



Riette van Laack
Hyman, Phelps & McNamara, P.C.
700 Thirteenth Street, N.W., Suite 1200
Washington, D.C. 20005

Re: GRAS Notice No. GRN 001147

Dear Dr. van Laack:

This letter corrects our response letter to GRN 001147 signed on July 5, 2024. The purpose of this revised letter is to correct the CAS registry number for hydrated copper sulfate hydroxide from “687159-65-4” to “678159-65-4”.

The Food and Drug Administration (FDA, we) completed our evaluation of GRN 001147. We received the notice that you submitted on behalf of Copperprotek SPA (Copperprotek) on March 22, 2023 and filed it on September 21, 2023. Copperprotek submitted amendments on December 5, 2023, January 4, January 17, January 22, March 28, and May 3, 2024, that clarified the particle size distribution, manufacturing process, technical effect, specifications, intended uses, dietary exposure, and safety information.

The subject of the notice is copper (II) ion for use as an antimicrobial agent in polyolefin food packaging at a maximum level of 100 mg/m². The packaging is intended to be used for fresh beef, fresh pork, cooked sausage, deli meat, fresh salmon, and fresh cheese.¹ The notice informs us of Copperprotek’s view that these uses of copper (II) ion are GRAS through scientific procedures.

Copperprotek provides information on the identity and composition of the copper microparticles that result in the generation of copper (II) ions. Copperprotek states that copper (II) ions originate from microparticles containing copper sulfate hydroxide salts including tricopper tetrahydroxide sulfate, tribasic copper sulfate (CAS registry number 12068-81-4), copper sulfate pentahydrate (CAS registry number 7758-99-8), sodium dicopper hydroxide sulfate monohydrate, and hydrated copper sulfate hydroxide (CAS registry number 678159-65-4). Copperprotek describes the microparticles as spherical in shape with a single non-amorphous structure comprised of the five copper sulfate species. Copperprotek provides information on particle size distribution noting that 95% of the particles are in the 1-5 µm range.

¹ Copperprotek states that the copper (II) ion-containing food packaging is not intended for use for infant formula.

Copperprotek describes the manufacturing process for the copper microparticles and their incorporation into LLDPE. Copperprotek states that the copper microparticles are produced by precipitation of copper sulfate with sodium hydroxide until the pH is between 4 and 6. The copper hydroxide precipitate/gel is emulsified in a copper sulfate solution followed by spray drying resulting in a light green powder. The copper microparticles are gravimetrically mixed with molten LLDPE and then extruded to form light green pellets. Copperprotek states that the manufacturing process is consistent with good manufacturing practices and that all materials and processing aids utilized in the manufacturing process are used in accordance with applicable U.S. regulations or are concluded to be GRAS for their respective uses.

Copperprotek provides specifications for the copper microparticles in LLDPE pellets that include copper content (3.5 – 4.5 % w/w), pellet size (2 – 7 mm), pellet solubility (99.9% insoluble), and limits for arsenic (<0.3 mg/kg), cadmium (<0.3 mg/kg), mercury (<0.3 mg/kg), and lead (<0.3 mg/kg). Copperprotek provides the results from the analyses of three non-consecutive batches to demonstrate that the copper microparticles in LLDPE can be manufactured to meet the specifications. Copperprotek indicates that the copper microparticles in LLDPE are stable for 24 months when stored at room temperature in dry conditions.

Copperprotek estimates dietary exposure to copper based on the results of migration studies on sheets of LLDPE containing the copper microparticles at the intended use level of 100 mg copper (II) ion /m². Using the highest migration amount for copper and food consumption data from the 2015-2018 National Health and Nutrition Survey (NHANES), Copperprotek estimates the eaters-only dietary exposure to copper from the proposed uses to range from 81 – 238 µg/p/d at the 90th percentile for the U.S. population groups 1-3 years, 4-8 years, 9-13 years, 14-18 years, 19-50 years, 51 years and older. Copperprotek also estimates the cumulative dietary exposure to copper from the background consumption of food and dietary supplements and the proposed uses to range from 966 – 3095 µg/p/d at the 90th percentile for the same U.S. population groups².

Copperprotek describes the absorption, distribution, metabolism, and excretion (ADME) properties of copper (II) ion which is the copper species released from the copper microparticles in LLDPE. Copperprotek states that copper (II) ion is reduced to copper (I) by epithelial cell reductase enzymes, and that copper (I) is primarily absorbed in the stomach and small intestine and transported to the liver by portal circulation. Copperprotek discusses several published oral toxicology studies in animals including long-term repeat-dose oral toxicology studies. Copperprotek also discusses a range of information on oral exposure to copper in humans. The weight of evidence suggests that the proposed dietary exposure to copper in humans from copper (II) ion is not

² Using food consumption data from 2015-2018 NHANES, FDA estimated the cumulative dietary exposure to copper from the background consumption of food, dietary supplements, drinking water and the proposed uses to be 1430 µg/p/d at the mean and 2610 µg/p/d at the 90th percentile for the U.S. population aged 2 years and older.

associated with adverse health effects.

Copperprotek states that the technical effect for copper microparticles in polyolefin food packaging is as an antimicrobial. Copperprotek provides results demonstrating this technical effect in fresh beef and processed meat.

Based on the totality of evidence, Copperprotek concludes that copper (II) ion is GRAS for its intended use.

Use in Products under USDA Jurisdiction

As provided under 21 CFR 170.270, during our evaluation of GRN 001147, we coordinated with the Food Safety and Inspection Service (FSIS) of the United States Department of Agriculture. Under the Federal Meat Inspection Act, the Poultry Products Inspection Act, and the Egg Products Inspection Act, FSIS determines the efficacy and suitability of ingredients used in meat, poultry, and egg products, and prescribes safe conditions of use. Suitability relates to the ingredient's effectiveness in performing its intended technical effect and the assurance that the ingredient's use will not result in products that are adulterated or misleading for consumers. FSIS has completed its review and has no objection to the use of copper (II) ion as an antimicrobial agent in polyolefin food packaging at a maximum level of 100 mg/m² on fresh meat and red meat sausage. The no objection does not extend to Modified Atmospheric Packaging. Regarding labeling, in lieu of a declaration of the copper film, a "use by" or a "use or freeze by" date will be acceptable. Due to the migration of copper into the products and the extension of shelf-life, copper (II) ion would not be considered a processing aid. FSIS requested that we advise you to seek regulatory guidance from its Risk Management and Innovations Staff (RMIS) about the use of copper (II) ion in meat, poultry and egg products. You should direct such an inquiry to Stephanie Hretz, Director, RMIS, Office of Policy and Program Development, FSIS by email at Stephanie.Hretz@usda.gov.

Standard of Identity

In the notice, Copperprotek states its intention to use copper (II) ion in packaging for food in several food categories, including foods for which standards of identity exist, located in Title 21 of the Code of Federal Regulations. We note that an ingredient that is lawfully added to food products may be used in a standardized food only if it is permitted by the applicable standard of identity.

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(l)(1)-(4) applies. In our evaluation of Copperprotek's notice concluding that copper (II) ion is GRAS under its intended conditions of use, we did not consider whether section 301(l) or any of its exemptions apply to foods containing copper (II) ion. Accordingly, our response should not be construed to be a statement that foods containing copper (II) ion, if introduced or delivered for introduction into interstate commerce, would not violate section 301(l).

Conclusions

Based on the information that Copperprotek provided, as well as other information available to FDA, we have no questions at this time regarding Copperprotek's conclusion that copper (II) ion is GRAS under its intended conditions of use. This letter is not an affirmation that copper (II) ion 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 001147 is accessible to the public at www.fda.gov/grasnoticeinventory.

Sincerely,

**Susan J.
Carlson -S**

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