Summary of the application: Tri-betahydroxybutyrin

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The applicant, Neuroenergy Ventures, Inc. (NEV), is seeking authorisation of tri-betahydroxybutyrin as a novel food in the context of Regulation (EU) 2015/2283. The compound tri-betahydroxybutyrin is a synthetic molecule and it is proposed for use as an ingredient in food for special medical purposes (FSMP).

As tri-betahydroxybutyrin does not have a significant history of consumption in the EU prior to May 1997, or a history of consumption in third countries, it should therefore be considered novel, falling under category 2(a)(i) in Regulation 2015/2283 'food with a new or intentionally modified molecular structure, where that structure was not used as, or in, a food within the Union before 15 May 1997'.

Five independent batches from independent manufacturing lots were sampled and analysed for relevant composition data. The FSMP compound is a clear to light yellow oil and is freely soluble in water. The main components present include tri-betahydroxybutyrin, along with di-betahydroxybutyrin (diester) and the acetylated diester. Microbiological analysis demonstrated the absence of specific bacteria, yeasts and moulds in the five batch samples. Stability analysis demonstrated that tri-betahydroxybutyrin remains stable when stored at ambient temperatures for up to 7 months.

Tri-betahydroxybutyrin is comprised of a glycerol backbone with 3 molecules of β-hydroxybutyrate esterified to it. The absorption and distribution process for the tri-betahydroxybutyrin is expected to be similar to any dietary triglyceride. Following ingestion, the esters of 3-hydroxybutyrate are expected to be cleaved from the glycerol backbone by lipases and esterases in the gut and systemically. As the liver cannot metabolise the liberated 3-hydroxybutyrate, it enters the systemic circulation where it will be available for distribution to the brain, heart and muscle.

The assessment of the safety of tri-betahydroxybutyrin is based on the metabolic fate of the compound and the totality of the evidence supporting the safety of glycerol tri-betahydroxybutyrin itself and pre-clinical and human evidence supporting the safety of a number of breakdown products. The safety of tri-betahydroxybutyrin is corroborated by the endogenous production of 3-hydroxybutyrate, and the safety of various ketogenic diets. The safety of tri-betahydroxybutyrin is derived from studies in animal models and humans, as well as extensive safety data on the metabolic precursor, which produces the same major metabolite of hydroxybutyrate, safety data on an extensive series of substances also producing the common metabolite, and the safety of various ketogenic diets that result in the same circulating metabolites.

Genotoxicity studies of tri-betahydroxybutyrin were reported to be negative, including a bacterial reverse mutation assay, an in vivo mouse micronucleus assay and an in vitro chromosomal aberrations assay. As part of a multigenerational study, rats were administered 1,3-butanediol, and a dominant lethal assay and cytogenic assay for chromosomal aberrations conducted in study subgroups were both negative. In addition, a bacterial reverse mutation assay on the isomer of the relevant metabolic precursor was negative. Several repeated dose studies have been conducted for the novel food or its closely metabolically related surrogates. The lowest NOAEL from these studies was for 1,3-butanediol in

a study conducted in dogs. The NOAEL from this study was estimated to be 750 mg/kg bw/day, following two years of test substance administration. This was the highest dose tested and revealed no adverse effects, suggesting that the true NOAEL is quite possibly much higher. A rat study conducted by similar design and of chronic duration using 1,3-butanediol resulted in a NOAEL of 5,000 mg/kg bw/day and was also the highest dose tested, further suggesting a higher true chronic NOAEL than tested. NOAEL values from prenatal and developmental studies utilising a number of the metabolically relevant surrogate molecules were also high, with the lowest NOAEL being 2,000 mg/kg bw/day, which was the only dose level tested. NOAEL values from other studies and utilizing other relevant test articles were higher, ranging from approximately 4,000 – 6,000 mg/kg bw/day. Because adverse effects were not typically revealed in preclinical studies, it is appropriate to also consider the clinical data, which suggest that direct consumption of doses up to approximately 2,000 mg/kg bw/day were well-tolerated. This dose of 2,000 mg/kg bw/day is approximately 140 g/person/day considering a 70 kg default body weight.

Thus, based on metabolic studies, animal studies, and clinical trials of related chemical compounds along with evidence related to the intake of ketogenic diets, it can be concluded that the novel food tri-betahydroxybutyrin, produced in accordance with current GMP and meeting appropriate food-grade specifications, is considered safe for use in a food for FSMP use by the EU population.