CBI Deleted Copy

1 Cargill Drive
Eddyville, IA 52553
USA

USDA National Organic Program
Program Manager
USDA/AMS/TM/NOP
Room 4008-So., Ag Stop 0268
1400 Independence Avenue, SW.
Washington, DC 20250

ATTN: Robert Pooler
Valerie Frances

September 27, 2007

Dear Robert, Dear Valerie:

The following document is the "CBI Deleted Copy" of our petition for non-shellfish derived REGENASURE® Glucosamine hydrochloride to be added to the National List of substances listed under 7 CFR 205.605 (a) or (b). I have updated the response to item #4.

If you have any questions or require additional information please let me know.

Best regards,

Randy Buren
Regulatory Affairs Specialist
Cargill Corn Milling
641-969-7745 (phone)
641-969-3774 (fax)
randy_buren@cargill.com

Petition for non-shellfish derived REGENASURE® Glucosamine hydrochloride to be added to the National List of substances listed under 7 CFR 205.605 (a) or (b)

Item A

REGENASURE® Glucosamine hydrochloride is hereby petitioned to be included in the National List for, "Nonagricultural (nonorganic) substances allowed in or on processed products labeled as "organic" or "made with organic (specified ingredients)."
7 CFR 205.605 (a) or (b)

Item B

1. **The substance's common name.**

   Glucosamine hydrochloride.

2. **The manufacturers name, address and telephone number.**

   Cargill, Incorporated
   #1 Cargill Drive
   Eddyville, Iowa 52553

   Phone: 888-734-3627

3. **The intended or current use of the substance such as a pesticide, animal feed, processing aid.**

   The current use for REGENASURE® Glucosamine HCl (hydrochloride) is as a dietary ingredient and/or a functional food ingredient. It is also listed in the International Nomenclature of Cosmetic Ingredients (INCI) and may be used as an ingredient in cosmetic products.

4. **A list of crop, livestock, or handling activities for which the substance will be used. If used for crops or livestock, the substance rate or method of application must be described. If used for handling (including processing), the substance's mode of action must be described.**

Upon addition to the national list, the intended use would be as an ingredient considered as a "Nonagricultural (nonorganic) substance (7 CFR 205.605)" used as a dietary ingredient, functional food ingredient or as a cosmetic ingredient in dietary supplements, functional foods or cosmetic products that meet the requirements to be labeled as "organic" or "made with organic".

5. **The source of the substance and detailed description of it's manufacturing or processing procedures from the basic component(s) to the final product. Petitioners with concerns for confidential business information can follow the guidelines in the Instructions for Submitting Confidential Business Information (CBI) listed in #13.**

Cargill, Incorporated produces REGENASURE® Glucosamine HCl through a unique process that utilizes a non-GMO, non-toxic and non-pathogenic strain of *Aspergillus niger*, produced through a dextrose based fermentation; whereas all other known commercial glucosamine products are derived from shellfish waste.

The specifications for REGENASURE® Glucosamine HCl are well defined and demonstrate that the manufacturing method is reproducible and produces comparable batches of the end product. The processing method carefully isolates glucosamine produced within the fungal biomass through acid hydrolysis of the fungal biomass, separation of glucosamine from the fungal biomass solids, and precipitation of glucosamine hydrochloride in crystal form. The processing method results in the formation of REGENASURE® Glucosamine HCl, which meets the specifications of the analytical methods of the USP-NF specifications for glucosamine hydrochloride.

Manufacturing Process for REGENASURE® Glucosamine HCl:
[CBI Deleted]

6. A summary of any available previous reviews by State or private certification programs or other organizations of the petitioned substance.

Not applicable.

7. Information regarding EPA, FDA, and State regulatory authority registrations, including registration numbers.

The Cargill manufacturing site is registered under the FDA's Bioterrorism Act and has received a registration number. In addition, the site has been issued a "Food Processing/Warehouse License" from the state of Iowa.

REGENASURE® Glucosamine HCl is produced in a facility which uses current food Good Manufacturing Practices (21 CFR Part 110 – FDA, 2005) and a comprehensive Hazard Analysis and Critical Control Point (HACCP) program, which is reviewed and updated annually.

8. The Chemical Abstract Service (CAS) number or other product numbers of the substance and labels of the products that contain the petitioned substance.

The CAS registry number for glucosamine hydrochloride is [66-84-2].
Labels from current products with glucosamine HCl can be found in **Appendix 1**.

9. The substance's physical properties and chemical mode of action including (a) chemical reactions with other substances, especially substances used in organic production; (b) toxicity and environmental persistence; (c) environmental impacts from it's use or manufacturer; (d) effects on human health; (e) effects on soil organisms, crops, or livestock.

(a) Non-shellfish glucosamine HCl would be used in a final product form (i.e. food supplement, functional food). No deleterious reactions are known to occur in these forms. This product would not be applicable to organic production substances applied to crops.

(b),(d) An excellent review of the toxicology of glucosamine and its safety in humans entitled, "Glucosamine effects in humans: a review of effects on glucose metabolism, side effects, safety considerations and efficacy" has been published by JW Anderson *et al.* (2005) (**Appendix 2**). This critical evaluation indicated that glucosamine is safe under current conditions of use and does not affect glucose metabolism.

(c) REGENASURE® Glucosamine HCl is manufactured in accordance with state and local environmental regulations. It would not be utilized for crop production.
(e) REGENASURE® Glucosamine HCl is made for human consumption and is not applicable to soil organisms, crops, or livestock.

10. Safety information about the substance including a Material Safety Data Sheet (MSDS) and a substance report from the National Institute of Environmental Health Studies.

Please see **Appendix 3** for the REGENASURE® Glucosamine HCl MSDS. As mentioned in the response to #7, Cargill's glucosamine hydrochloride is manufactured under the current food Good Manufacturing Practices (21 CFR Part 110 – FDA, 2005) and a comprehensive Hazard Analysis and Critical Control Point (HACCP) program. This product meets or exceeds the analytical specifications of the United States Pharmacopoeia USP monograph for glucosamine hydrochloride. A substance report from the National Institute of Environmental Health would not be applicable for our product, since it is not applied to crops for organic crop production.

11. Research information about the substance, which includes comprehensive substance research reviews and research bibliographies, including reviews and bibliographies, which present contrasting positions to those presented by the petitioner in supporting the substance's inclusion on or removal from the National List.

The research information available on glucosamine HCl is mainly in the form of clinical studies. This product has a safe history of use. Please see **Appendix 4** for a list of references on the use of glucosamine hydrochloride and it's efficacy.

12. A "Petition Justification Statement" which provides the justification of a synthetic substance on the National List under 7 CFR 205.605 (a) or (b)

This petition is requesting the permission for the use of REGENASURE® Glucosamine HCl as a "Nonagricultural (nonorganic) substance allowed in or on processed products labeled as "organic" or "made with organic (specified ingredients)." A non-synthetic form of glucosamine is not available. Glucosamine HCl would be added to products labeled as "organic" or "made with organic (specified ingredients)" at a level, which would be below the "maximum allowed" requirement.

The approval of REGENASURE® Glucosamine HCl under the 7 CFR 205.605 (a) or (b) list will allow consumers, who choose to only purchase organic products, the opportunity to consume glucosamine for health benefits in an

organic form. Numerous clinical studies have demonstrated the human health benefit of glucosamine (**Appendix 4**).

13. A Commercial Confidential Information Statement which describes the specific required information contained in the petition that is considered to be Confidential Business Information (CBI) or confidential commercial information and the basis for that determination. Petitioners should limit their submission of confidential information to that needed to address the areas for which this notice requests information.

Justification statements for CBI-Deleted material:

1. Page 3. The manufacturing process is considered confidential information falling under the category of "trade secret" (13 (b) from petition instructions).
2. Page 7, Appendix 1. Labels of customer products are considered confidential commercial information (13 (a) from the petition instructions).
3. Page 8, Appendix 2. The Anderson, J.W. et al. paper is copyrighted material and only the reference is listed in the CBI-deleted copy (13 (g) from petition instructions).

Appendix 1

Labels of products that contain glucosamine hydrochloride: [CBI-Deleted]

Appendix 2

Anderson, J.W., Nicolosi, R.J., Borzelleca, J.F., 2005. Glucosamine effects in humans: a review of effects on glucose metabolism, side effects, safety considerations and efficacy. Food and Chemical Toxicology 43, 187-201.

Pages 9 – 23 [CBI-deleted]

Appendix 3

REGENASURE® Glucosamine hydrochloride - MSDS

Date of Preparation: August, 3, 2001
Updated: April 4, 2005

Section 1 – Chemical Product and Company Identification	
Product Name:	D-glucosamine hydrochloride, 2-Amino-2-deoxy-D-glucose hydrochloride
CAS Number:	66-84-2
Manufacturer:	Cargill Acidulants 1 Cargill Drive Eddyville, IA 52553-5000
Emergency Telephone Number:	800/424-9300 (Chemtrec)

Section 2 – Composition / Information on Ingredients			
HAZARDOUS COMPONENTS:	% COMP	OSHA PEL	ACGIH TLV
None (This product does not meet any known hazard communication criteria.)	Minimum 98%	N/A	N/A

Section 3 – Hazards Identification		
Routes of Entry:	Eyes:	Yes
	Ingestion:	Yes
	Inhalation:	Yes
	Skin:	Yes
Health Hazards – Acute:	Eyes:	Severely irritating, may be abrasive.
	Ingestion:	May cause gastrointestinal irritation in excess.
	Inhalation:	Causes irritation to respiratory system.
	Skin:	May cause skin irritation.
Health Hazards – Chronic:	Small amounts handled during normal operations are not likely to cause injury.	
Signs and Symptoms of Exposure:	Irritation.	
Medical Conditions Generally Aggravated by Exposure:	None	
Effects of Overexposure:	None	

Section 4 – First Aid Measures		
First Aid and Emergency Procedures:	Eyes:	Flush eyes with water.
	Ingestion:	None
	Inhalation:	Treat symptomatically if breathing is not normal.
	Skin:	Wash with water.

Section 5 – Fire Fighting Measures		
Flash Point (Method Used):	N/A (N/A = not applicable)	
Flammable Limits:	Upper Explosive Limit:	N/A
	Lower Explosive Limit:	N/A
Extinguishing Media:	Water, foam, or carbon dioxide	
Special Fire Fighting Procedures:	Wear self-contained breathing apparatus.	
Unusual Fire and Explosion Hazards:	Fire may produce irritating or toxic fumes.	
NFPA Hazard Code: (4=extreme/severe: 3=high/serious; 2=moderate; 1=slight; 0-minimum)	Health:	0
	Flammability:	0
	Reactivity:	0

Section 6 – Accidental Release Measures	
Spill or Leak Procedures:	Follow all state and local requirements for non-hazardous waste disposal.
Neutralizing Chemicals:	None

Section 7 – Handling and Storage	
Handling and Storage Requirements:	Store in tightly closed container in a cool, dry, well ventilated area. Keep container closed when not in use to maintain product quality. Avoid contact with eyes, minimize dust generation, wash hands thoroughly after handling, and use in a well-ventilated area.

Section 8 – Exposure Controls / Personal Protection		
Respiratory Protection:	Use NIOSH approved respirator.	
Ventilation:	Local:	Use local exhaust ventilation.
	Mechanical:	N/A
	Special:	N/A
	Other:	N/A
Protective Gloves:	Wear impervious protective gloves as appropriate to prevent contact with skin.	
Eye Protection:	Use chemical safety goggles.	
Other Protective Clothing or Equipment:	Wear impervious protective clothing as appropriate to prevent contact with skin.	
Work/Hygienic Practices:	Follow good housekeeping procedures.	

Section 9 – Physical and Chemical Properties	
Appearance and Odor:	Off-white crystals with characteristic odor.
Boiling Point:	N/A
Evaporation Rate (Butyl Acetate = 1):	N/A
Melting Point:	Decomposes
Specific Gravity (Water = 1):	1.42 @ 100^0 F
Solubility in Water:	Soluble
Vapor Density (Air = 1):	N/A
Vapor Pressure (mmHg):	N/A

Section 10 – Stability and Reactivity	
Stability:	Stable under normal temperature and pressure
Conditions to Avoid:	N/A
Incompatibility (Materials to Avoid):	Strong oxidizing agent
Hazardous Decomposition or Byproducts:	Irritating and toxic fumes
Hazardous Polymerization:	Will not occur

Section 11 – Toxicological Information	
Toxicity Hazard Rating:	No specific data. Low order of toxicity.
OSHA Hazardous/Non-hazardous:	Non-hazardous

Section 12 – Ecological Information
This chemical is expected to be readily biodegradable. It is not known to cause significant adverse environmental impact, although pH depression can occur when spilled into water bodies.

Section 13 – Disposal Considerations	
Waste Disposal Method:	Dispose of in accordance to local, state, and federal regulations.

Section 14 – Transport Information	
DOT:	Not restricted
IATA:	Not restricted
HMIS Labeling:	Exempt

Section 15 – Regulatory Information

This product is included in the TSCA inventory of chemical substances in the USA, and in Canada on DSL list.
Not regulated by OSHA or IARC.

Section 16 – Other Information

The information given and the recommendations made herein apply to our product(s) alone and are not combined with other product(s). Such are based on our research and on data from other reliable sources that are believed to be accurate. No guarantee of accuracy is made. It is the purchaser's responsibility before using any product to verify this data under their own operation conditions and to determine whether the product is suitable for their purposes.

Technical Services
Cargill Acidulants
1 Cargill Drive
Eddyville, IA 52553-5000
800-535-1443

Appendix 4

Glucosamine hydrochloride efficacy document

Cargill™

Regenasure™ GLUCOSAMINE

TECHNICAL INFORMATION

Key Findings

- Chronic joint problems and arthritis affect close to 1/3 of American adults. C*DC, 2002*
- Orally administered glucosamine is rapidly absorbed. *Setnikar, 1993*
- Glucosamine is an important building block of the joint tissue that forms a cushioning layer at the end of bones. *IOM, 2003*
- Glucosamine has a much lower incidence of side effects than NSAIDs, or even placebo. *Anderson, 2005*
- 1,500 mg of glucosamine is a typical daily dose. This level of supplementation has shown pain relief for people coping with regular knee pain. *Reginster, 2001, Clegg 2006, Herrero-Beaumont 2005*
- A 3-year study showed a 20-25% symptomatic improvement in the glucosamine group, while they worsened in the placebo group. *Pavelka, 2002*
- Joints in patients who took glucosamine narrowed by a mean of only 0.06 mm, compared to 0.31 mm in the placebo group. *Reginster, 2001*

GLUCOSAMINE EFFICACY INFORMATION

The efficacy of glucosamine has been evaluated through animal models and human clinical trials over many decades. Glucosamine is commonly used "as a single ingredient or in combination with other ingredients" as "a joint builder (to increase joint flexibility, to restore joint function, and to alleviate joint pain), and for osteoarthritis" (IOM 2003). Glucosamine is "a major building block of the water-loving proteoglycans" which are used to produce glycosaminoglycans, which bind water in the cartilage matrix (Theodosakis 2004). Glucosamine HCl has been radiolabled and administered to both rats and dogs (Setnikar 1984, 1986), showing it is readily absorbed.

In two recent meta-analyses (McAlindon 2000, Richy 2003), researchers reviewed the evidence for efficacy of glucosamine HCl and glucosamine sulfate for arthritic complaints. It was concluded that glucosamine was moderately efficacious for relief of arthritic complaints, and that glucosamine had highly significant efficacy on all aspects of knee osteoarthritis including joint space narrowing, pain, and mobility scores. In 2 recent major clinical trials (Clegg 2006, Herrero-Beuamont 2005) glucosamine was supplied at 1,500 mg/day to osteoarthritis patients, and positive results indicate that glucosamine reduced knee pain compared to a placebo, and that all treatments were well-tolerated by the study subjects.

Glucosamine is commonly found in several salt forms, including glucosamine hydrochloride (HCl), glucosamine sulfate and N-acetylglucosamine (IOM, 2003). "The counter anion of the glucosamine salt (i.e. chloride or sulfate) is unlikely to play any role in the action or pharmacokinetics of glucosamine" (PDR, 2001), as orally administered glucosamine HCl and glucosamine sulfate are both dissociated in the stomach and free glucosamine then enters the small intestine (Anderson 2005). Glucosamine HCl does contain 83% free base glucosamine compared to only 65% in glucosamine sulfate (PDR, 2001). It has been concluded through *in vitro* testing that glucosamine HCl and glucosamine sulfate have similar abilities to prevent or reduce cartilage degeneration (Karzel 1971, Karzel 1982, Fenton 2000). A direct comparison of glucosamine HCl to glucosamine sulfate (Karzel 1971, Karzel 1982) showed equality in stimulation of proteoglycan synthesis. A recent human clinical study directly compared glucosamine HCl and glucosamine sulfate on a glucosamine basis (versus a weight basis) and reported no difference in response among groups (Qiu 2005).

Cargill Acidulants
1 Cargill Drive
Eddyville, IA 52553-5000
1-888-REGENASURE
www.regenasure.com

GLUCOSAMINE HYDROCHLORIDE REFERENCES

2006: Clegg DO, Reda DJ, Harris CL et al. Glucosamine, chondroitin sulfate and the two in combination for painful knee osteoarthritis. N Engl J Med 2006; 354:795-808.

2005: Anderson JW, Nicolosi RJ, Borzelleca JF. Glucosamine effects in humans: a review of effects on glucose metabolism, side effects, safety considerations and efficacy. *Food Chem Toxicol*. 2005 Feb;43(2):187-201.

2005: Qiu GX, etal. A multi-central, randomized, controlled clinical trial of glucosamine hydrochloride/sulfate in the treatment of knee osteoarthritis. *Natl. Med. J. China*. 2005 Nov 16;85(43):3067-70.

2004: Theodosakis, Jason MD. The Arthritis Cure, The Revised Edition. St. Martins Press, 2004.

2003: Braham R, etal. The effect of glucosamine supplementation on people experiencing regular knee pain. *Br J Sports Med.* 2003; 37:45-49.

2003: Institute of Medicine. Safety review: Draft 3 prototype monograph on glucosamine. pp 1-84. 2003. Washington, DC, National Academy of Sciences. Ref Type: Report.

2003: Richy F, etal. Structural and symptomatic efficacy of glucosamine and chondroitin in knee osteoarthritis: a comprehensive meta-analysis. *Arch Intern Med.* 2003; 163:1514-1522.

2001: Hendler SS, etal. Glucosamine. *PDR for Nutritional Supplements*, First Edition. 2001. 186-189.

2000: Fenton JI, etal. *Osteoarthritis and Cartilage.* 2000;8, 444-451.

1999: Das A, etal. Combination of glucosamine and chondroitin in knee OA. *Osteoarthritis Cartilage.* 2000;8(5):343-350.

1999: Leffler CT, etal. "Glucosamine, chondroitin, and manganese ascorbate for degenerative joint disease of the knee or low back: a randomized, double blind, placebo-controlled pilot study." *Military Medicine* February 1999;164:2:85-91.

1986: Setnikar I, Giacchetti C, Zanolo G. Pharmacokinetics man. *Drug Res* 1986;36(1):729-735.

1984: Setnikar I, Giacchetti C, Zanolo G. Absorption, distribution and excretion of radioactivity after a single intravenous or oral administration of [^{14}C] Glucosamine to the rat. *Pharmotherapeutica* 1984; 3 (38) 538-558.

1982: Karzel K, etal. "Effect of hexosamine derivatives on mesenchymal metabolic processes of in vitro cultured fetal bone explants" *Z. Rheumatology* 1982 Sep-Oct;41(5):212-8.

1971: Karzel K, etal. "Effect of hexosamine derivatives and uronic acid derivatives on glycosaminoglycan metabolism of fibroblast cultures." *Pharmacology* 1971;5:337-345.

ADDITIONAL GLUCOSAMINE REFERENCES

2005: G. Herrero-Beaumont et al. Effects of Glucosamine Sulfate on 6-Month Control of Knee Osteoarthritis Symptoms vs. Placebo and Acetaminophen: Results from the Glucosamine Unum in Die Efficacy (GUIDE) Trial. American College of Rheumatology, presentation #1203, Nov. 2005.

2003: Scroggie DA, etal. The effect of glucosamine-chondrotin supplementation on glycosylated hemoglobin levels in patients with type 2 diabetes mellitus. *Arch Intern Med* 2003; 163:1587-1590.

2002: Centers for Disease Control and Prevention, press release.

2002: Pavelka K, etal. Glucosamine sulfate use and delay of progression of knee osteoarthritis: a 3-year, randomized, placebo-controlled, double-blind trial. *Arch Intern Med* 2002; 162:2113-2123.

2001: Nguyen P, etal. "A randomized double-blind clinical trial of the effect of chondroitin sulfate and glucosamine hydrochloride on temporomandibular joint disorders: a pilot study." *Cranio* 2001;Apr;19(2):130-9.

2001: Reginster JY et al. Long-term effects of glucosamine sulphate on osteoarthritis progression: a randomized, placebo-controlled clinical trial. *Lancet* 2001; 357:251-256.

2000: Beren J, etal. "The therapeutic effect of glucosamine HCl/chondroitin sulfate combination of type II collagen-induced arthritis in D/A rats." Published in the Proceedings of the Society for Experimental Biology and Medicine, 2000.

2000: Hungerford et al. "Use of Nutraceuticals in the Management of Osteoarthritis." *Journal of the American Nutraceutical Association* 2000; Vol.3, No. 1:23-27.

2000: Lippiello L, etal. "Dose response and synergistic effect of glucosamine HCl and chondroitin sulfate on in-vitro proteoglycan synthesis by bovine and human chondrocytes." Paper presented at the 67th annual meeting of the American Academy of Orthopedic Surgeons, Orlando, FL, 2000.

2000: McAlindon TE, etal. Glucosamine and chondroitin for treatment of osteoarthritis: a systematic quality assessment and meta-analysis. *J Amer Med Assoc* 2000; 283:1469-1475.

1999: Canapp SO, etal. "Scintographic evaluation of glucosamine HCl and chondroitin sulfate as treatment for acute synovitis in dogs." *American Journal of Veterinary Research* December, 1999;60(12):1550-1556.

1999: Lippiello L, etal. "Beneficial effect of cartilage disease-modifying agents tested in chondrocyte cultures and a rabbit instability model of osteoarthritis." *Arthritis & Rheumatology* September 1999;42(9)(supplement S256).

1998: Shankland WE. The effects of glucosamine and chondroitin sulfate on osteoarthritis of the TMJ: a preliminary report of 50 patients. *J Craniomandibular Practice* 1998; 16:230-235.

1993: Setnikar I, etal. Pharmacokinetics of Glucosamine in Man *Arzneimittel-Forschung.* 1993:43 (II), 10, 1109-1113.