Kristi O. Smedley, Ph.D.
Center for Regulatory Services, Inc.
5200 Wolf Run Shoals Rd.
Woodbridge, VA 22192

Re: GRAS Notice No. GRN 000931

Dear Dr. Smedley:

This letter corrects our letter signed on November 12, 2020, sent in response to GRN 000931. The purpose of this revised letter is to correct a typographical error, where "creatinine monohydrate" rather than "creatine monohydrate" was reported as the test substance in paragraph 3 on page 2 of our November 12, 2020 letter.

The Food and Drug Administration (FDA, we) completed our evaluation of GRN 000931. We received the notice that you submitted on behalf of AlzChem Trostberg GmbH (AlzChem) on March 5, 2020, and filed it on June 12, 2020. AlzChem submitted amendments to the notice on August 12, 2020, September 2, 2020, and October 7, 2020, that provided clarification on the batch analyses data, specifications, analytical methods, and safety studies.

The subject of the notice is creatine monohydrate for use as an ingredient in "energy" drinks, protein bars and powders, milk shakes, meal replacement powders and bars, meat analogs, and powdered drink mixes (excluding infant formula and foods under the jurisdiction of the United States Department of Agriculture) at a level of 1.12 grams (g)/serving (equivalent to 1.0 g creatine/serving). The notice informs us of AlzChem's view that these uses of creatine monohydrate are GRAS through scientific procedures.

AlzChem provides information about the chemical identity of creatine monohydrate. AlzChem describes creatine monohydrate as a colorless, odorless, powder that is designated by the CAS Registry No. 6020-87-7, and has a molecular formula of $C_4H_9N_3O_2 \cdot H_2O$ and a molecular weight of 149.1 g/mol.

AlzChem describes the manufacturing process for creatine monohydrate. AlzChem states that creatine monohydrate is produced through chemical synthesis from the reaction of sodium sarcosinate and cyanamide under controlled pH and temperature. Creatine monohydrate precipitates from the reaction solution. After cooling, the creatine monohydrate is separated from the solution using suction filtration and is then

washed several times with potable water. The wet cake is then vacuum-dried and packaged. AlzChem states that creatine monohydrate is produced using current good manufacturing practices.

AlzChem provides specifications for creatine monohydrate that include limits for creatine monohydrate (≥99.9%), creatinine (≤100 mg/kg), dicyandiamide (≤50 mg/kg), dihydrotriazine (≤3 mg/kg), arsenic (≤0.1 mg/g), mercury (≤0.1 mg/g), lead (≤0.1 mg/g), and cadmium (≤0.1 mg/g). AlzChem provides results of analyses of three non-consecutive batches to demonstrate that creatine monohydrate can be manufactured to meet the specifications. AlzChem states that all analytical methods are validated methods that are fit for purpose. AlzChem states that the creatine monohydrate powder is stable for a minimum of three years at room temperature in the original unopened container.

AlzChem estimates the dietary exposure to creatine monohydrate from existing dietary sources and the intended uses using food consumption data from the 2013-2014 National Health and Nutrition Examination Survey. AlzChem estimates exposure to creatine monohydrate from the intended use in the specified foods at a maximum use level of 1.12 g per serving (equivalent to 1 g/serving creatine). AlzChem estimates that the eaters-only dietary exposure to creatine from the intended uses of creatine monohydrate would be 0.9 g/p/d at the mean and 1.5 g/p/d at the 90th percentile for the U.S. population. AlzChem also provides a cumulative dietary exposure to creatine from background sources of creatine and from the intended uses of creatine monohydrate. AlzChem estimates the cumulative eaters-only exposure for creatine to be 0.6 g/p/d and 1.4 g/p/d at the mean and 90th percentile, respectively for the U.S. population.

AlzChem discusses published data and information supporting the safety of creatine monohydrate, including studies that examined creatine monohydrate intake, metabolism, and effects on liver and kidney functions in rodents and humans. Creatine is normally found in skeletal muscle, but also in heart muscle, brain and testes of vertebrates. Creatine also occurs in commonly consumed foods like meat and fish. AlzChem states that the endogenous synthesis and metabolism of creatine are well known; and that humans absorb, metabolize, and irreversibly breakdown creatine to creatinine, which is excreted via the urine. AlzChem discusses a published study in which an oral dose of 2 g/kg bw/d creatine monohydrate did not exhibit any adverse effect on kidney function in healthy rats and those with already impaired kidney function. AlzChem discusses several published human studies that demonstrate that: (i) oral intake of up to 7 g/d creatine monohydrate for more than 12 months, with or without a loading phase, did not show any evidence of liver toxicity in healthy adults, athletes, post-menopausal women, cardiac patients, and type 2 diabetic patients; (ii) oral intake of up to 25 g/d for 4 years showed no adverse effects on renal function in healthy individuals; and (iii) short and long-term supplementation (up to 30 g/d for 5 years) is safe and well-tolerated in healthy individuals, as well as in infant and elderly patients.

AlzChem further discusses the opinions of several international regulatory bodies (i.e., European Scientific Committee for Food, the European Food Safety Authority,

Norwegian Scientific Committee for Food Safety, and Spanish Agency for Food Safety and Nutrition), which evaluated creatine monohydrate as a food additive and as a dietary supplement, and suggested that the consumption of doses up to 3 g/d is unlikely to pose any risks to humans.

Based on the totality of data and information presented in the notice, AlzChem concludes that creatine monohydrate is GRAS for its intended use in food.

Potential Labeling Issues

Under section 403(a) of the Federal Food, Drug, and Cosmetic Act (FD&C Act), a food is misbranded if its labeling is false or misleading in any way. Section 403(r) of the FD&C Act lays out the statutory framework for labeling claims characterizing a nutrient level in a food or the relationship of a nutrient to a disease or health-related condition (also referred to as nutrient content claims and health claims). If products containing creatine monohydrate bear any nutrient content or health claims on the label or in labeling, such claims are subject to the applicable requirements and are under the purview of the Office of Nutrition and Food Labeling (ONFL). The Office of Food Additive Safety did not consult with ONFL on this issue or evaluate any information in terms of labeling claims. Questions related to food labeling should be directed to ONFL.

Section 301(ll) of the FD&C Act

Section 301(ll) of the FD&C Act prohibits the introduction or delivery for introduction into interstate commerce of any food that contains a drug approved under section 505 of the FD&C Act, a biological product licensed under section 351 of the Public Health Service Act, or a drug or a biological product for which substantial clinical investigations have been instituted and their existence made public, unless one of the exemptions in section 301(ll)(1)-(4) applies. In our evaluation of AlzChem's notice concluding that creatine monohydrate is GRAS under its intended conditions of use, we did not consider whether section 301(ll) or any of its exemptions apply to foods containing creatine monohydrate. Accordingly, our response should not be construed to be a statement that foods containing creatine monohydrate, if introduced or delivered for introduction into interstate commerce, would not violate section 301(ll).

Conclusions

Based on the information that AlzChem provided, as well as other information available to FDA, we have no questions at this time regarding AlzChem's conclusion that creatine monohydrate is GRAS under its intended conditions of use. This letter is not an affirmation that creatine monohydrate is GRAS under 21 CFR 170.35. Unless noted above, our review did not address other provisions of the FD&C Act. Food ingredient manufacturers and food producers are responsible for ensuring that marketed products are safe and compliant with all applicable legal and regulatory requirements.

In accordance with 21 CFR 170.275(b)(2), the text of this letter responding to GRN 000931 is accessible to the public at www.fda.gov/grasnoticeinventory.

Sincerely,

Susan J. Carlson -S

Digitally signed by Susan J. Carlson -S
Date: 2020.12.03 13:49:16 -05'00'

Susan Carlson, Ph.D.
Director
Division of Food Ingredients
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