

ADVISORY COMMITTEE ON NOVEL FOODS AND PROCESSES**ISOMALTULOSE****Issue**

The Committee is asked to consider an initial opinion from the German Competent Authority on an application for authorisation of Isomaltulose for use as a food ingredient under the Novel Foods Regulation (EC) No. 258/97.

The Committee is asked whether it agrees with the initial opinion and whether they have any further comments to make on the application. The Committee's advice will form the basis for the UK's formal response.

Introduction

1. On 1 December 2004, the European Commission forwarded the German Competent Authority's (CA) initial opinion on an application made under Article 4(1) of Regulation (EC) No 258/97 from a German company, Südzucker. Under the time scales set out in the regulation, the UK and other Member States have until 30 January 2005 to provide comments or objections to the initial opinion.
2. The German CA has sought advice from their Federal Institute for Risk Assessment, and has issued a positive opinion for this novel food ingredient.
3. A translation of the German Initial Assessment Report and the full dossier from the applicant, including annexes, are attached as Annexes 1 and 2 respectively.

Background

4. The application from Südzucker is for the placing on the market of isomaltulose as a novel food ingredient in the EU. Isomaltulose is a reducing disaccharide composed of a glucose and fructose molecule, joined by a 1,6-glycosidic bond. Although reported to occur naturally in honey and sugar cane extract, levels are too low to be significant. The applicant synthesises isomaltulose through the enzymatic rearrangement of sucrose using sucrose glucosylmutase from the micro-organism *Protaminobacter rubrum*. Relative to sucrose, isomaltulose has a sweetening potential of 42%.
5. Members will recall considering a similar application submitted to the UK CA by Cargill Cerestar BVBA for authorisation of isomaltulose as a novel food ingredient. Cerestar's application was discussed at the Committee's meetings in November 2003 and January 2004. The UK's initial opinion on the application was forwarded to Member States in April 2004, when the Committee concluded that they were "satisfied by the evidence provided by Cerestar that the range of uses for isomaltulose is acceptable, subject to the applicants' adherence to the

specification and production parameters described in the application dossier. Isomaltulose containing foods should comply with existing legislation and should not make claims that are likely to mislead consumers. The applicant should establish a post-launch monitoring scheme to determine the patterns of consumption and to ascertain whether the use of isomaltulose leads to any misunderstanding of the energy content of foods in which it is used". The applicant has responded to comments and questions from the other Member States and a decision on authorisation is expected early in 2005.

6. In accordance with the European Commission Regulation 258/97, isomaltulose has been classified as a pure chemical or simple mixture from a non-GM source (class 1.2). The requirements for a submission for this class are as follows:

I	Specification of the NF	X
II	Effect of the production process applied to the NF	X
III	History of the organism used as the source of the NF	X
IV	Effect of the genetic modification on the properties of the host organism	-
V	Genetic stability of the GMO	-
VI	Specificity of expression of novel genetic material	-
VII	Transfer of genetic material from GM microorganisms	-

VIII	Ability to survive in and colonise the human gut	-
IX	Anticipated intake/extent of use of the NF	X
X	Information from previous human exposure to the NF or its source	-
XI	Nutritional information on the NF	X
XII	Microbiological information on the NF	X
XIII	Toxicological information on the NF	X

7. The key issues for consideration are presented below under the headings taken from the European Commission guidelines on scientific information necessary to support applications for placing on the market of novel foods or novel food ingredients.

I Specification of the Novel Food (NF)

Annex 2 p.11-14

8. The NF is a disaccharide derived from sucrose through the use of an immobilised enzyme preparation from *P.rubrum*. The applicant has provided compositional data on isomaltulose see Annex 2 page 11.
9. The applicant has evaluated the stability of the NF using 8* batches from 1998 and in boiled sweets. These showed no relevant changes when re-analysed after two years storage at ambient conditions. The applicant also evaluated the stability of isomaltulose in acid solution and at a high temperature, which has showed that it is not hydrolysed at pH1 or pH2 and is stable up to 120 °C.
10. The German CA has made no comments on the specification of the NF.
11. When assessing Cerestar's isomaltulose application the Committee requested further analyses on heavy metals to be carried out on the final product.

* Incorrectly given as 9 batches in the German CA's initial opinion.

Südzucker have carried out such tests on its NF, which showed the absence of metallic contaminants (such as lead and cadmium), at the limit of detection of the methods used.

II Effect of the production process applied to the NF

Annex 2 p.15-17

12. Isomaltulose is produced from an aqueous solution of food grade sucrose, which is derived from non-GM sugarbeet, which is passed through a column with an enzyme preparation consisting of *P.rubrum*. The resulting liquid isomaltulose is subjected to ion exchange, evaporation and centrifugation to produce isomaltulose crystals. The production process is described in more detail in annex 2 (pages 15-17) and a flow chart can be seen in annex 2 on page 93.
13. The first steps of isomaltulose manufacture (enzymatic re-arrangement of sucrose to isomaltulose by *P.rubrum*) has been commercially utilised in the EU by the applicant company for the production of isomalt, a polyol which has a long history of use and is authorised as a food additive in the EU in accordance with Directive 94/35/EC. The EC Scientific Committee on Food gave this product and method of production a favourable opinion in 1984.
14. The applicant has integrated its own quality assurance system according to DIN EN ISO 9001, which is certified and will be regularly checked by an accredited body. The production process is also conducted according to the principles of Good Manufacturing Practice and HACCP. The applicant is of the view that these controls will ensure the safety of the production and will ensure that any adverse effects from such sources can be excluded.
15. The German CA have made no comment on the production process but were of the view that the quality assurance procedures were all in accordance with current EU Directives in force in the EU.
16. Südzucker's manufacturing process is very similar to that described in Cerestar's isomaltulose application (see para 5 above).

III History of the organism used as the source of the NF

Annex 2 p.18

17. German CA are of the opinion that the source of material for the novel food (non-GM sugarbeet) has a reliable history of food use.

IX Anticipated intake and extent of use of the NF

Annex 2 p.20-21

18. The applicant intends that their isomaltulose will be used as an ingredient in a variety of products as an alternative of sugar where it is intended to partly replace glucose, fructose, sucrose and starch hydrolystates, and has assumed that the overall intake of the average glucose and fructose in the diet will not change. A complete list of products and the levels at which isomaltulose will be added can be found below. These products will not be restricted locally and there are no plans to target these products to a particular consumer group.

Proposed food uses and use levels of isomaltulose as a food ingredient		
Food category	Proposed food used	Approx.levels (%)
Beverages	Soft drinks such as: <ul style="list-style-type: none"> • energy drinks • sports and isotonic drinks • instant drink preparations 	5-15
	Teas	5-15
	Beer and related beverages	5-15
Cereal and Cereal products	Breakfast cereals	20-30
	Cereal bars	15-20
Soups, toppings, desserts		15-30
Milk-based products		10-20
Confectionery/bakery	Hard candies	99
	Soft candies, toffees, gelees	45-50
	Chewing gum	25-30
	Chocolate and related products	25-50
	Comprimates ¹ , tablets	98-99
	Baked goods	25
	Ice creams	30
Fondants, filling, cremes	90	
Others	Jams, marmalade	25-40
	Nutritive formulae	10-20
	Energy-reduced foods	10-40

19. The applicant has estimated potential intake of isomaltulose allowing for 10-fold safety margins based on the information from Japan in 2002 were it was marketed. The applicant has calculated that, in Japan, consumers would consume approximately 1g per day, which is equivalent to a sugar replacement rate of 2.5%. For Europe, the applicant has reported that data suggests that the sugar consumption is about double that of Japan. Therefore, the applicant has assumed that consumption would be approximately 2g of isomaltulose/day or 20g/day for high consumers 20g/day. Assuming gram for gram replacement of other sugars, this would not result in an increase in metabolisable glucose or fructose.

20. Compared with the earlier application from Cerestar, the range of food to be marketed containing isomaltulose is wider in the Südzucker application and includes a number of broad categories, such as “baked goods”, “energy reduced foods, “fondants, fillings, crèmes” and “milk-based products” (Annex 3).

¹ This is a term, which has been used, in the original dossier.

21. With respect to Cerestar's application, the Committee were concerned that the use of isomaltulose could result in an overall increase in energy intake due to the misinterpretation of any claims made for reduced sweetness or delayed energy release. The German CA has made no comment on the anticipated intake of the novel food.
22. In its opinion the German CA mentioned that the applicant provided an estimate of the projected intake of isomaltulose in Germany (Annex 1, page 2). Unfortunately the annex providing details of these estimates was not circulated to Member States.

X Information from previous human exposure to the NF or its source

Annex 2 p.22

23. Small quantities of isomaltulose have been found in honey and cane sugar. Quantitative analysis of Spanish honey have shown that isomaltulose was detected in all samples of honey, ranging between 0.1-0.7%. Consumption of honey in Germany has been estimated by the applicant, who has determined that the average intake of isomaltulose is below <10 g/year.
24. The applicant has stated that isomaltulose has been approved as a food ingredient within the same category as sucrose in Japan since 1983 and has been marketed in Japan since 1985. In 1992 isomaltulose was accepted as a functional/health ingredient under their regulation for food for specified health use (FOSHU). No side effects have been reported to date.
25. The German CA has made no comment on previous exposure of the NF.

XI Nutritional information on the Novel Food

Annex 2 p.23-28

26. Isomaltulose is a disaccharide, which is hydrolysed in the small intestine into fructose and glucose, in a similar way to sucrose. However, it is metabolised much more slowly, at a rate of one-fifth to one-quarter of that of sucrose. But the overall intake of metabolisable glucose and fructose is the same, resulting in a lower glycaemic and a reduced insulin response.
27. The stability of the linkage between glucose and fructose makes isomaltulose more resistant to oral fermentation, which would result in lower plaque formation. Animal and human studies have confirmed that isomaltulose has a low cariogenic potential.
28. The functional properties of isomaltulose are the main reason for its intended use. The applicant has confirmed that isomaltulose is intended to be used for its low glycaemic and tooth friendly properties and it is envisaged that it will help reduce the negative health effects, which are associated with high glycaemic diets.
29. When assessing Cerestar's isomaltulose application the Committee were otherwise content with the nutritional properties of isomaltulose, but had concerns over the vagueness of the target market and possibility for misinterpretation by the public.

XII Microbiological Information

Annex 2 p.29-30

30. Non-viable *P.rubrum* cells are used in the production of isomaltulose. The German CA notes that *P.rubrum* as a enzymatic processing aid is classed as risk group 1 micro-organism, according to current scientific knowledge; the handling of bacteria in this group presents no risk to humans and vertebrates. After processing the micro-organisms are destroyed using formaldehyde.
31. Analysis for *P.rubrum* using an agar-based medium was carried out on several batches of isomaltulose. These analyses verified the absence of viable *P.rubrum*. It has been reported in scientific literature that *P.rubrum* is not pathogenic and has a lower order of toxicity (further information can be found in Annex 2 p.29 and 119).
32. The microbiological status of isomaltulose is also checked on a regular basis as part of "in-process-control" measures. The applicant has carried out analyses for aerobic mesophilic bacteria, *E.coli*/coliforms, yeast and mould. Results show that microbial cell count is typically below 10cfu/10 TSG, yeast and mould were even lower and *E.coli*/coliforms were not detected.
33. The German CA considers that the information supplied by the applicant to assure microbiological safety is satisfactory.
34. When assessing Cerestar's isomaltulose application the Committee were also satisfied with the information supplied by Cerestar and that the *P. rubrum* was suitable for food use and would cause no safety concerns.

XIII Toxicological information

Annex 2 p. 31-34

35. Independent toxicologists have reviewed and evaluated the safety data on isomaltulose, which are summarised in the application dossier and detailed in the safety evaluation report in Annex 2 (pages 31-34 and 130-149 respectively).
36. *In vitro* studies in rats, pigs and humans confirmed that isomaltulose is hydrolysed by sucrase/isomaltulase complex. *In vivo* biochemical studies in rats, pigs, dogs, healthy and diabetic humans showed that isomaltulose is completely digested in the small intestine but again less rapidly digested compared with sucrose. Intravenous *In vivo* studies in rats, dogs investigated the systemic fate of isomaltulose, which showed that intravenously administered isomaltulose is only partly hydrolysed in rats and dogs. In humans, isomaltulose was rapidly excreted indicating no systemic metabolism. A number of subchronic, mutagenicity and embryotoxicity/teratogenicity studies showed that isomaltulose is well tolerated at high levels without toxicity (Annex 2, pages 130-149).
37. The German CA has made no comment on the toxicological information.
38. Previously when assessing Cerestar's isomaltulose application the Committee was satisfied that the isomaltulose from other manufacturers was sufficiently similar to the applicant's product for the toxicological studies to be relevant. The Committee was content that the toxicological data were sufficient to demonstrate the safety of isomaltulose.

Allergenicity

Annex 2 p.34

39. The applicant has addressed the issue of allergenicity and is of the view that as isomaltulose is a carbohydrate similar to sucrose, glucose and fructose, no allergenic risk to humans is anticipated from the compound itself.
40. Several filtration and purification processes involved during the production of the NF remove *P.rubrum* (which is used as a processing aid). Therefore, protein from *P.rubrum* will not be present in the final product. Samples of isomaltulose were analysed for protein using the Bradford method. No protein was detected and the applicant has concluded that protein amounts if any would be below 1µg/g or 1mg/kg of isomaltulose.
41. When assessing Cerestar's isomaltulose application the Committee previously considered that the level of protein to be sufficiently low to cause no problems with allergenicity, taking into account the quantities that might be consumed.

Labelling

Annex 2 p.37

42. The applicant has provided suggested text for the labelling of their products. According to the applicant "Isomaltulose" will be clearly displayed on product and shall be included in the list of ingredients. In order to provide further information to the consumer regarding isomaltulose, the applicant has proposed to place a footnote on the packaging, which states that "Isomaltulose is composed of glucose and fructose like sugar but is digested more slowly".
43. With regard to the nutritional labelling of products, isomaltulose shall appear under carbohydrates (e.g. equivalent to lactose or maltose) and when calculating the calorific content of the final product and will contribute 4kcal/g (17kJ/g) in line with other carbohydrates. In their opinion, Germany CA have stated that it would be useful to indicate on the labelling that the energy content of isomaltulose is identical to that of saccharose.
44. When the Committee evaluated the application submitted by Cerestar, members commented on the labelling of isomaltulose. The Committee concluded that any claims referring either to reduced sweetness of isomaltulose or to the rate of energy release should be accompanied by a statement of the energy equivalence of the novel ingredient with other sugars, presented in a way that cannot be construed as misleading to consumers.

Committee Action Sought

45. The Committee is asked whether it agrees with the initial opinion from the German CA that isomaltulose produced by Südzucker should be granted authorisation as a novel food ingredient and whether it wished to make any additional comments on the application.

Secretariat
January 2005

Annexes attached

Annex 1: A translation of the German Competent Authority's Initial Assessment Report on the application made by Südzucker to place on the market the novel food ingredient isomaltulose. **CONFIDENTIAL**

Annex 2: Application dossier for the request for an approval of isomaltulose as a novel food (including annexes as listed). **CONFIDENTIAL**

Annex 3: Comparison of novel food applications submitted to the UK and German Competent Authorities by Cerestar and Südzucker respectively.

ADVISORY COMMITTEE ON NOVEL FOODS AND PROCESSES

Comparison of novel food applications submitted to the UK and German Competent Authorities by Cerestar and Südzucker respectively.

- 1) The range of foods intended to be marketed containing isomaltulose is wider in the Südzucker application. The categories supplied are also more vague than those included in the Cerestar application. The table below illustrates the differences and similarities in the uses for the two applications:

Food Use	Proposed use levels (%)	
	Cerestar (UK)	Südzucker (Germany)
Dilutable soft drinks	20	5-15
Energy drinks	5.5	5-15
Sports and isotonic drinks	7.0	5-15
Energy reduced soft drinks	7.0	-
Regular soft drinks	5.5	-
Instant drink preparations	-	5-15
Beer and related beverages	-	5-15
Teas	-	5-15
Sandwich biscuits	20	-
Cereal bars	10	15-20
Breakfast cereals	30	20-30
Soups, toppings, desserts	-	15-30
Milk-based products	-	10-20
Energy and diet meal bars	15	-
Meal replacements (dry wt)	20	10-20
Milk based meal replacements (dry wt)	20	-
Candy and chocolate bars	25	25-99
Energy tablets	97	-
Comprimates, tablets	-	98-99
Chewing gum	-	25-30
Baked goods	-	25
Ice creams	-	30
Fondants, fillings, cremes	-	90
Jams, marmalades	-	25-40
Energy reduced foods	-	10-40

- 2) The Südzucker application highlights the glycaemic and non-cariogenic properties of isomaltulose as the main purpose of its incorporation in foods. Cerestar intend to use the product as a carbohydrate source with reduced sweetness when compared to sucrose. Its incorporation as an ingredient will modify the organoleptic properties of the foods.
- 3) The ACNFP had concerns over the intended market for this ingredient and considered that its use may lead to misunderstandings by the consumer that

“reduced sweetness” would be seen as “reduced energy”. Cerestar provided a clear labelling suggestion that could not be misconstrued at the request of the ACNFP.

- 4) Sudzucker have provided the following labelling suggestion for their isomaltulose product: “Isomaltulose is composed of glucose and fructose like sugar but is digested more slowly”. This suggestion does not seem as clear as that requested by the ACNFP when the Cerestar’s application was assessed.
- 5) The Südzucker application mentions the possibility of this product being used in diabetic foods (Annex 2 page 40). However, it does not make any specific mention of this in the list of proposed products to include isomaltulose.

**Secretariat
January 2005**