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Opinion of the Panel on Food Additives, Flavourings, Processing Aids, Materials in Contact with Food and Cosmetics of the Norwegian Scientific Committee for Food Safety

Adopted 12 March 2008

Evaluation of the relevance of the Southampton study on hyperactive behaviour and artificial food colours in combination with sodium benzoate in Norway

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SUMMARY

The Norwegian Food Safety Authority (Mattilsynet) has asked the Norwegian Scientific Committee for Food Safety (Vitenskapskomiteen for mattrygghet, VKM) whether it is necessary to perform a national risk assessment related to the results from the Southampton study on hyperactive behaviour and artificial food colours in combination with sodium benzoate. The case has been assessed by the Panel on Food Additives, Flavourings, Processing Aids, Materials in Contact with Food and Cosmetics (Panel 4).

A study by Southampton University showing a possible association between the intake of two mixtures of artificial food colours together with the preservative sodium benzoate and the occurrence of Attention Deficient Hyperactivity Disorder (ADHD) in children was published in 2007. The trial was commissioned by the UK Food Standards Agency (FSA) as a result of an earlier study, which could not be clearly interpreted due to some limitations in the study design.

The increase in hyperactivity reported in the Southampton study after children were challenged with artificial food colours and sodium benzoate in two different mixtures (A and B) were considered small, and the findings were not consistent between the two age groups and the two mixtures. The study provides a limited support to an increase in hyperactive behaviour from mixtures of artificial food colours and sodium benzoate.

Available data suggest a limited use of these artificial food colours in food products sold on the Norwegian market today. The Panel therefore considers the results of the Southampton study to be of little relevance in Norway. No additional Norwegian risk assessment is considered necessary. However, it is recommended that the future use of these artificial food colours on the Norwegian market is monitored.

SAMMENDRAG (In Norwegian)

Vitenskapskomiteen for mattrygghet (VKM) har på oppdrag fra Mattilsynet blitt bedt om å vurdere om det er nødvendig å gjennomføre en nasjonal risikovurdering relatert til resultatene fra en ny britisk studie (Southampton-studien) som antyder at en blanding av syntetiske fargestoffer og konserveringsmidlet natriumbenzoat kan medføre økt hyperaktivitet hos barn. Saken ble vurdert av Faggruppen for tilsetningsstoffer, aroma, matemballasje og kosmetikk (Faggruppe 4).

En studie utført ved Southampton University publisert i 2007 viser en mulig sammenheng mellom inntaket av to blandinger av syntetiske fargestoffer og natriumbenzoat og en økning i ADHD (”Attention Deficient Hyperactivity Disorder”) hos barn. Studien ble utført på oppdrag fra UK Food Standards Agency (FSA) på bakgrunn av en tidligere studie hvor resultatene var vanskelige å tolke som følge av noen begrensninger i studien.

Den rapporterte økningen i hyperaktivitet blant barn som hadde drukket to ulike blandinger (A og B) inneholdende syntetiske fargestoffer og natriumbenzoat fra Southampton-studien vurderes som liten og funnene er ikke konsekvente på tvers av alder og de to blandingene. Studien gir en begrenset støtte til en økning av hyperaktivitet etter eksponering for syntetiske fargestoffer og natriumbenzoat.

De tilgjengelige dataene tyder på en begrenset bruk av disse syntetiske fargestoffene i matvarer på det norske markedet per i dag. Faggruppen vurderer derfor resultatene fra Southampton-studien som lite relevante for Norge. Det er ikke funnet nødvendig å utføre en ny risikovurdering. Faggruppen anbefaler at bruken av disse syntetiske fargestoffene i matvarer på det norske markedet blir overvåket.

CONTRIBUTORS

Persons working for VKM, either as appointed members of the Committee or as *ad hoc* experts, do this by virtue of their scientific expertise, not as representatives for their employer. The Civil Services Act instructions on legal competence apply for all work prepared by VKM.

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Assessed by

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BACKGROUND

Hyperkinetic Disorder (HKD), also known as Attention Deficient Hyperactivity Disorder (ADHD), is regarded as a neurological disorder where the cause of the disease is thought to be multifunctional, including both genetic and environmental factors. In Norway, the prevalence is anticipated to be 3 to 5% among children and adolescent below 18 years old, reported by The Directorate for Health and Social Affairs (Asheim *et al.*, 2007). ADHD typically has onset in early childhood and is characterised by specific patterns of behaviour, like inattention, impulsivity, hyperactivity and reduced ability to concentrate.

Since the 1970s, there has been speculated about a causal relationship between food additives and ADHD. Although a number of studies have been published, cited in Bateman *et al*. (2004), no clear evidence of hyperactivity caused by food additives has been provided.

A new study by Southampton University showing a possible association between the intake of two mixtures of certain artificial food colours together with the preservative sodium benzoate and the occurrence of ADHD in children was published in 2007 (McCann *et al.*, 2007). The trial was commissioned by the UK Food Standards Agency (FSA) as a result of an earlier study, which could not be clearly interpreted because of some limitations in the study design (Bateman *et al.*, 2004).

In September 2007, the UK Committee on Toxicity of Chemicals in Food, Consumer Products and the Environment (COT) published a statement concerning the trial report by McCann *et al.* prior to publication of the findings (COT, 2007). The Federal Institute for Risk Assessment (BfR) in Germany has recently published an opinion where they assessed the findings of the recent British trial and examined their relevance for the assessment of the health risk to children from the additives concerned (BfR, 2007).

This opinion by the Norwegian Scientific Committee for Food Safety (VKM) on the new trial by Southampton University is based on the publication of the study, the COT opinion and the opinion from BfR. The Southampton study is at present also being evaluated by the European Food Safety Authority (EFSA).

TERMS OF REFERENCE

Based on the results from the recent study performed at the Southampton University, the Norwegian Food Safety Authority finds it necessary to ask for a risk assessment of the association between intake of food additives and hyperactivity. The Norwegian Scientific Committee for Food Safety (VKM) is asked to answer the following questions.

- Is it necessary to perform a national evaluation of food additives and hyperactivity before EFSA has finalised its evaluation?
- Do VKM find it necessary to perform a national risk assessment after the risk assessment by EFSA is available?
- VKM is asked to evaluate the importance of combined exposure to artificial food colours and sodium benzoate.
- Possible lack of knowledge or data should be further described.

OPINION

Hazard characterisation

Design of the Southampton study

The description of the study design is taken from the recent opinions from COT and BfR (COT, 2007; BfR, 2007).

The placebo-controlled double blind study was conducted with 153 children aged 3 years and 144 children aged 8-9 years. 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" to high level hyperactivity was represented.

The participating families were instructed to avoid foods containing the additives examined 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 of day and duration of exposure).

Table 1. The test phase of the trial lasted six weeks. The design was as follows (adapted from BfR, 2007):

Week	**1**	**2**	**3**	**4**	**5**	**6**
Content of 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 (Table 1). The children were given one drink per day which they were supposed to drink at home so that parents could monitor compliance.

The children were given Mix A, Mix B or placebo for seven days in weeks 2, 4 and 6 and placebo during weeks 1, 3 and 5 (Table 1). Mix A contained the additives Tartrazine (E102), Ponceau 4R (E124), Sunset Yellow FCF (E110) and Carmoisine (E122) and the preservative sodium benzoate (E211) (Table 2). This mix corresponded to the additive mix previously used in the Isle of Wight study (Bateman *et al.*, 2004). Mix B contained the artificial food colours Quinoline Yellow (E104), Allura Red AC (E129), Sunset Yellow FCF (E110) and Carmoisine (E122), as well as the preservative sodium benzoate (E211) (Table 2). With regard to composition and dose, Mix B was intended to reflect more current eating habits.

Table 2. Composition of the food additive challenge mixtures used in the Southampton trial (McCann *et al.*, 2007), adapted from (COT, 2007).

Name of Additive (E number)	ADI [1] (mg/kg bw)	Mix A 3-year-olds mg/day (mg/kg bw day)[2]	Mix B 3-year-olds mg/day (mg/kg bw day)[2]	Mix A 8- to 9-year-olds mg/day (mg/kg bw day)[3]	Mix B 8- to 9-year-olds mg/day (mg/kg bw day)[3]
Tartrazine (E102)	7.5	7.5 (0.50)	0	9.36 (0.30)	0
Ponceau 4R (E124)	4	5.0 (0.33)	0	6.25 (0.20)	0
Sunset Yellow FCF (E110)	2.5	5.0 (0.33)	7.5 (0.50)	6.25 (0.20)	15.6 (0.50)
Carmoisine (E122)	4	2.5 (0.17)	7.5 (0.50)	3.12 (0.10)	15.6 (0.50)
Quinoline yellow (E104)	10	0	7.5 (0.50)	0	15.6 (0.50)
Allura Red AC (E129)	7	0	7.5 (0.50)	0	15.6 (0.50)
Total artificial food colours per day (mg)		20	30	25	62.5
Volume of drink given daily (ml)		300	300	625	625
Concentration of colour in mg/L		66.7	100	40	100
Sodium benzoate (E211)	5	45 (3)	45 (3)	45 (1.45)	45 (1.45)

[1]The acceptable daily intake (ADI) is an estimate of the amount of a substance in food or drink, expressed on a body weight basis, that can be ingested daily over a lifetime by humans without appreciable health risk
[2]Based on average body weight of 15 kg for a 3-year-old
[3]Based on average body weight of 31 kg for an 8-year-old

The total amount of artificial food colours in Mix A for the 3-year-old children was 20 mg/day and 25 mg/day for the older children. In Mix B, the total amount of artificial food colours was 30 mg/day for the 3-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 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- to 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. Confounders like gender,

baseline GHA score, pretrial diet, maternal education level and maternal social class were taken into account in the statistical assessment).

Results from the Southampton study

The interpretation of results is taken from McCann *et al.* (2007) and the recent opinions from COT and BfR (COT, 2007; BfR, 2007).

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 (Table 3).

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- to 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 group of 8- to 9-year-old children only (Table 3).

Table 3. Summary of analysis of changes in GHA scores following challenge with Mix A or B compared with placebo, for the whole cohort (primary analysis) and a sub-group consuming ≥ 85% of the challenge drinks and no missing data (*post-hoc analysis*), adapted from (COT, 2007).

		Mix A	**Mix B**
Whole sample (primary analysis)	3-year-olds (n = 140)	0.20 (0.01 to 0.39)*	0.17 (-0.03 to 0.36)
	8- to 9-year-olds (n = 136)	0.08 (-0.02 to 0.17)	0.12 (0.03 to 0.22)*
≥ 85% consumption and no missing GHA data (*post-hoc analysis*)	3-year-olds (n = 73)	0.32 (0.05 to 0.60)*	0.21 (-0.06 to 0.48)
	8- to 9-year-olds (n = 91)	0.12 (0.02 to 0.23)*	0.17 (0.07 to 0.28)*

*Statistically significant (at $p < 0.05$)
Scores are expressed as mean standard deviation units (SDU) with 95% confidence intervals in parentheses

When the measurement numbers for hyperactivity resulting from the assessment of parents, teachers, external experts and the computer test were evaluated individually (disaggregated analysis, Table 4), not as a GHA, then only the results that 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.

Table 4. Summary of disaggregated analysis of changes in behaviour measures assessed following challenge with Mix A or B compared with placebo, based on subgroup consuming ≥ 85% of the challenge drinks, adapted from (COT, 2007).

	Mix A		Mix B	
	3-year-olds	8- to 9-year-olds	3-year-olds	8- to 9-year-olds
Parental score	0.49 (0.09 to 0.89)*	0.03 (-0.10 to 0.16)	0.36 (-0.04 to 0.76)	0.13 (0.00 to 0.25)*
Teacher score	0.03 (-0.11 to 0.16)	-0.01 (-0.12 to 0.09)	0.08 (-0.05 to 0.21)	0.01 (-0.09 to 0.11)
Classroom observation score	0.10 (-0.07 to 0.27)	0.08 (-0.07 to 0.22)	-0.01 (-0.18 to 0.16)	0.05 (-0.09 to 0.19)
Computer-based task score	N.D.	0.08 (-0.16 to 0.32)	N.D.	0.20 (-0.04 to 0.43)

*Statistically significant (at $p < 0.05$)
Scores are expressed as mean SDU with 95% confidence intervals in parentheses
N.D.: not determined

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.

Comments by VKM
The observed increase in hyperactivity in children after being challenged with artificial food colours and sodium benzoate in two different mixtures (A and B) were considered small, and the findings were not consistent across age groups or across the different mixtures. A significant increase in hyperactivity was found for 3-year-olds challenged with Mix A and for 8- to 9-year-olds challenged with Mix B. However, only the parental scores showed a significant increase in hyperactivity in the disaggregated analysis of changes of behaviour.

Exposure characterisation

There are no market data in Norway for the use of the artificial food colours examined in the Southampton study. However, it should be noted that before 2001 these artificial food colours were generally not permitted for use in food in Norway. The colours were authorised for use in accordance with EC legislation in 2001. According to the industry (Ministry of Foreign Affairs, 2000) and a limited market survey, the use of these artificial food colours in products on the Norwegian market today is probably very low.

A limited survey of the use of artificial food colours was carried out in Norway (January/February 2008). The artificial food colours are permitted for use in several food products like sweets, beverages, desserts, jam, soups, sauces, mustard and some products less relevant for children. Thirty-two desserts, 11 mustards, 31 jams, 15 soups and 20 sauces were controlled for the content of artificial food colours, and none of these food products were found to contain the artificial food colours used in the Southampton study. These food

products were not controlled for addition of sodium benzoate, but it is expected that several brands contain sodium benzoate.

The labelling of a total of 120 different sweets and candy products was controlled and only 9 brands of sweets were found to contain Quinoline Yellow (E 104). Tartrazine (E 102) and Allura Red AC (E 129) were found in 2 brands, while only one brand was found to contain Sunset Yellow FCF (E 110). Only for the brands containing E 102, E 129 and E 110, the colours were found to be in a mixture. The other artificial food colours, Ponceau 4R (E 124) and Carmoisine (E 122), were not found in any of the sweets checked.

Quinoline Yellow (E 104) was the only of the artificial food colours tested in the Southampton study found in beverages in Norway. It was found in 3 of the 36 beverages that were checked.

This limited survey on the use of artificial food colours is assumed to be representative for the products found on the marked in Norway.

The preservative sodium benzoate (E 211) is present in many food products in Norway. In a recent report where the total intake of sodium benzoate from food was estimated it was found that benzoic acid from beverages contributed with approximately 50% of the estimated intake. Young children (1- to 2-year-olds) who consume high amounts of beverages are at risk of exceeding the acceptable daily intake (ADI) for benzoic acid (VKM, 2007).

Based on these findings, it could be concluded that the likelihood for children in Norway to be exposed to the artificial food colours examined in the Southampton study is very low.

Risk characterisation

It is not known which of the single food additives in Mix A and B, or the combination, which might be responsible for the possible effect on hyperactivity.

It is also noted that only a small increase in hyperactivity was found after challenge with artificial food colours and sodium benzoate in children in the Southampton study, and there was a lack of consistency across age groups and type of mixture.

It is unlikely that a 3-year-old child in Norway may be regularly exposed both to Quinoline Yellow and sodium benzoate from sweets and beverages in the doses used in the Southampton study. It is even less likely that a child in Norway would be exposed to all the artificial food colours and sodium benzoate corresponding to Mix A or B in the Southampton study.

Taking into account the low use of these artificial food colours in food products on the Norwegian market resulting in very limited intake among Norwegian children, the Panel concludes that the risk of being exposed to the combinations of food additives used in the Southampton study is negligible, and therefore the risk is low for the possible effects described in this study.

Combined exposure

The Southampton study, which has used combinations of artificial food colours and sodium benzoate, cannot clarify whether the reported effects are caused by single compounds or mixtures of these. No additional studies have been found on possible combined effects of artificial food colours and sodium benzoate.

CONCLUSIONS

The increase in hyperactivity reported in the Southampton study after children were challenged with artificial food colours and sodium benzoate in two different mixtures (A and B) were considered small, and the findings were not consistent between the two age groups and the two mixtures. The study provides a limited support to an increase in hyperactive behaviour from mixtures of artificial food colours and sodium benzoate.

Available data suggest a limited use of these artificial food colours in food products sold on the Norwegian market today. The Panel therefore considers the results of the Southampton study to be of little relevance in Norway. No additional Norwegian risk assessment is considered necessary.

The Southampton study, which has used combinations of artificial food colours and sodium benzoate, cannot clarify whether the reported effects are caused by single compounds or mixtures of these. No additional studies have been found on possible combined effects of artificial food colours and sodium benzoate.

It is recommended that the future use of these artificial food colours on the Norwegian market is monitored.

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