

# Choline

**Choline** /ˈkoʊliːn/[<sup>[1]</sup><sup>[2]</sup> is a water-soluble vitamin-like essential nutrient.<sup>[3]</sup><sup>[4]</sup><sup>[5]</sup> It is a basic constituent of lecithin, which is present in many plants and animal organs.<sup>[6]</sup> The term *cholines* refers to the class of quaternary ammonium salts containing the *N,N,N*-trimethylethanolammonium cation (X<sup>−</sup> on the right denotes an undefined counteranion).<sup>[3]</sup>

The cation appears in the head groups of phosphatidylcholine and sphingomyelin, two classes of phospholipid that are abundant in cell membranes. Choline is the precursor molecule for the neurotransmitter acetylcholine, which is involved in many functions including memory and muscle control.

Some animals cannot produce choline, but must consume it through their diet to remain healthy. Humans make choline in the liver. Whether dietary or supplemental choline is beneficial or harmful to humans has not been determined.<sup>[7]</sup> Possible benefits include reducing the risk of neural tube defects and fatty liver disease. It has also been found that intake of choline during pregnancy can have long-term beneficial effects on memory for the child.<sup>[5]</sup>

According to the US Institute of Medicine, there is not enough evidence to establish a Recommended Daily Intake for choline. The Australian and New Zealand national nutrition bodies note that while deficiency has been seen during experiments, there have been no reports of choline deficiency in the general population.<sup>[8]</sup> All three have published an "Adequate Intake" value, discussed below. The European Union's food safety authority says there are no Recommended Daily Intakes in the EU and "no indications of inadequate choline intakes available in the EU".<sup>[9]</sup>

Methionine and folate are known to interact with choline while homocysteine is undergoing methylation to produce methionine. Recent studies have shown that choline deficiency may have adverse effects, even when sufficient amounts of methionine and folate are present.<sup>[5]</sup>

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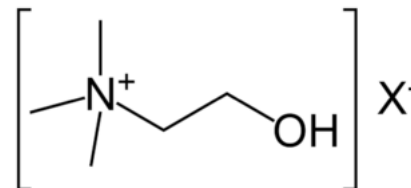
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## Choline



## Names

Preferred IUPAC name

2-Hydroxy-*N,N,N*-trimethylethan-1-aminium

### Other names

2-Hydroxy-*N,N,N*-  
trimethylethanaminium  
Bilineurine  
(2-  
Hydroxyethyl)trimethyla  
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## Identifiers

CAS Number	62-49-7 ( <a href="http://www.commonchemistry.org/ChemicalDetail.aspx?ref=62-49-7">http://www.commonchemistry.org/ChemicalDetail.aspx?ref=62-49-7</a> ) ✓
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3D model (JSmol)	Interactive image ( <a href="http://chemapps.stolaf.edu/jmol/jmol.php?model=C%5BN%2B%5D%28C%29%28C%29CCO">http://chemapps.stolaf.edu/jmol/jmol.php?model=C%5BN%2B%5D%28C%29%28C%29CCO</a> )
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Beilstein Reference	1736748
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## History

Choline was first isolated by Adolph Strecker from pig and ox bile (Greek: *χολή*, *chole*) in 1862.<sup>[10]</sup> When it was first chemically synthesized by Oscar Liebreich in 1865,<sup>[10]</sup> it was known as **neurine** until 1898 when it was shown to be chemically identical to choline.<sup>[11]</sup> In 1998, choline was classified as an essential nutrient by the Food and Nutrition Board of the Institute of Medicine (USA).<sup>[12]</sup>

## Chemistry

Choline is a quaternary ammonium salt with the chemical formula  $(\text{CH}_3)_3\text{N}^+(\text{CH}_2)_2\text{OHX}^-$ , where  $\text{X}^-$  is a counterion such as chloride (see choline chloride), hydroxide or tartrate. Choline chloride can form a low-melting deep eutectic solvent mixture with urea with unusual properties.<sup>[13]</sup> The salicylate salt is used topically for pain relief of aphthous ulcers.<sup>[14][15]</sup>

### Choline hydroxide

Choline hydroxide is one of the class of phase transfer catalysts that are used to carry the hydroxide ion into organic systems, and, therefore, is considered a strong base. It is the least-costly phase transfer catalyst, and is used as an effective method of stripping photoresists in circuit boards.<sup>[16]</sup> Choline hydroxide is not completely stable, and it slowly breaks down into trimethylamine.<sup>[17]</sup>

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ChemSpider	299 ( <a href="http://www.chemspider.com/Chemical-Structure.299.html">http://www.chemspider.com/Chemical-Structure.299.html</a> )✓
DrugBank	DB00122 ( <a href="https://www.drugbank.ca/drugs/DB00122">https://www.drugbank.ca/drugs/DB00122</a> )✓
ECHA InfoCard	100.000.487 ( <a href="https://echa.europa.eu/substance-information/-/substanceinfo/100.000.487">https://echa.europa.eu/substance-information/-/substanceinfo/100.000.487</a> )
EC Number	200–655–4
Gmelin Reference	324597
IUPHAR/BPS	4551 ( <a href="http://www.guidetopharmacology.org/GRAC/LigandDisplayForward?tab=summary&amp;ligandId=4551">http://www.guidetopharmacology.org/GRAC/LigandDisplayForward?tab=summary&amp;ligandId=4551</a> )
KEGG	C00114 ( <a href="http://www.kegg.jp/entry/C00114">http://www.kegg.jp/entry/C00114</a> )✓
PubChem CID	6209 ( <a href="https://pubchem.ncbi.nlm.nih.gov/compound/6209">https://pubchem.ncbi.nlm.nih.gov/compound/6209</a> )
UNII	N91BDP6H0X ( <a href="https://fdasis.nlm.nih.gov/srs/srsdirect.jsp?regno=N91BDP6H0X">https://fdasis.nlm.nih.gov/srs/srsdirect.jsp?regno=N91BDP6H0X</a> )✓
InChI	
SMILES	
Properties	
Chemical formula	C <sub>5</sub> H <sub>14</sub> NO <sup>+</sup>
Molar mass	104.17080
Density	1.09 g/ml
Boiling point	305 °C (581 °F; 578 K)
Solubility in water	500 mg/ml
Except where otherwise noted, data	

# In humans

## Physiology

Choline and its metabolites are needed for three main physiological purposes: structural integrity and signaling roles for cell membranes, cholinergic neurotransmission (acetylcholine synthesis), and a major source for methyl groups via its metabolite, trimethylglycine (betaine), which participates in the S-adenosylmethionine (SAME) synthesis pathways.<sup>[18][19]</sup>

## Fish odor syndrome

Choline is a precursor to trimethylamine, which some persons are not able to break down due to a genetic disorder called trimethylaminuria. Persons suffering from this disorder may suffer from a strong fishy or otherwise unpleasant body odor, due to the body's release of odorous trimethylamine. A body odor will occur even on a normal diet – *i.e.*, one that is not particularly high in choline. Persons with trimethylaminuria are advised to restrict the intake of foods high in choline; this may help to reduce the sufferer's body odor.<sup>[20]</sup>

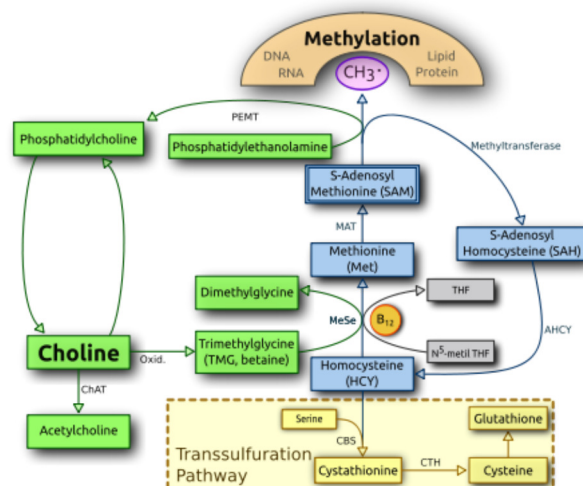
## Food sources of choline

The following are choline values for a selection of foods in quantities that people may consume in a day.

are given for materials in their standard state (at 25 °C [77 °F], 100 kPa).

✓ verify (what is ✓✗ ?)

Infobox references



Choline metabolism.

Animal and plant foods	Food amount (imperial)	Food amount (metric)	Choline (mg)	Choline (mg) in 100g food	Calories	% of diet to meet AI (smaller is better) <sup>[a 1]</sup>
<u>Raw beef liver</u>	5 ounces	142g	473	333	192 <sup>[nb 1]</sup>	9
<u>Cauliflower</u>	1 pound	454g	177	39	104 <sup>[nb 2]</sup>	13
<u>Large egg</u>	1	50g	147	294	78 <sup>[nb 3]</sup>	12
<u>Broccoli</u>	1 pound	454g	182	40	158 <sup>[nb 4]</sup>	19
<u>Cod fish</u>	0.5 pound	227g	190	84	238 <sup>[nb 5]</sup>	28
<u>Spinach</u>	1 pound	454g	113	25	154 <sup>[nb 6]</sup>	30
<u>Wheat germ</u>	1 cup	113g	202	179	432 <sup>[nb 7]</sup>	47
<u>Soybeans, mature, raw</u>	1 cup	186g	216	116	86 <sup>[nb 8]</sup>	51
<u>Milk, 1% fat</u>	1 quart	946mL (976g)	173	18	410 <sup>[nb 9]</sup>	52
<u>Firm tofu</u>	2 cups	504g	142	28	353 <sup>[nb 10]</sup>	55
<u>Sunflower seeds (kernels), raw</u>	1 cup	140 g	77	55	584 <sup>[21]</sup>	
<u>Chicken</u>	0.5 pound	227g	150	66	543 <sup>[nb 11]</sup>	80
<u>Cooked kidney beans</u>	2 cups	354g	108	31	450 <sup>[nb 12]</sup>	92
<u>Uncooked quinoa</u>	1 cup	170g	119	70	626 <sup>[nb 13]</sup>	116
<u>Peanuts</u>	1 cup	146g	77	53	828 <sup>[nb 14]</sup>	237
<u>Almonds</u>	1 cup	143g	74	52	822 <sup>[nb 15]</sup>	244

Besides cauliflower, other cruciferous vegetables may also be good sources of choline.<sup>[22]</sup>

The USDA Nutrients Database (<http://ndb.nal.usda.gov/ndb/nutrients/report?nutrient1=421&nutrient2=&nutrient3=&fg=&max=25&subset=0&offset=25&sort=c&totCount=4681&measureby=m>) has choline content for many foods.

## Adequate Intake instead of Recommended Dietary Allowance

The Australian, New Zealand, and European Union national nutrition bodies note there have been no reports of choline deficiency in the general population.<sup>[23][9]</sup> The USA joins these three in not publishing a Recommended Dietary Allowance (RDA), due to lack of consensus evidence. They have, however, published Adequate Intake (AI) values. The US Institute of Medicine (IOM) notes that these figures are based on just one study and that there was little data and the choline made by the body (assuming a dietary intake of zero) may be enough for some groups.<sup>[24]</sup> Australia, New Zealand and Canada use the figures published by the US IOM. The European Food Safety Authority (EFSA) published its own Adequate Intake values, most recently in 2016.<sup>[9][25]</sup> For U.S. dietary supplement labeling purposes the amount in a serving is expressed as a percent of Daily Value (%DV) based on the AI. For choline, as shown in Reference Daily Intake, 100% of the Daily Value is 550 mg.

Group	EFSA Adequate Intake	US IOM Adequate Intake	US IOM Upper Limit
<b>Infants</b>	(mg/day)	(mg/day)	(mg/day)
0–6 months	-	125	ND
7–12 months	160	150	ND
<b>Children</b>			
1–3 yrs	140	200	1000
4–6 yrs	170	250	1000
7–8 yrs	250	250	1000
9–10 yrs	250	375	1000
11–13 yrs	340	375	2000
<b>Males</b>			
14 yrs	340	550	3000
15+ yrs	400	550	3500 (3000 for 15–18 yrs)
<b>Females</b>			
14 yrs	340	400	3000
15–18 yrs	400	400	3000
19+ yrs	400	425	3500
<b>If pregnant</b>	480	450	3500 (3000 if ≤ 18 yrs)
<b>If lactating</b>	520	550	3500 (3000 if ≤ 18 yrs)

## Average or common intakes

Studies on a number of different populations have found that the average intake of choline was below the Adequate Intake.<sup>[5][26][27]</sup> In the United States, a recently published government survey on food consumption reported that for men and women ages 20 and older the average choline intakes were, respectively, 402 and 278 mg/day. For post-menopausal women, 280 mg/day<sup>[28]</sup>

## Health effects of dietary choline

Choline deficiency may play a role in liver disease, atherosclerosis, and possibly neurological disorders.<sup>[5]</sup> One sign of choline deficiency is an elevated level of the liver enzyme ALT.<sup>[4]</sup> If low choline intake causes an elevated homocysteine level, it raises the risk for preeclampsia, premature birth, and very low birth weight.<sup>[5]</sup>

Involvement of choline in long-term health and development of clinical disorders, such as cardiovascular diseases, cognitive decline in aging and regulation of blood lipid levels, has not been well-defined.<sup>[29]</sup>

## As a dietary supplement

The US Food and Drug Administration requires that infant formula not made from cow's milk be supplemented with choline.<sup>[30]</sup> Choline-providing dietary supplement ingredients include: choline chloride, choline bitartrate, citicoline (CDP-choline), L-alpha-glycerophosphocholine (Alpha-GPC), lecithin, phosphatidylcholine.

## Medical imaging

Because of its involvement in biologic processes, several medical imaging techniques have been developed to monitor relative concentration and kinetics of choline in different diseases. Radiolabeling one of the nitrogen methyl groups on choline with carbon-11 allows it to be used as a tracer in PET imaging studies. Carbon-11 is radioactive with a half-life of 20.38 minutes.<sup>[31]</sup> By monitoring the gamma radiation resulting from the decay of carbon-11, the uptake and retention of carbon-11 choline in different parts of the body can be measured.

One of the first uses of carbon-11 choline in PET imaging was with Alzheimer's disease patients.<sup>[32]</sup> Choline is the precursor to neurotransmitter acetylcholine whose cholinergic activity is impaired in many neurodegenerative diseases including Alzheimer's.<sup>[33]</sup> While there was uptake of the tracer in the brain, no pharmacokinetic pattern was found.

Carbon-11 choline has found more success in cancer systems imaging. Choline is a precursor for the synthesis of phospholipids in our cells.<sup>[34]</sup> When a cell is about to divide, it synthesizes these phospholipids to generate enough material to build the cell membranes of the two daughter cells. Thus it was hypothesized that highly proliferative tumors would uptake more choline than the surrounding healthy tissue. This was first tested in brain tumors after successful demonstration of choline uptake in the brain.<sup>[35]</sup> It was found that these brain tumors had over 10x the uptake of carbon-11 choline than the surrounding brain tissue. Furthermore, because of the low choline uptake in healthy brain tissue, carbon-11 choline was found to be a superior PET tracer than fluorine-18 Fludeoxyglucose (FDG) when delineating brain tumors.<sup>[36]</sup> Carbon-11 choline has also been used to detect tumors in the colon<sup>[37]</sup> and esophagus<sup>[38]</sup> and lung metastases.<sup>[39]</sup>

Prostate cancer is another disease where carbon-11 choline PET imaging has found success. As with the brain, there is too much signal from the surrounding tissue, especially the bladder, to accurately measure tumor uptake with fluorine-18 FDG. While it was shown carbon-11 choline could be used to detect the initiation of prostate cancer,<sup>[40]</sup> its value was found in detecting prostate cancer recurrence when it is the most deadly.<sup>[41][42][43][44]</sup> In 2012, the U.S. Food and Drug Administration approved carbon-11 choline as an imaging agent to be used during a PET scan to detect recurrent prostate cancer.<sup>[45][46]</sup>

## Pregnancy and brain development

The human body can produce choline by methylation of phosphatidylethanolamine by N-methyltransferase (PEMT) to form phosphatidylcholine in the liver, or it may be consumed from the diet. It has been demonstrated that both *de novo* production and dietary consumption are necessary, as humans eating diets lacking choline develop fatty liver, liver damage, and muscle damage. However, because of the close interplay between choline, folate, methionine, and vitamin B<sub>12</sub>, (whose pathways overlap), the function of choline can be complex.

To begin with, methionine can be formed two ways, either from methyl groups derived from folate, or from methyl groups derived from betaine (which gets its methyl groups from choline). Changes in one of these pathways is compensated for by the other, and if these pathways do not adequately supply methyl groups to produce methionine, the precursor to methionine, homocysteine, rises.



Maximum intensity projection of a PET/CT with choline: Note the physiologic accumulation in the liver, pancreas, kidney, bladder, spleen, bone marrow and salivary glands. A bone metastasis is in the left pubic bone.

Choline in food exists in either a free or esterified form (choline bound within another compound, such as phosphatidylcholine, through an ester linkage). Although all forms are most likely usable, some evidence indicates they are unequally bioavailable (able to be used by the body). Lipid-soluble forms (such as phosphatidylcholine) bypass the liver once absorbed, while water-soluble forms (such as free choline) enter the liver portal circulation and are generally absorbed by the liver.<sup>[47]</sup> Both pregnancy and lactation increase demand for choline dramatically. This demand may be met by upregulation of PEMT via increasing estrogen levels to produce more choline *de novo*, but even with increased PEMT activity, the demand for choline is still so high that bodily stores are generally depleted. This is exemplified by the observation that *Pemt* <sup>-/-</sup> mice (mice lacking functional PEMT) will abort at 9–10 days unless fed supplemental choline.<sup>[48]</sup>

While maternal stores of choline are depleted during pregnancy and lactation, the placenta accumulates choline by pumping choline against the concentration gradient into the tissue, where it is then stored in various forms, most interestingly as acetylcholine, (an uncommon occurrence outside of neural tissue). The fetus itself is exposed to a very high choline environment as a result, and choline concentrations in amniotic fluid can be ten times higher than in maternal blood. This high concentration is assumed to allow choline to be abundantly available to tissues and cross the blood-brain barrier effectively.<sup>[48]</sup>

### Functions in the fetus

Choline is in high demand during pregnancy as a substrate for building cellular membranes, (rapid fetal and mother tissue expansion), increased need for one-carbon moieties (a substrate for addition of methylation to DNA and other functions), raising choline stores in fetal and placental tissues, and for increased production of lipoproteins (proteins containing "fat" portions).<sup>[49][50][51]</sup> In particular, there is interest in the impact of choline consumption on the brain. This stems from choline's use as a material for making cellular membranes, (particularly in making phosphatidylcholine). Human brain growth is most rapid during the third trimester of pregnancy and continues to be rapid to approximately five years of age.<sup>[52]</sup> During this time, the demand is high for sphingomyelin, which is made from phosphatidyl choline (and thus from choline), because this material is used to myelinate (insulate) nerve fibers.<sup>[53]</sup> Choline is also in demand for the production of the neurotransmitter acetylcholine, which can influence the structure and organization of brain regions, neurogenesis, myelination, and synapse formation. Acetylcholine is even present in the placenta and may help control cell proliferation/differentiation (increases in cell number and changes of multiuse cells into dedicated cellular functions) and parturition.<sup>[54][55]</sup>

Choline uptake into the brain is controlled by a low-affinity transporter located at the blood-brain barrier.<sup>[56]</sup> Transport occurs when arterial plasma choline concentrations increase above 14  $\mu\text{mol/l}$ , which can occur during a spike in choline concentration after consuming choline-rich foods. Neurons, conversely, acquire choline by both high- and low-affinity transporters. Choline is stored as membrane-bound phosphatidylcholine, which can then be used for acetylcholine neurotransmitter synthesis later. Acetylcholine is formed as needed, travels across the synapse, and transmits the signal to the following neuron. Afterwards, acetylcholinesterase degrades it, and the free choline is taken up by a high-affinity transporter into the neuron again.<sup>[57]</sup>

### Neural tube closure

While folate is most well known for preventing neural tube nonclosure (the basis for its addition to prenatal vitamins), folate and choline metabolism are interrelated. Both choline and folate (with the help of vitamin B<sub>12</sub>) can act as methyl donors to homocysteine to form methionine, which can then go on to form SAM (S-Adenosyl methionine) and act as a methyl donor for methylation of DNA. Dietary choline deficiency alone without concurrent folate deficiency can decrease SAM concentration, suggesting that both folate and choline are important sources of methyl groups for SAM production.<sup>[48]</sup> Inhibition of choline absorption and use is associated with neural-tube defects in mice, and this may also

occur in humans.<sup>[47]</sup> A retrospective case control study (a study that collects data after the fact, from cases occurring without the investigator causing them to occur) of 400 cases and 400 controls indicated that women with the lowest daily choline intake had a four-fold greater risk of having a child with a neural-tube defect than women in the highest quartile of intake.<sup>[27]</sup>

### Choline and long-term memory

In humans, the brain continues to develop after birth, and does not become similar to its adult structure until around four years of age. By feeding infants formula instead of milk, and presumably through differences in choline amount in the breast milk of mothers consuming different choline levels, the still-developing brain of an infant may be impacted, which may, in part, contribute to the differences seen between individual adult humans in memory and recall.<sup>[48]</sup>

### Choline and lactation

The human mammary gland is composed of several cell types, including adipose (fat cells), muscle, ductal epithelium, and mammary epithelium (referred to sometimes as lactocytes). The mammary epithelium is the site for excretion of raw materials into the milk supply, including choline. This occurs, for the fat portion of the milk, by apocrine secretion, where vacuoles containing materials bud off the cell into the lumen (storage) of the alveolus (milk secretion gland). From here the milk will be released upon stimulation with oxytocin via suckling.<sup>[58]</sup>

### Choline in milk

Choline can be found in milk as free choline, phosphocholine, glycerophosphocholine, sphingomyelin, and phosphatidylcholine, and choline levels within breast milk are correlated with choline levels in maternal blood.<sup>[59][60]</sup> Choline consumed via breast milk has been shown to impact blood levels of choline in breast-fed infants – indicating that choline consumed in breast milk is entering the neonatal system.<sup>[60]</sup> Choline may enter the milk supply either directly from the maternal blood supply, or choline-containing nutrients may be produced within the mammary epithelium.<sup>[61]</sup> Choline reaches the milk through a transporter specific for choline from the maternal blood supply (against a concentration gradient) into the mammary epithelial cells.<sup>[62]</sup> At high concentrations (greater than that typically seen in humans), choline can diffuse across the cell membrane into the mammary epithelium cell. At more normal concentrations, it passes via what is believed to be a calcium/sodium-dependent, phosphorylation-related, active transporter into the cell.<sup>[63]</sup>

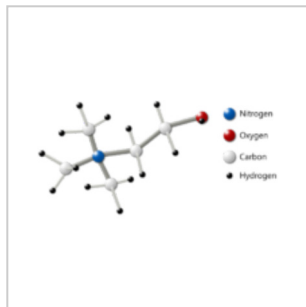
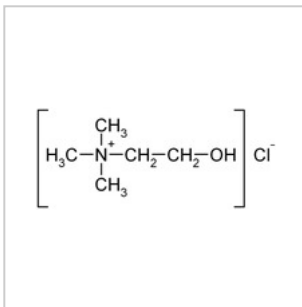
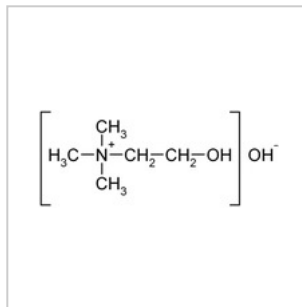
### Differences between breast milk and formula

Human milk is rich in choline, but formulas derived from other sources, particularly soy, have lower total choline concentrations than human milk.<sup>[48][64][65]</sup> Bovine milk and bovine-derived formulas had similar or higher glycerophosphocholine compared to human milk, and soy-derived formulas had lower glycerophosphocholine content. Phosphatidylcholine and sphingomyelin concentrations were similar between bovine formulas and human milk, but soy-derived infant formulas had more phosphatidylcholine than human or bovine sources. Soy-derived formulas had less sphingomyelin than human milk, which is a concern, since sphingomyelin is used for producing myelin, which insulates neurons. Free choline concentrations in mature human milk were 30–80% lower than those found in bovine milk or formulas. Mature human milk also has lower free choline than colostrum-transitional human milk. Phosphocholine is particularly abundant in human milk.<sup>[66]</sup>

## Additional images

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Choline (C<sub>5</sub>H<sub>14</sub>NO<sup>+</sup>)Choline chloride

Choline hydroxide

## See also


- Acetylcholine
- Cytidine diphosphate choline
- Dimethylethanolamine


## Notes

- Percentage of diet calculated using 2500 daily calories for an average adult male and 550mg for Adequate Intake (AI) using the figures from the table. As an example, even though peanuts contain some choline, they are a poor source given their 237% of diet to meet AI requirement, which means that a person who ate nothing but peanuts would have less than half of AI. Nearly identical figures are obtained for an average adult female when using 2000 calories and 425mg as assumptions; therefore, separate columns for male and female are not necessary.

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