NIAGEN®

Nicotinamide Riboside (NR)

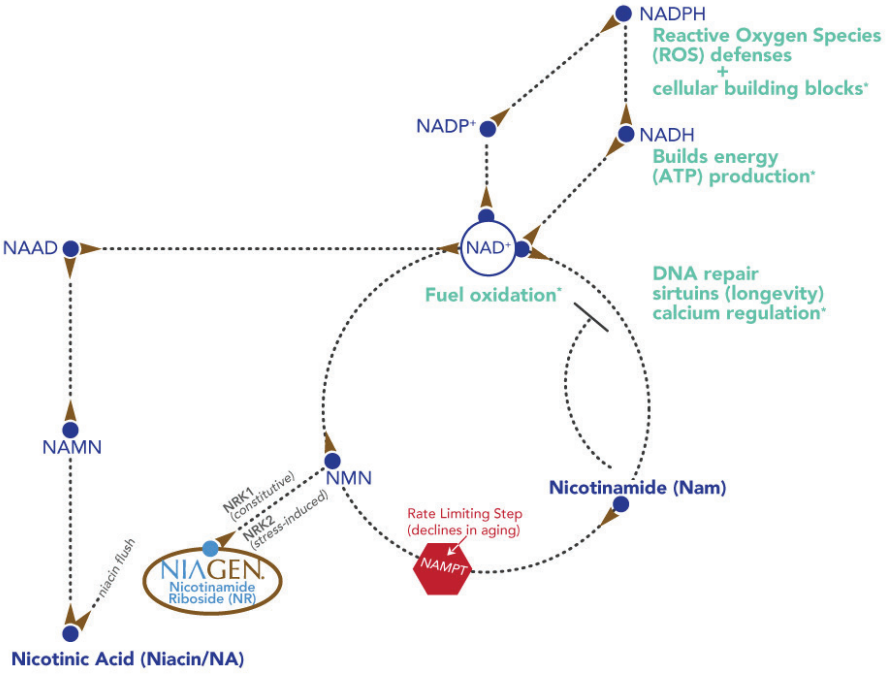
What is Nicotinamide Riboside (NR)?

NR is a next-generation vitamin B3 that has been found to be naturally-occurring in milk in trace amounts.[1] The metabolism of NR is unique from that of other more commonly known forms of vitamin B3, nicotinamide and nicotinic acid. Specifically, NR has been shown in a pre-clinical study to be the most effective form of vitamin B3, increasing nicotinamide adenine dinucleotide (NAD+) more than nicotinic acid and stimulating NAD+-consuming activities better than nicotinamide.[2]

Nicotinic acid (also known as niacin) and nicotinamide (also known as niacinamide) were discovered in the 1930's to be the factors that cured pellagra.[3] Niacin is known to cause severe flushing.[4] In 2004, nicotinamide riboside emerged as a newly discovered NAD+ precursor[5] and does not bind to the receptor responsible for flushing.[6]

NR has pre-clinically demonstrated that it is superior to both niacin and nicotinamide, both of which are standard forms of vitamin B3 commonly used in vitamin supplements and foods.[2] NR is not reliant upon a conversion step requiring the enzyme "NAMPT"[7, 8] (see Figure below). The activity level of NAMPT determines the amount of nicotinamide that is converted into NAD+[9], which is why this particular step in the process is often referred to as the "rate limiting step".[10] As normal aging occurs, the activity of NAMPT is thought to decrease.[11-15] NR can be used by the cell to make NAD+ without this enzymatic step.

Figure – NAD+ synthesis from nicotinic acid, nicotinamide, and nicotinamide riboside



Why is NR Important?

NR is important because it is a potent and bioavailable pre-cursor to NAD+.[2, 5, 16-18] NAD+ is essential to life and is known to be vital to functions that ensure proper cellular and energy metabolism.[19] The most well-known function of NAD+ is the transferring of electrons to the machinery in the cell that produces ATP, the energy currency of all cells.[20, 21]

NAD+ is increasingly being shown to have important functions beyond electron transfer. One of the most promising potential roles for NR as a pre-cursor to NAD+ is activation of sirtuins, enzymes associated with a wide variety of functions related to metabolism and longevity.[8, 22-24]

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Sirtuins – The "Anti-Aging Proteins"

- The sirtuins are proteins that have been shown to perform vital longevity functions in mice and in cellular models.[8, 22-24]
- Increasingly, there is support for the hypothesis that decreased cellular NAD+ results in a decline in sirtuins activity.[12, 25]
- A pre-clinical study published in 2016 in the journal ***Nature Communications*** demonstrated that NR is a more potent activator of sirtuin acitvity than nicotinamide and surpasses nicotinic acid at increasing NAD+.[2]

Human Studies of NR

The first human study of NIAGEN® nicotinamide riboside was published in 2016 in the journal *Nature Communications*.[2] This study reported dose dependent increases in the NAD+ metabolome following oral administration of 100, 300, and 1000 mg single doses of NIAGEN® in adults.

Three additional published clinical trials of NIAGEN® have continued to demonstrate its safety and efficacy at increasing NAD+ even at doses as high as 2,000 mg/d administered for as long as 12 weeks.[16-18] Recent published trials have also highlighted the promise of NIAGEN® for supporting cardiovascular[18] and liver[17] health.

There is much interest in the potential for meaningful health benefits of nicotinamide riboside. As a result, many additional human trials are being conducted with NIAGEN®. Selected clinical trials are listed below.

Human studies of NIAGEN® nicotinamide riboside are registered on the U.S. National Institutes of Health website: www.clinicaltrials.gov (search "nicotinamide riboside").

Study Title	Research Institution	Trial ID #
Nicotinamide Riboside and Mitochondrial Biogenesis	Cambridge University Hospitals NHS Foundation Trust University of Cambridge; MRC Mitochondrial Biology Unit	NCT03432871
Nicotinamide Riboside in Systolic Heart Failure	University of Washington National Heart, Lung, and Blood Institute (NHLBI)	NCT03423342
Effects of Nicotinamide Riboside on Metabolism and Vascular Function	Iowa State University	NCT03501433
Nicotinamide Riboside in LVAD Recipients	University of Washington American Heart Association	NCT03727646
NR and Metabolic Health (insulin sensitivity in overweight and obese adults)	Maastricht University Medical Center Dutch Heart Foundation	NCT02835664
Study to Evaluate the Effect of Nicotinamide Riboside on Immunity	National Heart, Lung, and Blood Institute (NHLBI)	NCT02812238
The Effects of NAD on Brain Function and Cognition	University of Texas Health Science Center, San Antonio University of Texas South Texas Veterans Health Care System	NCT02942888
Trial of Nicotinamide Riboside and Co-enzyme Q10 in Chronic Kidney Disease	University of Washington; National Institute of Diabetes and Digestive and Kidney Diseases (NIDDK)	NCT03579693
Nicotinamide Riboside in Chemo-induced Peripheral Neuropathy	National Cancer Institute (NCI) University of Iowa	NCT03642990
Nicotinamide Riboside for Diabetic Neuropathy (NiRiD) A Randomized Controlled Trial of Nicotinamide	University of Maryland US Department of Veterans Affairs	NCT03685253
Supplementation in Early Par-kinson's Disease: the NOPARK Study	Haukeland University Hospital	NCT03568968
The Effect of Nicotinamide Riboside on Skeletal Muscle Function in Heart Failure Subjects	National Heart, Lung, and Blood Institue (NHLBI) National Institutes of Health Clinical Center (CC)	NCT03565328
NAD+ Therapy for Improving Memory and Cerebrovascular Function in Pa-tients with MCI	National Institute on Aging (NIA)	NCT03482167

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Claims Supported by Science

- Clinically demonstrated to significantly increase NAD+*
- Promotes mitochondria health*
- Promotes healthy cellular metabolism*
- Promotes healthy aging*

Regulatory Status of NIAGEN®

NIAGEN® has two successful New Dietary Ingredient Notifications with the FDA (NDIN 882, 1062) for daily recommended intake of not more than 300 mg/d.

NIAGEN® is generally recognized as safe (FDA GRAS Notice No. 635) for use in vitamin waters, protein shakes, nutrition bars, gum, chews, and powdered beverages. Maximum use level 0.0057% by weight.

NIAGEN® Patents

NIAGEN® has more than 20 issued process and use patents with more pending.

Potential NIAGEN® Applications

NIAGEN® can be used in capsules, tablets, melts or in powder form as a dietary supplement. It can also be included in functional foods and beverages in the following categories: vitamin waters, protein shakes, nutrition bars, gum, chews, and powdered beverages.

References

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