

amino scope®



KYOWA HAKKO BIO'S NEWS FROM AROUND THE GLOBE • WINTER 2017



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Science Update

Kyowa Hakko Bio (KHB) India seminar in Mumbai

by Sandeep Somavanshi



India is a rapidly-growing market for the Nutraceutical Industry due to rising awareness of the importance of health and fitness, as well as changes in lifestyle trends. The nutraceuticals market is likely to rise above US \$6.1 billion by 2020, growing at compound annual growth rate (CAGR) from the current level of US \$2.8 billion at about 17%.

The goal of the seminar was to inform potential customers about nutraceutical value with various applications of KHB branded ingredients and to encourage general awareness of Kyowa's amino acids.

The half-day seminar had a good response, with 25 delegates from different backgrounds (such as R&D, business development, marketing, and regulatory) in attendance. Leading pharmaceutical and nutraceutical companies like Cipla, Alkem, Meyer Organics, Lyka Labs, and others joined the event.



Dr. Kamiya presented KHB's innovation fermentation technology and the special applications of KHB's key products, including L-Omithine, L-Citrulline, Oligosaccharides, Setria® Glutathione, Sustamine® L-Alanyl-L-Glutamine,

and ATP. An interesting and interactive Q&A at the event was appreciated and well-received by attendees. The KHIN team worked together and coordinated effectively to make the event a grand success.



Research on Kyowa's original L-Citrulline/L-Arginine combination for Pre-Workout

by Yuki Nakamura

A double-blind, randomized, placebo-controlled, human clinical trial was recently published in Bioscience, Biotechnology, and Biochemistry investigating the effects of combined oral L-citrulline and L-arginine supplementation in 45 healthy males.

Oral L-citrulline plus L-arginine supplementation (1 g each) significantly increased plasma L-arginine levels, compared with 2 g of L-citrulline or L-arginine in the subgroup within the normal range of blood arginine at baseline (Figure 1; Suzuki T et al., 2016). The combination of L-citrulline and L-arginine is thought to help improve sports performance via enhancing nitric oxide (NO) production.

NO is a vital signaling molecule produced in the body that is biosynthesized endogenously from L-arginine by various nitric oxide synthase (NOS) enzymes. Emerging evidence suggests that increasing L-arginine levels may help increase NO production, which in turn may help enhance sports performance by increasing blood flow to muscle tissues.

Oral L-citrulline supplementation is known to be a more effective way to increase L-arginine levels in the body compared to L-arginine itself. L-arginine is trapped in intestinal and hepatic cells after oral ingestion, which leads to low bioavailability. On the other hand, L-citrulline is poorly metabolized in the intestines and liver, and is converted to L-arginine in the kidneys. Therefore, oral L-citrulline supplementation effectively supplies L-arginine.

We recently found in an animal

study that co-supplementation of L-citrulline and L-arginine more rapidly increased plasma L-arginine levels than L-citrulline or L-arginine alone (Figure 2; Morita M et al., 2014).

Furthermore, the current human clinical study showed that the combination effectively increased plasma L-arginine levels in healthy individuals. L-citrulline is known to suppress arginase activity and inhibit L-arginine degradation (Figure 3). The combination of L-citrulline and L-arginine may effectively enhance NO production, leading to a more beneficial effect in sports performance than L-citrulline or L-arginine alone.

Kyowa filed an international patent application of the combination, and the patent has been granted in the US and in Japan. Additional clinical trials are also being planned to demonstrate the effects on sports performance.

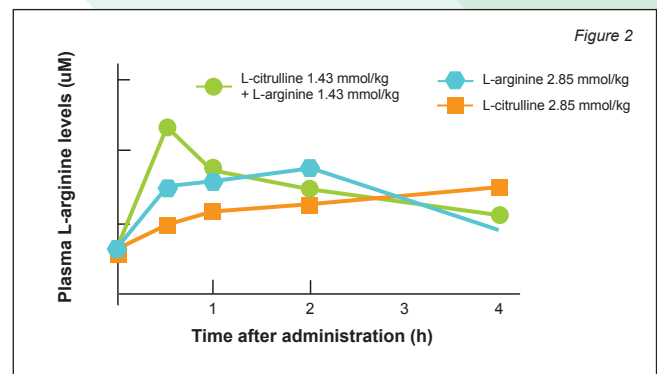
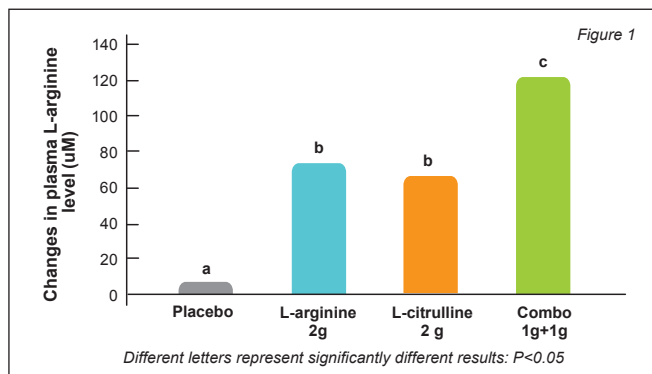
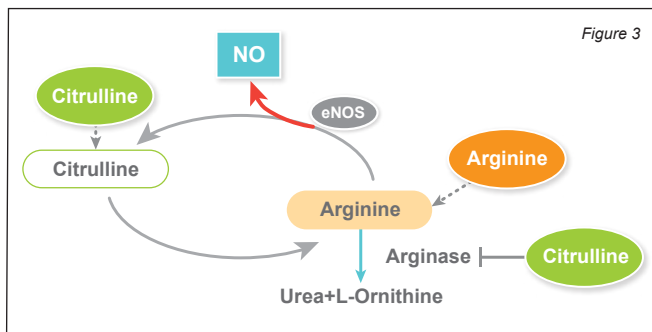


Figure 1: Subgroup analysis of changes in plasma L-arginine levels at 1 hour after supplementation. (Placebo: n=7, L-arginine: n=9, L-citrulline: n=8, L-citrulline+L-arginine: n=10)

Figure 2: Time course of changes in plasma L-arginine concentration (rats)

Figure 3: A proposed mechanism of action



References.

- Morita M, Hayashi T, Ochiai M, Maeda M, Yamaguchi T, Ina K, Kuzuya M. Oral supplementation with a combination of L-citrulline and L-arginine rapidly increases plasma L-arginine concentration and enhances NO bioavailability. *Biochem Biophys Res Commun.* 454(1): 53-7, 2014.
- Suzuki T, Morita M, Hayashi T, Kamimura A. The effects on plasma L-arginine levels of combined oral L-citrulline and L-arginine supplementation in healthy males. *Biosci Biotechnol Biochem.* 2016 Sep 26: 1-4. [Epub ahead of print]

Product News

by Takeshi Ikeda

Patent on Sustamine® for enhancing endurance performance now in EU and Australia

A patent on a method to enhance endurance by Sustamine intake has recently been established in both the EU and Australia. Kyowa filed an international patent application for the invention in 2011 and transferred it into the US, Europe, Canada and Australia. Endurance performance is the central focus for Sustamine, and the patent should promote product development globally.

Sustamine helps promote rehydration by enhancing electrolytes and water absorption. Sustamine is a dipeptide consisting of L-alanine and L-glutamine (AlaGln) with superior solubility and stability in water compared to L-glutamine alone. Certain amino acids such as L-glutamine are co-transported with Na⁺ in the intestine and promote electrolytes and water absorption (Figure 1). It has been reported that AlaGln promotes rehydration better than L-glutamine (Lima AA et al., 2002).

Sustamine may help improve endurance performance by promoting rehydration during exercise. Prolonged endurance exercise causes a progressive water and electrolyte loss via sweating for thermoregulation and leads to a significant performance decrement. Therefore, it is critical for athletes to rehydrate efficiently for maintaining exercise performance. It has been reported in several clinical studies that Sustamine supplementation during exercise may provide ergogenic benefits in endurance performance.

The first clinical study published in 2010 reported that Sustamine supplementation with water (5 or 20

g/L) significantly increased time to exhaustion during endurance exercise of cycle ergometer in 10 college-aged males (Figure 2). The clinical study in 10 women basketball players at the University of Central Florida also showed that rehydration with Sustamine (2 or 4 g/L) significantly improved basketball skill performance and visual reaction time (Hoffman JR et al., 2012).

The other study reported that Sustamine ingestion with a commercially available sports drink (600 mg or 2 g/L) significantly improved time to exhaustion during high-intensity running exercise (McCormack WP et al., 2015). These ergogenic effects should be mediated by enhanced water and electrolyte absorption from the gut during exercise.

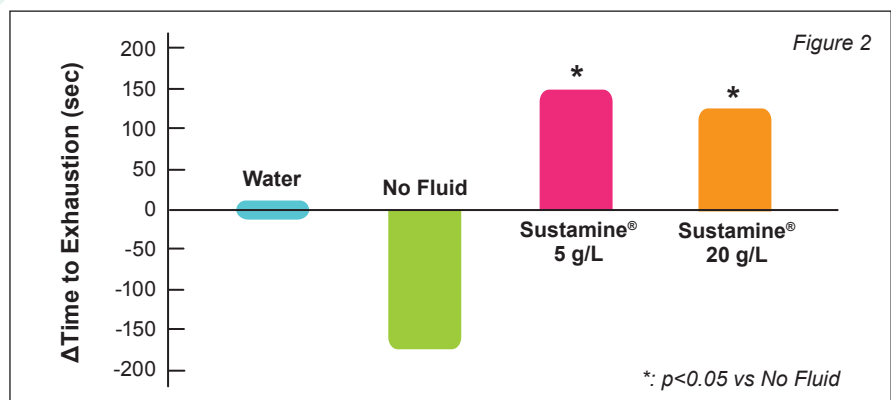
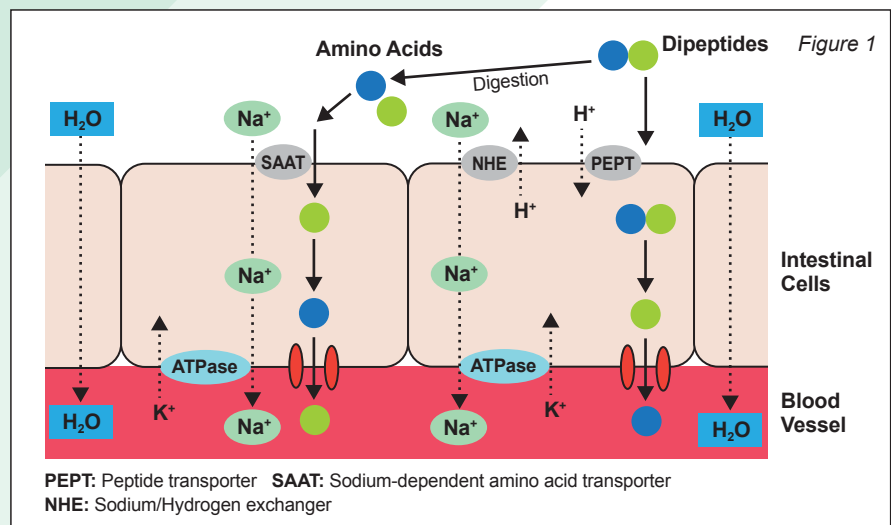


Figure 1: Mechanism of action

Figure 2: Improvement in endurance performance with hydration stress (Hoffman JR et al. 2010)

Reference: Hoffman JR, Ratamess NA, Kang J, Rashti SL, Kelly N, Gonzalez AM, Stec M, Anderson S, Bailey BL, Yamamoto LM, Hom LL, Kupchak BR, Faigenbaum AD, Maresh CM. Examination of the efficacy of acute L-alanyl-L-glutamine ingestion during hydration stress in endurance exercise. *J Int Soc Sports Nutr.* 7:8, 2010.

Hoffman JR, Williams DR, Emerson NS, Hoffman MW, Wells AJ, McVeigh DM, McCormack WP, Mangine GT, Gonzalez AM, Fragala MS. L-alanyl-L-glutamine ingestion maintains performance during a competitive basketball game. *J Int Soc Sports Nutr.* 9(1):4, 2012.

Lima AA, Carvalho GH, Figueiredo AA, Gifoni AR, Soares AM, Silva EA, Guerrant RL. Effects of an alanyl-glutamine-based oral rehydration and nutrition therapy solution on electrolyte and water absorption in a rat model of secretory diarrhea induced by cholera toxin. *Nutrition.* 18(6):458-62, 2002.

McCormack WP, Hoffman JR, Pruna GJ, Jajtner AR, Townsend JR, Stout JR, Fragala MS, Fukuda DH. Effects of L-Alanyl-L-Glutamine Ingestion on One-Hour Run Performance. *J Am Coll Nutr.* 34(6):488-96, 2015.



Power up for your best-ever performance

Intense activity and workouts dehydrate your body and drain cells of glycogen, the energy stores that power your muscles. Sustamine® is a unique, clinically tested ingredient that combines the amino acids L-Glutamine and L-Alanine to assist with hydration.* Sustamine may also support immune and intestinal health, as well as exercise performance.* It's also rapidly absorbed for faster recovery.* Want to power up your sports performance? Look for products formulated with pure, vegetarian, allergen-free Sustamine.*

 **SUSTAMINE®**
Rehydrate. Replenish. Recover.

Find products with Sustamine at www.sustamine.com



Follow Sustamine®

*These statements have not been evaluated by the Food and Drug Administration. This product is not intended to diagnose, treat, cure, or prevent any disease.

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Look for brands with Sustamine® in their formulations



BioKyowa

by Joel Melka

BioKyowa is working hard to improve their quality systems to meet the ever-changing requirements from customers and regulatory authorities. There are two exciting changes underway at BioKyowa in 2017. The first is changing the analytical method used to measure heavy metals in their products. This change is due to customers requesting more information on specific heavy metal analyses, and from a revision by United States Pharmacopeia (USP) to the Elemental Impurities method in USP Drug Products and Dietary Supplements. The new USP testing method needs to be in place by January 1, 2018.

The currently used USP standard testing method for heavy metals is a rudimentary colorimetric method that uses a pass/fail standard for a No More Than (NMT) amount of heavy metals contained in the product based on lead content. The same is true for the arsenic testing method being used. This means that BioKyowa currently reports a value of NMT 10ppm heavy metals and NMT 1ppm for arsenic. Based on more precise measurements from outsourced testing of heavy metals in their products.

BioKyowa knew that their product's elemental impurity concentrations were substantially lower than what was being reported. The new USP monograph changes gave BioKyowa the opportunity to justify the purchase of a new Perkin Elmer Inductively Coupled Plasma-Optical Emission Spectrometer 8000 (ICP-OES) to provide a better testing method and reporting value to their customers.

An ICP-OES uses a technique in which the composition and concentration of elements can be determined in a given sample. The sample is dissolved in a solution (mostly water)

and is pumped through a nebulizer that sprays the sample into a chamber that contains an argon plasma. The heat energy applied to the sample atoms (6000K-7000K) causes their electrons to reach an excited state. As the electrons return to their low energy position, emission rays (spectrum rays) are released that can be used for elemental identification and determination of the concentration of each element.

Instrument validation testing of their new ICP-OES was performed by BioKyowa over the past three months. Results show that the new instrument corroborates previously outsourced testing, in that heavy metal impurity levels in their products are very low. The new instrument has a 50 ppb level of detection for lead, mercury, cadmium and arsenic.

Testing in BioKyowa's food grade products (L-glutamine, L-arginine and L-citrulline) has resulted in measured values of less than 50 ppb! Establishing this testing method for use in 2017 is considered another vital component in BioKyowa's tool kit for meeting their customer's ever evolving needs for highest quality products.

The second change underway at BioKyowa is that they are working diligently to comply with the Food Safety Modernization Act (FSMA). BioKyowa, like all other food ingredient manufacturers, is overseen by FDA regulations.

FSMA focuses on the prevention of food safety issues, detection and response to food safety problems, and improving the food safety of imported foods. The majority of all food product recalls are due to food allergens and microorganisms that cause foodborne illnesses. The new FSMA regulations emphasize food safety through being proactive on reducing and preventing these hazards.

BioKyowa is currently re-examining their risk based hazard analyses, improving Good Manufacturing Practices, and strengthening programs such as Allergens, Environmental Monitoring and Supply Chain Management, in order to meet the new FSMA regulations and to ensure their customers are supplied with the highest quality and the safest amino acids.



Marketing News

by Elyse Lovett

Raising Consumer Awareness in 2016

In the past few years, we have seen a growing trend in digital marketing. From Millennials all the way up to baby boomers, people are relying heavily on information from the Internet, specifically social media and manufacturer's websites, in the supplement industry. There has been an increasing demand for interactive and sharable content. Kyowa Hakko USA heard the demands of our consumers and increased our online consumer awareness presence in 2016.



Alongside traditional print advertising, Kyowa Hakko USA featured two advertorials in Prevention Magazine's online publication. The advertorials titled "Keep Up With Cognizin®," For the Evolution Of Your Mind" and "Find out What's Missing From Your Detox," highlighted information and benefits on Cognizin® Citicoline and Setria® Glutathione. During the promotion months, the advertorial was the number one traffic driver to both our

Cognizin and Setria websites, with over 1,000 referral sessions for each.

For Cognizin, the campaign generated an impressive 1.9 million online impressions and 4.5 million print impressions. For Setria, the campaign generated an impressive 4 million online impressions and 4.5 million print impressions.

In raising consumer awareness even greater in 2016, Kyowa Hakko USA featured Setria and Cognizin in two separate BuzzFeed campaigns. BuzzFeed is a global cross-platform network that includes mobile apps, Facebook, Snapchat, YouTube, and many other digital platforms. The BuzzFeed Setria campaign, "What's Your Antioxidant IQ," was viewed by over 75,000 people and reached a millennial audience that skewed female. The BuzzFeed Cognizin campaign "11 Things You Didn't Know About Your Own Mind," was viewed by almost 100,000 people and again reached a millennial audience that skewed females over males.



We created our first Setria e-book with Whole Foods magazine, which launched in Q4 2016. The e-book featured topics including the "master antioxidant" glutathione, the key roles of Setria Glutathione, why glutathione decreases, and why

Setria has superior absorption. The e-book is on Whole Foods Magazine's website and is available for customer use.



Our 2016 advertising campaign generated the most impressions we have had with a mix of digital and print ads. We will continue with a strong advertising plan for 2017, with an increased number of digital ads. We created a new ad for our Setria Performance Blend and will include our new customer logos on the ad in 2017. Our consumer advertising campaign will continue with magazines like Scientific American Mind, Psychology Today, Clean Eating, Prevention, Fitness RX, and Muscle & Fitness.

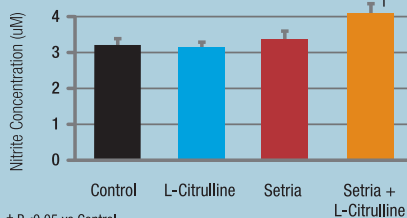
Consumer Media impressions for 2016

Cognizin: 12.2 million impression
Pantesin: 3.9 million impressions
Setria: 12.4 million impressions
Sustamine: 5.0 million impressions
Setria Performance Blend: 3.4 million impressions



Get a competitive edge with Setria® Performance Blend**

Get help achieving the strength-training results you want by maintaining the increase in nitric oxide production post-workout.* New research in resistance-trained males suggests that Setria® glutathione may support NO production when combined with L-citrulline.* This Setria® Performance Blend may help sustain NO levels, which could lead to reduced fatigue and speed recovery.* If you're looking to gain an edge, add Setria® Performance Blend to your workout.*

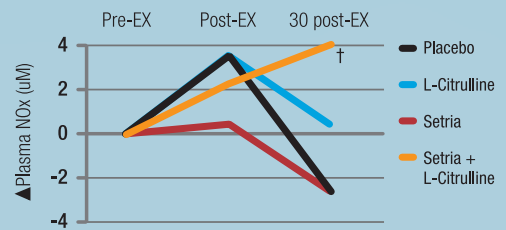


In-vitro results suggest that cells supplemented with a combination Setria Glutathione and L-Citrulline underwent increases in nitrite formation compared to the control.

McKinley-Barnard et al. Journal of the International Society of Sports Nutrition (2015) 12:27.

*These statements have not been evaluated by the Food and Drug Administration. This product is not intended to diagnose, treat, cure, or prevent any disease.

** Patent pending



One week of daily oral supplementation with 200 mg of Setria glutathione and 2 grams of L-Citrulline showed significant increases in plasma NO levels 30 min. post exercise.

McKinley-Barnard et al. Journal of the International Society of Sports Nutrition (2015) 12:27.

Setria® Performance Blend may

1. Support NO levels post-workout*
2. Sustain NO levels post-workout*
3. Aid in vasodilation to help fuel muscles*

Setria®
Performance Blend

Find products with Setria at www.setriaglutathione.com



Tradeshows & Conferences

by Oksana Ritchie

Health Ingredients Europe – November 2016

Recognized as the world's leading global event for food and beverage innovation, the Health Ingredients exhibition takes place in a different major European city every other year. From November 29th to December 1st, 2016, it was Frankfurt's turn to host the event which showcases the most diverse range of new and innovative ingredients and services. Focusing on ingredients and solutions for food and drink formulation, dietary supplements, nutraceuticals, and personal care products, it is an essential meeting place for the industry.

In addition to exhibiting at Health Ingredients, Kyowa Hakko Europe also attended the Sports Nutrition

Conference that was held in the same city and was run in association with the European Specialist Sports Nutrition Alliance (ESSNA). The conference highlighted 'Innovation and Opportunity in Sports Nutrition'.

Both events were a huge success, with the sports conference being sold out and HI attracting record numbers of both exhibitors and visitors. It was Kyowa's first time attending HI and our primary focus was on promoting our branded ingredients, such as Cognizin®, Sustamine®, and Setria®. Our visitor numbers surpassed all expectations with attendees from all across Europe and beyond showing great interest in our products and reinforcing both the market need and potential. Needless to say, we have already booked our stand for 2018!



Upcoming Events



Integrative Healthcare Symposium Annual Conference
February 23-25, 2017
New York, NY USA



ExpoWest – Engredea
March 9-12, 2017
Anaheim, CA USA
Booth 305



Ingredient Marketplace
April 18-20, 2017
Orlando, FL USA
Booth K43



Vitafoods
May 9-11, 2017
Geneva, Switzerland
Stand L142
Speaking Session: *Cognizin® Citicoline's Breakthrough Benefits for Cognition*



FUNCTIONAL FOOD EXPO
Functional Food Expo
June 8-9, 2017
Barcelona, Spain
Stand C03



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Kyowa Hakko Bio Italia S.R.L.

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