William J. Rowe
GRAS Associates, LLC
11810 Grand Park Ave, Suite 500
North Bethesda, MD 20852

Re: GRAS Notice No. GRN 001155

Dear Mr. Rowe:

The Food and Drug Administration (FDA, we) completed our evaluation of GRN 001155. We received the notice that you submitted on behalf of Fresh Inset S.A. (Fresh Inset) on September 6, 2023, and filed it on November 15, 2023. Fresh Inset submitted amendments to the notice on February 12, 2024, and March 12, 2024, regarding the manufacturing process, specifications, and dietary exposure.

The subject of the notice is 1-methylcyclopropene and α-cyclodextrin complex (1-MCP complex) for use as an ethylene inhibitor on stickers placed inside food packaging for cut fresh produce (sliced melon, pineapple, apple, mushroom, and shredded cabbage/coleslaw) at a maximum level of 9.086 µg of 1-MCP per kg of fresh produce to extend the shelf life of the fresh produce.[1] The notice informs us of Fresh Inset's view that this use of 1-MCP complex is GRAS through scientific procedures.

Fresh Inset describes 1-MCP complex as a complex of 1-MCP (CAS Registry Number 3100-04-7) and α-cyclodextrin. Fresh Insets states that 1-MCP is a colorless gas at room temperature that volatizes from moist surfaces and water and is chemically unstable. Fresh Inset states that 1-MCP is complexed with α-cyclodextrin to improve stability.

Fresh Inset describes the method of manufacture for 1-MCP complex. First, toluene is mixed with sodium amide at a 15:1 ratio under an inert gas in a reactor equipped with a condenser and airtight stirrer. After bringing the mixture to reflux, 3-chloro-2-methylpropene (3-CMP) is added dropwise until all the starting material is consumed. The escaping gases are passed through sulfuric acid whereupon 1-MCP is collected by condensation in a condenser cooled to -78 °C. 1- MCP is heated to its boiling point (48 to 54 °F) and is stirred into α-cyclodextrin dissolved in a small amount of water. The resulting precipitate consisting of α-cyclodextrin and approximately 5% (w/w) of 1-MCP is filtered, washed, and diluted with α-cyclodextrin to adjust the content of 1-MCP to 3.3% (w/w). Fresh Inset states that 1-MCP complex is manufactured in accordance with current good manufacturing practices.

[1] Fresh Inset states that 1-MCP complex is not intended for use in any products under the jurisdiction of the U.S. Department of Agriculture or in infant formula.

Fresh Inset provides specifications for 1-MCP complex that includes content of 1-MCP (3.3 ± 0.165%) and limits for 3-chloro-2-methylpropene (≤ 0.02% of the 1-MCP content), 1-chloro-2-methylpropene (≤0.02% of the 1-MCP content), methylidene cyclopropane (≤1.96% of the 1-MCP content), and toluene (<0.05% of the 1-MCP content). Fresh Inset provides the results from the analyses of five non-consecutive batches to demonstrate that 1-MCP complex can be manufactured to meet these specifications.

Fresh Inset estimates the dietary exposure to 1-MCP based on the intended uses of 1-MCP complex and using food consumption data from the 2017-2020 National Health and Nutrition Examination Survey (NHANES). Fresh Inset estimates the mean and 90th percentile eaters-only dietary exposure to 1-MCP for the total U.S. population to be 0.71 µg/person (p)/d and 1.48 µg/p/d, respectively.[2] Fresh Inset states that the intended uses of 1-MCP are substitutional for the uses of 1-MCP specified in GRN 000585.[3]

Fresh Inset performed an updated literature search through July 2023, and summarizes published data and information supporting the safety of 1-MCP complex for use as an ethylene inhibitor for cut produce. Fresh Inset discusses the results of published genotoxicity, acute and subchronic (oral and inhalation) toxicity, reproductive and developmental toxicity, and endocrine disruption studies on 1-MCP. Based on the ADME study, Fresh Inset notes that 1-MCP has little possibility to accumulate in tissues or blood. Fresh Inset states that 1-MCP is not genotoxic and does not show any adverse effects up to 22.4 and 26.5 mg/kg bw/d of 1-MCP in male/female rats in the 91-day study, and up to 4.1 mg 1-MCP/kg bw/d in the 90-day dog study.

Based on the data and information provided in the submission, Fresh Inset concludes that 1-MCP complex is GRAS under the conditions of its intended use.

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 Fresh Inset's notice concluding that 1-MCP complex 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 1-MCP complex. Accordingly, our response should not be construed to be a statement that foods containing 1-MCP complex, if introduced or delivered for introduction into interstate commerce, would not violate section 301(ll).

[2] OFAS estimated the mean and 90th percentile eaters-only dietary exposures to 1-MCP for the U.S. population aged 2 years and older to be 0.711 µg/p/d (0.013 µg/kg bw/d) and 1.48 µg/p/d (0.028 µg/kg bw/d), respectively, using food consumption data from the 2017-2020 NHANES.

[3] The subject of GRN 000585 is 1-MCP complex. We evaluated this notice and responded in a letter dated January 29, 2016, stating that we had no questions at that time regarding the notifier's GRAS conclusion.

Conclusions

Based on the information that Fresh Inset provided, as well as other information available to FDA, we have no questions at this time regarding Fresh Inset's conclusion that 1-MCP complex is GRAS under its intended conditions of use. This letter is not an affirmation that 1-MCP complex 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 001155 is accessible to the public at www.fda.gov/grasnoticeinventory.

Sincerely,

Susan J. Carlson -S

Digitally signed by Susan J. Carlson -S
Date: 2024.04.23 13:04:34 -04'00'

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