Isomaltulose

Tweede beoordeling van de veiligheid voor de consument, volgens de Europese verordening 258/97 betreffende nieuwe voedingsmiddelen en nieuwe voedselingrediënten

Isomaltulose

Second opinion regarding consumer safety, in accordance with European Regulation 258/97 concerning novel foods and novel ingredients

Gezondheidsraad:
Commissie Veiligheidsbeoordeling nieuwe voedingsmiddelen (VNV)

Health Council of the Netherlands
Committee on the Safety Assessment of Novel Foods

aan/to

de minister van Volksgezondheid, Welzijn en Sport/
the Minister of Health, Welfare and Sport

de minister van Landbouw, Natuur en Voedselkwaliteit/
the Minister of Agriculture, Nature and Food Quality

Nr 2004/01VNV, Den Haag, 15 juni 2004
No. 2004/01VNV, The Hague, June 15, 2004

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Deze publicatie kan als volgt worden aangehaald:
Gezondheidsraad. Commissie Veiligheidsbeoordeling nieuwe voedingsmiddelen. Isomaltulose. Den Haag: Gezondheidsraad, 2004; publicatie nr 2004/01VNV.

Preferred citation:
Health Council of the Netherlands. Committee on the Safety Assessment of Novel Foods. Isomaltulose. The Hague: Health Council of the Netherlands, 2004; publication no. 2004/01VNV.

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Uw kenmerk : VGB/VL 2483347
Ons kenmerk : 2004/01VNV, U-865/MR/cv/622-CW
Datum : 15 juni 2004

Mijnheer de minister,

Dit schrijven dient ter beantwoording van de adviesaanvraag over de veiligheid van nieuwe voedingsmiddelen en nieuwe voedselingrediënten, die door u mede namens de Minister van Landbouw, Natuur en Voedselkwaliteit aan de Gezondheidsraad is voorgelegd. Aan de orde is een zogenoemde tweede beoordeling, conform de Europese verordening 258/97, van isomaltulose. Dit nieuwe voedselingrediënt wordt gemaakt door enzymatische omvorming van sucrose (suiker). De aanvrager is de firma Cargill die isomaltulose, geproduceerd door het dochterbedrijf Cerestar, op de Europese markt wil brengen. Isomaltulose komt niet direct beschikbaar voor de consument, maar zal worden verwerkt in verschillende categorieën levensmiddelen waaronder dranken, bakkerijproducten, maaltijdvervangers en zoetwaren. De beoordeling is verricht door de Commissie 'Veiligheidsbeoordeling nieuwe voedingsmiddelen' van de Gezondheidsraad (Commissie VNV).

De eerste beoordeling van de aanvraag voor markttoelating is verricht door het *Advisory Committee on Novel Foods and Processes* (ACNFP) van het Verenigd Koninkrijk. De ACNFP heeft isomaltulose beoordeeld als veilig voor de toepassing als voedselingrediënt. Ten overvloede wijst de ACNFP erop dat levensmiddelen die isomaltulose bevatten moeten voldoen aan bestaande regelgeving en niet vergezeld mogen gaan van claims die de consument kunnen misleiden. Volgens de ACNFP zou de aanvrager marktmonitoring moeten uitvoeren om het consumptiepatroon van isomaltulose-houdende voedingsmiddelen vast te stellen en om na te gaan of er bij de consument geen misvattingen zijn aangaande het energiegehalte van deze nieuwe producten. De ACNFP is bezorgd dat de aan isomaltulose toegeschreven eigenschappen van "verminderde zoetheid" en "vertraagde energieafgifte" verkeerd door consument geïnterpreteerd

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kunnen worden, en daarom meent zij dat dergelijke uitspraken vergezeld moeten gaan van de vermelding dat isomaltulose energetisch gelijkwaardig is aan suiker. De bevoegde autoriteit, de Engelse *Food Standards Agency*, heeft het advies van de ACNFP overgenomen.

De Commissie VNV baseert haar oordeel op de informatie in het dossier (voor een samenvatting zie Bijlage D), het rapport van de eerste beoordeling door de ACNFP (zie Bijlage E) en de wetenschappelijke literatuur. De Commissie VNV stemt grotendeels in met de Engelse beoordeling. De kwaliteit van het productieproces lijkt gewaarborgd. De zuiverheid van het product is minstens 99 % en het bevat geen chemische of microbiologische verontreinigingen.

Voor de productie van isomaltulose wordt een enzympreparaat gebruikt afkomstig van *Protaminobacter rubrum*. Deze bacterie heeft geen ziekteverwekkende eigenschappen en kent een geschiedenis van gebruik in de EU sinds 1984, toen de zoetstof isomalt werd toegelaten. Bij de industriële bereiding van dit voedseladditief is isomaltulose een tussenproduct. De Commissie VNV is het eens met de ACNFP dat dit een belangrijke ondersteuning is voor de veilige toepassing van dit enzympreparaat.

Vanuit voedingskundig oogpunt is er geen bezwaar tegen het gebruik van isomaltulose. Dit komt van nature voor in geringe hoeveelheden in rietsuiker en honing. Isomaltulose is minder dan half zo zoet als sucrose. Het bestaat net als sucrose uit één glucose- en één fructosemolecuul maar verschilt van sucrose in de manier waarop deze beiden chemisch gekoppeld zijn. Alhoewel isomaltulose langzamer wordt verteerd dan sucrose wordt het wel volledig opgenomen door het lichaam. De voedingswaarde is dan ook gelijk aan die van sucrose.

Bij het gebruik zoals de aanvrager voorstelt, komt de gemiddelde isomaltulose-inneming neer op een vervanging van zo'n 10 % van de gewone suikerinneming. De Commissie VNV tekent aan dat de voedselconsumptiegegevens die de aanvrager voor de Engelse consument afleidt, gezien de aannames, slechts een globale indicatie zijn. Daarnaast is het onbekend in hoeverre deze resultaten representatief zijn voor de Europese bevolking. De populatiegroep met de hoogste inneming uit het door de aanvrager voorgestelde productassortiment zijn jongens van 11-18 jaar oud. Met het scenario dat de aanvrager schetst zouden grootverbruikers onder hen (97,5 percentiel) bijna één ons isomaltulose per dag consumeren. Dit is vergelijkbaar met een inneming van zo'n 42 % van de totale suikerconsumptie in de vorm van isomaltulose. Uit de voedselconsumptiegegevens blijkt dat

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per kg lichaamsgewicht jonge kinderen het meeste isomaltulose binnen krijgen, en in het geval van een *worst case* scenario bedraagt dit 4 gram per kg.

Er zijn geen nadelige effecten waargenomen in de gebruikelijke onderzoeken naar mutageniteit, teratogeniteit/embryotoxiciteit, subchronische toxiciteit en ook niet in 26-weken onderzoeken. De toxicologische onderzoeken met isomaltulose bij proefdieren die in het dossier zijn opgenomen betreffen allen producten van andere firma's. De aanvrager heeft aanvullende informatie verstrekt waaruit de ACNFP concludeert, dat het isomaltulose van deze aanvraag voldoende vergelijkbaar is met de onderzochte producten. De Commissie VNV is het eens met de ACNFP dat uit de resultaten van toxicologische testen blijkt dat isomaltulose een veilig product is.

Aanvullend op de eerste beoordeling meldt de Commissie VNV dat in het dossier de resultaten worden geëvalueerd van negen mensgebonden onderzoeken[a]. Vier hiervan betreft het product van de aanvrager en de hoogst geteste eenmalige dosering was bijna 80 gram. De Commissie VNV stemt in met de aanvrager dat deze resultaten bevestigen dat isomaltulose bij het voorgestelde gebruik goed wordt verdragen en dat er geen nadelige gezondheidseffecten optreden. De Commissie tekent hierbij aan dat het dossier geen informatie bevat over twee zeldzame erfelijke afwijkingen in het fructosemetabolisme[b], te weten fructose intolerantie (fructose–aldolase deficiëntie, incidentie 1:20.000) en fructose 1,6-diphosphatase deficiëntie (incidentie onbekend). Mensen met zo'n aangeboren stofwisselingstoornis kunnen géén of maar weinig fructose verdragen. Voor deze groep consumenten is de door de aanvrager voorgestelde tekst op het etiket dat isomaltulose een bron van glucose en fructose is net als suiker, belangrijk.

Isomaltulose valt niet onder de categorie-aanduiding 'Suiker' en moet apart worden vermeld op de ingrediëntendeclaratie. Etikettering dient in overeenstemming te zijn met Richtlijn 2000/13/EG en artikel 8 van Verordening (EG) 258/97. De Commissie VNV onderkent het probleem van mogelijke misleiding van de consument dat de ACNFP voorziet als bepaalde kenmerken inzake de zoetheid en de snelheid van energieafgifte van isomaltulose op het etiket

[a] In één van de onderzoeken is de tolerantie bestudeerd van dagelijkse isomaltuloseconsumptie bij 60 gezonde vrijwilligers waarbij de hoeveelheid over een periode van 12 weken toenam tot 48 gram per dag. Dit onderzoeksrapport is niet in het dossier opgenomen, maar wordt wel besproken in een door derden gepubliceerd overzichtsartikel dat deel uitmaakt van het dossier.

[b] Essentiële fructosuria (fructokinase deficiëntie, incidentie 1:130.000) is een onschuldige erfelijke stofwisselingstoornis die niet als een ziekte wordt beschouwd.

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Gezondheidsraad **Vice-voorzitter**
Health Council of the Netherlands

worden verwoord. Evenals de ACNFP vindt zij het belangrijk dat het etiket vermeldt dat isomaltulose energetisch gelijkwaardig is aan suiker.

Ik onderschrijf de conclusies van de Commissie VNV.

Hoogachtend,

Prof. dr JGAJ Hautvast

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Letter to the Dutch Minister of Health, Welfare and Sport

On June 15, professor JGAJ Hautvast, Vice-president of the Health Council of the Netherlands wrote as follows to the Minister of Health, Welfare and Sport:

This letter has been prepared in reply to your request for advice regarding the safety of novel foods and food ingredients, also made on behalf of the Minister of Agriculture, Nature and Food Quality. The subject in question is a so-called second opinion, in accordance with European Regulation 258/97, concerning isomaltulose. This novel food ingredient is produced via enzymatic conversion of sucrose (sugar). The applicant, Cargill Incorporated, wishes to introduce isomaltulose (which is manufactured by its business unit, Cerestar) to the European market. Isomaltulose will not be directly available for consumers, but will be incorporated in foods of various categories, such as beverages, cereal products, instant meal replacements and confectionery products. This assessment was carried out by the Health Council Committee on Safety Assessment of Novel Foods (VNV Committee).

The initial assessment of the application for market authorization was carried out by the *Advisory Committee on Novel Foods and Processes* (ACNFP), in the United Kingdom. The ACNFP's assessment was that isomaltulose is safe for use as a food ingredient. Perhaps unnecessarily, the ACNFP points out that foodstuffs which contain isomaltulose must comply with existing legislation and must not be associated with claims that might mislead consumers. According to the ACNFP, the applicant must carry out market monitoring to establish the pattern of consumption for isomaltulose-containing foodstuffs and to determine whether consumers have mistaken ideas con-

cerning the energy content of these products. The ACNFP is concerned that the characteristics of 'reduced sweetness' and 'delayed energy release' could be misinterpreted by consumers. Accordingly, it feels that any such claims should be accompanied by a statement of the energy equivalence of the novel ingredient with other sugars. The competent authority, the UK Food Standards Agency, has adopted the ACNFP's recommendations.

The VNV Committee based its views on the information contained in the dossier (see Annex D for the summary), on the report of the initial assessment by the ACNFP (see Annex E), and on the scientific literature. The VNV Committee is largely in agreement with the British assessment. It appears that, in terms of quality, the production process incorporates the necessary safeguards. The product is at least 99% pure, and is free of chemical and microbiological contaminants.

Isomaltulose is produced using an enzyme preparation derived from *Protaminobacter rubrum*. This non-pathogenic bacterium has been used in the EU since 1984, when isomalt (a sweetener) was admitted to the European market. Isomaltulose is an intermediate product in the industrial preparation of this food additive. The VNV Committee concurs with the ACNFP that this is important evidence of the safety of this enzyme preparation.

From the nutritional point of view, there is no objection to the use of isomaltulose. This is a naturally occurring substance, which is present at low concentrations in cane sugar and honey. Isomaltulose is less than half as sweet as sucrose. Like sucrose, it consists of one molecule of glucose and one of fructose. It differs from sucrose with respect to the type of glycosidic linkage between these two molecules. While it is digested more slowly than sucrose, isomaltulose is nevertheless fully absorbed by the body. The nutritional value is therefore equivalent to that of sucrose.

When used in accordance with the applicant's suggestion, average isomaltulose intake amounts to a replacement of about 10 % of normal sugar intake. The VNV Committee notes that the food consumption data for British consumers is only a rough indication, given the assumptions made by the applicant when deriving this data. Furthermore, it is not known to what extent these results are representative of the population of Europe as a whole. The applicant has outlined a worst case scenario for the population group with the highest intake figures from all proposed food categories. These are male teenagers aged from 11 to 18, and the amount involved is almost one hundred grams of isomaltulose per day. This is comparable to an intake of around 42 % of total sugar consumption, in the form of isomaltulose, by 'heavy users' in this category (97.5 percentile). The food consumption data reveals that, per kg of body weight, young children ingest the largest amounts of isomaltulose. In the worst case scenario, this would be four grams per kg.

No adverse effects were observed in the course of the usual tests for mutagenicity, teratogenicity/embryotoxicity, and subchronic toxicity, nor in 26-week studies. The tox-

icological tests described in the dossier, in which isomaltulose was administered to experimental animals, all used products manufactured by other companies. On the basis of additional information provided by the applicant, the ACNFP has concluded that the isomaltulose on which this application is based, is sufficiently similar with the products used in these tests. The VNV Committee concurs with the ACNFP that the toxicological data shows isomaltulose to be a safe product.

In addition to the initial assessment, the VNV Committee reports that the dossier contains assessments of the results of nine studies on human subjects*. Four of these involved the applicant's own product, and the highest single dose tested was almost 80 grams. The Committee concurs with the applicant that these results confirm that isomaltulose is well tolerated when used as described in the application dossier and that no adverse health effects occur. The Committee notes that the dossier does not contain information on two rare hereditary disorders of the fructose metabolism**. These are fructose intolerance (fructose-aldolase deficiency, incidence 1:20.000) and fructose1,6-diphosphatase deficiency (incidence unknown). People suffering from these inborn errors have no or a reduced tolerance for fructose. The information on the label that isomaltulose is a source of glucose and fructose as proposed by the applicant is important for this group of consumers.

Isomaltulose does not fall within the 'Sugar' category, and should therefore be listed separately on the ingredients declaration. Labelling should conform to Directive 2001/13/EC and Article 8 of European Regulation (EC) 258/97. The VNV Committee recognises the problem, foreseen by the ACNFP, that consumers could be misled as a result of statements referring to the sweetness or the rate of energy release. The Committee agrees with the ACNFP that the label should include information on the energy equivalence of the novel ingredient with sugar.

I endorse the conclusions and recommendations of the VNV Committee,

(signed) professor JGAJ Hautvast

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* One of the studies dealt with the tolerance of daily isomaltulose consumption in 60 healthy volunteers. Over a period of twelve weeks, the amount was increased to a final level of 48 grams per day. While the report of this study was not included in the dossier, it was discussed in a survey article published by other researchers, a copy of which was included in the dossier.

** Essential fructosuria (fructokinase deficiency, incidence 1:130.000) is considered a harmless metabolic abnormality and not a disease.

Literatuur/Literature

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(Regulation (EC) No 258/97 of the European Parliament and of the Council of 27 January 1997 concerning novel foods and novel food ingredients. Official Journal of the European Communities 1997; L43: 1-6).

EG97a Aanbeveling (EG) nr. 97/618/EG van de Commissie van 29 juli 1997 betreffende de wetenschappelijke aspecten en de presentatie van de informatie die nodig is om aanvragen voor het in de handel brengen van nieuwe voedingsmiddelen en nieuwe voedselingrediënten te ondersteunen alsmede het opstellen van de verslagen van de eerste beoordeling uit hoofde van Verordening (EG) nr. 258/97 van het Europees Parlement en de Raad. Publicatieblad van de Europese Gemeenschappen 1997; L253: 1-36
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A	De adviesaanvraag/Request for advice
B	De commissie/The committee
C	EU-procedure/EU-procedure
D	Samenvatting van het dossier/Executive summary of the dossier
E	Eerste beoordeling/First assessment

Bijlagen/Annexes

Bijlage **A**

De Adviesaanvraag/Request for advice

Op 18 augustus 1999 schreef de Minister van Volksgezondheid, Welzijn en Sport aan de Voorzitter van de Gezondheidsraad (brief kenmerk GZB/VVB 993428):

Sinds mei 1997 is in de Europese Unie de Verordening (EG) 258/97 van kracht inzake nieuwe voedingsmiddelen en nieuwe voedselingrediënten. Daarmee werd de veiligheidsbeoordeling onderdeel van een communautaire procedure.

Met u is reeds de mogelijkheid besproken de beoordeling door de Gezondheidsraad te laten uitvoeren. Ik verzoek u dan ook mede namens de Staatssecretaris van Landbouw, Natuurbeheer en Visserij, in deze eerste fase van uitvoering van de Europese Verordening (EG) 258/97 gedurende een aantal jaren, de veiligheidsbeoordeling gestalte te geven. Voor het onderbrengen bij de Gezondheidsraad pleit het experimentele karakter dat de beoordeling de eerste jaren zal hebben. Dit experimentele karakter komt voort uit het feit dat het een nieuw soort beoordeling betreft van deels nieuwe categorieën van voedingsmiddelen of voedselingrediënten. Het is namelijk een veiligheidsbeoordeling vóór het op de markt brengen van met name voedingsmiddelen van een genetisch gemodificeerde oorsprong en zogenaamd functional foods (nutriceutica). Daarnaast ga ik ervan uit dat de onafhankelijke wetenschappelijke advisering door de Gezondheidsraad het vertrouwen van de Europese Commissie en de andere lidstaten in het Nederlandse oordeel nog versterkt.

Mijn beleid is erop gericht een zo groot mogelijke openheid en transparantie te realiseren van de gevolgde procedure en de beoordeling om de consument vertrouwen te geven in de veiligheid van de

nieuwe voedingsmiddelen. Ik verzoek de Gezondheidsraad hieraan bij te dragen door bijvoorbeeld inzage te geven in de dossiers waarvoor een aanvraag wordt ingediend, waarbij uiteraard bedrijfsvertrouwelijke gegevens worden beschermd en door de criteria, waarop de veiligheid zal worden beoordeeld, te publiceren.

De Minister van Volksgezondheid, Welzijn en Sport,
w.g. dr E Borst-Eilers

English translation

On 18 August 1999, the Minister of Health, Welfare and Sport wrote as follows to the President of the Health Council of the Netherlands (under reference GZB/VVB 993428):

Since May 1997, Regulation (EC) 258/97 concerning novel foods and novel food ingredients has been in force in the European Union. Under the Regulation, the safety of novel foods has to be assessed as part of a community procedure.

Following discussions regarding the possibility of the Health Council making such assessments, the State Secretary for Agriculture, Nature Management and Fisheries and I wish the Council to take responsibility for safety assessment for a period of several years during the fist phase of implementation of European Regulation (EC) 258/97. It is considered appropriate that the Health Council should initially take on this role because the assessment activities will be of an experimental nature, involving both a new form of assessment (i.e. pre-marketing assessment) and, in many cases, new categories of foodstuff (primarily foodstuffs with a genetically modified basis and functional foods or nutraceuticals). We also feel that if assessments are made by a body with the Council's independent scientific status, this will support the validity of the Netherlands' opinion in the eyes of the European Committee and other member states.

My wish is to make the procedure and the assessment as open and transparent as possible, so as to enhance consumer trust in the safety of novel foods. I would like the Health Council to support this objective by, for example, allowing perusal of the application dossier (insofar as consistent with the need to protect the confidentiality of commercially sensitive information) and publishing the criteria upon which safety assessments are made.

The Minister of Health, Welfare and Sport,
(signed) dr E. Borst-Eilers

Bijlage **B**

De commissie/The committee

- Prof. dr EG Schouten, *voorzitter/chairman*
  hoogleraar epidemiologie; Wageningen Universiteit and Researchcentrum/ professor of epidemiology; Wageningen University and Research centre
- Prof. dr CAFM Bruijnzeel-Koomen
  hoogleraar dermatologie/allergologie; Academisch Ziekenhuis Utrecht/professor of dermatology/allergology; Academic Hospital Utrecht
- Ir EJ Kok
  toxicoloog; RIKILT-DLO Wageningen/toxicologist; State Institute for Quality Control of Agricultural Products, Wageningen
- Dr CF van Kreijl
  moleculair-bioloog; RIVM Bilthoven/molecular biologist; National Institute of Public Health and the Environment, Bilthoven
- Prof. dr P van der Laan
  emeritus hoogleraar statistiek; Technische Universiteit Eindhoven/professor of statistics; Technical University Eindhoven
- Dr FM Nagengast
  gastro-enteroloog; Academisch Ziekenhuis Nijmegen/gastro-enterologist; Academic Hospital Nijmegen
- Dr ir JMA van Raaij
  voedingsfysioloog; Wageningen Universiteit and Researchcentrum/ food physiologist; Wageningen University and Research centre

- Prof. dr ir G Schaafsma
  hoogleraar voeding; TNO Voeding, Zeist/professor of nutrition; TNO Nutrition and Food Research, Zeist
- Dr GJA Speijers
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- Prof. dr WJ Stiekema
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- Ir R Top, *adviseur/advisor*
  Ministerie van VWS; Den Haag/Ministry of Health, Welfare and Sport; The Hague
- Prof. dr WM de Vos
  hoogleraar microbiologie; Wageningen Universiteit en Researchcentrum/ professor of microbiology; Wageningen University and Research centre
- Dr RA Woutersen
  toxicoloog, toxicologisch patholoog; TNO Voeding, Zeist/toxicologist, toxicologic pathologist; TNO Nutrition and Food Research, Zeist
- Dr ir F van der Wilk, *adviseur/advisor*
  COGEM, Bilthoven/Committee on Genetic Modification, Bilthoven
- Dr ir M Rutgers, *secretaris/scientific staff member*
  Gezondheidsraad, Den Haag/Health Council of the Netherlands, The Hague

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Layout: J van Kan; Gezondheidsraad, Den Haag/Health Council of the Netherlands, The Hague.

Bijlage **C**

EU-procedure/EU-procedure

Als een fabrikant een nieuw voedingsmiddel op de markt brengt, dient de veiligheid voor de consument gewaarborgd te zijn. In 1997 werd de Europese verordening van kracht waarin de procedure is geregeld voor de goedkeuring voor marktintroductie van een nieuw voedingsmiddel (EG97). Bij deze procedure zijn verschillende actoren betrokken. De aanvrager moet beoordelen of het product werkelijk 'nieuw' is, dat wil zeggen dat het nog niet eerder in de Europese Unie in substantiële mate voor menselijke voeding is gebruikt en ook niet wezenlijk gelijkwaardig is aan een bestaand product. (Voor een wezenlijk gelijkwaardig product kan worden volstaan met een kennisgeving van de marktintroductie.) Ook moet het niet gaan om een levensmiddelenadditief, aroma of extractiemiddel, omdat deze producten op een andere wijze worden beoordeeld. Voor een nieuw voedingsmiddel in de zin van de Europese verordening moet de aanvrager een veiligheidsdossier overleggen volgens aanbevelingen van de Europese Commissie (EG97a). Deze aanbevelingen zijn gebaseerd op rapporten van verschillende instanties die zich met het onderwerp nieuwe voedingsmiddelen bezighouden, te weten de OECD (OECD93, OECD96) en de WHO/FAO (FAO96, WHO91). Ook de Gezondheidsraad heeft zich al eerder over dit onderwerp gebogen (GR92). Sinds het verschijnen van de aanbevelingen van de EU wordt in internationaal verband gewerkt aan explicitering en aanpassing aan de stand van de wetenschap (GR02).

De fabrikant levert het volgens de richtlijnen samengestelde dossier in bij het land waar het product het eerst op de markt zal komen. Daarop komt de nationale veiligheids-beoordelingsautoriteit in actie. In Nederland is dat de Minister van Volksgezondheid, Welzijn en Sport. Zij heeft de Gezondheidsraad verzocht haar van advies te dienen. De

Voorzitter van de Gezondheidsraad heeft hiertoe de commissie Veiligheidsbeoordeling nieuwe voedingsmiddelen (commissie VNV) ingesteld.

De commissie beoordeelt op basis van de huidige stand van de wetenschap of de door de fabrikant geleverde gegevens juist en volledig zijn en of zij het eens is met diens conclusies. Zij maakt een verslag van haar bevindingen — ook volgens de Europese aanbevelingen (EG97a, deel III) — en biedt dat de minister aan. De minister formuleert het Nederlandse oordeel over een voedingsmiddel en brengt dat in bij het Europese overleg in het Permanent Comité voor de voedselketen en de diergezondheid. Alle Europese lidstaten worden uitgenodigd hun oordeel (de zogeheten tweede beoordeling) te geven over het dossier en over de eerste beoordeling alvorens genoemd Comité een eindoordeel velt. Als een dossier veel vragen oproept, gaat er een adviesvraag van de Europese Autoriteit voor voedselveiligheid (EAV). Komt men dan nog niet tot overeenstemming dan beslist de Europese Ministerraad. Sinds 18 april 2004 moeten veiligheidsdossiers van voedingsmiddelen van genetisch gemodificeerde oorsprong rechtstreeks ingediend worden bij de EAV (EG03).

English translation

When manufacturers bring novel foodstuffs onto the market, consumer safety has to be ensured. In 1997, a European Regulation (EG97) came into force, laying down the procedure for approving the market introduction of novel foodstuffs. The procedure recognizes various actors. The applicant must decide whether a product is a novel foodstuff, i.e. a substance that has not previously been available for human consumption to any substantial extent within the European Union and is not substantially equivalent to any existing product. (If a foodstuff is substantially equivalent to any existing product, it is sufficient to inform the authorities of its market introduction). Food additives, aromas and extracts are excluded from the provisions of the directive, since they fall within the scope of an established assessment regime. Before marketing a novel foodstuff, the applicant must compile a safety dossier that complies with the Recommendations of the European Commission (EG97a). These Recommendations are based on reports by a number of bodies that have studied the issue of novel foodstuffs, in particular the OECD (OECD93, OECD96) and the WHO/FAO (FAO96, WHO91). The Health Council of the Netherlands has also considered the question earlier (GR92). Since publication of the EU recommendations, international efforts have been made to clarify and adapt the latest scientific knowledge in the field (GR02).

Having compiled a dossier in line with the guidelines, the manufacturer has to submit it to the competent authority in the country where the product is to be marketed first. This dossier is assessed by the national safety assessment authority. In the Netherlands, this is the Minister of Health, Welfare and Sport, who is advised by the Health Council.

The President of the Health Council has created a Committee on the Safety Assessment of Novel Foods (VNV Committee) to advise the minister on behalf of the Council.

On the basis of the scientific state of the art, the committee has to decide whether the information provided by the manufacturer is accurate and complete and whether the manufacturer's conclusions are sound. The committee then draws up a report on its findings for the minister; this report must also comply with the European Recommendation (EG97a, part III). After considering the report, the minister formulates the Netherlands' opinion regarding the foodstuff in question, which is discussed at European level in the Standing Committee on the Food Chain and Animal Health. All other European member states are invited to express a 'second opinion' regarding the dossier and the first opinion. The Standing Committee then arrives at a final judgement. If a dossier is particularly contentious, the European Commission calls upon the European Food Safety Authority (EFSA) for advice. If consensus still cannot be reached, the issue is referred to the European Council of Ministers. From April 18th 2004 safety dossiers of food from genetically modified origin have to be submitted to EFSA directly (EC03).

Bijlage **D**

Samenvatting van het dossier/ Executive summary of the dossier

APPLICATION FOR THE APPROVAL OF ISOMALTULOSE

Regulation (EC) No 258/97 of the European Parliament and the Council of 27th January 1997 concerning novel foods and novel food ingredients

SUMMARY

Applicant: Cargill, Incorporated,
a Delaware corporation,
with its principal place of business at
15407 McGinty Road West, Wayzata,
Minnesota 55391 (USA),

Acting through,
Cerestar Food & Pharmaceutical Specialties,
one of its Business Units,

c/o Cerestar Research and Development Centre
Havenstraat 84
B-1800 Vilvoorde (Belgium)

October 22, 2003

APPLICATION FOR THE APPROVAL OF ISOMALTULOSE:

USE AS A NOVEL FOOD INGREDIENT IN EUROPE

CONTENTS

1.0 ADMINISTRATIVE DATA

The application is submitted by:

Applicant: Cargill, Incorporated, a Delaware corporation, with its principal place of business at 15407 McGinty Road West, Wayzata, Minnesota 55391 (USA),
Acting through,
Cerestar Food & Pharmaceutical Specialties, one of its Business Units,
c/o Cerestar Research and Development Centre
Havenstraat 84
B-1800 Vilvoorde (Belgium)

Hereinafter referred to as Cerestar

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2.0 APPLICATION

This application seeks approval for the use of isomaltulose, obtained by enzymatic rearrangement of sucrose, as a novel food ingredient in Europe. Approval is sought under *Regulation (EC) No 258/97 of the European Parliament and of the Council of 27th January 1997 concerning novel foods and novel food ingredient*s (hereafter referred to as EC 258/97).

Article 1(2) of EC 258/97 states that the regulation "…shall apply to the placing on the market within the Community of foods and food ingredients which have not hitherto been used for human consumption to a significant degree within the Community…" and which fall under one of six categories of novel foods and novel food ingredients. The lack of a significant prior history of human consumption in the European Community dictates that isomaltulose will be considered under category (c), pertaining to "foods and food ingredients with a new or intentionally modified primary molecular structure". Isomaltulose is thus considered a novel food/food ingredient.

3.0 IDENTIFICATION OF ESSENTIAL INFORMATION REQUIREMENTS

The application dossier ("Application for the Approval of Isomaltulose") was prepared pursuant to the *Commission Recommendation of 29 July 1997 concerning the scientific aspects and the presentation of information necessary to support applications for the placing on the market of novel foods and novel food ingredients* (hereafter referred to as the Commission Recommendation of 1997).

Section 4 of the Commission Recommendation of 1997 outlines recommendations made by the Scientific Committee on Food (SCF) pertaining to the "Scientific Classification of Novel Foods for the Assessment of Wholesomeness", which facilitates the safety and nutritional evaluation of a given novel food/food ingredient. Of the six classes identified, isomaltulose would be allocated a Class 1 designation (pure chemicals or simple mixtures from non-GM sources), since it is manufactured by conventional methods as a pure chemical, with no use of genetic modification. Isomaltulose is further classified under sub-class 1.2 (the source of the NF has no history of food use in the Community) of the SCF categorization. However, isomaltulose does occur as an intermediate product in the production of isomalt (E953), an additive permitted for use in food since 1984, which is manufactured by both Cerestar and Südzucker and involves the use of the same microorganism as that used in the preparation of isomaltulose.

Pursuant to Table II, Part I, under the Commission Recommendation of 1997, the essential information requirements corresponding with this classification are outlined as follows:

I. Specification of the novel food

II. Effect of the production process applied to the novel food

III. History of the organism used as the source of the novel food

IX. Anticipated intake/extent of use of the novel food

XI. Nutritional information on the novel food

XII. Microbiological information on the novel food

XIII. Toxicological information on the novel food

For each category (I through XIII), structured schemes have been developed (Part I of the Commission Recommendation of 1997), which consist of a decision-tree-like set of questions designed to elicit sufficient data for a comprehensive safety and nutritional evaluation of the novel food. This data is provided in the application dossier ("Application for the Approval of Isomaltulose").

4.0 EXECUTIVE SUMMARY

Under Regulation (EC) No 258/97 on Novel Foods and Food Ingredients, Cerestar seeks approval to market isomaltulose, obtained by enzymatic rearrangement of sucrose, for use as a novel food ingredient in Europe. Cerestar submitted an application in accordance with Commission Recommendation 97/618/EC, concerning the scientific aspects of information necessary for the placing on the market of novel foods and novel food ingredients.

Specifications and Manufacturing

Isomaltulose is a naturally occurring reducing dissacharide, composed of a glucose and fructose molecule, linked by a 1,6-glycosidic bond. Its sweetness is approximately 42% that of sugar.

The production of isomaltulose by Cerestar is initiated by dissolving food-grade sucrose in water and subsequently treating the resulting solution with a biocatalyst obtained from a non-viable, non-pathogenic strain of *Protaminobacter rubrum* (Porter *et al*., 1991). Once the enzymatic rearrangement is complete, the residual biomass material is removed by filtration. The crude isomaltulose product is then sequentially subjected to several stages of purification, including demineralisation, crystallisation, and washing. Drying and cooling of isomaltulose complete the production process, resulting typically in a product of 99% or greater purity. Results of analysis for representative batches of isomaltulose demonstrate compliance with final product specifications.

Previous Human Exposure

Isomaltulose has been identified to occur naturally in honey at levels of up to 1% as well as in sugar cane extract at low levels. Moreover, in Japan, isomaltulose has been used in yoghurt, chewing gum, and candy since 1985.

Estimated Intake of the Novel Food

The individual proposed food-uses and their maximum usage levels for isomaltulose in the E.U. are summarized in the following Table:

Table 4-1 Summary of the Individual Proposed Food-Uses and Use-Levels for Isomaltulose in the E.U.		
Food Category	**Proposed Food-Use**	**Use-Levels for IM (%)**
Beverages	Dilutable Soft Drinks	20.0
	Energy Drinks	5.5
	Energy Reduced Soft Drinks	7.0
	Regular Soft Drinks	5.5
	Sports and Isotonic Drinks	7.0
Cereals and Cereal Products	Biscuits, Sandwich-Type with Filling	20.0
	Cereal Bars	10.0
	Coated Ready-to-Eat Breakfast Cereals	30.0
	Energy and Diet Meal Bars	15.0
Miscellaneous Beverages	Meal Replacements, Dry Weight	20.0
	Milk Based Meal Replacements, Dry Weight	20.0
Sugar, Preserves, and Confectionery	Candy and Chocolate Bars	25.0
	Energy Tablets	97.0

Isomaltulose is proposed for use as a nutritive sweetener, in a variety of food products including soft drinks, fillings in baked goods, grain and meal replacement products. Under the conditions of intended use, male teenagers were estimated to have the highest intake of isomaltulose on an all-user basis by the U.K. population, from all-proposed food-uses, with mean and 97.5th percentile intakes of 37.8 and 97.8 g/day, respectively. On a body weight basis, children were identified as having the highest intakes, with mean and 97.5th percentile all-user isomaltulose intakes of 1.6 and 4.0 g/kg body weight/day, respectively. These intake levels represent a "worst case" exposure estimate.

Labelling

The designation 'isomaltulose' shall be displayed on the labelling of the product as such or in the list of ingredients of foodstuffs containing it.

In a prominently displayed footnote related to the designation isomaltulose by means of an asterisk (*) the words "Isomaltulose, like sugar, is a source of glucose and fructose which undergoes slower digestion and absorption" shall be displayed.

The words of the footnote shall have a typeface of at least the same size as the list of ingredients itself.

Safety of the Novel Food

Metabolic data in animals and humans, toxicity data in rats, and clinical studies, have been used to support the safety of isomaltulose. Metabolism studies have indicated that prior to absorption isomaltulose is almost completely hydrolyzed in the small intestine to the simple sugars, fructose and glucose. Both metabolites are subsequently utilized in well-characterized carbohydrate pathways. The metabolic fate of isomaltulose is equivalent to that of sucrose, which also is metabolized to glucose and fructose.

Results of subchronic and chronic studies, as well as human data, have consistently demonstrated a lack of any toxicologically significant effects relevant to the conditions of the intended uses in foods. No treatment-related adverse effects were observed in a 13-week study in rats administered dietary levels of isomaltulose up to a maximum of 10% (approximately 7,000 and 8,100 mg/kg body weight, for males and females, respectively) or in a 26-week oral gavage study in which rats were administered a maximum isomaltulose dose of 4,500 mg/kg body weight/day. Furthermore, isomaltulose provided in the diet at concentrations of up to 10% (approximately 7 g isomaltulose/kg body weight/day), the highest dose tested, demonstrated no evidence of developmental toxicity in rats. The safety of isomaltulose was further verified in several clinical trials involving administration of oral bolus doses of isomaltulose as high as 1 g/kg body weight (approximately 70 g isomaltulose) to healthy as well as diabetic individuals and ileostomy patients. No physiological or adverse effects were observed in these studies. Tolerance studies conducted with sucrose or combinations of glucose and fructose demonstrated that bolus doses of up to 100 g were well tolerated without incidence of gastrointestinal effects. Since, isomaltulose, like sucrose, is metabolized to equal parts of glucose and fructose, these studies provide additional support that intake of up to 100 g isomaltulose, throughout the day, would be well tolerated. Furthermore, the absorption of fructose is facilitated by the presence of glucose, especially when both are ingested in equal amounts. Therefore, the gastrointestinal effects apparent following consumption of fructose alone would not be expected with isomaltulose.

Safety of the Microorganism Protaminobacter rubrum

The safety of the microorganism utilized in the production of isomaltulose has been confirmed in a 14-day toxicity study in which mice and rabbits received intravenous administrations consisting of viable cells as well as the growth medium. Study results demonstrated *Protaminobacter rubrum* to be non-pathogenic and possessing only a low order of toxigenicity. The production of isomaltulose and isomalt, however, involves the use of non-viable cells only. Furthermore, the microorganism has an established history of use in the production of isomalt

(E953), which was approved for use in food by the SCF in 1984. In fact, isomaltulose is an intermediate in the manufacturing process of isomalt.

Conclusion

In conclusion, there is a substantial body of evidence to support the safety of isomaltulose, which meets the criteria of a novel food ingredient based on its lack of prior history of use in the European Community. On the basis of the available toxicology data, its nutritional equivalence to sucrose, and the established use of the microorganism *Protaminobacter rubrum* in the production of isomalt, it is concluded that isomaltulose does not present a significant risk for human health at the levels of intake, which would result from its intended uses in food.

Bijlage **E**

Eerste beoordeling/First assessment

19 Mar 2004

ADVISORY COMMITTEE FOR NOVEL FOODS AND PROCESSES

OPINION ON AN APPLICATION UNDER THE NOVEL FOODS REGULATION FOR THE APPROVAL OF ISOMALTULOSE AS A FOOD INGREDIENT

Applicant: **Cerestar (Cargill Cerestar BVBA)**

Responsible Person: **Yves Le-Bail Collet**

Novel Food: I **somaltulose**

EC Classification: **1.2**

INTRODUCTION

1. An application has been submitted by Cerestar to the UK Competent Authority on 30th October 2003 for approval of isomaltulose for use in a range of food products. A copy of the Application dossier was placed on the FSA web-site at the same time.

2. The present application for authorisation of isomaltulose was prepared pursuant to Commission Recommendation (97/618/EC) of 29 July 1997 concerning the scientific aspects and presentation of information necessary to support applications for the placing on the market of novel foods and novel food ingredients. Isomaltulose has been classified as a pure chemical or simple mixture from a non-GM source (class 1.2). The information presented in the dossier is structured accordingly and is considered below under the schemes outlined in this Commission Recommendation.

I. Specification of the novel food

Application Dossier, p 4-7

3. Certificates and methods for most analyses are to be found in the application dossier in appendix A. These analyses show isomaltulose to be a stable product under normal conditions and when subjected to heat treatments and of high purity containing low levels of arsenic and mercury. The certificates of analysis for the raw materials can be found in

appendix B. Batch on batch variation was assessed by testing five non-consecutive batches for composition. The results of these analyses on the samples indicate a narrow range of variation in composition and contaminants. Isomaltulose is produced via enzymatic conversion of sucrose using the non-pathogenic bacteria *Protaminobacter rubrum*.

Discussion. *The Committee requested further analyses on heavy metals to be carried out on the final product. Members accepted the additional data offered reassurance of the heavy metal content of the novel food. Otherwise, Members were satisfied that the analyses carried out by the applicant on the raw materials, the final product and the bacteria, P. rubrum demonstrated the safety of the novel food. The applicants' response is tabulated below.*

Summary of Metal Analysis Results					
Specification Parameter	**Manufacturing Lot**				
	(Batch 1)	**(Batch 2)**	**(Batch 3)**	**(Batch 4)**	**(Batch 5)**
Arsenic (ppb)	<100	<100	<100	<100	<100
Cadmium (ppb)	<10	<10	<10	<10	<10
Lead (ppb)	<20	<20	<20	21	<20
Mercury (ppb)	<5	<5	<5	<5	<5
Nickel (ppb)	<50	<50	<50	<50	<50

II. Effect of the production process applied to the novel food

Application dossier, p 8-19

4. The production process uses food-grade sucrose dissolved in water that is treated with a crude enzyme preparation consisting of *P. rubrum* cell mass killed using formaldehyde. After the enzymatic conversion the cells are removed by filtration. The product is then purified by demineralisation, crystallisation, washing, drying and cooling, producing a final isomaltulose product of at least 99% purity. Formaldehyde is not detectable in the final product.

Discussion. *The Committee was content that the production process is controlled and that the in-process monitoring steps were sufficient to ensure a safe and consistent product. The Committee was also reassured that the micro-organism P. rubrum is used in the commercial production of isomalt in the EU.*

III. History of the organism used as a source of the novel food

Application dossier, p 20

5. No information is supplied under this heading, as isomaltulose is not sourced from an organism but from food grade sucrose.

IX. Anticipated intake/extent of use of the novel food

Application dossier, p 21-27

6. The applicant intends to use their isomaltulose product as an ingredient in beverages and a variety of other products where it would partly replace other sugars as a source of energy. The availability of these products will not be restricted geographically and there are no plans to target these products at a particular consumer group.

7. The applicant has stated that the highest intake figures from all proposed food categories when related to body weight were found amongst children with mean and 97.5th percentile intakes of 1.6 and 4.0g /kg body weight/day respectively. The lowest intake figures were found amongst the female adults group with a mean intake of 0.2g/kg body weight/day and a 97.5th percentile intake of 0.6g/kg body weight/day.

Discussion. *The Committee had concerns over the intended market and 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. This issue is addressed in the labelling section below.*

XI. Nutritional information on the novel food

Application dossier, p 28-29

8. Isomaltulose is hydrolysed to equal amounts of fructose and glucose and absorbed almost completely in the small intestine in a similar way to sucrose.

9. Isomaltulose is metabolised at a rate of one-fifth to one quarter that of sucrose, but the final calorific value is the same as sucrose because both disaccharides are cleaved to form glucose and fructose. Isomaltulose is also characterised by a reduced sweetness when compared to sucrose. These functional properties will not be used to target products containing isomaltulose at specific consumer groups but they will be used to alter the organoleptic and physical properties of the products in which it is used.

Discussion. *The Committee had a concern over the study using 8 ileostomy patients outlined on page 48 of the dossier. Members were concerned over the possibility of a*

polymorphism in the population for isomaltulose metabolism that may cause problems. The applicant is of the opinion that there is no such polymorphism in the population as isomaltulose is metabolised by the same route as sucrose. The applicant has provided an expert confirming this view.

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. These concerns are addressed in the response from the applicant that can be found in section IX.

XII. Microbiological information on the novel food

Application dossier, p 30

10. Microbiological information is presented under schemes XII and XIII in the application dossier.

11. The purity of the stock suspension of *P. rubrum* is verified at the time of its preparation and the absence of mycotoxins and contaminating micro-organisms is also routinely demonstrated. *P. rubrum* has also been demonstrated to be non-pathogenic and has a low order of toxicity (Application dossier, p. 32-34)

12. Specifications for most raw materials including micro-organism screens were reproduced in the application.

Discussion. *The Committee was satisfied with the information supplied by the applicant and considered the production process, quality control measures and the nature of the final product to be sufficient to ensure no unintentional microbiological contamination of the product. They were also satisfied that the P. rubrum was suitable for food use and would cause no safety concerns.*

XIII. Toxicological information on the novel food

Application dossier, p 31-63

13. A number of toxicological studies have been provided to demonstrate the safety of isomaltulose including chronic and sub-chronic animal studies, developmental studies and various human studies. The toxicological tests described in the dossier have primarily been carried out on isomaltulose products from the applicant and two other manufacturers.

Discussion. *The Committee was satisfied that the isomaltulose products produced by other manufacturers of isomaltulose were sufficiently similar to the product produced by the applicant for the toxicological studies to be relevant. The Committee was content that the toxicological data provided by the applicant were sufficient to demonstrate the safety of isomaltulose.*

Allergenicity

Application dossier, p 54

14. The applicant has addressed the possibility that protein from the *P. rubrum* may be released during the production process, or protein from other raw materials may pass into the final product. The presence of protein in the final product has been estimated to be 5.2ppm, based on a measured nitrogen concentration of 0.8ppm and a standard conversion factor of 6.25. The protein figure may be an overestimate, since the calculation assumes that all nitrogen is in the form of protein.

Discussion. *The Committee considered this level of protein to be sufficiently low to cause no problems with allergenicity, taking into account the quantities that might be consumed.*

Labelling

15. The applicant provided the following labelling suggestion:

> "The designation 'isomaltulose' shall be displayed on the labelling of the product in the list of ingredients of foodstuffs containing it. In a prominently displayed footnote related to the designation isomaltulose by means of an asterisk (*), the words 'isomaltulose is like sugar, a source in equal parts of glucose and fructose, but has a slower rate of digestion and absorption' or 'Isomaltulose, like sugar, is a source of glucose and fructose which undergoes slower digestion and absorption' shall be displayed. The words of the footnote shall have a typeface of at least the same size as the list of ingredients itself."

Discussion. *The Committee was content that the labelling was sufficiently clear so that diabetics in particular would be aware that products containing isomaltulose were a source of glucose. In response to the Committee's earlier concern over the possibility of increasing calorific intake because of reduced sweetness and to clarify the exact role of isomaltulose as an ingredient the applicant has provided the following revised labelling suggestion:*

"Isomaltulose, like sugar, is a source of glucose and fructose, which undergoes slower digestion and absorption. A gram of isomaltulose provides as much total energy/calories as a gram of sugar, but over a prolonged period of time".

The Committee noted the inclusion of a statement about the energy content, but was concerned that the final part of the statement could lead to this information being misunderstood by consumers. 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".

OVERALL DISCUSSION

16. The Applicant has provided a clear specification of the proposed novel food and indicated, on the basis of analysis from a number of non-consecutive batches that the specification is achievable. The production process differs very little from that used in the production of isomalt, an approved sweetener in the EU.

17. Given that isomaltulose is an isomer of sucrose and is broken down to glucose and fructose in the GI tract in a similar way to sucrose, no additional nutritional concerns were raised from the consumption of the novel food. The information supplied by the applicant offers sufficient reassurance that consumption of the novel food does not give rise to any toxicological concerns.

18. The applicant has demonstrated that the novel food is stable under normal conditions and also when subject to raised temperatures. The applicant has also demonstrated that the novel food is microbiologically safe.

19. The proposed labelling of the product is acceptable, nevertheless the applicant should be reminded of the need to comply with food labelling legislation and ensure that the labelling and presentation of the products does not mislead the consumer, particularly in relation to their energy content.

20. While the projected levels of isomaltulose intake do not give rise to any toxicological concern, the effect of substitution for sucrose on the overall pattern of extrinsic sugar consumption is unknown. The Committee noted concerns that the consumption of extrinsic sugars is already undesirably high and recommended that the applicant undertakes post-market monitoring to demonstrate the pattern of consumption of

isomaltulose-containing products and to establish whether consumers correctly understand the energy content of such products compared with their existing counterparts

Conclusion

The Advisory Committee on Novel Foods and Processes is 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.

March 2004