

KYOWA

Unlocking Cognitive Potential

Danielle Citrolo, PharmD

Vice President of Scientific and Regulatory Affairs  
Kyowa Hakko U.S.A., Inc.

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COMPANY OVERVIEW



KYOWA

Date of Incorporation

**February 23, 1907**

●

Number of Group Companies

**178**

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Number of Employees

**30,000+**

KIRIN HOLDINGS COMPANY, LTD.

Joy brings us together



KIRIN

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KYOWA

KYOWA HAKKO BIO CO., LTD.

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Kyowa Hakko USA

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SALES & MANUFACTURING PLANTS



KYOWA



Sales Offices

Head Office: Chiyoda, Tokyo

Kyowa Hakko USA, Inc.


Kyowa Hakko Europe GmbH

Kyowa Hakko Bio Italia S.R.L.

Kyowa Hakko Pharmaceutical CO., LTD. Beijing Branch

Kyowa Hakko Pharmaceutical CO., LTD. Shanghai Branch

Kyowa Hakko Bio Singapore PTE, LTD



Manufacturing Plants

BioKyowa, Inc. USA

Shanghai Kyowa Amino Acid Co., LTD

Thai Kyowa Biotechnologies Co., LTD

Kyowa Hakko Bio Co., LTD

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DIETARY SUPPLEMENT & NUTRITION PRODUCTS

Setria

Glutathione

Cognizin

For the evolution of your mind

VELOX

Patented Performance Blend

Pantesin

Supports a healthy heart

Setria

Performance Blend

IMMUSE

Immune Support

EYEMUSE

Inspire Your View

Amino Acids

L-Arginine

L-Citrulline + L-Citrulline (VELOX)

L-Citrulline

L-Glutamine

Nucleic Acids

Citicoline (Cognizin)

Postbiotics

Kirin Holdings Co. Ltd.

Product Offerings:

Lactococcus lactis strain Plasma (IMMUSE)

Lactosaccharides paracasei K005119 (EYEMUSE)

Vitamins

Vitamin K<sub>2</sub>

Vitamin B Derivatives

Kyowa Pharm Chemical Co.

Product Offerings:

Vitamin B<sub>6</sub> derivatives

Pantesin® L080

Pantesin® HP55

Vitamin B<sub>12</sub> derivatives

Pyridoxal 5'-phosphate

New Product Development

Human Milk Oligosaccharides (HMOs)

2 - Fucosylactose

3 - Sialyllactose Sodium Salt

6 - Sialyllactose Sodium Salt

Peptides

L-Alanyl-L-Glutamine

L-Glutathione Reduced (Setria)

L-Glutathione + L-Citrulline

(Setria® Performance Blend)

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AGENDA

The Role of Cognizin in Enhancing Focus and Attention

- Citicoline Overview
- Citicoline Metabolism and MoA
  - How does citicoline work?
- Citicoline Human Studies
  - Potential as Nootropic

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TRENDS IN COGNITIVE HEALTH: SUPPLEMENTS

Brain Supplement Sales and Growth

- In 2020, the brain health market grew to a **\$1 billion** value.
- The pandemic effect set the market up for **post-pandemic growth**, and projections now show an **8.1% gain** for 2022.

Year	Brain Health Sales (\$B)	Brain Health Growth (%)
2017	809	4.0
2018	911	5.0
2019	967	6.0
2020	1,028	6.0
2021	1,086	5.0
2022e	1,174	8.0
2023e	1,264	7.0
2024e	1,354	7.0
2025e	1,524	8.0

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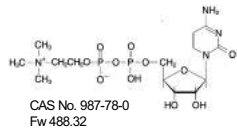
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## What is Citicoline?



- A mononucleotide comprising cytosine, ribose, pyrophosphate and choline.
- An endogenous intermediate in the biosynthesis of structural membrane phospholipids, and Acetylcholine, a nerve system activator.

### Citicoline



### Application

USA: Dietary Supplement, Food/Beverage (GRAS)

EU: Dietary Supplement (Novel Food)

Asia:

- Japan: Pharmaceutical
- China: Pharmaceutical (as sodium salt)

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## AGENDA



- Citicoline Overview
- Citicoline Metabolism and MoA
  - How does citicoline work?
- Citicoline Human Studies
  - Potential as Nootropic

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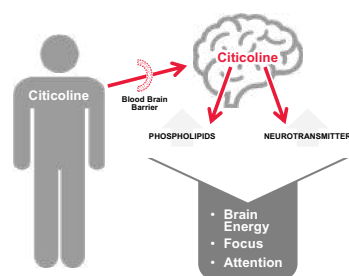
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## How Does Citicoline Work?



Citicoline metabolizes to raise Acetylcholine levels and provide Phospholipid support

- Citicoline exists in our cells and is specifically critical for optimal brain cell performance.
- Citicoline is sourced for multiple Phospholipids which is a brain nutrient to consist of brain cell membrane.
- Citicoline also supports Neurotransmitters, the way our brain cells communicate, to activate the nerves system.

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What is Citicoline?

Citicoline enhances brain function mainly via synthesis of **Phospholipids** that is a key component of brain cell membranes, and produce **Acetylcholine**, a nerve system activator.

Citicoline

Phospholipids ↑

Acetylcholine ↑

Brain cell component

Activate Nerve System

Overall Brain Health

- Short Term Benefit
  - ✓ Focus
  - ✓ Attention
  - ✓ Brain energy
- Long Term Benefit
  - ✓ Memory
  - ✓ Cognitive health

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Features and Benefits

Cognizin® Citicoline works as a Brain Nutrient to support acute performance as well as long term brain health.

Cognizin® is ideal for many different use occasions:

- Multitaskers
- Professional Workers
- Athletes
- E-Gamers
- Working Parents

COGNIZIN® CITICOLINE

BRAIN HEALTH

BRAIN PERFORMANCE

BRAIN SUPPORT

Brain cell membrane turnover

Neurotransmitters (e.g., Dopamine)

Mitochondria function

Memory/Long Term Support

Focus Attention

Brain Energy

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AGENDA

- Citicoline Overview
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Citicoline: Potential as a Nootropic

Definition of Nootropics

"Nootropics are drugs, supplement, and other substances that are claimed to improve cognitive function, particularly executive function, attention, memory, creativity, or motivation, in healthy individuals."

Oxford Dictionary  
Current Neuropharmacology, 13 (1), 5-11, 2015

Several human studies have shown Citicoline has a function to increase brain energy production, improve focus and attention, and memory in healthy subjects.

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Cognizin® Citicoline Human Studies

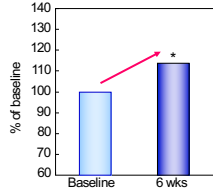
Cognizin® Citicoline Increases Energy in Brain

- Subjects:** 16 physically and mentally healthy individuals (8M and 8F, 47.3±5.4 y, BMI = 25.3 ± 5.2)
- Dose:** Citicoline 500 mg or 2000 mg/day (n = 8 each)
- Term:** 6 wks
- Index:** Measurement of β-NTP as cellular energy by 31P-MRS in the frontal lobe: Anterior Cingulate Cortex (ACC)

ACC: area responsible for focus, attention, concentration



β-NTP levels



\* Significant changes from baseline

Silver MM et al., NMR in Biomedicine, 21(10): 1066-75, 2008

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Cognizin® Citicoline Studies

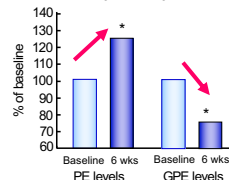
Cognizin® Citicoline Increases Phospholipid Synthesis (observed in humans)

Oral citicoline supplementation increased phospholipids synthesis in brain.

- Subjects:** 16 physically and mentally healthy individuals (8M and 8F, 47.3±5.4 y)
- Dose:** Citicoline 500 mg or 2,000 mg/day (n=8 each)
- Term:** 6 wks
- Index:** Membrane phospholipids in frontal lobe (ACC) measured by 31P-MRS; PE (anabolite) and GPE (catabolite)

ACC: Anterior cingulate cortex  
PE: Phosphoethanolamine  
GPE: Glycerophosphoethanolamine

\* Significant changes from baseline



Silver MM et al., NMR in Biomedicine, 21(10): 1066-75, 2008

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Cognizin® Citicoline Human Studies


### Cognizin® Citicoline Increases Attention


- Design:** Double-blind, randomized, placebo-controlled three-arm study
- Subject:** 60 middle-aged women (40-60 y.o.)
- Dose:** Citicoline 250 mg/day or 500 mg/day
- Term:** 1 month
- Measurement:** Continuous Performance Test (CPT)

- ✓ On a PC screen "A, B, C, ..., X" appear in random letters.
- ✓ When letters other than "X" appear, press the Space bar.
- ✓ The test runs for 14 minutes and the timing of the display changes.

PC screen: 「C, Z, A, X, J, P, X, L, W, R, X, X, .....」



**Commission Errors:**  
Participants incorrectly presses the space bar in response to "X"



**Omission Errors:**  
Participant fails to press the space bar in response to any letter other than "X"

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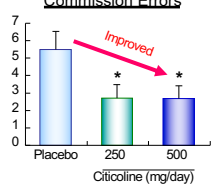
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Cognizin® Citicoline Human Studies


### Cognizin® Citicoline Increases Attention

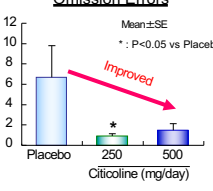
Oral Citicoline supplementation (250 mg/day) for 1 month improved attention in middle-aged women.

#### Commission Errors



Citicoline (mg/day)	Mean ± SE
Placebo	~5.5 ± 0.5
250	~2.5 ± 0.5*
500	~2.2 ± 0.5*

#### Omission Errors



Citicoline (mg/day)	Mean ± SE
Placebo	~6.5 ± 1.5
250	~1.5 ± 0.5*
500	~1.2 ± 0.5*

Mean ± SE  
\*: P<0.05 vs Placebo

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Cognizin® Citicoline Human Studies


### Cognizin® Citicoline Improves Motor Speed and Attention in Adolescents

- Design:** Randomized, placebo controlled, double blinded study
- Subjects:** Healthy adolescent males (N=75, 13-18 y.o.)
- Dose:** Citicoline (N=51, 250 or 500 mg/day) or Placebo (N=25)
- Term:** 28 days
- Measurements:** Finger tap test, Ruff 2&7 selective attention test MOSES interview (Side effects)

Table 3. Baseline Demographic Characteristics—Between-Group Differences.

	Treatment (n = 51)	Placebo (n = 24)	P
Age ± SD	15.41 ± 1.70	15.71 ± 1.73	0.98
Education (years) ± SD	9.00 ± 1.76	9.42 ± 1.82	0.48
Height (cm) ± SD	171.14 ± 9.24	171.95 ± 10.76	0.64
Weight (kg) ± SD	61.74 ± 14.80	63.90 ± 14.34	0.82
IQ (WASI) ± SD	106.04 ± 10.23	107.33 ± 9.50	0.45

Note: WASI = Wechsler Adult Intelligence Scale.

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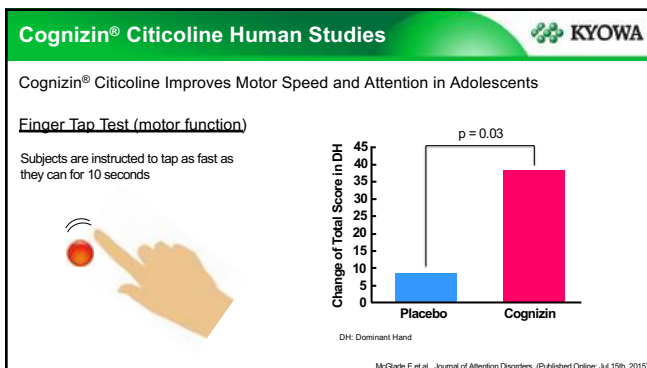
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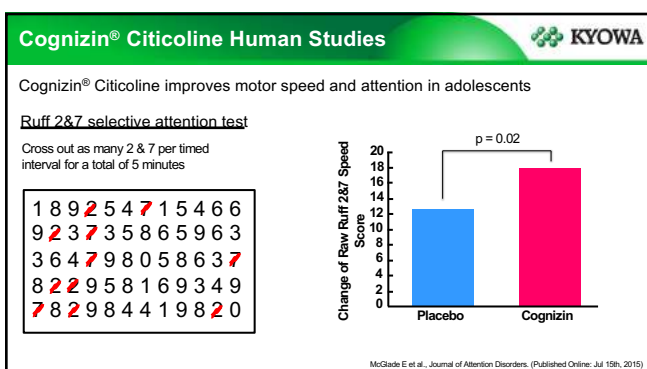
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**Cognizin® Citicoline Human Studies** 

Cognizin® Citicoline Improves Memory

- Design:** Randomized placebo-controlled parallel, double-blind study
- Subjects:** Healthy male/female age 50-85 years with AAMI\*
- Dose:** Citicoline 500 mg/day (two-piece capsule) or placebo
- Term:** 12 weeks
- Outcome:** Cognitive test battery, which includes 7 tests

\*Age-associated memory impairment (AAMI).

In order to investigate citicoline efficacy for memory properly, screened healthy subjects who have no health conditions that would prevent from fulfilling the study requirements but complaint or self-report memory loss.

NIH has proposed criteria for defining AAMI:

- (1) Males and females at least 50 years old
- (2) Complaints of memory loss and memory test performance that is at least 1 standard deviation (SD) below the mean established for young adults on a standardized test
- (3) Evidence of adequate intellectual function
- (4) Absence of dementia

J. Nutr. 21 August 2021, 2153-2160

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Cognizin® Citicoline Human Studies

Method – Cognitive Test Battery

- A web-based platform for the assessment of cognitive function.
- Use several tasks to assess distinct components of cognition for evaluate memory function.

Memory

Spatial Span

The patient will have to try to remember a sequence of flashing boxes that appear on the screen one after the other.

Memory

Paired Associates

The patient must remember which object appeared in which box. Next, one at a time, objects appear in the center of the screen, and patients must point out which box each object was located in.

Verbal

Digit Span

A sequence of numbers appears on the screen, one at a time. At the sound of the beep, users click the numbers in the same order.

Attention

Feature Match

The patient will have to determine whether the array in the two boxes are identical or different by clicking MATCH or MISMATCH.

This is just an example, please visit their website to see more details

[www.kyowa-pharmaceuticals.com/citicoline](http://www.kyowa-pharmaceuticals.com/citicoline)

J. Nutr. 21 August 2021, 2153-2160

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Cognizin® Citicoline Human Studies

Cognizin® Citicoline Improves Memory

- Citicoline significantly improved episodic memory.
- Other outcomes is not statistically significant though, showed a trend.

Short-Term Spatial Memory

Working Memory

Episodic Memory

Data showed as LS mean +/- SEM. ANCOVA was used to assess differences between test groups. \*P<0.00625

J. Nutr. 21 August 2021, 2153-2160

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Cognizin® Citicoline Human Studies

Cognizin® Citicoline Improves Memory

- Composite memory, calculated using the scores of 4 memory tests\*, also significantly improved.
- Conclusion  
Dietary supplementation of citicoline for 12-week improved overall memory performance, especially episodic memory, in healthy older males and females with AAMI.

Composite Memory

\*A within-group significance observed only in Citicoline

Data showed as LS mean +/- SEM. ANCOVA was used to assess differences between test groups. \*P<0.00625, due to adjustment of multiplicity (error correction) using the Bonferroni correction.

\*To avoid "cherry picking", shown in the FDA guidance, it is appropriate

- To combine several tests into a single variable
- To account for multiplicity.

J. Nutr. 21 August 2021, 2153-2160

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Summary

**Citicoline** is a mononucleotide comprising cytosine, ribose, pyrophosphate and choline.

Several human studies have shown **Cognizin® Citicoline** has a function to increase brain energy production, improve focus and attention, and memory in healthy subjects.

**Citicoline** is an endogenous intermediate in the biosynthesis of structural membrane Phospholipids, and Acetylcholine, a nerve system activator.

**Citicoline** has a potential as a Nootropic and applications for dietary supplements, sports/esports supplement or energy drinks.



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Thank you!

If you need more information, please email  
[info@kyowa-usa.com](mailto:info@kyowa-usa.com)

KYOWA HAKKO U.S.A., Inc.  
[www.kyowa-usa.com](http://www.kyowa-usa.com) [www.cognizin.com](http://www.cognizin.com)



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