

RESEARCH MONOGRAPH · COMPOUND PROFILE

NAD⁺

An obligate intracellular dinucleotide cofactor essential for hundreds of enzymatic reactions, supplied for research use as the oxidized free acid form for parenteral or topical research.

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ABSTRACT

Nicotinamide adenine dinucleotide (NAD⁺; CAS 53-84-9; molecular formula C₂₁H₂₇N₇O₁₄P₂; molecular weight 663.43) is a small-molecule pyridine dinucleotide cofactor that functions in three biologically distinct roles: as the dominant cellular electron-transfer cofactor in oxidative metabolism (where it cycles between the oxidized NAD⁺ and reduced NADH forms), as the substrate for the sirtuin family of NAD⁺-dependent deacetylases (which hydrolyze NAD⁺ to nicotinamide and ADP-ribose), and as the substrate for poly-ADP-ribose polymerases (PARPs) and the CD38 ecto-enzyme (both of which also consume NAD⁺). Cellular NAD⁺ concentrations are tightly regulated and decline substantially with age in humans and other mammals; the age-related decline correlates with reduced sirtuin activity, impaired DNA damage repair, and a constellation of metabolic dysfunctions that has motivated substantial research interest in NAD⁺ supplementation as a geroprotective intervention. The research-grade product supplied as "NAD⁺" is the oxidized free acid form, which has poor oral bioavailability but is suitable for parenteral administration in research models. Better-characterized parenteral approaches use NAD⁺ precursors (nicotinamide riboside NR and nicotinamide mononucleotide NMN), which are more efficiently absorbed orally and converted intracellularly to NAD⁺. Direct NAD⁺ administration in research-grade dosing has been used in study of cellular bioenergetics, neurological function, and metabolic endpoints. The compound is not approved by any regulatory authority for human or veterinary use as a therapeutic; NAD⁺ is also widely available as a food supplement under separate regulatory frameworks.

Compound identification

Nomenclature and synonyms

The compound is referred to as NAD⁺, NAD, beta-nicotinamide adenine dinucleotide, DPN⁺, coenzyme I, codehydrogenase I, or diphosphopyridine nucleotide. The CAS number is 53-84-9 (free acid). Sodium and other salt forms have separate CAS numbers. The PubChem CID is 925.

A point of nomenclature confusion is the relationship between NAD⁺ and the related cofactors NADH (the reduced form), NADP⁺ (the phosphorylated derivative used in anabolic biochemistry), and NADPH (the reduced phosphorylated form). The four forms have related structures but distinct biological roles. NAD⁺ supplementation in research-grade dosing addresses the oxidized non-phosphorylated pool; the cellular machinery interconverts the four forms as needed.

The relationship to NAD⁺ precursors is also worth noting. Nicotinamide riboside (NR) and nicotinamide mononucleotide (NMN) are biosynthetic intermediates that the cell converts to NAD⁺ through dedicated kinase and adenylyltransferase activities. NR and NMN are more efficiently absorbed orally and have been characterized in human clinical trials more extensively than NAD⁺ itself.

Structural chemistry

NAD⁺ is a dinucleotide consisting of nicotinamide ribonucleotide and adenosine ribonucleotide joined by a pyrophosphate linker. The molecular formula is C₂₁H₂₇N₇O₁₄P₂; the average molecular weight of the free acid is 663.43 g/mol; common salt forms include the monosodium and disodium derivatives.

The biologically active redox center is the nicotinamide ring, which can accept a hydride from a substrate (forming NADH) or transfer a hydride to a downstream electron acceptor (regenerating NAD⁺). The redox potential of the NAD⁺/NADH couple is approximately minus 320 millivolts, which positions NAD⁺ as a moderately oxidizing cofactor under cellular conditions.

The compound is highly polar, with multiple ionizable groups including the two pyrophosphate phosphates (pKa values approximately 1 and 6), the adenine N-1 (pKa approximately 4), and the nicotinamide carboxamide. At physiological pH the dinucleotide carries a net negative charge of approximately minus 2.

Physicochemical properties

NAD⁺ is supplied as a white to slightly yellowish powder or fine crystalline powder. The lot of record (Kodiac biolabs lot 20260124) is described as a white to yellowish crystalline powder consistent with the reference description. Solubility in water is high; concentrations up to 100 mg/mL are routinely prepared. Solubility in 0.9 percent saline and PBS is also high. Solubility in DMSO and other organic solvents is poor.

NAD⁺ is sensitive to alkaline pH (degradation at pH above 8) and to elevated temperature (rapid decomposition above 60 degrees Celsius). Aqueous solutions are stable at neutral pH and refrigerated temperature for at least 7 days; longer storage requires lyophilization or freezing. NAD⁺ is also light-sensitive; protect solutions from prolonged direct UV exposure.

The lyophilized powder is stable at minus 20 degrees Celsius for at least 24 months under standard light protection in the original sealed vial. Reconstituted solutions should be aliquoted and frozen for storage beyond a few days; freeze-thaw cycles are permissible but should be limited to 5 to 10 cycles.

Discovery and developmental history

Origin in classical biochemistry

NAD⁺ was discovered in 1906 by Arthur Harden and William John Young, who identified a heat-stable factor in yeast extracts (which they called "cozymase") that was essential for fermentation activity. The factor was subsequently characterized in the 1930s as nicotinamide adenine dinucleotide and assigned its modern structural description through the work of Otto Warburg, Hans von Euler-Chelpin, and others. Warburg shared the 1931 Nobel Prize in Physiology or Medicine in part for work on cellular respiration and the pyridine nucleotide cofactors; von Euler-Chelpin shared the 1929 Nobel Prize in Chemistry for the structural characterization of cozymase.

The 20th century characterization of NAD⁺ focused predominantly on its role as an electron-transfer cofactor. The recognition of its non-redox roles as a substrate for sirtuins, PARPs, and CD38 emerged in the late 20th and early 21st centuries through work on cellular signaling, DNA damage repair, and aging biology.

NAD⁺ supplementation as a geroprotective intervention

Cellular NAD⁺ concentrations decline with age in mammals, with measured declines in human plasma and tissue ranging from 30 to 60 percent between young adulthood and old age. The age-related decline correlates with reduced sirtuin activity (which requires NAD⁺ as a substrate), impaired DNA damage repair (which depends on NAD⁺-dependent PARP activity), and metabolic dysfunctions consistent with mitochondrial decline. The geroprotective hypothesis is that restoring cellular NAD⁺ to younger levels would partially restore sirtuin and PARP function and reduce age-related dysfunction.

Clinical trials of NAD⁺ precursors (NR, NMN) have demonstrated that oral supplementation raises plasma and tissue NAD⁺ concentrations measurably; downstream functional benefits in humans are less clearly established and remain an active area of research. Direct intravenous NAD⁺ has been used in research-grade settings and in some uncontrolled clinical practice for addiction recovery and post-COVID-19 fatigue, though the evidence base for these uses is limited.

Mechanism of action

Redox cofactor

The most fundamental role of NAD⁺ is as the dominant cellular electron-transfer cofactor in catabolic metabolism. The cofactor accepts hydride from glycolysis (at the glyceraldehyde-3-phosphate dehydrogenase step), from the citric acid cycle (multiple enzymes), from beta-oxidation of fatty acids, and from amino acid catabolism. The reduced form NADH is then re-oxidized at Complex I of the electron transport chain, with the released energy used to pump protons across the inner mitochondrial membrane. Hundreds of cellular dehydrogenases use NAD⁺ or NADH as cofactors.

Sirtuin substrate

The sirtuin family of NAD⁺-dependent deacetylases (SIRT1 through SIRT7 in humans) catalyzes the removal of acetyl groups from lysine residues on histones, transcription factors, and metabolic enzymes. The reaction consumes one molecule of NAD⁺ per deacetylation event, producing nicotinamide and 2'-O-acetyl-ADP-ribose as products. Sirtuin activity is therefore tied directly to cellular NAD⁺ availability; declining NAD⁺ with age reduces sirtuin activity and impairs the deacetylation events that regulate metabolism, mitochondrial biogenesis, DNA repair, and lifespan.

PARP substrate

Poly-ADP-ribose polymerases (PARP1, PARP2, and others) catalyze the addition of ADP-ribose chains to target proteins, primarily in the DNA damage response. The reaction consumes NAD⁺ at high stoichiometry; PARP1 activation in response to DNA damage can deplete cellular NAD⁺ within minutes. Chronic low-level DNA damage in aging cells is one of the proposed drivers of the age-related NAD⁺ decline; the depletion is a feedback consequence of accumulated DNA damage and the PARP response to it.

CD38 substrate

CD38 is an ecto-enzyme expressed on the surface of immune cells (and intracellularly in some tissues) that hydrolyzes NAD⁺ to nicotinamide and ADP-ribose, producing the calcium-mobilizing second messenger cyclic ADP-ribose as a side product. CD38 activity rises with age in many tissues, and CD38-mediated NAD⁺ consumption is a major driver of the age-related NAD⁺ decline. CD38 inhibitors are an active drug-development class for the same indication space as NAD⁺ supplementation.

Limits of the mechanistic model

The biochemistry of NAD⁺ as a cofactor and substrate is exceptionally well established. The age-related decline in cellular NAD⁺ is well documented across multiple species. The connection between restored NAD⁺ and improved cellular function in animal models is also well documented. The translation to human clinical benefit is less clear; clinical trials of NAD⁺ precursors have generally shown raised NAD⁺ levels but variable downstream functional benefits, and direct intravenous NAD⁺ administration has not been rigorously evaluated in randomized controlled trials.

Pharmacokinetics

Routes of administration

Intravenous administration of free-acid NAD⁺ produces high transient plasma concentrations and brief tissue exposure. Subcutaneous administration is occasionally used in research settings. Oral NAD⁺ administration is poorly bioavailable; the dinucleotide is hydrolyzed in the intestinal lumen to nicotinamide riboside and other precursors, which are then absorbed and reconverted to NAD⁺ intracellularly. NAD⁺ precursors (NR, NMN) are more appropriate for oral dosing and are characterized more extensively in clinical pharmacokinetics. Topical NAD⁺ has been used in dermatologic preparations.

Plasma half-life and tissue distribution

The plasma half-life of free NAD⁺ following intravenous administration is short, on the order of 5 to 15 minutes, due to rapid hydrolysis by serum nucleotidases and uptake by tissues. The relevant duration of biological effect is on the order of hours to days, reflecting the persistence of the NAD⁺ pool that has been replenished. Tissue distribution following intravenous administration is broad; uptake is observed in liver, kidney, skeletal muscle, brain (limited), and other tissues.

Metabolism and excretion

NAD⁺ is hydrolyzed by serum and tissue nucleotidases at the pyrophosphate linker, producing NMN and AMP. NMN is then dephosphorylated to NR, which can be taken up by cells and reconverted to NAD⁺ through the NRK pathway. Alternatively, the cofactor may be consumed intracellularly through the sirtuin, PARP, and CD38 reactions, producing nicotinamide as the dominant metabolite. Nicotinamide is recycled through the salvage pathway (nicotinamide phosphoribosyltransferase, NAMPT) or excreted as its methylated derivatives via renal routes.

Reported research dose ranges

Research-grade dosing varies substantially based on the intended endpoint and route. Subcutaneous administration in rodent studies typically uses 5 to 50 milligrams per kilogram daily; intravenous administration uses 50 to 500 milligrams per dose. Allometric scaling places the equivalent human exposure in the range of 700 micrograms to 70 milligrams per kilogram per dose, or approximately 50 milligrams to 5 grams per dose for a 70 kg subject.

The dose range commonly used in uncontrolled clinical practice for "NAD+ infusions" is 250 to 1000 milligrams per intravenous infusion, administered over 1 to 4 hours. Higher doses (above 500 milligrams) are sometimes associated with chest tightness, flushing, and gastrointestinal symptoms during infusion; slow administration mitigates these effects. Investigators should treat the published dose ranges as approximate guidance and should not exceed the upper end without specific experimental justification.

Sourcing and quality verification

Synthesis route

NAD⁺ is produced commercially by enzymatic synthesis from nicotinamide and ATP, using nicotinamide phosphoribosyltransferase and nicotinamide mononucleotide adenyltransferase as catalysts. Chemical synthesis is also possible but more expensive. The product is purified by ion-exchange chromatography and lyophilized.

The lot of record (Kodiak biolabs lot 20260124) was sourced from the supplier of record and shipped in lyophilized form. The vendor analytical report records 99.60 percent purity by HPLC.

Common adulterants and impurities

The research-grade NAD⁺ supply chain has documented patterns of substandard product. Reported issues include:

1. Substitution of NAD⁺ with the related cofactor NADP⁺ (the phosphorylated derivative). The two compounds have different molecular weights (NAD⁺ at 663.43; NADP⁺ at 743.41) and different biological activities. UV-visible spectroscopy and mass spectrometry distinguish them.
2. Substitution with the reduced form NADH (which is biologically distinct and which oxidizes back to NAD⁺ on storage in air). UV-visible spectroscopy resolves this readily; NADH absorbs at 340 nm, NAD⁺ does not.
3. Contamination with the precursor nicotinamide, NMN, or NR, which can produce some of the downstream effects but is not the same compound.
4. Decomposition products from improper storage at elevated pH or temperature, including ADP-ribose and free nicotinamide.
5. Endotoxin contamination from non-pyrogen-controlled synthesis.

Independent verification by HPLC, mass spectrometry, and UV-visible spectroscopy on every batch is essential. The vendor COA is necessary but not sufficient. Kodiak biolabs is in the process of establishing third-party verification

through Janoshik Analytical.

Analytical standards

Reverse-phase HPLC on a C18 column with isocratic or gradient elution from aqueous phosphate buffer (pH 6.5 to 7.0) to acetonitrile, monitoring at 260 nm (the dominant adenine absorbance), is the standard purity assay. Identity confirmation by LC-MS yields a deprotonated molecular ion at 662.1 m/z. UV-visible spectroscopy provides additional identity confirmation through the characteristic A260/A280 absorbance ratio of approximately 2.4 for NAD⁺.

Reconstitution and handling

Solvent system

NAD⁺ dissolves readily in water and 0.9 percent saline. PBS at neutral pH is also suitable. Bacteriostatic water is the standard vehicle for solutions intended for parenteral administration with storage beyond a single use. Avoid alkaline buffers (above pH 8); NAD⁺ degrades rapidly at alkaline pH.

Reconstitution protocol

A 500 mg vial reconstituted in 5 mL produces a 100 mg/mL solution; in 10 mL produces a 50 mg/mL solution. Dissolution is rapid; allow 30 to 60 seconds for full dissolution. The solution should be slightly yellow to colorless; deeper yellow color indicates oxidation product accumulation. Filter through a 0.22 micron sterile filter prior to parenteral use.

Storage stability

Lyophilized NAD⁺ in the unopened vial: stable at minus 20 degrees Celsius for at least 24 months. Reconstituted aqueous solutions: stable at 2 to 8 degrees Celsius for 7 to 14 days at neutral pH. Aliquot and freeze for longer storage; up to 10 freeze-thaw cycles are permissible. Avoid prolonged exposure to room temperature; degradation is significant after 24 to 48 hours at room temperature.

Stack interaction considerations

NAD⁺ is occasionally combined with sirtuin-activating compounds (resveratrol, pterostilbene) on the rationale that NAD⁺ supplementation supports sirtuin substrate availability and the small molecules support sirtuin allosteric activation. The combination is mechanistically reasonable but not extensively studied in controlled comparison.

Combination with MOTS-c is occasionally reported in research-grade protocols on the rationale that both compounds intersect with mitochondrial energetics and AMPK pathway activity. The mechanistic case is plausible but not formally established.

NAD⁺ is sometimes combined with NAD⁺ precursors (NR or NMN) in research-grade protocols on the assumption that the combination provides redundant routes to elevated cellular NAD⁺. The combination is generally well tolerated but the additional benefit over either compound alone is not well characterized.

Pharmacokinetic interactions with CYP-substrate compounds are not expected. NAD⁺ has no documented receptor-level interactions with conventional small-molecule pharmacotherapy at standard research doses.

References

1. Harden A, Young WJ. The alcoholic ferment of yeast-juice. Proceedings of the Royal Society of London B 78:369-375 (1906). Foundational disclosure of "cozymase."
2. Verdin E. NAD⁺ in aging, metabolism, and neurodegeneration. Science 350:1208-1213 (2015). Comprehensive review of the geroprotective hypothesis.
3. Imai S, Guarente L. NAD⁺ and sirtuins in aging and disease. Trends in Cell Biology 24:464-471 (2014). Sirtuin-NAD⁺ axis review.
4. Yoshino J, Mills KF, Yoon MJ, Imai S. Nicotinamide mononucleotide, a key NAD(+) intermediate, treats the pathophysiology of diet- and age-induced diabetes in mice. Cell Metabolism 14:528-536 (2011). NMN supplementation effects.
5. Trammell SA, Schmidt MS, Weidemann BJ, et al. Nicotinamide riboside is uniquely and orally bioavailable in mice and humans. Nature Communications 7:12948 (2016). NR pharmacokinetics.
6. Camacho-Pereira J, Tarrago MG, Chini CCS, et al. CD38 dictates age-related NAD decline and mitochondrial dysfunction through an SIRT3-dependent mechanism. Cell Metabolism 23:1127-1139 (2016). CD38-mediated NAD⁺ decline.
7. Martens CR, Denman BA, Mazzo MR, et al. Chronic nicotinamide riboside supplementation is well-tolerated and elevates NAD⁺ in healthy middle-aged and older adults. Nature Communications 9:1286 (2018). NR human pharmacokinetics.
8. Mendelsohn AR, Larrick JW. The NAD⁺/PARP1/SIRT1 axis in aging. Rejuvenation Research 20:244-247 (2017). PARP-NAD⁺ axis review.
9. PubChem. Compound CID 925 (NAD⁺). National Library of Medicine. Accessed 2026-04.
10. Vendor Certificate of Analysis, Kodiak biolabs lot 20260124. kodiak.org/pages/lab-results.

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