THE APPLICATION TO AMEND THE *AUSTRALIA AND NEW ZEALAND FOOD STANDARDS CODE* TO ALLOW FOR THE USE OF COGNIZIN® CITICOLINE AS A NUTRITIVE SUBSTANCE IN FORMULATED CAFFEINATED BEVERAGES

EXECUTIVE SUMMARY

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Kyowa Hakko Bio Co., Ltd. ("Kyowa") is seeking to amend Schedules 3 (Identity and Purity), 28 (Formulated Caffeinated Beverages), and 26 (Food Produced using Gene Technology) of the *Australia New Zealand Food Standards Code* to include citicoline as a nutritive substance. Citicoline, also known as cytidine diphosphate choline (cytidine 5'-diphosphocholine), is a complex organic molecule that functions as an intermediate in the biosynthesis of cell membrane phospholipids.

Kyowa's Cognizin® brand citicoline is a high-purity ingredient that contains no less than 98.0% citicoline on a dry weight basis, and meets the specifications for citicoline established previously for Cognizin® in the European Union (EU) and the United States (U.S.), and the specifications for citicoline in the *Japanese Pharmacopoeia* and the *United States Pharmacopeia* Dietary Supplements Compendium. The results of stability studies demonstrate that Kyowa's Cognizin® citicoline is stable under various conditions representative of a wide range of food matrices, and support that the ingredient would be uniformly incorporated into the food matrices to which it is intended to be added.

The manufacturing process for Kyowa's Cognizin® citicoline utilises a modified strain of *Escherichia coli* B expressing enzymes from safe donor strains that catalyse the biosynthesis of citicoline using glucose and choline chloride as substrates. Kyowa's Cognizin®, produced by fermentation using the same modified strain of *E. coli* B as a processing aid, is currently marketed in the EU and the U.S. The results of batch analyses of Kyowa's Cognizin® citicoline demonstrate that the manufacturing process results in a product that consistently meets specifications and does not contain any production organism, as residual DNA and proteins are not present in the final product.

Kyowa's Cognizin® citicoline is intended to be added to formulated caffeinated beverages intended for consumption by adults at a level of 250 mg/serving (or 69 mg/100 mL), with the nutritive purpose to be helpful for the maintenance of cognitive function. It is expected that consumption of citicoline as an ingredient in energy drinks will be similar to that calculated for the same use and use level in the U.S. (*i.e.,* up to 512 mg/day).

Kyowa's Cognizin® citicoline is Generally Recognized as Safe for use in a variety of food and beverages in the U.S., at levels providing up to 1,505 mg citicoline/day. In the EU, Cognizin® citicoline is permitted for use as a novel food ingredient in food supplements for middle-aged to elderly adults (providing up to 500 mg/day), and in foods for particular nutritional uses (specifically foods for special medical purposes) at levels of up to 250 mg/serving (providing up to 1,000 mg/day).

Following comprehensive searches of the published scientific literature, no studies were identified that indicated any adverse health effects related to consumption of citicoline. The intended use and nutritive purpose (*i.e.,* to be helpful for the maintenance of cognitive function) of Kyowa's Cognizin® in formulated caffeinated beverages in Australia and New Zealand is supported by the information characterising the metabolism and safety of citicoline, non-clinical and clinical studies of Kyowa's Cognizin® and other citicoline products (alone or as components of FCBs), and the history of safe consumption from background consumption of cytidine and choline as natural constituents of the diet. Overall, the available evidence supports the safety and suitability of the use of citicoline as a nutritive substance in formulated caffeinated beverages.