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**REPORT FROM THE COMMISSION TO THE EUROPEAN PARLIAMENT AND
THE COUNCIL**

ON THE PROGRESS OF THE RE-EVALUATION OF FOOD ADDITIVES

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EXECUTIVE SUMMARY

Food additives are subject to a safety evaluation before they are permitted for use in the European Community. It is also a requirement that they are re-evaluated whenever necessary in light of changing conditions of use and new scientific information. European Parliament and Council Directives 2003/114/EC and 2003/115/EC require the Commission to present a status report to the European Parliament and the Council on the re-evaluations of food additives which have been carried out.

This report provides a summary of the recent additive re-evaluations undertaken by the Scientific Committee on Food (SCF) and the European Food Safety Authority (EFSA) and describes the related actions taken by the European Commission on the basis of the scientific opinions.

Some of the additive evaluations were undertaken when the SCF was first established in the 1970's. Therefore the Commission felt that it is timely to request that the EFSA undertake to review the evaluations of all currently permitted food additives. This report additionally describes the rationale and priority setting for this review by the EFSA.

1. INTRODUCTION

The authorisation of food additives for use in foods is harmonised in the European Community. Framework Directive 89/107/EEC¹ lays down the general principles for the use and authorisation of food additives, whereas three specific directives on sweeteners (Directive 94/35/EC²), colours (Directive 94/36/EC³) and on additives other than colours and sweeteners (Directive 95/2/EC⁴) lay down the rules on which additives may be used in which foods and their conditions of use. This legal framework is complemented by three Commission Directives laying down specifications (specific purity criteria) for the authorised food additives (Directives 95/31/EC⁵, 95/45/EC⁶ and 96/77/EC⁷).

The authorisations are based on three criteria:

- the food additive does not pose a safety risk to the health of the consumer,
- there is a technological need for the use and,
- the consumer is not misled by the use of a food additive.

According to the framework Directive 89/107/EEC, the Scientific Committee on Food (SCF), now replaced by the European Food Safety Authority (EFSA), must be consulted before the adoption of provisions likely to affect public health, such as the drawing up of lists of additives and the conditions for their use. Accordingly, food additives have been evaluated for their safety by the SCF or EFSA prior to their authorisation.

Directive 89/107/EEC also requires that food additives must be kept under continuous observation and re-evaluated whenever necessary in the light of changing conditions of use and new scientific information.

Accordingly some food additives have been re-evaluated in recent years when new scientific data had been requested or became otherwise available.

There are a number of reasons why the Commission has considered it appropriate to start a systematic re-evaluation of food additives:

- (1) The Commission has recently adopted a proposal for a new Regulation⁸ on food additives as announced in the White Paper on Food Safety. In this context, the Commission has proposed to formalise its intention and introduce a requirement for a systematic re-evaluation of all authorised food additives.

¹ Council Directive 89/107/EEC, OJ L 40, 11.2.1989, p. 27.

² European Parliament and Council Directive 94/35/EC, OJ L 237, 10.9.1994, p. 3.

³ European Parliament and Council Directive 94/36/EC, OJ L 237, 10.9.1994, p. 13.

⁴ European Parliament and Council Directive No 95/2/EC, OJ L 61, 18.3.1995, p. 1.

⁵ Commission Directive 95/31/EC, OJ L 178, 28.7.1995, p. 1.

⁶ Commission Directive 95/45/EC, OJ L 226, 22.9.1995, p. 1.

⁷ Commission Directive 96/77/EC, OJ L 339, 30.12.1996, p. 1.

⁸ COM(2006) 428 final.

- (2) The report from the Commission on Dietary Food Additive Intake in the European Union⁹ published in 2001 has shown that the intake of some food additives has the potential to exceed the Acceptable Daily Intake (ADI).
- (3) In the context of the amendment of Directive 95/2/EC and Directive 94/35/EC on sweeteners (Directives 2003/114/EC¹⁰ and 2003/115/EC¹¹), the Commission has been required to present a status report about the re-evaluation of food additives to the European Parliament and the Council, in particular for those additives that were identified as possibly exceeding the ADI in the 2001 intake report.
- (4) A report entitled “Food additives in Europe 2000¹²” was submitted by the Nordic Council of Ministers to the Commission. This provides a good basis for the prioritisation of additives for re-evaluation. It examines whether the safety evaluations on food additives undertaken by the SCF are still valid and adequate in the light of present day standards for safety assessments. Furthermore, it examines whether significant new toxicological studies have been published since the latest SCF evaluation of a substance.

Consequently, the Commission has asked the EFSA to re-evaluate all currently permitted food additives in the EC.

This report is elaborated as a response to the requirements laid down in Directives 2003/114/EC and 2003/115/EC. The European Commission’s mandate is to submit a report to the European Parliament and the Council outlining the progress made in the re-evaluations of additives and setting a provisional calendar for future re-evaluations.

This report describes the safety evaluation which applies to food additives prior to their authorisation and lists examples of recent re-evaluations of authorised food additives. It also gives an overview on the organisation of the on-going re-evaluation of food colours and describes other on-going re-evaluations. Further detail relating to recent re-evaluations is provided in an accompanying staff working paper.

2. SAFETY EVALUATION

Prior to their authorisation food additives are evaluated for safety by the independent scientific bodies that advise the Commission. The SCF, created in 1974, undertook this task until May 2003. The task of the SCF was to advise the Commission on any problem relating to the protection of the health and safety of persons arising or likely to arise from the consumption of food, in particular on nutritional, hygienic and toxicological issues.

⁹ COM(2001) 542 final.

¹⁰ OJ L 24, 29.1.2004, p. 65.

¹¹ OJ L 24, 29.1.2004, p. 58.

¹² Food Additives in Europe 2000, Status of safety assessments of food additives presently permitted in the EU, Nordic Council of Ministers, TemaNord 2002:560.

Therefore, although the legislation on the authorisation and use of food additives was only fully harmonised and completed by 1995, there is a long history of evaluating the safety of food additives in the EC.

Since May 2003 the SCF was replaced by the EFSA established by Framework Regulation (EC) No 178/2002 of 28 January 2002¹³.

Similarly to the SCF, the EFSA provides independent scientific advice on all matters linked to food and feed safety. EFSA's risk assessments provide risk managers with a sound scientific basis for defining policy driven legislative or regulatory measures required to ensure a high level of consumer protection with regard to food safety.

In addition to establishing technological need and value to consumers of a proposed food additive, it is necessary to evaluate the implications for the health of the consumer due to the presence of that additive in food.

Within the EFSA, it is usually the Panel on food additives, flavourings, processing aids and materials in contact with food (AFC) which carries out the risk assessment in relation to food additives and issues the opinions on their safety.

Information that should be submitted in order to carry out a safety evaluation of a food additive is laid down in the guidance document¹⁴ that was developed by the SCF (adopted in July 2001). Subsequently this guidance document was endorsed by the AFC panel in its second meeting on 9 July 2003. The SCF first issued guidelines for the safety assessment of food additives¹⁵ in 1980. Since that time, a number of other guidance documents have been published on the principles for assessment of food additive safety, including by the Joint FAO/WHO Expert Committee on Food Additives (JECFA),¹⁶ and there is now considerable international consensus on these general principles.

In accordance with the SCF guidelines, the aim of toxicological testing is to determine whether the substance, when used in the manner and in the quantities proposed, would pose any appreciable risk to the health of consumers. Such testing should provide not only information relevant to the average consumer, but also relevant to those population groups whose pattern of food consumption, physiological status or health status may make them vulnerable, e.g. young age, pregnancy, diabetes, etc. A general framework covering core tests and other tests is given in the guidelines. Core tests include tests on metabolism and toxicokinetics, subchronic toxicity, genotoxicity, chronic toxicity and carcinogenicity as well as tests on reproduction and developmental toxicity. Other tests include studies on immunotoxicity, allergenicity, food intolerance, neurotoxicity and *in vitro* studies as alternatives to *in vivo* studies.

¹³ Regulation (EC) No 178/2002 of the European Parliament and of the Council, OJ L 31, 1.2.2002, p. 1.

¹⁴ Guidance on submissions for food additive evaluations by the Scientific Committee on Food (opinion expressed on 11 July 2001). http://europa.eu.int/comm/food/fs/sc/scf/out98_en.pdf

¹⁵ Guidelines for the Safety Assessment of Food Additives (Opinion expressed on 22 February 1980, 10th Series). http://europa.eu.int/comm/food/fs/sc/scf/reports/scf_reports_10.pdf

¹⁶ IPCS/JECFA (1987) Environmental Health Criteria 70: Principles for the Safety Assessment of Food Additives and Contaminants in Food. World Health Organization, Geneva.

As stated in the guidelines, the studies required will depend on the chemical nature of the additive, its intended uses and levels of use in food, whether it is a new additive or a re-examination of an existing additive. In addition to laboratory tests, it may be possible to use human data derived from medical use, epidemiologic studies, or on critically exposed groups. However, it is recognised that for new food additives, a safety evaluation generally relies on experimental data largely derived from investigations in laboratory animals. If the biological action of a substance has been ascertained qualitatively and quantitatively in a range of tests on laboratory animals, the likely effects on man can then be estimated by careful extrapolation by toxicologists.

3. PRIORITY SETTING

3.1. Colours

Synthetic colours were among the first additives to be evaluated, therefore, many of the evaluations date back to the 1970's and 1980s'. For some of these colours many new studies have become available and the results of these studies should be included in the evaluation.

The report of the Nordic Council (Food Additives in Europe 2000) draws the same conclusion by giving some natural colours priority. The report concludes that they have only been tested to a very limited extent and that the evaluations were based more on assumptions. For instance some were considered acceptable as long as they were derived from food and that consumption as a colour would not significantly differ from that which could be expected from consuming the foods in question. However, since the specifications for these colours also allow for other sources and there is a tendency by food producers to replace synthetic colours by natural ones, it is not certain that these conditions are still met. So a new safety assessment is needed. The report gives a low to medium priority for the re-evaluation of synthetic colours.

The report of the Nordic Council therefore suggested that most natural colours are given a higher priority re-evaluation than the synthetic colours.

3.2. Miscellaneous food additives

The re-evaluation of nitrites and nitrates was set as a priority following the judgement of the Court of Justice in case C-3/00 Denmark against Commission¹⁷. Additionally, Directive 2003/114/EC lays down as a matter of priority the re-evaluation of polysorbates.

Moreover, the report of the Nordic Council has given a medium priority to some additives in the group of antioxidants and preservatives. However, the categorisations are less homogeneous than those concerning colours or sweeteners.

¹⁷ C-3/00 Judgment of 20/03/2003, Denmark / Commission (Rec.2003, p.I-2643).

3.3. Sweeteners

The safety evaluation of most sweeteners is recent. Therefore, sweeteners should have the lowest priority for re-evaluation. However, due to recent studies published on the safety of aspartame, the EFSA has recently re-evaluated aspartame with high priority.

4. OUTCOME AND STATUS OF RECENT AND ONGOING RE-EVALUATIONS

The outcomes and status of some recent and ongoing re-evaluations is provided below, further details relating to these and other re-evaluations is available in a Commission Staff Working Paper¹⁸.

4.1. Nisin (E 234) and Natamycin (E 235)

Nisin is authorised for food preservation by Directive 95/2/EC. Nisin is permitted in ripened cheese and processed cheese, certain puddings, clotted cream and mascarpone.

Natamycin is also authorised for food preservation by Directive 95/2/EC. Natamycin is permitted for the surface treatment on cheese and on dried cured sausages.

The Scientific Steering Committee adopted an opinion on antimicrobial resistance in 28 May 1999¹⁹. On the basis of this opinion, the Commission adopted on 20 June 2001 a Communication on a Community strategy against antimicrobial resistance²⁰. Action 9 listed in the Communication is to review the use of two authorised antimicrobial agents in food: nisin and natamycin.

The re-evaluation of nisin was completed by January 2006 and the AFC Panel adopted an opinion on nisin with the following conclusions²¹:

Nisin has a double mode of antimicrobial action; binding to lipid II and subsequent inhibition of cell wall synthesis as well as forming pores in the cytoplasmic membrane. Nisin is used as a food preservative and has currently no therapeutic use. There are no reports of sporadic nisin resistant bacterial mutants showing cross-resistance to therapeutic antibiotics. The Panel considered that this is probably due to the differences in the antimicrobial mode of action between therapeutic antibiotics and nisin and that antibiotic resistance to nisin is not likely to be an issue in relation to its use in food.'

Similarly to nisin, the Commission has asked the EFSA to issue an opinion on the safety of using natamycin as a food additive and also to address the issue of antimicrobial resistance and the use of natamycin. This re-evaluation should be completed by mid 2007.

¹⁸ [reference to be added].

¹⁹ Opinion of the Scientific Steering Committee on Antimicrobial Resistance 28 May 1999 (available from http://ec.europa.eu/food/fs/sc/ssc/out50_en.pdf)

²⁰ COM(2001) 333 final.

²¹ The EFSA Journal (2006) 314, 1-16.

4.2. Para-hydroxybenzoates (E 214 – 219)

Para-hydroxybenzoates are permitted for use as preservatives in some meat coatings, potato and cereal based snacks, coated nuts, certain confectionery items and dietary food supplements in liquid form by Directive 95/2/EC.

The SCF evaluated para-hydroxybenzoates (parabens) in 1994²² and established a temporary ADI of 0-10 mg/kg bw, as the sum of methyl, ethyl and propyl p-hydroxybenzoic acid esters and their sodium salts.. The ADI was made temporary because the SCF considered that the toxicological information available showed some inadequacies and uncertainties. The SCF therefore requested a new oral teratogenicity study in the rat.

In 2000, the SCF reiterated its wish to review the safety of parabens. At its last meeting in April 2003, the SCF noted that no data had been submitted by the food industry in support of the parabens and drew attention to its statement of October 2000, that the temporary ADI should be withdrawn if no further data were submitted.

In addition, Directive 2003/114 requested the Commission and the EFSA to review the conditions for the use of E 214 – 219 p-hydroxybenzoates and their sodium salts before 1 July 2004.

The re-evaluation was completed in July 2004 when the AFC Panel adopted an opinion²³ with the following conclusions:

‘The Panel established a full group ADI of 0-10 mg/kg bw for the sum of methyl and ethyl p-hydroxybenzoic acid esters and their sodium salts.... The Panel considered that propyl paraben should not be included in this group ADI because propyl paraben, contrary to methyl and ethyl paraben, had effects on sex hormones and the male reproductive organs in juvenile rats.

The Panel is unable to recommend an ADI for propyl paraben because of the lack of a clear NOAEL.’

Consequently, the Commission proposed in October 2004 to withdraw E 216 propyl p-hydroxybenzoate and E 217 sodium propyl p-hydroxybenzoate from Directive 95/2/EC²⁴. The amendment to Directive 95/2/EC was adopted by the European Parliament and the Council on 5 July 2006²⁵.

4.3. Nitrites and nitrates (E 249 – E 252)

Sodium and potassium salts of nitrite and nitrate are permitted for preservation of meat products, cheese and certain fish products by Directive 95/2/EC.

In light of the judgement of the Court of Justice in Case C-3/00, Denmark v. Commission, the Commission consulted the EFSA for advice on the current

²² Opinion on p-hydroxybenzoic acid alkyl esters their sodium salts. Expressed on 25 February 1994. Reports of the Scientific Committee for Food, Thirty-Fifth Series. CEC, Luxembourg. p. 9-12.

²³ The EFSA Journal (2004) 83, 1- 26.

²⁴ (COM(2004) 650 final).

²⁵ Directive 2006/52/EC, OJ L 204, 26.7.2006 p. 10.

authorisations of nitrite and nitrate in meat products in relation to the effect of nitrites and nitrates on the microbiological safety of meat products, in particular related to *Clostridium botulinum*.

The re-evaluation was completed in November 2003 and the Scientific Panel on Biological Hazards adopted an opinion²⁶.

The Panel confirmed that nitrite contributes to microbiological safety and also to the flavour, colour and anti-oxidative stability of meat products. Levels up to 100 mg/kg of added nitrite might suffice for preservation of many products, but some might require up to 150 mg/kg. The Panel noted that nitrate provides no direct protection against the growth of *Clostridium botulinum* in most meat products. However, the use of nitrate as a reservoir of nitrite appears necessary, in particular, in traditionally-cured meat products.

The Panel recommended that the levels of nitrite and nitrate are set down in the legislation as “added amount”. It was of the opinion that the added amount of nitrite rather than the residual amount contributes to the inhibitory activity against *C. botulinum*.

In order to keep the level of nitrosamines as low as possible by lowering the levels of nitrites and nitrates added to food whilst maintaining the microbiological safety of food products, the European Parliament and the Council have adopted Directive 2006/52/EC amending Directive 95/2/EC to change the current authorisations for nitrates and nitrites. In this amendment the general principle of controlling ingoing amounts of nitrates and nitrites applies, however for certain traditionally manufactured products the use is controlled by residual amounts.

4.4. Benzoic acid and its salts (E 210 – E213)

Benzoic acid and its salts are widely used as food preservatives and permitted for use by Directive 95/2/EC.

The SCF first evaluated the safety of benzoic acid and its salts in 1994. In this opinion²⁷, the Committee raised questions about developmental toxicity and genotoxicity and asked for further studies in these two areas. In view of these data requests, the Committee set only a temporary ADI of 0 – 5 mg/kg bw based on an overall NOAEL of 500 mg/kg bw/day from long-term and multigeneration studies.

In September 2002, the SCF had completed the re-evaluation of its earlier opinion in the light of new information and adopted an opinion²⁸ with the following conclusions:

On the basis of these data and the other types of study previously evaluated by the Committee, the Committee can establish a full Group ADI of 0 - 5 mg/kg bw for

²⁶ The EFSA Journal (2003) 14, 1-31.

²⁷ Opinion on benzoic acid and its salts. Expressed on 24 February 1994. Reports of the Scientific Committee for Food, Thirty-Fifth Series. CEC, Luxembourg, p. 33-39.

²⁸ Opinion of the Scientific Committee on Food on Benzoic acid and its salts (expressed on 24 September 2002).

benzoic acid and its salts including benzyl alcohol and related benzyl derivatives used as flavourings.’

4.5. Cyclamic acid and its sodium and calcium salts (E 952)

Cyclamic acid and its sodium and calcium salts are intense sweeteners, with a sweetness approximately 30 times that of sucrose. They are permitted for use in several low calorie foods and beverages by Directive 94/35/EC.

The SCF evaluated the safety of cyclamate, cyclohexylamine and dicyclohexylamine in 1984²⁹ and established a temporary ADI of 0-11 mg/kg bw, expressed as cyclamic acid, for cyclamic acid and its sodium and calcium salts. The Committee reviewed cyclamate again in 1988, 1991 and 1995 and confirmed the temporary ADI.

In March 2000, the SCF revised its opinion³⁰ on cyclamate again. The Committee concluded that a full ADI for cyclamate could now be established. However, although the new epidemiological data revealed no indications of harmful effects of cyclamate on humans, the Committee decided to lower the ADI for this substance from 11 to 7 mg/kg bw. The reason for this was that new scientific evidence had shown the conversion rate of cyclamate to cyclohexylamine and dicyclohexylamine in the body to be higher than was previously thought.

Consequently, the authorisations for the use of cyclamates were revised in Directive 2003/115/EC to reflect the change in the acceptable daily intake.

4.6. Aspartame (E 951)

Aspartame is an intense sweetener with a sweetness approximately 200 times that of sucrose. It is permitted for use in several low calorie foods and beverages by Directive 94/35/EC. Salt of aspartame acesulfame (E 962) is also permitted by Directive 94/35/EC. Owing to the phenylalanine content of aspartame, persons suffering from the genetic disease phenylketonuria (PKU) must take into account the consumption of aspartame into their daily intake of phenylalanine, therefore under EU legislation products containing aspartame must contain the warning ‘contains a source of phenylalanine’.

²⁹ Commission of the European Communities (1985). Report of the Scientific Committee for Food on Sweeteners (opinion expressed on 14 September 1984). Reports of the Scientific Committee for Food (Sixteenth Series). CEC, Luxembourg, EUR 10210 EN.

³⁰ Revised opinion on cyclamic acid and its sodium and calcium salts (Expressed on 9 March 2000).

The SCF initially evaluated aspartame during 1984³¹ and established an ADI of 40 mg/kg bodyweight. Subsequently the SCF re-examined aspartame in 1988³², 1997³³ and most recently in 2001 the Committee reviewed the safety of aspartame by considering over 500 papers published in the scientific literature since the earlier SCF assessment (papers published between 1988 and 2001). As a result of this review in 2002³⁴ the Committee concluded that after reviewing the data available to date there was no evidence to suggest a need to revise the outcome of the earlier risk assessment or the ADI previously established for aspartame.

In June 2005, the European Commission became aware of a new study carried out at the Ramazzini research centre in Italy by Soffritti et al.^{35 36} The Commission asked the EFSA to urgently assess the new study and advise whether it is necessary to revise the previous opinion on aspartame carried out by the SCF in 2002.

After considering the data provided by the research institute in December 2005 and April 2006 the EFSA adopted an opinion on 3rd May 2006³⁷. This opinion concluded that, on the basis of the data provided, there is no reason to further review the previous scientific opinion on the safety of aspartame nor to revise the ADI established by the SCF.

5. ON-GOING RE-EVALUATION OF FOOD COLOURS

As mentioned above, the Commission requested the EFSA to re-evaluate food colours as a priority. There are 46 currently permitted colours which can be subdivided into three groups; natural, synthetic and mineral colours. In order to collate and summarise the existing information on the colours, the EFSA published in November 2004 two calls for tenders; one for gathering information on synthetic colours³⁸ and one for natural colours³⁹. In its call for tenders the EFSA also outlined its strategy for re-evaluation of the safety assessments.

³¹ SCF (1985). Sweeteners. Reports of the Scientific Committee for Food (Sixteenth Series), EUR 10210 EN, Commission of the European Communities, Luxembourg.

³² SCF (1989). Sweeteners. Reports of the Scientific Committee for Food (Twenty-first Series), EUR 11617 EN, Commission of the European Communities, Luxembourg.

³³ SCF (1997). Minutes of the 107th Meeting of the Scientific Committee for Food, held on 12-13 June 1997 in Brussels. Available at:
http://europa.eu.int/comm/food/fs/sc/oldcomm7/out13_en.html

³⁴ Opinion of the Scientific Committee on Food: Update on the Safety of Aspartame (expressed on 4 December 2002).

³⁵ Soffritti, M., Belpoggi, F., Esposti D.D, and Lambertini, L. (2005). Aspartame induces lymphomas and leukaemias in rats. *Eur. J. Oncol.*, 10, 107-116.

³⁶ Soffritti, M., Belpoggi, F., Esposti, D.D., Lambertini, L., Tibaldi, E., and Rigano, A. (2006). First Experimental Demonstration of the Multipotential Carcinogenic Effects of Aspartame Administered in the Feed to Sprague-Dawley Rats. *Env. Health Perspect.*, 114, 379 – 385.

³⁷ The EFSA Journal (2006) 356, 1-44.

³⁸ Call for tender No EFSA/AFC/ADD/Tender/02/2004.

³⁹ Call for tender No EFSA/AFC/ADD/Tender/01/2004.

In 2005, the EFSA selected a contractor to prepare summary reports, including toxicity and non-toxicity data, to be used in the re-evaluation of the currently permitted natural and synthetic colours. During the first year of the contract the contractor will prepare summary reports for ten natural colours and ten synthetic colours.

The actual re-evaluation is being undertaken by the AFC Panel and commenced in 2006.