Donald Schmitt, MPH
ToxStrategies, Inc.
739 Thornapple Drive
Naperville, IL
60540

Re: GRAS Notice No. GRN 001036

Dear Mr. Schmitt:

The Food and Drug Administration (FDA, we) completed our evaluation of GRN 001036. We received the notice that you submitted on behalf of Cargill, Inc. (Cargill) on October 26, 2021, and filed it on February 1, 2022. Cargill, submitted an amendment to the notice on May 27, 2022 that clarified the identity, intended uses, use level, specifications, dietary exposure, and safety information.

The subject of the notice is the complexation products of iron (II) with sodium citrate (iron citrate) for use as an anticaking agent in salt at a maximum use level of 156 mg/kg (equivalent to 30 mg/kg as iron). The notice informs us of Cargill's view that this use of iron citrate is GRAS through scientific procedures.

Cargill describes iron citrate as a dark green/red aqueous solution comprised of at least 22% by weight of the complexation products of iron and citrate (1:1) with an ionization level of ≥3.5 but ≤4 and a pH of 5–10. Cargill states that the nominal empirical chemical formula for iron citrate is $Na_{x+1}FeC_6H_{5-x}O_7$ (x = 0.5–1.0) and the molecular weight is 278.93–289.92 g/mol.

Cargill describes the manufacturing method for iron citrate. It is prepared by mixing a ferrous iron salt and sodium citrate in water, with sodium hydroxide added to adjust the pH. The solution is then filtered and cooled as necessary and transferred to storage containers. Cargill states that iron citrate is manufactured in accordance with current good manufacturing practices using food grade raw materials and processing aids.

Cargill provides specifications for iron citrate that include limits for total iron (>3.5%), citrate (>11.5%), pH (5-10), density (>1.2 g/ml), water (≤78%), arsenic (≤1 mg/kg), lead (≤3 mg/kg), mercury (≤1 mg/kg), cadmium (≤1 mg/kg), and maximum ratios (on a molar basis) of chloride, sulfate, and sodium *vs.* iron (2.2:1, 1.2:1, and 5.6:1, respectively). Cargill provides analytical results from four non-consecutive batches to demonstrate that iron citrate can be manufactured to meet the specifications. Cargill states that iron citrate is stable for at least 4 months when stored at 2-20°C in a closed container out of direct sunlight or in an amber bottle.

To estimate dietary exposure to iron citrate, Cargill uses reported dietary exposures to sodium based on food consumption data from the 2013-2016 the National Health and Nutrition Examination Survey (NHANES) and presumes that all salt contained iron citrate at a level of 156 mg/kg. Cargill estimates the mean dietary exposure to iron citrate from the intended uses to be 1.3 mg/person (p)/day (d) (0.25 mg iron/p/d) for the US population aged >1 year.[1] Cargill notes that iron citrate will be used as an alternative to, not in addition to, other anticaking agents used in salt. Cargill further notes that it is unlikely that iron citrate will replace all other anticaking agents currently added to salt.

Cargill describes the history of safe use of the iron-based compounds ferric citrate and ferrous citrate in dietary food products. Cargill notes that several other iron compounds are recognized as GRAS for their intended uses in food including as an anti-caking agent in salt.

Cargill discusses the absorption, distribution, metabolism, and excretion (ADME) properties of iron citrate and its components. Cargill notes that iron balance in the body is highly conserved with only a small quantity lost each day via fecal excretion. Cargill states that citric acid (citrate) is an intermediate in the citric acid cycle; the majority of citrate is filtered and reabsorbed by the kidney and a small portion is excreted in urine. Citing published studies Cargill also notes that ferric citrate is not mutagenic or genotoxic. Cargill discusses many oral toxicology studies in rodents performed by different groups. These studies were conducted for different durations varying from approximately 2 weeks through 96 weeks. Cargill notes that collectively the animal toxicology studies are relevant in the context of determination of human iron exposure as established by the Institute of Medicine's (IOM's) dietary reference intake as well as the tolerable upper limit (UL) values of iron for various age groups.

Cargill notes that the potential iron intake resulting from iron citrate as an anti-caking agent in salt (0.16 - 0.26 mg/p/d) is well below the IOM UL values[2]. Cargill also notes that the consumption of iron citrate in salt is expected to have a negligible contribution on background dietary intake of iron. Cargill concludes that consumption of iron citrate used as an anti-caking agent in salt is not expected to have any adverse health concerns from the level of exposure to ferrous citrate or iron. In addition to discussing IOM's recommended daily allowances (RDAs) and the tolerable upper intake levels (ULs) for iron intake across different age and sex groups and life stages, Cargill also discusses the JECFA-established provisional maximum tolerable daily intake (PMTDI) for dietary iron in adults (0.8 mg/kg body weight (bw)/d, or 56 mg/p/d based on a 70-kg adult). In addition, a JECFA evaluation of citric acid concluded that the acceptable daily intake (ADI) for this substance was "not limited."

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[1] Using more recent food consumption data from the 2015-2018 NHANES, FDA estimates the dietary exposure to iron citrate to be 1.3 mg/p/d (0.25 mg iron/p/d) at the mean and 2.0 mg/p/d (0.38 mg iron/p/d) at the 90th percentile for the US population aged 2 years and older.

[2] IOM provides a UL for iron consumption of 45 mg/person/day for adults (>14 years old) and 40 mg/person/day for children (1-13 years old). These values, along with the daily potential iron intake resulting from iron citrate calculated by Cargill, are calculated by age category independent of body weight.

Based on the totality of evidence, Cargill concludes that iron citrate is GRAS for its intended use.

Potential Requirement for a Color Additive Petition

There is no GRAS provision for color additives. In the notice, Cargill describes iron citrate as dark green/ red. As such, the use of iron citrate in food products may constitute a color additive use under section 201(t)(1) of the FD&C Act and FDA's implementing regulations in 21 CFR Part 70. Under section 201(t)(1) and 21 CFR 70.3(f), a color additive is a material that is a dye, pigment, or other substance made by a synthetic process or similar artifice, or is extracted, isolated, or otherwise derived from a vegetable, animal, mineral, or other source. Under 21 CFR 70.3(g), a material that otherwise meets the definition of a color additive can be exempt from that definition if it is used (or is intended to be used) solely for a purpose or purposes other than coloring. Our response to GRN 001036 is not an approval for use as a color additive nor is it a finding of the Secretary of the Department of Health and Human Services within the meaning of section 721(b)(4) of the FD&C Act. Questions about color additives should be directed to the Division of Food Ingredients in the Office of Food Additive Safety.

Section 301(ll) of the Federal Food, Drug, and Cosmetic Act (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 Cargill's notice concluding that iron citrate 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 iron citrate. Accordingly, our response should not be construed to be a statement that foods containing iron citrate if introduced or delivered for introduction into interstate commerce, would not violate section 301(ll).

Conclusions

Based on the information that Cargill provided, as well as other information available to FDA, we have no questions at this time regarding Cargill's conclusion that iron citrate is GRAS under its intended conditions of use. This letter is not an affirmation that iron citrate 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 001036 is accessible to the public at www.fda.gov/grasnoticeinventory.

Sincerely,

Susan J. Carlson -S

Digitally signed by Susan J. Carlson -S
Date: 2022.10.06 17:47:55 -04'00'

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