



Michel Donat, Pharm. D.
Société des Produits Nestlé S.A.
Avenue Nestlé 55, 1800 Vevey
SWITZERLAND

Re: GRAS Notice No. GRN 000959

Dear Dr. Donat:

The Food and Drug Administration (FDA, we) completed our evaluation of GRN 000959. We received Société des Produits Nestlé S.A.'s (Nestlé's) notice on June 1, 2020, and filed it on October 2, 2020. Nestlé submitted an amendment to the notice on December 18, 2020, providing clarification on the intended uses as well as an updated dietary exposure estimate.

The subject of the notice is iron milk proteinate for use as a dietary source of iron in conventional food and beverages.¹ Nestlé intends to use iron milk proteinate at levels consistent with current good manufacturing practice (cGMP) in accordance with the principles of FDA's fortification guidelines and fortification policy.² The notice informs us of Nestlé's view that this use of iron milk proteinate is GRAS through scientific procedures.

Our use of the term, "iron milk proteinate," in this letter is not our recommendation of that term as an appropriate common or usual name for declaring the substance in accordance with FDA's labeling requirements. Under 21 CFR 101.4, each ingredient must be declared by its common or usual name. In addition, 21 CFR 102.5 outlines general principles to use when establishing common or usual names for nonstandardized foods. Issues associated with labeling and the common or usual name of a food ingredient are under the purview of the Office of Nutrition and Food Labeling (ONFL) in the Center for Food Safety and Applied Nutrition. The Office of Food Additive Safety did not consult with ONFL regarding the appropriate common or usual name for "iron milk proteinate."

Nestlé provides information on the identity and composition of iron milk proteinate. Nestlé describes iron milk proteinate as a white to off-white powder that is highly soluble in water. Iron milk proteinate is a complex of ferric iron linked to sodium caseinate. The backbone is comprised of phosphoserine residues of casein that function as the binding sites for ferric ions which are stabilized by inorganic phosphate.

¹ Nestlé does not intend to use iron milk proteinate in infant formula or in any products under the jurisdiction of the United States Department of Agriculture.

² 21 CFR 104.20

Nestlé describes the manufacturing process for iron milk proteinate. Nestlé states that iron milk proteinate is produced by adding ferric salt to a solution of casein in the presence of orthophosphate. First, sodium caseinate powder is added to heated deionized water until it is completely dissolved. The dissolved caseinate solution is then cooled to ambient temperature, and a dipotassium hydrogen orthophosphate solution is added. Next, a ferric salt solution is gradually added while maintaining a neutral pH. The resulting solution is then stirred, pasteurized, concentrated, and spray-dried. Nestlé states that all raw materials and processing aids are food grade and are used in accordance with an applicable regulation, have been previously concluded to be GRAS for their intended use, or have been the subject of an effective food contact notification.

Nestlé provides specifications for iron milk proteinate that include limits for protein ($\geq 50\%$), moisture ($< 8\%$), fat ($< 1\%$), ash ($\geq 27\%$), sodium ($< 5\%$), iron ($\geq 2\%$), phosphorus ($\geq 3\%$), arsenic (< 1 mg/g), lead (< 0.5 mg/g), cadmium (< 0.5 mg/g), and microorganisms. Nestlé provides results from the analyses of five non-consecutive batches to demonstrate that iron milk proteinate can be manufactured to meet the specifications. Nestlé states that the powder form of iron milk proteinate has been shown to be stable for a minimum of six months at 20 °C and 37 °C.

Nestlé estimates the dietary exposure to iron from the background diet (food and dietary supplements) using food consumption data from the 2015-2016 National Health and Nutrition Examination Survey. Nestlé assumes that iron from iron milk proteinate would be the sole source of iron in the diet and therefore, all exposure to iron from the background diet would be as a result of the consumption of iron milk proteinate. Nestlé estimates the eaters-only dietary exposure to iron from background sources to be 16 mg/p/day (d) at the mean and 28 mg/p/d at the 90th percentile for the U.S. population aged 1 year and older. Presuming that iron comprises 2.7% of iron milk proteinate on average, Nestlé estimates the exposure to iron milk proteinate to be 608 mg/p/d at the mean and 1,034 mg/p/d at the 90th percentile for the U.S. population aged 1 year and older. Nestlé further notes that the intended uses of iron milk proteinate will be substitutional for other iron-containing ingredients currently in use in the U.S. marketplace. Therefore, the intended uses of iron milk proteinate will not increase the current dietary exposure to iron for the U.S. population.

Nestlé discusses published safety data on iron milk proteinate and its components (iron, phosphate, and casein). Nestlé states the dietary exposure to iron in the U.S. population arising from current iron fortification practices is below the upper limit (UL) of 45 mg/d established by the Institute of Medicine (IOM, 2006).³ Nestlé discusses the results of *in vitro* and *in vivo* studies to demonstrate that iron milk proteinate is soluble, readily digested to peptides, and has a similar iron bioavailability as ferrous sulfate. Nestlé states that because iron milk proteinate has similar bioavailability to ferrous sulfate, animal toxicity studies of ferrous sulfate are relevant to the safety evaluation of iron

³ Nestlé states that the results of an updated literature search through May 2020 indicate that there have not been any published studies since the 2006 IOM review that would contradict the previous safety conclusions.

milk proteinate. Nestlé summarizes published 31-day, 61-day, and 7-week repeated dose oral toxicity studies using ferrous sulfate in rats and mice, as well as developmental studies demonstrating no toxicologically relevant effects. Nestlé also notes that the uses of a number of iron compounds are either the subjects of previous GRAS notices⁴ or are GRAS affirmed with no limitations other than cGMP. Nestlé states that their intended uses of iron milk proteinate do not appreciably increase the U.S. population's existing exposure to phosphorus and therefore, it is not expected to pose any safety concerns. Nestlé summarizes published short-term, subchronic, and chronic toxicity studies conducted with various phosphates and polyphosphates, as well as human clinical studies. Nestlé states that casein and caseinates are natural components of milk and have a history of safe consumption in the human diet. Nestlé summarizes the safety conclusion for casein and caseinates in a review conducted previously by the Select Committee on GRAS Substances (SCOGS).

Nestlé includes the statement of a panel of individuals (Nestlé's GRAS panel). Based on its review, Nestlé's GRAS panel concluded that iron milk proteinate is safe under the conditions of its intended use.

Based on the totality of the data and information, Nestlé concludes that iron milk proteinate is GRAS for its intended use.

Standards of Identity

In the notice, Nestlé states its intention to use iron milk proteinate in several food categories, including foods for which standards of identity exist, located in Title 21 of the CFR. 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.

Allergen Labeling

The FD&C Act requires that the label of a food that is or contains an ingredient that contains a "major food allergen" declare the allergen's presence (section 403(w)). The FD&C Act defines a "major food allergen" as one of eight foods or food groups (i.e., milk, eggs, fish, Crustacean shellfish, tree nuts, peanuts, wheat, and soybeans) or a food ingredient that contains protein derived from one of those foods. Iron milk proteinate requires labeling under the FD&C Act because it contains proteins derived from milk.

Potential Labeling Issues

Under section 403(a) of the 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

⁴ We evaluated GRN 000019 (ferrous bisglycinate chelate), GRNs 000152 and 000178 (sodium iron EDTA), GRN 000271 (ferrous ammonium phosphate), and GRN 000441 (sodium ferrous citrate), and we responded in letters dated September 30, 1999, December 9, 2004, January 11, 2006, May 29, 2009, and May 10, 2013, respectively, that we had no questions at that time regarding the notifiers' GRAS conclusions.

nutrient to a disease or health-related condition (also referred to as nutrient content claims and health claims). If products containing iron milk proteinate 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) in the Center for Food Safety and Applied Nutrition. 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(II) of the Federal Food, Drug, and Cosmetic Act (FD&C Act)

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


Conclusions

Based on the information that Nestlé provided, as well as other information available to FDA, we have no questions at this time regarding Nestlé's conclusion that iron milk proteinate is GRAS under its intended conditions of use. This letter is not an affirmation that iron milk proteinate 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 000959 is accessible to the public at www.fda.gov/grasnoticeinventory.

Sincerely,

Susan J.
Carlson -S

 Digitally signed by Susan J.
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Susan Carlson, Ph.D.
Director
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