Choline and Citicoline

Common Acronyms

CNS	Chinese Nutrition Society
CRN	Council for Responsible Nutrition
DRI	dietary reference intake
DRV	dietary reference value
EC SCF	European Commission Scientific Committee on Food
EFSA	European Food Safety Authority
EVM	Expert Group on Vitamins and Minerals
ICMR-NIN	Indian Council of Medical Research - National Institute of Nutrition
IOM	Institute of Medicine
IU	international unit
LOAEL	lowest observed adverse effect level
LOEL	lowest observed effect level
NIH	National Institute of Health
KNS	Korean Nutrition Society
NOEL	no observed effect level
NOAEL	no observed adverse effect level
RCT	randomized clinical trial
SUL	safe upper level
UF	uncertainty factor
UL	tolerable upper intake level

Introduction

Choline is a quaternary amine that exists in free and esterified forms (Obeid and Karlsson 2023; Shim and Park 2022). It is essential, at all ages, for liver, muscle, and brain function, especially during fetal development. This nutrient is a component in cell and organelle membranes and has roles in various physiological processes, including DNA and histone methylation, nerve myelination, cell membrane signaling, lipid transport, and signal transduction pathways (IOM 1998; Wallace et al. 2018; Kansakar et al. 2023; WHO 2011). Choline serves as a precursor for

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several metabolites, including acetylcholine, phosphatidylcholine, sphingomyelin, and betaine (WHO 2011; Kansakar et al. 2023; Obeid and Karlsson 2023).

Choline is produced endogenously in the human liver, though not at sufficient levels to meet daily requirements. Most individuals need to consume choline from dietary sources and/or supplementation to prevent deficiency (Wallace et al. 2018; Derbyshire 2019; Korsmo et al. 2020; Derbyshire and Obeid 2020). The most common sources of choline in foods are fat-soluble phospholipids (i.e., phosphatidylcholine and sphingomyelin) or water-soluble compounds (i.e., phosphocholine, glycerolphosphocholine, and free choline) (Wallace et al. 2018; NIH 2022). Dietary lecithin provides dietary choline, primarily in the form of phosphatidylcholine. Despite often being used interchangeably with the term, "phosphatidylcholine," lecithin is a natural complex mixture of phospholipids (mainly of phosphatidylcholine, phosphatidylethanolamine, phosphatidylinositol, and phosphatidic acid), together with various amounts of other substances, e.g., triglycerides, fatty acids, and carbohydrates (Drake 2023; EFSA 2017). The amount of choline naturally occurring in foods ranges from 2-356 mg per serving of nuts, vegetables, or meats (Wallace et al. 2018; NIH 2022; Drake 2023).

Several forms and sources of choline are found in dietary supplements, including choline bitartrate, choline chloride, lecithin, phosphatidylcholine, and alpha-glycerophosphocholine (AGPC or choline alfoscerate); in addition, citicoline is used as a source of supplemental choline (NIH 2022; Drake 2023; Kansakar et al. 2023).

The current chapter focuses on the derivation of UL values for supplemental choline (including sources such as phosphatidylcholine and AGPC listed above) and citicoline in adults.

Bioavailability

Free choline, phosphocholine, and glycerophosphocholine are absorbed into the lumen of the small intestine by transporter proteins (IOM 1998; NIH 2022). Because it is water soluble, choline is absorbed into the aqueous phase of plasma and into the portal circulation and phosphorylated in the liver. The fat-soluble phospholipids (i.e., phosphatidylcholine and

sphingomyelin) are absorbed intact, incorporated into chylomicrons, and released into the lymphatic circulation. The phospholipids are distributed to tissues and other organs, including the brain and placenta (EFSA 2016; NIH 2022). Unabsorbed choline is metabolized into trimethylamine (in the gut) and betaine (in the liver and kidney) (IOM 1998; JECFA 2011; EFSA 2016; WHO 20111). Choline is eliminated by the kidney within eight hours of absorption (Obeid and Karsen 2023).

Following oral administration, citicoline is absorbed and rapidly hydrolyzed into choline and cytidine, with cytidine being further broken down in the gastrointestinal tract and liver into uridine (EFSA 2013; Secades 2016). Ingested citicoline yields approximately 21% choline; for example, 500 mg of citicoline provides approximately 106 mg of choline. Following absorption, citicoline and its metabolites are involved in choline and pyrimidine metabolic pathways and then incorporated into tissues. Elimination primarily occurs through respiratory CO_2 and urinary excretion (EFSA 2013; Secades 2016).

Safety Considerations

Choline

Human studies conducted with high interventional doses of choline are limited to older studies previously reviewed by the IOM (1998). Fishy body odor, vomiting, salivation, sweating, and gastrointestinal effects were considered by the IOM in its hazard assessment. Such effects were reported in studies of patients with tardive dyskinesia and cerebellar ataxia at levels of 10,000 or 16,000 mg per day choline (as choline chloride or choline bitartrate) (Growdon et al 1977a,b; Gelenberg et al. 1979; Lawrence et al. 1980). These exposure levels are approximately 20-30 times the adequate intake (AI) levels established for adults by the IOM (1998) and the EFSA (2016) of 425-500 mg per day and 400-520 mg per day, respectively.

In a small, uncontrolled pilot trial, seven patients with Alzheimer senile dementia (male and female; minimum age 70 years) were given choline at 4,000 mg per day (as choline chloride) for two weeks, followed by 7,500 mg per day for an additional two weeks (Boyd et al. 1977). Nausea and diarrhea were experienced by “some” patients at 7,500 mg per day; these same

patients had a "small" decrease in blood pressure. No changes in blood pressure, and no incidences of nausea, diarrhea, or "evidence of peripheral cholinergic stimulation" were observed at the 4,000 mg dose level. This study was identified by the IOM as the basis for deriving its UL value for choline, which the IOM referred to as "a single case report" with "a slight hypotensive" effect at the higher dose (see *Official Reviews* section).

No effects on blood pressure were reported in any of the other clinical trials included in CRN's assessment. In addition, two studies included blood pressure measurements *a priori* in the study methods; both reported no changes in this parameter following choline intervention (Jacobson et al. 2021; Yamashita et al. 2023). As described in CRN's Methodology chapter, human clinical trial data published since the IOM (1998) report were searched for, screened, and assessed for relevance to deriving CRN's UL value for adult supplemental use of choline. Studies identified that met the inclusion criteria for the current chapter are discussed below. In addition, studies with other forms of choline were considered, primarily AGPC and phosphatidylcholine, due to their higher concentration of choline. A full literature review is outside the scope of this chapter; however, an overview of the information reviewed is summarized below.

Three studies conducted with choline in non-pregnant adults were identified; no side effects were reported (Columbo and Rohr 2016; Wallace et al. 2012; Yamashita et al. 2023). Wallace et al. (2012) administered placebo or 1,000 mg choline (as choline bitartrate) per day for twelve weeks to postmenopausal women. No side effects were reported in this randomized, double blind, placebo-controlled trial. Two additional clinical trials demonstrated a lack of any adverse effects associated with choline at 300 mg per day (from egg yolk) or 365 mg per day (as choline bitartrate) for twelve weeks (Columbo and Rohr 2016; Yamashita et al. 2023). Of note, the safety evaluation in the study by Yamashita et al. (2023) included physical, hematological, clinical chemistry, and urinalysis parameters.

No adverse effects were reported in six studies conducted with choline in pregnant individuals (Jiang et al. 2013; Caudill et al. 2018; Taesuan et al. 2021; Yan et al. 2012; Loinard-González et al. 2022; Jacobson et al. 2018). In three dietary intervention trials, pregnant volunteers received 480 or 930 mg choline per day (380 mg from the study diet + 100 or 550 mg choline [as choline chloride]) starting from the end of the second trimester or during the third trimester until delivery

(Jiang et al. 2013; Caudill et al. 2018; Yan et al. 2012). In the studies by Loinard-González et al. (2022) and Taesuan et al. (2021), 25 or 550 mg per day of choline was administered starting at the beginning of the second trimester until delivery. Finally, Jacobson et al. (2018) studied the impact of choline supplementation on the adverse effects associated with heavy alcohol consumption during pregnancy.[1] Following twelve weeks of supplemental intake of 0 or 2,000 mg per day (starting at a mean gestation age of 20 weeks), no serious adverse effects were reported (Jacobson et al. 2018). The only side effects observed were an increase in nausea and indigestion; in addition, no changes in blood pressure measurements were seen in the participants.

The safety of lower levels of choline intake has been demonstrated in studies with other sources of choline. For example, a review published in 2025 by Grenata and colleagues summarized the findings of fifteen studies (RCTs, prospective and retrospective cohort studies, and one systematic review), concluding most studies on AGPC reported "excellent tolerance and minimal side effects, typically mild in nature, at doses of up to 1200 mg/day." The ten intervention trials administered 400-1,200 mg AGPC per day for up to 180 days. Since AGPC contains approximately 40% choline, this equates to approximately 160-480 mg per day of choline (Chemi S.p.A. 2023; Granata et al. 2025). One population-based, retrospective cohort study reported that an increase in 10-year incident stroke risk was associated with the use of AGPC, noting that further studies on this potential risk are needed (Lee et al. 2021; see below for additional discussion on cardiovascular disease [CVD] risk and choline). Intervention studies with phosphatidylcholine, which contains approximately 13% to 15% choline, provide additional information for consideration (Drake 2023; Ross et al. 2016; EFSA 2017). For example, in a study published by Ross et al. (2013, 2016), there were no adverse effects following supplemental intakes of 6,300 mg phosphatidylcholine per day (3,600 in the morning plus 2,700 in the evening). This dose level corresponds to approximately 900 mg choline per day starting from a mean of 17 weeks of gestation until delivery.

[1] Typically, studies with concomitant exposures are excluded following the criteria outlined in CRN's methodology (see Methods chapter). This study was reviewed and included as an exception, as it provides additional information relevant to safety at dose levels between 1,000 and 4,000 mg choline per day.

Choline Intake and Risk of Cardiovascular Disease

Several observational epidemiological studies have evaluated associations between dietary choline intake and cardiovascular disease (CVD) outcomes, including mortality, stroke, and prevalence of coronary artery disease across multiple populations, including the National Health and Nutrition Examination Survey (NHANES) (e.g., Jieru et al. 2024; Lin et al. 2024; Wang et al. 2024; Zhou et al. 2023), the Jackson Heart Study cohort (Millard et al. 2018), the EPIC cohort (Dalmeijer et al. 2008), the CARDIA study (Shea et al. 2024), and the Nurse's Health Study (NHS) and Health Professionals Follow-Up Study (HPFS) (Bertoia et al. 2014; Zheng et al. 2016). The findings of these studies are mixed, with some reporting beneficial, adverse, or null outcomes. Pooled analyses have identified associations between dietary intake and/or biomarkers of choline exposure and CVD outcome (Yang et al. 2023; Sharifi-Zahabi et al. 2024); however, these analyses are limited by the quality and robustness of the evidence. Interpretation of observational epidemiological evidence requires careful consideration of sources of bias due to the lack of randomization or controlled, experimental environments. Uncertainties attributable to biases, and in particular exposure characterization and confounding, are key to interpretation of hazard and risk based on such epidemiological studies, as discussed below (Schaefer et al. 2025).

Confounding by dietary factors is a critical source of bias in epidemiological studies. Key sources of dietary choline include legumes, cereal and animal-based foods such as dairy, eggs, beef, liver, and chicken (NIH 2022), which are foods independently associated with negative cardiovascular outcomes (e.g., elevated cholesterol).[2] Observational evidence that fails to adequately adjust for the source of dietary choline intake, and other dietary considerations attributed to animal-based foods such as caloric, cholesterol, and saturated fat intake, cannot definitively establish a clear relationship between dietary choline intake and CVD outcomes.

[2] As stated by Zheng et al. (2016), "Our previous data showed that dietary phosphatidylcholine is derived mainly from intakes of egg, red meat, and fish." In the study population described by Nagata et al. (2015), "For choline intake, the major food groups were eggs (25.5%), seafood (15.2%), and meats (14.8%) in men" with comparable findings in women. Yang et al. (2020) reported that approximately 22-23% and 15-17% of choline comes from red meat and eggs, respectively, in black and white populations, with 23% and 13.6% of choline coming from egg and red meat sources in Chinese populations.

Another common source of bias in observational studies is exposure estimation methods. Many studies estimated choline intake through food frequency questionnaires, which are subject to recall bias and may fail to characterize day-to-day variability in dietary intake, may not account for changes in dietary patterns over time, and may be subject to reporting bias (i.e., underreporting of dietary behaviors that are perceived as "negative" or overreporting dietary behaviors perceived as "beneficial"). Studies measuring choline intake through serum measurement of metabolites from the choline pathway (e.g., Dai et al. 2020; Shea et al. 2024) provide a direct quantitative estimate of choline intake. However, plasma choline may not be a reliable biomarker in isolation, as dietary choline is converted to betaine in a rapid two-step process (Abratte et al. 2009). Due to the rapid conversion of choline to betaine, single measurements of serum concentrations may not be representative of long-term behaviors (Böckmann et al. 2022, 2023) and cannot account for other dietary behaviors and unhealthy dietary patterns associated with increased CVD risks.

Considerations of biological plausibility, including investigation of plausible mechanisms or modes of action, can increase confidence in hazard characterization determinations based on uncertain observational epidemiological evidence (Schaefer et al. 2025). Choline that is not absorbed following ingestion undergoes microbial degradation in the gut and can be converted to trimethylamine-N-oxide (TMAO), via a trimethylamine (TMA) intermediate, which has been shown to promote atherosclerosis in animals (EFSA 2016; Drake 2023). However, the composition of the gut microbiome, as well as factors such as obesity and metabolic syndrome status and renal dysfunction appear to play a key role in TMAO formation and concentrations (Wallace et al. 2018; He et al. 2022; Canyalles et al. 2023; Obeid and Karlsson 2023). In addition, investigations of the relationship between plasma choline and TMAO are mixed (Drake 2023). The currently available evidence varies and raises questions as to whether TMAO is a causal factor for CVD risk or a predictor of CVD status attributable to reverse causality. Therefore, any implications of this potential mode of action on the association between choline and risk of CVD cannot be extrapolated at this time.

Long-term human clinical trials (conducted for up to 12 months) provide clear, quantitative measurements of choline intake[3] and report on biometrics and adverse events related to CVD

[3] As choline or from forms such as phosphatidylcholine or citicoline

(e.g., changes in blood pressure, serum lipoproteins, weight gain, stroke, myocardial infarction) (Wallace et al. 2012; Yamashita et al. 2023; Karner et al. 2014; Nakazaki et al. 2021; Hall et al. 2020; Alvarez-Sabín et al. 2013; Brown et al. 2012). Although clinical trials do not evaluate effects over chronic, lifetime durations, statistically significant precursors to overt CVD (e.g., changes in serum lipoproteins, blood pressure, weight gain) were not identified and no significant increases in cardiac adverse events were reported in these studies. In addition, a meta-analysis of three trials did not identify a difference in serious cardiovascular adverse events when comparing citicoline (as a source of choline) with placebo, although the evidence was considered low quality and uncertain (Marti-Carvajal et al. 2020).

Due to the uncertainties attributable to exposure measurement and confounding biases, a conclusion regarding the relationship between dietary choline and CVD outcomes cannot be confidently reached from the current observational epidemiological evidence. This conclusion is consistent with the EFSA (2016) Panel determination that the "association between choline intake and disease outcomes might be confounded by uncertainties inherent to the methodology used for the assessment of choline intakes, and by the effect of other dietary, lifestyle, or undefined factors on the disease outcomes investigated." As such, the EFSA (2016) Panel excluded observational evidence using biomarkers of exposure (e.g., serum choline) and "conclude[d] that the data on choline intake and risk of CVD cannot be used to derive DRVs for choline." However, as new data become available, this area of research may warrant additional consideration.

Citicoline

As described in CRN's Methodology chapter, human clinical trial data published since the IOM (1998) report were searched for, screened, and assessed for relevance to deriving CRN's UL value for adult supplemental use of citicoline. Ten clinical trials were identified that met the inclusion criteria. A full literature review is outside the scope of this chapter; however, an overview of the information identified and reviewed is summarized below.

No serious adverse effects associated with citicoline supplementation were reported across the ten studies identified, which tested doses ranging from 300-2,000 mg per day for four weeks to three years. Most studies reported specifically on the incidence of adverse events or side effects; only

one study did not include monitoring for such in the methodology. Three intervention studies that included a placebo control group and a citicoline group receiving 1,000 mg per day for up to 12 months reported no differences in adverse events between groups (Alvarez et al. 1999; Cotroneo et al. 2013; Alvarez-Sabín et al. 2013). In a study lacking a placebo control group, Hall et al. (2020) gave 1,000 mg citicoline per day to ten patients with Fragile X-associated tremor/ataxia syndrome (FXTAS) for twelve months; no serious adverse effects were attributed to citicoline in this small patient population.

Citicoline was administered at doses of 2,000 mg per day for 90 days in the Citicoline Brain Injury Treatment Trial (COBRIT) (Zafonte et al. 2012). This phase 3, randomized, double-blind, placebo-controlled trial was conducted in patients with traumatic brain injury across eight trauma centers. The incidence of adverse events was not significantly different between groups. While outside the inclusion criteria due to concomitant exposures to recreational drugs, a randomized, double-blind, placebo-controlled trial in 60 adults with a depressive disorder and methamphetamine dependence reported citicoline was well tolerated (Brown and Gabrielson 2012). Citicoline was used as add-on therapy in this dose-escalating study, starting with 500 mg per day and increasing to 2,000 mg per day for the last four weeks (total of 12 weeks).

Official Reviews

IOM (1998). The IOM found the adverse effects of excess choline intake to include mild hypotension and fishy body odor. "Slight hypotension," with nausea and diarrhea, was identified as the critical effect for deriving the UL value for choline based on the Boyd et al. (1977) study, which the IOM referred to as "a single case report." Based on this study, the IOM identified a LOAEL of 7,500 mg per day for total intake from all sources. An UF of 2 was selected to account for the limited data on hypotension, as well as interindividual variability in response to cholinergic effects. Thus, the IOM UL for choline is 3,500 mg per day (rounded down from 3,750) for adults, including pregnant and lactating individuals.[4] The IOM noted that sensitive populations with the following conditions "may be at risk of adverse effects with choline intakes at the UL": trimethylaminuria (fish odor syndrome), renal disease, liver disease, depression, and

[4] Age 19 years and older; UL value of 3 grams per day for age 14-18 years

Parkinson's disease. Of note, the IOM concluded that the hepatotoxicity in question was due to the salicylate in choline magnesium trisalicylate, and not due to the choline component. The IOM also discussed the association of fishy body odor, vomiting, salivation, sweating, and gastrointestinal effects in patients with tardive dyskinesia and cerebellar ataxia receiving 10,000 or 16,000 mg per day for up to six weeks (Growdon et al. 1977a,b; Gelenberg et al. 1979; Lawrence et al. 1980). The IOM noted that fishy body odor may also occur in healthy populations at these higher levels of intake. Citicoline was not evaluated by the IOM.

EVM (2003). The UK's EVM did not include choline or citicoline in the list of vitamins and minerals for which ULs were set.

EFSA (2016). The EFSA has not derived an UL for choline. It its 2016 *Dietary Refence Values for Choline*, the EFSA summarized the UL derivation from the IOM (1998). In addition, the Panel assessed the potential health consequences related to excess choline intake and various outcomes, concluding that the available data could not be used to derive DRV values for choline based on risk of CVD due to the lack of a significant association (see *Safety Considerations* section) or risk of cancer (colon/rectum, breast, esophageal, prostate, and ovarian) due to inconsistent or limited data.

EFSA (2013). The EFSA (2013) evaluated citicoline as a novel food ingredient (as a food supplement) aimed at a target population of middle-aged and elderly adults (not children) at a maximum level of 500 mg per day and in foods for particular nutritional uses for medical purposes up to 250 mg per serving, with a daily consumption level not to exceed 1,000 mg per day. The EFSA evaluated animal and human data and concluded that the novel food ingredient, citicoline, is safe under the proposed uses and use levels. While the EFSA's focus was on evaluating the safety of citicoline as a novel food, the Panel stated that numerous human clinical studies published since 1997 provided support that citicoline was well tolerated and did not raise safety concerns up to 2,000 mg per day of citicoline for up to 12 weeks or up to doses of 1,000 mg of citicoline for 9 months in healthy subjects and patients.

CNS (2023). An UL value for choline of 3,000 mg per day in adults was set by the CNS. The CNS did not derive an UL for citicoline.

ICMR-NIN (2020). The ICMR-NIN did not include choline or citicoline in the list of vitamins and minerals for which ULs were set.

KNS (2020). The KNS published its general approach to evaluating data for setting DRI values. However, choline was excluded from assessment due to an "insufficient basis for establishing [its] reference intake"; therefore, an UL value was not derived. The KNS did not evaluate citicoline.

CRN Recommendations

CRN has not previously derived UL values for choline and citicoline. The goal of this chapter was to derive UL values for supplemental choline and citicoline in adults following CRN's updated methodology. While not all human clinical trials are specifically designed to evaluate adverse effects, no new trials since the IOM (1998) assessment were identified that reported any serious adverse effects. As with any assessment in which not all available data are reviewed, inherent uncertainties with the risk assessment and selection of the UL are recognized.

CRN's methodology for deriving a supplemental intake UL prioritizes data from human studies, when available. The tables below summarize the key human clinical studies considered in deriving an UL value for supplemental intake by CRN according to its principal points of departure for risk assessment (as described in the CRN Methods). As described in the Methods, if the supplemental intake dose-response relationship is identified from the strongest data and assessed conservatively, no additional uncertainty factor is needed (that is, the implicit UF is 1.0 to a NOAEL). If a LOAEL is used, the UF must be greater than unity (1.0) and should be appropriate for the conversion to a NOAEL.

Choline

As summarized in the *Safety Considerations* section, 14 human clinical trials were identified that met the inclusion criteria for this chapter; in addition, studies on related sources of choline

were considered, where relevant.[5] Studies identified in the search that are most pertinent[6] to deriving ULs for choline and citicoline based on CRN's methodology are presented in the table below.

Key Studies Considered for the CRN UL for Choline in Adults

Reference	Study Design	Participant Description	No. of Subjects	Dose(s) (mg/day)[a]	Duration	NOAEL (mg/day)	LOAEL (mg/day)
Key studies from IOM (1998)							
Boyd et al. 1977	Uncontrolled pilot trial	Alzheimer patients with senile dementia	7	0, 4,000, 7,500 (as choline chloride)	2 weeks at each dose	4,000[b]	7,500
Key studies identified in update							
Ross et al. 2013, 2016	Randomized, double blind, placebo-controlled trial	Healthy pregnant women	100	0, 900 (as phosphatidyl-choline)	~23 weeks	900	N/A
Wallace et al. 2012	Randomized, double blind, placebo-controlled trial	Postmenopausal women	42	0, 1,000 (as choline bitartrate)	12 weeks	1,000	N/A
Jacobson et al. 2018	Randomized, double blind, placebo-controlled trial	Pregnant women with heavy alcohol use[d]	70	0, 2,000	12 weeks	2,000	N/A

N/A, not applicable
[a] Presented as milligrams choline
[b] IOM concluded the available data on choline were inadequate to identify a NOAEL for excess choline intake.
[c] From 17.2 ± 2.1 weeks after mother's last menstrual period up to delivery
[d] Studies with concomitant exposures are typically excluded following CRN's methodology. This study was included as an exception to provide additional information relevant to the dose levels between 1,000 and 4,000 mg choline per day.

As summarized in the Official Reviews section, the UL value of 3,500 mg per day derived previously by the IOM (1998) was based on "small" hypotensive effects observed at 7,500 mg choline per day but not at 4,000 mg per day in the same patient population (Boyd et al. 1977). CRN notes the limitations in the Boyd et al. (1977) include the small population size, short duration, and lack of control group. In addition, there are no human clinical studies that have administered choline at doses between the 4,000 mg per day from the Boyd et al. (1977) study and the 2,000 mg per day in the Jacobson et al. (2018) study. However, in the nine human clinical trials identified since the 1998 IOM report for this chapter, no serious adverse effects were reported following intervention with choline up to 2,000 mg per day for up to twelve weeks

[5] Literature search conducted May 2025.
[6] Where numerous relevant studies were identified, those most pertinent to the UL derivation are included in the table as representative studies. Prioritization was given to studies at dose levels informing the UL and studies with higher weighting based on CRN's Methods (e.g., duration, number of participants, randomization, etc.).

(Columbo and Rohr 2016; Wallace et al. 2012; Yamashita et al. 2023; Jiang et al. 2013; Caudill et al. 2018; Taesuan et al. 2021; Yan et al. 2012; Loinard-González et al. 2022; Jacobson et al. 2018). This finding is also supported by clinical trials with phosphatidylcholine and AGPC as sources of choline.

The IOM UL for choline has been established since 1998. Since that time, no new data have become available that identify any serious adverse effects in clinical trials with choline, nor sufficient evidence from epidemiological studies to establish a relationship between choline intake any adverse outcome (e.g., CVD risk). Therefore, despite the limitations noted in the Boyd et al. (1997) study, a modified approach to CRNs methodology was implemented. Based on the available dataset and lack of serious adverse effects in clinical trials, the longstanding UL derived by the IOM is supported by CRN as its supplemental UL for adults. This UL value was derived by the IOM based on the 7,500 mg per day LOAEL value from Boyd et al. (1977) and applying an UF of 2, yielding an UL of 3,500 mg per day.

Given the uncertainties in the available observational epidemiological evidence, including inconsistencies in reported effects and high risk of bias, and a lack of adverse effects on relevant parameters in human clinical trials, the potential relationship between increased risk of CVD and choline intake is not suitable for UL development. However, as this area of research continues to grow, additional data may become available warranting revision of this assessment.

Quantitative Summary for Choline in Healthy Adults

CRN (2025) UL, supplemental intake	3,500 mg/day
IOM (1998) UL, total intake	3,500 mg/day
EC SCF/EFSA	Not determined
EVM (2003)	Not determined
CNS (2023), total intake	3,000 mg/day
ICMR-NIN (2020)	Not determined
KNS (2020)	Not determined

Citicoline

As summarized in the *Safety Considerations* section, ten human clinical trials were identified that met the inclusion criteria for citicoline.[7] Studies identified in the search that are most pertinent[8] to deriving ULs for choline and citicoline based on CRN's methodology are presented in the tables.

Key Studies Considered for the CRN UL for Citicoline in Adults

Reference	Study Design	Participant Description	No. of Subjects	Dose(s) (mg/day)	Duration	NOAEL (mg/day)
Zafonte et al. (2012)	Randomized, double-blind, placebo-controlled	Patients with traumatic brain injury	1,213	0, 2,000	90 days	2,000
Alvarez-Sabín et al. (2013)	Open-label, randomized, parallel	Patients with stroke	347	0, 1,000	12 months	1,000
Cotroneo et al (2013)	Open-label, placebo-controlled	Elderly with mild vascular cognitive impairment	349	0, 1,000	9 months	1,000
Alvarez et al. (1999)	Randomized, double-blind, placebo-controlled	Patients with Alzheimer's disease	30	0, 1,000	4 weeks	1,000

No serious adverse effects were reported in any human intervention studies published since 1998 meeting the inclusion criteria; these studies included doses ranging from 300-2,000 mg citicoline per day for four weeks to three years. The COBRIT trial provides the largest and most robust clinical study on citicoline, which administered 2,000 mg per day for 90 days with no differences in adverse events reported between placebo and citicoline groups (Zafonte et al. 2012). Additional studies have demonstrated a lack of adverse effects at 1,000 or 2,000 mg per day for up to 12 months (Brown and Gabrielson 2012; Alvarez et al. 1999; Cotroneo et al. 2013; Alvarez-Sabín et al. 2013). Therefore, 2,000 mg per day is selected as the NOAEL for citicoline for adults following the CRN process. As described in CRN's Methods, if the supplemental intake dose-response relationship is identified from the strongest data and assessed conservatively, no

[7] Literature search conducted June 2025.
[8] Where numerous relevant studies were identified, those most pertinent to the UL derivation are included in the table as representative studies. Prioritization was given to studies at dose levels informing the UL and studies with higher weighting based on CRN's Methods (e.g., duration, number of participants, randomization, etc.).

additional uncertainty factor is needed (that is, the implicit UF is 1.0). Consistent with CRN's methodology, an UF of 1 is applied to yield an UL of 2,000 mg per day for adults for supplemental citicoline. This UL would yield approximately 424 mg choline per day, well below the UL of 3,5000 mg choline per day derived in this chapter.

Quantitative Summary for Citicoline in Healthy Adults

CRN (2025) UL, supplemental intake	2,000 mg/day
IOM	Not evaluated[a]
EC SCF/EFSA	Not evaluated
EVM (2003)	Not evaluated
CNS (2023), total intake	Not evaluated
FSSAI (2018)	Not evaluated
ROK (2020)	Not evaluated

[a] Scientific opinion on use as a novel food ingredient only; no UL evaluated

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