SINCE 1985
Organic trade association

May 3, 2012

Ms. Michelle Arsenault
National Organic Standards Board
USDA-AMS-NOP
1400 Independence Avenue, SW
Room 2648-So, Ag Stop 0268
Washington, DC 20250-0268

Docket: AMS–NOP–12–0017

RE: Handling Committee – Choline & Inositol

Dear Ms. Arsenault:

Thank you very much for this opportunity to provide comment on the NOSB Handling Committee Recommendations on Choline and Inositol.

OTA is the membership-based business association for organic agriculture and products in North America. OTA is the leading voice for the organic trade in the United States, representing organic businesses across 49 states. Its members include growers, shippers, processors, certifiers, farmers' associations, distributors, importers, exporters, consultants, retailers and others. OTA's Board of Directors is democratically elected by its members. OTA's mission is to promote and protect the growth of organic trade to benefit the environment, farmers, the public and the economy.

OTA ***supports*** the Handling Committee's Recommendation to allow Choline and Inositol in infant formula labeled "organic" or "made with organic (specified ingredients or food group(s)". We understand that choline and inositol are mandated for non-milk based infant formulas and accordingly will be allowed under 21 CFR 107.100 per the NOP Proposed Rule on Nutrient Vitamins and Minerals[1]. However, because these nutrients are essential for infants and because they are found in breast milk, infant formula manufacturers have been adding them to milk-based formulas for a long time as well. This recommendation, in combination with the Proposed Rule for Nutrient Vitamins and Minerals, will secure their allowance in both milk-based and non-milk-based certified organic infant formulas.

OTA ***does not support*** the Handling Committee's recommendation to allow choline ***only*** in agricultural products, other than infant formula, labeled "made with organic (specified ingredients or food groups(s))". The Handling Committee recommendation claims that there is no compelling reason to think that choline is essential to handling organic food therefore it should be allowed in the "made with" category only. OTA has found published scientific information that shows choline to be an essential nutrient. We have not however found published scientific information showing inositol to be

[1] Sunset Review 2012 for Nutrient Vitamins and Minerals: Docket number AMS-NOP-10-0083, Published January 12, 2012

recognized as essential in the human diet. OTA supports the allowance of nutrients that are consistent with OFPA and the evaluation criteria for allowed substances as listed in § 205.600. As a result, we're concerned about the precedent that will be set and the confusion that will be created by allowing non-essential nutrients in the "made with" category only.

Choline is recognized as essential

In 1998, the Food and Nutrition Board of the IOM evaluated numerous research studies about choline to set Dietary Reference Intakes (DRIs). As a result of the evaluation, choline was officially recognized as an essential nutrient by IOM (1). DRIs have now been set for infants, children, adolescents, adults, pregnant women and breastfeeding women. While choline is found in a wide variety of foods, the most concentrated sources being liver, eggs, and wheat germ (2), strict vegetarians who do not consume eggs or milk may not be able to obtain enough choline through diet alone (3). Research also shows that choline recommendations may be sub-optimal for a large percentage of the population for a number of different factors (4). Given the importance of choline in a wide range of critical functions in the human body coupled with less than optimal intakes among the population, several nutrition research institutes are recommending that dietary guidance be developed to encourage the intake of choline-rich foods. We have included a fairly recent nutrition review titled "Choline: an essential nutrient for public health" (Attachment A).

The decision to call a nutrient "non-essential" because it's not specifically listed as essential by FDA in the Code of Federal Regulations ignores valid and published scientific information by respected organizations such as The National Research Council/National Academy of Sciences, the Institute of Medicine (IOM) of the National Academies, USDA's Agricultural Research Service (ARS), and the Centers for Disease Control and Prevention (CDC). In its Final Board Recommendation in 1995 on the Use of Nutrient Supplementation in Organic Foods, NOSB provided a definition of the term "Accessory Nutrients" to make it clear exactly what it was referring to. The NOSB definition was as follows: The term "accessory nutrients means nutrients not specifically classified as a vitamin or mineral but found to promote optimal health." NOSB cited five examples of nutrients or nutrient groups that met this definition at that time (omega-3 fatty acids, inositol, choline, carnitine, and taurine). NOSB also included the following Annotation for Nutrient Vitamins and Minerals:

> *Accepted for use in organic foods for enrichment or fortification when required by regulation or recommended by an independent professional organization.*

Instead of accepting the NOSB recommended annotation, NOP decided that the most appropriate reference was the FDA Nutritional Quality Guidelines for Foods found at 21 CFR 104.20. As described above, NOP has proposed a similar but updated annotation. OTA supports the NOP Proposed Rule to allow nutrient vitamins and minerals as per their allowance under 21 CFR 104.20, 107.100 and 107.10. We also acknowledge that there are additional nutrients that may be essential but are not specifically listed in one of those three references. In order to be allowed in NOP certified products, they must undergo NOSB review and meet OFPA and NOP criteria for addition to the National List.

Consistent with the evaluation criteria for allowed ingredients found at § 205.600 of the NOP regulations, OTA agrees that any substance added to the National List must be essential or necessary for the handling of organically produced agricultural products. NOSB intended to avoid the random addition of nutrients to organic foods but was determined to permit fortification in those instances where an independent professional organization deemed fortification was appropriate. We believe the committee needs to stay aligned with the intent of the original NOSB and take a closer look at the essentiality of choline as recommended by respected independent professional organizations.

Allowing non-essential nutrients in the "made with" category only

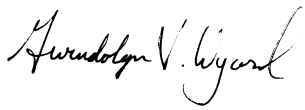
OTA is concerned about the precedent that will be set by allowing non-essential nutrients in the "made with" category only and the increased confusion it will likely cause around an already confusing label category. We believe the "made with" label category should in its most basic sense simply refer to a certified product that contains at least 70% organic ingredients. We understand there is an allowance for 30% non-organic agricultural ingredients in a "made with" product, however non-agricultural ingredients must be on the National List at § 205.605 and if listed they should meet OFPA and National List criteria.

There is already considerable confusion surrounding the meaning of the "made with" label. OTA believes it sets a bad precedent to use the "made with" label to represent products that contain ingredients that are somehow non-essential or not completely compatible with OFPA criteria and organic principles. We encourage the Board to carefully consider the potential impact of their recommendations on choline and inositol and to focus on the OFPA and National List criteria and add substances to the National List for use in "organic" and "made with (specified ingredients or food group(s)" accordingly.

In conclusion, OTA supports the rational and safe addition of nutrients to foods in order to preserve a balance of nutrients in the consumer diet. We also support the maximum freedom of choice for organic consumers, and believe that NOP certified products should be nutritionally equal to their conventional counterparts. The 1995 Board endorsed the fortification of organic foods with vitamins, minerals and accessory nutrients as deemed appropriate, and we would like to see the organic sector continue to support this intent. We urge the Board to carefully consider any further comments that document choline as an essential nutrient, and vote to add choline to the National List.

On behalf of our members across the supply chain and the country, OTA thanks the National Organic Standards Board for the opportunity to comment.

Respectfully submitted,



Gwendolyn Wyard
Associate Director of Organic Standards and Industry Outreach
Organic Trade Association (OTA)

CC: Laura Batcha
Executive Vice President
Organic Trade Association (OTA)

References

1. Food and Nutrition Board, Institute of Medicine. Dietary Reference Intakes: Thiamin, Riboflavin, Niacin, Vitamin B-6, Vitamin B012, Pantothenic Acid, Biotin, and Choline. Washington, D.C.: National Academy of Sciences; 1998. p. 390-422.

2. Zeisel, S. H. and Da Costa, K.-A. (2009), Choline: an essential nutrient for public health. Nutrition Reviews, 67: 615–623. doi: 10.1111/j.1753-4887.2009.00246.x.

3. Linus Pauling Institute. 2008. Micronutrient information center: Choline. Originally written by Higdon, J. in 2003; updated by Drake, V. and reviewed by Zeisel, S.H. in 2008. Retrieved September 2, 2011 from http://lpi.oregonstate.edu/infocenter/othernuts/choline/ 677.

4. Dietary Reference Intakes, Institute of Medicine of the National Academies, National Academies Press, Washington, DC, 2006.

Attachment A: Choline: an essential nutrient for public health – Nutrition Reviews, 2009.

Published in final edited form as:
Nutr Rev. 2009 November ; 67(11): 615–623. doi:10.1111/j.1753-4887.2009.00246.x.

Choline: An Essential Nutrient for Public Health

Steven H. Zeisel, M.D., Ph.D. and
Nutrition Research Institute, Department of Nutrition, School of Public Health and School of Medicine, University of North Carolina at Chapel Hill, CB#7461, Chapel Hill, NC 27599, (919) 843-4731, Steven_zeisel@unc.edu

Kerry-Ann da Costa, Ph.D.
Department of Nutrition, School of Public health and School of Medicine, The University of North Carolina at Chapel Hill, CB#7461, Chapel Hill, NC 27599, (919) 966-7346, kdacosta@unc.edu

Abstract

Choline was officially recognized as an essential nutrient by the Institute of Medicine (IOM) in 1998. There is a significant variation in the dietary requirement for choline that can be explained by common genetic polymorphisms. Because of its wide-ranging roles in human metabolism, from cell structure to neurotransmitter synthesis, choline-deficiency is now thought to have an impact on diseases such as liver disease, atherosclerosis and possibly neurological disorders. Choline is found in a wide variety of foods. Egg yolks are the most concentrated source of choline in the American diet, providing 680 milligrams per 100 grams. Mean choline intakes for older children, men, women and pregnant women are far below the Adequate Intake established by the IOM. Given the importance of choline in a wide range of critical functions in the human body, coupled with less than optimal intakes among the population, dietary guidance should be developed to encourage the intake of choline-rich foods.

Keywords

Choline; eggs; homocysteine; memory; methylation; methyl group; neural tube defects; phosphatidylcholine; pregnancy

Introduction

Choline was officially recognized as an essential nutrient by the Institute of Medicine in 1998.[1] Its role in the body is complex. It is needed for neurotransmitter synthesis (acetylcholine), cell-membrane signaling (phospholipids), lipid transport (lipoproteins), and methyl-group metabolism (homocysteine reduction).[2] It is the major dietary source of methyl groups via the synthesis of S-adenosylmethionine (AdoMet).[3] At least 50 AdoMet-dependent reactions have been identified in mammals, and it is likely that the number is much higher.[3] Such methylation reactions play major roles in biosynthesis of lipids, the regulation of several metabolic pathways, and detoxification in the body.[3] Choline is required to make the phospholipids phosphatidylcholine, lysophosphatidylcholine, choline plasmalogen, and sphingomyelin—essential components for all membranes.[4] It plays important roles in brain and memory development in the fetus and appears to decrease the risk of the development of neural tube defects.[5,6]

Correspondence to: Steven H. Zeisel.

The importance of choline in the diet extends into adulthood and old age. In a study of healthy adult subjects deprived of dietary choline, 77% of the men and 80% of the postmenopausal women developed signs of subclinical organ dysfunction (fatty liver or muscle damage). Less than half of premenopausal women developed such signs.[7] Ten percent of the subjects studied developed fatty liver, muscle damage, or both when they consumed the Adequate Intake (AI) of choline. The damage was reversed when they consumed a high-choline diet. Plasma choline concentration has been found to vary in response to diet, decreasing approximately 30 percent in humans fed a choline-deficient diet for 3 weeks.[4] Based on estimated dietary intakes and studies reporting liver damage with lower choline intakes, the Institute of Medicine, Food and Nutrition Board set the AI for choline at 425 milligrams/per day for women aged 19 and older, and 550 milligrams/per day for men aged 19 and older.

Choline can be acquired from the diet and via *de novo* biosynthesis through the methylation of phosphatidylethanolamine (PE) to phosphatidylcholine (PC). However, de novo synthesis of choline alone is not sufficient to meet human requirements.[1] Dietary choline from a variety of choline-containing foods is absorbed by the intestine and uptake is mediated by choline transporters.[8] The major fate of choline is conversion to PC (also known as lecithin), which occurs in all nucleated cells.[8] PC is the predominant phospholipid (>50%) in most mammalian membranes.[9] Recent studies indicate that choline is recycled in the liver and redistributed from kidney, lung, and intestine to liver and brain when choline supply is low.[8] Upon entry into the cell, choline is immediately phosphorylated to phosphocholine, or oxidized to betaine in some cell types such as hepatocytes.[8] Betaine is important because of its role in the donation of methyl groups to homocysteine to form the essential amino acid methionine.[10] While there are metabolic pathways for the interconversion of choline, phophatidylcholine, glycerophosphocholine, phosphocholine and sphingomyelin, the conversion of choline to betaine is irreversible.[10]

Any consideration of the requirements for choline and methionine needs to consider the close interrelationships with other methyl donors. Choline, methionine, and folate metabolism interact at the point that homocysteine is converted to methionine.[1] Perturbing the metabolism of any one of these methyl donors reveals the complex interactions of the metabolic pathways, as compensatory changes occur in the enzymes and vitamin co-factors involved in the reactions.[1,10] In rats, severe folate deficiency causes secondary hepatic choline deficiency.[4] Humans fed with total parenteral nutrition solutions devoid of choline, but adequate for methionine and folate, develop fatty liver and liver damage.[1] In healthy humans consuming adequate folate and methionine, inadequate choline intake can result in fatty liver or muscle damage that resolves when a source of dietary choline is provided.[4,7] Because of its wide-ranging role in human metabolism, from cell structure to neurotransmitter synthesis, choline deficiency is now thought to have an impact on diseases such as nonalcoholic fatty liver disease, atherosclerosis (via lipoprotein secretion), and possibly neurological disorders.[8] Therefore, getting adequate choline in the diet is important throughout life for optimal health.

Pregnancy and Lactation

Pregnancy and lactation are times when demand for choline is especially high and the supply of choline is critical. The recommended Adequate Intake (AI) for pregnant women is 450 mg/d; 550 mg/d for lactating women. Large amounts of choline are delivered to the fetus across the placenta and choline concentration in amniotic fluid is 10-fold greater than that present in maternal blood.[9] Plasma or serum choline concentrations are significantly higher in pregnant women, compared to nonpregnant women (10.7 microM of free choline and 2,780 microM of bound choline in nonpregnant women, compared to 16.5 microM and 3,520 microM at 36 to 40 weeks pregnancy)[11] and are 6- to7-fold higher in the fetus and newborn than they are in adults.[12] The transport of choline from mother to fetus depletes maternal plasma choline in

humans.[13] Thus, despite enhanced capacity to synthesize choline during pregnancy, the demand for this nutrient exceeds the supply and stores can be depleted. Because human milk is rich in choline, lactation further increases maternal demand, resulting in extended depletion of tissue stores.[14]

Neural Tube Defects

Several nutritional factors have been implicated in the occurrence of neural tube defects (NTDs). Foremost among those factors has been the role of periconceptional intake of folic acid.[5] Similar to folic acid, choline is involved in the methylation of homocysteine to methionine. Some research indicates that choline and methionine intakes may be factors in reducing risk of NTDs as well, independent of folate intake from food and supplements.[5,6] The inhibition of choline uptake and metabolism in mouse embryos results in NTDs.[15]

Shaw et al.[5] found that women in the lowest quartile for dietary choline intake had four times the risk of giving birth to a child with a neural tube defect, compared with women in the highest quartile of intake. Decreased risks of NTD-affected pregnancies were found for higher periconceptional intakes of choline for all NTDs as well as for spina bifida and anencephaly separately. The association remained strong after adjusting for maternal pre-pregnancy weight, height, education, race, ethnicity, periconceptional vitamin use, dietary folate intake, dietary methionine intake and total energy intake. Since choline and folate metabolism intersect at the pathway for methyl-group donation, it is reasonable to hypothesize that methylation reactions are the mechanism they share in common that influence neural tube closure.[9]

Memory Development

Recent studies show that choline supplementation during critical periods of neonatal development can have long-term beneficial effects on memory. (See Table 1) During later periods of pregnancy, the memory center of the brain (the hippocampus) is developing. In rodents, choline supplementation or depletion during this critical phase causes lifelong changes in brain structure and function. [9,13] Adult rodents typically experience a decline in memory as they age. Offspring exposed to extra choline *in utero* did not show this change with age.[16]

Pregnant rats supplemented with choline experience multiple modifications in the developmental patterns of gene expression known to influence learning and memory.[17] The likely mechanism for these effects of choline involves DNA methylation, altered gene expression, and associated changes in stem cell proliferation and differentiation.[18] In humans, the hippocampus continues to develop after birth, and it closely resembles the adult structure by 4 years of age. Extrapolating from rodent data, human sensitivity to the developmental effects of choline would occur in utero and continue up to age 4 years.[18] A study of pregnant women and their children found no association between choline concentrations in maternal and cord blood and intelligence levels in their children at 5 years of age.[19] Currently, there are no published studies in humans examining whether choline supplementation during pregnancy enhances memory performance in offspring.

A study of rat pups exposed to ethanol during the neonatal brain growth spurt, a developmental period that would be equivalent to postnatal development in humans, and treated with choline chloride, found that choline supplementation reduced the severity of fetal alcohol effects even after the alcohol exposure.[20] The findings suggest that early dietary intervention with choline may reduce the severity of some fetal alcohol effects. Moreover, the ability of choline to attenuate ethanol's effects was evident months after choline treatment, suggesting that choline's effects are long lasting.[20]

The second half of pregnancy is characterized by a strong inverse relation between plasma betaine and homocysteine.[21] Elevated maternal homocysteine concentrations are a risk factor for several adverse pregnancy events, including preeclampsia, prematurity and very low birth weight, and have been suggested to have an important role as a marker of pregnancy complications and adverse pregnancy outcomes.[22] Though most studies have found a clear inverse association between maternal choline levels and homocysteine, Molloy et al.[23] found a highly significant positive association between maternal choline levels and maternal homocysteine levels, suggesting that the high fetal demand for choline stimulates de novo synthesis of choline in the maternal liver with a resultant increase in homocysteine. Regardless of the specific mechanism that raises homocysteine, the recommendation remains the same—to increase choline intake by diet or supplementation to attenuate de novo synthesis and reduce homocysteine levels.[23] These findings may indicate a need for intervention to ensure optimal choline intakes during pregnancy.[23]

Heart Disease

When choline stores are inadequate, there is a diminished capacity to methylate homocysteine to methionine, and plasma levels of homocysteine increase.[24] Elevated levels of homocysteine have been associated with greater risk for several chronic diseases and conditions including cardiovascular disease,[25] cancer,[26] cognitive decline[27] and bone fractures.[28] Intakes of choline and betaine have been associated with lower homocysteine levels, whether intake of each nutrient is considered independently or in combination and whether the source is from food or supplements.[29,30] Homocysteine can also be methylated to form methionine via another pathway involving vitamins B12 and folic acid. Methionine can, in turn, be converted to S-adenosyl methionine. Deficiency of either vitamin B12 or folic acid can result in elevated plasma homocysteine concentrations and increased risk for chronic disease.[31]

Olthof et al. found in a group of men, aged 50–71, with elevated homocysteine levels, that a high daily dose of choline (2.6 g), supplemented as phosphatidylcholine, lowered fasting as well as plasma homocysteine concentrations after a methionine-loading test.[32] The choline supplementation was as effective as folic acid in lowering fasting homocysteine levels. Olthof suggested that if elevated homocysteine concentration causes cardiovascular disease, choline intake may reduce cardiovascular disease risk.

Inflammation

Findings from the ATTICA study indicated that subjects whose diets were rich in choline and betaine had the lowest levels of several inflammatory markers, including C-reactive protein (CRP), homocysteine, interleukin-6 and tumor necrosis factor.[33] These findings were significant after adjusting for various sociodemographic, lifestyle and clinical characteristics of the participants. Higher combined dietary intakes of choline and betaine were associated with lower concentrations of all of the inflammatory markers measured in the study. This is similar to the findings of Cho et al.[34] who found that among 1,960 participants in the Framingham Offspring Study, the combined dietary intakes of choline and betaine were associated with lower homocysteine concentrations. Most recently, findings from the Nurses' Health Study revealed that those with the highest consumption of dietary choline had improved plasma levels of biomarkers for inflammation, including adiponectin, high-molecular-weight adiponectin, resistin and CRP.[35] Elevated CRP has recently been recognized by the National Heart, Lung and Blood Institute as a useful marker for cardiovascular disease.[36]

The associations found between cardiovascular disease risk factors and typical dietary intakes of choline and betaine have not translated into increased risk from cardiovascular disease.[37,38] Analysis of findings from the PROSPECT-EPIC cohort of 16,165 women in the Netherlands, aged 49–70, suggested that regular dietary intakes of betaine and choline were not associated

with cardiovascular disease risk.[38] However, even those in the highest quartile of choline intake fell below the current AI of 425 mg/d for women and the range of intake was small.

Breast Cancer

Choline deficiency in cell and rodent models is associated with DNA damage and apoptosis.[39,40] Cells grown in choline-deficient medium have greater membrane fragility than cells grown in control medium.[39] Induced choline deficiency in a group of 51 men and women aged 18–70 for 42 days also showed increased DNA damage and apoptosis in lymphocytes.[400] High dietary intakes of choline have recently been associated with a decreased risk for breast cancer. In the first study to examine the association between choline and breast cancer, Xu et al.[41] found that breast cancer risk was reduced 24% among women with high dietary intakes of choline. The association did not vary substantially with menopausal status or cancer type (invasive vs *in situ*).

Dietary Recommendations And Genetic Variations That Affect Choline Requirements

The recommended adequate intake (AI) for choline has been set at 425 mg/d for women, 450 mg/d for pregnant women, 550 mg/d for lactating women and 550 mg/d for men.[1] However, an Estimated Average Requirement (EAR) has not been set because of a lack of sufficient human data.[1,7]

The potential public health implications of not consuming enough of this essential nutrient have only recently begun to be examined. The development of a database of the choline content of foods now makes it possible to track the dietary choline intakes of populations and correlate intakes with the incidence of disease.[42]

There is a significant variation in the dietary requirement for choline that can be explained by common genetic polymorphisms.[41,45,43] Understanding dietary choline requirement and its modulation by genetic polymorphism has public health significance, especially in regards to its role in brain development.[13] Current recommended intakes do not take into consideration these genetic variations as a modulator of dietary requirement. When the AI for choline was established in 1998, it was assumed that less than 5% of the population would be affected. It is now clear that as much as 50% of the population may have genetic polymorphisms that increase dietary methyl requirements, of which choline is a major source, leaving them susceptible to choline deficiency.[44,45]

When fed a choline-deficient diet, some men and women developed fatty liver and liver and muscle damage, whereas others did not. Premenopausal women who are carriers of a very common single nucleotide polymorphism (SNP) have been found to be 15 times as likely as non-carriers to develop signs of choline deficiency on a low-choline diet.[45] Studies are underway to identify other genetic differences that contribute to individual variability in dietary requirements for choline.[46]

DNA methylation influences the expression of some genes and depends upon the availability of methyl groups from AdoMet. Alterations in DNA methylation, with resulting changes in gene expression, can have important consequences for embryogenesis and carcinogenesis; dietary choline availability during pregnancy influences the development of the brain in the fetus via choline-mediated alterations in the birth, migration and death of cells in the brain.[44] Research is ongoing to identify genetic polymorphisms in choline related genes that affect their function, be it via changes in the regulation of the gene, which in turn could increase the requirement for choline in the diet. Identification of common polymorphisms that affect dietary requirements for choline could allow for the identification of individuals, especially pregnant women, for whom choline needs may exceed current recommendations. [18]

Dietary choline requirements are an excellent example of nutrigenomics (the science of molecular-level interactions between nutrients and other dietary bioactives and the response of genes). Endogenous biosynthesis of choline is regulated by estrogen via gene estrogen response elements. DNA methylation is influenced by the availability of choline, and common genetic polymorphisms have major effects on the dietary requirement for this nutrient. These interactions have important health implications.[46]

Prevalence of Suboptimal Choline Intakes

At the time the AI for choline was established in 1998, it wasn't known whether there were significant numbers of people who were choline deficient. It was known, however, that there were many who were folate deficient,[1] which can impact choline status. There is now evidence that current choline recommendations may be suboptimal for a large percentage of the population. Women appear to depend upon a combination of dietary choline intake and high rates of endogenous estrogen-induced biosynthesis of choline to sustain normal pregnancy.[13] There is, however, a real possibility that women in the U.S. may not get enough choline during pregnancy.[5,13] The AI set by the Institute of Medicine for choline during pregnancy is 450 mg/d and for lactation 550 mg/d. Dietary choline intake among women varies from <300 mg/d to >500 mg/day. Intakes at the lower end of that range could increase the risk of having a baby with a neural tube birth defect.[5,13]

In a subset of subjects from the Nurses' Health Study, the cutoff for the 95th percentile of choline intake was 411 mg/d, which suggests that most of women within this population were not meeting the recommended intake.[29] Though many foods contain choline, there is at least a twofold variation in dietary intake in humans.[13] A study of 16 adult women and 16 adult men, ages 18 – 67, found that only 6 of the 16 women met or exceeded the AI for choline.[47] A recent analysis of data from NHANES 2003–2004 revealed that for older children, men, women and pregnant women, mean choline intakes are far below the AI. Ten percent or fewer had usual choline intakes at or above the AI.[48]

Additional analysis of NHANES 2003–2004 data found that choline intake decreases with age and that adults ages 71 and older consumed an average of about 264 milligrams per day, about one-half of the AI for choline.[49]

Food Sources of Choline

Choline is found in a wide variety of foods. (Table 2) The U.S Department of Agriculture recently released an updated version of its first database of choline content in foods, including more than 630 foods.[42] Among the most concentrated sources of dietary choline are liver, eggs, and wheat germ. In foods, choline is found in free and esterified form (such as phosphocholine, glycerophosphocholine, phosphatidylcholine, and sphingomyelin).[18] Human milk is rich in choline compounds. Soy-derived infant formulas have lower total choline concentrations than do human milk and bovine milk-derived formulas.[50] Foods rich in the related compound, betaine, include wheat bran, wheat germ, quinoa, beets, spinach and spaghetti.[42]

Dietary information obtained from the Nurses' Health Study and the Nurses' Health Study 2 revealed that animal products, including eggs, milk, chicken, beef, and pork to be the biggest contributors of choline in the diets of the female subjects.[29]

Though eggs are a more concentrated source of choline[42], in the Nurses' Health Study and Nurses' Health Study 2, milk provided the largest percentage of dietary choline, because it was consumed more frequently. However, NHANES 2003–2004 data showed that eggs contributed a relatively higher share of total choline intake for those whose intake was at or above the AI, compared to others.[48] Eggs also provide more choline per kilocalorie compared to most other

foods, including milk. To get the same amount of choline found in a single egg (125 mg/72 calories; most of the choline is in the egg yolk – 680 mg/100g), one would need to consume 3 ¼ cups of nonfat milk (270 calories) or 3 ½ ounces of wheat germ (366 calories). In addition, adding an egg to the diet each day would increase the number of pregnant women meeting the AI from 10% to more than 50% and for older men and women from 5% to 20%.

Health Professional Awareness and Dietary Recommendations for Choline Intake

Given the importance of choline in a wide range of critical functions in the human body, coupled with less than optimal intakes among the population and evidence that as much as 50% of the population carry genetic variations that make it necessary to consume choline at levels greater than the AI, it is advised that dietary guidance be developed to encourage the intake of choline-rich foods. However, there are currently two major impediments to this goal.

Current dietary guidance from a variety of health organizations recommends limiting intake of cholesterol to less than 300 milligrams day; less than 200 milligrams a day for those with existing cardiovascular disease,[51] which de facto limits consumption of eggs, one of the richest sources of choline (and cholesterol) in the American diet. One large egg contains 212 milligrams of cholesterol and 125 milligrams of choline.[42,52] Secondly, health professionals, including physicians and registered dietitians, have limited knowledge about the biological importance of choline and are relatively unaware of the best dietary sources. A recent survey of health professionals found that of several nutrients, including calcium, vitamin D, protein, folate, iron, and vitamins E and A, choline was the least likely to be recommended. Only about 10% of those surveyed said that they were likely to recommend foods containing choline to their patients. Among OB/GYNs, who care for the population with the greatest choline needs, only about 6% were likely to recommend foods containing choline for healthy pregnant women.[53] It is evident that the current lack of awareness, knowledge and education among both health professionals and the public regarding the important role of choline in the diet may have negative health consequences.

Conclusions

There is an immediate need to increase awareness among health professionals and consumers of choline as an essential, but currently suboptimal, nutrient, and further, to highlight the critical role it plays throughout life, especially for pregnant and lactating women. New analysis of NHANES data indicates that for the majority of the population choline consumption is far below current dietary recommendations. Increasing awareness of the pervasiveness of suboptimal choline intakes must become the focus of public health efforts in order to promote optimal health. Education regarding the richest food sources of choline can assist in reaching this goal.

Acknowledgments

The authors would like to thank Densie Webb, Ph.D., R.D. for assistance in preparing this article.

Funding

Preparation of the article was made possible with an unrestricted education grant from the Egg Nutrition Center. The authors have no funding to declare.

References

1. Food and Nutrition Board, Institute of Medicine. Dietary Reference Intakes: Thiamin, Riboflavin, Niacin, Vitamin B-6, Vitamin B012, Pantothenic Acid, Biotin, and Choline. Washington, D.C.: National Academy of Sciences; 1998. p. 390-422.

2. Penry J, Manore M. Choline: an important micronutirent for maximal endurance-exercise performance? Int J Sport Nutr Exerc Metab 2008;18:191–203. [PubMed: 18458362]

3. Stead L, Brosnan J, Brosnan M, Vance D, Jacobs R. Is it time to reevaluate methyl balance in humans. Am J Clin Nutr 2006;83:5–10. [PubMed: 16400042]

4. Zeisel S. Choline, an essential nutrient for humans. FASEB 1991;5:2093–2098.

5. Shaw G, Carmichael S, Yang W, Selvin S, Schaffer D. Periconceptional dietary intake of choline and betaine and neural tube defects in offspring. Am J Epidemiol 2004;160:102–109. [PubMed: 15234930]

6. Rees W, Wilson F, Maloney C. Sulfur amino acid metabolism in pregnancy: the impact of methionine in the maternal diet. J Nutr 2006;136:1701S–1705S. [PubMed: 16702342]

7. Fischer L, da Costa K, Kwock L, Stewart P, Lu T, Stabler S, Allen R, Zeisel S. Sex and menopausal status influence human dietary requirements for the nutrient choline. Am J Clin Nutr 2007;85:1275–1285. [PubMed: 17490963]

8. Li Z, Vance D. Phosphatidylcholine and choline homeostasis. J Lipid Res 2008;49:1187–1194. [PubMed: 18204095]

9. Zeisel S. Perinatal choline influences brain structure and function. Nutr Rev 2006;64:197–203. [PubMed: 16673755]

10. Zeisel S, Mar MH, Howe J, Holden J. Concentrations of choline-containing compounds and betaine in common foods. J Nutr 2003;133:1302–1307. [PubMed: 12730414]

11. Ozarda I, Uncu G, Ulus I. Free and phospholipid-bound choline concentrations in serum during pregnancy, after deliver and in newborns. Arch Physiol Biochem 2002;110:393–399. [PubMed: 12530624]

12. Zeisel S. Developmental changes in rat blood choline concentration. Biochem J 1981;198:565–570. [PubMed: 7034731]

13. Zeisel S. Choline: Critical role during fetal development and dietary requirements in adults. Annu Rev Nutr 2006;26:229–250. [PubMed: 16848706]

14. Steegers-Theunissen R, Boers G, Trijbels F, et al. Maternal hyperhomocysteinemia: a risk factor for neural-tube defects? Metabolism 1994;4:1475–1480. [PubMed: 7990699]

15. Fisher M, Zeisel S, Mar M, Sadler T. Inhibitors of choline uptake and metabolism cause developmental abnormalities in neurulating mouse embryos. Teratology 2001;64:114–122. [PubMed: 11460263]

16. Meck W, Williams C. Metabolic imprinting of choline by its availability during gestation: implications for memory and attentional processing across the lifespan. Neurosci Biobehav Rev 2003;27:385–399. [PubMed: 12946691]

17. Mellott T, Follettie M, Diesl V, Hill A, Lopez-Coviella I, Blusztago J. Prenatal choline availability modulated hippocampal and cerebral cortical gene expression. FASEB J 2007;21:1311–1323. [PubMed: 17264169]

18. Zeisel S. The fetal origins of memory: the role of dietary choline in optimal brain development. J Pediatr 2006;149:S131–S136. [PubMed: 17212955]

19. Signore C, Ueland P, Troendle J, Mills J. Choline concentrations in human maternal and cord blood and intelligence at 5 yr of age. Am J Clin Nutr 2008;87:896–902. [PubMed: 18400712]

20. Thomas J, Biane J, OBryan K, O'Neill T, Dominguez H. Choline supplementation following third-trimester-equivalent alcohol exposure attenuates behavioral alterations in rats. Behav Neurosci 2007;121:120–130. [PubMed: 17324056]

21. Velzing-Aarts F, Holm P, Fokkema M, van der Dijs F, Ueland P, Muskiet F. Plasma choline and betaine and their relation to plasma homocysteine in normal pregnancy. Am J Clin Nutr 2005;81:1283–1289.

22. Vollset S, Refsum H, Irgens L, et al. Plasma total homocysteine, pregnancy complications, and adverse pregnancy outcomes: the Hordaland Homocysteine Study. Am J Clin Nutr 2000;71:962–968. [PubMed: 10731504]

23. Molloy A, Mills J, Cox C, et al. choline and homocysteine interrelations in umbilical cord and maternal plasma at delivery. Am J Clin Nutr 2005;82:836–842. [PubMed: 16210714]

24. da Costa KA, Gaffney C, Fischer L, Zeisel S. Choline deficiency in mice and humans is associated with increased plasma homocysteine concentration after a methionine load. Am J Clin Nutr 2005;81:440–444. [PubMed: 15699233]

25. The Homocysteine Studies Collaboration, 2002. Homocysteine and risk of ischemic heart disease and stroke. J Am Med Assoc 2002;288:2015–2022.
26. Wu L, Wu J. Hyperhomocysteinemia is a risk factor for cancer and a new potential tumor marker. Clin Chim Acta 2002;322:21–28. [PubMed: 12104077]
27. Seshadri S, Beiser A, Selhub J, Jacques P, Rosenberg I, D'Agostino R, Wilson P, Wolf P. Plasma homocysteine as a risk factor for dementia and Alzheimer's disease. N Engl J Med 2002;346:476–483. [PubMed: 11844848]
28. van Meurs J, Dhonukshe-Rutten, Pluijm S, van der Klift M, et al. Homocysteine levels and the risk of osteoporotic fracture. N Engl J Med 2004;350:2033–2041. [PubMed: 15141041]
29. Chiuve S, Giovannucci E, Hankinson S, et al. The association between betaine and choline intakes and the plasma concentrations of homocysteine in women. Am J Clin Nutr 2007;86:1073–1081. [PubMed: 17921386]
30. Atkinson W, Elmslie J, Lever M, Chambers S, George P. Dietary and supplementary betaine: acute effects on plasma betaine and homocysteine concentrations under standard and postmethionine load conditions in healthy male subjects. Am J Clin Nutr 2008;87:577–585. [PubMed: 18326594]
31. Jacques P, Bostom A, Wilson P, Rich S, Rosenberg I, Selhub J. Determinants of plasma total homocysteine concentration in the Framingham Offspring cohort. Am J Clin Nutr 2001;73:613–621. [PubMed: 11237940]
32. Olthof M, Brink E, Katan M, Verhoef P. Choline supplemented as phosphatidylcholine decreases fasting and postmethionine-loading plasma homocysteine concentrations in healthy men. Am J Clin Nutr 2005;82:111–117. [PubMed: 16002808]
33. Detopoulou P, Panaglotakos B, Antonopoulou S, Pittsavos C, Stefanadis C. Dietary choline and betaine intakes in relation to concentrations of inflammatory markers in health adults: the ATTICA study. Am J Clin Nutr 2008;87:424–430. [PubMed: 18258634]
34. Cho E, Zeisel S, Jacques P, et al. Dietary choline and betaine assessed by food-frequency questionnaire in relation to plasma totoal homocysteine concentration in the Framingham Offspring Study. Am J Clin Nutr 2008;83:905–911. [PubMed: 16600945]
35. Fargnoli JL, Fung TT, Olencauk DM, Chamberland JP, Hu FB, Mantzoros CS. Adherence to healthy eating patterns is associated with higher circulating total and high-molecular-weight adiponectin and lower resistin concentrations in women from the Nurses' Health Study. Am J Clin Nutr 2008;88:1213–1324. [PubMed: 18996855]
36. U.S. Department of health and Human Services, National Institutes of Health, National, Heart, Lung and Blood Institute. Statement from Elizabeth G. Nabel, M.D., Director, National Heart, Lung, and Blood Institute on New Findings on the Role of Inflammation in Prevention of Coronary Heart Disease. [Accessed November 13, 2008]. www.nih.gov/news/health/nov2008/nhlbi-`10.htm
37. Bidulescu A, Chambless L, Siega-Riz A, Zeisel S, Heiss G. Usual choline and betaine dietary intake and incident coronary heart disease: the Atherosclerosis Risk in Communities (ARIC) Study. BMC Cardiovasc Disord 2007;7:20. [PubMed: 17629908]
38. Dalmeijer G, Olthof M, Verhoef P, bots M, van der Schouw Y. Prospective study on dietary intakes of folate, betaine, and choline and cardiovascular disease risk in women. Eur J Clin Nutr 2008;62:386–394. [PubMed: 17375117]
39. da Costa K, Badea M, Fischer L, Zeisel S. Elevated serum creatine phosphokinase in choline-deficient humans: mechanistic studies in C2C12 mouse myoblasts. Am J Clin Nutr 2004;80:163–170. [PubMed: 15213044]
40. da Costa K, Niculescu M, Craciunescu, Fischer L, Zeisel S. Choline deficiency increases lymphocyte apoptosis and DNA damage in humans. Am J Clin Nutr 2006;84:88–94. [PubMed: 16825685]
41. Xu X, Gammon M, Zeisel S, et al. Choline metabolism and risk of breast cancer in a population-based study. FASEB J 2008;22:1–8. [PubMed: 18166582]
42. [Accessed July 11, 2008]. http://www.nal.usda.gov/fnic/foodcomp/Data/Choline/Choln02.pdf
43. da Costa K, Kozyreva O, Song J, Galanko J, Fischer L, Zeisel S. Common genetic polymorphisms affect the human requirement for the nutrient choline. FASEB J 2006;20:1336–1344. [PubMed: 16816108]
44. Niculescu M, Zeisel S. Diet, methyl donors and DNA methylation: Interactions between dietary folate, methionine and choline. J Nutr 2002;132:2333S–2335S. [PubMed: 12163687]

45. Kohlmeier M, da Costa K, Fischer LM, Zeisel SH. Genetic variation of folate-mediated one-carbon transfer pathway predicts susceptibility to choline deficiency in humans. Proc Natl Acad Sci U S A 2005;102:16025–16030. [PubMed: 16236726]

46. Zeisel S. Gene response elements, genetic polymorphisms and epigenetics influence the human dietary requirement for choline. IUBMB Life 2007;59:380–387. [PubMed: 17613168]

47. Fischer L, Scearce J, Mar M-H, et al. Ad libitum choline intake in healthy individuals meets or exceeds the proposed adequate intake level. J Nutr 2005;135:826–829. [PubMed: 15795442]

48. Jensen, H.; Batres-Marques; Carriquiry, A.; Schalinske, K. Choline in the diets of the U.S,. Population: NHANES, 2003–2004; Presented at the National Nutrient Data Bank Conference; 2007.

49. Keast, D. Food sources of choline in the diets of US older adults: NHANES, 2999-2004; Presented at the National Nutrient Data Bank Conference; 2007.

50. Holmes-McNary M, Cheng WL, Mar MH, Fussel S, Zeisel S. Choline and choline esters in human and rat milk and in infant formulas. Am J Clin Nutr 1996;64:572–576. [PubMed: 8839502]

51. National Heart, Lung, and Blood Institute. Bethesda, Maryland: US Department of Health and Human Services, Public Health Service, National Institutes of Health; 2002. Third Report of the National Cholesterol Education Program (NCEP) Expert Panel on Detection, Evaluation, and Treatment of High Blood Cholesterol in Adults (Adult Treatment Panel III). publication no. (NIH) 02–5215

52. [Accessed July 11, 2008]. http://www.nal.usda.gov/fnic/foodcomp/search

53. StrategyOne Health Professionals Survey. 2007 Apr.

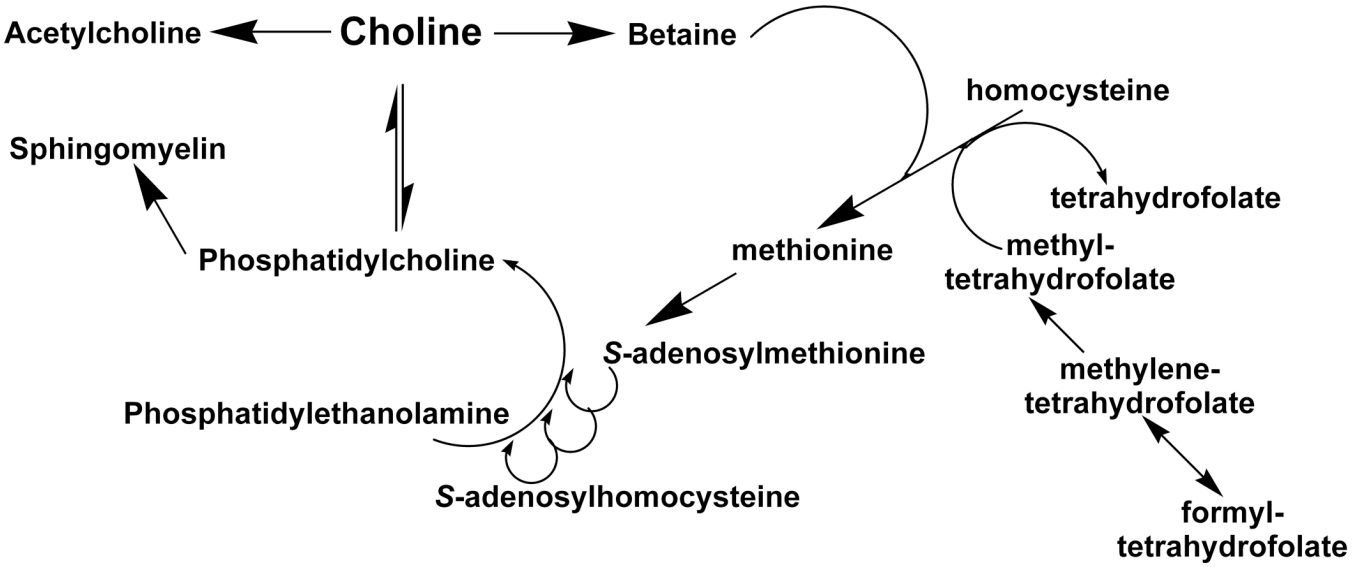


Figure 1.
Metabolic pathway of choline

Nutr Rev. Author manuscript; available in PMC 2009 November 25.

Table 1

Effect of Maternal Choline Supplementation on Brain Function in Animals

Reference	Animal model	Choline Dose	Measurements	Length	Outcome	Significance
Glenn et al. (2008)Error! Bookmark not defined.[16]	32 Male and female rats	Maternal diet supplemented with 5 g/kg vs control (1.1 g/kg)	Response to novel environments/ objects ;hippocampal plasticity in adulthood	Tested at 1 and 24 months of age	Increase in exploration behavior in prepubertal females and an attenuation in the decline in exploration with age. Evidence of long-lasting effects of prenatal choline supplementation on markers of hippocampal plasticity.	$p<0.05$
Stevens et al. (2008)Error! Bookmark not defined.[17]	34 Male and female rats	Maternal diet supplemented with 5 g/kg vs normal (1.1g/kg) vs deficient (0g/kg	Sensory inhibition in offspring as assessed by five sensory inhibition parameters	Tested at 11 to 12 months of age	Rats gestated on deficient choline showed abnormal sensory inhibition in 2 out of 5 parameters when tested at adulthood; rats gestated on normal or supplemented choline showed normal sensory inhibition.	$p<0.01$
Stevens et al. (2008)Error! Bookmark not defined.[18]	27 Male and female mice	Maternal diet supplemented with 5 g/kg vs normal (1.1 g/kg)	Sensory inhibition in offspring as assessed by three sensory inhibition parameters	Tested at 10 to 12 weeks of age	Gestational choline supplementation produced permanent improvement in sensory inhibition in two out of three parameters tested in adult offspring.	$p<0.001$
Cheng et al. (2008)Error! Bookmark not defined.[19]	32 Male and female rats	Maternal diet supplemented with 5 g/kg vs normal (1.1 g/kg) during days 12–17 of gestation	Animals were trained in a series of differential reinforcement schedules and their responses evaluated. Two time periods were selected and compared.	Tested at 7 months	Gestational choline supplementation at days 12–17, resulted in long-lasting effects exhibited by the establishment of more precise and enduring memories of the training procedures	$p<0.01$
Cheng et al. (2008)Error! Bookmark not defined.[20]	12 Male rats	Maternal diet supplemented with 3.5 g/kg vs control (1.1 g/kg) during days 12–17 of gestation	Animals were trained and tested on auditory and visual signals at two different time intervals and two levels of intensity	Tested at 20 months	Prenatal choline supplementation enhanced auditory and visual responses in aged rats	<0.01
Wong-Goodrich et al. (2008)Error! Bookmark not defined.[21]	Experiment 160 Male rats	Maternal diets were either choline deficient, sufficient (1.1g/kg) or supplemented (5 g/kg) on gestation days 12–17. **Experiment 1** Offspring	**Experiment 1** Animals were trained and tested for hippocampally mediated spatial	**Experiment 1** Trained at 70 days of age for 24 days. After 10 days retrained for 14 days.	In utero availability of choline affects cognitive and	<0.05

Reference	Animal model	Choline Dose	Measurements	Length	Outcome	Significance
	Experiment 234 Male rats	were divided into 2 groups (one group received a choline-deficient diet; another received 5.0g/kg of choline). The animals were returned to a 1.1 g/kg choline diet and given two additional retraining sessions. **Experiment 2** One group of offspring was given a control diet (1.1 g/kg); the other group was given a choline supplemented diet for 12 weeks.	navigation, memory and plasticity at three time intervals. **Experiment 2** Tested for spatial memory, dentate cell proliferation and neurogenesis.	After 10 more days, animals were retrained again for 14 days. **Experiment 2** At 15 months of age, animals were trained for 4 days on a water-maze.	hippocampal responses when offspring are exposed to changes in the choline supply as adults.	

Table 2

Selected Food Sources of Choline (milligrams per serving)

Food	Choline
Chicken, liver, cooked (3 oz)	247
Soy flour, defatted (1 cup)	201
Salmon, sockeye, smoked (3 oz)	187
Egg, whole, raw, fresh (1 large)	125
Quinoa, uncooked (1/2 cup)	60
Chicken, broilers or fryers, meat and skin, roasted (3 oz)	56
Turkey sausage, cooked (3 oz)	55
Wheat germ, toasted, plain (2 tbsp)	50
Milk, nonfat, fluid, with added vitamin A (8 ounces)	38
Cauliflower, cooked, boiled (1/2 cup)	24
Peas, green, frozen, cooked, drained (1/2 cup)	22
Bacon, pork, cured, cooked (2 pieces)	20
Almonds (1 oz)	15
Broccoli, cooked, boiled, drained (1/2 cup)	15
Frankfurter, beef (1)	15
Oat bran, raw (1/2 cup)	15
Pecans (1 oz)	15
Tomato paste, canned (2 tbsp)	12
Flaxseed (2 tbsp)	11

Source: USDA Database for the Choline Content of Common Foods, Release Two, January 2008; USDA National Nutrient Database for Standard Reference, Release 20.