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Original Submission

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September 15, 1999

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

Based on Sec. 170.36 Notice for a claim for exemption based on a GRAS determination, we are submitting the following information regarding the use of cetylpyridinium chloride (CPC) as an antimicrobial treatment for various food products. This particular use of CPC is exempt from the premarket approval requirements of the Federal Food, Drug, and Cosmetic Act because the notifier has determined that such use is GRAS. The following documentation follows the outline for submitting a "Notice of a claim for exemption based on GRAS determination."

Sincerely,

Curtis W. Coleman
President, Safe Foods Corporation

Dr. Amy L. Waldroup
Professor

1999 SEP 21 A 8:50

1999 SEP 20 P 5:22

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Part I. Claim for Exemption (actual form code (c) (1))

- 1). Name and Address of Notifier: Mr. Curtis W. Coleman, President, Safe Foods Corporation, 1505 Rebsamen Park Road, Little Rock, AR 72202-1857.
- 2). Common or Usual Name of the Substance: Cetylpyridinium chloride or CPC.
- 3). Conditions of Use: CPC will be used to treat various types of raw and fully cooked food products. This may include: poultry, red meat, fish and shellfish, eggs, fruits, vegetables, cereal grains, nutmeats, and dairy products. Regardless of food type, the level of CPC to be utilized will not exceed 1.0%, and will in most cases not exceed 0.5%. CPC will be utilized as an antimicrobial treatment to control pathogens of concern including *Salmonella*, *Campylobacter*, *Listeria*, *E. coli*, and *Shigella*.

A high percentage of the population already consumes this substance in mouthwashes, mouthrinses, and throat lozenges. Basically, all portions of the population could consume this substance either in the previously described applications, or from foods treated with CPC.

- 4). Basis for GRAS Determination: Scientific Procedures.
- 5). Data and Information: The data and information that are the basis for this application of cetylpyridinium chloride for GRAS status are available for the Food and Drug Administrator's (FDA) review and copying at reasonable times. The data and information can be obtained from Mr. Curtis W. Coleman, President, Safe Foods Corporation at 1505 Rebsamen Park Road, Little Rock, AR 72202-1857, phone: (501) 663-2383 or cwcoleman@safefoods.net.

Part II. Identity of Substance (actual form code (c) (2))

- 1). Chemical Name: cetylpyridinium chloride.
- 2). Chemical Abstract Service (CAS) Registry Number: 6004-24-6.
- 3). Empirical Formula: $C_{21}H_{38}N \cdot Cl$.
- 4). Structural Formula:

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5). Quantitative Composition: $C_{21}H_{38}N \cdot Cl$ has a formula weight of 340.05; $C_{21}H_{38}N \cdot Cl \cdot H_2O$ has a formula weight of 358.07; and $C_{21}H_{40}ClNO$ has a molecular weight of 358.01 and a mass of 339.99. Calculated elemental content is C: 70.45%; H: 11.26%; Cl: 9.90%; O: 4.47%; and, N: 3.91%.

6). Method of Manufacture: CPC can be prepared by the interaction of cetyl chloride and pyridine under pressure at an elevated temperature. In aqueous solution, CPC is synthesized by alkylation of pyridine with cetyl chloride to yield the monohydrate of the quaternary salt of pyridine and cetyl chloride.

Part III. (actual form code (c) (3))

1). Self-limiting Levels of Use: Not Applicable.

Part IV. (actual form code (c) (4))

A. Scientific Procedures (actual form code (c) (4) (i) (A))

1). Safety and Probable Consumption: CPC has been safely used in mouthwashes, rinses and throat lozenges since 1940 (Huyck, 1944). In the draft of the Dental Plaque Subcommittee Report (FDA, 1998) it is stated that "cetylpyridinium chloride at concentrations of 0.045 to 0.1% with minimally 72 to 77% chemically available cetylpyridinium chloride is safe and effective for use in mouthrinse formulations as an over-the-counter antigingivitis, antiplaque agent." In this claim of exemption, no greater than 1.0% CPC will be used to treat various foodstuffs. This does not mean that treated foods will contain 1.0% CPC. This simply implies that the food item may come in contact with less than or equal to 1.0% CPC. Assuming 100% uptake of CPC by a treated food, the actual level of CPC in any food should never exceed 880 mg/kg or 0.88 g/kg.

Using residual data from the literature that is specific for poultry and catfish treated with 0.1 or 0.4% CPC, residual levels of CPC in this foods is likely to be in the range of 17.8 to 33.3 mg/kg (Compadre *et al.*, 1998). When diluted in the typical volume of gastrointestinal fluid, this amount of CPC will be below the amount required for the reduction of bacteria such as *E. coli* (Compadre *et al.*, 1996). Moreover, the routine use of CPC lozenges has not been implicated in altering gastrointestinal microflora. If a person were to consume the maximum recommended dose of CepacolTM lozenges in a day (12 lozenges), approximately 0.6 g or 600 mg of CPC would be consumed. If a person was to use one of the many available mouthwashes, like ScopeTM or ActTM, once a day, then 0.014 g or 14 mg of CPC (this calculation utilizes a 20% accidental swallowing rate which is common) would be consumed each day. In comparison, if 25% of all the red meat, poultry, fish, and shellfish consumed in this country were treated with 1.0% CPC, a typical person would consume approximately 535 to 1000 mg (0.5 to 1 g) of this chemical annually. This would equate to taking 20 CepacolTM lozenges per year or gargling 72 times in a year. For treatment of fruits and vegetables, the absorption rate of CPC should be negligible due to the extreme lipophilic properties of this chemical.

B. (Actual form code (c) (4) (i) (B))

1). Inconsistent Reports: There are no reports of investigations of other information that appear to be inconsistent with GRAS determination.

C. (Actual form code (c) (4) (i) (C))

1). Based on the information provided in sections above (c) (1), (c) (2), (c) (3), (c) (4) (i) (A), and (c) (4) (i) (B), there is consensus among experts qualified by scientific training and experience to evaluate the safety of substances, including CPC, added to food and there is reasonable certainty that the substance is not harmful under the intended conditions of use as specified in this claim of exemption.

Part V. CPC as an Antimicrobial Agent (not a required section of exemption)

CPC is a quaternary ammonia compound that has been safely used in some commercially available mouthwashes, throat sprays, and throat lozenges (0.045 to 1.4% CPC) for over 20 years (Barnes *et al.*, 1976; Ciancio *et al.*, 1978; Ashley *et al.*, 1984; Frost and Harris, 1994). In these types of products CPC is added to provide protection against plaque and gingivitis.

According to Huyck (1944), CPC inhibits bacterial metabolism through the formation of weakly ionized compounds from the interaction of basic cetylpyridinium ions with the acid groups of bacteria. In solution, as little as 0.002% CPC applied at room temperature resulted in close to a 90% reduction in *Salmonella typhimurium* (Breen *et al.*, 1995). There are, however, conflicting reports regarding the effects of CPC on bacterial attachment, specifically attachment of *Salmonella typhimurium*, to chicken skin (Breen *et al.*, 1995; Kim and Slavik, 1996). Breen *et al.* (1995) stated that CPC was "extremely effective at both inhibiting and reversing attachment of viable *S. typhimurium* cells to chicken skin." However, Kim and Slavik (1996) used scanning electron micrographs to show that "CPC does not detach cells from chicken skin."

Application of CPC to Poultry. In the first reported study of CPC application to poultry skin (Breen *et al.*, 1995), a 10-minute pretreatment of chicken skin with 0.1% CPC at 77° F diluted with 0.008 M buffered phosphate saline at pH 7.2 "completely inhibited the attachment of *Salmonella typhimurium*." The same treatment concentration and exposure time at 95° F, resulted in an 84% reduction in attachment. In these trials, 2.5 cm² (1 square inch) chicken drumstick skin samples were treated with 5 ml of various concentrations of CPC ranging from 0 to 0.1%. Considering this volume of treatment solution per skin surface area (5 ml/2.5 cm²), and utilizing the equations for surface area of poultry carcasses (Thomas, 1978), it was determined that approximately 1.3 gallons of CPC solution would be required per processed chicken. It should be noted that in these trials the CPC was not mixed with any other chemical prior to treatment, as is the case in later studies conducted by these and other researchers.

In later studies it was reported that a 3-minute treatment with 0.4% solution of CPC plus 5% glycerin in 0.008M buffered phosphate saline at pH 7.2 to *Salmonella*-inoculated chicken drumstick skin resulted in a 4.8 log reduction in *Salmonella typhimurium* (Breen *et al.*, 1997). It was observed that when CPC was used in concentrations greater than 0.1% the CPC would quickly precipitate. The addition of 5.0% glycerin to the antimicrobial treatment serves to keep the CPC in solution. These researchers also stated that pretreatment of chicken skin with CPC could reduce carcass to carcass cross contamination during poultry slaughter because a 10-minute application of 0.8% CPC to chicken drumstick skin prevented bacterial attachment. In these studies the temperature of the CPC solution was not reported and each 2.5 cm² (1 square inch) skin sample was treated with 5 ml of CPC solution. Again, this would equate to using approximately 1.3 gallons of CPC solution per processed chicken carcass.

In a study conducted by Kim and Slavik (1996), CPC was evaluated for effectiveness in removing and/or killing attached *Salmonella typhimurium* on chicken skin. In this study the authors sprayed or immersed chicken skin samples in 0.1% CPC. Spray application was at either 59° F or 122° F for 1 minute. Immersion treatments were applied at room temperature for 1 minute, 1 minute plus 2 minutes "rest" time, or 3 minutes. Spraying, regardless of treatment temperature, resulted in 87 to 98% reduction in salmonellae levels. The amount of spray per unit of skin surface area was not reported. Immersion treatments, regardless of application time, resulted in salmonellae reductions similar to those noted for the spray applications. In the immersion treatments, 2.5 ml CPC solution was applied to 10 cm² skin samples. At this application rate, this would equate to approximately 21 ounces (0.16 gallon) per processed chicken carcass.

In trials conducted at the University of Arkansas pilot poultry processing plant prechill carcasses obtained from a local commercial facility were treated with 10 to 12 ounces (0.08 to 0.09 gallon) of 0.2% or 0.5% CPC applied at room temperature in an on-line mist cabinet (30 seconds followed by 2 minute rest period). This application would follow the inside-outside bird washer in a commercial facility, and would be applied in the same manner as an acidified sodium chlorite product (SanovaTM, Alcide Corp., Redmond, WA) which is presently approved and utilized as an antimicrobial treatment in some poultry plants. These same concentrations (0.2% and 0.5%) were also evaluated as a prechill dip (immersion) for 10 seconds at room temperature. All CPC treatments, regardless of application method or concentration, significantly reduced aerobic plate count (APC), *E. coli*, other coliforms, and *Campylobacter* on postchill broilers (Brown and Waldroup, 1999, unpublished data). The 0.5% CPC dip resulted in the greatest reductions in all groups of organisms. For this treatment there was a 99.7% reduction in APC, and a > 99.9% reduction in *E. coli*, other coliforms and *Campylobacter*. In fact, *E. coli*, other coliforms, and *Campylobacter* could not be recovered from any of the chicken carcasses dipped in 0.5% room temperature CPC for 10 seconds.

In a second trial conducted in the same pilot processing facility, a 0.5% CPC 10-second room temperature prechill dip resulted in a 99.3% reduction in APC, *E. coli* and other coliforms could not be recovered from chilled carcasses (Waldroup *et al.*, 1999, unpublished data). A 10-second room temperature mist application of 0.5% CPC resulted

in a 92% reduction in APC with greater than 90% reductions in *E. coli* and other coliforms. Mist applications at 0.75% and 1.0% CPC further reduced microbial levels to 99% for APC and 93% for *E. coli* and other coliforms. There was no statistical improvement in reductions in APC, *E. coli* or coliforms when the CPC concentration in the mist application was increased from 0.75% to 1.0%.

In the trial just described, all prechill carcasses were inoculated with 30,000 *Salmonella typhimurium* cells prior to the prechill dip or mist treatments. At postchill, more than 75% of control carcasses were still positive for *Salmonella*. No *Salmonella* could be recovered from carcasses treated with CPC, regardless of concentration or method of application. This finding supports the *Salmonella* inhibition studies in the literature (Breen *et al.*, 1995; 1997; Kim and Slavik, 1996). It should be noted, however, that there are some findings in the present study that needs further explanation. Our laboratory traditionally enumerates *Salmonella typhimurium* by standard dilution and direct plating. This practice is consistent with methods used in all the previous published studies with CPC and chicken skin. When this is done, there is a lower detection level associated with the assay. In the two studies conducted by Breen *et al.*, (1995 and 1997), the lower detection level for *Salmonella typhimurium* was not published but is calculated to be 32 cfu/ml in the 1995 study and 5 cfu/ml in the 1997 study. In the 1996 study conducted by Kim and Slavik (1996), the lower detection level was not reported and can not be calculated using the information in the manuscript. In every study reported there was no preenrichment to allow for recovery of sublethally stressed cells. In fact, in the latter study the samples were direct plated on XLD agar which is highly selective for *Salmonella*, but inhibitory to sublethally stressed cells.

In our recent studies, we direct-plated for *Salmonella typhimurium*, but also allowed the entire whole carcass rinse fluid (400 ml) to preenrich for 24 hours, and then streak-swabbed the enriched sample. This allowed for a lower detection level of <1 cfu/ml for samples which are not positive by direct plating, but which are positive after overnight enrichment. Using this procedure we recovered 50 to 100% *Salmonella typhimurium* from the same samples. Thus, if the direct-plated samples are negative, but the 24-hour enriched original sample is positive for *Salmonella*, then one can conclude that at least one organism was recovered in the whole carcass rinse. This organism then had 24 hours to replicate to sufficient levels to allow for detection. One might argue that preenrichment gives the organism every chance at recovery, but this is how the USDA/FSIS *Salmonella* samples are being assayed. Current *Salmonella* performance standards are based on incidence, not level, of *Salmonella*, and one cell will result in a positive sample.

Our most recent study was conducted in a commercial broiler processing facility over a three-day period. Postchill broilers were sprayed with room temperature 0.4% CPC for 2 to 3 seconds. In this commercial trial APC, *E. coli*, other coliforms and *Campylobacter* were significantly reduced by the CPC treatment by 99.3%, 87.1%, 86.0%, and 99.4%, respectively. Incidence of *Salmonella* in the control group of carcasses was 17% and in the treated group of carcasses was 14%.

Application of CPC to Other Foods. Cutter and Dorsa (1998) used 1.0% CPC to treat beef samples. These authors reported complete removal of *Salmonella typhimurium* and *E. coli* O157:H7 from beef treated with a fecal slurry containing these organisms. Even after 35 days of refrigerated storage, vacuum packaged beef samples which had been initially treated with 1.0% CPC were free of these two pathogens. The authors reported no adverse organoleptic properties as determined by flavor, color, and texture of the cooked product.

Catfish skins (2.5 cm² or 1.0 square inch) were treated for 3 minutes with 5 ml of CPC ranging in concentration from 0.0% to 0.8% (Compadre *et al.*, 1998). Regardless of CPC concentration all treatments contained 5.0% glycerin and were diluted in 0.008 M phosphate buffer saline. Prior to antimicrobial treatment, catfish skin samples were inoculated with *Listeria monocytogenes*. At CPC concentrations of 0.2% and higher, *Listeria monocytogenes* could not be recovered from the skins, equating to a 3.67 log reduction in initial levels. However, there was no attempt in the methodology to recover any sublethally injured cells or to determine if there was a measurable amount of residual CPC in the microbial assay.

References:

Ashley, F.P., A. Skinner, P. Jackson, and R.F. Wilson, 1984. The effect of a 0.1% cetylpyridinium chloride mouth rinse on plaque and gingivitis in adult subjects. *Br. Dent. J.* 157:191-195.

Barnes, G.P., D.W. Roberts, R.V. Katz, and J.D. Woolridge, 1976. Effects of two cetylpyridinium chloride-containing mouthwashes on bacterial plaque. *J. Periodontol.* 47:419-422.

Breen, P.H., C.M. Compadre, E.K. Fifer, H. Salari, D.C. Serbus, and D.L. Lattin, 1995. Quaternary ammonium compounds inhibit and reduce the attachment of viable *Salmonella typhimurium* to poultry tissues. *J. Food Sci.* 60:1191-1196.

Breen, P.J., H. Salari, and C.M. Compadre, 1997. Elimination of *Salmonella* contamination from poultry tissues by cetylpyridinium chloride solutions. *J. Food Prot.* 60:1019-1021.

Ciancio, S.G., M.L. Mather, and R.D.H. Bunnell, 1978. The effect of a quaternary ammonium-containing mouthwash on formed plaque. *Pharmacol. Therapeut. Dent.* 3:1-6.

Compadre, C.M., P.J. Breen, H. Salari, X. Zhou, and A. Handie, 1998. Pre-commercialization studies of cetylpyridinium chloride as an antimicrobial agent for the treatment of food products. *Proc. Food Safety Consortium*, pp. 15-27.

FDA, 1998. Draft Dental Plaque Subcommittee Report on Cetylpyridinium Chloride. Food and Drug Administration, Center for Drug Evaluation and Research, Division of OTC Drug Products (HFD-560), 9201 Corporate Blvd., Rockville, MD 20850.

Frost, M.R. and M.P.W. Harris, 1994. An in vitro study to assess the efficacy of antiplaque agents in mouthwash formulations. *Microbios* 79:101-108.

Huyck, C.L., 1944. Cetylpyridinium chloride. *Am. J. Pharm.* 116:50-59.

Kim, J.W., and M.F. Slavik, 1996. Research note: Cetylpyridinium chloride (CPC) treatment on poultry skin to reduce attached *Salmonella*. *J. Food Prot.* 59:322-326.

Thomas, N.L., 1978. Observations of the relationship between the surface area and weight of eviscerated carcasses of chickens, ducks and turkeys. *J. Food Technol.* 13:81-86.

Cutter, C.N., and W.J. Dorsa, 1998. Antimicrobial activity of chlorine washes against pathogenic bacteria on beef surfaces. *Reciprocal Meat Conference Proc.* Page 51.

End Submission

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Pages 000078. 000081-000091, 000093-000102, 000105 – 000108 not included.



AM



September 23, 1999

Dr. Linda Kahl
Office of Premarket Approval
FDA - Center for Food Safety
200 C St. S.W.
Washington, DC 20204

Dear Dr. Kahl,

Enclosed are four copies of Safe Foods Corporation's amended first page of our self-affirmed GRAS petition. The change was made according to your phone conversation with Curtis Coleman.

Please let me know if there is anything else I can do to help you.

Thank you,

U
Kathryn Coleman
enclosure

1999 SEP 24 P 3:26

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Part I. Claim for Exemption (actual form code (c) (1))

- 1). Name and Address of Notifier: Mr. Curtis W. Coleman, President, Safe Foods Corporation, 1505 Rebsamen Park Road, Little Rock, AR 72202-1857.
- 2). Common or Usual Name of the Substance: Cetylpyridinium chloride or CPC.
- 3). Conditions of Use: CPC will be used to treat various types of raw and fully cooked food products. This may include: poultry, red meat, fish and shellfish, eggs, fruits, vegetables, cereal grains, nutmeats, and dairy products. Regardless of food type, the level of CPC to be utilized will not exceed 1.0%, and will in most cases not exceed 0.5%. CPC will be utilized as an antimicrobial treatment to control pathogens of concern including *Salmonella*, *Campylobacter*, *Listeria*, *E. coli*, and *Shigella*.

A high percentage of the population already consumes this substance in mouthwashes, mouthrinses, and throat lozenges. Basically, all portions of the population could consume this substance either in the previously described applications, or from foods treated with CPC.

- 4). Basis for GRAS Determination: Scientific Procedures.
- 5). Data and Information: The data and information that are the basis for this application of cetylpyridinium chloride for GRAS status are available for the Food and Drug Administrator's (FDA) review and copying at reasonable times, or the information will be sent to the FDA upon the Agency's request. The data and information can be obtained from Mr. Curtis W. Coleman, President, Safe Foods Corporation at 1505 Rebsamen Park Road, Little Rock, AR 72202-1857, phone: (501) 663-2383 or cwcoleman@safefoods.net.

Part II. Identity of Substance (actual form code (c) (2))

- 1). Chemical Name: cetylpyridinium chloride.
- 2). Chemical Abstract Service (CAS) Registry Number: 6004-24-6.
- 3). Empirical Formula: $C_{21}H_{38}N \cdot Cl$.
- 4). Structural Formula:

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1999 OCT 13 P 3: 11

October 12, 1999

Dr. Linda Kahl
Office of Premarket Approval
Food and Drug Administration
1110 Vermont Avenue, N. W.
Washington, DC 20201

Dear Dr. Kahl:

First, thank you for your gracious assistance and direction regarding the submission of our GRAS notification for cetylpyridinium chloride as used in Cecure®.

I have a somewhat unusual request. As you may know, Safe Foods Corporation acquired the rights to the patents for Cecure from the University of Arkansas for Medical Sciences in Little Rock. Dr. Harry P. Ward is Chancellor of the University. FDA Commissioner Dr. Jane Henney, who is one of Dr. Ward's close friends, is speaking in Little Rock on October 28 at a symposium at which Dr. Ward will be specially honored.

At that event we would like for Dr. Henney to be able to present to Dr. Ward a letter from the FDA advising Safe Foods Corporation and the University of Arkansas for Medical Sciences of its receipt and acceptance of the GRAS notification which has been submitted.

Please let me know if I may be of assistance in any way in facilitating this.

Thank You and Best Regards.

Curtis W. Coleman
President and CEO

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Dec. 30, 1999

CW Coleman @ Safe Foods . net

David. Zeitz @ USDA. GOV

VIEW OR CHANGE THE FILE

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File: CWCOLEMA NOTE
Dr. Martin:

I hope this finds you having enjoyed a very Blessed Christmas and a happy holiday season!

We need to meet with you and Dr. David Zeitz and the other members of the committee with which we last met last summer as soon as possible, preferably between now and January 16 if at all possible.

Our requested agenda:

- (1) What is necessary to establish Cecure(TM) (the CPC formulation) as an "antimicrobial" (in contrast to a "food processing aid")?
- (2) What is necessary to gain approval for Cecure(TM) for automatic online reprocessing in poultry processing plants?
- (3) What is necessary to gain "food additive" status for Cecure(TM)?

We expect that 1 1/2 hours will be adequate for the meeting. Our party will

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VIEW OR CHANGE THE FILE

C10

File: CWCOLEMA NOTE

We expect that 1 1/2 hours will be adequate for the meeting. Our party will include:

Dr. Amy Waldroup, University of Arkansas
Dr. Jim Marsden, Kansas State University
Mrs. Kathryn Coleman, Safe Foods Corporation
Curtis Coleman, Safe Foods Corporation

Please let me know how I may be of assistance to facilitate such a meeting. We will, of course, be glad to adjust our schedule as much as possible to accommodate yours and the committee's.

Thank you again for your always courteous and gracious assistance,

Curtis Coleman

c: Dr. David Zeitz

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January 10, 2000

Robert L. Martin, Ph.D.
Supv. Consumer Safety Officer
Division of Petition Control
Direct Additives Branch (HFS-217)
Center for Food Safety and Applied Nutrition
Food and Drug Administration
200 C. Street SW
Washington, DC 20204

Andrew D. Laumbach, Ph.D.
Division of Petition Control, HFS-215
Office of Premarket Approval
Center for Food Safety and Applied Nutrition
Food and Drug Administration
200 C Street SW
Washington, D. C. 20204

VIA FACSIMILE: 202-418-3131
CONFIRMED Federal Express Priority Letter

RE: GRAS Notice (GRN) No. 000031

Dear Dr. Martin and Dr. Laumbach:

Please accept this request to immediately withdraw our GRAS notification submitted 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), and designated by the FDA as GRN No. 000031. Please also confirm your acceptance of our request and the withdrawal of this notification.

Thank You and Best Regards,

Curtis W. Coleman
President and CEO

c: Dr. David Zeitz
Dr. Amy Waldroup

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