ORIGINAL SUBMISSION
November 1, 2016

Office of Food Additive Safety (HFS-200)
Center for Food Safety and Applied Nutrition
Food and Drug Administration
5001 Campus Drive
College Park, Maryland 20740

Subject: Notice of a GRAS Exclusion for Alpha-Cyclodextrin

Dear Sir/Madam:

In accord with 21 C.F.R. part 170, subpart E, Wacker Chemical Corporation hereby submits the enclosed notice that the general use of its alpha-cyclodextrin in processed and ultra-processed foods (other than beverages) at a level of up to 3% (w/w) as consumed, and in certain beverages at a level of up to 1.05% (w/v) as consumed, is excluded 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).

Sincerely,

Ricardo Carvajal

RC/sas
Enclosures
GRAS NOTICE FOR ALPHA-CY CloDExTRIN
SUBMITTED BY WACKER CHEMICAL CORPORATION

Part 1 – Signed statements and certification

(1) Applicability of 21 C.F.R. part 170, subpart E

We submit this GRAS notice in accordance with 21 C.F.R. part 170, subpart E.

(2) Name and address of the notifier

Company: Wacker Chemical Corporation
Name: Helmut Reuscher Ph.D.
Address: 3301 Sutton Road, Adrian, Michigan 49221-9397
Phone: (517) 264-8794
Fax: (517) 264-8795

(3) Name of the notified substance

Alpha-cyclodextrin

(4) Applicable conditions of use of the notified substance

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

As explained in detail in this notice, the substance is to be used in (1) processed foods other than beverages (products that are directly derived from whole foods and recognized as such), (2) ultra-processed foods other than beverages (products that are formulated mostly or entirely from substances derived from whole foods), and (3) certain types of beverages. Some of these foods may constitute meat or poultry products falling under the jurisdiction of the U.S. Department of Agriculture. The substance is not intended to be used in infant foods.

(b) Levels of use in such foods

The substance may be used in processed and ultra-processed foods other than beverages at a level of up to 3% (w/w) as consumed, and in diet soft drinks at a level of up to 1.05% (w/v) as consumed. These use levels will supersede the corresponding use levels specified in GRN 000155. The use levels for the other types of beverages specified in GRN 000155 would remain unchanged, and are listed in Table 1.
Table 1  Food categories and use levels for alpha-cyclodextrin

<table>
<thead>
<tr>
<th>Food category</th>
<th>Maximum use level (%)</th>
<th>Present GRN</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Processed and ultra-processed foods (as consumed)</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Breads, rolls, cakes, baking mixes, refrigerated dough</td>
<td>5</td>
<td>3</td>
</tr>
<tr>
<td>Brownies and bars</td>
<td>7</td>
<td>3</td>
</tr>
<tr>
<td>Crackers (sweet and non-sweet)</td>
<td>10</td>
<td>3</td>
</tr>
<tr>
<td>Coffee whiteners (dry), formula diets, meal replacements, nutritional supplements</td>
<td>1</td>
<td>3</td>
</tr>
<tr>
<td>Ready-to-eat breakfast cereals</td>
<td>2 to 9</td>
<td>3</td>
</tr>
<tr>
<td>Instant rice, pasta, and noodles (prepared)</td>
<td>2</td>
<td>3</td>
</tr>
<tr>
<td>Condiments</td>
<td>3</td>
<td>3</td>
</tr>
<tr>
<td>Reduced fat spreads</td>
<td>20</td>
<td>3</td>
</tr>
<tr>
<td>Dressings and mayonnaise</td>
<td>5</td>
<td>3</td>
</tr>
<tr>
<td>Yogurt, milk beverage mixes, and frozen dairy desserts</td>
<td>2.5</td>
<td>3</td>
</tr>
<tr>
<td>Pudding mixes (dry)</td>
<td>1</td>
<td>3</td>
</tr>
<tr>
<td>Snack foods</td>
<td>1</td>
<td>3</td>
</tr>
<tr>
<td>Canned and dry soups (prepared)</td>
<td>2</td>
<td>3</td>
</tr>
<tr>
<td>Hard candy</td>
<td>15</td>
<td>3</td>
</tr>
<tr>
<td>Chewing gum</td>
<td>10</td>
<td>3</td>
</tr>
<tr>
<td><strong>Beverages (as consumed)</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Diet soft drinks</td>
<td>1</td>
<td>1.05</td>
</tr>
<tr>
<td>Beverage mixes, fruit juices, instant coffees and teas</td>
<td>1</td>
<td>1</td>
</tr>
<tr>
<td>Vegetable juices, soy milk and non-soy (imitation) milk</td>
<td>2</td>
<td>2</td>
</tr>
</tbody>
</table>

a As per Agency Response Letter GRN 000155.

(c) Purpose for which the substance is used

The substance is for general use in foods.

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

The population expected to consume the substance consists of members of the general population who consume at least one of the products described above.

(5) Basis for the GRAS determination

The statutory basis for our conclusion of GRAS status is through scientific procedures in accordance with 21 C.F.R. §§ 170.30(a) and (b).
(6) Exclusion from premarket approval

The notified substance is not subject to the premarket approval requirements of the FDC Act based on our conclusion that the notified substance is GRAS under the conditions of its intended use.

(7) Availability of data and information

If the Food and Drug Administration (FDA) asks to see the data and information that are the basis for our conclusion of GRAS status either during or after FDA’s evaluation of our notice, we will agree to make the data and information available to FDA. Further, upon FDA’s request, we will allow the Agency to review and copy the data and information during customary business hours at the above address, and will provide FDA with a complete copy of the data and information either in an electronic format that is accessible for the Agency’s evaluation or on paper.

(8) Applicability of FOIA exemptions

None of the data and information in Parts 2 through 7 of our GRAS notice are exempt from disclosure under the Freedom of Information Act, 5 U.S.C. § 552.

(9) Certification

We certify that, to the best of our knowledge, our GRAS notice is a complete, representative, and balanced submission that includes unfavorable information, as well as favorable information, known to us and pertinent to the evaluation of the safety and GRAS status of the use of the substance.

Name: Helmut Reuscher Ph.D.
Title: Director

Date

Please address correspondence to:

Ricardo Carvajal
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Part 2 – Identity, method of manufacture, specifications, and physical or technical effect

(1) Identity of the notified substance

(a) Chemical name

Alpha-cyclodextrin; α-cyclodextrin; α-CD; alpha-dextrin; α-dextrin

(b) Chemical Abstracts Service (CAS) Registry Number

10016-20-3

(c) Empirical formula

\((\text{C}_6\text{H}_{10}\text{O}_5)_6\)

(d) Structural formula

Alpha-cyclodextrin (hereinafter “α-CD”) is the cyclic polymer of six α-1,4-linked glycopyranosyl units.

(e) Characteristic properties

Cyclodextrins are cyclic α-(1-4)-linked maltooligosaccharides. α-CD is a ring-shaped molecule made up of six glucose units linked by α-1,4-bonds. The circular molecules of α-, β- and γ-CD are shaped like a hollow truncated cone or torus. Because the hydrogen atoms and the oxygen atoms of the glycosidic bonds are facing the inner side of the torus, while the hydroxyl groups are located on the outer side, cyclodextrins have a hydrophobic cavity and, at the same time, a hydrophilic outer surface which
makes them water-soluble. The hydrophobic cavity enables cyclodextrins to form inclusion complexes with a variety of organic compounds. The diameter of the cavity provides for a certain selectivity of the complexation of “guest” molecules, i.e., the bigger ring of the 8-membered γ-CD can accommodate a wider variety of guest molecules than the smaller rings of α- and β-CD. Large guest molecules may complex with more than one cyclodextrin molecule (Le Bas & Rysanek, 1987).

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 dextrins” 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.

The formation of an inclusion complex with a guest molecule is the basis for many applications of cyclodextrins in food, cosmetics, and pharmaceutical preparations (Hedges et al., 1995; Nagatomo, 1985; Loftsson & Masson, 2001). The formation of complexes between cyclodextrins and guest molecules is reversible, and excess water would in most cases result in a dissociation of the complex (Hedges et al., 1995; Nagatomo, 1985; Loftsson and Masson, 2001). 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.

**Any known toxicants that could be in the source**

The potential impurities of α-CD are residues of the cyclodextrin-glycosyltransferase (CGTase, EC 2.4.1.19, CAS 9030-09-5) preparation, residual starch, linear maltooligosaccharides, maltose, glucose and β-cyclodextrin.

The CGTase preparation is obtained from a recombinant strain of *Escherichia coli* K12. *E. coli* K12 is a nonpathogenic and nontoxicigenic host organism which has been used for the production of other food ingredients such as chymosin or γ-cyclodextrin and which is recognized as safe (FDA, 1990, 2000). The *E. coli* K12 strain belongs to risk group 1 in the classification of human etiologic agents (NIH, 2002), and is also recommended as a safe host organism by the EU Commission (EU Commission, 1997). The gene coding for the α-CGTase stems from *K. oxytoca*, strain M5a1, which has been well characterized (Randriamahefa,
1994) and has been used for many years in biotechnological research and applications. The vector used for introduction of the α-CGTase gene in the *E. coli* K-12 host is derived from the pJF118EH vector which is derived from pBR322, a widely used mobilization-defective vector that is considered to be safe (EU Commission, 1997). The α-CGTase preparation has been subjected to Ames tests in *S. typhimurium* strains TA 1535, TA 1537, TA 98, TA 100 and *E. coli* WP2 uvrA with and without metabolic activation, as well as in a chromosome aberration test in cultured human lymphocytes, without any evidence of a genotoxic effect (Bär, et al. 2004). In a 13-week subchronic toxicity study in rats, the α-CGTase preparation did not produce any adverse effects at levels of up to 260 mg TOS/kgbw/d, which was the highest dose level tested (Bär et al., 2004).

α-CD does not contain any CGTase activity because the enzyme is inactivated by heat and is removed completely during the α-CD production process. DNA from the CGTase source organism (*E. coli* K12) could not be detected either using sensitive polymerase chain reaction (PCR) techniques. Any non-proteinaceous, hydrophilic or lipophilic by-products present in the CGTase preparation would also be removed by the applied purification steps. The absence of protein was demonstrated by appropriate analytical tests.

The complexant, 1-decanol, is efficiently removed during purification. Analysis of five α-CD pilot batches showed 1-decanol residues of <15 ppm. 1-Decanol has FEMA GRAS status (FEMA No. 2365) (Hall and Oser, 1965) and is approved FDA for use in foods as a synthetic flavoring substance (21 C.F.R. § 172.515) and as a synthetic fatty alcohol (21 C.F.R. § 172.864). In addition, 1-decanol was evaluated by the Joint FAO/WHO Expert Committee on Food Additives (JECFA) as a flavoring substance and determined to not pose safety concerns at estimated daily intakes (for eaters only) of 7 and 28 µg/person/day in the United States and Europe, respectively (WHO, 1998). In the EU, 1-decanol is listed in the Register of Flavoring Substances under FL No 02.024 (Commission Decision 2002/113/EC).

**(2) Description of method of manufacture**

α-, β- and γ-Cyclodextrins (CDs) 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 transfers it to the C-4 position of the non-reducing end to produce α-, β- or γ-CD.
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).

α-CD is produced using CGTase from a recombinant strain of Escherichia coli K12, harboring the CGTase gene of Klebsiella oxytoca, and applying the solvent process for separation of the obtained α-CD.

In the first step of α-CD production, food-grade, liquefied starch is treated with CGTase under controlled pH and temperature conditions. 1-Decanol is added as a complexant to precipitate formed α-CD. The complex is removed and purified by dissolution in water and re-precipitation. The complexant is separated from α-CD by decantation and steam distillation. Obtained by crystallization, α-CD is a white powder with a purity of ≥ 98.0%.

(3) Specifications for food-grade material

The specifications for food-grade α-CD are provided below:

Assay: ≥ 98% of α-CD (on an anhydrous basis)
Ash (residue on ignition): ≤ 0.1%
Reducing sugars: ≤ 0.5%
Heavy metals (as Pb): ≤ 5 ppm
Lead: ≤ 0.5 ppm
Volatile organics: ≤ 20 ppm

The “volatile organics” are residues of the complexant 1-decanol. Additional purity criteria are included in the company’s internal specifications, such as microbiological purity and optical density.

(4) Data and information bearing on physical or other technical effect

Our GRAS notice does not include data and other information bearing on physical or other technical effect because such data and other information are not necessary to demonstrate safety.
Part 3 – Dietary exposure

(1) Introduction

As described in detail in Part 6 of this notice, α-CD is the subject of GRN 000155, to which FDA responded with a “no questions” letter in 2004. In 2012, the GRAS uses of α-CD were extended to encompass use as a flavor adjunct (carrier, stabilizer) pursuant to a self-determination. Since 2012, further food technological benefits of α-CD were discovered (Li et al., 2014). Alpha-CD was found, for example, to be a useful whipping agent for preparing fat-reduced mousses, confectionary and bakery fillings, fruit-based desserts, baked snacks and certain dairy-based products such as yogurt. It also can be used as an emulsifier over a wide range of fat levels to prepare products such as mayonnaises, dressings and cake icings. Other possible applications include use in baked goods such as cakes, muffins, pancakes and waffles. Some but not all of these applications are included in the list of proposed uses specified in GRN 000155 (see Table 1 in Part 1 of this GRN, and also in Appendix 2). Furthermore, it is possible that additional useful food applications of α-CD will be discovered in future. Therefore, it is necessary to (a) overhaul the list of intended uses of alpha-cyclodextrin that was considered in GRN 000155, and (b) revise the calculation of the estimated intakes that may result from the new range of intended uses.

Considering furthermore that not only the composition of foods is changing over time but also new types of food are occasionally developed, a mere update of the existing list of foods that might contain added α-CD may be a short-lived solution. Therefore, we here apply a different, more flexible, yet with regard to the safety assessment still conservative approach for estimating the intake of α-CD that may result from the extended range of uses.

(2) Consumption of processed and ultra-processed foods

The common denominator of all foods that contain added α-CD, be it as an ingredient of the basic matrix of the food or be it as an ingredient of one of the components of the food (such as, for example, its glazing or filling), is that such foods by definition are “processed” or even “ultra-processed.”

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1 Because only a few of the proposed uses encompassed by GRN 000155 actually materialized, the present intake of α-CD by the US population is orders of magnitude below the estimated intakes that were presented in GRN 000155 (i.e., 0.21 and 0.43 g/kg bw/d for the mean and the 90th percentile consumer, respectively).
According to the 2010 Dietary Guidelines for Americans Report, a processed food is “any food other than a raw agricultural commodity that has been subject to washing, cleaning, milling, cutting, chopping, heating, pasteurizing, blanching, cooking, canning, freezing, drying, dehydrating, mixing, packaging, or other procedures that alter the food from its natural state. Processing also may include the addition of other ingredients to the food, such as preservatives, flavors, nutrients, and other food additives or substances accepted for use in food products, such as salt, sugars, and fats (USDA, 2010).”

Definitions of processed and ultra-processed foods have been published and examples were provided (Moubarac et al., 2014). Of note is that each of these

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2 “Processed foods are ready-to-consume products which are manufactured to make them durable and more palatable and attractive. They are directly derived from foods and recognizable as versions of the original foods. Generally produced to be consumed as part of meals or dishes, or may be used, together with ultra-processed products, to replace food-based freshly prepared dishes and meals. Processes include canning and bottling using oils, sugars or syrups, or salt and methods of preservation such as salting, salt-pickling, smoking and curing. Examples of processed food are canned or bottled vegetables and legumes preserved in brine; peeled or sliced fruits preserved in syrup; tinned whole or pieces of fish preserved in oil; salted nuts; un-reconstituted processed meat and fish such as ham, bacon, smoked fish; cheese. Ultra-processed foods are formulated mostly or entirely from substances derived from foods. Typically they contain little or no whole foods. They are durable, convenient, accessible and highly or ultra-palatable. Typically they are not recognizable as versions of foods, although they may imitate the appearance, shape and sensory qualities of foods. Many ingredients are not available in retail outlets. Some ingredients are directly derived from foods, such as oils, fats, flours, starches and sugar. Others are obtained by further processing of food constituents. They contain preservatives; stabilizers, emulsifiers, solvents, binders, bulkers; sweeteners, sensory enhancers, colors and flavors; processing aids and other additives. Their bulk may come from added air or water. Micronutrients may ‘fortify’ the products. Most are designed to be consumed by themselves or in combination as snacks. They displace food-based freshly prepared dishes, meals. Processes include hydrogenation, hydrolysis; extruding, molding. Examples are chips (crisps), many types of sweet, fatty or salty snack products; ice-cream, chocolates, candies (confectionary); French fries (chips), burgers and hot dogs; poultry and fish ‘nuggets’ or ‘sticks’ (‘fingers’); breads, buns, cookies (biscuits); breakfast cereals; pastries, cakes, cake mixes; ‘energy’ bars; preserves (jams), margarines: desserts; canned, bottled, dehydrated, packaged soups, noodles; sauces; meat, yeast extract; soft, carbonated, cola, ‘energy’ drinks; sugared, sweetened milk drinks, condensed milk, sweetened including ‘fruits’ yoghurts; fruit and fruit ‘nectar’ drinks; instant coffee, cocoa drinks; no-alcohol wine, beer; pre-prepared meat, fish, vegetables, cheese, pizza, pasta dishes; infant formulas, follow-on milks, other baby products; ‘health’, ‘slimming’ products such as powdered or ‘fortified’ meal and dish substitutes.”
categories (including the category of unprocessed/minimally processed foods) comprises liquid foods (i.e., beverages), semi-liquid foods, and solid foods.

When these definitions were applied to the food intake data of the 2007/2008 National Health and Nutrition Examination Survey (NHANES), it was determined that 64.7% of the ingested dietary energy was provided in the United States by ultra-processed foods and 4.9% by processed foods. Furthermore, it was found that the combined value (i.e., 69.6%) was slightly higher for the US than for Canada (62.0%) and the UK (63.4%) (Baraldi et al., 2013; Moubarac et al., 2013b).

More recent data from the UK which are based on the UK National Diet & Nutrition Survey (2008-2012) are in keeping with this observation (Adams & White, 2015). Conceivably, a saturation point is reached for the consumption of ultra-processed foods when they account for about two thirds of the daily energy intake (Solberg, 2014). In turn this means that unprocessed and minimally processed foods (as defined in Moubarac et al., 2014) provide still about one third of the daily energy intake, even in affluent Western societies.

Since foods to which α-CD has been added are by definition processed or ultra-processed foods, this food consumption data provides a basis for estimating the maximum daily intake of α-CD regardless of the exact type of food or food component in which α-CD is used at present or might be used in future.

(3) Intake of α-CD from its combined uses in processed and ultra-processed foods (other than beverages)

The daily intake of α-CD from its use at a given level in processed and ultra-processed foods may be estimated from the total energy intake from such foods. The total energy intake with foods of any type is about 50 kcal/kg bw/d for the 90th percentile adult subject (Bär & Würtzen, 1990). This value was first proposed and applied twenty-five years ago in Europe. As it has been demonstrated by

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3 Based on the more recent NHANES 2009-2010 data, ultra-processed and processed food account for 57.9 and 9.4% of the ingested dietary energy, respectively (Martinez Steele et al., 2016).

4 An analysis of purchases of packaged foods (including beverages) showed that 15.9 and 61.0% of the food energy was provided by moderately and highly processed products, respectively (Poti et al., 2015). However, since food waste was not taken into account and foods without a bar-code were not included (such as fresh fruits), this analysis tends to overestimate the consumption of processed foods.
Swinburn et al. (2009) and is illustrated in Figure 1 at Appendix 1, this value is still fully applicable also to the current U.S. population with a higher than European average body weight.

Figure 1 presents the data points of the daily energy expenditure and the body weight of 1399 U.S. adults. The black line is the corresponding regression line. The red line depicts the relationship between the daily metabolizable energy (ME) intake with food (i.e., solid and liquid foods together) and the body weight for a fixed arbitrary value of 50 kcal/kg bw. As may be seen from the distribution of these data points, more than 90% of U.S. adults have a daily ME intake below 50 kcal/kg bw.

For the purpose of the present report, a person’s daily energy expenditure is considered to be identical to its daily ME intake (Seale et al., 1990). The 90th percentile ME intake of 50 kcal/kg bw/d stems from the combined intake of both solid and liquid foods (such as soft drinks and milk which contribute a significant amount of energy to the total daily energy intake of U.S. residents). On average, indeed 21% of the per capita energy intake was contributed by beverages in 2002 (Duffey & Popkin, 2007). Accordingly, the 90th percentile consumer of food energy who consumes 50 kcal/kg bw/d obtains about 40 kcal/kg bw/d from solid and semi-solid foods and 10 kcal/kg bw/d from beverages.

Applying an average energy density of 2 kcal/g to foods other than beverages (Hansen, 1979; Kant & Graubard, 2005), this daily ME intake of 40 kcal/kg bw corresponds to a food intake of 20 g/kg bw/d. If 70% of this amount, i.e., 14 g/kg bw/d, is obtained from processed or ultra-processed food (Baraldi et al., 2013; Moubarac et al., 2013a) and if all of that food contained α-CD at the highest technologically feasible concentration of 3%, an α-CD intake of about 420 mg/kg bw/d would result for the 90th percentile consumer.

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5 Reading example: For a person with a body weight of 100 kg, the average energy expenditure is about 3260 kcal, i.e., 32.6 kcal/kg bw.

6 While in people with increasing body weight the energy intake is slightly higher than the energy expenditure, this difference is small on a daily basis.

7 A somewhat smaller contribution (15%) of beverages to the total daily energy intake was reported from a more recent analysis of US food purchase data (Poti et al., 2015). However, since food wasting was not considered in that study (which is likely bigger for foods than beverages), this data does not invalidate the earlier reported value of 20% which is derived from food consumption data (Duffey & Popkin, 2007).

8 A somewhat lower value of about 1.5 kcal/g has been proposed by others for foods including milk products (Douglass et al., 1997).
Applying the same calculation to the mean consumer who ingests 28.5 kcal/kg bw/d corresponding to 11.4 g food (excluding beverages)/kg bw/d and thus 7.98 g/kg bw/d processed and ultra-processed food, an α-CD intake of about 239 mg/kg bw/d is obtained. For the mean and 90th percentile adult consumer with an average body weight of 70 kg, daily α-CD intakes of 16.7 g and 29.4 g, respectively, would result from such a ubiquitous use of α-CD at the highest feasible concentration (3%) in each and every processed and ultra-processed food (except beverages). These calculated α-CD intakes are clearly overestimates because they are based on the assumption that 80% of the total daily energy intake is provided by solid or semi-solid foods of which 70% is processed or ultra-processed and contains α-CD at the highest feasible concentration (3%).

(4) Intake of α-CD from its use in certain types of beverages

For estimating the α-CD intake with beverages, the ingested volumes rather than the ingested energy must be considered and taken as a basis, because both the energy density of beverages varies widely (from about 0–70 kcal/100 mL) and the liquid intake varies widely (from about 15–40 mL/kg bw/d). With such widely varying parameters, it is difficult to make a reasoned “worst case” estimation of the daily α-CD intake from its use in beverages. Instead, the food consumption data that were presented in GRN 000155 may be applied. The description of the beverages in which α-CD is intended to be used is still valid and so are the projected maximum use levels, except for diet soft drinks in which the maximum is to be adjusted from 1% to 1.05%. The projected intakes of α-CD from its use in beverages were estimated from U.S. food consumption data as described in GRN 000155. The two-day average intake per user of such products was estimated at 3.5 g/d (mean) and 7.5 g/d (90th percentile) for users (age 2 years and older) of such products. The increase of the maximum use concentration of α-CD in soft drinks from 1% to 1.05% would increase these values by not more than about 0.1-0.2 g/d.

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9 In comparison to the estimated daily α-CD intakes of 11.4 g for the mean and 19.8 g for the 90th percentile consumer, which were regarded to be GRAS as per GRN 000155, here the projected intakes are about 2-times higher.

10 According to GRN 000155, α-CD is intended to be used in beverage mixes, diet soft drinks, fruit juices, instant coffee, instant tea, and formula diets at a level of 1% (beverage as consumed) and in vegetable juices as well as soy and non-soy imitation milk at a level of 2%.
(5) Intake of α-CD from its combined use in processed and ultra-processed foods and in certain types of beverages

The intakes of α-CD from its use in solid foods and semi-solid foods on the one hand in certain types of beverages on the other hand are additive.

For the mean adult consumer, an α-CD intake of 16.7 g/d would result from its use at the highest intended concentration in all processed and ultra-processed foods and an intake of 3.6 g/d would result from its use in the specified types of beverages. For the 90\textsuperscript{th} percentile adult consumer, an α-CD intake of 29.4 g/d from all processed and ultra-processed food and 7.9 g/d from specified beverages is estimated.

Quite clearly, these are hypothetical figures which in reality will never be attained because there exists other ingredients available that may substitute for α-CD in formulating certain types of food and beverages. In some corresponding earlier cases, market share adjustments have therefore been made and were accepted in some GRAS Notices [e.g., for D-psicose (10% share) in GRN 000400, isomaltulose (5-10% share) in GRN 000184, etc.]. However, while the market reality demonstrates the existence of competition among food additives of similar functionality, the estimation of market shares is somewhat speculative and is, therefore, not applied in this report.

The presented intake estimates of α-CD pertain to adult consumers. This raises the question about the projected intakes among children. Since the fractional consumption of processed and ultra-processed is similarly high (but not higher) in children and since the energy intake per kg body weight is also not much higher than in adults, the α-CD intake on a per kg body weight basis is expected to also be similar. Only for beverages (soft drinks) a slightly higher intake (on a per body weight basis) may be expected. On the other hand, it should be recognized that α-CD is not absorbed as such but is, like most other soluble dietary fibers, degraded by the intestinal microbiota to common end-products of fermentation. Therefore, there is no systemic exposure to α-CD and a comparative estimation of intakes per kg body weight for children vs. adults would be quite misleading. Any concern about an "over-consumption" of α-CD among children from the intended uses of α-CD is, therefore, not warranted.
Part 4 – Self-limiting levels of use

The levels at which α-CD would become self-limiting are above the levels specified in Table 1 in Part 1 of this notice.
Part 5 – Experience based on common use in food before 1958

Because the statutory basis for our conclusion of GRAS status is not through experience based on common use in food, our notice does not include evidence of a substantial history of consumption of the notified substance for food use by a significant number of consumers prior to January 1958.
Part 6 – Narrative

(1) Introduction

Alpha-CD is a cyclic oligomer consisting of six glucose units joined "head-to-tail" by α-1,4-glycosidic bonds. It is produced from food-grade starch by means of cyclodextrin glycosyltransferase ("CGTase"), an amylolytic enzyme which hydrolyzes the amylose molecule and at the same time ties the resulting oligomers to a ring. Alpha-CD formed in this way is separated from the reaction mixture by complexation with 1-decanol, isolation of the insoluble complex, disintegration of the recovered complex at elevated temperature in the presence of water, re-precipitation of the complex, removal of 1-decanol from the recovered complex by steam stripping and isolation of α-CD from the aqueous phase by crystallization. Alpha-CD is produced in accordance with current Good Manufacturing Practice (cGMP) for food ingredients and complies with the Food Chemicals Codex ("FCC") monograph for α-CD.

Wacker introduced α-CD as a food ingredient in the U.S. food market in 2005 after having received a “no further questions” letter from FDA in response to its GRAS notice, GRN 000155 (FDA, 2004)(Appendix 2). The conditions under which the use of α-CD was generally recognized as safe for the first time, based on scientific procedures, are specified in GRN 000155 and the FDA's subsequent reply (FDA, 2004). These uses comprise the then expected application of α-CD for the fiber supplementation of foods and beverages and its use as carrier or stabilizer for flavors (i.e., as a flavor adjuvant), carrier, stabilizer or solubilizer of colors, vitamins and fatty acids as well as for improving the ‘mouthfeel’ of beverages. The maximum levels of α-CD considered at that time for defined categories of processed foods were shown in Section 3 (b) of GRN 000155. The FDA’s response letter to GRN 000155 is attached to this report as Appendix 2 for reference.

In early 2012, interest arose in the use of α-CD as flavor adjunct, i.e., as carrier and stabilizer of flavors, in certain types of food that were not covered by GRN 000155. The use level of α-CD as flavor adjunct was given with ≤ 750 mg/kg food (as consumed). The range of foods in which the use of flavors with α-CD was considered feasible comprised any type of processed food except:

(a) liquid foods, i.e., beverages which were already contained in GRN 000155 (i.e., diet soft drinks, beverage mixes, fruit juices, instant coffees and teas, vegetable juices, soy milk and non-soy (imitation) milk, soups and milk beverage mixes), and
(b) foods with a standard that would preclude the use of added flavors or α-CD as a flavor adjunct.
The foods in which α-CD was intended to be used as a flavor adjunct were, therefore, described collectively as “solid foods” and “semi-liquid foods such as yogurts, frozen dairy desserts, sauces, and relishes”, i.e., any processed food other than liquid foods as described above under item (a).

For assessing the safety of these additional potential uses of α-CD, Wacker convened a panel of scientific experts, to assess the safety of α-CD as a flavor adjunct in foods. The maximum additional intake of α-CD that would result from its use as a flavor adjunct in foods other than liquid foods was estimated at not more than 0.75 and 1.4 g/d for the 70-kg mean and 90th percentile consumer, respectively. This estimated additional intake of α-CD was considered small in comparison to the estimated daily intakes of 11.4 g for the mean and 19.8 g for the 90th percentile consumer that were calculated from food consumption data of the 1994-1996 and 1998 Continuing Surveys of Food Intakes by Individuals and that were considered GRAS as per GRN 000155. Based on the assessment of the pivotal, then publicly available safety studies of α-CD and considering that single (bolus) α-CD doses of 10 - 25 g α-CD were well tolerated by adult human subjects, the proposed additional uses of α-CD as a flavor adjunct in foods other than liquid foods were considered to be generally recognized as safe based on scientific procedures.

(2) Safety assessment of α-CD used as an ingredient of processed and ultra-processed foods (other than beverages) at a level of up to about 3% (in food as consumed) and in certain types of beverages at a level of up to about 1.05% (as consumed)

A substantial body of evidence is available for the safety assessment of α-CD as a food ingredient. The pivotal, publicly available safety studies have been reviewed earlier by Wacker’s GRAS Expert Panel (Anderson et al., 2004) and authoritative food safety assessment bodies (WHO, 2002, 2005; FSANZ, 2004; EFSA, 2007). Since then, additional studies with α-CD have been published. The pertinent studies were retrieved from a comprehensive search of the scientific literature conducted through March 16, 2016 and their results are included in this report.

Investigations on the metabolic fate of ingested α-CD demonstrate that α-CD is not digested to glucose in the GI-tract to any relevant degree; i.e., its disposition in the GI tract is similar to that of other soluble dietary fibers (Diamantis & Bär, 2002; van Ommen et al., 2004).
The toxicity of α-CD was examined in standard in-vitro and in-vivo toxicity tests including cytotoxicity\textsuperscript{11} and genotoxicity tests, subchronic (3-month) oral toxicity studies in rats (Lina & Bär, 2004a) and dogs (Lina & Bär, 2004b), and oral embryotoxicity/teratogenicity studies in mice, rats and rabbits (Price et al., 1996; NTP, 1994a, b; Waalkens-Berendsen & Bär, 2004; Waalkens-Berendsen et al., 2004). α-CD was administered with the daily diet to rats and mice at dietary concentrations of up to 20% and to dogs at concentrations of up to 5%. In all these studies, α-CD was well tolerated and did not elicit adverse effects.\textsuperscript{12}

The human intestinal tolerance to oral doses of α-CD was demonstrated in a study on the glycemic impact of a single dose of α-CD. In this study, twelve healthy, fasted, 23–24 year old, male volunteers consumed a bolus dose of 25 g α-CD together with 100 g white bread without experiencing any untoward intestinal effects (Diamantis & Bär, 2002). In other human studies in which the effects of α-CD on the glycemic impact of starch or sucrose were examined, single bolus doses of 2–10 g α-CD were similarly well tolerated (Jarosz et al., 2013; Buckley et al., 2006; Gentilcore et al., 2011). The tolerance to repeated oral doses of α-CD was demonstrated by two studies with α-CD intakes of 6 g/d for periods of 2 months in healthy adults (Comerford et al., 2011) and 3 months in obese diabetic subjects (Grunberger et al., 2007) and in one study at intakes of 30 g/d for 7 days (Park et al., 2012).

An interaction of ingested α-CD with the absorption of soluble vitamins or other lipophilic nutrients is not expected because the cavity of the α-CD molecule is too small to accommodate molecules of this size. Furthermore, there is direct evidence for the absence of complex formation of α-CD with vitamins D\textsubscript{3}, E and K\textsubscript{1} from an in-vitro experiment (Okada et al., 1988). An interference with the absorption of other lipophilic nutrients is also not expected because ingested α-CD will efficiently be degraded by the intestinal microbiota.

The intake of α-CD of 29.4 g/d that would result for the 70-kg, “heavy” (i.e., 90\textsuperscript{th} percentile) consumer from its proposed use as an ingredient in processed and ultra-processed foods (excluding beverages) at the technologically maximally feasible level of 3% is higher than the 90\textsuperscript{th} percentile intake (19.8 g/day for the “heavy”

\textsuperscript{11} The results of recent tests of the in-vitro cytotoxicity of α-CD and its derivatives on Caco-2 cells and human erythrocytes and on immortalized murine microvascular endothelial cells are in line with the results of earlier similar studies that have been taken into consideration in previous safety assessments of α-CD already (Roka et al., 2015; WHO 2002; EFSA, 2007; FSAZ, 2004).

\textsuperscript{12} A recent study in which dogs received α-CD in two daily doses of 6 g α-CD each provides further support for the gastrointestinal tolerance of this substance (Guevara et al., 2015).
consumer) that has been determined to be "generally recognized as safe" in GRN 000155. However, this higher intake is still within the range of α-CD single doses (≤ 15 g) and daily doses (≤ 30 g) that were well tolerated by adult human subjects.

Thus, the pivotal, publicly available safety studies in animals and tolerance studies in humans of α-CD demonstrate that the proposed uses of α-CD as an ingredient in processed and ultra-processed foods (excluding beverages) and in certain types of beverages as described in Table 1 in Part 1 of this GRN do not present a risk to human health.

(3) Conclusions

In summary, the GRAS determination based on scientific procedures of the proposed uses of α-CD as an ingredient of processed and ultra-processed food as defined herein (but excluding infant foods) at levels of up to 3% (in the foods as consumed) and in certain specified types of beverages at a concentration of up to 1.0–1.05% relies on:

(1) the nature of α-CD – a soluble dietary fiber in the form of a cyclic oligomer of six units of glucose that is not absorbed from the gastro-intestinal tract (it is degraded by intestinal microbiota to usual end-products of fermentation); and

(2) published animal toxicity studies and human tolerance studies.

It is further supported by the corresponding conclusion of internationally recognized experts, e.g., FAO/WHO (JECFA) ("ADI not specified"), EFSA, and FSANZ. Finally, an independent panel of scientific experts, qualified by training and experience to evaluate the safety of food ingredients, concluded that under the conditions of intended use in foods, Wacker’s α-CD is GRAS through scientific procedures. The panel’s opinion is included at Appendix 3.
Part 7 – List of supporting data and information


Appendix 1
Relation between body weight and energy flux in US adults 
[energy flux = total energy expenditure (TEE) measured by the 
doubly labeled water technique]. (Pearson's correlation $r = 0.65$, $P < 0.0001$; $n = 1399$). Black line: linear regression 
(Swinburn et al., 2009). Red line: Energy expenditure = 50 
kcal/kg bw (inserted by authors of this report).
Appendix 2
Diane McColl
Hyman, Phelps & McNamara, P.C.
700 Thirteenth Street, N.W.
Suite 1200
Washington, D.C. 20005-5929

Re: GRAS Notice No. GRN 000155

Dear Ms. McColl:

The Food and Drug Administration (FDA) is responding to the notice, dated June 25, 2004, that you submitted on behalf of Wacker Chemical Corporation (Wacker) in accordance with the agency’s proposed regulation, proposed 21 CFR 170.36 (62 FR 18938; April 17, 1997; Substances Generally Recognized as Safe (GRAS); the GRAS proposal). FDA received the notice on June 28, 2004, filed it on June 30, 2004, and designated it as GRAS Notice No. GRN 000155.

The subject of the notice is alpha-cyclodextrin. The notice informs FDA of the view of Wacker that alpha-cyclodextrin is GRAS, through scientific procedures, for use in selected foods for fiber supplementation, as a carrier or stabilizer for flavors (flavor adjuvant), colors, vitamins and fatty acids, and to improve mouth-feel in beverages. These uses are described in Table 1.

Table 1
Food categories and use levels for alpha-cyclodextrin
## Food category

<table>
<thead>
<tr>
<th>Food category</th>
<th>Maximum use level (percent)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Breads, rolls, cakes, baking mixes, refrigerated dough</td>
<td>5</td>
</tr>
<tr>
<td>Brownies and bars</td>
<td>7</td>
</tr>
<tr>
<td>Crackers (sweet and non-sweet)</td>
<td>10</td>
</tr>
<tr>
<td>Diet soft drinks, beverage mixes, fruit juices, instant coffees and teas,</td>
<td>1</td>
</tr>
<tr>
<td>coffee whiteners (dry), formula diets, meal replacements, and nutritional</td>
<td></td>
</tr>
<tr>
<td>supplements</td>
<td></td>
</tr>
<tr>
<td>Vegetable juices, soy milk and non-soy (imitation) milk</td>
<td>2</td>
</tr>
<tr>
<td>Ready-to-eat breakfast cereals</td>
<td>2 to 9*</td>
</tr>
<tr>
<td>Instant rice, pasta, and noodles (prepared)</td>
<td>2</td>
</tr>
<tr>
<td>Condiments</td>
<td>3</td>
</tr>
<tr>
<td>Reduced fat spreads</td>
<td>20</td>
</tr>
<tr>
<td>Dressings and mayonnaise</td>
<td>5</td>
</tr>
<tr>
<td>Yogurt, milk beverage mixes, and frozen dairy desserts</td>
<td>2.5</td>
</tr>
<tr>
<td>Pudding mixes (dry)</td>
<td>1</td>
</tr>
<tr>
<td>Snack foods</td>
<td>1</td>
</tr>
<tr>
<td>Canned and dry soups (prepared)</td>
<td>2</td>
</tr>
<tr>
<td>Hard candy</td>
<td>15</td>
</tr>
<tr>
<td>Chewing gum</td>
<td>10</td>
</tr>
</tbody>
</table>

* The notifier states that use level in ready-to-eat cereals will vary based on weight of serving size (i.e., if less than 20 g/cup the level is 2 percent; 20-43 g/cup the level is 9 percent; greater than or equal to 43 g/cup the level is 5 percent).

As part of its notice, Wacker reports that a panel of individuals (Wacker's GRAS panel) has evaluated the data and information that are the basis for Wacker's GRAS determination. Wacker considers the members of its GRAS panel to be qualified by scientific training and experience to evaluate the safety of substances added to food. Wacker's GRAS panel report discusses the following information concerning alpha-cyclodextrin: 1) the manufacturing process and specifications; 2) estimated daily intake; 3) absorption, distribution, metabolism, and excretion; 4) published toxicological studies conducted in animals; 5) published studies that concern cellular and genetic effects; and 6) published studies conducted with humans. Wacker's GRAS panel concludes that, based on scientific procedures, alpha-cyclodextrin meeting appropriate food grade specifications and manufactured in accordance with current good manufacturing practices, is GRAS under the conditions of intended use.

The alpha-cyclodextrin is intended for use in selected solid, semi-liquid, and liquid foods. According to the notifier, alpha-cyclodextrin has nutritional properties similar to fermentable dietary fiber, is stable under food processing conditions, and has a low viscosity in aqueous solutions. Structurally, alpha-cyclodextrin is shaped like a hollow truncated cone or torus. The
cavity of alpha-cyclodextrin is hydrophobic and the outer surface is hydrophilic. Alpha-cyclodextrin is water soluble and can form inclusion complexes with lipophilic substances. The formation of reversible inclusion complexes is the basis for alpha-cyclodextrin applications.

Alpha-cyclodextrin (CAS Registry No. 10016-20-3), also known as cyclohexa-amylose, cyclomalto-hexose or alpha-dextrin, has an empirical formula of \((\text{C}_{6}\text{H}_{10}\text{O}_{5})_{6}\) and molecular weight of 973 Daltons. Structurally, alpha-cyclodextrin is a cyclic polymer of six alpha-1,4-linked glycopyranosyl units.

The notifier describes their manufacturing process for alpha-cyclodextrin. In the first step of alpha-cyclodextrin production, food-grade, liquefied starch is treated with a cyclodextringlycosyltransferase (CGTase, EC 2.4.1.19, CAS 9030-09-5) under controlled pH and temperature conditions. The CGTase is obtained from a recombinant strain of *Escherichia coli* K12, harboring the CGTase gene of *Klebsiella oxytoca*. Alpha-cyclodextrin is precipitated from the enzymatic reaction mixture by addition of 1-decanol. The precipitate is further purified by dissolution in water and re-precipitation. The 1-decanol is separated from alpha-cyclodextrin by decantation and steam distillation. The final alpha-cyclodextrin product is obtained by crystallization and is a white powder with a purity of ≥ 98.0 percent. The notifier provides additional specifications including limits on the maximum levels of volatile organic compounds, heavy metals, and lead (less than 0.5 parts per million).

Using the foods and use levels summarized in Table 1 and the two day consumption data from the United States Department of Agriculture (USDA) Continuing Survey of Food Intakes by Individuals 1994-96, 98 (CSFII), the notifier calculated an estimate of the daily intake (EDI) of alpha-cyclodextrin. The notifier estimates the mean and 90th percentile intake (users only and of all age groups combined) of alpha-cyclodextrin from the intended uses in Table 1 (except chewing gum) to be 11.4 and 19.8 g/person/day. The calculation also includes a mean "per eating occasion" intake of 3.9 g/person. The notifier used a separate survey on chewing gum use in the United States to provide an additional EDI for alpha-cyclodextrin ingested from chewing gum as 0.9 g/person/day.

The notifier reports that the Joint FAO/WHO Expert Committee on Food Additives (JECFA) evaluated alpha-cyclodextrin in June 2001 for technological uses in food. On the basis of the available safety studies on alpha-cyclodextrin and studies on the related beta- and gamma-cyclodextrin, JECFA allocated an Acceptable Daily Intake (ADI) of "not specified" for alpha-cyclodextrin. The notifier reports that the 63rd meeting of JECFA in 2004 also determined an ADI of "not specified" for alpha-cyclodextrin.

Wacker's GRAS panel discusses published studies regarding absorption, distribution, metabolism, excretion, bioavailability, toxicity and mutagenicity conducted with alphacyclodextrin in humans and various animal species. In summary, alpha-cyclodextrin is not digested by the mammalian digestive enzymes; however, it is completely fermented by the intestinal microbiota. Less than 1 percent of the alpha-cyclodextrin is absorbed; however, this amount is not metabolized and is excreted unchanged in the urine. Two 13-week toxicity studies with rats and dogs provide no evidence for adverse reactions in the gastrointestinal tract, the kidneys, the liver or any other organs or tissues at alpha-cyclodextrin intakes of up to 20 percent of the diet (13 g/kg bw/day in rats and 10 g/kg bw/day in dogs). The notifier states that the EDI calculations indicate that the intake of alpha-cyclodextrin per eating occasion (3.9 g/person) would be below the doses that were tolerated by adult volunteers who experienced no side-effects (10 g/person) or minimal intestinal symptoms (25 g/person). Based on these studies, the GRAS panel concludes that alpha-cyclodextrin is safe for its intended uses.
Based on the information provided by Wacker, as well as other information available to FDA, the agency has no questions at this time regarding Wacker's conclusion that alpha-cyclodextrin is GRAS under the intended conditions of use. The agency has not, however, made its own determination regarding the GRAS status of the subject use of alpha-cyclodextrin. As always, it is the continuing responsibility of Wacker to ensure that food ingredients that the firm markets are safe, and are otherwise in compliance with all applicable legal and regulatory requirements.

In accordance with proposed 21 CFR 170.36(f), a copy of the text of this letter, as well as a copy of the information in the notice that conforms to the information in proposed 21 CFR 170.36(c)(1), is available for public review and copying on the homepage of the Office of Food Additive Safety (on the Internet at http://www.cfsan.fda.gov/~lrd/foodadd.html).

Laura M. Tarantino, Ph.D.
Director
Office of Food Additive Safety
Center for Food Safety and Applied Nutrition

(1) The lead specification is a maximum level of 0.5 ppm; however, batch analysis records included in GRN 000155 indicate a lead level of less than 1 ppm. FDA notes that a maximum lead level of 1 ppm is within the specifications described in the Food Chemicals Codex (5th edition) for beta- and gamma-cyclodextrin.

(2) ADI 'not specified' is used to refer to a food substance of very low toxicity which, on the basis of the available data (chemical, biochemical, toxicological and other) and the total dietary intake of the substance arising from its use at the levels necessary to achieve the desired effects and from its acceptable background levels in food, does not, in the opinion of the Committee, represent a hazard to health. For that reason, and for the reasons stated in the individual evaluations, the establishment of an ADI expressed in numerical form is not deemed necessary. An additive meeting this criterion must be used within the bounds of good manufacturing practice, i.e. it should be technologically efficacious and should be used at the lowest level necessary to achieve this effect, it should not conceal food of inferior quality or adulterated food, and it should not create a nutritional imbalance.
Expert Panel Consensus Statement concerning the Generally Recognized as Safe (GRAS) status of alpha-Cyclodextrin for Use in Processed and Ultra-processed Foods and Certain Beverages Based on Scientific Procedures

Prepared for:
Hyman, Phelps & McNamara, P.C.
700 Thirteenth Street NW, Suite 1200
Washington, D.C. 20005

April 08, 2016
1. INTRODUCTION

The undersigned, an independent panel of experts qualified by their scientific training and national and international experience to evaluate the safety of food and food ingredients (the "Expert Panel"), was specially convened by Wacker Chemical Corp. (formerly Wacker Biochem Corp.) and asked to evaluate the safety and Generally Recognized as Safe (GRAS) status of alpha-cyclodextrin (hereinafter "alpha-CD") for general use in processed and ultra-processed foods as defined herein (excluding beverages) at levels of up to 3%, and in certain specified types of beverages at concentrations up to 1.05%.

Pivotal, publicly available safety studies were critically reviewed previously by Wacker's GRAS Expert Panel (Anderson et al., 2004) and authoritative food safety assessment bodies (WHO, 2002, 2005; FSANZ, 2004; EFSA, 2007). At the request of Wacker, Albert Bár Ph.D. performed a comprehensive search of the scientific literature through 16 March 2016 relating to the safety/toxicity and dietary intake/consumption of alpha-CD and summarized the results of the pertinent studies and other information for consideration by the Expert Panel in a dossier, "Alpha-Cyclodextrin", dated March 2016. The Expert Panel critically evaluated that summary and other available data and information believed to be pertinent to the safety of alpha-CD under the intended conditions of use.

Following an independent, critical and collaborative evaluation of the data and information, the Expert Panel independently and jointly unanimously concluded that Wacker's alpha-CD, manufactured consistent with current Good Manufacturing Practice (cGMP) and meeting appropriate food-grade specifications, is safe and Generally Recognized As Safe (GRAS) based on scientific procedures for use in processed and ultra-processed foods as defined herein (but excluding beverages) at levels up to 3% in the foods as consumed, and in certain specified types of beverages as consumed at a concentration up to 1.05% of alpha-CD.
2. BACKGROUND

Wacker's GRN 000155 (submitted on 25 June 2004) provided the FDA with a summary of the basis for Wacker's GRAS determination for the then-intended uses of alpha-CD. The safety of these uses of alpha-CD was supported by data on its absorption, distribution, metabolism and excretion. The toxicological studies included acute toxicity studies in mice and rats, subchronic oral toxicity studies in rats and dogs, embryotoxicity/teratogenicity studies in mice, rats and rabbits, standard genotoxicity tests, and a study in humans which provided data on the gastrointestinal tolerance of 25-g single doses of alpha-CD. Data on the safety of 1-decanol were also considered because trace amounts of this processing aid may be present in alpha-CD (not more than 20 ppm as per FCC specifications).

Detailed reports of the pivotal safety studies on which the Panel based its report are publicly available (Lina & Bår 2004a, b; Waalkens-Berendsen & Bår, 2004; Waalkens-Berendsen et al., 2004).

Following review of Wacker's GRAS Notice (GRN 000155), FDA issued a response letter (22 December 2004) stating that the agency had no questions regarding Wacker's conclusion that the intended uses of alpha-CD described in the GRAS Notice are GRAS based on scientific procedures (FDA, 2004).

The safety of alpha-CD has also been critically reviewed and summarized by the Joint FAO/WHO Expert Committee on Food Additives ("JECFA") which allocated an ADI "not specified" on two separate occasions for alpha-CD for use as a food-technological additive and as a nutritive substance (dietary fiber) resulting in an estimated daily intake of alpha-CD of 11.4 and 19.8 g/d for the mean and 90th percentile consumer, respectively (WHO, 2002, 2005). Food Standards Australia/New Zealand (FSANZ) performed its own safety assessment of alpha-CD (FSANZ, 2004), confirmed JECFA's ADI "not specified" and authorized alpha-CD as a novel food in Australia/NZ.

The latest assessment of the safety of alpha-CD was conducted by the European Food Safety Authority (EFSA) (EFSA, 2007). The EFSA Panel also concluded that there are no safety concerns for the consumption of alpha-CD which was subsequently authorized as a novel food without limitations of use by the European Commission (Commission Decision 2008/413/EC). As of March 16, 2016, no data were identified in the scientific literature that would conflict with EFSA's conclusion on the safety of alpha-CD.
3. EXPANDED USE OF ALPHA-CD IN PROCESSED AND ULTRA-PROCESSED FOODS

In view of proposed new applications of alpha-CD in foods that are not covered by GRN 000155 and considering the more flexible authorization of alpha-CD as a novel food in the European Union, Wacker requested the Expert Panel to assess the safety of the use of alpha-CD in any kind of processed and ultra-processed foods (except beverages) at levels of up to 3% and in certain specified beverages at concentration of up to 1.05%.

Based on publicly available data on the consumption of defined processed and ultra-processed foods in the US (Baraldi et al., 2013; Moubarac et al., 2013) coupled with published data on (a) the food intake per kg bw for the 290th percentile of US consumers (Swinburn et al., 2009), (b) an average energy density of 2 kcal/g food (other than beverages) (Hansen 1979; Kant & Graubard, 2005), and (c) an approximately 80:20 ratio of energy intake from foods and beverages (Duffey & Popkin, 2007), the intake of alpha-CD from its combined use in all processed and ultra-processed foods at a level of 3% was estimated at 420 mg/kg bw/d or 29.4 g/d for the 90th percentile consumer with a body weight of 70 kg. The additionally proposed use of alpha-CD in beverages specified in GRN 000155 at a level of 1.05% would result in an estimated alpha-CD intake of 7.5 g/d for the 90th percentile consumer of such beverages (calculation based on intake data presented in GRN 000155).

Single doses of 25 g and repeated doses of 2 x 15 g/d alpha-CD for 7 days were well tolerated by humans (Diamantis & Bär, 2002, Park et al., 2012). The weight of evidence including extensive toxicological data and human data and the opinions of international experts including JECFA, FSANZ AND EFSA, support the safety of the intended uses of alpha-CD.
4. CONCLUSION

We, the Expert Panel, have individually and collectively critically evaluated published and unpublished data and information pertinent to the safety of Wacker’s alpha-CD summarized in a dossier ("Alpha-Cyclodextrin") and other information deemed pertinent, and unanimously conclude that Wacker’s alpha-CD, produced consistent with current Good Manufacturing Practice (cGMP) and meeting appropriate food-grade specifications, is safe for use as an ingredient for general use in processed and ultra-processed foods as defined herein (but excluding beverages) at levels up to 3% in the foods as consumed, and in certain specified types of beverages as consumed at a concentration up to 1.05%.

We further conclude that the proposed use of Wacker’s alpha-CD is Generally Recognized As Safe (GRAS) based on scientific procedures for use as an ingredient for general use in processed and ultra-processed foods as defined herein (but excluding beverages) at levels up to 3% in the foods as consumed, and in certain specified types of beverages as consumed at a concentration up to 1.05%.

It is our opinion that other qualified experts would concur with these conclusions.

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Virginia Commonwealth University School of Medicine  
Richmond, Virginia  

Robert Nicolosi, Ph.D.  
Professor Emeritus Department of Clinical Laboratory & Nutritional Sciences,  
UMass Lowell, Lowell MA 01075

1 The Expert Panel considered the safety, but not the suitability, of the proposed use of alpha-CD as an ingredient in processed and ultra-processed meat and poultry products.
REFERENCES


