

BALCHEM CORPORATION

Balchem Corporation, a producer of a range of nutritional ingredients for the food and feed (including choline salts marketed to the global infant formula industry), appreciates the opportunity to submit comments on FSANZ Proposal P1028 – Infant Formula

Q.1.24 Do you support inclusion of a mandatory requirement for choline in infant formula? Please provide your rationale.

A mandate for choline in infant formula would be consistent with the worldwide position of the nutrient in this product application. Choline is a required component of infant formula in many markets, with typical addition within the range of 7 to 50 mg/100 kcal (1.7 to 12 mg/100 kJ), as specified in standards of national authoritative bodies.

The biological reasons for choline's importance to newborns are its role in brain development, which continues at a fast pace in the months after birth, and in ongoing cognitive function. Choline is a precursor of numerous cellular metabolites that are important for their diverse purposes in the human body (1). Choline is needed to make phosphatidylcholine (PC), an important primary structural component of the phospholipid membranes of all cells, including glial and neuronal cells. (This phospholipid is also needed in the construction of very low density lipoproteins, which has an important function in fat transport.) Choline is also a precursor of the phospholipid sphingomyelin (SM), which is important in the myelin sheath of neurons, and in the metabolism of molecules that function in intracellular signaling, specifically diacylglycerol and ceramide. Perhaps most significant is its necessity for the synthesis of acetylcholine, the primary agent of neurotransmission in cholinergic neurons.

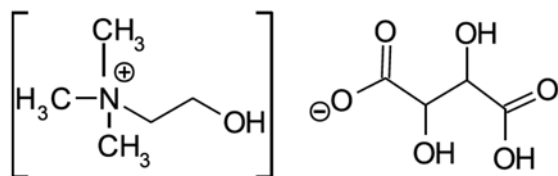
In the first months of life, an infant will receive choline from breast milk, infant formula, or a combination thereof. Infant formula composition is intended to resemble the composition of breast milk (3-6), particularly with regard to certain bioactive micronutrients, including choline. The quantity and form(s) of choline in breast milk and infant formula will influence the circulating levels of choline in infants (7). An infant's level of choline at birth and in its first newborn weeks is several fold higher than a typical adult level (5-10), presumably reflecting a need to support continued rapid growth during this time. Choline nutriture remains extremely important as a child is weaned from breast milk. Many commercial solid food preparations, "follow-up" formulas, and "toddler milks" in international markets now also contain choline.

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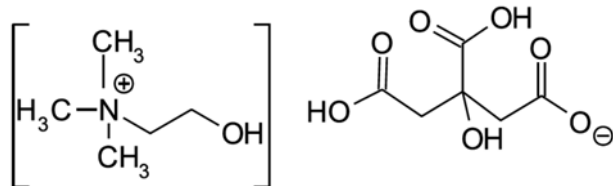
Q1.25 What is the technological justification can you provide for the use of choline citrate and/or choline hydrogen tartrate in infant formula?

The bioavailability is comparable to forms listed in Table 9.1.

Choline hydrogen tartrate is simply an alternative name for **choline bitartrate** (CAS Number 87-67-2); they are the same substance. The United States Pharmacopeia and Food Chemicals Codex monographs for choline bitartrate clearly designate that it should be the **choline L(+) bitartrate form**.



Choline citrate is, like choline bitartrate and choline chloride, a water-soluble salt. Where choline bitartrate is made from tartaric acid, choline citrate is made with citric acid instead. These salts are similar in their solubility and the ease with which they dissociate in solution.



Choline citrate is listed for use as a choline source in infant formula and follow-up formula, processed cereal-based food and baby food in Europe (*Regulation (EU) No 609/2013 of the European Parliament and of the Council of 12 June 2013 on food intended for infants and young children, food for special medical purposes, and total diet replacement for weight control*).

All three salts are bioavailable sources of choline cation, though the active load differs in each molecule.

- choline chloride is ~74% (w/w) choline
- choline citrate is ~35% (w/w) choline
- choline bitartrate is ~41% (w/w) choline

All forms are hygroscopic, with choline chloride being the most deliquescent. Choline chloride is typically used in spray dried infant formula products, whereas choline bitartrate and choline citrate are often used in dry-blended nutrient premixes used in infant formula.

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Q1.26 If you have provided a technological justification for these forms of choline can you provide:

(a) reference to a specification for choline citrate and/or choline hydrogen tartrate in an internationally accepted monograph of specifications (including those referenced in Standard 1.3.4)?

Choline hydrogen tartrate = choline bitartrate, which is covered in both Food Chemicals Codex and United States Pharmacopeia monographs.

(b) evidence to demonstrate safety can you provide for the use of choline citrate and/or choline hydrogen tartrate in infant formula?

Choline hydrogen tartrate = choline bitartrate.

Both choline hydrogen tartrate and choline citrate have been used in EU infant formula products for decades.

Thank you, once again, for the opportunity to provide comment on this proposal.

Kristine V. Lukasik, Ph.D.

Senior Director – Corporate Regulatory Affairs

Balchem Corporation

52 Sunrise Park Road, New Hampton, NY 10958, USA

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Reference List

- (1) Zeisel SH, Blusztajn JK. Choline and human nutrition. *Annu Rev Nutr* 1994;14:269-96.
- (2) Niculescu M, Zeisel SH. Diet, methyl donors and DNA methylation: Interactions between dietary folate, methionine and choline. *J Nutr* 2002;132:2333S-5S.
- (3) 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.
- (4) Zeisel SH, Char D, Sheard NF. Choline, phosphatidylcholine and sphingomyelin in human and bovine milk and infant formulas. *J Nutr* 1986;116:50-8.
- (5) Zeisel SH. Choline and choline esters as required nutrients during pregnancy and lactation. In: Zeisel SH, Szuhaj BF, editors. *Choline, Phospholipids, Health and Disease*. Champaign, IL: AOCS Press; 1998. p. 131-42.
- (6) Zeisel SH. Choline and phosphatidylcholine are important components of an infant's diet. In: Huang YS, Sinclair SJ, editors. *Lipids in Infant Nutrition*. Champaign, IL: AOCS Press; 1998. p. 192-212.
- (7) Ilcol YO, Ozbek R, Hamurtekin E, Ulus IH. Choline status in newborns, infants, children, breast-feeding women, breast-fed infants and human breast milk. *J Nutr Biochem* 2005;16:489-99.
- (8) Ilcol YO, Urncu G, Ulus IH. Free and phospholipid-bound choline concentrations in serum during pregnancy, after delivery, and in newborns. *Arch Phys Biochem* 2002;110(5):393-9.
- (9) Zeisel SH. Choline availability in the neonate. In: Dowdall MJ, Hawthorne JN, editors. *Cellular and Molecular Basis of Cholinergic Function*. Chichester, U.K.: Horwood Press; 1987. p. 709-19.
- (10) Zeisel SH, Epstein MF, Wurtman RJ. Elevated choline concentration in neonatal plasma. *Life Sci* 1980;26:1827-31.

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