

The following is an extract from:

Nutrient Reference Values for Australia and New Zealand
Including Recommended Dietary Intakes

ENDORSED BY THE NHMRC ON 9 SEPTEMBER 2005

© Commonwealth of Australia 2006

ISBN Print 1864962372
ISBN Online 1864962437

The Nutrient Reference Values (NRVs) was a joint initiative of the Australian National Health and Medical Research Council (NHMRC) and the New Zealand Ministry of Health (MoH). The NHMRC would like to thank the New Zealand MoH for allowing the use of the NRV material in the development of this website.

NHMRC publications contact:

Email: nhmrc.publications@nhmrc.gov.au
Internet: <http://www.nhmrc.gov.au>
Free Call: 1800 020 103 ext 9520

CHOLINE

BACKGROUND

Choline is a precursor for a number of compounds including the neurotransmitter acetylcholine and the membrane constituents phospholipid and sphingomyelin, platelet activating factor and betaine, which is required by kidney cells and plays a role in donating methyl groups to homocysteine to form methionine. It is also important for lipid and cholesterol transport and metabolism if methyl groups.

There is some evidence that choline may improve cognitive function and memory at all ages and, by extension, choline deficiency has been implicated in poor performance for groups such as the institutionalised elderly (Fioravanti & Yanagi 2004, McDaniel et al 2003). There is also evidence that choline may reduce serum and urinary carnitine (Hongu & Sachan 2003).

Choline can be made in the body, but the ability of the body to produce enough depends on the methyl-exchange relationships between choline and folate, Vitamin B₁₂ and methionine (Zeisel & Blusztajn 1994). The dietary essentiality of choline was demonstrated in a study of healthy men with normal folate and vitamin B₁₂ status who developed liver damage with lower plasma choline and phosphatidylcholine concentrations when fed a choline-deficient diet (Zeisel et al 1991). However, few countries have included choline in their nutrient intake recommendations.

There is little information about requirements for most age and gender groups. Evidence from animal studies suggests that females may have a lower requirement than males. Female rats are less sensitive to choline deficiency than male rats, perhaps because of an enhanced capacity to form choline *de novo* (Tessitore et al 1995). If this is true for women, it is possible that the enhanced capacity may decrease after menopause (Lindblad & Schersten 1976) as animal experiments again have shown that oestrogens increase hepatic phosphatidyl-ethanolamine-*N*-methyltransferase activity (Drouva et al 1986, Young 1971).

Choline is widely distributed throughout the food supply, mostly in the form of phosphatidylcholine in membranes. Milk, liver, eggs and peanuts are particularly good sources. Vegetarians consuming significant quantities of refined products have a risk of becoming choline deficient. Wheat germ and dried soybeans are good sources of choline for this group (Zeisel et al 2003). Endogenous biosynthesis of choline does not meet physiological requirements and chronic deficiency leads to hepatic dysfunction.

Choline is absorbed in the small intestine both intact and after bacterial metabolism to betaine. Some betaine is also formed by oxidation of choline in liver and kidney (Bianchi & Azzone 1964, Weinhold & Sanders 1973). There appear to be no competitors for the choline transporter mechanism in the gut. The tissues of the body accumulate choline by diffusion and mediated transport (Zeisel 1981) and a specific carrier mechanism allows transport across the blood-brain barrier. This carrier has very high capacity in the neonate.

Although choline is essential, there appear to have been no reports of deficiency in the general population. Deficiencies have been seen in experimental situations and also in total parenteral nutrition (Buchman et al 1992, 1993, 1995, Chalwa et al 1989, Shapira et al 1986, Sheard et al 1986). Individuals with obesity, insulin resistance or diabetes, and middle-aged women have a propensity to develop fatty liver syndrome. This may in part be due to deficiencies of nutrients such as carnitine, essential fatty acids or choline, but there is little evidence. Given the propensity of visceral obesity in western countries including Australia and New Zealand, consideration of choline intake, amongst other nutrients, needs to be further explored.

Markers of liver dysfunction and plasma concentrations have been used to assess choline requirements, but both have limitations. Animal experiments show that hepatic choline and choline metabolites in liver decrease in choline deficiency (Zeisel et al 1989). Phosphocholine concentration in liver correlates highly with dietary choline and is also sensitive to modest changes in dietary intake. However, it is not easy to measure (Cohen et al 1995).

Plasma concentration of choline varies in response to diet (Buchman et al 1993, Burt et al 1980, Chalwa et al 1989, Sheard et al 1986, Zeisel et al 1991). The disadvantage of using it as a functional marker is that concentrations do not decline to less than 50% of normal, possibly due to hydrolysis of membrane phospholipids to maintain plasma levels (Savendahl et al 1997). Plasma phosphatidylcholine concentrations also decrease in choline deficiency, but phosphocholine concentrations are also influenced by factors that change plasma lipoprotein levels, so it is not a specific marker for choline deficiency (Zeisel et al 1991).

RECOMMENDATIONS BY LIFE STAGE AND GENDER

<i>Infants</i>	AI	Choline
0–6 months	125 mg/day	
7–12 months	150 mg/day	

Rationale: The AI for 0–6 months was calculated by multiplying the average intake of breast milk (0.78 L/day) by the average concentration of choline in breast milk, and rounding. Breast milk from well-nourished mothers contains an average of 160 mg/L of choline delivered as choline, phosphocholine, glycerophosphocholine, phosphatidylcholine and sphingomyelin (Holmes-McNary et al 1996, Zeisel et al 1986). Infant formulas derived from soy or bovine milk contained significantly less phosphocholine than human milk (Holmes-McNary et al 1996). The AI was thus set at 125 mg/day (160 mg/L x 0.78 L/day and rounded), or 18 mg/kg for the reference weight of 7 kg at this age.

Although the free choline moiety is adequately provided by infant formulas and bovine milk, re-evaluation of the concentration of other choline esters, in particular glycerophosphocholine and phosphocholine, may be warranted. As there are no data on the availability of choline from foods for this age group, the AI for 7–12 months was set by using the reference body weight ratio methods to extrapolate either from the AI for 0–6 months or that for adults. This gave a figure of 150 mg/day.

<i>Children & adolescents</i>	AI	Choline
All		
1–3 yr	200 mg/day	
4–8 yr	250 mg/day	
Boys		
9–13 yr	375 mg/day	
14–18 yr	550 mg/day	
Girls		
9–13 yr	375 mg/day	
14–18 yr	400 mg/day	

Rationale: As there are no data to set EARs, AIs for children and adolescents were set by extrapolating from the adult data on a body weight basis and allowing for growth needs.

Adults	AI	Choline
Men		
19–30 yr	550 mg/day	
31–50 yr	550 mg/day	
51–70 yr	550 mg/day	
>70 yr	550 mg/day	
Women		
19–30 yr	425 mg/day	
31–50 yr	425 mg/day	
51–70 yr	425 mg/day	
>70 yr	425 mg/day	

Rationale: As data are too limited to allow the setting of an EAR, an AI for adults was set using data from experimental studies. In one study, an intake level of 500 mg/day (approximately 7 mg/kg body weight) prevented alanine aminotransferase abnormalities in healthy men (Zeisel et al 1991). This estimate is uncertain, but is within the range of adequacy for patients on total parenteral nutrition for whom 2 mg/kg/day (150 mg/day for the standard body weight of men) did not prevent deficiency and 31 mg/kg/day (about 2400 mg/day) did. The AI is therefore set at 550 mg/day for men (7 mg/kg body weight x 76 kg and rounding up). Animal data have suggested that women may use choline more efficiently. The female AI was set using the data from men and adjusting for body weight (7 mg/day x 61 kg), and rounding.

Pregnancy	AI	Choline
14–18 yr	415 mg/day	
19–30 yr	440 mg/day	
31–50 yr	440 mg/day	

Rationale: There are limited data on the needs for choline in pregnancy. The AI is based on the fetal and placental accumulation of choline plus turnover in the mother. From the data of Pompfret et al (1989), Widdowson (1963) and Welsch (1976), the combined fetal and placental choline content has been estimated at 312 mg/kg (FNB:IOM 1998). Assuming there is no additional synthesis in pregnancy and no contribution from fetal and placental synthesis, the additional requirement is 3,000 mg (assuming a 3 kg fetus and 7 kg organs of pregnancy) which equates to 11 mg/day. The AI was therefore set by adding 11 mg/day and rounding.

Lactation	AI	Choline
14–18 yr	525 mg/day	
19–30 yr	550 mg/day	
31–50 yr	550 mg/day	

Rationale: Needs in lactation increase, as a substantial amount of choline is secreted in breast milk. For an average volume of 0.78 L/day of breast milk with an average choline content of 160 mg/L, the increase is 125 mg/day which was added to the mother's requirement.

UPPER LEVEL OF INTAKE - CHOLINE

Infants

0–12 months **Not possible to establish. Source of intake should be breast milk, formula and food only**

Children and adolescents

1–3 yr **1,000 mg/day**

4–8 yr **1,000 mg/day**

9–13 yr **1,000 mg/day**

14–18 yr **3,000 mg/day**

Adults 19+ yr

Men **3,500 mg/day**

Women **3,500 mg/day**

Pregnancy

14–18 yr **3,000 mg/day**

19–50 yr **3,500 mg/day**

Lactation

14–18 yr **3,000 mg/day**

19–50 yr **3,500 mg/day**

Rationale: The data used to set the UL included a single case report of hypotension and several studies involving cholinergic effects and body odour effects after large choline doses. There are no data to establish a NOAEL. A LOAEL of 7.5 g/day was derived from the study of Boyd et al (1977) of seven dementia patients receiving choline therapy and reports of hypotension, cholinergic responses and fishy body odour in other patients undergoing treatment (Gelenberg et al 1979, Growdon et al 1977a,b, Lawrence et al 1980). In these studies, intakes of 4 g/day showed no effect in terms of hypotension, nausea, diarrhoea or other cholinergic effects but at 7.5 g/day or over, these effects were reported in some patients. A UF of 2 was selected because of limited data, giving a UL of 3.5 g/day (3,500 mg/day) after rounding down. There are no data to suggest that during pregnancy or lactation, there is increased susceptibility, so the same UL was set.

For infants, there were no data on which to set a UL. The only source should be breast milk, formula and food. For older children and adolescents, the UL was set on a body weight basis from the adult value, and rounded down.

REFERENCES

- Bianchi G, Azzone GF. Oxidation of choline in rat liver mitochondria. *J Biol Chem* 1964;239:3947–55.
- Boyd WD, Graham-White J, Blackwood G, Glen I, McQueen J. Clinical effects of choline in Alzheimer senile dementia. *Lancet* 1977;2:711.
- Buchman AL, Dubin M, Jenden D, Moukarzel A, Roch MH, Rice K, Gorbein J, Ament ME, Eckhart CD. Lecithin increases plasma free choline and decreases hepatic steatosis in long-term total parenteral nutrition patients. *Gastroenterology* 1992;102:1363–70.
- Buchman AL, Moukarzel A, Jenden D, Roch MH, Rice K, Ament ME. Low plasma free choline is prevalent in patients receiving long term parenteral nutrition and is associated with hepatic aminotransferase abnormalities. *Clin Nutr* 1993;12:33–7.
- Buchman AL, Dubin M, Moukarzel A, Jenden D, Roch MH, Rice K, Gorbein J, Ament ME. Choline deficiency: A cause of hepatic steatosis during parenteral nutrition that can be reversed with intravenous choline supplementation. *Hepatology* 1995;22:1399–403.

- Burt ME, Hanin I, Brennan MF. Choline deficiency associated with total parenteral nutrition. *Lancet* 1980;2:638–9.
- Chalwa RK, Wolf DC, Kutner MH, Bonkovsky HL. Choline may be an essential nutrient in malnourished patients with cirrhosis. *Gastroenterology* 1989;97:1514–20.
- Cohen BM, Renshaw PF, Stoll AL, Wurtman RJ, Yurgelun-Todd D, Babb SM. Decreased brain choline uptake in older adults. An in vivo proton magnetic resonance spectroscopy study. *JAMA* 1995;274:902–7.
- Drouva SV, LaPlant E, Bechet JJ, Clauser H, Kordon C. Estradiol activates methylating enzymes involved in the conversion of phosphatidylethanolamine to phosphatidylcholine in rat pituitary membranes. *Endocrinology* 1986;119:2611–22.
- Fioravanti M, Yanagi M. Cytidine diphosphocholine (CDP choline) for cognitive and behavioural disturbances associated with chronic cerebral disorders in the elderly. *Cochrane Database Syst Rev*. 2004;(2):CD000269.
- Food and Nutrition Board: Institute of Medicine. *Dietary Reference Intakes for Thiamin, Riboflavin, Niacin, Vitamin B6, Folate, Vitamin B12, Pantothenic Acid, Biotin, and Choline*. Washington DC: National Academy Press, 1998.
- Gelenberg AJ, Doller-Wojcik J, Growdon JH. Choline and lecithin in the treatment of tardive dyskinesia: preliminary results from a pilot study. *Am J Psychiatry* 1979;136:772–6.
- Growdon JH, Crowden EL, Wurtmann RJ. Huntington's disease: Clinical and chemical effects of choline administration. *Ann Neurol* 1977a;1:418–22.
- Growdon JH, Crowden EL, Wurtmann RJ, Wiener W. Oral choline administration to patients with tardive dyskinesia. *N Engl J Med* 1977b;297:524–7.
- Holmes-McNary MQ, Cheng WL, Mar MH, Fussell S, Zeisel SH. Choline and choline esters in human and rat milk and in infant formulas. *Am J Clin Nutr*. 1996;64:572–6.
- Hongu N and Sachan DS. Carnitine and choline supplementation with exercise alter carnitine profiles, biochemical markers of fat metabolism and serum leptin concentrations in healthy women. *J. Nutr* 2003;133:84–9.
- Lawrence CM, Millac P, Stout GS, Ward JW. The use of choline chloride in ataxic disorders. *J Neurol Neurosurg Psychiatry* 1980;43:452–4.
- Lindblad L, Schersten T. Incorporation rate in vitro of choline and methyl-methionine into human hepatic lecithins. *Scand J Gastroenterol* 1976;11:587–91.
- McDaniel MA, Maier SF, Einstein GO. "Brain-specific" nutrients: a memory cure? *Nutrition* 2003;19:957–75.
- Pomphret EA, daCosta KA, Schurman LL, Zeisel SH. Measurement of choline and choline metabolite treatment upon rat liver. *J Nutr Biochem* 1989;1:533–41.
- Savendahl L, MarM-H, Underwood LE, Zeisel SH. Prolonged fasting in humans Results in diminished plasma choline concentrations but does not cause liver dysfunction. *Am J Clin Nutr* 1997;66:622–5.
- Shapira G, Chalwa RK, Berry CJ, Williams PJ, Roy RGB, Rudman D. Cysteine, tyrosine, choline and carnitine supplementation of patients on total parenteral nutrition. *Nutr Int* 1986;2:334–9.
- Sheard NF, Zeisel WB. The fish odor syndrome. Trimethylaminuria. *JAMA* 1986;251:253–5.
- Tessitore L, Sesca E, Greco M, Pani P, Dianzani M. Sexually differentiated response to choline in choline deficiency and ethionine intoxication. *Int J Exp* 1995;76:125–9.
- Weinhold PA, Sanders R. The oxidation of choline by liver slices and mitochondria during liver development in the rat. *Life Sci* 1973;13:621–9.

- Welsch F. Studies on accumulation and metabolic fate of (*N*-Me³H)choline in human term placenta fragments. *Biochem Pharmacol* 1976;25:1021–30.
- Widdowson EM. Growth and composition of the fetus and newborn. In: Asali N, ed. *Biology of gestation, Vol 2*. New York: Academic Press, 1963. Pp 1–51.
- Young DL. Estradiol-and testosterone-induced alterations in phosphatidylcholine and triglyceride synthesis in hepatic endoplasmic reticulum. *J Lipid Res* 1971;12:590–5.
- Zeisel SH, Blusztajn JK. Choline and human nutrition. *Ann Rev Nutr* 1994;14:269–96.
- Zeisel SH, Char D, Sheard NF. Choline, phosphatidylcholine and sphingomyelin in human and bovine milk and infant formulas. *J Nutr* 1986;116:50–8.
- Zeisel SH, daCosta KA, Franklin PD, Alexander EA, Lamont JT, Sheard NF, Beiser A. Choline, an essential nutrient for humans. *FASEB* 1991;5:2093–8.
- Zeisel SH, Mar MH, Howe JC, Holden JM. Concentrations of choline containing compounds and betaine in common foods *J Nutr* 2003;133:1302–7.
- Zeisel SH. Dietary choline: Biochemistry, physiology and pharmacology. *Ann Rev Nutr* 1981;1:95–121.
- Zeisel WB, Zola T, da Costa K, Pomphret EA. Effect of choline deficiency on S-adenosylmethionine and methionine concentration in the rat liver. *Biochem J* 1989;259:725–9.