David Tsivion, Ph.D.
DouxMatok Ltd.
9 Shimshon Street
Petach-Tikva 49517
ISRAEL

Re: GRAS Notice No. GRN 000996

Dear Dr. Tsivion,

This letter revises our response letter to GRN 000996 signed on February 4, 2022. The purpose of this revised letter is to include the additional amendment submitted by the notifier on February 4, 2022.

The Food and Drug Administration (FDA, we) completed our evaluation of GRN 000996. We received DouxMatok Ltd.'s (DouxMatok's) notice on March 1, 2021 and filed it on June 17, 2021. DouxMatok submitted amendments to the notice on October 5, 2021 and February 4, 2022 that provided clarifications on the physical characterization, including particle size distribution, specifications, method of manufacture, dietary exposure, information related to safety, and the updated literature search.

The subject of the notice is synthetic amorphous silica (SAS) for use as a carrier to deliver and improve the perception of sweetness of white sugar at levels up to 0.30 g/100g.[1,2] The notice informs us of DouxMatok's view that this use of SAS is GRAS, through scientific procedures.

DouxMatok provides information on the identity and composition of SAS as a fine white powder in the form of silica gel (CAS 112926-00-8) with an average particle size ranging from 4.5 to 5.3 micrometers (µm).

DouxMatok describes the manufacturing process of SAS. Silica gel is produced by mixing alkali metal silicate solution with sulfuric acid or hydrochloric acid under controlled conditions resulting in a hydrosol made up of particles; upon drying, they adhere to form aggregates. DouxMatok states that physical parameters such as pore size, particle size distribution, and surface area are controlled by process conditions; primary particles range from 5 nm to 50 nm and cluster via Si-O-Si covalent bonds that further aggregate to particles ranging in size from 2.4 to 15 µm. These aggregates can be

[1] DouxMatok notes that SAS is not intended for use in infant formula or in foods that fall under the purview of the U.S. Department of Agriculture.
[2] 21 CFR 170.3 (n)

milled to the desired final particle size and DouxMatok states that SAS in the solid powder forms does not exist as nanoparticles. DouxMatok states that the mean diameter of SAS aggregates or agglomerates formed is typically above 100 nanometers. DouxMatok states that SAS is manufactured consistently with current good manufacturing practices (cGMP).

DouxMatok provides specifications for SAS that include appearance, loss on ignition (≤ 8.5% (w/w)), loss on drying (≤ 7% (w/w)), silica (≥ 99.4% (w/w)), average particle size (4.5 to 5.3 µm), limits for heavy metals, including lead (≤ 4.5 mg/kg), and microorganisms. DouxMatok provides results from five non-consecutive lots of SAS to demonstrate that it can be manufactured to meet specifications. DouxMatok also states that SAS conforms to the specifications for silicon dioxide in Food Chemicals Codex (12th Edition, FCC, 2021).

DouxMatok provides an estimate of dietary exposure to SAS from the intended use based on average daily food consumption data from the 2015-2016 National Health and Nutrition Examination Survey (NHANES). DouxMatok estimates the mean and 90th percentile eaters-only dietary exposure to SAS to be 46 mg/p/d and 103 mg/p/d, respectively for the U.S. population aged 2 years and older. DouxMatok also estimates the mean and 90th percentile cumulative dietary exposure to SAS to be 160 mg/p/d and 245 mg/p/d, respectively, for the U.S. population ages 2 years and older, by considering a background dietary exposure of 107 mg/p/d to SAS. DouxMatok states that use of SAS is self-limiting.

DouxMatok states that SAS in the form of silica gel used in white sugar has the same chemical identity as the ingredients that were previously concluded to be GRAS in GRN 000321 and 000554[3], and incorporates safety narratives from them. DouxMatok states that the majority of SAS is excreted in the feces and not expected to undergo significant intestinal absorption; further, any small quantities of soluble SAS that are absorbed will be excreted unchanged in the urine. DouxMatok summarizes published and unpublished safety studies evaluated by EFSA, OECD, JECFA, and ECETOC, as corroborative information. DouxMatok states that an updated literature search through August 2020 identified no new studies that would contradict their GRAS conclusion.

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

Based on the totality of the data and information, DouxMatok concludes that SAS is GRAS for its intended use.

[3] We evaluated GRNs 000321 and 000554 and responded in letters dated August 18, 2010 and May 14, 2015, respectively, stating that we had no questions at the time regarding the notifiers' GRAS conclusions.

Standards of Identity

In the notice, DouxMatok states its intention to use SAS 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.

Potential Labeling Issues

Under section 403(a) of the Federal Food, Drug, & Cosmetic (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 SAS 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(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 DouxMatok's notice concluding that SAS 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 SAS. Accordingly, our response should not be construed to be a statement that foods containing SAS, if introduced or delivered for introduction into interstate commerce, would not violate section 301(ll).

Conclusions

Based on the information that DouxMatok provided, as well as other information available to FDA, we have no questions at this time regarding DouxMatok's conclusion that SAS is GRAS under its intended conditions of use. This letter is not an affirmation that SAS 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 000996 is accessible to the public at www.fda.gov/grasnoticeinventory.

Sincerely,

Susan J. Carlson -S

Digitally signed by Susan J. Carlson -S
Date: 2022.02.17 15:28:23 -05'00'

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