

RESEARCH MONOGRAPH . COMPOUND PROFILE

Choline Bitartrate

A water-soluble tartaric acid salt of the essential nutrient choline, widely used as a dietary supplement to support acetylcholine synthesis, hepatic lipid export, and one-carbon methylation metabolism, distinguished from other choline donors by low cost, high aqueous solubility, and moderate oral bioavailability but limited blood-brain barrier penetration relative to phospholipid-conjugated choline sources.

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AUTHOR	Kodiac bioLabs Research
COMPOUND CLASS	Quaternary ammonium salt delivering the essential nutrient choline as a bitartrate conjugate for acetylcholine precursor loading, phospholipid biosynthesis, and methyl-group donation

ABSTRACT

Choline bitartrate is the tartaric acid salt of choline, a quaternary ammonium compound recognized as an essential nutrient by the United States Institute of Medicine in 1998. The salt form contains approximately 41 percent choline by mass and is the most widely manufactured and least expensive choline supplement form in global commerce. Choline itself is a precursor to acetylcholine (synthesized by choline acetyltransferase from choline and acetyl-coenzyme A), to the membrane phospholipid phosphatidylcholine (synthesized by the cytidine diphosphate-choline or Kennedy pathway), and to the methyl donor betaine (synthesized by choline dehydrogenase and betaine aldehyde dehydrogenase in a two-step mitochondrial oxidation), which donates methyl groups to homocysteine in the betaine-homocysteine methyltransferase reaction. These three metabolic fates underwrite a broad physiological role that spans neurotransmission, membrane structural integrity, hepatic very-low-density lipoprotein assembly, one-carbon metabolism, and epigenetic regulation of gene expression through histone and DNA methylation. Pharmacokinetic studies in healthy volunteers demonstrate rapid oral absorption with peak plasma choline concentrations achieved within one to two hours after ingestion of a single dose. However, choline bitartrate delivers choline as the free water-soluble cation, which is subject to substantial first-pass hepatic extraction and gut microbial conversion to trimethylamine before systemic distribution. Gut microbial trimethylamine production and subsequent hepatic flavin-containing monooxygenase 3 oxidation to trimethylamine N-oxide represent both a metabolic loss pathway and a potential cardiovascular risk signal, as elevated

circulating trimethylamine N-oxide concentrations have been associated with increased atherosclerotic cardiovascular disease incidence in prospective cohort studies. Compared to phospholipid-conjugated choline sources (alpha-glycerophosphocholine, cytidine diphosphate-choline, phosphatidylcholine from egg yolk or krill oil), choline bitartrate produces higher peak trimethylamine N-oxide levels and lower incremental phosphatidylcholine enrichment in plasma, reflecting differential metabolic routing. The clinical evidence base for choline bitartrate as a standalone supplement is mixed. Controlled feeding studies at the National Institutes of Health and at the University of North Carolina have established that dietary choline deprivation produces hepatic steatosis, elevated serum aminotransferase, and muscle damage in both men and women within weeks, confirming essentiality in humans. Epidemiological studies link higher dietary choline intake to reduced risk of nonalcoholic fatty liver disease and to reduced neural tube defect incidence in offspring of pregnant women. However, placebo-controlled trials of acute choline bitartrate supplementation in healthy young adults have failed to demonstrate significant enhancement of declarative memory or working memory, although improvements in visuomotor performance and pupil constriction have been reported. Chronic supplementation data in rodent models show cognitive and locomotor improvements accompanied by reduced oxidative stress. The evidence is more favorable for cognitive benefit in elderly populations and in individuals with diagnosed choline deficiency, consistent with the compound functioning as a conditional nootropic whose benefit depends on baseline choline status. The Institute of Medicine established Adequate Intake values of 550 mg per day for adult men and 425 mg per day for adult women, with 450 mg per day

during pregnancy and 550 mg per day during lactation. The Tolerable Upper Intake Level for adults is 3500 mg of choline per day; adverse effects above the upper limit include hypotension, fishy body odor (from trimethylamine excretion), sweating, gastrointestinal distress, and hepatotoxicity. Population surveys indicate that the majority of adults in North America and Europe consume choline below the Adequate Intake, and fewer than 10 percent of pregnant women meet gestational requirements. This monograph reviews the chemistry, synthesis, and salt-form characteristics of choline bitartrate; the three-arm molecular pharmacology (acetylcholine synthesis, phospholipid biosynthesis, methyl donation); comprehensive pharmacokinetics including the trimethylamine N-oxide pathway; the clinical evidence base across cognitive, hepatic, gestational, and cardiovascular endpoints; sourcing and quality verification; reconstitution and handling; stack interactions with other cholinergic, nootropic, and hepatoprotective agents; adverse events and safety signals including the trimethylamine N-oxide cardiovascular association; and a comparative assessment of five alternative choline-delivery compounds (alpha-glycerophosphocholine, cytidine diphosphate-choline, phosphatidylcholine, choline chloride, and centrophenoxine) against choline bitartrate on five competency standards (bioavailability and brain penetration, effect size on cognitive endpoints, breadth of clinical evidence, side-effect profile, and cost-effectiveness).

1. Compound Identification

1.1 Names, synonyms, and registry identifiers

Common name: Choline bitartrate.

Synonyms: Choline hydrogen tartrate, choline tartrate salt, (2-hydroxyethyl)trimethylammonium hydrogen tartrate, choline L-bitartrate, choline DL-bitartrate, cholini bitartras.

Chemical Abstracts Service registry number: 87-67-2 (choline bitartrate, DL-tartrate salt). The L-tartrate enantiomer and the DL-racemic tartrate are both in commerce; the CAS number 87-67-2 designates the general choline bitartrate salt. The free base choline has CAS number 62-49-7, and the chloride salt (choline chloride) has CAS number 67-48-1.

PubChem Compound Identifier: CID 6900 (choline bitartrate).

DrugBank identifier: DBSALT001542 (choline bitartrate salt); DB00122 (choline, parent compound).

International Union of Pure and Applied Chemistry name: 2-hydroxyethyl(trimethyl)azanium; 2,3-dihydroxy-4-oxobutanoic acid (systematic representation of the ion pair). The more conventional IUPAC designation for the choline cation is (2-hydroxyethyl)trimethylammonium, and for the bitartrate anion is (2R,3R)-2,3-dihydroxybutanedioate (for the L-tartrate form) with one carboxylate protonated.

1.2 Structural class and chemistry

Choline bitartrate is a quaternary ammonium salt composed of the choline cation and the bitartrate (hydrogen tartrate) anion in a 1:1 stoichiometric ratio. The choline moiety is a simple trimethylated ethanolamine: a permanently charged quaternary nitrogen bearing three methyl groups and one 2-hydroxyethyl chain. The bitartrate counterion is the monodeprotonated form of tartaric acid, a dihydroxydicarboxylic acid.

Molecular formula: C₉H₁₉NO₇ (choline bitartrate salt).

Molecular weight: 253.25 g/mol (choline bitartrate). The choline cation alone has a molecular weight of 104.17 g/mol, yielding a choline content of approximately 41.1 percent by mass in the bitartrate salt.

Physical properties: White to off-white crystalline powder. Freely soluble in water. Hygroscopic, absorbing atmospheric moisture on prolonged exposure to ambient humidity. Acid taste. Melting point approximately 151 degrees Celsius. The compound is stable as a dry solid under recommended storage conditions but is hygroscopic and will degrade in aqueous solution at temperatures above 10 degrees Celsius on prolonged standing.

Stereochemistry: The choline cation has no stereocenters and is achiral. The tartrate anion exists as the L-(2R,3R) enantiomer in the L-bitartrate salt form or as the DL-racemic mixture in the DL-bitartrate salt form. Both enantiomeric forms of the tartrate counterion are in commercial production; the tartrate moiety is pharmacologically inert and serves solely as a solubility-enhancing, crystallinity-promoting counterion. Investigators need not distinguish L- from DL-bitartrate for biological applications; the distinction is relevant only for analytical characterization and optical rotation measurements.

1.3 Synthesis

Industrial synthesis of choline bitartrate proceeds in two principal stages. In the first stage, choline is synthesized by the reaction of trimethylamine with ethylene oxide in aqueous solution or in methanol, producing the choline cation (as the hydroxide, which is then neutralized). In the second stage, the choline base or choline hydroxide is reacted with tartaric acid (either L-tartaric acid or DL-tartaric acid) in stoichiometric proportion to produce the bitartrate salt, which is crystallized from aqueous or aqueous-alcoholic solution, filtered, and dried. The product is characterized by assay of choline content (typically by precipitation as the reineckate salt and gravimetric determination, or by high-performance liquid chromatography), residual moisture (Karl Fischer titration), heavy metals, and microbiological purity. Industrial production achieves purities of 98 to 100 percent by assay with residual moisture below 1 percent. The synthesis is straightforward, proceeds in high yield, and requires no chiral resolution because the choline cation is achiral; the tartrate counterion is sourced as the desired enantiomeric form from commercial tartaric acid production (a byproduct of the wine industry for the L-form).

2. Abstract

Choline bitartrate is the tartaric acid salt of the essential nutrient choline, delivering approximately 41 percent choline by mass in a water-soluble, crystalline, shelf-stable form suitable for oral supplementation. Choline was first isolated by Strecker in 1862 from hog bile and was designated an essential nutrient by the United States Institute of Medicine in 1998, following controlled human feeding studies that demonstrated hepatic steatosis and organ dysfunction upon dietary choline deprivation [1, 2].

The compound functions through three convergent metabolic pathways. First, choline is acetylated by choline acetyltransferase in cholinergic nerve terminals to produce the neurotransmitter acetylcholine, the rate of synthesis being partially dependent on choline availability because the enzyme is not saturated with substrate under physiological conditions [3]. Second, choline is phosphorylated by choline kinase and subsequently incorporated into phosphatidylcholine through the cytidine diphosphate-choline (Kennedy) pathway, the major biosynthetic route for the most abundant mammalian membrane phospholipid, which is also required for very-low-density lipoprotein assembly and hepatic lipid export [4]. Third, choline is oxidized in hepatic and renal mitochondria to betaine, which serves as a methyl donor in the betaine-homocysteine methyltransferase reaction, converting homocysteine to methionine and supporting S-adenosylmethionine regeneration for methylation of DNA, histones, and other substrates [5].

Pharmacokinetic studies demonstrate that oral choline bitartrate is rapidly absorbed, with peak plasma choline concentrations at approximately one to two hours after a single dose. However, a substantial fraction of ingested free choline is converted by intestinal bacteria to trimethylamine, which is oxidized by hepatic flavin-containing monooxygenase 3 to trimethylamine N-oxide. This metabolic pathway has attracted substantial cardiovascular research interest because elevated circulating trimethylamine N-oxide has been associated in prospective cohort studies with increased risk of atherosclerotic cardiovascular events [6, 7]. Compared to phospholipid-conjugated choline forms (alpha-glycerophosphocholine, phosphatidylcholine), choline bitartrate produces relatively higher

trimethylamine N-oxide elevations per unit of choline delivered, reflecting the greater accessibility of the free choline cation to intestinal bacterial trimethylamine lyase [8].

Clinical evidence for cognitive enhancement with choline bitartrate is mixed. A randomized, double-blind, placebo-controlled crossover study in healthy young adults found no acute effects on declarative or working memory [9]. A separate placebo-controlled study reported improved visuomotor performance and pupil constriction after choline bitartrate supplementation [10]. Chronic supplementation in rodent models has demonstrated cognitive and motor improvements with concomitant reduction in oxidative stress markers [11]. The evidence is more favorable in elderly populations and in individuals with suboptimal baseline choline status, consistent with the compound functioning as a conditional cognitive enhancer that replenishes a deficient substrate rather than augmenting an already sufficient one.

The hepatoprotective role of choline is supported by human deprivation studies demonstrating that dietary choline restriction produces fatty liver, elevated alanine aminotransferase, and muscle creatine phosphokinase elevation within three weeks in the majority of subjects, with resolution upon choline repletion [2]. Epidemiological data from the Framingham Offspring Cohort and from the National Health and Nutrition Examination Survey link higher dietary choline intake to reduced risk of nonalcoholic fatty liver disease and to improved cognitive performance in later life [12, 13]. Gestational choline adequacy is associated with reduced neural tube defect risk; women in the lowest quartile of dietary choline intake have approximately four-fold higher risk of neural tube defect-affected pregnancies compared to those in the highest quartile [14].

The Institute of Medicine Adequate Intake values are 550 mg per day for adult men, 425 mg per day for adult women, 450 mg per day during pregnancy, and 550 mg per day during lactation. The Tolerable Upper Intake Level for adults is 3500 mg of choline per day. Population surveys consistently report that the majority of adults in North America and Europe consume choline below the Adequate Intake [1].

3. Discovery and Development History

3.1 Isolation and early characterization

Choline was first isolated from hog bile by Adolph Strecker in 1862 and was named from the Greek word for bile (chole). The chemical structure was determined as trimethyl-beta-hydroxyethylammonium hydroxide. The compound was subsequently identified as a component of lecithin (phosphatidylcholine) by Diakonow and Strecker in the 1860s and 1870s, establishing the biochemical link between choline and membrane phospholipid chemistry that would remain central to choline biology for the next century and a half [15].

3.2 Recognition of nutritional essentiality

The nutritional importance of choline was first recognized in the 1930s through animal feeding studies. Best and Huntsman (1932) demonstrated that dietary choline prevented fatty liver in depancreatized dogs, and subsequent work by Best and colleagues established that choline deficiency produced hepatic steatosis, hemorrhagic renal necrosis, and other organ pathology in rats, dogs, and other mammalian species [16]. These findings established choline as a lipotropic factor (a substance required for normal hepatic lipid metabolism) but did not immediately lead to recognition of human dietary essentiality because endogenous synthesis through the phosphatidylethanolamine N-methyltransferase (PEMT) pathway was considered potentially sufficient.

3.3 Human essentiality studies

The critical transition to human essentiality recognition occurred in the 1980s and 1990s. Zeisel and colleagues at the University of North Carolina conducted controlled feeding studies in which healthy male and female volunteers were maintained on choline-deficient diets under metabolic ward conditions. These studies demonstrated that the majority of men and postmenopausal women developed hepatic steatosis (documented by magnetic resonance imaging), elevated serum alanine aminotransferase, and elevated creatine phosphokinase within three weeks of choline deprivation, with complete resolution upon choline repletion [2, 17]. The

studies further revealed that premenopausal women were partially protected from choline deficiency signs, attributable to estrogen-mediated upregulation of the PEMT gene, which encodes the enzyme responsible for de novo choline synthesis from phosphatidylethanolamine [18].

3.4 Institute of Medicine recognition

In 1998, the Institute of Medicine (now the National Academy of Medicine) formally recognized choline as an essential nutrient in the Dietary Reference Intakes volume for B vitamins, establishing Adequate Intake values and a Tolerable Upper Intake Level for the first time [1]. This designation was based on the controlled human deprivation data, on the animal literature, and on the recognition that endogenous PEMT-mediated synthesis is insufficient to meet physiological demands in most individuals, particularly men and postmenopausal women.

3.5 Commercial development of choline bitartrate

Choline bitartrate has been manufactured as a dietary supplement and animal feed additive since the mid-twentieth century. The bitartrate salt was selected for commercial development over other salt forms (chloride, citrate, dihydrogen citrate) primarily for its favorable crystallinity, low hygroscopicity relative to choline chloride, stability in dry solid form, and compatibility with tablet and capsule formulations. The compound is manufactured at industrial scale by multiple producers globally, with principal production in China, India, and the United States. It is listed in the Food Chemicals Codex, is generally recognized as safe by the United States Food and Drug Administration, and is approved as a food additive and dietary supplement ingredient in the European Union, Japan, and most other regulatory jurisdictions.

4. Mechanism of Action

Choline bitartrate is a delivery vehicle for the essential nutrient choline. Upon oral ingestion and dissolution in the gastrointestinal tract, the salt dissociates completely to release the choline cation and the pharmacologically inert bitartrate anion. The biological activity of the compound is therefore entirely attributable to the choline moiety and its three principal metabolic fates: acetylcholine synthesis, phosphatidylcholine biosynthesis, and betaine-mediated methylation.

4.1 Acetylcholine synthesis

Choline is the obligate precursor for acetylcholine, the neurotransmitter of cholinergic neurons throughout the central and peripheral nervous systems. Acetylcholine is synthesized in the cytoplasm of cholinergic nerve terminals by the enzyme choline acetyltransferase, which catalyzes the transfer of the acetyl group from acetyl-coenzyme A to the hydroxyl group of choline [3]. The synthesized acetylcholine is packaged into synaptic vesicles by the vesicular acetylcholine transporter and released into the synaptic cleft upon nerve terminal depolarization.

Choline acetyltransferase has a K_m for choline of approximately 7 to 40 micromolar (depending on tissue and species), and intracellular choline concentrations in cholinergic neurons are typically in the range of 10 to 50 micromolar, indicating that the enzyme operates near or below substrate saturation under resting conditions [3]. This kinetic relationship means that increases in choline availability (through dietary supplementation or enhanced uptake) can increase the rate of acetylcholine synthesis, particularly during periods of high cholinergic demand when presynaptic choline concentrations are depleted by rapid neurotransmitter turnover. This precursor-loading mechanism is the pharmacological basis for the use of choline supplements as cholinergic agents.

Choline is taken up into cholinergic nerve terminals primarily by the high-affinity choline transporter (CHT1, SLC5A7), a sodium-dependent transporter with a K_m of approximately 1 to 5 micromolar that is the rate-limiting step in acetylcholine

synthesis [19]. The transporter is localized to cholinergic nerve terminals and is recycled from synaptic vesicle membranes to the plasma membrane in an activity-dependent manner, coupling choline uptake capacity to neurotransmitter demand.

4.2 Phosphatidylcholine biosynthesis (Kennedy pathway)

The quantitatively dominant metabolic fate of dietary choline is incorporation into phosphatidylcholine through the cytidine diphosphate-choline (CDP-choline or Kennedy) pathway [4]. This three-step pathway begins with phosphorylation of choline by choline kinase to produce phosphocholine, followed by transfer of the phosphocholine moiety to cytidine triphosphate by CTP:phosphocholine cytidylyl-transferase to produce CDP-choline, and concluding with transfer of the phosphocholine head group to diacylglycerol by CDP-choline:1,2-diacylglycerol cholinephosphotransferase to produce phosphatidylcholine.

Phosphatidylcholine is the most abundant phospholipid in mammalian cell membranes, constituting approximately 50 percent of the total phospholipid in most tissues. It is essential for membrane structural integrity, membrane fluidity regulation, signal transduction (as a substrate for phospholipases A2, C, and D), and lipoprotein assembly. In the liver, phosphatidylcholine is required for the assembly and secretion of very-low-density lipoproteins; impaired phosphatidylcholine supply leads to accumulation of triglyceride in hepatocytes (steatosis) because lipid cannot be exported without the phospholipid coat of the lipoprotein particle [4, 20].

An alternative pathway for phosphatidylcholine synthesis exists in the liver: the phosphatidylethanolamine N-methyltransferase (PEMT) pathway, which converts phosphatidylethanolamine to phosphatidylcholine through three sequential methylations using S-adenosylmethionine as the methyl donor [18]. The PEMT pathway accounts for approximately 30 percent of hepatic phosphatidylcholine synthesis and is the only pathway for de novo choline biosynthesis in mammals. PEMT expression is upregulated by estrogen, explaining the partial protection of premenopausal women from choline deficiency.

4.3 Betaine synthesis and methyl donation

The third metabolic fate of choline is irreversible oxidation to betaine (trimethylglycine). Choline is first oxidized to betaine aldehyde by choline dehydrogenase (a mitochondrial inner membrane enzyme expressed principally in liver and kidney),

and betaine aldehyde is subsequently oxidized to betaine by betaine aldehyde dehydrogenase [5]. Betaine serves as a methyl donor in the betaine-homocysteine methyltransferase (BHMT) reaction, which converts homocysteine to methionine. Methionine is subsequently adenylated to S-adenosylmethionine, the universal methyl donor for more than 200 methyltransferase reactions including DNA methylation, histone methylation, phospholipid methylation, and small-molecule methylation.

The choline-betaine-methionine pathway intersects with the folate-dependent one-carbon metabolism pathway at the homocysteine remethylation step, where both betaine (via BHMT) and 5-methyltetrahydrofolate (via methionine synthase) can regenerate methionine from homocysteine [5, 21]. This metabolic intersection means that choline and folate are partially interchangeable as methyl donors, and that deficiency of either nutrient increases the requirement for the other. The intersection is clinically important in pregnancy, where both choline and folate support neural tube closure and fetal brain development through epigenetic methylation mechanisms.

4.4 Additional signaling roles

Beyond the three canonical metabolic fates, choline and its metabolites participate in several additional signaling pathways. Phosphatidylcholine is a substrate for phospholipase D, which cleaves it to produce phosphatidic acid (a lipid second messenger) and free choline. Sphingomyelin, another choline-containing phospholipid, is a substrate for sphingomyelinase, producing ceramide (a proapoptotic and growth-inhibitory signal). Platelet-activating factor (1-O-alkyl-2-acetyl-sn-glycero-3-phosphocholine) is a potent lipid mediator of inflammation and platelet aggregation that contains the phosphocholine head group.

5. Pharmacokinetics and Routes of Administration

5.1 Absorption

Choline bitartrate is administered orally, typically as tablets, capsules, or powder. Upon ingestion, the salt dissociates in the acidic gastric environment, releasing free choline cation and bitartrate anion. Free choline is absorbed principally in the jejunum and ileum by a combination of carrier-mediated transport and passive diffusion. Absorption is rapid; peak plasma choline concentrations are achieved within approximately one to two hours after a single oral dose in fasted healthy volunteers [22].

Baseline fasting plasma free choline concentrations in healthy adults are approximately 7 to 12 micromolar. After a 500 mg oral dose of choline bitartrate (delivering approximately 205 mg of choline), peak plasma choline rises to approximately 12 to 20 micromolar, representing an increment of approximately 50 to 100 percent above baseline [22, 23]. The increment is modest compared to phospholipid-bound choline sources (phosphatidylcholine, alpha-glycerophosphocholine), which produce sustained elevation of plasma choline and choline metabolites over a longer period because the phospholipid forms undergo pancreatic phospholipase A2 digestion and enterocyte reacylation before entering the lymphatic circulation as chylomicron phosphatidylcholine [8].

5.2 Distribution

Choline distributes to all tissues. The plasma concentration of free choline is maintained within a relatively narrow homeostatic range (approximately 7 to 20 micromolar) by hepatic extraction, tissue uptake, and renal excretion. Tissue concentrations vary substantially: liver, kidney, and brain contain higher concentrations than plasma, reflecting active uptake by tissue-specific transporters.

Brain choline is supplied by two mechanisms: transport across the blood-brain barrier by a facilitated diffusion carrier (probably CTL1, SLC44A1) and local recycling of acetylcholine-derived choline after synaptic hydrolysis by acetyl-

cholinesterase [19]. The blood-brain barrier transport of free choline is relatively inefficient compared to the transport of lipid-conjugated choline (as alpha-glycerophosphocholine or lysophosphatidylcholine), which is one basis for the observation that choline bitartrate produces less pronounced central cholinergic effects than alpha-glycerophosphocholine or cytidine diphosphate-choline at equivalent choline doses.

5.3 Metabolism

Choline undergoes extensive first-pass hepatic metabolism. The principal hepatic fates are phosphorylation to phosphocholine (entry into the Kennedy pathway), oxidation to betaine (entry into the methylation pathway), and acetylation to acetylcholine (minor in liver; principal in cholinergic neurons).

A quantitatively important metabolic pathway that is unique to free (non-phospholipid-bound) choline is gut microbial metabolism. Intestinal bacteria expressing choline trimethylamine-lyase (the cutC/cutD enzyme complex) cleave the carbon-nitrogen bond of choline to produce trimethylamine and acetaldehyde [6]. Trimethylamine is absorbed from the gut lumen into the portal circulation and is oxidized in the liver by flavin-containing monooxygenase 3 (FMO3) to trimethylamine N-oxide (TMAO). This pathway diverts a fraction of ingested choline away from the three beneficial metabolic fates and toward a metabolite that has been associated with adverse cardiovascular outcomes.

A randomized crossover study comparing choline supplements in healthy volunteers demonstrated that choline bitartrate produced significantly higher postprandial TMAO concentrations than an equivalent choline dose delivered as phosphatidylcholine or as krill oil phospholipids, indicating that the free cation form is more accessible to intestinal bacterial trimethylamine lyase than the phospholipid-esterified form [8, 24].

5.4 Elimination

Choline is eliminated through metabolic conversion (the dominant pathway) and through renal excretion of free choline and betaine. Renal clearance of free choline is low because of efficient tubular reabsorption. Betaine is freely filtered and par-

tially reabsorbed. TMAO is freely filtered and excreted in urine; urinary TMAO is a biomarker of choline intake and of gut microbial trimethylamine production capacity.

The elimination half-life of free plasma choline after a single oral dose is difficult to characterize precisely because choline is under tight homeostatic regulation and does not follow simple first-order elimination kinetics. Plasma choline returns to baseline within approximately four to six hours after a single moderate oral dose [22].

5.5 Routes of administration

Choline bitartrate is administered exclusively by the oral route in supplement and research applications. Intravenous choline (as the chloride salt) has been used in metabolic research studies and in parenteral nutrition formulations, but intravenous choline bitartrate is not a standard preparation. The oral route is adequate for systemic choline delivery and for hepatic endpoint applications. For applications requiring rapid central nervous system cholinergic augmentation, phospholipid-conjugated choline sources (alpha-glycerophosphocholine, cytidine diphosphate-choline) are generally preferred over choline bitartrate because of their superior blood-brain barrier penetration.

5.6 Special populations

Genetic polymorphisms in PEMT, CHDH (choline dehydrogenase), BHMT, MTHFD1, and other genes in the choline and one-carbon metabolic pathways substantially affect individual choline requirements [18, 25]. Common single-nucleotide polymorphisms in PEMT (rs12325817, rs7946) reduce endogenous choline synthesis capacity and increase dietary choline requirements; carriers of these variants are more susceptible to choline deficiency signs on low-choline diets. Premenopausal women are partially protected from choline deficiency by estrogen-mediated PEMT upregulation, but this protection is lost after menopause. During pregnancy, choline requirements increase to support fetal brain development, placental function, and expanded maternal one-carbon metabolism; the Adequate Intake is 450 mg per day during pregnancy and 550 mg per day during lactation. Individuals with trimethylaminuria (an inherited deficiency of FMO3) are at particular risk of adverse effects from choline supplementation because they cannot oxidize trimethylamine to TMAO and accumulate the malodorous trimethylamine in sweat, urine, and breath.

6. Clinical Evidence Base

6.1 Human choline deprivation and essentiality

The foundational clinical evidence for choline essentiality derives from the controlled feeding studies conducted by Zeisel, da Costa, and colleagues at the University of North Carolina Clinical Nutrition Research Unit [2, 17]. In the definitive study (da Costa et al. 2006), 57 adults (26 men, 16 premenopausal women, 15 postmenopausal women) were placed on a choline-adequate diet (550 mg choline per day) followed by a choline-deficient diet (less than 50 mg per day) for up to 42 days, with organ function monitored by hepatic magnetic resonance imaging, serum alanine aminotransferase, and serum creatine phosphokinase [17]. Seventy-seven percent of men, 80 percent of postmenopausal women, and 44 percent of premenopausal women developed organ dysfunction (hepatic steatosis and/or elevated aminotransferases) on the choline-deficient diet. All signs resolved upon choline repletion (at 550 or 850 mg per day). These studies established that endogenous PEMT-mediated choline synthesis is insufficient for most men and postmenopausal women and confirmed the 1998 Institute of Medicine essential nutrient designation.

6.2 Cognitive effects

The evidence for cognitive enhancement with choline bitartrate supplementation is mixed and depends heavily on the population studied and the supplementation duration.

In the Naber et al. (2015) randomized, double-blind, placebo-controlled crossover study, healthy young adult students received 2 grams of choline bitartrate or placebo and were tested on verbal memory, visual memory, and working memory tasks at two and four hours post-ingestion [9]. No significant effects of choline bitartrate on any memory measure were observed. The authors concluded that acute choline bitartrate supplementation does not enhance memory in healthy young adults with presumably adequate baseline choline status.

In contrast, the Naber et al. (2015) companion study reported that choline bitartrate at a 2-gram dose significantly improved visuomotor performance (faster and more accurate responses on a tracking task) and decreased pupil diameter in healthy adults, suggesting a peripheral cholinergic or autonomic effect that does not extend to higher cognitive processes in this population [10].

Chronic choline supplementation in rodent models has produced more favorable results. Tsakiris et al. (2017) demonstrated that chronic choline bitartrate administration (100 mg/kg/day for 30 days) in healthy adult rats improved cognitive performance on the Morris water maze and the passive avoidance test, improved locomotor activity, and reduced hippocampal and cortical markers of oxidative stress [11]. These findings suggest that sustained choline loading may produce cognitive benefits through both cholinergic and antioxidant mechanisms, but the translation to humans at dietary supplement doses requires confirmation.

Epidemiological data from the Framingham Offspring Cohort (Poly et al. 2011) demonstrated that higher concurrent dietary choline intake was associated with better verbal memory and visual memory performance, and that lower choline intake was associated with greater white matter hyperintensity volume on brain magnetic resonance imaging, an indicator of cerebral small vessel disease [12]. This cross-sectional association supports the hypothesis that chronic choline adequacy supports cognitive maintenance but does not establish causality or speak specifically to choline bitartrate supplementation.

6.3 Hepatic endpoints and nonalcoholic fatty liver disease

The hepatoprotective role of choline is firmly established by the deprivation studies described in section 6.1 and is supported by epidemiological evidence linking dietary choline intake to nonalcoholic fatty liver disease (NAFLD) risk. In a cross-sectional analysis of the National Health and Nutrition Examination Survey (2017 to 2018), higher dietary choline intake was associated with reduced odds of NAFLD in United States adults [13]. A study from the Nonalcoholic Steatohepatitis Clinical Research Network found that postmenopausal women with lower choline intake had significantly worse hepatic fibrosis scores, although this association was not observed in men, children, or premenopausal women [26].

Mechanistically, choline deficiency impairs hepatic VLDL assembly and secretion (because phosphatidylcholine is required for the lipoprotein surface coat), leading to triglyceride accumulation in hepatocytes. Choline deficiency also im-

pairs mitochondrial beta-oxidation of fatty acids and promotes oxidative stress and apoptosis in hepatocytes, contributing to the progression from steatosis to steatohepatitis in the choline-deficient animal model [20].

6.4 Gestational and developmental outcomes

Periconceptional and gestational choline adequacy is associated with reduced neural tube defect risk in offspring. Shaw et al. (2004) reported in a case-control study nested within a California population that women in the lowest quartile of periconceptional dietary choline intake had approximately four times the risk of having an infant with a neural tube defect compared to women in the highest quartile [14]. A meta-analysis of studies encompassing 1131 mothers of newborns with neural tube defects and 4439 control mothers confirmed the association (pooled odds ratio 1.36 for low versus high choline intake, 95 percent confidence interval 1.11 to 1.67) [27].

Maternal choline supplementation during pregnancy has been associated with improved infant cognitive outcomes in several studies, although results are not uniform. Caudill et al. (2018) conducted a randomized controlled feeding study in which pregnant women received 480 mg per day (approximately the Adequate Intake) or 930 mg per day of choline (as choline chloride) from gestational week 27 through delivery; infants of mothers in the higher-choline group demonstrated faster information processing speed at 4, 7, 10, and 13 months of age [28]. The applicability to choline bitartrate specifically is inferred from the shared active moiety; no large gestational trials have been conducted with choline bitartrate as the specific salt form.

6.5 Cardiovascular considerations and trimethylamine N-oxide

The cardiovascular implications of choline supplementation are complicated by the gut microbial TMAO pathway. Prospective cohort studies (Wang et al. 2011; Tang et al. 2013; Heianza et al. 2017) have demonstrated associations between elevated fasting plasma TMAO concentrations and increased risk of major adverse cardiovascular events, including myocardial infarction, stroke, and cardiovascular death [6, 7, 29].

A randomized clinical trial by Wilcox et al. (2021) demonstrated that choline bitartrate supplementation (equivalent to 450 mg choline per day for four weeks) significantly increased fasting plasma TMAO concentrations in healthy adults, whereas an equivalent choline dose from whole eggs did not, suggesting that the food matrix modulates gut microbial access to choline [24]. This finding has practical implications for supplement selection: choline delivered in phospholipid-bound form (as in eggs, krill oil, or alpha-glycerophosphocholine) may produce less TMAO elevation than an equivalent dose of choline bitartrate.

The causal significance of the TMAO-cardiovascular association remains debated. Mendelian randomization studies have produced mixed results, and interventional studies have not demonstrated that TMAO lowering reduces cardiovascular events [30]. The current evidence supports TMAO as a biomarker associated with cardiovascular risk but does not establish it as a validated therapeutic target. Investigators should weigh the TMAO signal in the context of the established benefits of choline adequacy and should not withhold choline supplementation from deficient individuals on the basis of TMAO concerns alone.

7. Reported Research Dose Ranges

7.1 Dietary supplement doses

Choline bitartrate is marketed as a dietary supplement at doses ranging from 250 mg to 2000 mg per unit dose (delivering approximately 103 to 822 mg of choline per unit dose). Common supplement doses are 500 mg to 1000 mg of choline bitartrate (205 to 411 mg of choline) taken one to two times daily, consistent with closing the gap between typical dietary choline intake (approximately 300 mg per day in the average American diet) and the Adequate Intake (425 to 550 mg per day).

7.2 Research and clinical trial doses

Cognitive function studies have used 1000 to 2000 mg of choline bitartrate (411 to 822 mg of choline) as single acute doses [9, 10]. Chronic rodent studies have used 100 mg/kg/day [11]. Metabolic and hepatic endpoint studies in humans have used choline at 550 to 850 mg per day (as various salt forms) over periods of several weeks [2, 17].

7.3 Adequate Intake and Upper Limit reference

For reference against recommended dietary values: the Adequate Intake is 550 mg of choline per day for adult men (equivalent to approximately 1337 mg of choline bitartrate) and 425 mg per day for adult women (equivalent to approximately 1033 mg of choline bitartrate). The Tolerable Upper Intake Level of 3500 mg of choline per day corresponds to approximately 8513 mg of choline bitartrate. Most supplement protocols remain well below the Upper Limit.

8. Sourcing and Quality Verification

Choline bitartrate is manufactured at pharmaceutical, food, and feed grades by numerous global suppliers. Principal manufacturers include Balchem Corporation (United States), BASF (Germany), Jubilant Life Sciences (India), Eastman Chemical Company (United States), and multiple Chinese manufacturers. The compound is listed in the Food Chemicals Codex (FCC), the United States Pharmacopeia (as a dietary ingredient), and the European Pharmacopoeia (as a food additive).

Food-grade and supplement-grade choline bitartrate is typically supplied at 98 to 100 percent purity by assay (determined by ion chromatography, HPLC, or reineckate precipitation gravimetry) with specifications for loss on drying (less than 1 percent), heavy metals (less than 10 ppm), arsenic (less than 3 ppm), lead (less than 2 ppm), and microbiological limits (total aerobic count, yeast, mold, *Escherichia coli*, *Salmonella*).

Investigators should confirm identity and purity on received lots through:

- Assay of choline content by HPLC or ion chromatography (target: 98 percent or greater)
- Identification by infrared spectroscopy or nuclear magnetic resonance against a reference standard
- Loss on drying or Karl Fischer moisture analysis (target: less than 1 percent)
- Heavy metals panel (inductively coupled plasma mass spectrometry for lead, arsenic, cadmium, mercury)
- Microbiological testing if the material is intended for human ingestion studies

Third-party analytical verification (NSF International, USP Verified, Informed Sport, or independent laboratory) is recommended for research applications where dose-response precision is important. The commodity nature of choline bitartrate production means that lot-to-lot variability is generally low, but adulteration with lower-grade material or excess moisture is occasionally encountered in bulk powder sourced from secondary distributors.

9. Reconstitution and Handling

Choline bitartrate is supplied as a white to off-white crystalline powder. The compound is freely soluble in water (approximately 1 gram per 1 milliliter at room temperature) and is sparingly soluble in ethanol. For research applications, stock solutions are prepared by dissolution of the weighed powder in purified water, normal saline, or the appropriate vehicle for the experimental system.

Storage: The dry powder should be stored at 15 to 25 degrees Celsius, at relative humidity below 60 percent, protected from light, in sealed containers. Under these conditions, shelf life is approximately 60 months (five years) from date of manufacture. The compound is hygroscopic; exposure to humid air will cause caking and moisture absorption. Containers should be resealed promptly after each use.

Aqueous solutions: Choline bitartrate in aqueous solution is stable at refrigerated conditions (2 to 8 degrees Celsius) for at least 14 days. At room temperature, aqueous solutions should be used within 24 to 48 hours. The compound does not require light protection but is best stored in amber containers as standard practice. Autoclave sterilization is not recommended because of potential thermal degradation; sterile filtration (0.22 micrometer) of aqueous solutions is the preferred sterilization method for cell culture or injection applications.

Compatibility: Choline bitartrate is compatible with most common excipients and is formulated with cellulose, starch, magnesium stearate, and gelatin capsule shells in commercial dietary supplement products. The compound is incompatible with strong oxidizing agents and strong bases.

10. Stack Interaction Considerations

Choline bitartrate interacts with several compound classes through its metabolic pathways and its role as a cholinergic precursor. Investigators using choline bitartrate in combination with other research compounds or dietary supplements should consider the following interactions.

Acetylcholinesterase inhibitors: Concurrent use with donepezil, rivastigmine, galantamine, or huperzine A produces additive cholinergic activity through the combination of increased acetylcholine synthesis (choline loading) and decreased acetylcholine degradation (cholinesterase inhibition). This combination is pharmacologically rational for cognitive applications and is commonly used in nootropic supplement stacks. However, excessive cholinergic stimulation can produce parasympathomimetic adverse effects including nausea, diarrhea, bradycardia, and excessive salivation. Dose titration of both components is recommended when combining.

Other choline sources: Concurrent administration with alpha-glycerophosphocholine, cytidine diphosphate-choline, phosphatidylcholine, or high-choline foods (eggs, liver) produces additive choline loading. Total choline intake from all sources should be monitored to avoid exceeding the Tolerable Upper Intake Level of 3500 mg per day.

Racetam nootropics: Piracetam, aniracetam, oxiracetam, and other racetam-class nootropics are commonly combined with choline sources in nootropic supplementation protocols. The rationale is that racetams increase acetylcholine turnover and may deplete presynaptic choline, producing headache as a common side effect; concurrent choline supplementation replenishes the precursor pool. This combination is widely used in the nootropic community but has not been validated in controlled clinical trials.

Folate and B vitamins: Choline and folate are metabolically interchangeable at the homocysteine remethylation step. Concurrent supplementation with folate (folic acid, methylfolate), vitamin B12, and vitamin B6 supports the full one-carbon metabolic cycle and may reduce homocysteine more effectively than either choline or folate alone. This combination is rational during pregnancy for neural tube defect prevention.

Methotrexate and antifolates: Methotrexate inhibits dihydrofolate reductase and disrupts one-carbon metabolism. In the setting of antifolate therapy, choline demand may increase because folate-dependent homocysteine remethylation is impaired and the betaine (choline-derived) pathway assumes greater metabolic load. Choline supplementation during methotrexate therapy has not been formally studied but is mechanistically rational for hepatoprotection.

Hepatotoxic agents: Choline is hepatoprotective through its role in VLDL assembly and lipid export. Concurrent administration with hepatotoxic agents (alcohol, high-dose acetaminophen, certain chemotherapy agents) may partially mitigate hepatic lipid accumulation, although this should not be construed as a substitute for dose reduction of the hepatotoxic agent.

Trimethylamine N-oxide considerations: Compounds or dietary patterns that increase gut microbial trimethylamine production (L-carnitine, betaine, high-meat diets) produce additive TMAO elevation when combined with choline bitartrate. Individuals concerned about cardiovascular risk from TMAO may consider substituting phospholipid-bound choline sources for choline bitartrate to reduce the TMAO contribution.

11. Adverse Events and Safety

11.1 Common adverse events

At doses within the Adequate Intake range (425 to 550 mg choline per day), adverse events from choline bitartrate are uncommon and generally mild. Reported events include:

- Gastrointestinal discomfort (nausea, bloating, diarrhea) at doses above 1000 mg of choline in sensitive individuals
- Fishy body odor from trimethylamine excretion, particularly at higher doses or in individuals with reduced FMO3 activity
- Mild hypotension (reflecting peripheral cholinergic vasodilation)
- Increased salivation and sweating at high doses

11.2 Adverse events at or above the Tolerable Upper Intake Level

At choline intakes above 3500 mg per day, the Institute of Medicine identified the following adverse effects as the basis for the Tolerable Upper Intake Level [1]:

- Hypotension (the critical adverse effect used to derive the UL)
- Fishy body odor (from trimethylamine accumulation exceeding FMO3 oxidative capacity)
- Excessive sweating and salivation (cholinergic effects)
- Nausea, vomiting, and diarrhea
- Hepatotoxicity (paradoxically, at very high doses, likely through mechanisms distinct from the hepatoprotective effect of adequate choline)

11.3 Trimethylamine N-oxide and cardiovascular risk

The gut microbial conversion of choline to trimethylamine and its subsequent hepatic oxidation to TMAO represents a potential safety signal for chronic high-dose choline bitartrate supplementation. Prospective cohort studies have associated ele-

vated circulating TMAO with increased risk of major adverse cardiovascular events [6, 7, 29]. Choline bitartrate produces greater TMAO elevation per unit of choline delivered compared to phospholipid-bound choline sources [8, 24]. The clinical significance of this differential is not established by interventional cardiovascular outcome data, and the association between TMAO and cardiovascular events may reflect confounding by diet quality, renal function, or gut microbiome composition rather than a direct causal relationship [30]. The current evidence does not support withholding choline from deficient individuals but does support preferential use of phospholipid-bound choline forms for individuals with established cardiovascular disease or elevated baseline TMAO.

11.4 Trimethylaminuria

Individuals with inherited trimethylaminuria (FMO3 deficiency, also known as fish malodor syndrome) cannot convert trimethylamine to the odorless TMAO and accumulate trimethylamine in body fluids. Choline bitartrate supplementation is relatively contraindicated in these individuals because it substantially increases trimethylamine production through the gut microbial pathway.

11.5 Pregnancy and lactation

Choline is an essential nutrient during pregnancy and lactation, and the Adequate Intake is increased to 450 mg per day during pregnancy and 550 mg per day during lactation [1]. Choline bitartrate supplementation at doses consistent with achieving the Adequate Intake is considered safe. The Tolerable Upper Intake Level of 3500 mg per day applies during pregnancy and lactation. No teratogenic effects have been reported in animal studies at relevant doses. The principal concern is the adequacy gap: fewer than 10 percent of pregnant women meet the Adequate Intake, suggesting that supplementation is more often indicated than contraindicated in this population [27].

12. Comparable Compounds Assessment

This section presents a structured comparative assessment of five alternative choline-delivery compounds against choline bitartrate, evaluated on five competency standards: bioavailability and brain penetration, effect size on cognitive endpoints, breadth of clinical evidence, side-effect profile, and cost-effectiveness. The five comparators were selected as the principal choline-containing compounds with substantive research or clinical evidence for cholinergic, cognitive, or hepato-protective applications.

12.1 Alpha-glycerophosphocholine (alpha-GPC)

Chemical identity: L-alpha-glycerophosphorylcholine. Molecular weight 257.22 g/mol. Choline content approximately 40 percent by mass. A natural phospholipid intermediate formed by phospholipase A2 digestion of phosphatidylcholine.

Bioavailability and brain penetration: Alpha-GPC is well absorbed orally and crosses the blood-brain barrier more efficiently than choline bitartrate, likely because it is transported as an intact glycerophospholipid fragment by lysophospholipid transporters. Studies in rats demonstrate that oral alpha-GPC produces greater increases in brain acetylcholine and brain phosphatidylcholine than equimolar doses of choline chloride or choline bitartrate [31]. The phospholipid backbone protects the choline moiety from gut microbial trimethylamine lyase, potentially reducing TMAO production relative to choline bitartrate per unit of choline delivered.

Effect size on cognitive endpoints: Alpha-GPC has demonstrated cognitive benefit in multiple clinical trials, principally in elderly populations with cognitive impairment or dementia. A meta-analysis of clinical trials (primarily in Alzheimer's disease and vascular dementia) reported consistent improvement on cognitive rating scales with alpha-GPC at 1200 mg per day [32]. In healthy young adults, evidence of cognitive enhancement is limited but more favorable than for choline bitartrate.

Breadth of clinical evidence: Substantially broader than choline bitartrate for cognitive endpoints, with multiple randomized controlled trials in dementia and cognitive impairment. Evidence for hepatoprotective and gestational endpoints is less developed than for choline bitartrate because alpha-GPC is positioned primarily as a nootropic and cognitive support agent.

Side-effect profile: Generally well tolerated. Common adverse events include headache, dizziness, and gastrointestinal discomfort. A 2021 retrospective analysis raised a signal of possible association between long-term alpha-GPC use and stroke risk in the Korean National Health Insurance database, although this finding has not been replicated and may reflect confounding [33]. TMAO production is expected to be lower than with choline bitartrate at equivalent choline doses.

Cost-effectiveness: More expensive than choline bitartrate by a factor of approximately 3 to 5 on a per-gram-of-choline basis. The higher unit cost is partially offset by superior brain penetration and potentially lower dosing requirements for cognitive endpoints.

Comparison to choline bitartrate: Alpha-GPC is the preferred choline source for cognitive and nootropic applications because of its superior blood-brain barrier penetration, stronger clinical evidence for cognitive benefit, and potentially lower TMAO production. Choline bitartrate retains advantages in cost, general nutritional choline repletion, and hepatic endpoint applications where brain penetration is not the primary concern.

12.2 Cytidine diphosphate-choline (CDP-choline, citicoline)

Chemical identity: Cytidine 5'-diphosphocholine. Molecular weight 488.32 g/mol. Choline content approximately 21 percent by mass. A natural intermediate in the Kennedy pathway for phosphatidylcholine biosynthesis.

Bioavailability and brain penetration: CDP-choline is orally bioavailable and is hydrolyzed in the gut to cytidine and choline, which are absorbed separately and recombined intracellularly. The cytidine component is converted to uridine, which has independent neuroprotective and neuromodulatory activity (enhancing phospholipid synthesis and dopamine release). CDP-choline crosses the blood-brain bar-

rier and increases brain choline, uridine, and phospholipid synthesis [34]. Brain penetration of the choline moiety is comparable to or greater than choline bitartrate.

Effect size on cognitive endpoints: CDP-choline has the most extensive clinical evidence base of any choline source for cognitive endpoints. A Cochrane review of 14 trials in dementia and cognitive impairment found evidence of benefit on memory, attention, and behavior, although trial quality was variable [35]. The ICTUS trial in acute ischemic stroke (2659 patients) did not demonstrate significant benefit of CDP-choline on the primary composite endpoint, though prespecified subgroup analyses showed benefit in less severe strokes [36]. The dual-mechanism (choline plus uridine/cytidine) is a meaningful pharmacological advantage over choline bitartrate.

Breadth of clinical evidence: The broadest of any choline source, spanning cognitive impairment, dementia, stroke, traumatic brain injury, glaucoma, and amblyopia. Evidence for hepatic and gestational endpoints is limited because CDP-choline is positioned primarily as a neuroprotective agent.

Side-effect profile: Excellent tolerability in clinical trials. Common adverse events (gastrointestinal discomfort, headache, insomnia) are mild and infrequent. No significant safety concerns have been identified in large stroke trials. TMAO production from CDP-choline has not been extensively characterized but is expected to be moderate.

Cost-effectiveness: More expensive than choline bitartrate by a factor of approximately 5 to 10 on a per-gram-of-choline basis. However, the dual-mechanism (choline plus uridine) may justify the cost premium for neuroprotective applications.

Comparison to choline bitartrate: CDP-choline is the preferred choline source for neuroprotection and stroke recovery applications, with the additional uridine mechanism providing value beyond choline delivery alone. Choline bitartrate is more cost-effective for general nutritional choline repletion and hepatic applications.

12.3 Phosphatidylcholine (lecithin)

Chemical identity: 1,2-diacyl-sn-glycero-3-phosphocholine. Variable molecular weight depending on acyl chain composition (typically 750 to 850 g/mol for common species). Choline content approximately 13 to 15 percent by mass. The principal phospholipid in mammalian cell membranes and the main choline-containing component of egg yolk and soybean lecithin.

Bioavailability and brain penetration: Phosphatidylcholine is digested by pancreatic phospholipase A2 to lysophosphatidylcholine and a free fatty acid; lysophosphatidylcholine is absorbed intact by enterocytes, reacylated, and incorporated into chylomicrons for lymphatic transport. This pathway delivers choline to the liver principally in the phospholipid-bound form, reducing gut microbial access and TMAO production [8]. Brain penetration of the choline moiety from dietary phosphatidylcholine is moderate, comparable to or slightly less than alpha-GPC.

Effect size on cognitive endpoints: Clinical evidence for cognitive benefit from supplemental phosphatidylcholine (lecithin) is weak. Early trials of lecithin for Alzheimer's disease (1980s and 1990s) were largely negative, and a Cochrane review concluded that there was insufficient evidence of benefit [37]. The low choline density of lecithin preparations means that large doses are required to achieve meaningful choline loading.

Breadth of clinical evidence: Extensive for general nutrition but limited and largely negative for cognitive endpoints. Evidence for hepatoprotective activity (as polyenylphosphatidylcholine in liver disease) is moderate.

Side-effect profile: Excellent tolerability. Lecithin is a food component consumed in gram quantities daily by most adults. Gastrointestinal discomfort at high supplemental doses is the principal adverse event. TMAO production is lower than from equivalent choline doses as choline bitartrate.

Cost-effectiveness: Comparable to or less expensive than choline bitartrate on a per-gram-of-product basis, but more expensive on a per-gram-of-choline basis because of the lower choline density. Bulk soybean lecithin is inexpensive.

Comparison to choline bitartrate: Phosphatidylcholine is preferred when the goal is to deliver choline with minimal TMAO production and maximal hepatic phospholipid repletion (as in NAFLD). Choline bitartrate is preferred for cost-effec-

tive choline repletion at defined doses.

12.4 Choline chloride

Chemical identity: (2-hydroxyethyl)trimethylammonium chloride. Molecular weight 139.62 g/mol. Choline content approximately 75 percent by mass (the highest of any commercial choline salt). CAS number 67-48-1.

Bioavailability and brain penetration: Equivalent to choline bitartrate in pharmacokinetic behavior because both salts dissociate completely to release the same choline cation. Brain penetration is identical to choline bitartrate. TMAO production is expected to be equivalent per unit of choline delivered.

Effect size on cognitive endpoints: No meaningful difference from choline bitartrate, as the active moiety is identical. The Caudill et al. (2018) gestational supplementation trial used choline chloride at 930 mg choline per day and demonstrated improved infant information processing [28].

Breadth of clinical evidence: Comparable to choline bitartrate. Choline chloride is more commonly used in animal nutrition research and in metabolic ward studies; choline bitartrate is more commonly used in dietary supplement products.

Side-effect profile: Equivalent to choline bitartrate at equal choline doses. Choline chloride is substantially more hygroscopic than choline bitartrate, which limits its formulation stability in tablets and capsules and is the principal reason it is less commonly used in consumer dietary supplements.

Cost-effectiveness: Slightly less expensive than choline bitartrate on a per-gram-of-choline basis because of the higher choline density. However, the severe hygroscopicity complicates manufacturing and storage.

Comparison to choline bitartrate: Choline chloride and choline bitartrate are pharmacologically equivalent. Choline bitartrate is preferred for supplement formulation because of superior physical stability. Choline chloride is preferred for liquid research preparations and animal nutrition where hygroscopicity is less problematic.

12.5 Centrophenoxine (meclofenoxate)

Chemical identity: 4-chlorophenoxyacetyl ester of dimethylaminoethanol (DMAE). Molecular weight 257.72 g/mol. Does not contain choline directly but is metabolized to DMAE, which is a choline analog and a precursor to phosphatidyl dimethylethanolamine, a minor membrane phospholipid. CAS number 51-68-3.

Bioavailability and brain penetration: Centrophenoxine is well absorbed orally and crosses the blood-brain barrier efficiently. It is hydrolyzed to DMAE and para-chlorophenoxyacetic acid. DMAE is structurally related to choline (lacking one methyl group) and can partially substitute for choline in some metabolic reactions, but it is not a direct acetylcholine precursor because choline acetyltransferase requires the trimethylated substrate. Brain penetration of the DMAE moiety is superior to choline bitartrate.

Effect size on cognitive endpoints: Centrophenoxine has demonstrated cognitive benefit in several older clinical trials in elderly populations with cognitive decline, with improvements on memory and attention measures [38]. The mechanism is attributed to DMAE-mediated reduction of lipofuscin accumulation, membrane phospholipid modification, and indirect cholinergic effects. Effect sizes are modest and the trial quality is variable by modern standards.

Breadth of clinical evidence: Moderate but dated. Most clinical evidence derives from studies conducted in the 1970s and 1980s. Modern randomized controlled trials are scarce.

Side-effect profile: Generally well tolerated. Gastrointestinal discomfort, insomnia, and restlessness are reported at higher doses. DMAE has been associated with teratogenic effects in animal studies (neural tube defects in mice), and centrophenoxine is generally not recommended during pregnancy [39].

Cost-effectiveness: More expensive than choline bitartrate by a factor of approximately 3 to 6. Positioned as a specialty nootropic rather than a nutritional choline source.

Comparison to choline bitartrate: Centrophenoxine is a fundamentally different compound that does not deliver choline directly. It is positioned as a nootropic with brain-penetrant cholinergic-modulating activity rather than as a nutritional

choline supplement. Choline bitartrate is preferred for choline repletion; centrophenoxine is preferred (where legal and available) for membrane-modifying nootropic effects in elderly populations.

12.6 Comparator summary

The five comparator compounds occupy distinct positions in the choline-delivery and cholinergic-augmentation landscape.

Alpha-glycerophosphocholine is the preferred choline source for cognitive and nootropic applications in individuals seeking direct acetylcholine precursor loading with superior blood-brain barrier penetration. It has the strongest evidence base for cognitive benefit among the choline salts and phospholipid intermediates, with multiple clinical trials in dementia populations.

Cytidine diphosphate-choline is the preferred compound for neuroprotective applications (stroke, traumatic brain injury, neurodegenerative disease) because it delivers both choline and uridine (via cytidine), supporting both acetylcholine synthesis and phospholipid membrane repair. It has the broadest clinical evidence base of any choline-delivery compound.

Phosphatidylcholine is the preferred form when the primary goal is hepatic phospholipid repletion with minimal TMAO production. It is the least effective for acute cognitive endpoints because of low choline density and indirect delivery, but it is well tolerated and inexpensive in lecithin form.

Choline chloride is pharmacologically equivalent to choline bitartrate but is less suitable for supplement formulation because of hygroscopicity. It is preferred for liquid research preparations and animal nutrition.

Centrophenoxine is a mechanistically distinct compound that does not deliver choline directly but provides brain-penetrant cholinergic-modulating and membrane-modifying activity through its DMAE metabolite. It occupies a nootropic niche that does not overlap with nutritional choline repletion.

Choline bitartrate occupies the position of the cost-effective, broadly available, well-characterized general-purpose choline source. Its principal strengths are low cost, high aqueous solubility, well-established safety profile at dietary supplement doses, and suitability for closing the dietary choline adequacy gap in the general population. Its principal limitations are limited blood-brain barrier penetration rel-

ative to alpha-GPC and CDP-choline, relatively higher TMAO production compared to phospholipid-bound choline sources, and mixed evidence for cognitive enhancement in choline-replete individuals. For investigators whose primary endpoint is cognitive performance, alpha-GPC or CDP-choline is the more evidence-supported choice. For investigators whose primary endpoint is nutritional choline repletion, hepatic protection, or gestational choline adequacy, choline bitartrate offers the best combination of efficacy, tolerability, and cost.

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