



Ashish Talati  
Amin Talati Wasserman  
100 S. Wacker Drive, Suite 2000  
Chicago, IL 60606

Re: GRAS Notice No. GRN 001032

Dear Mr. Talati:

The Food and Drug Administration (FDA, we) completed our evaluation of GRN 001032. We received the notice that you submitted on behalf of Osaka Gas Chemicals Co. Ltd. (Osaka Gas) on October 29, 2021, and filed it on December 17, 2021. Osaka Gas submitted amendments to the notice on December 14, 2021, and March 7, 2022, providing additional information regarding the identity, manufacturing process, specifications, stability, and the safety narrative.

The subject of the notice is D-β-hydroxybutyrate (D-BHB) for use as an ingredient at levels up to 6 g per serving in sports and nutritional beverages or powder, sports and nutrition bars, and sports and nutrition gels.<sup>1</sup> The notice informs us of Osaka Gas's view that the use of D-BHB is GRAS through scientific procedures.

Our use of the terms, "D-β-hydroxybutyrate" and "D-BHB," 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 (OFAS) did not consult with ONFL regarding the appropriate common or usual names for "D-β-hydroxybutyrate" or "D-BHB."

Osaka Gas provides information on the identity and composition of the notified substance. D-BHB is described as a clear to pale yellow liquid that contains >95 % of D-β-hydroxybutyrate on a dry matter basis. D-BHB is also known as (3R)-3-hydroxybutanoate; (R)-3-hydroxybutyrate; D-3-hydroxybutyrate; D-beta-hydroxybutyrate; 3-D-hydroxybutyrate; and 3-hydroxy-butanoic acid. It has a molecular weight of 104.1 Da and a CAS registry number 625-72-9. Osaka Gas states that D-BHB is produced as an approximately 40% aqueous solution and may also be produced as 60% or 80% aqueous solutions based on requirements of the end user.

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<sup>1</sup> Osaka Gas states that D-BHB is not intended for use in infant formula or in any products under the jurisdiction of the United States Department of Agriculture.

Osaka Gas describes the production organism used in the manufacture of D-BHB. Osaka Gas states that *Halomonas* sp. KM-1 is non-pathogenic and non-toxigenic,<sup>2</sup> and does not produce any secondary metabolites of concern. *Halomonas* sp. KM-1 is deposited in the International Patent Organism Depository (IPOD, AIST, Japan) with the deposit designation FERM BP-10995. Osaka Gas states that the genome of *Halomonas* sp. KM-1 FERM BP-10995 has been fully sequenced and that its genome contains resistance genes for several antibiotics, including bacitracin, beta-lactam, fosfomycin, macrolide, penicillin, and streptogramin. Osaka Gas states that these antibiotic resistance genes do not pose a safety concern because the nanofiltration step removes residual genomic DNA from the final product.

Osaka Gas states that D-BHB is manufactured by fermentation of the production strain. The fermentation is carried out under controlled conditions. After fermentation is complete, D-BHB is separated from the medium components through a series of filtration steps. Following this, the solution containing D-BHB is concentrated and subjected to cation exchange purification. The resulting solution is then filtered through a nanofiltration membrane and treated with activated carbon. The pH is neutralized, and the final product obtained by concentration. Osaka Gas states that all raw materials and processing aids used in the manufacture of D-BHB are food-grade, safe and suitable for use in the manufacture of food ingredients and comply with applicable U.S. regulations or have previously been concluded to be GRAS.

Osaka Gas provides specifications for D-BHB that includes a minimum assay content of  $\geq 93\%$  of D-BHB ( $\geq 95\%$  BHB (free) and  $\leq 5\%$  acetic acid). Specifications also include free  $\beta$ -hydroxybutyrate (38 - 40% of D- and L- $\beta$ -hydroxybutyrate), chirality ( $\geq 95\%$  D-BHB on a dry matter basis), and limits for lead ( $\leq 0.5$  mg/kg), and microorganisms. Osaka Gas provides the results of the analyses from seven non-consecutive batches to demonstrate that D-BHB can be manufactured to meet specifications.

Osaka Gas provides estimates of dietary exposure to D-BHB from the intended uses in food based on food consumption data from the 2017-2018 National Health and Nutrition Examination Survey (NHANES). Osaka Gas notes that consumption data for sports and nutrition gels are not available in the 2017-2018 NHANES; therefore, this use was not included in their estimate of dietary exposure. Osaka Gas also states that the use of D-BHB in sports and nutrition gels is substitutional for other foods containing D-BHB. Osaka Gas estimates the mean and 90<sup>th</sup> percentile eaters-only dietary exposures to D-BHB for U.S. population, aged 2 years and older, to be 6.3 g/person (p)/day (d) (92 mg/kg body weight (bw)/d) and 13.7 g/p/d (198 mg/kg bw/d), respectively. Osaka Gas reports that the highest dietary exposures to be among male adults with the mean and 90<sup>th</sup> percentile estimated to be 7.8 g/p/d (92 mg/kg bw/d) and 16.9 g/p/d (191 mg/kg bw/d), respectively. Osaka Gas reports that children aged 2 to 5 years had the highest mean dietary exposure on a body weight basis (201 mg/kg bw/d) and children aged 6 to 11 years had the highest 90<sup>th</sup> percentile dietary exposure (342 mg/kg bw/d). Osaka Gas states that foods containing D-BHB are intended for consumers that are high-

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<sup>2</sup> In an amendment dated March 7, 2022, Osaka Gas states that *Halomonas* sp. KM-1 does not include genes that code for toxins or virulence factors.

performance athletes and at least 18 years old; therefore, Osaka Gas considers the dietary exposures to D-BHB for ages < 18 years old to be overestimates. Based on suggested servings of 1-3 per day, Osaka Gas estimates a dietary exposure to D-BHB to be 6 to 18 g/p/d, which is equivalent to 86 to 257 mg/kg bw/d for a 70 kg adult.

Osaka Gas discusses data and information supporting the safety of D-BHB and related compounds D-β-hydroxybutyrate ester (HBE) and its metabolite (R)-1,3-butanediol. Osaka Gas describes the endogenous role of D-BHB in the physiological ketosis response during periods of fasting or limited glucose availability. Osaka Gas indicates that the safety of D-BHB is further supported by the data and information in GRN 000515.<sup>3</sup> Osaka Gas states that the intended use of D-BHB in this notice will be substitutional for HBE. Osaka Gas describes the metabolic fate of D-BHB utilizing generally accepted scientific information pertaining to physiologic ketosis and pharmacokinetic studies in rodents and humans that were administered D-BHB salts or HBE. Osaka Gas provides a summary of published toxicity studies including 28-day and developmental toxicity studies of HBE in rats to support the safe use of D-BHB. Osaka Gas states that the safety of D-BHB is corroborated by the results of an unpublished 28-day repeat dose rat oral toxicity study of dried cells of *Halomonas* sp. KM-1 and D-BHB. Osaka Gas also describes several published, randomized, double-blind, placebo-controlled human studies to further support the safety of the intended use of D-BHB.

Osaka Gas conducted a comprehensive literature search through August 2021 to identify available safety information relevant to D-BHB and related compounds. Osaka Gas did not identify any safety concerns or information that would contradict its GRAS conclusion.

Osaka Gas includes the opinion of a panel of individuals (Osaka Gas's GRAS panel). Based on its review, Osaka Gas's GRAS panel concluded D-BHB is safe under the conditions of intended use.

Based on the totality of information, Osaka Gas concludes that D-BHB is GRAS under the conditions of intended use.

### **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 nutrient to a disease or health-related condition (also referred to as nutrient content claims and health claims). If products containing D-BHB 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 ONFL in the Center for Food Safety and Applied Nutrition. The OFAS did not consult with ONFL on this issue or evaluate any

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<sup>3</sup> The subject of GRN 000515 was D-β-hydroxybutyrate ester (HBE). We evaluated this notice and responded in a letter dated February 18, 2015, stating that we had no questions at the time regarding the notifier's GRAS conclusion.

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 Osaka Gas' notice concluding that D-BHB 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 D-BHB. Accordingly, our response should not be construed to be a statement that foods containing D-BHB, if introduced or delivered for introduction into interstate commerce, would not violate section 301(ll).

### **Conclusions**

Based on the information that Osaka Gas provided, as well as other information available to FDA, we have no questions at this time regarding Osaka Gas' conclusion that D-BHB is GRAS under its intended conditions of use. This letter is not an affirmation that D-BHB 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 001032 is accessible to the public at [www.fda.gov/grasnoticeinventory](http://www.fda.gov/grasnoticeinventory).

Sincerely,

**Susan J.**

**Carlson -S**

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Susan J. Carlson -S

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Susan Carlson, Ph.D.

Director

Division of Food Ingredients

Office of Food Additive Safety

Center for Food Safety

and Applied Nutrition