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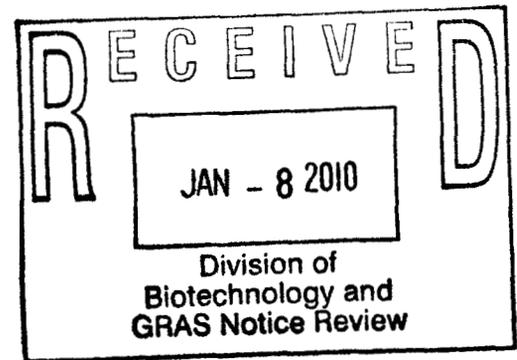
000001

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January 7, 2010

Via E-mail and Overnight Mail

Dr. Robert L. Martin
Office of Food Additive Safety (HFS-255)
Center for Food Safety and Applied Nutrition
Food and Drug Administration
University Station Building
4300 River Road, Room 2045
College Park, MD 20740-3835



Re: GRAS Notification for Arginine When Used in Solution Containing other approved GRAS Substances for Addition to Pork and Poultry

Dear Dr. Martin:

Oh behalf of our client, Dr. Ranzel Nickelson, II (the “Notifier”), we submit this letter in triplicate to notify the U.S. Food and Drug Administration (“FDA”) of the Notifier’s conclusion that the use of arginine as set forth in this document is exempt from the premarket approval requirements applicable to food additives¹ under the Federal Food, Drug, and Cosmetic Act (“FDC Act”), 21 U.S.C. § 301 *et seq.*, because such use is generally recognized as safe (“GRAS”). 21 C.F.R. § 170.30. We also include an additional copy for FDA to forward onto USDA’s Food Safety and Inspection Service (“FSIS”).

A GRAS Notification for arginine for use a brine solution for addition to meats (pork and beef) and poultry was previously submitted May 4, 2009. FDA had no questions with the conclusion that arginine is GRAS for use as an ingredient in brine solution to be injected into beef subprimals or mixed with ground beef to form beef patties. See FDA “No Questions” Letter (November 2, 2009), GRAS Notice No. GRN 290. We understand from conversations with FDA that FDA desired to make its response to GRAS Notice No. GRN 290 consistent with a separate FSIS suitability petition, and thus, FDA did not explore the pork and poultry question in its review of GRAS Notice No. GRN 290. This present GRAS notification revives the use of arginine in pork and poultry. All of the information contained in this GRAS notification is substantively the same as that submitted in connection with GRAS Notice No. GRN 290, including the clarifications to FDA’s questions submitted on

¹ 21 U. S.C. § 348(b)-(f).

Dr. Robert L. Martin
Office of Food Additive Safety (HFS-255)
Food and Drug Administration
January 7, 2010
Page 2

August 7, 2009. We note that a suitability petition for the use of arginine in pork and poultry will be submitted to FSIS, and we encourage FDA and FSIS to coordinate their reviews.

I. Name and Address of the Notifier

Ranzell "Nick" Nickelson II, Ph.D.
455 Sansom Blvd
Saginaw, TX 76179
817-821-7133 office
817-249-7951 fax

II. Common or Usual Name of the Substance

The common or usual name for the substance is "L-Arginine."² This document will refer to the substance as "arginine."

III. Intended Use

Arginine will be added via a brine solution to pork and poultry. The solution will contain arginine and other approved GRAS substances and will be injected into the pork and poultry to enhance the flavor, tenderness, and juiciness of the pork/poultry. The scope of this petition includes pork and poultry.

IV. Basis for the GRAS Determination

The Notifier concludes that arginine is generally recognized as safe for the intended use outlined in this document through scientific procedures.

V. Availability of Data and Information

The data and information that are the basis for the GRAS determination are available for CFSAN's review and copying at reasonable time at Dr. Nickelson, 455 Sansom Blvd, Saginaw, TX 76179, or, upon request, can be sent to CFSAN for review.

² See Food Chemicals Codex, 6th Ed. (2008-2009), L-Arginine (Attachment 1).

Dr. Robert L. Martin
Office of Food Additive Safety (HFS-255)
Food and Drug Administration
January 7, 2010
Page 3

VI. Identity, Manufacturing Process, and Specifications of Arginine

The arginine meets the specifications set forth in the FCC. Suppliers would assure that the arginine meets FCC specifications through a letter of guaranty and certificate of analysis.³

VII. Self-Limiting Levels of Use

The Notifier uses food-grade arginine in a brine solution, which is comprised of arginine and other approved GRAS substances. Arginine is added at 0.2-0.6% (depending on muscle type and desired pump level).⁴ The % values are measured by dry weight. The solution is made under current good manufacturing processes.

As there is some cost associated with arginine, the Notifier has made every effort to insure that minimum levels are used to achieve desired results. Thus, the minimum amount of arginine is added to achieve the intended results.

The amount of brine injected (pumped) into pork/poultry ranges from 10-20% based on the initial weight of the pork/poultry. That is, if the initial weight of the pork/poultry is 100 g, then 10-20 g of the brine solution is injected into the pork/poultry. Pork/poultry are injected with a chilled solution to desired pump level. The solution is added to the ground pork/poultry at 6-8% prior to forming into patties. For ground pork/poultry, the solution is added directly by pouring it into the final blender prior to forming. Note, the focus of the GRAS Notification is the arginine and not the brine solution.

In laboratory evaluations of different levels and concentrations, the Notifier developed a model using fresh ground pork/poultry. 50 grams of ground pork/poultry was weighed, blended for 15 seconds, and then filtered for 15 minutes. The filtrate is measured and compared to a water control. The Notifier then calculated % Retention Over Control (ROC) to determine optimum levels. The ROC studies demonstrated that there is a law of diminishing returns on the use of arginine. The Notifier also used equivalent levels of Sodium Tripolyphosphate as benchmarks.

As mentioned above, data is being submitted FSIS to support the suitability of the use of arginine in pork and poultry via a brine solution. This information on suitability is incorporated by reference in this document.

³ See Food Chemicals Codex, 6th Ed. (2008-2009), L-Arginine.

⁴ For current suitability studies, arginine is used at 0.3%.

Dr. Robert L. Martin
Office of Food Additive Safety (HFS-255)
Food and Drug Administration
January 7, 2010
Page 4

VIII. GRAS Determination Through Scientific Procedures

It is common knowledge that arginine is one of the naturally occurring amino acids in meat and poultry protein.⁵ Arginine is reported to be from 6.52 to 6.98% of pork/poultry protein, depending on species.⁶ The total protein content of pork/poultry is 21-24% (local data), so the level of arginine in pork/poultry is approximately 1.5% or 15,000 ppm.

A study published in *Regulatory Toxicology and Pharmacology* in 2008 assessed the safety of arginine when added to the diet. See Shao, A., Hathcock, J.N., *Risk Assessment for the amino acids taurine, L-glutamine, and L-arginine*, *Regulatory Toxicology and Pharmacology*, 50(2008):376-399 (Attachment 2). The study states that “experts have generally acknowledged the absence of adverse effects from [orally administered] supplemental amounts [of arginine] in humans.” This risk assessment scrutinized data from published human clinical trials, of which there was “a fairly robust human clinical trial dataset.” The study reviewed 38 published human clinical trials and observed, “None of the clinical trials reviewed found any systemic and credible hazard or adverse effects related to [arginine] administration. Therefore, by definition, there is no basis for identifying a NOAEL [no observed adverse effect level] or LOAEL [lowest observed adverse effect level]. In the absence of either of those two values a UL [upper level of intake] usually is not set.”

⁵ The Free Dictionary by Farlex, citing The Columbia Electronic Encyclopedia (2007) (“[O]ne of the 20 amino acids commonly found in animal proteins.”), *available at* <http://encyclopedia2.thefreedictionary.com/arginine> (last visited 5/1/09); The Free Dictionary by Farlex, citing Encyclopedia Concise Britannica (2008) (“One of the essential amino acids, particularly abundant in histones and other proteins associated with nucleic acids. It plays an important metabolic role in the synthesis of urea, the principal form in which mammals excrete nitrogen compounds. Arginine is used in medicine and biochemical research, in pharmaceuticals, and as a dietary supplement.”), *available at* <http://encyclopedia2.thefreedictionary.com/arginine> (last visited 5/1/09); McGraw-Hill Concise Dictionary of Modern Medicine (2002) (“Biochemistry: A 'facultatively' essential amino acid that contains a guanido group with a pKa > 12, which carries a positive charge at physiological pH; it becomes an essential amino acid when the body is under stress or injured. Sources: Turkey, chicken and other meats.”); American Heritage Medical Dictionary (2007) (“An amino acid obtained from the hydrolysis or digestion of plant and animal protein.”).

⁶ See U.S. Department of Agriculture, Agricultural Research Service. 2009. USDA National Nutrient Database for Standard Reference, Release 22. Nutrient Data Laboratory Home Page, <http://www.ars.usda.gov/ba/bhnrc/ndl>.

Dr. Robert L. Martin
Office of Food Additive Safety (HFS-255)
Food and Drug Administration
January 7, 2010
Page 5

Based on the dosage used in the clinical trials and the quality of the trials, the researchers selected 20 g/d as the OSL (observed safe level) for supplemental arginine. The researchers acknowledged the conservative nature of their exclusive reliance on human data, but stated that the advantage to this approach is that the level identified as save warrants an extremely high level of confidence.

The intended use of arginine falls well below 20 g/d.⁷ The solution is injected into pork/poultry at levels between 10-20%. The solution addition level anticipated for ground pork/poultry is 6-8%. The level of arginine is 0.2%-0.6% in the solution. Thus, the level of arginine used in the solution represents only approximately 5% of the arginine already present in pork/poultry tissue or 600 ppm of finished raw product. In other words, the naturally occurring arginine is present at levels more than 20 times greater than that being added by the solution. The naturally occurring arginine and the added arginine would be indistinguishable in laboratory analysis. Exposure through consumption would be 0.12%⁸ for the added arginine if the pork/poultry was injected to the maximum level of 20%. For a 4 ounce serving, there would be 0.12 g of arginine.

As stated earlier, arginine is a naturally occurring component of pork and poultry protein, and the arginine used in the solution is indistinguishable from naturally occurring arginine in the pork/poultry. Any byproducts produced by the addition of arginine to pork/poultry would be consistent with the naturally existing byproducts from arginine present in pork/poultry.

The arginine meets FCC specifications, and the arginine used in the solution is indistinguishable from naturally occurring arginine in the pork/poultry. The arginine is added to the pork/poultry during processing and does not significantly increase the amount of arginine naturally found in the food.

⁷ The amount of added Arginine that is retained in the meat and poultry depends on the muscle and the species. For purposes of the safety assessment to determine maximum theoretical consumption levels, it is assumed that all of the Arginine that is injected via the brine solution into the pork/poultry is retained.

⁸ Thus, if the Arginine is present at 0.6% of the brine solution, and the brine solution is added at the maximum level of 20% to the pork/poultry, the Arginine would be added at 0.12% (i.e., $0.006 \times 0.20 = 0.0012$) to the pork/poultry based on their initial weight of the pork/poultry. In other words, if the initial weight of the pork/poultry was 100 g, then 0.12 g of Arginine would be added via the brine solution to the pork/poultry.

Dr. Robert L. Martin
Office of Food Additive Safety (HFS-255)
Food and Drug Administration
January 7, 2010
Page 6

To further support the safety of the intended use described in this document, we note that FDA has classified arginine as an approved food additive under the use conditions defined in 21 C.F.R. § 172.320. The regulation stipulates that the addition of arginine to food is safe under several conditions, one of which is that the amount of the arginine added for nutritive purposes plus the amount naturally present in free and combined (as protein) form must not exceed 6.6% by weight of total protein (expressed as free amino acid) of the finished food.

The addition of arginine via the brine solution in pork/poultry does not introduce any novel safety issues apart from those considered by FDA in its consideration of the arginine use described in 21 C.F.R. § 172.320. The minimum amount of arginine is added to achieve the desired effect, and the amount of arginine added plus the amount naturally present in free and combined form does not exceed 6.6% by weight of total protein (expressed as free amino acid) of the finished food. The added arginine will result in a PER of protein consistent with pork/poultry protein. Moreover, although the arginine is added for a different purpose, it is the same food substance as that provided for in 21 C.F.R. § 172.320 and it is added at or below the levels indicated in 21 C.F.R. § 172.321. Therefore, no novel safety issues arise from the addition of arginine via the brine solution to pork/poultry.

Moreover, FDA recently issued a “no questions” letter in response to GRAS Notification No. GRN 290 for the use of arginine in subprimal beef and ground beef. See FDA “No Questions” Letter (November 2, 2009), GRAS Notice No. GRN 290.⁹ The addition of arginine via the brine solution in pork/poultry does not introduce any novel safety issues apart from those considered by FDA in its review of GRAS Notice No. GRN 290.

Also, the use of arginine as a flavoring agent has been determined to be safe by the Joint FAO/WHO Expert Committee on Food Additives (JECFA). JECFA states:

No safety concern at current levels of intake when used as a flavouring agent.
Not evaluated using the Procedure for the Safety Evaluation of Flavouring Agents; the substance is a macronutrient and a normal component of protein

⁹ In connection with GRAS Notice No. GRN 290, a suitability petition was submitted to FSIS, and FSIS concluded that the data supported the use. FSIS currently lists “an aqueous solution of arginine, potassium hydroxide, salt, and water” as a pH control agent in brine solutions for beef subprimals or beef patties. *See* FSIS’s Safe and Suitable Ingredients Used in the Production of Meat and Poultry Products, Directive 7120.1 (Amendment 21) (1/5/2010), *available at* <http://www.fsis.usda.gov/oppde/rdad/FSISDirectives/7120.1Amend21.pdf>.

Dr. Robert L. Martin
Office of Food Additive Safety (HFS-255)
Food and Drug Administration
January 7, 2010
Page 7

and, as such, human exposure through food is orders of magnitude higher than the anticipated level of exposure from use as a flavouring agent.

See Summary of Evaluations Performed by the Joint FAO/WHO Expert Committee on Food Additives, Arginine, available at http://incem.org/documents/jecfa/jeceval/jec_156.htm.

Finally, arginine has been the subject of extensive study as a drug to treat a wide variety diseases and symptoms (e.g., to measure growth hormone levels in people who might have related deficiencies and to treat people with inborn errors of urea synthesis).¹⁰ It is well recognized in the medical community for its therapeutic uses.¹¹ Arginine is also widely sold in the U.S. as a dietary supplement, and we have found over two hundred 30-day notification letters submitted to FDA pursuant to FDCA § 403(r)(6) for dietary supplements that contains arginine.¹²

¹⁰ See MayoClinic.com. Arginine (L-arginine). 2008. http://www.mayoclinic.com/health/l-arginine/NS_patient-arginine ("Arginine is considered a semi-essential amino acid because even though the body normally makes enough of it, supplementation is sometimes needed....Early evidence suggests that arginine may help treat medical conditions that improve with vasodilation, such as chest pain, clogged arteries (called atherosclerosis), coronary artery disease, erectile dysfunction, heart failure, intermittent claudication/peripheral vascular disease, and blood vessel swelling that causes headaches (vascular headaches). Arginine also triggers the body to make protein and has been studied for wound healing, bodybuilding, enhancement of sperm production (spermatogenesis), and prevention of wasting in people with critical illnesses."); see also Wikipedia.com. Arginine. <http://en.wikipedia.org/wiki/Arginine> (last visited 4/21/2009).

¹¹ See Mosby's Dictionary of Complementary and Alternative Medicine (2005) ("[A]n essential amino acid that has been used as an adjunct therapy in congestive heart failure, erectile dysfunction, peripheral vascular disease (PVD), and angina pectoris. It may also be useful in the treatment of upper respiratory ailments, type II diabetes, and various hematologic conditions.").

¹² See e.g., Kohli, R., et al., Dietary L-Arginine Supplementation Enhances Endothelial Nitric Oxide Synthesis in Streptozotocin-Induced Diabetic Rats, The American Society for Nutritional Sciences J. Nutr. 134:600-608. March 2004, available at <http://jn.nutrition.org/cgi/content/abstract/134/3/600>.

Dr. Robert L. Martin
Office of Food Additive Safety (HFS-255)
Food and Drug Administration
January 7, 2010
Page 8

The references above support the conclusion that there is a consensus among experts qualified by scientific training and experience to evaluate the safety of substances added to food that arginine is safe when added to food as described in this document.

Very truly yours,

Robert G. Hibbert

Attachments

cc: Catherine Rockwell, DAM, FSIS
Dr. Ranzel Nickelson, II

1

Pages 000011-000012 have been removed in accordance with copyright laws. Please see appended bibliography list of the references that have been removed from this request.

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000013

Pages 000014-000037 have been removed in accordance with copyright laws. Please see appended bibliography list of the references that have been removed from this request.

SUBMISSION END

000038

Reference List for Industry Submission, GRN 000317

<i>Pages</i>	<i>Author</i>	<i>Title</i>	<i>Publish Date</i>	<i>Source</i>	<i>BIB_Info</i>
000011-000012	NA	Monographs/L-Arginine	NA	FCC	NA
000014-000037	Shao, Andrew; Hatchcock, John N.	Risk assessment for the amino acids taurine, L-glutamine	2008	Regulatory Toxicology and Pharmacology	Volume 50, pgs 376-399

NA- Not applicable

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PAGES 1 -24 WERE DELETED exemption(b)(4)

Williams, Stacey

From: Hibbert, Robert G. [Robert.Hibbert@klgates.com]
Sent: Thursday, March 18, 2010 5:01 PM
To: Williams, Stacey
Subject: RE: GRN 317: notifying entity

Dr. Williams:

Thank you for your inquiry. For the sake of consistency I would request that we go ahead and designate Edge Food Products as the notifying entity for GRN 317. If we can do anything else to assist in your review please do not hesitate to contact me.

Best regards,

Bob Hibbert
K&L Gates
1601 K Street, N.W.
Washington, DC 20006-1600
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From: Williams, Stacey [mailto:Stacey.Williams@fda.hhs.gov]
Sent: Thursday, March 18, 2010 4:26 PM
To: Hibbert, Robert G.
Subject: GRN 317: notifying entity

Good afternoon Dr. Hibbert,

I wanted to follow-up with you to discuss the representation of Dr. Nickelson vs. Standard Meat Company or Edge Food Products, LLC (Edge Food Products). Previously, (GRN 290) the notice came in to our office on with the notifying entity being listed as Dr. Nickelson and was later changed to Edge Food Products in the response letter. I wanted to follow-up with you to determine what we should expect to list as the notifying entity in any future correspondence regarding GRN 317. I would like to clarify this information now in order to prevent any possible delays that may occur in responding to your GRAS notice. I look forward to your response and as always, if you have any questions or concerns, feel free to contact me.

Best regards,

Stacey Williams

Stacey Williams, Ph.D.
Consumer Safety Officer
U.S. Food and Drug Administration
Center for Food Safety and Applied Nutrition
Office of Food Additive Safety
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301-436-1291

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6/28/2010

June 22, 2010

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Stacey Williams, Ph.D
Consumer Safety Officer
U.S. Food & Drug Administration
Center for Food Safety & Implied Nutrition
Office of Foods Additive/Safety
4300 River Road
College Park, MD 20740-3835

Dear Ms. Williams:

This follows our recent discussions regarding the status of GRN 000317, a pending GRAS notification, and will confirm our request that the Edge Food Products be specified as the notifying entity.

If you have any further questions regarding this matter, please do not hesitate to contact me.

Sincerely,

Robert G. Hibbert
Counsel to Edge Products LLC