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April 30, 2001

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Office of Premarket Approval (HFS-200)
Center for Food Safety and Applied Nutrition
U.S. Food and Drug Administration
200 C St. SW
Washington, DC 20204

Subject: Notice of a GRAS Exemption for Erythritol

Dear Sir/Madam:

Pursuant to the proposed rule outlined at 62 Fed. Reg. 18939 (April 17, 1997), Cerestar Holding, B.V. hereby submits notification that use of erythritol as a flavor enhancer, formulation aid, humectant, nutritive sweetener, stabilizer and thickener, sequestrant, and texturizer in foods is exempt from the premarket approval requirements of the Federal Food, Drug, and Cosmetic Act because the notifier has determined that such use is generally recognized as safe (GRAS). To facilitate your review, this notification is submitted in the format suggested under proposed 21 C.F.R. § 170.36(c) (see 62 Fed. Reg. at 18961). Also enclosed is an electronic copy (Microsoft Word 97) of the GRAS Exemption Claim (GRAS Exemption Claim.doc) and Additional Information (GRAS Additional Information.doc) documents.

Sincerely,

Diane B. McColl
Counsel to Cerestar Holding, B.V.

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GRAS Exemption Claim

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GRAS EXEMPTION CLAIM

We hereby claim that the use of erythritol as a flavor enhancer, formulation aid, humectant, nutritive sweetener, stabilizer and thickener, sequestrant, and texturizer in foods is exempt from the premarket approval requirements of the Federal Food, Drug, and Cosmetic Act because we have determined that such use of erythritol is generally recognized as safe (GRAS).

(1) Name and address of the notifier:

Peter de Cock
Global Business Development Manager
Cerestar Holding B.V.
Havenstraat 84, B-1800 Vilvoorde
Phone: 011 232 2 257 0654
Fax: 011 32 2 257 0780

(2) Common or usual name of the substance that is the subject of the GRAS exemption claim:

Erythritol

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

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

Bakery fillings, cakes and cookies, chewing gum, dairy drinks, fat-based cream used in modified fat/calorie cookies, cakes and pastries, hard candies, frozen dairy desserts, puddings, reduced and low calorie carbonated and non-carbonated beverages, soft candies, sugar substitutes, and yogurt.

(b) Levels of use in such foods:

	Maximum Use
Bakery fillings (fruit, custard, cream, pudding)	15%
Cakes and cookies (regular and dietetic)	15%
Chewing gum	60%
Dairy drinks (chocolate and flavored milks)	3.5%
Fat-based cream used in modified fat/calorie cookies, cakes and pastries	60%
Hard candies (including pressed candy, mints and cough drops)	99%
Frozen dairy desserts (regular ice cream, soft serve, sorbet)	10%
Puddings (instant, phosphate set)	10%
Reduced- and low-calorie carbonated and non-carbonated beverages	3.5%
Soft Candies (non-chocolate, plain chocolate, chocolate coated)	60%
Sugar substitutes (carrier)	100%
Yogurt (regular and frozen)	10%

(c) Purposes for which the substance is used:

Flavor enhancer, formulation aid, humectant, nutritive sweetener, stabilizer and thickener, sequestrant, texturizer.

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

Members of the general population who consume at least one of the food categories described above.

(4) Basis for the 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 Cerestar Holding B.V.'s GRAS determination are available for the Food and Drug Administration's (FDA's) review and copying at reasonable times at the offices of the notifier, or will be sent to FDA upon request.

25 April 01

Peter de Cock
Global Business Development Manager
Cerestar Holding B.V.

Please address correspondence to:

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ADDITIONAL INFORMATION

(1) Identity of the notified substance

(a) Chemical name

1,2,3,4-butanetetrol

Synonyms: *meso*-erythritol, tetrahydroxybutane, erythrol, erythrite, erythroglucin, antierythrite, and phycite

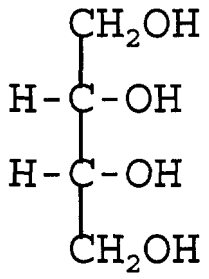
(b) Chemical Abstracts Service (CAS) Registry Number

149-32-6 (*meso*-erythritol)

(c) Empirical formula

$C_4H_{10}O_4$

(d) Structural formula



(e) Method of manufacture

Erythritol is manufactured through pure culture fermentation using a non-toxigenic, non-pathogenic microorganism that acts upon a carbohydrate-based medium. The fermentation broth containing erythritol is separated from the organisms and subjected to purification treatment similar to those for the carbohydrate sweeteners and sugar alcohols, *e.g.*, ion-exchange resin, activated charcoal, ultrafiltration and crystallization. The final product is a material containing not less than 99.5% erythritol.

(i) Fermentation Process

The manufacturing process for erythritol is based on the fermentative conversion of glucose into erythritol catalyzed by a microorganism named *Moniliella pollinis* (previously named *Tomentosa var. pollinis*) followed by separation and purification from the fermented liquor.

For the fermentation process, the strain inoculum preparation is transferred under aseptic conditions into a flask containing sterile medium. The sterile media used for the seed cultures and for the production cultures contain glucose syrup, corn steep liquor, and antifoaming agents. All ingredients used are of food grade quality or food compatible. The fermentation apparatus is operated under aeration and maintained at a specified temperature range.

(ii) Purification Process

For product purification, the fermented broth is heated to kill the microorganisms. All the production microorganisms, *Moniella pollinis,* are killed by this treatment.

The concentrated hot erythritol solution is pumped into a crystallizer and cooled to induce crystallization of the product. Alternatively, the crystallization can take place partly or totally during the evaporation process. The crystals are then separated from the mother liquor by centrifugation and washed with demineralized water. The erythritol crystals are then redissolved in demineralized water, and the solution is passed through an ion exchange resin station consisting of an anionic and cationic resin, which is used only for food applications. Additionally, the solution may be decolorized by treatment with activated charcoal. The erythritol solution is then further purified using ultrafiltration (cut-off 5 kD) and crystallized again by cooling or by evaporation. The crystals are centrifuged, washed with demineralized water and dried in a hot air stream, sifted, and packed in bags. The resulting erythritol is at least 99.5% pure.

(iii) Production Microorganism

The production organism, *Moniliella pollinis,* is both non-toxicogenic and non-pathogenic.

(f) Characteristic properties

Erythritol is a naturally occurring four-carbon sugar alcohol, which is the reduced sugar alcohol analogue of the four-carbon monosaccharide, erythrose. Erythritol occurs widely in nature and has been found in to occur naturally in several foods, including wine, sake, beer, mushrooms, watermelon, pears, grapes and soy sauce at levels up to 0.13% (w/v)(Goossens and Röper, 1994; Shindou *et al.*, 1988, 1989). It also exists endogenously in the tissues and body fluids of humans and animals (Goossens and Röper, 1994; Horning *et al.*, 1974; Oku and Noda, 1990; Spencer, 1967).

Erythritol exists as a white, odorless crystal in the form of a tetragonal prism. It is heat stable and non-hygroscopic. Erythritol is also stable under acid and alkaline conditions. It has a melting point of 119 to 123°C, a boiling point of 329-331°C, a heat of fusion of 311-323 J/g and a heat of solution of -180 J/g. It is very soluble in water, slightly soluble in alcohol, and practically insoluble in fats and ether.

Erythritol has a sweetness of about 60-80% that of sucrose, depending on the food in which erythritol is present (Goossens and Röper, 1994). It is noncariogenic (21 C.F.R. § 101.80) and has a caloric value of 0.2 kcal/gram.

(g) Any content of potential human toxicants

None.

(h) Specifications for food-grade material

The specifications for erythritol are as described at pages 10-11 of Food Chemicals Codex IV (Second Supp. 2000) (FCC, 2000).

(2) Information on any self-limiting levels of use

None.

(3) Detailed summary of the basis for the notifier's determination that a particular use of the notified substance is exempt from the premarket approval requirements of the Federal Food, Drug and Cosmetic Act because such use is GRAS

The published scientific literature contains numerous safety studies supporting the safety of erythritol for food use. In October 1996, an Expert Panel of independent experts, qualified by training and relevant national and international experience to

evaluate the safety of foods and food ingredients, conducted a comprehensive and critical review of the available data and information, both published and unpublished, and unanimously concluded that under the conditions of intended use in foods erythritol is GRAS based on scientific procedures (Berndt *et al.*, 1996). The 1996 GRAS determination was confined to more limited uses of erythritol than those that are the subject of this notification. Specifically, the 1996 GRAS determination encompassed use of erythritol in foods (% use levels) as follows: (1) sugar substitutes (100%); (2) hard candies (50%); (3) soft candies (40%); (4) reduced- and low-calorie beverages (1.5%); (5) fat-based cream for use in cookies, cakes, and pastries (60%); (6) dietetic cookies and wafers (7%); and (7) chewing gum (60%) (Berndt *et al.*, 1996). A copy of the published Expert Panel review is enclosed.

In December 1996, Cerestar Holding B.V. (Cerestar), Mitsubishi Chemical Corp., and Nikken Chemicals Co., Ltd. jointly submitted the currently pending GRAS affirmation petition (GRASP 7G0422) for the above-described uses of erythritol. In December 1997, FDA approved a dental health claim for erythritol. *See* 21 C.F.R. § 101.80; *see also* 62 Fed. Reg. 63653 (Dec. 2, 1997).

In 1998, in anticipation of the review of erythritol by the Joint FAO/WHO Expert Committee on Food Additives (JECFA), a second review of the biochemical, metabolic, toxicological, and clinical data, concluding that erythritol was safe for its intended use in foods, was also published (Munro *et al.*, 1998). At its 53rd meeting, JECFA evaluated the safety of erythritol and established an acceptable daily intake (ADI) "not specified" for erythritol for use as a sweetening agent (WHO, 2000a,b). JECFA assigns an ADI "not specified" to substances that, on the basis of the available data, the total dietary intakes resulting from use at levels necessary to achieve the desired effect, and background levels in food, do not represent a hazard to health. Copies of the 1998 Expert Panel review, as well as the 2000 JECFA toxicological monograph and report on erythritol are enclosed.

At the request of Cerestar alone, the Expert Panel reconvened in May 2000 to review the expanded uses of erythritol that are the subject of this GRAS Notification. The Panel concluded that under the conditions of the expanded uses in foods, erythritol meeting appropriate food grade specifications and manufactured in accordance with current good manufacturing practices, is GRAS based on scientific procedures. A copy of the "Expert panel opinion concerning expanded uses of erythritol" is enclosed.

(4) Probable Consumption of the Substance

Erythritol is intended for use as a flavor enhancer, formulation aid, humectant, nutritive sweetener, stabilizer and thickener, sequestrant, and texturizer. As discussed in Section 3 above, the 1996 safety review evaluated erythritol it for use in the following foods: (1) sugar substitutes; (2) hard candies; (3) soft candies; (4) reduced- and low-calorie beverages; (5) fat-based cream for use in cookies, cakes, and pastries; (6) dietetic cookies and wafers; and (7) chewing gum (Berndt *et al.*, 1996). For such uses, the user population mean and 90th percentile intakes were estimated to be 6.9 g/day and 16.9 g/day, respectively. Applying a market share adjustment and assuming that erythritol would replace all xylitol use (20% of total polyol use), a user population mean and 90th percentile consumption of 1g/day and 4 g/day, respectively, was projected.

The expanded uses for erythritol that are the subject of this GRAS Notification require a separate calculation of probable consumption. Exposure calculations estimate the user population mean and 90th percentile intakes to be 14.1 g/day and 30.8 g/day respectively. Applying a market share adjustment and assuming that erythritol would replace all xylitol use (20% of total polyol use), a user population mean and 90th percentile consumption of 4.9 g/day and 11.9 g/day, respectively, corresponding to 0.09 and 0.23 g/k bw/day is projected. Because of their higher food intake relative to body weight, young children aged 1 to 3 years may consume up to 1g/kg bw/day (90th percentile).

(5) 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 substances added to food that there is reasonable certainty that the substance is not harmful under the intended conditions of use.

See the enclosed 1996 and 1998 published reviews of the data supporting the GRAS status of erythritol, the 2000 WHO report and toxicological monograph supporting an ADI "not specified" for erythritol, and the May, 2000 "Expert Panel Opinion Concerning Expanded Uses of Erythritol." The Expert Panel that reviewed erythritol consisted of William O. Berndt, Ph.D., University of Nebraska Medical Center, Joseph F. Borzelleca, Ph.D., Medical College of Virginia, W. Gary Flamm, Ph.D., Flamm Associates, and Ian C. Munro, Ph.D., FRCPath, CanTox Health Sciences International.

References

Berndt W.O., Borzelleca J.F., Flamm G., Munro I.C. (1996). Erythritol: a review of biological and toxicological studies. *Regulatory Toxicology and Pharmacology* 24: S191.

Berndt W.O., Borzelleca J.F., Flamm G., Munro I.C. (2000). Expert panel opinion concerning expanded uses of erythritol, May 18, 2000 (unpublished report).

FCC, (2000). Food Chemicals Codex IV (Second Supp. to the Fourth Edition). National Academy Press, Washington DC, pp. 10-11.

Goossens J. and Röper H. (1994). Erythritol: A new bulk sweetener. *International Food Ingredients* 1/2: 27-33.

Horning E.C., Horning M.G., Szafranek J., Van Hout P., German A.L., Thenot J.P. and Pfaffenberger C.D. (1974). Gas phase analytical methods for the study of human metabolites. Metabolic profiles obtained by open tubular capillary chromatography. *Journal of Chromatography* 91, 367-378.

Munro I.C., Berndt W.O., Borzelleca J.F., Flamm W.G., Lynch B.S., Kennepohl E., Bär A., and Modderman J. (1998). Erythritol: an interpretive summary of biochemical, metabolic, toxicological and clinical data. *Food and Chemical Toxicology* 36: 1139-74.

Oku T. and Noda K. (1990). Influence of chronic ingestion of newly developed sweetener, erythritol on growth and gastrointestinal function of the rats. *Nutrition Research* 10, 987-996.

Shindou T., Sasaki Y., Miki H., Eguchi T., Hagiwara K. and Ichikawa T. (1989). Identification of erythritol by HPLC and GS-MS and quantitative measurement in pulps of various fruits. *Journal of Agricultural and Food Chemistry* 37, 1474-1476.

Shindou T., Sasaki Y., Miki H., Eguchi T., Hagiwara K. and Ichikawa T. (1988). Determination of erythritol in fermented foods by high performance liquid chromatography. *Shokuhin Eiseigaku Zasshi* 29, 419-422 (includes English translation).

Spencer N. (1967). Ion exchange chromatography of polyols. *Journal of Chromatography* 30, 566-571.

WHO, (2000a). Sweetening agent: erythritol. In *Evaluation of certain food additives and contaminants.* WHO Technical Report Series 896, §3.2, pp. 18-22. ICPS International Programme on Chemical Safety in Cooperation with the Joint FAO/WHO Expert Committee on Food Additives (JECFA). World Health Organization, Geneva.

WHO, (2000b). Erythritol. In *Safety evaluation of certain food additives and contaminants.* WHO Food Additives Series: 44, pp. 15-70. ICPS International Programme on Chemical Safety in Cooperation with the Joint FAO/WHO Expert Committee on Food Additives (JECFA). World Health Organization, Geneva.

Enclosures

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EXPERT PANEL OPINION CONCERNING EXPANDED USES OF ERYTHRITOL

The undersigned, an independent panel of recognized experts (the "Expert Panel"), qualified by their scientific training and relevant national and international experience in evaluating the safety of food and food ingredients, were requested by Cerestar Holdings BV ("Cerestar") to conduct a comprehensive review of pertinent data and information to determine whether certain expanded uses of erythritol in foods are "generally recognized as safe" ("GRAS") based on scientific procedures. Attached are *curriculum vitae* evidencing the qualifications of the Expert Panel members.

Previously, the safety of erythritol was critically evaluated by the Expert Panel (Bernt *et al.*, 1996). The Panel then concluded that the use of erythritol as a flavor enhancer, formulation aid, humectant, nutritive sweetener, stabilizer and thickener, sequestrant, and texturizer in a number of foods is GRAS based on scientific procedures. For such uses, the Panel estimated the user population mean and 90th percentile intakes to be 6.9 g/day and 16.9 g/day, respectively. Applying a market share adjustment and assuming that erythritol would replace all xylitol use (20% of total polyol use), the Panel projected a user population mean and 90th percentile consumption of 1 g/day and 4 g/day, respectively.

In the course of reviewing the expanded uses of erythritol, the Expert Panel reviewed intake estimates for both the current GRAS uses and the expanded uses combined, the publicly available data and information present in the pending petition for U.S. Food and Drug Administration (FDA) affirmation of the GRAS status of the current uses of erythritol (GRASP 7G0422 submitted jointly by Cerestar Holding Company B.V, Mitsubishi Chemical Corporation and Nikken Chemicals Company, Ltd.), and additional relevant information.

Following independent, critical evaluation of such data and information, the Expert Panel met on May 18, 2000 with representatives of Cerestar. After thorough discussion of the data and information, the Panel concluded that under the conditions of combined current and expanded uses in foods, erythritol meeting appropriate food grade specifications and manufactured in accordance with current good manufacturing practices, is "generally recognized as safe" based on scientific procedures. A summary of the basis for the Panel's conclusion is provided below.

Dietary Exposure

The combined current and expanded uses of erythritol are shown in the attached Table 1. The Panel estimated the user population mean and 90th percentile intakes to be 14.1 g/day and 30.8 g/day, respectively. Applying a market share adjustment and assuming that erythritol would replace all xylitol use (20% of total polyol use), the Panel projected a user population mean and 90th percentile consumption of 4.9 g/day and 11.9 g/day, respectively, corresponding to 0.09 and 0.23 g/k bw/day. Because of their higher food intake relative to body weight, young children aged 1 to 3 years may consume up to 1 g/kg bw/day (90th percentile).

Safety Assessment

Erythritol has been extensively evaluated in a number of toxicological and clinical studies. The preclinical studies include acute, subchronic, chronic, carcinogenicity, reproductive and developmental toxicity, and mutagenicity. High dose effects (e.g., 10% of diet, equivalent to approximately 5 g/kg bw) noted in animal studies such as laxation and diuresis are considered to be physiological responses to osmotic loading, and are not toxicologically significant.

The clinical studies provided information to compare the metabolism and pharmacokinetics of erythritol in humans and animals, and to assess the possibility for the development of effects associated with changes in water balance, both in normal individuals and persons with diabetes. In evaluating the exposures resulting from the current and expanded uses, the Panel considered in particular the potential for laxation, perturbation of renal function, and the possible sensitivity of children.

Transient minor gastrointestinal effects, consisting of loose stools, nausea, gurgling, and flatulence, were reported in the clinical studies after erythritol administration, but only after large acute bolus (liquid) doses and/or administration on an empty stomach. From the studies which evaluated gastrointestinal effects, the laxation threshold for erythritol cannot be clearly defined. However, the data suggest that the laxation threshold is in excess of 0.6 to 0.8 g/kg bw/day under all conditions and is likely greater than 1.0 g/kg bw/day under intended conditions of use. Also, the laxation threshold for erythritol has been reported to be about 4-fold greater than that for sorbitol.

From the clinical studies by Bornet *et al.* (1996a,b) and Tetzloff *et al.* (1996), the threshold for osmotic diuresis can be established. The results of a study in which erythritol was administered in food indicate no overt diuretic effect of a single 0.4 or 0.8 g/kg bw dose (Bornet *et al.*, 1996b). Progressive, statistically significant increases in sodium and chloride excretion and urine osmolality were seen in the study, however, these effects were not accompanied by increased water consumption or increased urinary volume. The increased urinary osmolality could be attributed to the presence of erythritol in the urine. In the Tetzloff *et al.* (1996) repeat dose study, in which human volunteers received 1.0 g/kg bw/day of erythritol in food for 7 days , slight diuresis, in the form of non-significantly increased urine volumes and non-significantly decreased urine electrolyte concentrations were reported. Thus, the threshold for the appearance

of diuretic activity of erythritol under intended conditions of use appears to be in the range of 1.0 g/kg bw/day.

Diuretic effects are due to the increased plasma osmolar load associated with absorbed erythritol. An estimate of the renal capacity required to clear erythritol from the blood to prevent its accumulation can be determined from the available clinical and pharmacokinetic data. Based on the plasma kinetics described for mannitol, and erythritol, a normal healthy 70 kg adult consuming 40 grams of erythritol, would require a maximum of 15 to 25% of normal renal capacity to effectively clear erythritol. Renal function in children aged 1 year and older is essentially equivalent to that of adults when normalized for body weight. Therefore, while young children may experience transient exposures to higher amounts of erythritol because of their higher food intake relative to body weight compared to adults, such exposures would be readily handled by the kidneys.

Detailed analysis of the data provide no evidence to indicate that erythritol, under the conditions of combined current and expanded uses, would be associated with adverse health effects.

Conclusion

Based on our independent and collective critical evaluation of the pertinent data and information, the Expert Panel unanimously concludes that under the conditions of combined current and expanded uses in foods, erythritol meeting appropriate food grade specifications and manufactured and used in accordance with current good manufacturing practices, is "generally recognized as safe" based on scientific procedures.

By:

William O. Berndt, Ph.D.	18 May 00 Date
Joseph F. Borzelleca, PhD.	18 May 2000 Date
W. Gary Flamm, Ph.D.	May 18, 2000 Date
Ian C. Munro, Ph.D.	May 18/2000 Date

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Table 1. Combined Current and Expanded Uses of Erythritol

Food Category	Maximum Level of Erythritol
Bakery fillings (fruit, custard, cream, pudding)	15%
Cakes and cookies (regular and dietetic)	15%
Chewing gum	60%
Dairy drinks (chocolate and flavored milks)	3.5%
Fat-based cream used in modified fat/calorie cookies, cakes and pastries	60%
Hard candies (including pressed candy, mints and cough drops)	99%
Frozen dairy desserts (regular ice cream, soft serve, sorbet)	10%
Puddings (instant, phosphate set)	10%
Reduced- and low calorie carbonated and non-carbonated beverages	3.5%
Soft candies (nonchocolate, plain chocolate, chocolate coated)	60%
Sugar substitutes (carrier)	100%
Yogurt (regular and frozen)	10%

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SUBMISSION END

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