

Notification

**NEW DIETARY INGREDIENT – PREMARKET NOTIFICATION**

**December 1, 2004**

**1. MANUFACTURER/DISTRIBUTOR-**

**Distributor**

ArtJen Complexus Holdings Corp.  
510 Westcourt Place  
251 Goyeau Street  
Windsor, Ontario N9E 2T2  
Canada

**Manufacturers**

**Raw Material:**

Wacker Biochemical Corporation  
3301 Sutton Road  
Adrian MI 49221

**Finished Products:**

**Tablets:**

Nutricorp International  
A Division of Jamieson Laboratories  
4025 Rhodes Drive  
Windsor, Ontario N8W 5B5  
Canada

**Chewable Tablets:**

Archon Vitamin Corporation  
209 40<sup>th</sup> Street  
Irvington, NJ 07111

**2. NAME OF NEW DIETARY INGREDIENT-**

$\alpha$ -Cyclodextrin – Chemical Abstract Service (CAS) number [10016-20-3] - This material is manufactured by and purchased by us in bulk from Wacker Biochemical Corporation, 3301 Sutton Road, Adrian MI 49221. It is of note that Wacker is the world's major producer of "pure"  $\alpha$ -cyclodextrin. A copy of correspondence from Wacker confirming GMP compliance is included in Appendix A.

Appendix A contains a copy of a Wacker document that identifies this material as Cavamax W6®, which is their registered name for  $\alpha$ -cyclodextrin. This same document details the product specifications. In addition we have enclosed in Appendix A, a copy of a certificate of analysis for this material indicating that Wacker's delivered product may exceed their published specifications. In

addition we have enclosed in Appendix A copies of Wacker's procedures for the analysis of their  $\alpha$ -cyclodextrin.

We will market our tablets and chewable tablets under the Trade Name "FBCx™", the only active ingredient in these tablets will be  $\alpha$ -cyclodextrin [10016-20-3] obtained from Wacker Biochemical or other comparable source should one become available.

$\alpha$ -Cyclodextrin is a cyclic oligosaccharide consisting of  $\alpha$ -(1,4)-linked D-glucopyranose units. Like  $\beta$ - and  $\gamma$ -cyclodextrin,  $\alpha$ -cyclodextrin is naturally occurring and is produced commercially, in the case of Wacker Biochemical, by the enzymic action of cyclodextrin glucosyltransferase on corn starch.

### 3. Description of the Supplement-

The supplement will be in the form of tablets and/or chewable tablets. Each tablet will contain 1,053mg of  $\alpha$ -cyclodextrin. Chewable tablets will contain 2,000mg of  $\alpha$ -cyclodextrin. Our production-run tablets completely dissolve within 11 minutes and our chewable tablets are specified to release all of their  $\alpha$ -cyclodextrin within 5 minutes.

- i. Each tablet will contain 1,053mg of  $\alpha$ -cyclodextrin. Chewable tablets will contain 2,000mg of  $\alpha$ -cyclodextrin. The composition of each tablet is listed below in Table 1, manufactured by Nutricorp International, a division of Jamieson Laboratories, Windsor, ON Canada (Appendix B):

**Table 1. – Composition of Tablets**

Ingredient	Mass/Tablet (mg)	Example From Inactive Ingredient List
$\alpha$ -Cyclodextrin	1,053	
Dicalcium phosphate	348.6	007789777~378.78~MG
Microcrystalline Cellulose	160	009004346~1385.3~MG
Sodium Croscarmellose	16	TABLET~180~MG
Vegetable magnesium stearate	16	000557040~400.74~MG
Calcium silicate	6.4	007778189~170~MG
Hypromellose (hydroxypropylmethylcellulose)	16	009004653~60~MG
Polyethylene glycol	2.4	009004960~12.5~MG
Carnauba wax	1.2	008015869~300~MG

The composition of each chewable tablet is listed below in Table 2, manufactured by Archon Vitamin Corporation, Irvington, NJ.

**Table 2. – Composition of Chewable Tablets**

Ingredient	Mass/Tablet (mg)	Example From Inactive Ingredient List (mg)
$\alpha$ -Cyclodextrin	2,000	
Croscarmellose Sodium	80	TABLET~180~MG
Aspartame	10	053906697~65~MG
Stearic Acid	50	000057114~187.5~MG
Magnesium Stearate	10	000557040~50~MG
Silicon Dioxide	10	007631869~37.5~MG

The tablet and chewable tablet formulations as well as a copy of Jamieson's (Nutricorp's) Health Canada Establishment License and Archon's State of New Jersey GMP Certificate are included in Appendix B.

Prior to release of the tablets either Nutricorp or Archon is responsible for the quality control of their finished product, including microbiology testing.

ii It is recommended by us that persons consuming a normal or high fat containing diet who wish to decrease or maintain their body weight take, orally, two 1g tablets or one 2g chewable tablet within one hour, before, after or during the consumption of a fat containing meal; a total of approximately 6g of active ingredient per day. By our experimentation (1-3) this amount of  $\alpha$ -cyclodextrin is sufficient to reduce the bioavailability of 54g or approximately one-half of a normal adult's daily dietary fat intake. In the absence of dietary fat the  $\alpha$ -cyclodextrin passes through the small intestine and into the large intestine where it is metabolized by the micro flora as are, by definition, all soluble dietary fibers.

#### 4. Evidence of Safety-

Please find a listing of evidence below; copies of these documents have been attached in Appendix C:

- i. Joint FAO/WHO Expert Committee on Food Additives, Fifty-seventh meeting, Rome, 5-14 June 2001. Establishes that the *Acceptable Daily Intake* of  $\alpha$ -cyclodextrin is *Not Specified*.
- ii. Joint FAO/WHO Expert Committee on Food Additives, Sixty-third meeting, Geneva, 8-17 June 2004. This is a reevaluation of the data supplied by the manufacturer (Wacker). The levels of consumption are based in part upon our studies and confirms that the *Acceptable Daily Intake* of  $\alpha$ -cyclodextrin is *Not Specified*.
- iii. Correspondence by McColl, Diane B. of Hyman, Phelps & McNamara, P.C., to Gimber, Christian of Wacker Chemical Co.- This document

confirms that an independent panel of qualified scientific experts concluded, based upon scientific procedures, that  $\alpha$ -cyclodextrin is GRAS (Generally Recognized As Safe). This self affirmation is, according to personal communication with Wacker Biochemical, at a level of 20g/day and considers the levels that we propose to use. Note that this correspondence post dates our Patent Cooperation Treaty application (3) and all of our prior art identified in that application. Our intended uses and levels were identified in that application as well as our prior art listed in that application.

- iv. A discussion of scientific, peer-reviewed studies conducted in various animal species and human tissue culture follows; copies of these articles are attached in Appendix C:

#### **Safety Assessment of Published and Unpublished Data-**

- i. The attached document *Joint FAO/WHO Expert Committee on Food Additives, Fifty-seventh meeting, Rome, 5-14 June 2001* establishes that in the opinion of the FAO/WHO that  $\alpha$ -cyclodextrin at low doses, consistent with typical "carrier/preservative" type uses, is safe for human consumption to a *Not Specified* level.
- ii. The attached document *Joint FAO/WHO Expert Committee on Food Additives, Sixty-third meeting, Geneva, 8-17 June 2004*, is yet to be published in its entirety, however, we are given to understand (verbal communication) that this reevaluation of the data was precipitated by our disclosures that there are significant human health benefits from the consumption of  $\alpha$ -cyclodextrin as a food additive at levels sufficient to complex a portion of the fat consumed by humans in the average day. These levels, based upon an average North American diet, far exceed the 6 grams per day that we recommend. Please note that this document post dates our Patent Cooperation Treaty application (3) and all of our prior art identified in that application. Our intended uses and levels were identified in that application as well as our prior art listed in that application.
- iii. We have found (1-3) that growing male Wistar rats fed a high fat diet containing  $\alpha$ -cyclodextrin at a rate of 10% of the amount of fat in their diet gained weight at a rate that was identical to the control group consuming a normal fat-containing diet. In addition we found that at this low level of consumption that the  $\alpha$ -cyclodextrin ([10016-20-3] from Wacker Biochemical) elicited beneficial effects to the animal's blood lipid, insulin and leptin levels. Blood glucose levels remained unchanged. No adverse effects related to the inclusion of dietary  $\alpha$ -cyclodextrin were seen in any of our test animals. From these studies we have concluded that 6g of  $\alpha$ -cyclodextrin, distributed amongst fat-containing meals, taken orally each day will aid in human weight loss at a rate of approximately 1-1.5lbs per week with no deleterious side effects.

- iv. In human ciliary cell culture studies (4), designed to evaluate the effects of various cyclodextrins as drug carriers,  $\alpha$ -cyclodextrin was found to have no effect on ciliary beat frequency at what we would consider to be a high concentration of 2% (w/v). In addition the authors report that little effect was seen at levels below 5% (w/v). Even if we ignore the volume of food and water consumed by the average human on an average day, the small intestine receives 7-9 liters of water (5). Two percent of 7 liters would equate to 140g of  $\alpha$ -cyclodextrin or 23 times more than we recommend ingesting with fat-containing foods. The 5% figure quoted by the authors as exhibiting *mild to moderate and partially reversible effects* would necessitate the consumption of at least 280g or 46 times our recommend levels.
- v. Bär (6) states that  $\alpha$ -cyclodextrin is virtually indigestible by either salivary or pancreatic amylase but is metabolized by intestinal flora thus  $\alpha$ -cyclodextrin has the properties of a soluble dietary fiber. As there is no intestinal transport mechanism for  $\alpha$ -cyclodextrin, the fact that it is resistant to enzymic hydrolysis means that it will not be absorbed. The word “virtually” by definition allows for some small amount of hydrolysis to occur. It must be remembered that  $\alpha$ -cyclodextrin is a glucose polymer so that any hydrolysis that does occur will produce a linear oligosaccharide that would be subject to normal amylase digestion. In addition Bär concludes that  $\alpha$ -cyclodextrin may be safely incorporated into foods at *nutritionally significant levels* and that  $\alpha$ -cyclodextrin *has potential for use as a fully fermentable dietary fiber*. Although not defined, one could assume that these levels far exceed those used to stabilize additives or carry pharmaceuticals and are, at least, in the range that we propose to use.
- vi. Lina and Bär (7) studied the effects of  $\alpha$ -cyclodextrin (>98% purity) from Wacker-Chemie GmbH, parent company of Wacker Biochemical, on dogs. Using the same material that we propose using, this investigation involved animals receiving 0, 5, 10 and 20% (w/w) in their food for 13 weeks. At the 10 and 20% percent levels some reversible changes were seen in the size of the cecum and colon without any histological changes and consistent with consuming a non-digestible yet fermentable dietary fiber. The authors conclude that the No Adverse Effects Level (NOAEL) are 9.8 and 10.4 g  $\alpha$ -cyclodextrin/kg bw/day for male and female dogs respectively. This suggests  $\alpha$ -cyclodextrin is safe for a human male to consume approximately 784g of  $\alpha$ -cyclodextrin per day while a human female could safely consume 624g/day, Table 3. These levels are 104-130 times the level that we recommend for daily use. This study was funded by Wacker-Chemie GmbH. We conclude that this is strong evidence for the safety of  $\alpha$ -cyclodextrin from Wacker Biochemical at the levels that we propose for daily consumption.
- vii. Lina and Bär (8) studied the effects of  $\alpha$ -cyclodextrin (>98% purity) from Wacker-Chemie GmbH, parent company of Wacker Biochemical, on rats.

Using the same material that we propose using, this investigation involved two studies. The first four-week study was range finding. The second thirteen-week study established the NOAEL of 12.6g/kg bw/d for males and 13.9g/kg bw/d for females. Average human males and females would have to consume 1,008 g and 834g, respectively, per day to attain these levels. This is 139-168 times the levels that we recommend for daily use. This study was funded by Wacker-Chemie GmbH. We conclude that this is strong evidence for the safety of  $\alpha$ -cyclodextrin from Wacker Biochemical at the levels that we propose for daily consumption.

- viii. Van Ommen *et al.* (9) studied the absorption, distribution and metabolism of  $^{14}\text{C}$ - $\alpha$ -cyclodextrin in germ-free rats.  $^{14}\text{C}$ -labelled  $\alpha$ -cyclodextrin was prepared through the use of cyclodextrin glucosyltransferase to a purity of >99% (by HPLC), as does Wacker Biochemical. The unlabeled  $\alpha$ -cyclodextrin was supplied by and the research funded by Wacker Wacker-Chemie GmbH. By intravenous injection of  $^{14}\text{C}$ - $\alpha$ -cyclodextrin they found that  $\alpha$ -cyclodextrin is rapidly excreted unchanged from the blood stream by the kidneys,  $t_{1/2} = 26\text{min}$  for male and 21min for female rats. In addition to urine excretion, a minor amount, approximately 1.5% of the injected labeled material, appeared in the intestinal contents, suggesting the possibility of excretion either through bile or salivary secretions. These authors found no evidence of metabolism of  $\alpha$ -cyclodextrin by mammalian enzymes. They did find a small amount, approximately 2% of the total  $^{14}\text{C}$  label, in the blood in the form of  $^{14}\text{C}$  glucose; they were unable to rule out the possibility that  $^{14}\text{C}$  glucose was produced in the synthesis of the  $^{14}\text{C}$ - $\alpha$ -cyclodextrin. They found small amounts of  $^{14}\text{C}$  label in exhaled  $^{14}\text{CO}_2$  as well as some deposited in various organs. Van Ommen *et al.* attributed this to the microbial digestion of the small amount of material that found its way into the intestines. By administering labeled  $\alpha$ -cyclodextrin by gavage to germ-free rats and monitoring exhaled  $^{14}\text{CO}_2$  the authors found that there was almost no digestion of  $\alpha$ -cyclodextrin by mammalian enzymes. Conversely, in normal rats they found considerable amounts of  $^{14}\text{CO}_2$  in the breath and no  $^{14}\text{C}$ - $\alpha$ -cyclodextrin in the feces, indicating that the micro flora of the large intestine completely ferments  $\alpha$ -cyclodextrin. The authors conclude from these experiments that approximately 1% of the oral dose of  $\alpha$ -cyclodextrin that was administered to these rats was absorbed and subsequently rapidly eliminated by the kidneys. The authors conclude that, "*Overall, the metabolic fate of ingested  $\alpha$ -CD ( $\alpha$ -cyclodextrin) resembles, therefore, that of other naturally occurring, non-digestible yet fermentable glucans, such as resistant starch.*" From this rather large set of experiments we can conclude that  $\alpha$ -cyclodextrin ingested by humans would not be metabolized in the small intestine by human enzymes, rather it would be passed on to the large intestine and metabolized by the micro flora as are other soluble fibers. We conclude that this is strong evidence for the safety of  $\alpha$ -cyclodextrin from Wacker Biochemical at the levels that we propose for daily consumption.

- ix. Waalkens-Berendsen and Bär (10) studied the embryotoxicity and teratogenicity of  $\alpha$ -cyclodextrin ( $\geq 98\%$  purity) supplied by Wacker-Chemie GmbH. This study was funded by Wacker-Chemie GmbH. In this study pregnant Wistar rats were given  $\alpha$ -cyclodextrin in their food throughout their gestation at several levels up to 20% (w/w) of their solids; this equates to about 13g/kg bw/day. The authors concluded that there was no maternal toxicity, fetotoxicity, embryotoxicity or teratogenicity exhibited by the study animals and their offspring. The level of 13g/kg bw/day equates to a pregnant human consuming 780g/day or about 130 times the level that we recommend for non-pregnant females. It is of note that as weight gain is a normal part of pregnancy that we do not advise taking  $\alpha$ -cyclodextrin at all while pregnant. However, from this study we can conclude that there would be no harm caused if a pregnant human inadvertently ingested  $\alpha$ -cyclodextrin at our recommended levels during their pregnancy. We conclude that this is strong evidence for the safety of  $\alpha$ -cyclodextrin from Wacker Biochemical at the levels that we propose for daily consumption.
- x. Waalkens-Berendsen, Smits-van Prooijje and Bar (11) studied the embryotoxicity and teratogenicity of  $\alpha$ -cyclodextrin ( $>98\%$  purity) supplied by Wacker-Chemie GmbH. This study was funded by Wacker-Chemie GmbH. In this study pregnant New Zealand White rabbits were given  $\alpha$ -cyclodextrin in their food at several levels up to 20% (w/w) of their solids from day 0 to 29 of their pregnancy. 20% of solids represents about 5.9-7.5g/kg bw/day. The authors concluded that there was no maternal toxicity, adverse effects on maternal reproductive performance, fetotoxicity, embryotoxicity or teratogenicity exhibited by the study animals and their offspring. The levels of 7.5 g/kg bw/day equates to a pregnant human consuming 450g/day or about 75 times the level that we recommend for non-pregnant females. It is of note that as weight gain is a normal part of pregnancy that we do not advise taking  $\alpha$ -cyclodextrin at all while pregnant. However, from this study we can conclude that there would be no harm caused if a pregnant human inadvertently ingested  $\alpha$ -cyclodextrin at our recommended levels during their pregnancy. We conclude that this is strong evidence for the safety of  $\alpha$ -cyclodextrin from Wacker Biochemical at the levels that we propose for daily consumption.

With reference to articles above, Table 3 compares the amount of  $\alpha$ -cyclodextrin that was fed to various animal species and extrapolates that level to a “normal” adult human.

**Table 3 – Comparison of Amounts of  $\alpha$ -Cyclodextrin Fed to Various Animal Species**

Ref.	% $\alpha$ -CD In Diet	Food Intake	Body wt	$\alpha$ -Cyclodextrin	$\alpha$ -CD (g/day/human)
(7)	20%	0.55 kg/day male 0.50 kg/day female Species=Dog	13.0 kg 10.5 kg	NOAEL: 9.8 g/ $\alpha$ -CD kg bw/d male 10.4 female	784 g /day/80 kg male 624 g /day/60 kg female
(8)	20%	95.4 g/male/week 85.4 g/female/wk Species=Rat	187 g 158 g	NOAEL: 12.6 g/kg bw/d male, 13.9 female	1,008 g /day/80 kg male 834 g /day/60 kg female
(10)	20%	65.2 g/kg wt/day/rat (pregnant)	320 g	13.0 g/kg wt/day	782 g /day/60 kg female
(11)	20%	121 g/rabbit/day (pregnant)	4140 g	7.5 g/kg bw/day	450 g /day/60 kg female

$\alpha$ -CD:  $\alpha$ -Cyclodextrin

NOAEL: No adverse effects level

#### Conclusions:

Based upon all of the above data as well as our inability to find contradictory data we believe that  $\alpha$ -cyclodextrin is safe for human consumption as a dietary supplement at or above the levels that we propose for our products.

#### References:

1. Brogan, K., Artiss, J., Brucal, M., Moghaddam, M., and Jen, K-L.C. (2004). Effects of a new soluble dietary fiber on body weight regulation in rats. Obes Res 12:A110.
2. Artiss, J.D., Brogan, K., Brucal, M., Moghaddam, M., and Jen, K-L.C. (2004). The effects of a new soluble dietary fiber on weight gain and selected blood parameters in rats. Submitted to Int J Obes.
3. Jen, C and Artiss, JD. “Compositions comprising dietary fat complexer and methods for their use”. US and PCT application filed July 29, 2003. WO 2004/016101.
4. Agu, R., M. Jorissen, et al. (2000). "Safety assessment of selected cyclodextrins - effect on ciliary activity using human cell suspension culture model exhibiting vitro ciliogenesis." Int J Pharmaceu 193: 219-226.
5. Fox SI. Human Physiology, Eighth Edition, 2004, page 574. McGraw-Hill, NY, NY.
6. Bär, A. (2004). "Preface." Reg Toxicol Pharmacol 39: S1-S2.
7. Lina, B. and A. Bär (2004). "Subchronic (13-week) oral toxicity studies of a-

cyclodextrin in dogs." Regul Toxicol Pharmacol **39**: S27-S33.

8. Lina, B. and A. Bär (2004). "Subchronic oral toxicity studies with  $\alpha$ -cyclodextrin in rats." Regul Toxicol Pharmacol **39**: S14-S26.
9. Van Ommen, B., A. DeBie, et al. (2004). "Disposition of  $^{14}\text{C}$ -cyclodextrin in germ-free and conventional rats." Regul Toxicol Pharmacol **39**: S57-S66.
10. Waalkens-Berendsen, D. and A. Bär (2004). "Embryotoxicity and teratogenicity study with  $\alpha$ -cyclodextrin in rats." Regul Toxicol Pharmacol **39**: S34-S39.
11. Waalkens-Berendsen, D., A. Smits-van Prooije, et al. (2004). "Embryotoxicity and teratogenicity study with  $\alpha$ -cyclodextrin in rabbits." Regul Toxicol Pharmacol **39**:S40-S46.