報告資料1

食品添加物が児童の多動性に与える影響に関する論文について
（欧州食品安全機関の評価結果概要）

１．背景

昨年９月６日に公表された英国の医学誌 Lancet オンライン版において、食品添加物の混合物（合成着色料と保存料）を含む飲料水の摂取が児童の行動に与える影響についての研究結果が発表された。

欧州食品安全機関（EFSA：European Food Safty Authority）では本研究について評価を行い、その結果が本年 3 月 14 日に発表された。

２．EFSA 評価結果概要

EFSA の AFC パネル（食品添加物・香料・加工助剤及び食品と接触する物質に関する科学パネル）は、行動や児童精神医学、アレルギー、統計の専門家らの協力のもとにこの研究について検討し、本研究は、試験した添加物の混合物が一部のこどもの行動や注意力にわずかに影響を与えるという限られた証拠を提供するものであると結論した。しかしながら、観察された影響は、本研究における２つの年齢集団や２種類の混合物の間で一貫性がなかった。

全体的な証拠の重要度や以下に掲げるような相当の不確実性を考慮し、AFC パネルは、本研究による知見は食用着色料や安息香酸ナトリウムの ADI を変更する根拠にはならないと結論した。

- 子供の年齢や性、試験した２種類の混合物の影響及び観察者（保護者、教師、独立した観察者）における結果に一貫性がない
- 新しい指標（総合的多動性統合指標（Global Hyperactivity Aggregate, GHA））の臨床上の意義が不明
- 小さなエフェクトサイズの意義が不明
- 個々の添加物の影響を確認するための試験計画になっていない
- 用量反応性に関する情報がない
- 食品添加物の摂取による行動に対する影響の誘発について、生物学的に説明できようなメカニズムが考えにくい

efsa
European Food Safety Authority

Parma, 14 March 2008

PRESS RELEASE

EFSA evaluates Southampton study on food additives and child behaviour

Scientists at Europe's food safety watchdog have completed an assessment of a recent study[1] on the effect of two mixtures of certain food colours and the preservative sodium benzoate[2] on children's behaviour. The study, published last year by researchers at Southampton University in the United Kingdom (McCann *et al*, 2007), suggested a link between these mixtures and hyperactivity in children.

The European Food Safety Authority's (EFSA) AFC Panel[3], with the help of experts in behaviour, child psychiatry, allergy and statistics, concluded that this study provided limited evidence that the mixtures of additives tested had a small effect on the activity and attention of some children. However, the effects observed were not consistent for the two age groups and for the two mixtures used in the study.

Considering the overall weight of evidence and in view of the considerable uncertainties[4], 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 Panel concluded that the findings of the McCann *et al* study could not be used as a basis for altering the ADI[5] of the respective food colours or sodium benzoate.

---

[1] The study conducted by McCann *et al* (2007), commissioned by the UK Food Standards Agency, involved 153 children aged 3 years old and 144 children aged 8-9 years old from the general population, including children with normal to high level activity, but not children medicated for Attention Deficit Hyperactivity Disorder (ADHD). The study is published in The Lancet and can be found at http://www.thelancet.com/journals/lancet/article/PIIS0140673607613069/abstract
The UK's Committee on Toxicology evaluated the study and issued a comprehensive statement which can be found at http://cot.food.gov.uk/statements/cotstatements2007/colpreservchildren

[2] The additives included in the two mixtures given to the children were Tartrazine (E102), Quinoline Yellow (E104), Sunset Yellow FCF (E110), Ponceau 4R (E124), Allura Red AC (E129), Carmoisine (E122) and sodium benzoate (E211).

[3] The Panel on Food Additives, Flavourings, Processing Aids and Materials in Contact with Food.

[4] Lack of consistency in 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, independent assessor); the unknown clinical relevance of the effects measured; lack of information on dose-response; unknown relevance of the small effect size; the fact that mixtures were used and it is not possible to identify the effects of individual additives; the lack of a plausible biological mechanism that might explain the possible link between the consumption of colours and behaviour.

[5] ADI, or Acceptable Daily Intake, is a measure of the amount of a substance, such as a food additive, which can be consumed over a lifetime without an appreciable health risk. ADIs are expressed by milligrams (of the substance) per kilograms of body weight per day.

Among the limitations of the new study, was the inability to pinpoint which additives may have been responsible for the effects observed in the children given that mixtures and not individual additives were tested.

Although the findings from the study could be relevant for specific individuals showing sensitivity to food additives in general or to food colours in particular, it is not possible at present to assess how widespread such sensitivity may be in the general population.

The Panel assisted by behavioural experts considered that the significance of the effects on the behaviour of the children was unclear since it was not known if the small changes in attention and activity observed would interfere with schoolwork or other intellectual functioning.

Based on surveys conducted from 2002 to 2005 in sweets and soft drinks[6], the colours were shown to be frequently used. Sodium benzoate is also often present in soft drinks. The AFC Panel concluded that children who consume brightly coloured sweets and soft drinks could reach intake levels for some of the additives tested in the study that would be similar to the daily amounts given in that study.

The Panel evaluated the McCann *et al* study against the background of previous studies, going back to the 1970s, on the effect of food additives on behaviour and acknowledged that it is the largest study carried out on a suggested link between food additives and hyperactivity in the general population. The Panel noted that the majority of the previous studies used children described as hyperactive and these were therefore not representative of the general population.

The AFC Panel is currently re-evaluating the safety of all food colours authorised in the European Union on a case-by-case basis and the colours used in the McCann *et al* study are included in EFSA's review. Opinions on some of the colours concerned, such as Allura Red, are expected to be adopted by the end of the year.

The full text of the opinion is available on the EFSA website at:
http://www.efsa.europa.eu/EFSA/efsa_locale-1178620753812_1178694648892.htm

For media enquiries, please contact:
E-mail: Press@efsa.europa.eu

Steve Pagani, Head of Press Office
Tel.: +39 0521 036 149

[6] UK Food Standards Agency (FSA) (2002); unpublished survey by the Food Safety Authority of Ireland (FSAI) (2005); Union of European Beverage Associations (UNESDA) (2005).

Assessment of the results of the study by McCann *et al.* (2007) on the effect of some colours and sodium benzoate on children's behaviour [1]

Scientific Opinion of the Panel on Food Additives, Flavourings, Processing Aids and Food Contact Materials (AFC)

(Question No EFSA-Q-2007-171)

Adopted on 7 March 2008

PANEL MEMBERS

Fernando Aguilar, Herman Autrup, Sue Barlow*, Laurence Castle, Riccardo Crebelli, Wolfgang Dekant, Karl-Heinz Engel, Natalie Gontard, David Gott*, Sandro Grilli, Rainer Gürtler, John Chr. Larsen, Catherine Leclercq, Jean-Charles Leblanc, F. Xavier Malcata, Wim Mennes, Maria Rosaria Milana, Iona Pratt, Ivonne Rietjens, Paul Tobback, Fidel Toldrá.

SUMMARY

Following a request from the European Commission, the Panel on Food Additives, Flavourings, Processing Aids and Food Contact Materials (AFC) was asked to assess the results of a recent study on the effect of mixtures of additives on children's behaviour and provide an opinion on the findings, taking into account, if possible, other available scientific literature in the related area.

A recent study by McCann *et al.* (2007) has concluded that exposure to two mixtures of 4 synthetic colours plus a sodium benzoate preservative in the diet result in increased hyperactivity in 3-year old and 8- to 9-year old children in the general population. In an earlier study by the same research team there was some evidence for adverse behavioural effects of a mixture of 4 synthetic colours and sodium benzoate in 3-year old children on the Isle of Wight (Bateman *et al.*. 2004).

[1] For citation purposes: 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* (2008) 660, 1-5

* Two members of the Panel did not participate in the discussion on the subject referred to above because of possible conflict with declared interests.

In this recent study the effects of two combinations of Tartrazine (E102), Quinoline Yellow (E104), Sunset Yellow FCF (E110), Ponceau 4R (E124), Allura Red AC (E129), Carmoisine (E122) and sodium benzoate (E211) on children's behaviour were studied. Five of the six food colours belong to the class of synthetic azo dyes and one, Quinoline Yellow (E104), is a quinophthalone. Sodium benzoate is used as a preservative.

The study involved one hundred and fifty three 3-year old and one hundred and forty four 8- to 9-year old children, selected to represent a broad range of behaviour in the general population including children with normal to high level behavioural activity. Children who were medicated for ADHD were not included. A global hyperactivity aggregate (GHA) score was the main outcome of the study, and this parameter was based on aggregated z-scores of observed behaviours and ratings by teachers, class room observers and parents, plus, for 8- to 9- year old children, a computerised test of attention.

Mix A containing Tartrazine (E102), Ponceau 4R (E124), Sunset Yellow FCF (E110), Carmoisine (E122) and sodium benzoate significantly increased GHA scores for all 3-year old children compared to the placebo control GHA scores (effect size 0.20 [CI 0.01 to 0.39], $p<0.05$).

Mix B containing Sunset Yellow FCF (E110), Carmoisine (E122), Quinoline Yellow (E104), Allura Red AC (E129) and sodium benzoate had no effect on GHA scores in 3-year old children as compared to the placebo control GHA scores (effect size 0.17 [CI -0.03 to 0.36]).

This result persisted when analysis was restricted to 3-year old children who consumed more than 85% of juice and had no missing data (complete case group); in this analysis the effect of Mix A in the 3-year old children was still significantly increased compared to placebo control (effect size 0.32 [CI 0.05 to 0.60, $p<0.05$) but for Mix B no significant effect on GHA scores was observed (effect size 0.21 [CI -0.06 to 0.48]).

For the 8- to 9- year old children a significant effect of Mix A (effect size 0.12 [CI 0.02 to 0.23], $p<0.05$) or Mix B (effect size 0.17 [CI 0.07 to 0.28], $p<0.01$) was seen when analysis was restricted to those children consuming at least 85% of drinks with no missing data (complete case group). When all 8- to 9- year old children that completed the study were taken into account, Mix A had no effect on the GHA scores compared to the placebo control (effect size 0.08 [CI -0.02 to 0.17]) and Mix B had a significant effect on GHA scores (effect size 0.12 [CI 0.03 to 0.22] $p<0.05$).

The authors concluded that exposure to synthetic colours or a sodium benzoate preservative (or both) in the diet result in increased hyperactivity in 3-year old and 8- to 9-year old children in the general population.

Based on surveys conducted from 2002 to 2005, the target colours are more frequently used in sweets but also occur commonly in soft drinks and benzoate is frequently present in soft drinks. Children consuming brightly coloured sweets may be exposed to levels comparable to those considered in the protocol of the McCann *et al.* study for one or more of the food colours studied. Comparable levels may also be reached in those children who consume brightly coloured soft drinks. The level of exposure to sodium benzoate is also likely to occur.

The Panel considers that the steps taken for score normalisation and aggregation are mathematical transformations that might affect the assumptions of normality and independence of the data which are essential for the whole statistical analysis. Therefore, the authors' primary

analysis was repeated using a more justifiable and conventional statistical model, and this was supplemented by a set of additional analyses with the aim of aiding the interpretation of the results.

The Panel considers the re-analysis undertaken by EFSA, in which all single variables (minus the individual baseline value for that variable) were considered without normalisation, so that each subject served as its own reference, as the most adequate. This re-analysis was undertaken both at the level of the individual parameters as well as on the aggregated scores.

Based on the results obtained it was concluded that the analysis with the recalculated GHA score led to broadly similar conclusions to that in the original paper by McCann *et al*, except for the following:

(1) The Mix A versus placebo comparison was not statistically significant for the 3-year olds when all subjects were included (entire sample), while the significance for the $\geq$ 85% consumption and complete case groups was increased slightly;

(2) For the 8- to 9- year age group, the Mix A versus placebo comparison was no longer statistically significant in any of the three consumption groups.

In addition the data were analysed on the basis of a modified GHA score in which the parental scores were not included. The results from this analysis no longer revealed any statistically significant effects of Mix A or Mix B versus placebo, except for Mix B versus placebo in 8- to 9-year old completers.

A further analysis was carried out on the whole data set, comprising analysis of the single variables of parental scores, teacher scores and observer scores, and, in the case of 8- to 9-year old children, computer-based scores. There is a suggestion from these analyses that the statistically significant effects seen in the 3-year olds (Mix A versus placebo) and in the 8-to 9-year olds (Mix B versus placebo) are largely driven in the data by the parental scores and, in the older males in both comparisons, by the computer score.

The Panel notes that some, but not all, earlier studies have also reported effects of 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 Panel concludes that the McCann *et al.* study provides 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 some children selected from the general population, although the effects were not observed for all children in all age groups and were not consistent for the two mixtures. The findings may thus be relevant for specific individuals within the population, showing sensitivity to food additives in general or to food colours in particular.

However, it is not possible to assess the overall prevalence of such sensitivity in the general population and reliable data on sensitivity to individual additives are not available.

The clinical significance of the observed effects also remains unclear, since it is not known whether these small alterations in attention and activity would interfere with schoolwork and

other intellectual functioning. The clinical significance could possibly be clarified by assessments that used scales for functional impairment and diagnostic interviews, especially if a high proportion of children with high symptom scores were to be included in such a study.

There are thus a number of uncertainties that are apparent from this new research, some of which are echoed in earlier research. These include:

- 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.

The Panel concludes that the McCann *et al.* study provides 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, although the effects were not statistically significant for the two mixtures in both age groups.

Since mixtures and not individual additives were tested in the study by McCann *et al.*, it is not possible to ascribe the observed effects to any of the individual compounds.

The clinical significance of the observed effects also remains unclear.

In the context of 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 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.

Key words:

Hyperactivity, ADHD, children's behaviour, Southampton study, McCann, food additives, food colours.

Tartrazine, FD&C Yellow No. 5, E102, CAS 1934-21-0, Trisodium-5-hydroxy-1-(sulfonatophenyl)-4-(4-sulphonatophenylazo)-H-pyrazole-3-carboxylate, food colouring substance, EINECS number 217-699-5.

Ponceau 4R, New Coccine, E124, CAS Registry Number 2611-82-7, Trisodium 2-hydroxy-1-(4-Sulphonato-1-naphthylazo)-naphtalene-6,8-disulphonate, food colouring substance, EINECS number: 220-036-2.

Carmoisine, Azorubine, CI Acid Red 14 and CI food red 3, E122, CAS 3567-69-9, Disodium 4-hydroxy-3-(4-sulfonato-1-naphthylazo)naphthalene-1-sulfonate, food colouring substance EINECS number 222-657-4.

Quinoline Yellow, D&C Yellow No. 10, E104, CAS 8004-92-0, 2-(2-quinolyl)indan-1,3-dione-disulphonate, food colouring substance, EINECS number 305-897-5.

Allura Red AC, E129, CAS 25956-17-6, Food Red No. 40, FD&C Red No. 40, disodium, 2-hydroxy-1-(2-methoxy-5-methyl-4-sulphonatophenylazo)naphthalene-6- sulphonate, food colouring substance, EINECS number 247-368-0.

Sunset Yellow FCF, E110, Food Yellow No. 5, FD&C Yellow No. 6, E 110, CAS 2783-94-0, Disodium 2-hydroxy-1-(4-sulfonatophenylazo)naphthalene-6-sulfonate.

Sodium benzoate, benzoic acid, E 211, E 210, CAS 532-32-1, CAS 65-85-0, food preservative, EINECS number 208-534-8.

（参考）

（薬事・食品衛生審議会食品衛生分科会添加物部会資料（平成20年2月28日開催））

食品添加物が児童の多動性に与える影響に関する論文の発表について

2007年９月６日に公表された英国の医学誌Lancetオンライン版において、食品添加物の混合物（合成着色料と保存料）を含む飲料水の摂取が児童の行動に与える影響についての研究結果が発表された。

＜要約＞

方法：３歳児153名及び8/9歳児144名を対象とした、無作為化、二重盲検、プラセボ対照、クロスオーバー試験を行った。実験に供した飲料には「安息香酸ナトリウム及び合成着色料の混合物（A又はB）*1あるいはプラセボの混合物」が含まれていた。主要な結果の指標は、総合的多動性統合指標（Global Hyperactivity Aggregate, GHA *2）であり、分析はプロトコルに従って行った。

＊１）実験に使用された混合物の組成は以下のとおり。いずれも３歳児の場合の配合であり、8/9歳児に対してはこの1.25倍を使用した。

混合物A：食用赤色102号(5mg)、食用黄色4号(7.5mg)、食用黄色5号(5mg)、カルモイシン*(2.5mg)、安息香酸ナトリウム(45mg)

混合物B：食用赤色40号(7.5mg)、食用黄色5号(7.5mg)、カルモイシン*(7.5mg)、キノリンイエロー*(7.5mg)、安息香酸ナトリウム(45mg)

*我が国では指定外添加物

＊２）今回採用したGHAは、児童の多動性行動（注意力が持続しない、席をすぐ外す、話を聞かない等）について、教師と親が当該行動の頻度等に応じて得点付けを行った結果をもとにしている（8/9歳児ではコンピュータ試験の結果をさらに追加）。

結果：被験者のうち、３歳児16名及び8/9歳児14名は、行動に関連しない理由により試験を完了できなかったが、残りの被験者のデータについて分析を行った。

混合物Aは、3歳児全体に対するGHAにおいて、プラセボと比較して有意な影響を示した（GHA値0.20［95%信頼限界0.01 - 0.39］、p=0.044）。しかし、混合物Bでは有意な影響は見られなかった。この結果は、ジュースの85%以上を摂取し、データ欠落のない3歳児集団に限定しても同様であった（GHA値0.32［95%信頼限界0.05 - 0.60］、p=0.02）。また、8/9歳児では、飲料の少なくとも85%を消費しデータ欠落のない児童に限って分析した場合、混合物A（GHA値0.12［95%信頼限界0.02 - 0.23］、p=0.023）、混合物B（GHA値0.17［95%信頼限界0.07 - 0.28］、p=0.001）ともに有意な影響を示した。