Food Additives and Behaviour in Children Meeting minutes 14 February 2003

Wednesday 2 April 2003

10:30 am on Friday 14 February 2003, Conference Room 4, Aviation House, 125 Kingsway, London, WC2B 6NH

Present:

Professor Ian Kimber
(Chairman) Syngenta, Cheshire

Professor Eric Taylor
Institute of Psychiatry, London

Professor Peter Aggett
University of Central Lancashire

Dr Keith Godfrey
MRC Epidemiology Unit, Southampton University

Dr Alex Richardson
University of Oxford

Dr Vyvyan Howard
University of Liverpool

Mrs Jacquie Salfield
COT Consumer Representative

Dr Tim Marrs
Food Standards Agency

Mrs Sue Hattersley
Food Standards Agency

Dr Theresa Ekong
Food Standards Agency

Miss Karen Kyte
Food Standards Agency

Dr Lucy Foster
Food Standards Agency

Item 1: Welcome

1.1 The Chairman welcomed members to the second and final meeting of the ad hoc Working Group on Food Additives and Behaviour in Children.

Item 2: Apologies

2.1 Apologies were received from Professor John Warner Southampton General Hospital and Marion Castle Food Standards Agency.

Item 3: Minutes of the meeting held on 13 December 2002

3.1 The minutes of the first meeting, held on 13 December 2002, were agreed with amendments.

Item 4: Matters arising

4.1 Action points from the first meeting were discussed.

4.2 Referee comments on the Isle of Wight study

4.2.1 The report of the Isle of Wight study ("Do food additives cause hyperactivity and behaviour problems in a geographically defined population of 3 and 5 year olds?") has been sent to three scientific journals for consideration, but in each instance was not accepted for publication. At the first meeting of the Group, it was agreed that the contractors would let the Group have sight of the referees' concerns/comments, as these might inform the design of future investigations. The contractors had supplied the comments with a covering commentary from Professor Stevenson noting their response to specific referee comments. This was acknowledged to be very helpful and informative, and during the discussion, the principal points made were:

4.2.2 There was some concern by the referees that the self-selecting nature of those who continued to the end of the study may have resulted in a bias that could have affected the validity of the parental observations and the ability to generalise any findings to the wider population. However, it was noted that to achieve an efficient recruitment level while maintaining minimum bias would be difficult. One way of doing this might be to develop a design such those used for some psychological studies, whereby parents are not informed as to the true purpose of the study during recruitment. Doubts were also expressed about the feasibility of this.

4.2.3 There was some concern that statistically significant differences in behaviour between test and control groups had been observed in activity scores assessed by parents, but were not apparent in clinical assessments.

4.2.4 There had been a large placebo effect.

4.2.5 There was concern that the washout period of one week may not have been sufficient.

4.2.6 There was some concern by referees that the decision to adopt the statistical approach used in the study may have been made after the study had been carried out. The Group agreed that for future studies the primary objective and the statistical analysis should be clearly stated in the study proposal.

4.3 In considering how the design of future studies may be improved, it was noted that:

4.3.1 Less reliance on parental observations might produce more objective outcomes. This might be achieved by having 3-year-olds observed in a nursery setting by independent observers, or by using an older age group. However, it was also discussed and acknowledged that parents are much more likely than any independent /external observers to be sensitive to any real changes in the child's behaviour, because of their knowledge of and exposure to the child across a much broader range of settings and behaviours. The point was made that for this reason, to exclude parental ratings would remove the measure most likely to show change. Provided that the study blinding is successful, there would be no good reason to regard parental ratings as 'inferior' to those of others, and in many ways they could be considered superior.

4.3.2 For future studies, one could set an a priori hypothesis to test whether the findings are applicable to the general population or to a sub-group.

4.3.3 One suggestion was randomly to target smaller specific groups in smaller numbers, rather than adopt a population approach.

4.3.4 The possibility of a meta-analysis of published data in this area was discussed, but this was not favoured for number of reasons, including the heterogeneity of the studies.

4.3.5 In view of the above considerations, it was agreed that some of the referees felt that the contractors might have overstated the significance of their findings. While acknowledging that the study was well designed and conducted, a majority of the Group also considered that the results were not conclusive, a view also reached previously by the COT. (Minutes of the COT meeting of 5 September 2000 (item 4), TOX/MIN/2000/05 and minutes of the COT meeting of 1 May 2001 (item 5) TOX/MIN/2001/03).

4.4 The use of additives in the UK

4.4.1 At its first meeting, the Group had requested information on additive usage in the UK to facilitate its deliberations. Dr Lucy Foster of the Food Additives Branch presented a brief overview of the current usage of the additives examined in the Isle of Wight study. The principal points made were:

4.4.2 With regard to the use of colours in drinks, manufacturers were still using the additives sunset yellow, tartrazine and benzoates (often together), which had been examined in the Isle of Wight study. However, as these additives have been implicated in causing hyperactivity, manufacturers are moving away from these, towards using alternative, natural, colours.

4.4.3 A review of information collated from recently published Agency survey data on intense sweeteners in dilutable drinks prepared by carers and consumed by 1.5-4.5 year olds identified approximately one third of samples as containing sodium benzoate. This preservative was frequently used in combination with other preservatives, such as potassium sorbate and/or sodium metabisulphite.

4.4.4 A small number of dilutable drink samples (less than two per cent) was labelled as containing artificial colours such as carmoisine, sunset yellow, quinoline yellow and green S. For the majority of samples, colour was added as beta-carotene, or anthocyanins. Chlorophylls and caramels were also used to provide colour to a very small proportion of samples.

4.4.5 The Agency has recently conducted a survey of artificial colours in ‘ready to drink’ soft drinks, including sports/energy drinks. Publication of the results of this survey is anticipated in late Spring 2003.

4.4.6 An overview of information collated from an Agency survey on the use of artificial colours in confectionery (published April 2002) was presented. Of the 196 representative samples analysed in this survey, quinoline yellow was found to be most frequently used, occurring in approximately two thirds of packaged sweet samples. Sunset yellow, carmoisine and ponceau 4R occurred in almost one third of samples. Tartrazine was least frequently used, occurring in less than five per cent of samples.

4.5 A letter had been received from the Food Commission, raising several points of information, and noting the continued use of azo dyes in branded food products. Following a discussion of the letter, it was agreed that the secretariat would respond on behalf of the Agency, addressing specific issues raised in the letter.

4.6 A letter had also been received from the Food Additives and Ingredients Association, noting their concern that the Isle of Wight study had not adequately addressed the issue of the nutritional status of children studied, which may have had an impact on the parental observations. The Agency responded, addressing specific issues raised in the letter, and noted that the matter would be taken forward by putting out a research call for further studies based on the Group’s deliberations, which would take account of specific aspects, including the nutritional status of the children.

Item 5: Design of future studies

5.1 The Group considered the possible design of future studies, taking into account any lessons learned from the Isle of Wight study.

5.2 It was agreed that simple guidelines/advice would be drafted for potential contractors to aid the experimental design of studies that would produce conclusive results, but would not be overly prescriptive.
Action: The Food Standards Agency

5.3 Additives to be studied and doses

5.3.1 It was agreed that one objective of future studies would be to investigate additives examined previously in the Isle of Wight study. However, there was also a case for examining the additives that are more commonly used at present, and possibly additives that would most likely to be used as substitutes in future.

5.3.2 The question was asked as to how accurately the doses of additives examined in the Isle of Wight study reflected the normal exposure levels in children. Data on the consumption and exposure levels for E110, E121, E124 and E102 would be required by potential contractors, to ensure that dosage of colours used in any future study would accurately reflect current exposure levels to additives. The exposure data should be calculated at 97.5 percentile level to ensure adequate coverage.
Action: The Food Standards Agency

5.4 The design of new studies

5.4.1 The possible design of future studies was considered and a number of points were made.

5.4.2 One design approach could be parallel, allowing the simultaneous examination of different panels of additives, or sequential.

5.4.3 One important objective would be to carry out a repeat of the Isle of Wight study, looking at the same panel of additives and a placebo in a 2-arm cross-over trial. This would provide an opportunity to confirm or refute the study findings.

5.4.4 Another option would be a 3-armed study that would facilitate parallel examination of additives previously studied in the Isle of Wight study, a new panel of additives that would more accurately reflect current intake, and a placebo panel. However, such a design would be more complicated and could be difficult to manage successfully, and may compromise the basis of the investigation, for example by increasing the dropout rate.

5.4.5 A third option would be to consider a 3-arm crossover with the Isle of Wight panel of additives, a placebo arm, and a panel with natural colours with nutritional properties. Again, this could be difficult to manage successfully. Information on additive intakes in children and adults across EU would usefully inform this consideration.

5.4.6 It was noted that additives to be grouped together in crossover studies would have to be carefully selected.

5.4.7 It was noted that the design might comprise parallel or cross-over studies, with up to 3-arms, or a design that allowed number sequential studies.

5.5 Which age group

5.5.1 In considering which age group would be most appropriate for future studies, the following points were made:

5.5.2 Regardless of the age group of children to be examined, the background diet should be as stable as possible. This might be achieved by providing the diet, although doing this may introduce the

confounding effect of altering the nutritional content of the diets.

5.5.3 Future studies could use the same age group used in the Isle of Wight study, namely 3-5 year olds. This would make it easier to control the background diet, but would restrict the use of more objective end-points.

5.5.4 Another option would be to use older children. This would allow the use of more objective end-points, although the background diets would be more difficult to control.

5.6 The placebo

5.6.1 Future studies would need to address how to minimise the placebo effect and to ensure that both parents and children are truly blinded.

5.6.2 One way of achieving this would be to give the give the test and the control drinks in a carrier that was consumed throughout the entire study period.

5.6.3 It would be important to ensure that children are not able to distinguish between test and control drinks.

5.6.4 The vehicle for administering the test/placebo need not be restricted to drink.

5.7 The wash-out period

5.7.1 Future studies should ensure that the washout period is adequate. A period of 2-3 weeks was considered adequate.

5.8 The nutritional status of the children

5.8.1 It was possible that a behavioural effect of additives was only noted in a sub-group of the population of children, i.e. that with the poorest nutritional status.

5.8.2 Consideration should be given to providing recommendations on a baseline diet that would ensure good nutritional status. This would also facilitate the subsequent monitoring of the nutritional status of the children.

5.8.3 It may be useful to ask that nutritional diaries be kept, which would be available for analysis if required. The issue of how to effectively monitor compliance was considered, and how to deal with non-compliance.

5.9 Other end-points

5.9.1 The Group acknowledged that finding alternative psychological end points for 3-year olds would be difficult, although this would add power to the calculation. The use of attention span was appropriate for ADHD, but was only one of a number of useful measures for behaviour.

Item 6: Summary of agreed points

6.1 The Group agreed that there were concerns about the design of the Isle of Wight study that made it difficult to come to firm conclusions regarding the findings.

6.2 The Group agreed that it was feasible to design studies to determine whether a causal relationship exists between exposure to certain food additives and behavioural effects in children, and recommended that such studies should be funded.

6.3 The Group recommended that simple guidelines with clear objectives and expected outputs should be provided for potential contractors on experimental design for studies that would produce conclusive results.

6.4 The Group agreed that it would be important for contractors to agree on a statistical approach that

would be appropriate for future studies before commencement of the study.

6.5 It was agreed that it would be important to seek to substantiate the Isle of Wight study, using the same age group and the mix of additives as that used previously. However, consideration could also be given to studies with the older children and with a mix of additives that more accurately reflects current usage.

6.6 It was agreed that future studies should seek to minimise the placebo effect and to ensure that both parents and children are truly blinded.

6.7 It was agreed that future studies should ensure that the washout period is adequate.

6.8 It was agreed that future studies should make sure that the children being studied are receiving a baseline diet that will ensure good nutritional status. In addition, nutritional diaries should be available for subsequent analysis.