2007). Advances in genetic findings on attention deficit hyperactivity disorder. Psychological Medicine, 37, 1681-1692.
6. Murdoch RD, Pollock I, Young E, Lessof MH. (1987). Food additive induced

urticaria: studies of mediator release during provocation tests. J Roy Coll Phys, 4,:262-6.
7. Murdoch RD, Lessof MH, Pollock I, Young E. (1987).The effects of food additives on leukocyte histamine release in normal and urticarial subjects. J Roy Coll Phys, 4,:251-6.
8. Mannuzza S, Klein RG, Moulton JL (2002). Young adult outcome of children with: “situational “ hyperatctvity: A prospective, controlled follow-up study. Journal Of Abnormal Child Psychology, 30, 191-198.
9. Tsujii N, Okada A, Kaku R, Kuriki N, Hanada K, Matsuo J, Kusube T, Hitomi K (2007). Association between activity level and situational factors in children with attention deficit/ /hyperactivity disorder in elementary school. Psychiatry And Clinical Neurosciences, 61,181-185.
10. Whalen CK, Henker B, Ishikawa SS, Jamner LD, Floro JN, Johnston JA, Swindle R (2006). An electronic diary study of contextual triggers and ADHD: Get ready, get set, get mad. Journal Of The American Academy Of Child And Adolescent Psychiatry, 45, 166-174.
11. Scachter, HA, King J., Langford, S., Moher, D. (2001). How efficacious and safe is short-acting methylphenidate for the treatment of attention-deficit disorder in children and adolescents? A meta-analysis. Canadian Medical Association Journal, 165, 1475-1488
12.Kavale, A., Forness, S.R. (1983). Hyperactivity and diet treatment: a meta-analysis of the
Feingold hypothesis. Journal of Learning Disabilities, 16, 324-330.
13. Sonuga-Barke,E.J.S., Thompson,M., Stevenson,J. And Viney,D. (1997). Patterns of behaviour problems among pre-school children. Psychological Medicine, 27, 909-918.
14. Danckaerts M, Heptinstall E, Chadwick O, Taylor E (2000). A natural history of hyperactivity and conduct problems: self-reported outcome. European Child & Adolescent Psychiatry,9,26-38.
15. McGee R, Prior M, Williams S, Smart D, Sanson A. (2002). The long-term significance of
Teacher rated hyperactivity and reading ability in childhood: findings from two longitudinal
studies. Journal of Child Psychology and Psychiatry,43, 1004–17.
16. Blachman, D.R., & Hinshaw, S.P. (2002)**.** Patterns of friendship among girls with and without attention-deficit/hyperactivity disorder. Journal Of Abnormal Child Psychology, 30, 625-640.
17. COT Committee on toxicity, 2007. Statement on research project (T07040) investigating the
effect of mixtures of certain food colours and a preservative on behaviour in children.
http://www.food.gov.uk/multimedia/pdfs/committee/colpreschil.pdf
18. Needleman, H. L., Gunnoe, C., Leviton, A., Reed, R., Peresie, H., Maher, C. & Barrett, P. (1979). Deficits in psycholgic and classroom performance of children with elevated dentine lead levels. New England Journal of Medicine, 300, 689-695.

19. Needleman, H. (1983). The neuropsychological consequences of low level exposure to lead in childhood. In M. Rutter and R. Russell Jones (eds.) Lead versus Health: Sources and effects of low lead exposure. Chichester: John Wiley.
20.Rutter, M. (1983) Low level lead exposure: sources, effects and implications. In M. Rutter and R. Russell Jones (eds.) Lead versus Health: Sources and effects of low lead exposure. Chichester: John Wiley.

Appendix
The reliability and validity of the Global Hyperactivity Index (GHA)

The key feature of the GHA is that it is an aggregate of measures which themselves have well established psychometric properties.

For the 3 year olds

The Parent Rating was the Weiss-Werry-Peters (WWP) hyperactivity scale.[1] The WWP has been used in studies to assess hyperactivity in preschool children.[2] Inter-parent reliability has been found to be good (r=0.82).[3] In terms of validity it has been shown to predict behaviour problems in middle childhood [4] and to be sensitive to behavioural changes in drug trials. [5]

The Teacher Rating was the ADHD Rating Scale – IV (Teacher version: Pre-school).[6,7] Test-retest reliability coefficients for this measure are over .90 and concurrent validity with the Conners Teacher Rating Scale Revised range from .55 to .87.

For 8 year olds

The Parent Ratings was the ADHD Rating Scale – IV (Home version).[7,8] The parent scale has been shown to have acceptable psychometric properties including inter-rater reliability, test-retest reliability and internal consistency.[7] Scores on this measure also have adequate positive and negative predictive power in the diagnosis of ADHD. [9]

The Teacher Rating was the ADHD Rating Scale – IV (Teacher version) [6] As with the Parent/Home version, the ADHD Rating Scale-IV manual presents information on normative data and the acceptable psychometric properties of this scale.[7]

Response inhibition and attention was measured using the Conners' Continuous Performance Test II (CPTII).[10] The CPTII is a visual paradigm of 14 minutes duration and is used to evaluate attention and the response inhibition component of executive control. It has psychometric properties which have been well documented.[11] It has been used extensively with children with ADHD and a meta-analysis has shown it to be able to reliably differentiate children with ADHD from controls.[12]

For both 3 and 8/9 year olds

Observations were recorded using the Classroom Observation Code (COC).[13] The COC is one of the most thoroughly evaluated school observation coding systems. The COC has adequate interobserver reliability, discriminates between hyperactive and non-hyperactive children and has no detectable observer effect on child behaviour.[14, 15]

Psychometric properties of GHA

Given the situational specificity of hyperactivity it would be expected that the internal consistency of the GHA would be not be high and at baseline it is indeed modest for 3 year olds (α = .51) and somewhat higher for 8/9 year olds (α = .68). Evidence for the situational specificity of hyperactivity is shown by the highest correlation of the observational measure being with teacher ratings at each age.

The test-retest reliability of the GHA is best shown between baseline GHA and week 1 GHA, neither of which will be influenced by active challenges. This is good for 8/9 year olds (r_{tt}=0.89) but is somewhat lower (r_{tt} = 0.52) for 3 year olds.. The greater measurement error and the greater variability in the response to additives among the 3 year old children militated against detecting a significant effect of additives. For example see Table 3 and Table 4 in the Lancet paper.[16] For the entire sample the effect coefficient in models 2 for Mix B vs. placebo is .17 for 3 year olds and .12 for 8/9 year olds. However it is the latter which is significant as the 95% confidence intervals are smaller for 8/9 year olds (.03 to .22) compared to those for 3 year olds (-.03 to .36). Notwithstanding these wider confidence intervals (reflecting possibly a greater between child variability in the mix vs. placebo response and greater measurement unreliabilty) the study was able to replicate our previous finding of an adverse effect of mix A in 3 year old children.[17]

The GHA constructed in this way provides a multi-method, multi-source and multi-setting indicator of hyperactivity based upon measures with established psychometric characteristics. It was designed to detect increases in hyperactivity wherever they may occur - be it at home or at school.

References for Appendix

1. Routh D. Hyperactivity. In: Magrab P, editor. Psychological management of pediatric problems. Baltimore: University Park Press; 1978.p.3-8.
2. Hayward C, Killen J, Kraemer H, et al. (1998) Linking self-reported childhood behavioural inhibition to adolescent social phobia.. Journal of the American Academy of Child & Adolescent Psychiatry, 37**,**1308–16.
3. Mash EJ, Johnston C. (1983). Parental perceptions of child behaviour problems, parenting self-esteem and mother's reported stress in younger and older hyperactive and normal children. Journal of Consulting & Clinical Psychology, 51**,** 86–99.
4. Sonuga-Barke EJS, Thompson M, Stevenson J, Viney D (1997). Patterns of behaviour problems among pre-school children. Psychological Medicine, 27, 909-918.
5. Lewis, J.A. & Young, R. (1975). Deanol and methylphenidate in minimal brain dysfunction. Clinical Pharmacology and Therapeutics, 17, 534-540
6..DuPaul GJ, Power TJ, Anastopoulos AD, Reid R, McGoey K, Ikeda M. (1997). Teacher ratings of ADHD symptoms: Factor structure and normative data. Psychological Assessment, 9, 436-444.

7. DuPaul GJ, Power TJ, Anastopoulos AD, Reid R. (1998). AD/HD Rating Scale IV: Checklists, Norms and Clinical Interpretation. New York; Guilford Press.
8. DuPaul GJ, Anastopoulos AD, Power TJ, Reid R, Ikeda M, McGoey K,. (1998). Parent ratings of Attention-Deficity/Hyperactivity Disorder Symptoms: factor structure and normative data. Journal of Psychopathology and Behavioural Assessment , 20, 83-102.
9. Power TJ, Doherty BJ, Panichelli-Mindel SM, Karustis JL, Eiraldi RB, Anastopoulos AD, DuPaul GJ. (1998) The predictive validity of parent and teacher reports of ADHD symptoms. Journal of Psychopathology and Behavoural Assessment, 20, 57-81.
10. Conners CK. (1994). The Conners continuous performance test. Toronto, Canada: Multi-Health Systems.
11. Conner CK (2000). Conners' continuous performance test II: Technical guide. Toronto, Canada: Multi-Health Systems.
12. Losier BJ, McGrath PJ, Klein RM (1996). Error patterns on the continuous performance test in non-medicated and medicated samples of children with and without ADHD: A meta-analytic review. Journal Of Child Psychology And Psychiatry, 37, 971-987.
13. Abikoff H, Gittelman R. (1985). Classroom Observation Code: A modification of the Stony Brook code. Psychopharmacology Bulletin, 21, 901-909.
14. Abikoff H, Gittelman-Klein, R, Klein DF (1977). Validation of a Classroom Observation Code for hyperactive children. Journal of Consulting and Clinical Psychology, 45, 772-783.
15. Abikoff H, Gittelman R, Klein DF. (1980). Classroom Observation Code for hyperactive children: a replication of validity. Journal of Consulting and Clinical Psychology, 48*, 555-565.*
16.. McCann D. Barrett A, Cooper A, Crumpler D, Dalen L, Grimshaw K, Kitchen E, Lok K, Porteous L, Prince E, Sonuga-Barke E, Warner JO & Stevenson J (2007). 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, 1560-1567.
17. Bateman B, Warner JO, Hutchinson E, Dean T, Rowlandson P, Gant C, Grundy J, Fitzgerald C, 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. Archives of Disease in Childhood, 89, 506-511.