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FOOD ADDITIVES AND HYPERACTIVITY

Executive Summary

1. This paper provides an update to the Board following its discussions in September 2007 on the study from Southampton University on the possible effects of certain food colours and a preservative on children's behaviour. The European Food Safety Authority published its opinion on the study on 14 March 2008. The Agency has carried out research with consumers on the original advice given to parents regarding food colours and hyperactivity. Information has been collected from the food industry on the action it has taken regarding the use of certain artificial food colours, and its future plans. A technical workshop has been held in conjunction with the Food and Drink Federation on removing artificial colours from food and drink. The Executive has considered a number of options regarding the future use of certain colours in food and drink which could form the basis of advice to Ministers.

2. The Board is asked to:

   - **agree** advice to Ministers regarding the future use of the preservative sodium benzoate and the artificial colours used in the Southampton study in food and drink.

   - **agree** the FSA advice to parents regarding food colours and hyperactivity in children

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FOOD ADDITIVES AND HYPERACTIVITY

Issue

1. At its meeting in September 2007 the Board discussed the study from Southampton University on the possible effects of certain food colours and a preservative on children's behaviour. As food colours and preservatives are an EU competence, the Board wished to decide whether the evidence from the study constituted such a risk to public health that it overcame the threshold for unilateral action by a Member State. The Board concluded that it did not. The Board agreed that any action regarding the future use of the colours in the study would be needed at a European level, it noted that there were on-going processes in Europe on food additives and that EFSA was considering the study. The Executive was asked to return the issue of colours and hyperactivity to the Board as soon as the EFSA response to the Commission was known, to ensure that it was content with the position that was being taken. The EFSA opinion was published on 14 March 2008. In addition, the Board asked the Executive to re-look at the advice it had issued on its web site to see if this could be made more helpful to parents, and to bring this back to the Board. The Board also asked for a formal position from the industry on where it stood in respect of removing these additives from its produce to understand better how much of a practical issue this was. The FSA, in conjunction with the Food and Drink Federation, held a technical workshop with industry on 27 February to discuss these issues further. The Executive has considered a number of options which may form the basis of the UK negotiating position in any discussions with member states and the Commission following the publication of EFSA's opinion. The UK negotiating position will be decided by Ministers.

Strategic Aims

2. To ensure that all permitted food additives are safe for use, there is a technological need for their use, and that consumers can make informed choices about the additives they consume.

Background

Position from industry on removing colours and a preservative from food and drink

3. In September 2007 the Board asked to receive a formal position from the industry on where it stood in respect of removing these additives from its produce to understand better how much of a practical issue this was. Letters were sent to 8 trade associations and 21 companies requesting the following information:

- action taken already concerning the food colours used in the Southampton study;

- any future action planned and a timescale for this;

- action taken concerning sodium benzoate and future plans; and

- general information regarding the use of other permitted artificial food colours.

4. Responses were received from 5 trade associations and 6 individual companies. The responses were of a general nature rather than providing detailed information.

5. All respondents reported that steps had been taken to remove the colours used in the Southampton study. In own label products the use of artificial colours was reported to be discontinued. Some foods imported from outside of the UK may still contain colours. A limited number of foods were identified where alternatives to artificial colours were still being developed. It was reported that for a few products reformulation had been slow due to technical reasons e.g. alternative colours did not provide sufficient shelf life or processing stability, or the reformulated product was not acceptable to consumers. Examples of products which have been mentioned by industry as being particularly difficult to reformulate are canned/processed peas, mushy peas, tinned strawberries, rose-coloured sugar almonds, Turkish delight, and contrasting colour sponge cakes such as battenburg and angel cake. Those who responded reported that reformulation would be completed by the end of 2008.

6. The use of sodium benzoate is mainly restricted to soft drinks where it is a very effective preservative. Its use as a preservative in other foods appears to be limited with alternatives being developed.

7. With respect to other permitted artificial food colours it appears that the food and drink industry are taking steps to remove artificial colours from their products and reformulating where necessary, and where technologically possible.

8. Information regarding products which still contain the artificial colours used in the Southampton study and sodium benzoate is available on the action for additives web site[1] which was set up by the Food Commission following the publication of the Southampton study. The site works by inviting consumers to provide details of products they have found to contain artificial colours or sodium benzoate. Over 900 food and drink products are listed which fall broadly into 5 different categories – confectionary, soft drinks, bakery goods, savoury snacks, processed/mushy peas and jelly.

[1] www.actionforadditives.com

9. A technical workshop organised in conjunction with the FDF was held on 27 February. The purpose of the workshop was to help disseminate knowledge to companies who wish to move away from artificial colours. The invitation to the workshop was issued via regional food group co-ordinators and aimed primarily at SMEs. 26 people attended the workshop at Aviation House and 9 people participated via a video link to the FSA offices in Aberdeen. Sainsburys, Natural Food Colours Association, TNS-Worldpanel, Campden and Chorley Wood Food Research Association and the Organic Trade Group gave presentations at the workshop.

EFSA opinion on the Southampton study

10. The European Food Safety Authority's (EFSA) Panel on Food Additives, Flavourings, Processing Aids and Food Contact Materials (AFC) adopted an opinion on the Southampton study on 7 March. After some final editing, the opinion was published on 14 March (Annex 1). The Panel was assisted by behavioural experts in assessing the study and had the statistics reanalysed by EFSA's methodology unit. This reanalysis used the statistical approach undertaken by the authors and other approaches. These analyses confirmed the reported findings 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, although the effects were not statistically significant for the two mixtures in both age groups. The statistical reanalysis conducted by EFSA resulted in some minor differences, but overall would not alter the conclusions of the Committee on Toxicity (COT).

11. Like the COT, the EFSA Panel was unable to draw conclusions on the implications of the observed changes at the population level. The EFSA Panel also agreed with the COT that it was not possible to attribute causality to the association nor could the observed effects be ascribed to any of the individual compounds.

12. The EFSA Panel concluded that the findings of the study cannot be used as a basis for altering the Acceptable Daily Intake (ADI) of the respective food colours or sodium benzoate. This was based on the overall weight of evidence and in view of the considerable uncertainties, such as the lack of consistency and relative weakness of the effect and the absence of information on the clinical significance of the behavioural changes observed. The COT did not comment on whether the results could be used in reviewing the ADI as the purpose of its evaluation differed from that of EFSA.

13. The Chair of the COT has been consulted and agrees that the conclusions of the EFSA Panel are consistent with those previously reached by the COT. A comparison of the COT and EFSA analysis of the study from Southampton study is presented in Annex 2.

14. Professor Stevenson, the researcher who carried out the research at Southampton University, has forwarded a rejoinder to the Agency following the publication of the opinion from EFSA. This is attached at Annex 3.

Options for consideration regarding the future use of artificial colours

15. There are a number of possible options that could be pursued on the future use of artificial food colours, and the Board needs to consider its preferred option. This will be used to inform the UK position, which will be decided by Ministers, in discussions with the Commission and member states. Five options have been identified and are outlined in Annex 4 with pros and cons from the UK's view point. These options only apply to the colours used in the Southampton study and not to all artificial colours.

16. Sodium benzoate was present at a constant level in the mixtures used in the Southampton study whilst there was some variation in the results observed. The study was designed to look at mixtures of additives and so in its conclusions COT could not distinguish between possible effects of artificial colours and the preservative. One of the criteria for authorisation of additives is that of technological need and there seems to be a general view that preservation of food is a much stronger need than colouring it. There are alternatives to sodium benzoate available though in some cases they raise issues of effectiveness, cost and allergenicity.

FSA advice to parents regarding food colours and hyperactivity

17. When the research from Southampton University was published in September 2007 the FSA changed its advice to consumers to 'if a child shows signs of hyperactivity or ADHD then eliminating the colours used in the Southampton study from their diet might have beneficial effects'.

18. At its meeting in September 2007, the Board asked the Executive to re-look at the above advice to see if this could be made more helpful to parents, and bring this back to the Board. The Executive used consumer research to explore parents' understanding of the FSA advice. (Report attached at Annex 5.)

19. In addition the Welsh Food Advisory Committee discussed the FSA response to this research at its meeting on 6 September 2007 and again on 9 November 2007: their view is that it is unreasonable to expect parents to be monitoring their children for signs, or scales, of hyperactivity and that the FSA advice should recommend a general avoidance by all children of the colours in the Southampton study.

20. The major finding of the FSA consumer research was that, whilst the language and tone of the advice raised few objections, parents of children without ADHD or similar conditions widely misinterpreted the term 'hyperactivity' understanding it to

refer simply to a short-period of over-excited behaviour ('being hyper'). These parents therefore assumed the advice was aimed at them, and the paragraphs describing what is meant by hyperactivity came too late in the information provided to correct this assumption. Revising the advice, which included moving the paragraphs describing hyperactivity to the top, meant it was much less open to misinterpretation and respondents were much more likely to believe the advice was aimed primarily at parents of children with ADHD or similar conditions.

21. The view of the Welsh Food Advisory Committee that the FSA advice could have been broader to cover all children was raised in the September Board discussion. It was noted then that the advice was guided by the COT conclusions and that most benefit would be gained by those children who were demonstrating a level of hyperactive behaviour. The Executive still consider this is the case. The consumer research funded by the FSA shows that parents understand the advice provided in September 2007. The proposed revised advice, taking into account the consumer research, describes hyperactivity in the first instance. It also tells parents that if they have concerns on the basis of the information provided they might choose to avoid giving their child food and drink containing the artificial colours used in the Southampton study. The revised advice is presented in Annex 6.

Conclusion

22. The Executive has considered the options provided to the Board in Annex 4 regarding the future use of the artificial colours in food and drink. Option 5 is the preferred option - phasing out of these six colours in food and drink in the EU over a specific period. The basis for this is:

- the Southampton study is a scientific study of the highest quality;
- an accumulating body of evidence that there is an association between the consumption of certain food colours and children's behaviour;
- all food additives must be safe for use in order to be approved. The available evidence now leaves uncertainty as to whether that safety can be confidently asserted;
- the technological function of colours in food is about conferring a consumer choice benefit rather than a safety benefit; and
- a significant part of the UK food industry is already moving away from the use of artificial food colours in responding to consumer demand.

Board Action Required

23. The Board is asked to:

- **agree** advice to Ministers regarding the future use of the preservative sodium benzoate and the artificial colours used in the Southampton study in food and drink; and

- **agree** the FSA advice to parents regarding food colours and hyperactivity in children.

ANNEX 1

EFSA OPINION

This has been bound as a separate document

ANNEX 2

Comparison of EFSA and COT opinions of the Southampton Study

	EFSA	**COT**
Additional expertise	Clinical and statistical experts were members of the Working Group	Additional clinical and statistical experts assisted the COT. Unlike the EFSA panel, COT members' expertise includes paediatrics and research involving children
Limitations in the research	"*does not completely overcome the criticisms of the earlier Isle of Wight study*"	*"noted some limitations in the study design and analysis"* COT chair noted "t*here are constraints when conducting any research involving children".*
Study statistics	EFSA conducted a statistical reanalysis *"broadly similar conclusions to that in the original paper:* Significant differences compare to placebo were found in: Mix B in 8/9 year olds Mix A in 3 year olds with >85% consumption of the drinks	COT considered the statistical analysis conducted by the researchers and also paid attention to the trends *"Although not all risk estimates reached statistical significance, all showed a small increase in the mean GHA score associated with consumption of Mix A or Mix B. This does not automatically lead to the conclusions that the mixtures caused an increase in hyperactivity"*
Findings of the study	*"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 ADHD"*	*"supporting evidence suggesting that certain mixtures of artificial food colours together with the preservative sodium benzoate are associated with an increase in hyperactivity in children from the general population"*
Consistency	*"the effects were not statistically significant* *for the two mixtures in both age groups"* *"limited consistency of the results with respect to age and gender of the children, the effects of the two mixtures of additives tested*	*"changes in behaviour were not evident in all children in any one group and were not consistent across age groups or across the different mixtures used in the study."*

	and the type of observer (parent, teacher or independent observer)"	
Size of effect	*"the unknown relevance of the small effect size"* *" it is not known whether these small alterations in attention and activity would interfere with schoolwork and other intellectual functioning"*	*"the increases in mean levels of hyperactivity observed in this study were small relative to normal inter-individual variation"*
Relevance at population level	*The clinical significance of the observed effects ……. (b) for the population as a whole remains unclear"*	*"it is not possible to draw conclusions on the implications of the observed changes at the population level."*
Relevance to individual children	*The clinical significance of the observed effects (a) for the individual children in the study ……..remains unclear"*	*"if causal, this observation may be of significance for some individual children across the range of hyperactive behaviours, but could be of more relevance for children towards the hyperactive end of the scales"*
Possible sensitive subpopulation	*"changes in behaviour from either addition or withdrawal of additives from the diet were not observed in all children, suggesting there may be a subpopulation of individuals who are sensitive to food additives in general or to food colours in particular"* *" If a sensitive subpopulation does exist, it is not possible, from the currently available data, to assess the overall prevalence of such sensitivity and whether particular food additives may be implicated."*	*"suggest possible differential sensitivity to the particular mixtures used in this study"* *"However, the increases in GHA scores were not limited to individuals with the specific polymorphisms measures in the study"*
Influence of parental observations	*"the main contributors to the GHA scores were the parental scores"*	*"Parental reports were the only statistically significant discriminator of differences in children's behaviour"*
Effects of individual additives	*Since mixtures and not individual additives were tested in the study by McCann et al., it is not possible to ascribe the observed*	*"if the associations were causal, it is not possible to determine whether specific food additives within the mixtures were*

	effects to any of the individual compounds.	*responsible, or whether the association depended on the combined action of the mixture"* *"It is also not possible to extrapolate the findings to additives other than the specific combination in the mixtures used in this study."*
Biological mechanism	*"the lack of a biologically plausible mechanism for induction of behavioural effects from consumption of food additives"*	*"has not indicated any possible biological mechanism for the observations made, which might have provided evidence of causality or of the possible effects of individual additives or of other mixtures of additives."*
Existing evidence	*"The Panel noted that some, but not all, earlier studies have also reported effects of certain food colours on child behaviour, the majority of these studies being conducted on children described as hyperactive or with a clinical diagnosis of ADHD."*	*"the results of this study are consistent with, and add weight to, previous published reports of behavioural changes occurring in children following consumption of particular food additives"*
Implications for the ADI	*"the findings of the study cannot be used as a basis for altering the Acceptable Daily Intake (ADI) of the respective food colours or sodium benzoate"*	The COT did not comment on whether the results could be used in reviewing the ADI as the purpose of its evaluation differed from that of EFSA

ANNEX 3

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.

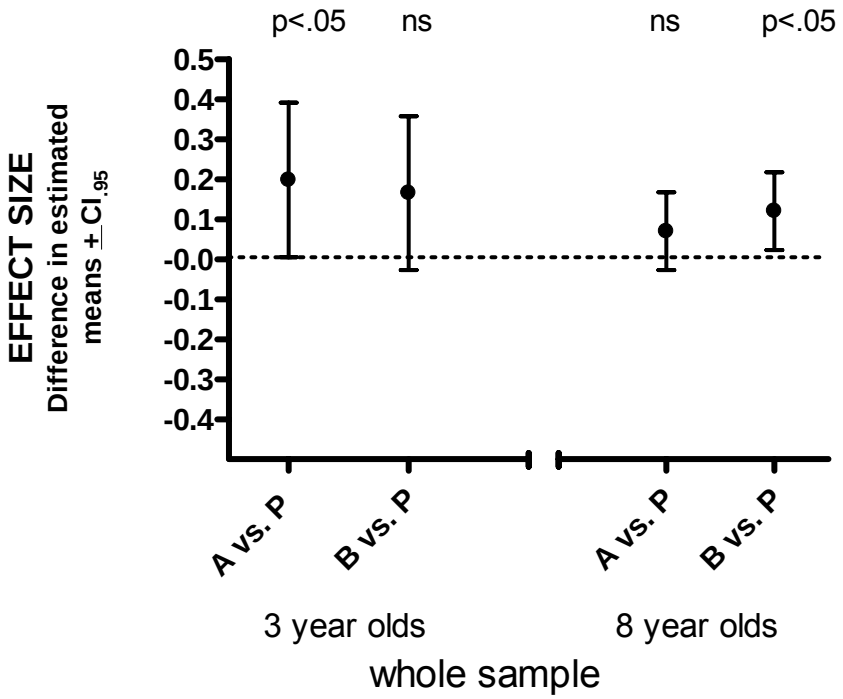

Figure. Effect sizes (+ 95% Confidence Intervals, CI) for Mix A vs. Placebo and Mix B vs. Placebo for 3 and for 8/9 year olds for the whole sample,
NB If 95% CI cut the zero line the effects are not significant at the .05 level.

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 the percentage of children scoring more than 1.5 SD above we predict that 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".

Jim Stevenson,
Donna McCann,
Edmund Sonuga-Barke,
John Warner

20 March 2008

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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.

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ANNEX 4

Options for consideration regarding the future use of certain artificial colours

Option 1 - Do nothing

Pros

- Consumers will notice no difference in the range of foods available.

Cons

- These artificial colours can continue to be used in food and drink.
- SMEs and companies from third countries will continue to use these colours.
- This option does not address consumer concern regarding the use of these colours in food and drink.

Option 2 – Point of sale notice of which colours are present in loose foods

Pros

- Provides consumers with more information on products which contain colours.

- Allows industry to continue to reformulate products and remove colours at its own pace.

Cons

- Many consumers don't have time to consult labels/notices and would prefer these artificial colours not to be there.

- Doesn't address concerns about children buying products with their own pocket money.

Option 3 - Removing colours from foods/drinks aimed primarily at, or consumed extensively by, children.

Pros

- The evidence concerns possible effects on children's behaviour. Removing the colours to a large extent from foods usually consumed by children is therefore a targeted response.

Cons

- Whilst it is possible to identify some products which are clearly aimed at children, there is likely to be a grey area which will lead to enforcement difficulties.

- Given the nature of family eating occasions there are unlikely to be many foods consumed by adults, which are not consumed by children as well – so the option becomes much the same as option 5.

Option 4 – Restricting the use of colours in the EU to certain limited food categories/products where there are no colouring alternatives.

Pros

- This would require mandatory action by the EU and therefore would ensure that these rules apply to all companies.

- Allows for continued use of colours in foods where there is no technological alternative.

Cons

- Some consumers may feel this does not go far enough but others may feel dissatisfied as they want to buy colourful foods (processed foods which still have a satisfying colour, celebration cakes etc) or complain products they have bought for many years are not the same colour.

- There will need to be criteria agreed for selecting the foods.

Option 5 – Phasing out the use of colours in food and drink in the EU over a specific period. Voluntary action by 2009 in the UK

Pros

- Many consumers would be content that action had been taken to protect consumers from the use of colours in food and drink.

- This would require mandatory action by the EU and therefore would ensure that these rules apply to all companies.

- Can vary end date for different situations. Where there are technical difficulties industry would have a longer time frame to complete reformulation. For other food and drink there would be a clear end point on a shorter time scale when reformulation must be completed by.

Cons

- Some consumers may feel dissatisfied as they want to buy colourful foods (processed foods which still have a satisfying colour, celebration cakes etc) or complain products they have bought for many years are not the same colour.

- Some products (where there are no satisfactory alternatives) may be lost from the market temporarily or even permanently.

ANNEX 5

REPORT FROM CRAGG ROSS DAWSON ON FSA ADVICE TO PARENTS REGARDING FOOD COLOURS

(This has been bound as a separate document)

ANNEX 6

Revised FSA advice to parents regarding food colours and hyperactivity

"Hyperactivity is a general term used to describe behavioural difficulties affecting learning, memory, movement, language, emotional responses and sleep patterns. In the context of this advice, it is when a child is over-active, can't concentrate and acts on sudden wishes without thinking about alternatives. There is no single test for diagnosing hyperactivity. Experts think it affects 2 to 5% of children in the UK. The figures are higher in the United States.

Attention deficit hyperactivity disorder (ADHD) is more than just hyperactive behaviour. It is linked to a specific pattern of behaviour, including reduced attention span and difficulties concentrating such that they affect the child's ability to learn and function at home and at school. Children with ADHD often have learning difficulties and behavioural problems.

Research funded by the FSA has suggested that consumption of mixes of certain artificial food colours and the preservative sodium benzoate could be linked to increased hyperactivity in children. It is important to remember that hyperactivity is also associated with many other factors in addition to certain additives, so dietary advice is part of the management not the total solution. Other factors include premature birth, genetics and upbringing.

If on the basis of this information you have concerns you might choose to avoid giving your child food and drinks containing the following artificial colours.

- sunset yellow FCF (E110)
- quinoline yellow (E104)
- carmoisine (E122)
- allura red (E129)
- tartrazine (E102)
- ponceau 4R (E124)

These colours are used in a number of foods, including some soft drinks, sweets, cakes and ice cream.

When colours are used in food, they must be declared in the list of ingredients as 'colour', plus either their name or E number. So if you choose to avoid certain additives, you can do this by checking the label.

If you buy any foods that are sold without packaging you will need to check with the person selling the product or with the manufacturer.

Some manufacturers and retailers have told the Agency that they are already working towards finding alternatives to these colours.