Glucosamine Hydrochloride

Handling/Processing

Identification of Petitioned Substance

Chemical Name:
D-glucosamine hydrochloride, 2-Amino-2-deoxy-D-glucose hydrochloride

CAS Number:
66-84-2

Other Names:

Other Codes:
European Inventory of Existing Commercial Chemical Substances (EINECS) No. 200-638-1

Trade Names:
REGENASURE® Glucosamine Hydrochloride

Characterization of Petitioned Substance

Composition of the Substance:

Glucosamine hydrochloride is used as a dietary ingredient and/or a functional food ingredient. It is also listed in the International Nomenclature of Cosmetic Ingredients and may be used as an ingredient in cosmetic products. The molecular formula for glucosamine hydrochloride is $C_6H_{13}NO_5 \cdot ClH$ and the molecular weight is 215.63 (U.S. EPA, Substance Registry Services).

Properties of the Substance:

Physical State	Crystalline
Color	Off-White
Melting Point	190 – 194° C
Specific Gravity	1.42 at 100° F
Water Solubility	Soluble
Incompatibility	Strong oxidizing agents
Stability	Stable under normal temperature and pressure

Specific Uses of the Substance:

Glucosamine is an amino monosaccharide that is an essential component of muco-polysaccharides and chitin. Glycosaminoglycans (muco-polysaccharides) are large complexes of negatively-charged carbohydrate chains that are incorporated into mucous secretions, connective tissue, skin, tendons, ligaments, and cartilage. Because glucosamine is a large component of joint tissue, the hypothesis that glucosamine supplements would provide symptomatic relief for osteoarthritis was developed more than 30 years ago (D'Ambrosio et al., 1981). Glucosamine supplements are widely used to relieve arthritic complaints (Houpt et al., 1999) and commercial products are on the market for this purpose. However, a study conducted looking at glucosamine supplementation as a means of cartilage preservation in patients with mild to moderate osteo-arthritis of the knee was negative. Glucosamine supplementation could possibly play a positive role in pain management of patients with osteo-arthritis, especially severe cases (HealthDay, 2009).

Approved Legal Uses of the Substance:

Glucosamine hydrochloride is not listed as Generally Recognized as Safe (GRAS) by the U.S. Food and Drug Administration (FDA).

Action of the Substance:

Glucosamine hydrochloride is used as a dietary ingredient and/or a functional food ingredient. It is also listed in the International Nomenclature of Cosmetic Ingredients and may be used as an ingredient in cosmetic products.

Status

U.S. Food and Drug Administration:

Glucosamine hydrochloride is not listed as Generally Recognized as Safe (GRAS) by the FDA. Cargill, Inc. submitted a notice on April 6, 2004 to the FDA that glucosamine hydrochloride is GRAS for use in select beverages as defined in 21 CFR 170.3(n)(3), (7), (16), (31), (36) at a maximum level of 0.75 grams per serving. The FDA received the notice on April 9, 2004 and assigned it as GRAS Notice No. GRN 000150. In a letter dated September 9, 2004, Cargill, Inc. asked that FDA cease to evaluation Cargill's notice in light of process related changes in the manufacture of glucosamine hydrochloride, with the understanding that Cargill may, in the future, submit another GRAS notification or make another appropriate submission for glucosamine chloride. The FDA ceased to evaluate glucosamine hydrochloride for GRAS status on September 9, 2004.

U.S. Environmental Protection Agency:

Glucosamine hydrochloride is included on the inventory of chemical substances for the Toxic Substances Control Act.

U.S. Pharmacopeia:

On August 16, 2007, the U.S. Pharmacopeia (USP) issued a USP certificate for glucosamine hydrochloride (LOT FOC363).

International:

Glucosamine hydrochloride is not allowed for use as a processing aid in organic food production by either the European Union (European Union, 2008) or Codex Alimentarius (Codex Alimentarius, 2008).

Glucosamine hydrochloride is included on the chemical inventory of the Domestic Substances List by the Canadian government.

Evaluation Questions for Substances to be used in Organic Handling

Evaluation Question #1: Is the petitioned substance formulated or manufactured by a chemical process? (From 7 U.S.C. § 6502 (21).)

Glucosamine hydrochloride is produced through a proprietary process that utilizes a non-genetically modified organism, *Aspergillus niger*, in a dextrose-based fermentation. After the fermentation, the glucosamine is isolated from the fungal biomass via acid hydrolysis. Subsequently, the glucosamine hydrochloride is filtered, crystallized, centrifuged, dried, and packaged for commercial use. More specific information is not available due to the proprietary nature of the manufacturing process.

Evaluation Question #2: Is the petitioned substance formulated or manufactured by a process that chemically changes the substance extracted from naturally occurring plant, animal, or mineral sources? (From 7 U.S.C. § 6502 (21).)

The glucosamine hydrochloride manufactured by the process described in the response to Evaluation Question 1 is slightly different chemically from glucosamine extracted from natural animal sources. The HCl moiety is added onto the synthesized glucosamine, due to the acid hydrolysis.

Evaluation Question #3: Is the petitioned substance created by naturally occurring biological processes? (From 7 U.S.C. § 6502 (21).)

Glucosamine is an amino monosaccharide that is an essential component of mucopolysaccharides and chitin. Glycosaminoglycans (mucopolusaccharides) are large complexes of negatively-charged carbohydrate chains that are incorporated into mucous secretions, connective tissue, skin, tendons, ligaments, and cartilage of animals and shellfish.

Evaluation Question #4: Is there a natural source of the petitioned substance? (From 7 CFR § 205.600 (b) (1).)

Glucosamine can be derived from shellfish waste.

Evaluation Question #5: Is there an organic agricultural product that could be substituted for the petitioned substance? (From 7 CFR § 205.600 (b) (1).)

There is not an organic agricultural product that can be substituted for glucosamine.

Evaluation Question #6: Are there adverse effects on the environment from the petitioned substance's manufacture, use, and disposal? (From 7 CFR § 205.600 (b) (2).)

The manufacturing process is confidential and so, little information is available. There is an acid hydrolysis step in the process and, therefore, the disposal of acidic waste may be an issue. The amount of waste to be disposed of is not known for each batch manufactured. Theoretically, the acidic waste could be neutralized, however, this may or may not be practical, depending on the amount of acidic waste produced.

Evaluation Question #7: Does the petitioned substance have an adverse effect on human health as defined by applicable Federal regulations? (From 7 CFR § 205.600 (b) (3).)

Acute Oral Toxicity

Oral administration of glucosamine at very large doses (5,000 to 15,000 mg/kg body weight) is well tolerated without documented toxicity. The LD_{50} for glucosamine for rats, mice, and rabbits exceed 5,000 mg/kg with a median value of >8,000 mg/kg (data from seven studies as summarized by Anderson et al., 2005). Glaza (2002) administered 5,000 mg glucosamine/kg BW orally to five male and five female rats. All animals were observed clinically, twice daily, for body weight changes, mortality, and morbidity. After 15 days, all animals were euthanized by over-exposure to carbon dioxide and subjected to macroscopic necropsy examination. The necropsy included examination of the external surface of the carcass and all organs and tissues in the thoracic, abdominal, pelvic, and oral cavities. No test material-related effects were observed. The acute oral LD_{50} of glucosamine hydrochloride is greater than 5,000 mg/kg.

Sub-chronic and Chronic Oral Toxicity

Echard et al. (2001) examined the effects of oral administration of glucosamine hydrochloride compared to a baseline diet in eight male spontaneously hypertensive rats and eight Sprague-Dawley rats for nine weeks. In this study, they fed 0.5% w/w or ~300 mg/kg (which was estimated at 10 to 20 times the usual human dose). It was concluded that there were no consistent effects on blood chemical parameters and organ histology, suggesting no overall toxicity of glucosamine in this nine week study involving these two strains of rats. In dietary studies cited by Setnikar et al., (1991b), rats ingested glucosamine sulfate at 2,700 mg/kg for 52 weeks and dogs ingested 2, 149 mg/kg for 26 weeks. There were no treatment-related adverse effects in either species.

Toxicity by the Parenteral Route

Setnikar et al., (1991a) investigated the effects of intravenous and intra-peritoneal administration in rats. The LD_{50} of glucosamine in rats for intra-peritoneal injection is ~5,247 mg/kg BW and for intravenous injection is 1,674 mg/kg BW. For mice, the LD_{50} of glucosamine for intra-peritoneal injection is 6,614 mg/kg BW while the LD_{50} for intravenous injection is >1,619 mg/kg BW.

Mutagenicity

Glucosamine was not mutagenic in the *E. coli* reverse mutation studies of Brusick et al., (1980). However. Nanjou et al., (1984) found glucosamine to induce strand breakage in the DNA of bactiophage, which the authors believed to be associated with the presence of an amino group.

Effects of Glucosamine on Glucose Metabolism in Humans

One of the main concerns is the effect of glucosamine on glucose metabolism and glucose homeostasis in humans. Anderson et al., (2005) concluded, from 32 clinical studies involving 3,073 subjects for an average of 17 weeks, that glucosamine had no adverse effects on glucose homeostasis. Glucosamine appears to be well-tolerated for periods up to three years. The usual dose of glucosamine was 1,500 mg/day in three doses, however, up to 3,200 mg/day were well-tolerated by subjects. Anderson et. al., (2005) also concluded from 13 clinical trials that glucosamine had no adverse effects on blood chemistries, hematological parameters, urinalysis, occult blood in feces, or cardiovascular parameters.

Therefore, based on the high LD_{50} calculated in the studies involving feeding glucosamine to rats, mice, and rabbits and the long-term human studies, it appears glucosamine, when used in nutritional supplements, has no adverse long-term effects.

In crystalline form, glucosamine hydrochloride is severely irritating to the eyes, as well as, irritating to the gastro-intestinal tract, respiratory system, and skin. Therefore, when handling glucosamine chloride in crystalline form, respiratory protection (an approved respirator), eye protection (safety goggles), skin protection (impervious clothing and gloves) should be used, in addition to following good housekeeping procedures.

Evaluation Question #8: Is the nutritional quality of the food maintained when the petitioned substance is used? (From 7 CFR § 205.600 (b) (3).)

Glucosamine hydrochloride is used as a nutritional supplement to relieve joint pain and is not normally part of any other foods to enhance handling/processing. The nutritional supplements containing glucosamine hydrochloride also have as ingredients (but not limited to): water, high fructose corn syrup, assorted fruit juices, chondroitin sulfate, preservatives, dyes, and flavors (both natural and artificial).

Evaluation Question #9: Is the petitioned substance to be used primarily as a preservative? (From 7 CFR § 205.600 (b) (4).)

Glucosamine hydrochloride is not used as a preservative.

Evaluation Question #10: Is the petitioned substance to be used primarily to recreate or improve flavors, colors, textures, or nutritive values lost in processing (except when required by law, e.g., vitamin D in milk)? (From 7 CFR § 205.600 (b) (4).)

Glucosamine hydrochloride is not used to recreate or improve flavors, colors, textures, or nutritive values lost in processing (except when required by law, e.g., vitamin D in milk).

Evaluation Question #11: Is the petitioned substance generally recognized as safe (GRAS) when used according to FDA's good manufacturing practices? (From 7 CFR § 205.600 (b) (5).)

Glucosamine hydrochloride is not generally recognized as safe (GRAS) when used according to FDA's good manufacturing practices. The FDA ceased its evaluation of glucosamine hydrochloride for GRAS status on September 9, 2004.

Evaluation Question #12: Does the petitioned substance contain residues of heavy metals or other contaminants in excess of FDA tolerances? (From 7 CFR § 205.600 (b) (5).)47

Glucosamine hydrochloride supplements do not contain residues of heavy metals or other contaminants in excess of FDA tolerances.

References

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