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  

October 31, 2005

Dear Dr. Martin:

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

The enclosed GRAS Notification is hereby submitted on behalf of 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 (PDF) of the Notification Claim and Additional Information documents.

Sincerely,

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

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

cc: A. Sentko
GRAS Notification – Exemption Claim for Isomaltulose (PALATINOSE™)

October 26, 2005

Content:

Part 1: GRAS Exemption Claim
Part 2: Additional Information
Part 3: References
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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
SÜDZUCKER AG Mannheim/Ochsenfurt, Business Unit Orafti/Palatinit;
General Manager, PALATINIT GmbH
Gottlieb-Daimler-Str. 12
D-68165 Mannheim
GERMANY
Telephone: 011 49 621 421 102
Faxline: 011 49 621 421 160
E-Mail: Hans-Ulrich Frech@Palatinit.de

US Regulatory Representative:

William A. Olson, Ph.D.
Center for Regulatory Services, Inc.
5200 Wolf Run Shoals Road
Woodbridge, VA 22192-5755
Telephone: 703 590 7337
Faxline: 703 580 8637
E-Mail: cfrsrv@aol.com

(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:

<table>
<thead>
<tr>
<th>Illustrative examples for the food categories isomaltulose can be used in</th>
<th>Examples for the description of the specific type of food within the given food category</th>
<th>Illustrative approx. use levels as consumed [%]</th>
</tr>
</thead>
<tbody>
<tr>
<td>Baked goods and baking mixes (21CFR170.3(n)(1))</td>
<td>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)</td>
<td>10-25</td>
</tr>
<tr>
<td>Beverages (21CFR170.3(n)(2); 21 CFR170.3(n)(3))</td>
<td>Breakfast cereals Cereal bars</td>
<td>5-20</td>
</tr>
<tr>
<td>Cereal-based products (21CFR170.3(n)(4))</td>
<td>Hard candies, cough drops etc Soft candies, toffees etc Chocolate and related products Compressed goods Fondants/frostings fillings, crèmes, toppings nougat</td>
<td>99</td>
</tr>
<tr>
<td>Confectionery and frostings (21CFR170.3(n)(9))</td>
<td>30-50</td>
<td>25-60</td>
</tr>
<tr>
<td>Chewing gum (21CFR170.3(n)(6))</td>
<td>Ice cream and other frozen dairy desserts</td>
<td>30</td>
</tr>
<tr>
<td>Frozen dairy desserts and mixes (21CFR170.3(n)(20))</td>
<td></td>
<td>15</td>
</tr>
<tr>
<td>Fruit and water ices (21CFR170.3(n)(21))</td>
<td></td>
<td>15-30</td>
</tr>
<tr>
<td>Gelatins, puddings, desserts etc (21CFR170.3(n)(22))</td>
<td></td>
<td>25-40</td>
</tr>
<tr>
<td>Jams and jellies, spreads (21CFR170.3(n)(28))</td>
<td></td>
<td>45</td>
</tr>
<tr>
<td>Nut and peanut spreads (21CFR170.3(n)(32))</td>
<td></td>
<td>3-20</td>
</tr>
<tr>
<td>Milk products (21CFR170.3(n)(31))</td>
<td>Juices including concentrates, dilutions, drink substitutes</td>
<td>1-10</td>
</tr>
<tr>
<td>Processed fruit and fruit juices or vegetable juices (21CFR170.3(n)(35); 21CFR170.3(n)(36))</td>
<td></td>
<td>10-25</td>
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<tr>
<td>Snack foods (21CFR170.3(n)(37))</td>
<td>e.g., table tops, granulated, liquid or tablet forms</td>
<td>2-99</td>
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<tr>
<td>Sugar substitutes (21CFR170.3(n)(42))</td>
<td></td>
<td>15-30</td>
</tr>
<tr>
<td>Sweet Sauces, toppings, syrups (21CFR170.3(n)(43))</td>
<td>Nutritive formulae/enteral nutrition Energy-reduced foods Meal replacement/slimming food</td>
<td>5-20</td>
</tr>
</tbody>
</table>
(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 insulinenic 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/Palatinitt, or will be sent to FDA upon request.

Sincerely,

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

Lutz Guderjahn, Ph.D.
Head of Business Development
Business Unit ORAFTI/PALATINIT
SÜDZUCKER AG Mannheim/Ochsenfurt
PART 2: Additional Information

I. Identity of the notified substance
A specification (parameters for identity and purity) for isomaltulose produced and intended to be marketed by SUDZUCKER/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_{2}O

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
PART 2: Additional Information

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

<table>
<thead>
<tr>
<th>Batch (LIMS No.)</th>
<th>200311449</th>
<th>200311450</th>
<th>200311451</th>
<th>200311452</th>
<th>200311453</th>
</tr>
</thead>
<tbody>
<tr>
<td>Water [%]</td>
<td>5.2</td>
<td>5.2</td>
<td>5.2</td>
<td>5.2</td>
<td>5.2</td>
</tr>
<tr>
<td>Isomaltulose [% TS*]</td>
<td>99.7</td>
<td>99.4</td>
<td>99.5</td>
<td>99.6</td>
<td>99.4</td>
</tr>
<tr>
<td>Total other saccharides [% TS]</td>
<td>0.3</td>
<td>0.4</td>
<td>0.4</td>
<td>0.3</td>
<td>0.5</td>
</tr>
<tr>
<td>Ash [% TS]</td>
<td>&lt;0.01</td>
<td>&lt;0.01</td>
<td>&lt;0.01</td>
<td>&lt;0.01</td>
<td>&lt;0.01</td>
</tr>
<tr>
<td>Lead [mg/kg TS]</td>
<td>&lt;0.03</td>
<td>&lt;0.03</td>
<td>&lt;0.03</td>
<td>&lt;0.03</td>
<td>&lt;0.03</td>
</tr>
</tbody>
</table>

* 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-\(\alpha\)-D-glucosyl-D-mannitol (1,1-GPM) and 6-O-\(\alpha\)-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)
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-hygrosopic 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 isomaltulose 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

![Figure 4: Solubility of Isomaltulose versus Sucrose in Water](image-url)
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 CO₂ directly at the point of sale). This marketing channel will not be open to isomaltulose containing beverages.
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 Süd Zucker. (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 Süd Zucker/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 Süd Zucker 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 (Zoetermeer, 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-carogenic 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


PART 3: References


PART 3: References


List of Annexes:

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


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

PALATINOSE™ Specification

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.

<table>
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<th>Parameter</th>
<th>SÜDZUCKER Specification on PALATINOSE™</th>
<th>Reference</th>
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<tr>
<td>Assay*</td>
<td>≥ 98 % isomaltulose</td>
<td>HPLC¹)</td>
</tr>
<tr>
<td>Description</td>
<td>White or colorless, crystalline, sweet substance faint isomaltulose specific odor</td>
<td></td>
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<tr>
<td>Water</td>
<td>≤ 6 %</td>
<td>Karl Fischer³)</td>
</tr>
<tr>
<td>Other saccharides*</td>
<td>≤ 2 %</td>
<td>HPLC¹)</td>
</tr>
<tr>
<td>Ash*</td>
<td>≤ 0.01 %</td>
<td>Conductivity⁴)</td>
</tr>
<tr>
<td>Lead*</td>
<td>≤ 0.1 mg/kg</td>
<td>AAS⁵)</td>
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* 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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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


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
Andere Saccharide
Veraschungsrückstand
Blei
Wasser

(min. 96%)
(max. 2%)
(max. 0,01%)
(max. 0,1 mg/kg)

(Die vorgenannten Werte sind jeweils auf das Trockengewicht bezogen.)

(max. 6%)


II. Auswirkungen des Herstellungsverfahrens

Nach Angabe des Antragstellers entspricht die Herstellung von Isomaltulose dem ersten von zwei Schritten bei der Herstellung des Stützungs mittels 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-

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.


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-Hydrolysat 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 Einaräumung eines zehnfachen Sicherheitszuschlages durch eine zukünftig zu erwartende Stel lung 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.

Informationen über eine frühere Exposition des Menschen


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 Stärkehdrolysate teilweise ersetzen.

Metabolisierung


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

**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 Blutzuckeraanstieg 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. Saccharose 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**


**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 gastrointestinalem 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 verzehnten, wurden gastrointestinale Störungen festgestellt. Bis zu einer
Zufuhr von 48 g war die gastrointestinal 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-Plasmacholesterol-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.


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.

Bewertung des allergenen Potentials

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.
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.

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

The application made by Südzucker AG for the authorisation of isomaltoolose (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, isomaltoolose (trade name Palatinose®) (B.I.1), including the following parameters:

- Isomaltoolose: min. 98%
- Other saccharides: max. 2%
- Ash residue: max. 0.01%
- Lead: max. 0.1 mg/kg
- Water: max. 6%

(The above figures refer in each case to dry weight).

The results of analytical tests carried out on a total of nine batches of isomaltoolose 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 isomaltoolose and isomaltoolose 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 isomaltoolose 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 isomaltoolose. 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, isomaltoolose, 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 metabolism. 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
In addition, various tests to detect mesophilic aerobic bacteria and *Escherichia coli*/*coli*form 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.

**Assessment of allergenic potential**

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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*NA- Not applicable*