ORIGINAL SUBMISSION

consultants to the regulated industry

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October 31, 2005

Dr. Robert Martin, Deputy Director
Division of Biotechnology and GRAS Notice Review
Office of Food Additive Safety (HFS 255)
Center for Food Safety and Applied Nutrition
Food and Drug Administration
4300 River Road
College Park, MD 20740-3835

REC'D NOV 1 - 2005

Dear Dr. Martin:

SUBJECT: GRAS Notification – Exemption Claim for Isomaltulose (Palatinose™)

The enclosed GRAS Notification is hereby submit on behalf SÜDZUCKER AG Mannheim/Ochsenfurt. This notice is in accordance with FDA proposed rule of April 17, 1997 (62 FR 18938), relating to the filing of a generally recognized as safe (GRAS) notification. SÜDZUCKER AG Mannheim/Ochsenfurt claims that the use of isomaltulose as a disaccharide carbohydrate is generally recognized as safe based on scientific procedures. It is therefore exempt from pre-market approval requirements of the Federal Food, Drug, and Cosmetic Act.

In conformity with the requirements outlined in the proposed rule, the attached information is included (*in triplicate*) with this exemption claim. Also enclosed is an electronic copy (PFD) of the Notification Claim and Additional Information documents.

Sincerely,

William A. Olson, Ph.D.
Consultant to
SÜDZUCKER AG Mannheim/Ochsenfurt

WAO:gbt
Isomaltulose GRAS Cover

Enclosures
GRAS Notification Exemption Claim for Isomaltulose (CD)
GRAS Notification (3 copies)

cc: A. Sentko

SÜDZUCKER

SÜDZUCKER / PALATINIT

GRAS Notification – Exemption Claim for Isomaltulose (PALATINOSE™)

October 26, 2005

Content:

Part 1: GRAS Exemption Claim
Part 2: Additional Information
Part 3: References
Part 4: Annexes

Form 00 601 / 15.000 / 09.2004

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GRAS EXEMPTION CLAIM

In accordance with FDA proposed rule of April 17, 1997 (62 FR 18938), relating to the filing of a generally recognized as safe (GRAS) notification, SÜDZUCKER AG Mannheim/Ochsenfurt hereby claims that the use of isomaltulose (Palatinose™) as a disaccharide carbohydrate intended for use in food and beverages is generally recognized as safe based on scientific procedures. It is therefore exempt from pre-market approval requirements of the Federal Food, Drug, and Cosmetic Act.

(1) Name and address of the notifier:

Hans-Ulrich Frech, Director
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(2) Common or usual name of the substance that is the subject of the GRAS exemption claim:

Isomaltulose, Palatinose™

(3) Applicable conditions of use of the notified substance:

(a) Foods in which the substance is to be used:

Isomaltulose is intended for use in foods (including beverages) in general as a carbohydrate source, replacing totally or partially sucrose or other highly digestible carbohydrates. Illustrative examples of food categories and food types in which isomaltulose can be used are presented in the table given under (b); neither the listed

food categories, nor the illustrative use levels, are intended to limit the food applications of isomaltulose. Potential users of products with isomaltulose are as described in (d) below.

(b) Levels of use in such foods:

Illustrative examples for the food categories isomaltulose can be used in	**Examples for the description of the specific type of food within the given food category**	**Illustrative approx. use levels as consumed [%]**
Baked goods and baking mixes (21CFR170.3(n)(1))		10-25
Beverages (21CFR170.3(n)(2); 21 CFR170.3(n)(3))	Specific soft-drinks such as energy drinks, sports and isotonic drinks Instant drink preparations Teas Beers and related beverages (e.g. light or alcohol-reduced beers)	1-10
Cereal-based products (21CFR170.3(n)(4))	Breakfast cereals Cereal bars	20-35 5-20
Confectionery and frostings (21CFR170.3(n)(9))	Hard candies, cough drops etc Soft candies, toffees etc Chocolate and related products Compressed goods Fondants/frostings fillings, crèmes, toppings nougat	99 30-50 25-50 98-99 90 15-55 45
Chewing gum (21CFR170.3(n)(6))		5-35
Frozen dairy desserts and mixes (21CFR170.3(n)(20))	Ice cream and other frozen dairy desserts	30
Fruit and water ices (21CFR170.3(n)(21))		15
Gelatins, puddings, desserts etc (21CFR170.3(n)(22))		15-30
Jams and jellies, spreads (21CFR170.3(n)(28))		25-40
Nut and peanut spreads (21CFR170.3(n)(32))		45
Milk products (21CFR170.3(n)(31))		3-20
Processed fruit and fruit juices or vegetable juices (21CFR170.3(n)(35); 21CFR170.3(n)(36))	Juices including concentrates, dilutions, drink substitutes	1-10
Snack foods (21CFR170.3(n)(37))		10-25
Sugar substitutes (21CFR170.3(n)(42))	e.g., table tops, granulated, liquid or tablet forms	2- >99
Sweet Sauces, toppings, syrups (21CFR170.3(n)(43))		15-30
Others	Nutritive formulae/enteral nutrition Energy-reduced foods Meal replacement/slimming food	5-20 5-40 5-20

Form 00 602 / 24.500 / 02.2004

(c) Purposes for which the substance is used:

Isomaltulose is a disaccharide to be used as a carbohydrate source, replacing totally or partially sucrose or other highly digestible carbohydrates. On a physical-chemical level it is similar to sucrose. From its chemical definition it is a sucrose-isomer consisting of glucose and fructose; however, compared to sucrose or glucose, it is less glycemic, less insulinemic and is non-cariogenic as the linkage between glucose and fructose is more stable than in sucrose. This is leading to a slow but complete hydrolysis and absorption in the small intestine.

Because of its low hygroscopicity isomaltulose is used for instant powder preparations. In solution, isomaltulose offers very low inversion rates and a low tendency to hydrolyze.

(d) Description of the population expected to consume the substance:

While isomaltulose is suitable for consumption by the general public, its cost, formulation characteristics and metabolic characteristics will lead to the development of foods in the "healthy lifestyle" segment, marketed to consumers who follow a low glycemic diet, who are interested in avoiding significant blood sugar variations, or who (such as those engaged in athletics) are interested in a slower glucose-fructose metabolic release.

(4) Basis for GRAS determination

The basis of the GRAS determination is through scientific procedures.

(5) Review and Copying Statement

The data and information that are the basis for this GRAS determination are available for the Food and Drug Administration's review and copying at reasonable times at the office of the US representative to Südzucker/Palatinit, or will be sent to FDA upon request.

Sincerely,

Hans-Ulrich Frech
General Manager Palatinit
Business Unit ORAFTI/PALATINIT
SÜDZUCKER AG Mannheim/Ochsenfurt

Lutz Guderjahn, Ph.D.
Head of Business Development
Business Unit ORAFTI/PALATINIT
SÜDZUCKER AG Mannheim/Ochsenfurt

I. Identity of the notified substance

A specification (parameters for identity and purity) for isomaltulose produced and intended to be marketed by SÜDZUCKER/PALATINIT is given in annex 1.

A. Chemical Name:

6-O-α-D-glucopyranosyl-D-fructofuranose, Monohydrate

B. CAS Registry Number

13718-94-0

C. Common Name

Isomaltulose, Palatinose™

D. Chemical Formula

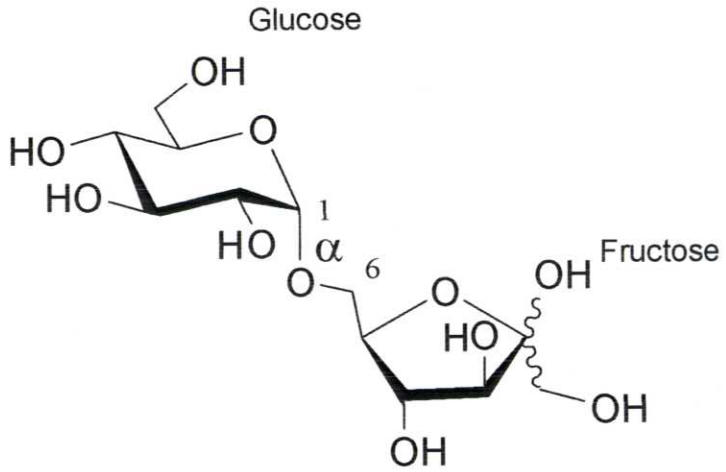
$C_{12} H_{22} O_{11} \times H_2O$

E. Definition

Isomaltulose is a reducing disaccharide consisting of one glucose and one fructose moiety linked by an alpha-1,6-glycosidic bond.

F. Structural Formula

Figure 1: Structural Formula of isomaltulose



G. Molecular Weight

360.6 (Monohydrate)

H. Assay

Not less than 98% of Isomaltulose on the dry weight basis

I. Description

White or Colorless, crystalline, sweet substance, faint Isomaltulose-specific odor.

J. Identification Test

Solubility – Soluble in Water
Thin layer chromatography – passes test

K. Purity

Water – Max. 6 % (Karl Fischer Method)
Other saccharides – Max. 2% on the dry weight basis (HPLC)
Ash – Max. 0.01% on the dry weight basis (Conductivity Ash Method)
Lead – Max. 0.1 ppm on the dry weight basis (Atomic Absorption Spectroscopy)

L. Analytical Aspects

Several batches were analysed to validate and verify the production process. The analytical results of 5 typical batches are listed in Table 1 below. The data show compliance with the specification as given in annex 1.

Table 1: Typical analyses of five isomaltulose batches from SÜDZUCKER

Batch (LIMS No.)	200311449	200311450	200311451	200311452	200311453
Water [%]	5.2	5.2	5.2	5.2	5.2
Isomaltulose [% TS*]	99.7	99.4	99.5	99.6	99.4
Total other saccharides [% TS]	0.3	0.4	0.4	0.3	0.5
Ash [% TS]	<0.01	<0.01	<0.01	<0.01	<0.01
Lead [mg/kg TS]	<0.03	<0.03	<0.03	<0.03	<0.03

* TS = Total solids

The batches for typical analysis were also analyzed for Kjeldahl nitrogen: Nitrogen was not detected (detection limit <0.01g/kg).
Protein tests were conducted according to Bradford. The detection limit using BSA as standard was 1 ppm. No protein was detectable.

M. Manufacturing Process

Up to now isomaltulose was an intermediate in the course of the isomalt[1]-production, a sugar alcohol that has been marketed in the U.S. since 1990. (see SÜDZUCKER's GRAS affirmation Petition 6G0321; accepted for filing by FDA in October 1990 (55 Fed.Reg. 42484, Oct. 19, 1990)). Now, isomaltulose is available as a final product.

In the following text, Figure 2 and Figure 3 the production process of isomaltulose as applied by SÜDZUCKER/PALATINIT is outlined.

Isomaltulose is manufactured from food-grade sucrose. An aqueous sucrose solution passes a column with an enzyme preparation consisting of immobilised non-viable cells of *Protaminobacter rubrum* (CBS 574.77), also called "biocatalyst".

The enzyme responsible for the conversion of sucrose into isomaltulose is sucrose-6-glucosylmutase (EC 5.4.99.11).

The biocatalyst used for isomaltulose production is the same as described in detail in SÜDZUCKER's GRAS affirmation Petition 6G0321 on isomalt. As already laid down in GRAS petition 6G0321, the potential pathogenicity and toxigenicity of *P. rubrum* was investigated on behalf of SÜDZUCKER with up to 10^{10} viable cells through intravenous injection in rabbits and mice followed for 14 days (Porter et al., 1991). The results showed that the viable enzyme producing organism is not pathogenic and shows only a low order of toxigenicity. The authors conclude that the *"findings provide a high degree of confidence that, if P. rubrum or its by-products should accidentally enter the final product, they will not present a hazard."*

SÜDZUCKER uses the biocatalyst as whole non-viable cells which are immobilised by entrapment in beads of calcium alginate gel. The immobilization system is consistent with the regulation for use of materials used as fixing agent in the immobilization of enzyme preparations (21 CFR 173.357). Calcium chloride is used as coagulation agent for alginate and

[1] In this case, the production for isomalt with a content of 1-O-α-D-glucosyl-D-mannitol (1,1-GPM) and 6-O-α-D-glucosyl-D-sorbitol (1,6-GPS) of >98 %.

sodium alginate is used for matrix formation; both are GRAS affirmed substances (21 CFR 184.1193 and 21 CFR 184.1724).

By the enzyme preparation, the α-1,2-linkage in sucrose is enzymatically converted into the α-1,6-linkage in isomaltulose. From the resulting solution commercial isomaltulose is obtained through crystallisation and drying. In addition, purification steps (filtration, ion exchange) are part of the process.

Figure 2: Enzymatic rearrangement of sucrose to isomaltulose (structural formulae)

Sucrose **Isomaltulose**

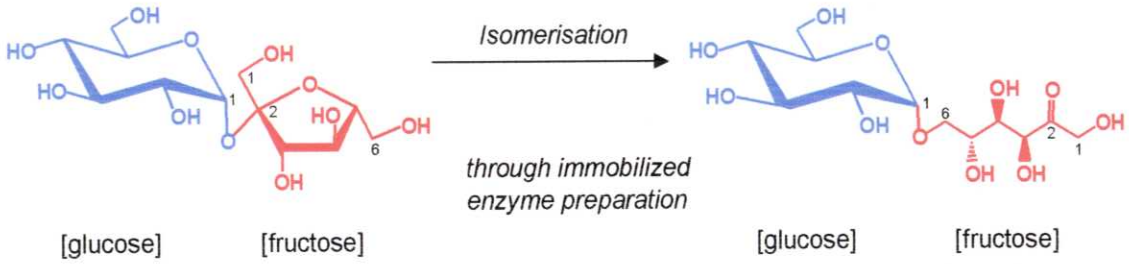
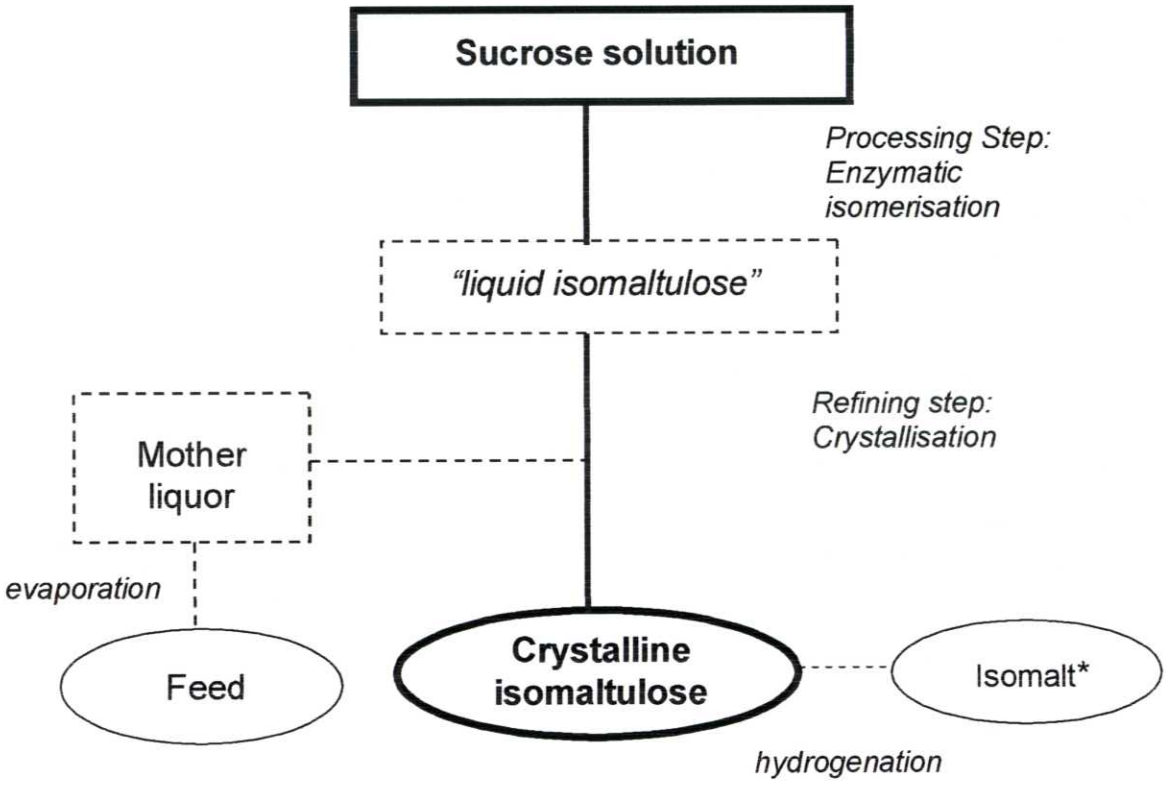


Figure 3: Production process of isomaltulose (SÜDZUCKER process)



** Content ≥ 98 % GPS + GPM*

The isomaltulose production is integrated in the SÜDZUCKER Quality Assurance System according to DIN EN ISO 9001, certified and regularly checked by an accredited body. Respective Standard Operation Procedures for raw materials, in-process as well as end product control are part of the QA system. The whole process is run in compliance with Good Manufacturing Practice as applicable to foods.
In addition to the quality assurance system, the production process was evaluated according to the principles of HACCP. This included basic processing steps, raw materials, processing aids, foreign bodies, potential environmental and microbial contaminants as well as food contact surfaces. In conclusion, the implemented GMP measures ensure that adverse health effects from such sources can be excluded.

N. Physical and chemical properties

General properties

Crystalline isomaltulose is a white substance similar to crystalline sucrose. Its melting range is about 122-124 °C and as such lower than that of sucrose (160-185 °C). Isomaltulose is practically non-hygroscopic and, unlike sucrose, remains so even on addition of citric acid (Schiweck et al., 1990; Kaga and Mizutani, 1985). The solution enthalpy of isomaltulose (-21.7 kJ/kg) is nearly the same as that of sucrose (-18.2 kJ/kg) and thus isomaltlulose does not have a cooling effect. Isomaltulose provides body/texture and mouth feeling (Schiweck et al., 1990).
Crystalline and chemical structure have been studied and confirmed by Dreissig and Lugar (1973).

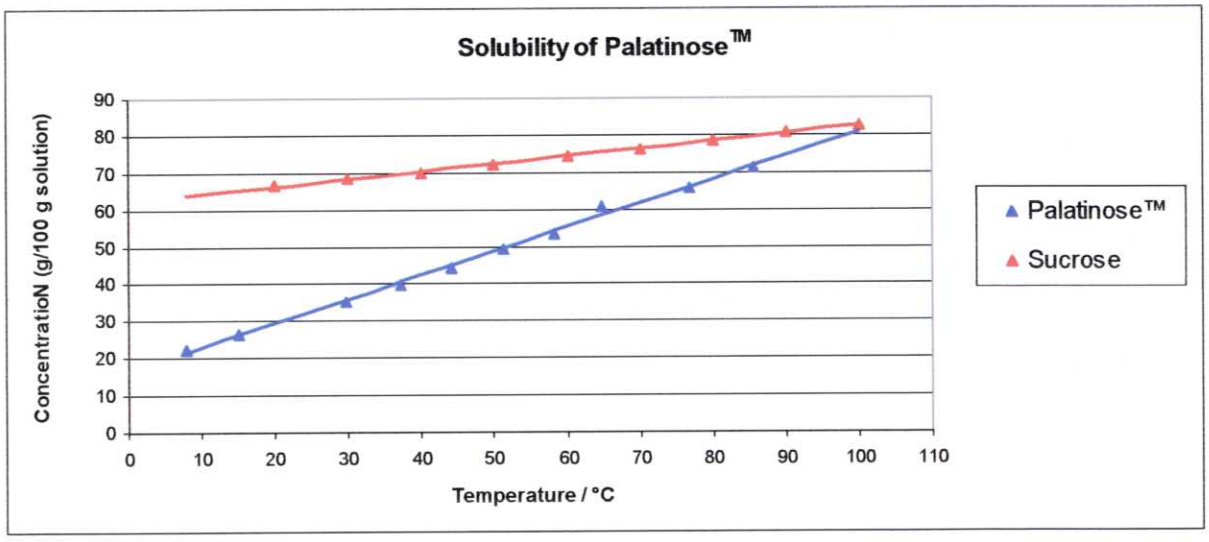
Viscosity

The viscosity of isomaltulose solutions is very similar (slightly lower) to that of sucrose solutions (Irwin and Sträter, 2001).

Solubility

Isomaltulose is soluble in water (approx. 0.5 g/g water). The solubility increases with rising temperatures, reaching 85 % of that of sucrose at about 80 °C. (Irwin and Sträter, 2001; Kaga and Mitzutani, 1985).

Figure 4: Solubility of Isomaltulose versus Sucrose in Water



O. Sensory properties

Isomaltulose provides a moderate sweetness, bulk and texture to foods.

Sweetness quality
The sweetness quality of isomaltulose is similar to sucrose; it is quickly sensed, refreshing and leaves no after-taste (Irwin and Sträter, 2001; Kaga and Mitzutani, 1985).

Sweetening power
The sweetening power of isomaltulose in comparison to a 10 % sucrose solution at 20 °C is about half that of sucrose, It rises with increasing concentrations. (Irwin and Sträter, 2001; Kaga and Mitzutani, 1985). Isomaltulose is also reported to mask off-flavors of some intense sweeteners, ingredients from fish, vegetables or soymilk (Irwin and Sträter, 2001; Anonymous 1985; Suzuki et al., 2003).

II. Information on self-limiting levels of use

Some substances may have a self-limiting use level; that is, the substance has a maximum concentration in food above which the food becomes unpalatable, unappealing, or otherwise unfit for human consumption.
For isomaltulose no such self-limiting use level that makes a product unfit for human consumption is known.

With respect to technological aspects, the solubility of isomaltulose in water (see Figure 4) might be regarded as a self-limiting level of use, e.g. transportation at room temperature of high-brix syrups containing isomaltulose is not possible due to the re-crystallization that will occur.
This has a direct impact on the potential market for isomaltulose as most beverages are produced and transported to a bottler as a high-brix syrup. The above described limitations regarding transportation of isomaltulose syrups will therefore result in increased incremental product costs as either isomaltulose has to be transported at lower temperatures in low brix-solution or a beverage company has to invest in additional equipment to turn isomaltulose into a solution after it is transported in crystalline form.

Furthermore the use of syrups is quite a common way for the "just-in-time" production of beverages in bars, cinemas and catering (so called post-mix systems in the "away from home market" where a beverage is produced via dilution of syrup with water and CO_2 directly at the point of sale). This marketing channel will not be open to isomaltulose containing beverages.

The price of isomaltulose will limit its use as well. As explained earlier, isomaltulose is made from sucrose. Therefore, isomaltulose production costs are significantly higher compared to sucrose. Its sweetening power is about half that of sucrose. Thus isomaltulose will be used in combination with other sweeteners as a functional ingredient, e.g. in order to reduce the glycemic response of a beverage. It will not be used to completely replace sucrose (or HFCS) in beverages. As an example, for a beverage this would mean roughly to use a mixture of 30% isomaltulose and 70% sucrose instead of 100% sucrose or HFCS.

III. Detailed summary of the basis for the notifier's determination that the particular use of the notified substance is exempt from pre-market approval requirements because the use is GRAS

Isomaltulose is an alpha-1,6- glucose-fructose combination and is absorbed as glucose and fructose in the small intestine. Based on this basic physiology, it can be concluded, that the safety of isomaltulose is similar to that of sucrose, an alpha-1,2-glucose-fructose combination.
A safety evaluation of isomaltulose was done by the TNO Nutrition and Food Research Institute (Zeist, The Netherlands) on the request of Südzucker. (Lina B.A.R. & Woutersen R.A.; Safety evaluation of isomaltulose (Palatinose®). TNO Report V2575, July 2000), taking all relevant studies into account (biological data and toxicological studies, metabolic studies and studies on gastrointestinal tolerance). The report is attached in annex 2 and concludes "that the use of isomaltulose as a sugar is of no health concern". A review of the biological and toxicological studies was published in the peer reviewed journal *Food and Chemical Toxicology* (Lina et al (2002) Isomaltulose (Palatinose®): A review of biological and toxicological studies. Fd. Chem.Toxicol. 40, 1375-1381;attached in annex 2)

In addition, based on a critical review of the scientific evidence (including e.g., physical and chemical identity information, manufacturing information, safety data and physiological data, intended uses and consumption estimates) another independent panel of experts qualified by scientific training and national and international experience concluded that isomaltulose is safe for human consumption. This assessment was part of the Novel Food approval process in accordance with Article 6 of Regulation (EU) No 258/97. (annex 3)
The complete file prepared by Südzucker/Palatinit (including copies of all references) and the initial assessment report prepared by the German Federal Institute for Risk Assessment was shared with the competent authorities of all 25 member states of the European Union and the safety of isomaltulose was confirmed by all member states, resulting in the authorization of Südzucker to place isomaltulose on the market of the Community as a novel food or novel food ingredient for use in foodstuffs. (Commission Decision of 25 July 2005, published in the Official Journal of the European Union on 29.7.2005 (L 199/90)). (annex 4)

Thus, independent panels of experts concluded that isomaltulose is generally recognized as safe (GRAS), based on scientific procedures, under the conditions of use in foods described herein.

IV. Probable Consumption of the Substance

Isomaltulose is intended to be used as a slow release carbohydrate source, in particular in those foods that contain significant amounts of carbohydrates like sucrose or other carbohydrates that are quickly absorbed to the blood stream. It is the purpose of isomaltulose to replace those quickly available carbohydrates completely or partially as isomaltulose is a carbohydrate that is more slowly hydrolyzed than sucrose. This leads to a lower blood glucose and insulin response. Isomaltulose provides the same calories as other carbohydrates as it is fully digestible. Further, pH-telemetry measurements showed that the oral flora can hardly use isomaltulose for their fermentation. Ph-telemetry measurements (Imfeld, 1993) did not show a drop down of the pH value below 5.7. These beneficial physiological properties will be the main reasons for using isomaltulose as a carbohydrate source.

While theoretically isomaltulose can be used at the same amount as sucrose is used, in practice, the intake level of sucrose will by far not be reached. Reasons for this are:

- Isomaltulose is significantly more expensive than sucrose is:
  Isomaltulose is produced from sucrose (sugar) via enzymatic rearrangement of the α-1,2 linkage to form an α-1,6 bond. Thus, sucrose is the starting material and the complete costs of production need to be added when calculating the price of isomaltulose. Substitution of low price carbohydrates like HFCS by isomaltulose is assumed to be negligible.
  Based on these significantly higher production costs, isomaltulose will be a high-price ingredient for added-value products with specific functional properties.

- Isomaltulose is less soluble in water compared to sucrose or HFCS which limits its use in high-brix syrups (see part II)

- Isomaltulose is less sweet than sucrose.

Thus, it is estimated that isomaltulose might replace the use of sucrose in the market at levels of approximately 5 to 10 %.

In the United States, the per capita per year consumption of total sweeteners estimated to be 102.1 pounds, of which 46.4 pounds are coming from the consumption of refined sugar while 55.7 pounds are coming from corn sweeteners. (Haley et al. Sweetener Consumption in the United States, USDA SSS-243-01, August 2005)

If 5-10 % of the refined sugar is replaced by isomaltulose it would lead to an intake of 2.3-4.6 pounds (1-2.1 kg) isomaltulose/person/year or approx. 3 to 6 g/person/day.

Additional intake information:

- Isomaltulose occurs in small quantities in honey. This was first found by Siddiqui and Furgala (1967) and later confirmed by Low and Sporns (1988). It has also been reported to be in cane sugar juice (Takazoe, 1985; Eggleston and Grisham, 2003).

  Quantitative analyses of 60 samples of Spanish honeys from various regions and sources (honeydew, nectar, forest) and our own analyses from sources worldwide using gas chromatographic methods were more recently carried out (Gomez Barez et al., 2000). Isomaltulose was detected in all samples tested and ranged from 0.1 to 0.7 %.

  Average consumption of honey in the German population is estimated between 1.1 and 1.4 kg/yr (Dutch 0.65 kg, French 0.25 kg). In the US, the average consumption of honey is 1.4 pounds/yr (0.64 kg). This means that on an average basis isomaltulose is ingested in milligram to gram quantities per year in these populations (< 10 g/yr).

- In Japan isomaltulose is marketed as food since 1985. In 2002, 5000t isomaltulose were marketed; in comparison sugar consumption amounted to more than 2 000 000 t (per capita intake 17 kg sugar in 2002).

- For Europe the sugar consumption is approx. 35 kg/yr or 100 g sugar/person//day).
  An estimation of the intake of isomaltulose in Germany was based on a 3 tier approach: estimation based on the total usage of sugars per person, estimation of the possible contribution of particular foodstuffs and estimation based on consumption surveys. It was assumed isomaltulose can replace 5-10% of the total sugar consumption by use of the relevant products. 20% was used as a maximum calculation. This resulted in the estimation of a daily average intake of isomaltulose of 15-35 g, assuming the alternative food product containing isomaltulose were chosen from the food selection at each opportunity. A particularly high level of consumption could, in an extreme case, possibly lead to a daily intake of up to approximately 100 g. All calculations are to be regarded as theoretical maximum amounts. The anticipated mean isomaltulose intake would probably be significantly lower in reality."(Expert Opinion of Prof. Dr. H. Heseker, University of Paderborn, Faculty of Sciences, Department of Nutrition and Consumer Education, 31.8.2004)

V. Basis for concluding, in light of the data and information described above, that there is consensus among experts qualified by scientific training and experience to evaluate the safety of the substances added to food and that there is reasonable certainty that the substance is not harmful under the intended conditions of use.

As laid down in section III, a safety evaluation was conducted by experts in the field of toxicology and food safety at TNO Nutrition and Food Research Institute (Zeist, The Netherlands) *(Lina B.A.R. & Woutersen R.A.; Safety evaluation of isomaltulose (Palatinose®). TNO Report V2575, July 2000)*) and published in the peer reviewed journal *Food and Chemical Toxicology (Lina et al (2002), Isomaltulose (Palatinose®): A review of biological and toxicological studies., Fd. Chem.Toxicol. 40, 1375-1381*). Both documents are attached in annex 2.

The experts concluded from reviewing the biological and toxicological data: *"A large body of in vitro and in vivo biochemical and toxicological studies in various species, including men, has been conducted to assess the safety of isomaltulose for use as a non-cariogenic sugar. Results on in vivo and in vitro studies show that isomaltulose is slowly but completely digested in the small intestine. The resulting monosaccharides glucose and fructose are absorbed and metabolized. Owing to complete cleavage and absorption, even high oral doses of isomaltulose do not result in gastrointestinal discomfort. Slower blood glucose and insulin responses may be particularly favorable for diabetic and pre-diabetic conditions. Toxicological and human studies did not reveal adverse effects. On the basis of the data presented in this paper, it is concluded that the use of isomaltulose as an alternative sugar would be of no health concern."* (Lina et al, Food and Chemical Toxicology, 2002)

Another independent expert panel, the German Federal Institute for Risk Assessment, evaluated all data as part of the Novel Food approval procedure in the European Union. Their assessment report is attached (annex 3). Data were distributed to all 25 member states of the European Union. The matter was discussed within the Standing Committee on the Food Chain and Animal Health, Section on General Food Law, during their meeting on 23rd June 2005. This committee plays a key role in the EU decision-making process as committee members are representatives of the EU Member States. The committee unanimously delivered a favorable opinion on the draft proposal of the EU Commission for the novel food approval of isomaltulose (one Member State absent). This resulted in the EU Commission decision on the 25th July 2005 to authorize SÜDZUCKER to place isomaltulose on the market for use in food in general (published in the Official Journal of the European Union on 29th July 2005 (annex 4).

Thus, independent panels of experts concluded that isomaltulose is generally recognized as safe (GRAS), based on scientific procedures, under the conditions of use in foods described herein.

List of References

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List of Annexes :

Annex 1: SÜDZUCKER/PALATINIT Specification for Palatinose™ (isomaltulose)

Annex 2: Lina B.A.R. & Woutersen R.A.; Safety evaluation of isomaltulose (Palatinose®). TNO Report V2575, July 2000

Lina, Jonker, & Kozianowski 2002 "Isomaltulose: a review of biological and toxicological studies", *Food and Chemical Toxicology*, vol. 40, pp. 1375-1381

Annex 3: Bundesinstitut für Risikobewertung (BfR), Berlin, Germany (Federal Institute for Risk Assessment)
Initial assessment report on the application made by SÜDZUCKER AG to place on the market the novel food ingredient isomaltulose (Palatinose ®) in accordance with Article 6 of Regulation (EC) No 258/97

Annex 4: European Union, Commission Decision of 25 July 2005, published in the Official Journal of the European Union on 29.7.2005 (L 199/90)
http://europa.eu.int/eur-lex/lex/LexUriServ/site/en/oj/2005/l_199/l_19920050729en00900091.pdf)

PALATINOSE™ Specification

Member of the Group SÜDZUCKER

PALATINOSE™ (Isomaltulose) is a disaccharide. Starting material for the PALATINOSE™ production is sugar. By an immobilized enzyme preparation sugar is converted to PALATINOSE™. Its chemical name is 6-O-α-D-glucopyranosyl-D-fructofuranose.

Parameter	SÜDZUCKER Specification on PALATINOSE™	Reference
Assay*	**≥ 98 % isomaltulose**	**HPLC[1)]**
Description	**White or colorless, crystalline, sweet substance faint isomaltulose specific odor**	
Identification		
Thin layer chromatography	**Passes test**	**TLC[2)]**
Solubility	**Soluble in water**	
Purity		
Water	**≤ 6 %**	**Karl Fischer[3)]**
Other saccharides*	**≤ 2 %**	**HPLC[1)]**
Ash*	**≤ 0.01 %**	**Conductivity[4)]**
Lead*	**≤ 0.1 mg/kg**	**AAS[5)]**

* **based on total solids**

1) Südzucker Standard Operation Procedure: Determination of the Composition of Palatinose™ as such and in food using HPLC

2) Südzucker Standard Operation Procedure: Identification of Palatinose™ using thin layer chromatography

3) Karl Fischer Method according to ICUMSA Method GS4/7/3-12 (1998)

4) Conductivity ash according to ICUMSA Method GS2/3-17 (2002)

5) Atomic Absorption Spectroscopy according to ICUMSA Method GS2/3-24 (1998)

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BfR

Risiken erkennen – Gesundheit schützen

24. September 2004

Bericht über die Erstprüfung des Antrags der Südzucker AG auf Inverkehrbringen der neuartigen Lebensmittelzutat Isomaltulose (Palatinose®) gemäß Artikel 6 der Verordnung (EG) Nr. 258/97

Der von Südzucker AG vorgelegte Antrag auf Zulassung von Isomaltulose (Handelsname: Palatinose®) als neuartige Lebensmittelzutat wurde vom Bundesinstitut für Risikobewertung im Hinblick auf die Kriterien gemäß Artikel 3 Absatz 1 der Verordnung (EG) Nr. 258/97 geprüft. Dem Bericht über die Erstprüfung wurde das in der Empfehlung der Kommission vom 29. Juli 1997 (97/618/EG) vorgegebene strukturierte Bewertungsschema für Lebensmittel der Kategorie 1.2, d.h. für reine Chemikalien oder einfache Mischungen aus nicht genetisch veränderten Quellen, deren Quelle bisher in der Gemeinschaft nicht als Lebensmittel verwendet wurde, zugrunde gelegt.

I. Spezifikation

Der Antragsteller hat Spezifikationen für die Identität und Reinheit der antragsgegenständlichen Isomaltulose (Handelsname: Palatinose®) aufgestellt (B.I.1), darunter für folgende Parameter:

Isomaltulose	min. 98%
Andere Saccharide	max. 2%
Veraschungsrückstand	max. 0,01%
Blei	max. 0,1 mg/kg
(Die vorgenannten Werte sind jeweils auf das Trockengewicht bezogen.)	
Wasser	max. 6%

Die Ergebnisse analytischer Untersuchungen von insgesamt neun Chargen Isomaltulose belegen, dass diese hinsichtlich der o.g. Parameter der vorgeschlagenen Spezifikation entsprechen. Die Gehalte anderer möglicher Metall-Kontaminanten (Cadmium, Nickel, Quecksilber und Arsen) lagen jeweils unterhalb der Nachweisgrenzen der angewandten Methoden.

Die chemische Stabilität von Isomaltulose und von Isomaltulose in Hartkaramellen wurde über einen Lagerzeitraum von zwei Jahren belegt.

II. Auswirkungen des Herstellungsverfahrens

Nach Angabe des Antragstellers entspricht die Herstellung von Isomaltulose dem ersten von zwei Schritten bei der Herstellung des Süßungsmittels Isomalt, welches in der EU gemäß Richtlinie 94/35/EG als Lebensmittelzusatzstoff zugelassen ist. Isomalt wurde durch den *Wissenschaftlichen Lebensmittelausschuss* (SCF) der Europäischen Kommission und durch das *Joint FAO/WHO Expert Committee on Food Additives* (JECFA) hinsichtlich der gesund-

heitlichen Unbedenklichkeit bewertet und zur Verwendung in Lebensmitteln akzeptiert (SCF, 1984 und 1987; JECFA, 1987).

Für die Herstellung der Isomaltulose wird als Ausgangsmaterial Saccharose mit Lebensmittel-Qualität (food-grade) eingesetzt, die aus konventionellen Zuckerrüben gewonnen wird. Durch Passage einer sterilisierten Saccharose-Lösung über ein Trägermaterial, das immobilisierte, abgetötete Zellen von *Protaminobacter rubrum* enthält, wird die α-1,2-glykosidische Bindung in Saccharose enzymatisch in die α-1,6-glykosidische Bindung überführt. Das Reaktionsprodukt Isomaltulose wird nach Filtration der Lösung, Ionenaustausch-Verfahren und Eindampfen durch Kristallisation und Trocknung gewonnen.

Der in einem Fließschema dargestellte Herstellungsprozess wird nach Angaben des Antragstellers von einem Qualitätssicherungssystem in Übereinstimmung mit GMP bzw. einem HACCP-Konzept begleitet. Dies schließt die Sicherheit aller verwendeten Chemikalien und Hilfsstoffe sowie Kontaktmaterialien unter Berücksichtigung der geltenden Richtlinien in der Europäischen Union (EU) ein.

III. Frühere Erfahrungen mit dem als Quelle des neuartigen Lebensmittels verwendeten Organismus

Das Ausgangsmaterial für die Herstellung von Isomaltulose ist aus konventionellen Zuckerrüben gewonnene Saccharose mit Lebensmittel-Qualität, welche eine sichere Tradition als Lebensmittel hat.

IX. Voraussichtlicher Konsum/Ausmaß der Nutzung

Isomaltulose ist zur Verwendung als Zutat in Getränken (5-15%), Getreide-Produkten, Suppen, Garnierungen und Desserts (15-30%), Produkten auf Milchbasis (10-20%), Backwaren und Konfekt (bis 99%) sowie anderen Produkten wie Marmeladen und Energie-reduzierten Lebensmitteln (10-40%) bestimmt und soll Glucose, Fructose, Saccharose und Stärke-Hydrolysate zum Teil ersetzen. Der Antragsteller geht davon aus, dass sich die Gesamt-Aufnahme an Glucose und Fructose nicht ändert.

Auf der Basis der im Jahr 2002 in Japan vermarkteten Isomaltulose und unter Einräumung eines zehnfachen Sicherheitszuschlages durch eine zukünftig zu erwartende Steigerung des Isomaltulose-Konsums, errechnet der Antragsteller einen Pro-Kopf-Verbrauch in Japan von 1 g/Tag, was einer 2,5 %-igen Zuckersubstitution entspräche. Da der Zuckerverbrauch der europäischen Bevölkerung als doppelt so hoch angenommen wird, schätzt der Antragsteller die maximale durchschnittliche Aufnahme für Europa auf 2 g/Tag bzw. 20 g/Tag bei hohem Verzehr.

Der Antragsteller hat nach Altersgruppen und Lebensmitteln differenzierte Schätzungen der Aufnahmemenge von Isomaltulose in Deutschland unter Nutzung verschiedener Berechnungsansätze vorgelegt. Für die Berechnungen wurden Verzehrsdaten der Nationalen Verzehrsstudie (NVS, 1985-1988) und Daten einer Multicenterstudie mit Kindern im Alter von 6

Monaten bis 5 Jahren (Verzehrsstudie zur Ermittlung der Lebensmittelaufnahme von Säuglingen (VELS), 2001-2002) verwendet. Zusätzlich wurden für die Aufnahmeschätzungen Agrar- und Absatzstatistiken zum Zuckerverbrauch und Absatz von Sportlergetränken bzw. Schokoriegeln herangezogen. Basierend auf diesen Verzehrsdaten wird die tägliche mittlere Isomaltulose-Zufuhr auf 15,9 g für Kinder von 1-4 Jahren, 34,8 g für Jungen von 11-18 Jahren und auf 23,8 g für die Gesamtbevölkerung geschätzt. Bei besonders hohem Verzehr können von Jungen bis zu 100 g Isomaltulose pro Tag aufgenommen werden.

X. Informationen über eine frühere Exposition des Menschen

Isomaltulose kommt in geringen Mengen in Honig (N.H. Low and P. Sporns (1988) Analysis and quantitation of minor di- and trisaccharides in honey, using capillary gas chromatography. Journal of Food Science 53 (2): 558-561) und in Rohrzuckersaft vor. Der Antragsteller schätzt die durchschnittliche Aufnahme von Isomaltulose durch den Verzehr von Honig in Deutschland auf < 10 g/Jahr.

In Japan wird Isomaltulose seit 1985 als Lebensmittelzutat verwendet und ist seit 1992 gemäß den *Food for Specified Health Use* (FOSHU)-Regelungen als funktioneller Lebensmittelinhaltsstoff in einer großen Zahl von Produkten akzeptiert, da es die Entwicklung von Karies reduziert. Nach Angabe des Antragstellers sind bisher keine Nebenwirkungen bekannt geworden.

XI. Ernährungswissenschaftliche Information

Die antragsgegenständliche Isomaltulose soll wegen der geringen kariogenen Eigenschaften und des geringen glykämischen Index höher glykämische und/oder kariogene Kohlenhydrate, wie Glucose, Fructose, Saccharose und Stärkehydrolysate teilweise ersetzen.

Metabolisierung
Isomaltulose wird durch den Isomaltase-Saccharase-Komplex in der Dünndarm-Mucosa hydrolytisch zu gleichen Teilen Glukose und Fruktose gespalten, wobei die Isomaltase den Hauptteil der Hydrolyse katalysiert. Dieser hydrolytische Spaltungsprozess läuft jedoch im Vergleich zur Saccharose wesentlich langsamer ab, die Hydrolyse-Rate der Isomaltulose beträgt nur 1/5 bis 1/4 der Saccharose. Daher steigt auch der Glukose- und Insulinspiegel nach oraler Verabreichung von Isomaltulose langsamer an und erreicht niedrigere Maximalwerte ((B.A.R. Lina, D. Jonker, G. Kozianowski (2002) Isomaltulose (Palatinose®): A review of biological and toxicologial studies. Food and Chemical Toxicology 40: 1375-1381). Dennoch gelangen, wie in den vom Antragsteller zitierten Fütterungs-Studien gezeigt wurde, unter den gegebenen Versuchsbedingungen und aufgenommenen Isomaltulose-Konzentrationen keine bzw. nur geringe Mengen unhydrolysierte Isomaltulose in den Dickdarm, wo sie beispielsweise zu kurzkettigen Fettsäuren fermentiert werden und Einfluss auf die fäkale Mikroflora ausüben könnten (Kashimura et al, 1990b).

Die Spaltungsprodukte werden durch aktive und passive Transportsysteme resorbiert und über den normalen Kohlenhydrat-Stoffwechselweg weiter metabolisiert. Isomaltulose weist mit 4 kcal/g den gleichen physiologischen Verbrennungswert wie Saccharose auf. Aufgrund

der langsameren Hydrolyse- und der dadurch bedingten langsameren Resorptionsrate steigt der Serumglukose- und Insulinspiegel im Vergleich zur Saccharose verzögert an. Aufgrund dieser sowohl bei gesunden Probanden als auch bei Diabetikern nachgewiesenen Eigenschaften soll Isomaltulose auch für Diabetiker und Verbraucher mit prädiabetischer Disposition geeignet sein (B.A.R. Lina et al., 2002). Nach der vom Antragsteller zitierten Humanstudie von Achten et al. (2003) weist Isomaltulose bei körperlicher Aktivität eine Oxidationsrate von 28 % im Vergleich zur Saccharose mit 63 % auf, was die Autoren der Studie auf die niedrigere Hydrolyserate von Isomaltulose zurückführen. Dies soll mit einer höheren Nutzung (Verbrauch) von Glykogen- und Fettreserven im Körper verbunden sein.

Glykämischer Index

Der Glykämischer Index klassifiziert Kohlenhydrat-haltige Lebensmittel nach ihrer Blutzucker-steigernden Wirkung und wird definiert als die Fläche unter der Kurve der Blutzuckerwerte. Zur Ermittlung des glykämischen Index wird der Blutzuckeranstieg nach Verzehr von 50 g Kohlenhydraten aus den entsprechenden Lebensmitteln gemessen. Der glykämische Index eines Lebensmittels wird im Vergleich zu Glukose, der ein Referenzwert von 100 zugewiesen wurde, ermittelt. Saccarose hat einen glykämischen Index von 70 und für Isomaltulose wurde an der Universität Sidney ein Glykämischer Index von 32 sowie ein Insulinämischen Index von 30 ermittelt.

Kariogene Eigenschaften

Die Bildung von Zahnkaries hat multifaktorielle Ursachen. Eine der Hauptursachen ist die Biosynthese von extrazellulären unlöslichen Glukanpolymeren auf der Zahnoberfläche und die Säurebildung aufgrund des enzymatischen Abbaus von Kohlenhydraten durch orale Plaque-bildende Bakterien, wie z.B. *Streptococcus mutans*. Ein pH-Wert unter 5.7 begünstigt die Demineralisierung des Zahnschmelzes. Zahlreiche *in vitro*-Studien belegen, dass Isomaltulose durch *Streptococcus mutans* und andere orale Plaque-bildende Bakterien nicht fermentiert wird, so dass die Säurebildung im Vergleich zu Saccharose und Glukose sehr gering ist und keine unlöslichen Glukane gebildet werden. Intraorale pH-Messungen beim Menschen zeigten, dass beim Verzehr von Isomaltulose-haltigen Süßwaren der pH-Wert oberhalb des kritischen pH-Wertes von 5.7 bleibt. Im Vergleich zu den traditionellen Zuckerarten gilt Isomaltose daher als weniger kariogen (T. Oku (1996) Oligosaccharides with beneficial health effects: A Japanese perspective. Nutrition Reviews 54 (11): 59-66).

Nebenwirkungen

Aufgrund der vollständigen Hydrolyse der Isomaltulose im Dünndarm und der anschließenden Resorption der Spaltprodukte Glukose und Fruktose, sind nach Aussage des Antragstellers auch bei höherer Isomaltulose-Zufuhr weder laxative Effekte noch eine Wirkung auf die Kolonflora zu erwarten, mit Ausnahme eines angeborenen oder durch eine Bürstensaum-Dystrophie erworbenen Saccharase-Isomaltase-Mangels. Die Antragsunterlagen enthalten einen Bericht über eine Studie zur Sicherheitsbewertung von Isomaltulose (Annex B XIII), die am TNO-Institut in den Niederlanden durchgeführt wurde. Weder in der Studie an 10 gesunden Männern (18-35 Jahre), denen in acht Mahlzeiten zwischen 0,25 und 0,75 g Isomaltulose pro kg Körpergewicht verabreicht wurden, noch in einer gastrointestinalen Toleranzstudie (randomisiert, doppel blind) an 60 weiblichen und männlichen Freiwilligen (Alter 24 Jahre +/- 9), die entweder Saccharose oder Isomaltulose in steigenden Konzentrationen über 12 Wochen verzehrten, wurden gastrointestinale Störugnen festgestellt. Bis zu einer

Zufuhr von 48 g war die gastrointestinale Toleranz von Isomaltulose mit der von Saccharose vergleichbar.

Auch die in einigen Studien untersuchten Lipid-Stoffwechselparameter (LDL, VLDL, HDL-C, Gesamtcholesterin und Triglyzeride) zeigten keine statistisch signifikanten Veränderungen im Vergleich zur Saccharose, bis auf die in einer Studie festgestellte signifikante Erhöhung der freien Fettsäuren und leichte Erhöhung der Gesamt-Plasmacholesterin-Konzentration.

XII. Mikrobiologische Informationen

Nach Einschätzung des Antragstellers enthält Isomaltulose keine Substanzen bakteriellen Ursprungs, die ein gesundheitliches Risiko darstellen könnten.

Die Saccharose wird vor der enzymatischen Behandlung gelöst, filtriert und sterilisiert. Die mikrobiologische Qualität des Produkts wird als Teil der Prozess-Kontrollmaßnahmen regelmäßig überprüft. In der kristallinen Isomaltulose sind die Bedingungen für mikrobielles Wachstum nicht gegeben.

Der als enzymatische Prozesshilfe verwendete Mikroorganismus *Protaminobacter rubrum* CBS 574.77 wird der Risikogruppe 1 zugerechnet, d.h. beim Umgang mit den dieser Risikogruppe zugeordneten Bakterien besteht nach dem Stand der Wissenschaft kein Risiko für Mensch und Wirbeltiere (Berufsgenossenschaft der chemischen Industrie, Merkblatt B006 2/97 ZH 1/346, Sichere Biotechnologie, Eingruppierung biologischer Agenzien: Bakterien). Zum Nachweis der Sicherheit des verwendeten Bakterien-Stammes wurde eine Publikation vorgelegt, in der die Pathogenität und Toxigenität von *P. rubrum* in Studien an Mäusen und Kaninchen untersucht wurde. Den Tieren wurden intravenös eine Zellsuspension mit lebenden Bakterien sowie zellfreie Überstände in verschiedenen Verdünnungen oder zellfreies Kultur-Medium verabreicht. Aus den Ergebnissen schließen die Autoren, dass *P. rubrum* nicht pathogen ist und geringe Toxigenität aufweist (Porter, 1991). Darüber hinaus wurde *P. rubrum* CBS 574.77 auf Aktivität gegenüber verschiedenen Gram negativen und Gram positiven Bakterien gestestet. Die Untersuchungsergebnisse zeigen, dass dieser Keim keine anti-mikrobiellen Eigenschaften aufweist.

Die Mikroorganismen werden nach der Anzüchtung mit Formaldehyd abgetötet. Nach Angabe des Antragstellers wurde *P. rubrum* in keiner der untersuchten Proben nachgewiesen (Annex B.XII.1-1). Darüber hinaus wurde auf Protein und Saccharose-6-Glucosylmutase-Aktivität untersucht (Annex B.XII.1-2). Zudem wurden routinemäßig erhobene Ninhydrin-in-Prozess-Kontrolldaten vorgelegt. Die vorgenannten Tests waren über einen Zeitraum von fünf Jahren stets negativ.

Des Weiteren wurden verschiedene Proben auf mesophile aerobe Bakterien und Escherichia coli/coliforme Keime (Indikatoren für den Hygienestatus von Lebensmitteln) sowie Hefen und Schimmelpilze untersucht. Es wurden nur niedrige Keimzahlen festgestellt, bei Hefen und Schimmelpilzen lag das Ergebnis häufig unterhalb der Nachweisgrenze.

Die Ergebnisse der mikrobiologischen Untersuchungen sind als zufriedenstellend anzusehen.

XIII. Toxikologische Informationen

Es wurden Fütterungsstudien an Ratten mit Isomaltulose über Zeiträume von bis zu 26 Wochen durchgeführt.

In der besonders relevanten subchronischen Fütterungsstudie an Wistar Ratten erhielten die Tiere über 13 Wochen Futter mit 2,5%, 5% oder 10% Isomaltulose. Eine Kontroll-Gruppe erhielt Futter mit 10% Saccharose. In den Test-Diäten war Isomaltulose auf Kosten von Saccharose enthalten, wobei die höchste Dosis einer Aufnahme von 7,0 bzw. 8,1 g Isomaltulose/kg Körpergewicht für männliche bzw. weibliche Tiere entsprach. Nach Angabe des Antragstellers wurde nicht vollständig aufgereinigte Isomaltulose mit einem niedrigeren Reinheitsgrad als Testmaterial verwendet, um höhere Konzentrationen möglicher unbekannter Kontaminanten zu erreichen.

In einer Studie zur Embryotoxizität/Teratogenität erhielten weibliche Wistar Albino-Ratten vom Tag 0 bis 21 der Schwangerschaft Futter mit 2,5%, 5% oder 10% Isomaltulose. Eine Kontroll-Gruppe erhielt Futter mit 10% Maisstärke. In den Test-Diäten war Isomaltulose auf Kosten von Maisstärke enthalten, wobei die höchste Dosis einer Aufnahme von ca. 6,9 g Isomaltulose/kg Körpergewicht entsprach.

Beide Studien wurden entsprechend den international anerkannten Empfehlungen durchgeführt und ergaben keine Hinweise auf toxikologisch relevante Effekte.

In Tests auf Genmutationen an Bakterien (Ames-Test) unter Verwendung der *Salmonella enterica* Typhimurium Stämme TA1535, TA98 und TA100 sowie TA1537 und TA1538 mit und ohne metabolische Aktivierung (S9-Mix) erwies sich Isomaltulose bis zur höchsten getesteten Konzentration von 4000 µg/Platte als nicht genotoxisch.

<u>Bewertung des allergenen Potentials</u>

Da Allergene in Lebensmitteln in der Regel Proteine sind und Isomaltulose zur Gruppe der Kohlenhydrate gehört, ist das Auftreten allergischer Reaktionen auch im Falle einer höheren Aufnahme von Isomaltulose nicht zu erwarten.

Das als Quelle für die enzymatische Prozesshilfe zur Produktion von Isomaltulose verwendete immobilisierte Bodenbakterium *P. rubrum* wird mit Hilfe mehrerer Filtrations- und Reinigungsschritte aus der Isomaltulose entfernt (vgl. Abschnitt XII), so dass die Möglichkeit einer Kontamination und somit auch einer allergenen Reaktion auf Rückstände des verwendeten Bakteriums im Endprodukt sehr gering ist.

Nach Angaben des Antragstellers sind keine allergischen Reaktionen nach dem Konsum von Isomalt, für dessen Herstellung das gleiche Bakterium verwendet wird, und Isomaltulose, das in Japan bereits vermarktet wird, bekannt geworden.

BfR

Schlussfolgerungen

Wir sehen die vorgelegten Informationen insgesamt als ausreichend an, um die Sicherheit der antragsgegenständlichen Isomaltulose zu belegen. Eine ergänzende Prüfung gemäß Artikel 7 der Verordnung (EG) Nr. 258/97 halten wir nicht für erforderlich.

Wir halten einen Kennzeichnungshinweis für sinnvoll, aus dem hervorgeht, dass der Energiegehalt der Isomaltulose mit dem von Saccharose identisch ist.

Des Weiteren weisen wir darauf hin, dass es sich aufgrund der Eigenschaften und der intendierten Verwendung der antragsgegenständlichen Isomaltulose u.E. um einen Zuckeraustauschstoff handelt, der somit den rechtlichen Bestimmungen für Lebensmittelzusatzstoffe unterliegt.

Federal Institute for Risk Assessment (BfR)

24 September 2004

Initial assessment report on the application made by *Südzucker AG* to place on the market the novel food ingredient isomaltulose (Palatinose®) in accordance with Article 6 of Regulation (EC) No 258/97

The application made by *Südzucker AG* for the authorisation of isomaltulose (trade name Palatinose®) as a novel food ingredient was assessed by the Federal Institute for Risk Assessment on the basis of the criteria defined in Article 3(1) of Regulation (EC) No 258/97. The initial assessment report was drawn up on the basis of the structured assessment scheme contained in the Commission Recommendation of 29 July 1997 (97/618/EC) for foods in Class 1.2, i.e. pure chemicals or simple mixtures from non-GM sources, the source of which has no history of food use in the Community.

I. Specification of the NF

The applicant has drawn up specifications for the identity and purity of the product in question, isomaltulose (trade name Palatinose®) (B.I.1), including the following parameters :

Isomaltulose	min. 98%
Other saccharides	max. 2%
Ash residue	max. 0.01%
Lead	max. 0.1 mg/kg
(The above figures refer in each case to dry weight).	
Water	max. 6%

The results of analytical tests carried out on a total of nine batches of isomaltulose show that they correspond to the proposed specifications, complying with the above-mentioned parameters. The content of other possible metallic contaminants (cadmium, nickel, mercury and arsenic) was in each case below the detection limits of the methods used.

The chemical stability of isomaltulose and isomaltulose in boiled sweets was proven over a storage period of two years.

II. Effect of the production process applied to the NF

According to the applicant, the manufacture of isomaltulose corresponds to the first of two stages which occur during the manufacture of the sweetener isomalt, which is authorised as a food additive in the EU in accordance with Directive 94/35/EC. Isomalt was assessed by the European Commission's Scientific Committee on Food (SCF) and by the Joint FAO/WHO Expert Committee on Food Additives (JECFA) in terms of its safety, and accepted for use in food (SCF, 1984 and 1987 ; JECFA, 1987).

Food-grade saccharose, obtained from traditional sugarbeet, is the raw material used to manufacture isomaltulose. A sterilised saccharose solution is passed through a carrier substance containing immobilised, dead *Protaminobacter rubrum* cells, and the α-1.2-glycoside bond in saccharose converts into the α-1.6-glycoside bond through enzyme activity. The product of this reaction, isomaltulose, is obtained after filtering the solution, ion-exchange, and evaporation by crystallisation and drying.

According to the applicant, the production process, which is shown in the form of a flowchart, is accompanied by a quality assurance system in accordance with GMP and

HACCP principles. This covers the safety of all chemicals and excipients used as well as contact materials, in accordance with the Directives in force in the European Union.

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

The source material for the manufacture of isomaltulose is food-grade saccharose derived from conventional sugarbeet which has a reliable history of food use.

IX. Anticipated intake/extent of use of the NF

Isomaltulose is intended for use as an ingredient in drinks (5–15%), cereal-products, soups, dressings and desserts (15–30%), milk-based products (10–20%), bread and confectionery (up to 99%), and other products such as jams and energy–reduced foods (10–40%) and will partly replace glucose, fructose, saccharose and starch hydrolysates. The applicant is assuming that the total intake of glucose and fructose will be unchanged.

On the basis of the isomaltulose placed on the market in Japan in 2002 and allowing for a tenfold safety margin to account for the expected future increase in the consumption of isomaltulose, the applicant calculates that there is an intake of 1 g per person per day in Japan, which is equivalent to a sugar replacement rate of 2.5 %. Since sugar consumption in Europe is assumed to be twice as high, the applicant estimates that the maximum average intake in Europe will be 2 g per day or 20 g per day at a high level of consumption.

The applicant has presented various estimates of isomaltulose intake in Germany, depending on age-group and foodstuff, using a variety of calculation methods. Consumption figures from the National Consumption Study (NVS, 1985–1988) and data from a multi-centre study of children aged from 6 months to 5 years (consumption study to determine the food intake of infants (VELS), 2001–2002) were used as the basis for the calculations. Intake estimates were also based on farming and sales statistics relating to sugar consumption and sales of sports drinks and chocolate bars. On the basis of these consumption figures, the average daily intake of isomaltulose is estimated at 15.9 g for children aged from 1–4 years, 34.8 g for adolescents aged from 11–18 years and 23.8 g for the total population. At particularly high consumption levels, it is possible for adolescents to consume up to 100 g isomaltulose per day.

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

Isomaltulose is found in low concentrations in honey (N.H. Low and P. Sporns (1988) Analysis and quantitation of minor di- and trisaccharides in honey, using capillary gas chromatography. Journal of Food Science 53 (2): 558-561) and in cane sugar syrup. The applicant estimates that the average intake of isomaltulose from the consumption of honey in Germany is < 10 g per year.

Isomaltulose has been used as a food ingredient in Japan since 1985 and has been accepted as a functional food ingredient in a large number of products since 1992 under the regulations applicable to Food for Specified Health Use (FOSHU), since it reduces the development of caries. According to the applicant, there have been no side effects so far.

XI. Nutritional information on the NF

The ingredient in question, isomaltulose, on account of its low caries-inducing properties and low glycaemic index, will partly replace caries–inducing carbohydrates or those with a higher glycaemic index, such as glucose, fructose, saccharose and starch hydrolysates.

Metabolisation

Isomaltulose is split by the hydrolytic action of the isomaltase-saccharase complex in the small intestinal mucosa into equal parts of glucose and fructose, with isomaltase catalysing most of the hydrolytic activity. This hydrolytic splitting process, however, is substantially slower compared with that of saccharose; the rate of hydrolysis of isomaltulose being only 1/5 to 1/4 of that of saccharose. Therefore glucose and insulin levels also rise more slowly after oral administration of isomaltulose and attain lower maximum levels ((B.A.R. Lina, D. Jonker, G. Kozianowski (2002) Isomaltulose (Palatinose®) : A review of biological and toxicological studies. Food and Chemical Toxicology 40:1375-1381). However, as demonstrated in the feed studies referred to by the applicant, under the given test conditions and at the isomaltulose concentrations administered, no or only a small quantity of unhydrolysed isomaltulose reached the large intestine, where it ferments into short-chain fatty acids, for example, and could affect faecal microflora (Kashimura et al, 1990b).

The products resulting from this splitting process are absorbed by active and passive transport systems and further metabolised via the normal process of carbohydrate metabolisation. At 4 kcal/g, isomaltulose has the same physiological calorific value as saccharose. The slower hydrolysis and consequently slower rate of absorption mean that serum glucose and insulin levels increase more slowly than is the case for saccharose. On account of these properties which were demonstrated in both healthy and diabetic subjects, isomaltulose is said to be suitable both for diabetics and for those of a prediabetic disposition (B.A.R. Lina et al, 2002). According to the study in humans carried out by Achten et al. (2003), referred to by the applicant, during physical activity, isomaltulose has an oxidation rate of 28%, compared with a rate of 63% for saccharose, which the authors of the study attribute to isomaltulose's lower rate of hydrolysis. This is associated with increased use (consumption) of glycogen and reserves of fat in the body.

Glycaemic index

The glycaemic index is a means of classifying foods containing carbohydrates according to their effect in triggering a rise in blood sugar levels and is defined as the area under the blood sugar level curve. The glycaemic index is obtained by measuring the rise in the blood sugar level after consuming 50 g of carbohydrate derived from the food in question. The glycaemic index of a food is given in comparison to glucose, which has a reference value of 100. Saccharose has a glycaemic index of 70 and isomaltulose obtained a glycaemic index of 32 and an insulin index of 30 at Sydney University.

Caries-inducing properties

The formation of dental caries is caused by many factors. One of the main causes is the biosynthesis of extracellular insoluble glucan polymers on the surface of the teeth and acid formation due to the enzymatic breakdown of carbohydrates by plaque-forming bacteria in the mouth such as *Streptococcus mutans*, for example. A pH-value below 5.7 favours the demineralisation of tooth enamel. Numerous *in vitro* studies prove that isomaltulose is not fermented by *Streptococcus mutans* and other oral plaque-forming bacteria, so that acid formation is minimal, compared with saccharose and glucose, and no insoluble glucans are formed. Measurements of the pH of the mouth in humans

showed that after consuming confectionery containing isomaltulose, the pH value remained above the critical level of 5.7. Compared with traditional forms of sugar, isomaltose is therefore less caries-inducing (T. Oku (1996) Oligosaccharides with beneficial health effects: A Japanese perspective. Nutrition Reviews 54 (11): 59-66).

Side effects

Owing to the total hydrolysis of isomaltulose in the small intestine, and the subsequent absorption of the split products, glucose and fructose, the applicant claims that even at higher intakes of isomaltulose there are unlikely to be laxative effects or effects on flora in the large intestine, except in the case of saccharase-isomaltase deficiency, which is either congenital or caused by brush-border dystrophy. The application documents contain a report of a study on the safety assessment of isomaltulose (Annex B XIII), carried out at the TNO-Institute in the Netherlands. No gastro-intestinal disturbances were observed among 10 healthy men (18-35 years of age) who received between 0.25 and 0.75 g of isomaltulose per kg of body weight in eight meals, nor during a gastro-intestinal tolerance study (random, double-blind) on 60 female and male volunteers (aged 24 years +/- 9), who consumed either saccharose or isomaltulose in increasing concentrations over 12 weeks. The gastro-intestinal tolerance of isomaltulose was comparable to that of saccharose up to an intake of 48 g.

The lipid metabolism parameters (LDL, VLDL, HDL-C, total cholesterol and triglycerides) examined in some studies also showed no significant variations compared with saccharose, except for a substantial increase in free fatty acids and a slight increase in total plasma cholesterol concentration observed in one study.

XII. Microbiological information on the NF

According to the applicant, isomaltulose contains no substances of bacterial origin likely to present a risk to health.

Saccharose is dissolved, filtered and sterilised before undergoing enzyme treatment. The microbiological quality of the product is checked regularly as part of process control measures. Crystalline isomaltulose does not provide the conditions necessary for microbial growth.

The microorganism *Protaminobacter rubrum* CBS 574.77, used as an enzymatic processing aid, is classed in Risk Group 1, i.e. according to present scientific knowledge, the handling of bacteria in this risk group presents no risk to humans and vertebrates (*Berufsgenossenschaft der chemischen Industrie,* (Trade Association for the Chemical Industry) *Merkblatt* B006 2/97 ZH 1/346, Safe Biotechnology, Classification of Biological Agents: Bacteria). As proof of the safety of the bacterial strain used, a publication was presented in which the pathogenicity and toxicogenicity of *P. rubrum* were tested in studies of mice and rabbits. A cell suspension with live bacteria as well as cell free surplus in various dilutions or cell-free culture medium was administered intravenously to the animals. The authors concluded from the results that *P. rubrum* is not pathogenic and has low toxicity (Porter, 1991). In addition, *P. rubrum* CBS 574.77 was tested for activity against various Gram negative and Gram positive bacteria. The test results show that this bacterium has no anti-microbial properties.

After cultivation, the microorganisms are destroyed using formaldehyde. According to the applicant, *P. rubrum* was not detected in any of the samples tested (Annex B.XII.1-1). In addition, a search for protein and saccharose-6-glucosylmutase activity was carried

out (Annex B.XII.1-2). Ninhydrin process control data were also presented on a routine basis. The above-mentioned tests were always negative over a five-year period.

In addition, various tests to detect mesophilic aerobic bacteria and *Escherichia coli*/coliform bacteria (indicators of the state of hygiene of foodstuffs) were carried out, as well as tests to detect yeasts and moulds. Only low bacterial counts were detected and in the case of yeasts and moulds the result was often below the detection limit.

The results of the microbiological tests are considered to be satisfactory.

XIII. Toxicological information on the NF

Feed studies were carried out on rats using isomaltulose over periods of up to 26 weeks.

In the case of the subchronic feed study in Wistar rats, which was of particular relevance, the animals received feed containing 2.5%, 5% or 10% isomaltulose over 13 weeks. A control group received feed containing 10% saccharose. The test diets contained isomaltulose instead of saccharose, the highest dose being an intake of 7.0 or 8.1 g isomaltulose per kg of body weight for male and female rats, respectively. According to the applicant, the substance used for the test was isomaltulose which had not been completely refined and had a lower degree of purity, in order to produce higher concentrations of potentially unknown contaminants.

During an embryotoxicity/teratogenicity study, female Wistar albino rats received feed containing 2.5%, 5% or 10% isomaltulose from days 0 to 21 of their pregnancy. A control group received feed containing 10% cornstarch. The test diets contained isomaltulose instead of cornstarch, the highest dose being an intake of around 6.9 g isomaltulose per kg of body weight.

Both studies were carried out in accordance with internationally recognised recommendations and showed no evidence of toxicologically significant effects.

In tests for genetic mutations of bacteria (Ames-test), using *Salmonella enterica Typhimurium*, strains TA1535, TA98 and TA100 and TA1537 and TA1538, with and without metabolic activation (S9 mix), isomaltulose proved not to be genotoxic, even at the highest concentration tested of 4000 µg/plate.

<u>Assessment of allergenic potential</u>

Since allergens in foodstuffs are usually proteins, and isomaltulose belongs to the carbohydrates group, there are unlikely to be allergic reactions to isomaltulose, even at high concentrations.

The immobilised soil bacterium, *P. rubrum*, used as the source for the enzymatic processing aid to produce isomaltulose, is removed from isomaltulose by several filtration and purification processes (cf. Section XII), so that the possibility of contamination and, consequently, an allergenic reaction to residues of the bacterium used in the final product is very small.

According to the applicant, there is no knowledge of any allergic reactions after eating isomalt, which is produced using the same bacterium, and isomaltulose, which is already on the market in Japan.

Conclusions

We consider the information presented to be sufficient to prove the safety of isomaltulose, for which authorisation is being sought. We do not consider it necessary to carry out an additional assessment, as provided for in Article 7 of Regulation (EC) No 258/97.

We think that it would be useful to indicate on the labelling that the energy content of isomaltulose is identical to that of saccharose.

In addition, we would point out that, given the properties and intended use of isomaltulose, we consider it to be a sugar substitute, making it subject to the legislation on food additives.

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SUBMISSION END

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