Risiken erkennen – Gesundheit schützen

Hyperactivity and Additives – Is there an association?

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A trial by Southampton University, commissioned by the British Food Standards Agency (FSA), examines a possible association between the intake of specific food additives (the food colourings E102, E104, E110, E122, E124, E129 and the preservative sodium benzoate E211) and the occurrence of Attention Deficit Hyperactivity Disorder (ADHD) in children.

The Federal Institute for Risk Assessment (BfR) has assessed the findings of this recent British trial and examined their relevance for the assessment of the health risk to children from the additives concerned. BfR is of the opinion that the trial does indeed produce some indications of a possible association between the intake of the examined additives and a negative effect on the children's behaviour. However, the observed effects are limited. The trial did not provide any clear evidence of a causal association between additive intake and the observed effects. The findings did not provide any information on the likely biological mechanism for a causal association of this kind either. The European Food Safety Authority (EFSA) also takes these indications of a possible association seriously and includes the trial findings in its current reassessment of all food additives authorised in the EU. BfR participates in this assessment.

As food additives must be included in the list of ingredients, consumers wishing to avoid any intake of the examined substances for precautionary reasons are able to refrain from consuming the corresponding foods and drinks.

1. Subject of the assessment

Southampton University has published the trial findings on a possible association between the intake of specific food additives and the onset of the Attention Deficit Hyperactivity Disorder (ADHD) in children (McCann *et al.* 2007). The trial was commissioned by the British Food Standards Agency (FSA) as the results of an earlier similar study (Isle of Wight Study, Bateman *et al.* 2004) could not be clearly interpreted because of some limitations in the study design.

The British Committee on Toxicity of Chemicals in Food, Consumer Products and the Environment (COT), which had already commented on the Isle of Wight Study (COT June 2001), has also evaluated the trial by Southampton University (COT September 2007) and extensively examined the trial report prior to publication of the findings.

The BfR opinion is based on a publication of the study design and the trial findings in The Lancet (McCann *et al.* 2007) and the COT opinion which was posted on the Internet.

2. Findings

The findings of the trial by Southampton University supply additional indications of a possible association between the intake of specific food additives and increased hyperactivity in children. However, the observed effects are low compared with normal inter-individual variation. Behavioural changes do not occur in all children in a group; nor do they occur in a statistically significant manner in all age and additive groups.

The trial does not supply any clear evidence of a possible causal association between additive intake and the observed effects. Nor can any biological mechanism be identified from the findings for a causal association of this kind.

Additives must be listed on the label. This means that consumers wishing to avoid any intake of the additives concerned for precautionary reasons can refrain from consuming these foods.

3. Reasons

According to Swanson *et al.* and Eigenmann and Haenggeli between 5 and 10% of children are deemed to be hyperactive. In most cases this is linked to the Attention Deficit Hyperactivity Syndrome (ADHS) (Swanson *et al*. 1998; Eigenmann and Haenggeli 2004). The factors which are discussed as the possible causes include genetic aspects (like the expression of polymorphisms concerning specific gene-encoding neurotransmitters) as well as food additives like phosphates, preservatives and colourings. There has been speculation for several years now about a possible causal association. In the 1970s an additive-free diet was proposed as treatment (Feingold 1975). Since then some contradictory or poorly interpretable studies have been published (e.g. Egger *et al.* 1992, Pollock and Warner 1990, Warner, 1993, Bateman *et al*. 2004), which have been the subject of controversial debate (Eigenmann and Haenggeli 2004, Stevenson *et al*. 2005). Further studies, which did not lead to any clear conclusions either, are cited in Bateman *et al*. (2004). Eigenmann and Haenggeli (2004) have commented in a critical manner on these studies. They believe that a careful clinical investigation of the patients concerned is necessary but question a causal association with additives. No clear evidence of hyperactivity caused by additives has been provided up to now. This may be due to methodological difficulties (like the appropriate consideration of a large number of possible confounders concerning behaviour and a lack of objective assessment criteria) and the resulting limitations of the studies.

In the trial by Southampton University (McCann *et al.* 2007), consideration was given to an earlier COT opinion concerning methodological limitations of the previous Isle of Wight Study (Bateman *et al.* 2004).

The placebo-controlled double blind study was conducted with 153 children aged 3 and 144 children aged between 8 and 9. The pre-school facilities and schools were selected in such a manner that already at the beginning of the study a wide range of behaviour of children from “normal” down to high level hyperactivity was represented.

The participating families were instructed to avoid foods containing the additives examined in the trial for the duration of the trial. This meant that intake of these additives was restricted to consumption of the prepared fruit juices to which specific additives had been admixed under defined conditions (amount, time and duration).

Over a period of three times seven days the children were given one of two additive mixes (Mix A or Mix B) or a placebo. Mix A contained the additives Tartrazine (E102), Ponceau 4R (E124), Sunset Yellow (E110) and Carmoisine (E122) and the preservative sodium benzoate (E211). This mix corresponded to the additive mix previously used in the Isle of Wight study. Mix B contained the food colourings Quinoline Yellow (E104), Allura Red AC (E129), Sunset Yellow (E110) and Carmoisine (E122) as well as the preservative sodium benzoate (E211). With regard to composition and dose, Mix B was intended to reflect more current eating habits.

The total amount of colouring in Mix A for the three-year-old children was 20 mg/day, for the older children 25 mg/day. In Mix B the total amount of colouring was 30 mg/day for the three-year-old children and 62.5 mg/day for the older children. The dose of sodium benzoate in both mixes (Mix A and Mix B) was 45 mg/day for both age groups.

The test phase of the trial lasted six weeks. The design was as follows:

Week	1	2	3	4	5	6
Content of the drink	Placebo	Mix A, Mix B or placebo	Placebo	Mix A, Mix B or placebo	Placebo	Mix A, Mix B or placebo

The allocation of the additive mixes or placebos in Weeks 2, 4 and 6 was done on a random basis. The children were given one drink per day which they were supposed to drink at home so that parents could monitor compliance.

The behaviour of the children was examined every week; however only the results of weeks 2, 4 and 6, in which they consumed the additive-containing drinks, were included in the evaluation. The behaviour of the children was assessed in three ways (four ways for older children) using specific criteria. The children's behaviour was assessed by parents at home, by teachers or educators in the classroom or pre-school facility and also by specially trained external experts. In addition the group of 8-9 year olds also took a computer-based attention test.

The numerical results of the various assessments (parents, teachers, external experts, computer test) were combined to give one overall Global Hyperactivity Aggregate (GHA).

In each case the results were assessed for the overall group of children and in addition for the respective groups of children who consumed at least 85% of the drinks. Furthermore, the measurement parameters were assessed individually, not as a GHA.

Possible confounders were taken into account in the statistical assessment (e.g. gender and base-line GHA).

For Mix A a statistically significant effect was only observed for the 3-year-old children and not for the older children when evaluating the entire cohort. The evaluation of the results of the children who had consumed at least 85% of the drinks revealed statistical significance in the 3-year-old children and in the older children.

In the case of Mix B a statistically significant effect was again only observed for the entire cohort in one age group, in this case in the 8-9 year-old children and not in the younger children. The evaluation of the results of the children who had consumed at least 85% of the drinks, revealed statistical significance (in contrast to Mix A) in the age group of 8-9 year-old children only.

When the measurement numbers for hyperactivity resulting from the assessment of parents, teachers, external experts and the computer test were evaluated individually, not as a GHA, then only the results which parents had recorded for Mix A in 3-year-old children and for Mix B in older children were statistically significant. All other results (evaluations by teachers and external experts and the results of the computer test) were not statistically significant. Although the effects went in the same direction, they were nevertheless very limited.

No statistically significant effect was observed for the parameters gender, earlier hyperactivity level, additive content of the foods consumed prior to commencement of the study, education and social class of the parents.

In addition the genetic status regarding various neurotransmitter systems was examined and correspondingly evaluated. According to McCann *et al.* (2007) the findings are to be published separately at a later date. COT, which apparently had access to the full trial report, comments in its opinion (September 2007) that there was a statistically significant association with the onset of hyperactivity (GHA) at least regarding two genetic parameters: in both age groups of children, who had consumed at least 85% of Mix A and in the group of 8-9 year-old children, who had consumed at least 85% of Mix B. Hence genetic causes cannot be completely ruled out. COT did, however, comment that in the so far unproven case of a causal association between genetic predisposition and hyperactivity, the observed effects were too limited to be able to identify risk groups on that basis.

The following section presents the COT comments and conclusions.

In its opinion COT appreciates the improved design of the trial by Southampton University concerning the possible association between the intake of specific food additives and the onset of ADHD compared to the Isle of Wight study. Nevertheless, it also identifies certain limitations concerning study design and evaluation in this trial, too. For instance the time of day when the children consumed the drinks was not defined which meant that the time between additive intake and assessment of behaviour varied. In the case of transient effects this can impact the result. Furthermore, the bodyweight of the children was not recorded which meant that the dose could not be adjusted. Inclusion of behaviour assessment for the respective placebo phases (weeks 1, 3 and 5) would have permitted statements on intra-individual variability.

The observed effects concerning hyperactivity in the children examined were not consistently statistically significant in both age groups and both additive groups (Mix A and Mix B). Although behaviour (measured as GHA) only changed slightly and this was only partially statistically significant, slightly amended behaviour was however observed in all groups given the additives. But this does not necessarily lead to the conclusion that the additive mixes caused an increase in hyperactivity.

The findings of the trial by Southampton University largely correlate with the findings of the Isle of Wight study although the effects measured in the study by Southampton University are more limited.

The uninterrupted duration of exposure in the Southampton University trial was seven days. In the opinion of COT it is not possible to predict whether longer exposure would lead to an exacerbation or weakening of the effects. Subject to the precondition that there is a causal association, the observed effects could be clinically relevant. Another question of importance in this context would be whether the effects are transient or persistent. This question cannot be answered in the trial under review. Transient effects would be less relevant for health than persistent ones.

No biological mechanism for a possible causal association between the intake of the corresponding additives and the onset of hyperactivity can be derived from the results of the trial by Southampton University. According to COT doubts remain about a causal association because of the lack of clear indications of an underlying biological mechanism. In its opinion

COT drew attention to the fact that it cannot be completely ruled out that the observed effects were random even if they were statistically significant in some groups.

COT considers the results of the trial by Southampton University as additional indications of a possible association between the intake of certain mixes of artificial colouring agents containing the preservative sodium benzoate and increased hyperactivity in children. To the extent that there is a causal association, this could be of importance for individual children particularly for those who are in any case clearly hyperactive. However, COT stresses that the mean levels of observed hyperactivity are low compared to normal inter-individual variation and that behavioural changes did not occur in all children in one group, did not occur uniformly across all age groups and not in an even manner for the intake of all additive groups. Hence it is not possible to draw any more extensive conclusions. Nor is it possible to extrapolate the results to other additives.

COT had an opportunity to extensively examine the trial report prior to publication of the findings. After short-term examination of the publication by McCann *et al*. (2007) BfR agrees with the conclusions in the COT opinion which was posted at the same time as the publication by McCann *et al*. (2007) on the Internet.

4. References

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