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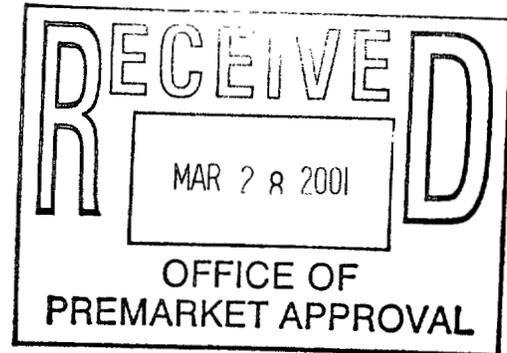


Original Submission

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WACKER

Wacker Biochem Corp.



March 23, 2001

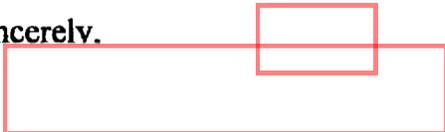
Office of Premarket Approval (HFS-200)
Center for Food Safety and Applied Nutrition
Food and Drug Administration
200 C St. SW
Washington, DC 20204

Subject: Notice of a GRAS exemption for beta-cyclodextrin

Dear Sir/Madam:

Pursuant to the proposed rule outlined at 62 Fed. Reg. 18939 (April 17, 1997), Wacker Biochem Corporation hereby submits notification that a particular use of a substance (beta-cyclodextrin, β -CD) 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). For ease of review by FDA, this notification is submitted in the format suggested under proposed 21 C.F.R. § 170.36(c) (62 Fed. Reg. at 18961). Also enclosed is an electronic copy (Microsoft Word 97) of the claim (GRAS Notification Claim.doc) and the additional information (GRAS Additional Info.doc).

Sincerely,


Dr. Gerhard Schmid, President
Wacker Biochem Corporation

DBC/MLB/dad

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■ Wacker Biochem Corp.
3301 Surton Road
Adrian, MI 49221-9397
(517) 264-8671

GRAS EXEMPTION CLAIM

We hereby claim that the use of beta-cyclodextrin (β -CD) for use as a flavor carrier and protectant 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 β -CD is generally recognized as safe (GRAS).

(1) Name and address of the notifier:

Dr. Gerhard Schmid, President
Wacker Biochem Corp.
3301 Sutton Road
Adrian, Michigan 49221-9397
517-264-8793
517-264-8795 (fax)

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

Beta-cyclodextrin; β -cyclodextrin

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

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

Baked goods prepared from dry mixes, breakfast cereal, chewing gum, gelatins and puddings, dry mix for soups, flavored coffee and tea, compressed candies, processed cheese products, flavored savory snacks and crackers, dry mix for beverages.

(b) Levels of use in such foods:

	<u>Maximum</u>
baked goods prepared from dry mixes	2%
breakfast cereal	2%
chewing gum	2%
gelatins and puddings	1%
dry mix for soups	0.2%
flavored coffee and tea	1%
compressed candies	2%
processed cheese products	1%
flavored savory snacks and crackers	0.5%
dry mix for beverages	1%

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(c) Purposes for which the substance is used:

Flavor carrier, protectant

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

Individuals consuming 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 Wacker Biochem Corporation'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.



Dr. Gerhard Schmid, President
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ADDITIONAL INFORMATION

(1) **Identity of the notified substance**

(a) **Chemical name**

Beta cyclodextrin; β -cyclodextrin; β -CD

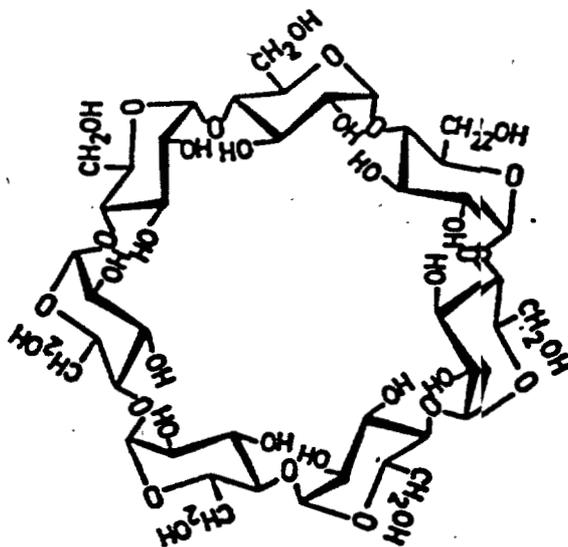
(b) **Chemical Abstracts Service (CAS) Registry Number**

7585-39-9

(c) **Empirical formula**

$(C_6H_{10}O_5)_7$

(d) **Structural formula**



(e) **Method of manufacture**

α -, β - and γ -Cyclodextrin (CD) are formed by the action of cyclodextrin-glycosyltransferases (CGTase, EC 2.4.1.19, CAS 9030-09-5) on starch. CGTases are amylolytic enzymes which are produced naturally by different strains of Bacilli and other species of bacteria (Sicard & Saniez, 1987; Schmid, 1989, 1991; Starnes, 1990; Tonkova, 1998). CGTases degrade starch by a cyclization reaction. There is evidence that the enzyme recognizes the 6, 7 or 8 glucose units from the non-reducing end of an amylose molecule, attacks the adjacent α -1,4-linkage, and

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transfers it to the C-4 position of the non-reducing end to produce α -, β - or γ -CD (Schmid, 1989). Typically, mixtures of α -, β - and γ -CD are formed by the action of CGTases on starch, with the β -form being predominant for thermodynamic reasons. Different CGTases produce α -, β -, and γ -CD in different proportions during the initial phase of the reaction. The ratio of the formed cyclodextrins is also influenced by other conditions such as the reaction time, temperature, and presence of ethanol (Goel & Nene, 1995).

Cyclodextrins are isolated from the enzymatic reaction mixture either by the “solvent process,” in which a suitable organic substance is added to form an insoluble complex with the cyclodextrins, or the “non-solvent process,” in which chromatographic separation techniques are applied (Sicard & Saniez, 1987; Schmid, 1991; Rendleman, 1993).

The product being considered here, is produced using CGTase from a genetically modified strain of Escherichia coli K12 and applying the solvent process for separation of the obtained β -CD.

In the first step of β -CD production, food-grade, liquefied starch is treated with CGTase under controlled pH and temperature conditions. Toluene is added as a complexant to precipitate formed β -CD. The complex is removed and purified by dissolution in water and re-precipitation. The complexant is separated from β -CD by decantation and steam distillation. According to the specifications of β -CD, total residue levels of toluene will not exceed 1 ppm. β -CD is obtained by crystallization as a white powder with a purity of $\geq 98.0\%$.

(f) Characteristic properties

β -CD is a ring-shaped molecule made up of seven glucose units linked by α -1,4-bonds. The circular structure of β -CD provides a hydrophobic cavity which allows complexes to be formed with a variety of molecules, while the hydrophilic outer surface makes β -CD water soluble. This enables cyclodextrins to form inclusion complexes with various organic compounds. This property forms the basis for numerous applications of cyclodextrins in foods, as well as pharmaceutical and cosmetic products (Szejtli, 1982; Nagatomo, 1985; Vaution et al., 1987; Pszczola, 1988; Allegre & Deratani 1994; Thompson, 1997). In foods, cyclodextrins can protect volatile compounds from evaporation, and chemically sensitive products from oxidation or photodegradation. Cyclodextrins also can stabilize emulsions and foams, mask certain undesirable tastes and odors, provide bulk, and improve texture (Hedges et al., 1995). The suitability of the different

cyclodextrins for these applications varies in relation to the size of the “guest” molecule, which the cyclodextrin ring should accommodate.

Cyclodextrins are cyclic α -(1-4)-linked maltooligosaccharides. α -, β -, and γ -cyclodextrin consist of 6, 7, and 8 glucose units, respectively. Cyclodextrins were first isolated by Villiers in 1891 from a culture medium of Bacillus amylobacter (Clostridium butyricum) grown on a medium containing starch. During studies on microbial food spoilage, Schardinger isolated Bacillus macerans, a heat-resistant cyclodextrin-producing microorganism. In recognition of his detailed investigations on cyclodextrins (from 1903-1911), these substances are referred to as “Schardinger dextrans” in the early literature (French, 1957). Meanwhile, many bacteria have been found to produce cyclodextrins from starch. On a commercial scale, cyclodextrins are produced today from starch using cyclodextrin glucosyltransferases, a group of bacterial amylolytic enzymes.

(g) Any content of potential human toxicants

The CGTase is obtained from a genetically modified strain of Escherichia coli K12. E. coli K12 is a nonpathogenic and nontoxic host organism which has been used for the production of other food ingredients such as chymosin and which is recognized as safe (FDA, 1990). The present strain expresses a CGTase gene of a Bacillus strain of the firmus/lentus group, an ubiquitous group of aerobic, gram-positive, alkalophilic, non-pathogenic microorganisms. For constructing this strain, a vector was used which is derived from pBr322, a widely used vector which is considered to be safe. The obtained CGTase preparation was non-mutagenic in Ames tests using S. typhimurium strains TA 1535, TA 1537, TA 98 and TA 100, with and without metabolic activation (S9-mix) (van Delft, 1997, cited in WHO, 1999). β -CD does not contain any CGTase activity because the enzyme is inactivated by heat and is removed completely during the β -CD production process. DNA from the CGTase source organism (E. coli K12) could not be detected either using sensitive PCR techniques. Any nonproteinaceous, hydrophilic or lipophilic by-products present in the CGTase preparation would also be removed by the applied purification steps.

Toluene is relatively non-toxic to experimental animals (WHO, 1981). According to the specifications of β -CD (FCC, 1997), total residue levels of toluene in β -CD will not exceed 1 ppm, i.e., the concentration which is acceptable also for bottled water (21 C.F.R. § 165.110).

(h) Specifications for food-grade material

The specifications for β -cyclodextrin are as described at pages 15-18 of Food Chemicals Codex IV (First Supp. 1997) (FCC, 1997).

(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 conducted using β -CD which include 52-week toxicity studies in rats and dogs; carcinogenicity studies in mice and rats; and, a 3-generation reproductive toxicity study in rats with a teratology phase. At its 41st and 44th meetings, JECFA evaluated the safety of β -CD and allocated an acceptable daily intake (ADI) of 0-5 mg/kg body weight/day for β -CD at the latter meeting based on a NOEL of 1.25% β -CD in the diet (equal to 470 mg/kg body weight/day) in a 1-year study in dogs and a safety factor of 100 (WHO, 1993, 1996).

(4) Probable Consumption of the Substance

β -CD is intended for use as a flavor carrier and protectant constituting up to 2% of the following foods: (1) baked goods prepared from dry mixes; (2) breakfast cereal; (3) chewing gum; (4) gelatins and puddings; (5) dry mix for soups; (6) flavored coffee and tea; (7) compressed candies; (8) processed cheese products; (9) flavored savory snacks and crackers; (10) dry mix for beverages. Exposure calculations, made in a pending GRAS affirmation petition, used survey data gathered by the Market Research Corporation of America and use levels of β -CD of up to 0.5% in the food categories listed above. As indicated by calculations for β -CD (GRASP 6G0421), a maximum of 12% of the flavors used in the food categories listed above use protectants; therefore, the estimated intake of β -CD assuming all flavors used for the above food categories use carriers/protectants was adjusted accordingly. Assuming replacement of all encapsulating

agents/protectants with β -CD (21 C.F.R. § 172.230), the estimated exposure of the total population to β -CD from the above listed food categories would be 1.44 mg/kg body weight/day¹ for the 90th percentile consumer (eaters only). When used at levels of up to 2%, as specified here, this intake level would approach the JECFA ADI of 5 mg/kg body weight/day. Given that (1) the use of encapsulating agents/protectants has significantly decreased in recent years (FEMA, 1999) and (2) a safety factor of 100 was used to establish the ADI, the increased exposure to β -CD from use levels of up to 2% in the above listed food categories does not present a safety concern.

(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.

The information in this notification was reviewed by an independent panel of experts:

I.C. Munro, Ph.D., CanTox, Inc.

G. A. Burdock, Ph.D., D.A.B.T.

W. G. Flamm, Ph.D., F.A.C.T.

Based on an independent, critical evaluation of proprietary data and information concerning the manufacture, safety and intended uses of β -CD provided by Wacker, publicly available data and information present in a pending GRAS affirmation petition (GRASP 6G0421) for β -CD submitted jointly by Cerestar U.S., Inc. and Roquette America, Inc., and additional relevant information found

¹ This estimate includes the use of β -CD in dry mixes for alcoholic beverages as indicated in the GRAS affirmation petition 1G0376.

in the published scientific literature, Drs. Munro, Burdock, and Flamm concluded that Wacker Biochem's β -CD product, meeting appropriate food grade specifications and manufactured in accordance with current good manufacturing practices, is generally recognized as safe based on scientific procedures.

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Submission End

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DIRECT DIAL (202) 737-4291

November 8, 2000

BY HAND DELIVERY

Dockets Management Branch
 Food and Drug Administration
 12420 Parklawn Drive (HFA-305)
 Room 1-23
 Rockville, Maryland 20857

Re: Docket No. 96G-0324; GRAS Affirmation Petition for β -Cyclodextrin

Dear Sir/Madam:

On October 7, 1997, we submitted, on behalf of Cerestar USA, Inc. ("Cerestar," formerly American Maize Products Co.), the enclosed opinion by qualified food safety experts (the "Expert Panel") confirming that under the conditions of intended use in foods, Cerestar's β -cyclodextrin (BCD) is "generally recognized as safe" ("GRAS") based on scientific procedures.

It has come to our attention that there was an inconsistency in the exposure estimates relied upon by the Expert Panel in 1997. Specifically, the estimated daily intake (EDI) described in the pending GRAS petition was based on a maximum use level of 2% BCD, whereas the actual food intake survey calculations were based on an expected use level of 0.5%. Upon discovering this discrepancy, the Expert Panel promptly re-evaluated the safety of Cerestar's BCD using the corrected intake calculations based on the 2% use level. Enclosed for your file is the "Amended Expert Panel Opinion of the GRAS Status of Beta-Cyclodextrin (BCD)" which was completed on August 29, 2000 by the Panel.

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96G-0324

Dockets Management Branch

HYMAN, PHELPS & MCNAMARA, P.C.

November 8, 2000

Page 2

Applying the adjusted EDI, the Expert Panel again concluded that Cerestar's BCD, meeting appropriate food grade specifications and used in conformity with current good manufacturing practice, is GRAS based on scientific procedures for its intended use as a flavor carrier/protectant at levels of up to 2% BCD in baked goods prepared from dry mixes; breakfast cereals; chewing gum; gelatins and puddings; dry mixes for soups; flavored coffee and tea; compressed candies (as tablets); processed cheese products; flavored savory snacks and crackers; and dry mix beverages.

Should you have any questions regarding the Amended Expert Panel Opinion confirming the GRAS status of Cerestar's BCD, please do not hesitate to contact us.

Sincerely,

Diane B. McColl
Counsel to Cerestar USA, Inc.

DBM/dmb
Enclosure

cc: Joseph F. Borzelleca, Ph.D.
George A. Burdock, Ph.D.
W. Gary Flamm, Ph.D.

Mike Fuelling, Esq.
Frances Turnak
Cerestar USA, Inc.

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Amended Expert Panel Opinion of the GRAS Status of Beta-Cyclodextrin (BCD)

In the autumn of 1997, the attached GRAS opinion statement was drafted and signed by Drs. Joseph F. Borzelleca, George A. Burdock and W. Gary Flamm. This statement addresses the use of BCD in ten food categories for use as a flavor carrier and protectant. The statement needs to be corrected to reflect accurately the estimated daily intake (EDI) to BCD by the upper 90th percentile consumers of the ten food categories. The need for this amendment resulted from an incorrect assumption that the EDI, given in the GRAS affirmation petition filed with FDA (6G0421), was based on a *maximum* use level of 2% BCD for the ten food categories as given below:

FOOD CATEGORY	Max. Level (% by weight)
Baked goods prepared from dry mixes	2
Breakfast cereal	2
Chewing gum	2
Gelatins and puddings	1
Dry mix for soup	0.2
Flavored coffee & tea	1
Compressed candy as tablets	2
Processed cheese products	1
Favored savory snacks and crackers	0.5
Dry mix beverages	1

Instead, the EDI was based on *expected* use levels (concentrations) up to 0.5% BCD in these food categories. As the petition (6G0421) seeks approval for use levels of BCD in food up to a maximum of 2%, not 0.5%, the Expert Panel has reconsidered the safety of such use levels for the purpose of this amendment and to correct the record accordingly.

Calculations, presented in the petition (6G0421), based on *expected* BCD use levels of up to 0.5%, combined with food intake survey data conducted by the Market Research Corporation of America (MRCA), resulted in an estimated exposure to BCD of 1.44 mg/kg body weight/day for the 90th percentile consumer. This estimate includes an adjustment for the fraction (or percent) of flavors in these ten food categories that currently use approved flavor protectants (microencapsulation) as described under 21 CFR §172.230, but assumed a total replacement of these protectants by BCD. As there are several such substances under FDA's food additive regulation (21 CFR §172.230) which have been used historically as flavor protectants, the above exposure estimate for BCD is unrealistic and will overstate actual exposure. Furthermore, as the use of flavor protectants has been declining significantly according to Lucas et al., 1999 (Flavor and Extract Manufacturers' Association of the United-States 1995 poundage and technical effects update survey. FEMA, Washington, D.C.), there is additional assurance exposure to BCD from its proposed, intended use will not reach or exceed the exposure estimate as based on total replacement of all currently used protectants. In view of these considerations, a 50% replacement of existing flavor protectants is considered adequately conservative. Adjusting the estimate accordingly reduces the exposure

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estimate to 0.72 mg/kg body weight/day. However, because the use level is up to a *maximum* of 2%, this estimate must be corrected. As the *maximum* level for each food category is about 4-fold higher on average than the level on which the estimate is based, the estimate of 0.72 mg/kg is multiplied by 4 raising the estimated exposure to BCD by the 90th percentile consumer to 2.88 mg/kg body weight/day.

As the estimated exposure is less than the ADI (acceptable daily intake) of 5 mg/kg body weight/day granted by the Joint WHO/FAO Expert Committee on Food Additives (JECFA) with which the Expert Panel concurs, the Panel concludes that BCD, meeting appropriate food grade specifications, is generally recognized as safe (GRAS) by scientific procedures for its intended use as a flavor carrier/protectant for the ten food categories identified in the original GRAS statement at levels up to 2% when used in conformity with current good manufacturing practice as described at 21 CFR §182.1(b).

Joseph F. Borzelleca, Ph.D., F.A.T.S.

29 August 2001
Date

George A. Burdock, Ph.D., D.A.B.T.

23 Aug 01
Date

W. Gary Flamm, Ph.D., F.A.C.T., F.A.T.S.

8/23/00
Date

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*EXPERT PANEL OPINION OF THE GRAS
STATUS OF BETA CYCLODEXTRIN*

The undersigned individuals were asked by Cerestar USA, Inc. (Cerestar) to review available relevant information on the safety of beta-cyclodextrin (BCD) for the purpose of determining whether certain specified uses of BCD in human foods would be generally recognized as safe (GRAS). As evidenced by the attached CV's the undersigned, Joseph F. Borzelleca, Ph.D., George A. Burdock, Ph.D., and W. Gary Flamm, Ph.D. (collectively the "Panel"), are well-established food safety experts, qualified by training and many years of relevant national and international experience in evaluating the safety of food ingredients.

Cerestar provided information on the safety, intended use and estimated consumer exposure to BCD, which was independently reviewed by Panel members. Publicly available data and information in the pending GRAS affirmation petition (6G0421) for BCD were made available to the Panel. In addition, the Panel, in coming to its conclusion concerning the GRAS status of BCD, relied on a search of the scientific literature, other relevant information and their respective years of professional experience addressing related matters. Traditional safety studies with BCD, conducted in accordance with FDA guidelines (FDA, 1982), have been published in the scientific literature and include: chronic (52-week) rat and dog studies; carcinogenicity studies in the rat and mouse; multigeneration studies with a teratology phase in the rat and extensive genotoxicity studies. Following independent review and consideration of the above data and information, a teleconference was held to discuss and review the findings with all Panel members.

BCD is a cyclic heptamer composed of seven glucose units joined by α -1,4 bond linkages. It is produced by the action of the enzyme, cyclodextrin glucosyl transferase, on hydrolyzed starch syrup. The enzyme is obtained from non-pathogenic and non-toxigenic strains of *Bacillus macerans*, *B. circulans* or related strains of *Bacillus*. BCD has the ability to form inclusion compounds with a range of molecules, generally of molecular mass of less than 250. It may serve as a carrier and protectant of food flavors by molecular inclusion.

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The Joint Expert Committee on Food Additives (JECFA) of the World Health Organization (WHO) and the Food and Agriculture Organization (FAO) has reviewed BCD at its forty-first and forty-fourth meetings. At the latter meeting, an acceptable daily intake (ADI) of 0-5 mg/kg bw was established based on a no effect level (NOEL) of 1.25% in the diet (equal to 470 mg/kg bw/day) in the 1-year study in dogs and a safety factor of 100. The Scientific Committee for Foods (SCF) of the European Union has also assigned BCD an ADI of 5 mg/kg bw/day.

In the report of the forty-fourth meeting (WHO, IPCS, 1996), the comment was made that, in the mouse carcinogenicity study, one male mouse in the 75 mg/kg bw group exhibited an inflammatory lesion of the lower gastrointestinal tract that was considered a possible cause of death. On the basis of this finding, the monograph suggested that the next lowest dose, 25 mg/kg bw, as the NOEL. However, these data were not used by JECFA to establish the ADI as the Committee considered the lesion to represent a species-specific reaction that was not relevant to setting an ADI. We agree, and have further found from our review of individual animal data and group mean values that no inflammatory lesions of the lower gastrointestinal tract were observed at doses above (225 and 675 mg/kg bw/day) or below 75 mg/kg bw in either the males or females. Based on this review and the above findings, the Panel believes that the inflammatory change found in the one male mouse cannot be regarded a treatment related effect. Accordingly, the above effect in the mouse, as JECFA and the SCF have concluded, should not be used to set an ADI. The Panel agrees with the decision of the JECFA and the SCF to consider the ADI for BCD to be 5 mg/kg bw/day as indicated above.

The uses intended for BCD are as a flavor carrier and protectant at 2% in the following foods: (1) chewing gum; (2) gelatin and puddings; (3) soups prepared from dry mixes; (4) coffee and tea products with added flavors; (5) compressed candies; (6) processed cheese products; (7) savory snacks-crackers with added flavorings; (8) baked goods prepared from dry mixes; (9) beverages prepared from dry mixes; (10) breakfast cereals. The above intended uses would collectively amount to 11 to 15 mg/kg bw/day for the upper 90th percentile consumer (eaters only) assuming all flavors used for the above food categories used carriers/protectants. This determination was made and supported by the petitioners in the pending GRAS affirmation petition using survey data gathered by the Market Research Corporation of America (MRCA). However, because only 14% of the flavors used in the

above foods are encapsulated (use protectants) according to the petitioners' calculations, estimated intake of BCD in these foods must be adjusted accordingly. Assuming BCD were to replace all encapsulating agents/protectants (see 21 CFR 172.230), the estimated amount consumed by the 90th percentile consumer (eaters only) would need to be multiplied by 14%. Hence, the estimated exposure to BCD from all of the above food categories for the 90th percentile consumer (eaters only) would be about 2 mg/kg bw/day, well below the JECFA and SCF ADI.

In conclusion, the Panel finds that BCD, meeting appropriate food grade specifications, is generally recognized as safe (GRAS) by scientific procedures for its intended use as a flavor carrier/protectant for the 10-food categories listed above when used in accordance with current good manufacturing practice as described at 21 CFR 182.1(b).

Joseph V. Borzelleca, Ph.D., F.A.T.S. 01 Oct 1997
Date

George A. Burdock, Ph.D., D.A.B.T. 28 Sept 97
Date

W. Gary Flamm, Ph.D., F.A.C.T. 9/26/97
Date

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August 31, 2001

Andrew Laumbach, Ph.D.
Consumer Safety Officer
Office of Food Additive Safety
Center for Food Safety and Applied Nutrition
Food and Drug Administration
200 C Street S.W.
Washington, D.C. 20204

Re: GRAS Notice for β -Cyclodextrin (GRN 74)

Dear Dr. Laumbach:

As requested, we have obtained additional information illustrating the extent to which the daily intake estimates derived from dietary survey information greatly exaggerate the likely dietary exposure to β -cyclodextrin.

We understand that, based on dietary survey data, the Food and Drug Administration (FDA) has determined that the estimated mean consumption of β -cyclodextrin under the conditions of intended use in food is 0.3 g/person/day. According to Census 2000, the United States population is 284.1 million so an intake of 0.3 g/person/day would require 84,420,000 g/day or 30,806 tons/year of β -cyclodextrin. If FDA's consumption estimate of 0.7 g/person/day for the heavy user (90th percentile) is applied to the total population, the demand for β -cyclodextrin would increase to 71,868.5 tons/year.

There is only a limited demand for use of β -cyclodextrin as a flavor protectant due to its technical properties and the availability of less costly alternatives. While β -cyclodextrin has been marketed in the United States since 1996, the actual amount of β -cyclodextrin used by the food industry is less than 50 tons/year. Hence, the FDA's estimated intakes are about 100-fold greater than the anticipated intakes based on actual production data.

We trust that this information is responsive to your request. If you have any additional questions, please do not hesitate to ask.

Sincerely,

 Dr. Gerhard Schmid
President
Wacker Biochem Corporation

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