

## Nitrite and nitrate in breast milk effects on infant health

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### Abstract

Human breast milk is the most ideal food in nature, containing essential nutrients that promote infant health and development. Breast milk is rich in nitrite and nitrate, and the proportion of these compounds vary with the composition of milk. The presence of nitrite and nitrate in breast milk indicates that they have an important impact on the growth and development of newborns. This article reviews that nitrite and nitrate in breast milk and their effects on infant health.

**Keywords:** Nitrate, nitrite, colostrum, neonate, necrotic enterocolitis

### Introduction

Nitrate and nitrite usually exist in the environment and are the most common nitrogenous compounds in nature [1]. As preservatives, they are widely used in the food industry for the fermentation and storage of meat, fish, and cheese [2]. Nitrite and nitrate, which form Nitrosamine and cause cancer, have always been dangerous substances. However, research shows that nitrite and nitrate can also be formed in the human body [3]. It is closely related to the signaling molecule of nitric oxide (NO) in human body [4]. NO is very important for the treatment of various diseases [5, 6].

Breast milk is the unique food necessary for the growth and development processes of infants and young children. The World Health Organization (WHO) recommends that infants aged 0-6 months should only breastfeed until the age of 2 years [7]. However, the breastfeeding rate in China has been low. In order to meet the needs of infants, infant formula is developed by simulating breast milk, but with the passage of time, it is still impossible to simulate the large and changing basic nutrients and immune characteristics of breast milk. Nitrate and nitrite widely exist in breast milk, especially in colostrum, containing high concentration nitrate. The fact that breast milk contains nitrate and nitrite indicates that they have significant physiological action for the growth and development processes of newborns.

### Safety of nitrate and nitrite

nitrate and nitrite can easily lead to Methemoglobin, especially infants aged 0-6 months.

Due to hypoxia, the skin color of infants is blue purple, also known as blue infant syndrome [8]. Nitrite can cause ferric ions (Fe<sup>2+</sup>) in oxyhemoglobin to be oxidized into ferric ions (Fe<sup>3+</sup>), significantly reduce the oxygen carrying function of oxyhemoglobin, cause infant anoxia and cyanosis, with blue purple skin [9, 10]. Nicotinamide adenine dinucleotide reductase in red blood cells, it can effectively reduce hemoglobin, making the hemoglobin level in the blood of healthy adults lower than 1%. Infants aged 0-6 months are sensitive to Methemoglobin caused by nitrite due to low gastric acid secretion, relatively easy oxidation of hemoglobin, immature Methemoglobin reductase system and other reasons [11, 12]. According to the analysis of infant Methemoglobin cases, WHO has stipulated the daily intake (ADI) of nitrate and nitrite in human body. The ADI for

nitrate and nitrite is 3.7mg/kg body weight and 0.06 mg/kg body weight respectively [13]. Some people believe that blue baby syndrome is related to groundwater contaminated with nitrate [14]. However, according to the current study, breast milk contains nitrate and nitrite (Table 1) [15].

**Table 1:** The measurement of nitrate and nitrite from breast milk

Phase	Nitrate (mg/100 mL)	Nitrite (mg/100 mL)
Colostrum	0.19±0.03	0.08±0.02
Transitional milk	0.52±0.10	0.001±0.001
Mature milk	0.31±0.02	0.001±0.001

It is estimated that the concentration of nitrite obtained by infants from colostrum can reach nearly 1 mg/kg, which is 14 times higher than that of the ADI for nitrite. Infants who are exclusively breastfed will not have any clinical problems [16]. Although the nitrate concentration received by mothers can reach up to 100 mg/L, but it can not influence the nitrate concentration in breast milk [17, 18].

### Changes of nitrate and nitrite

The composition of breast milk changes over time to adapt to changes in gut microbiota and metabolic requirements during infant growth [19]. Generally, milk from 2-3 days postpartum is called colostrum. Colostrum designed to meet the special needs of newborns is rich in protein and antibodies, with a yellow color, high consistency, high protein content, and low fat and sugar content. The protein concentration of colostrum is triple that of mature breast milk. The study also found that the nitrite concentration in colostrum is relatively high (Table 1). Ohta *et al.* found that the breast milk from the first day to the eighth day contained high concentrations of nitrite and nitrate, the concentration of which was 166~1246  $\mu$  M [20]. Hord *et al.* studied the changes of compounds such as nitrate and nitrite in breast milk over time and found that the nitrite content in colostrum is up to about 10  $\mu$  M [15]. Iizuka *et al.* reported that the concentration range of nitrate in colostrum ranges from 86.6 to 278.7  $\mu$  M, with an average concentration of 180.6  $\pm$  63.1  $\mu$  M; the concentration range of nitrite is 19.3~82.4  $\mu$  M, with an average concentration of 43.6  $\pm$  5.3  $\mu$  M [21]. Cekmen *et al.* found that the concentration of nitrite in the breast milk of healthy mothers was higher and the concentration of nitrite in the breast milk of preeclampsia

patients decreased from  $82.20 \pm 12.01 \mu\text{M}$  to  $56.09 \pm 11.18 \mu\text{M}$ , 30 days later, the concentration of nitrite was  $53.28 \pm 10.25 \mu\text{M}$  and  $37.75 \pm 12.10 \mu\text{M}$  [22]. Changes in the ratio of nitrate to nitrite in breast milk to meet the changing metabolic needs for infants during growth (Table 1). Nitrate is transformed into nitrite with nitrate reductase, and nitrite can be decomposed by gastric acid into an important signaling molecule of NO [21]. The reduction from nitrate to nitrite usually needs the participation of symbiotic bacteria in the body. However, human beings do not have nitrate reductase before childbirth. The baby's gastrointestinal tract is sterile and quickly colonized by bacteria from the mother's vagina, skin, and rectum [23]. Therefore, newborns do not have any nitrate reducing bacteria at birth, but colostrum contains high concentrations of nitrite. This enables infants to overcome the natural loss of life in the early stages of development [24]. When microbial symbiosis exists in mouth cavity, the nitrate-nitrite-NO pathway is established, and then nitrate becomes the main component of breast milk.

### Implication for infant health

The nitrate-nitrite- NO pathway plays an important role in the process of hypoxic vasodilation, stable blood pressure, ischemic reperfusion and platelet function changes. In adults, due to the existence of this pathway, the supply of nitrite produced by oral symbiotic microorganisms to reduce dietary nitrate is constant [25]. If the pathway is interrupted, it can lead to elevated blood pressure and increased platelet aggregation [26]. In addition, NO produced by this pathway is closely related to the integrity of gastric mucosa and blood flow. Lizuka *et al.* used chemiluminescence NO analyzer to determine the production of NO in neonatal stomach. It was found that the level of NO in gastric gas in breast fed newborns was significantly higher than that in formula fed newborns. The peak value was 2 to 5 days after the birth at  $6.03 \pm 5.73$  and  $2.24 \pm 15.71$  ppm respectively [21]. As nitrate-nitrite- NO pathway has not been established on the early growth and development in infants, newborns use nitrite in breast milk to make up for the function of nitrate-nitrite- NO pathway.

Necrotic enterocolitis (NEC) is the main reason of gastrointestinal diseases in premature infants, and its incidence rate is getting higher and higher [27]. The main pathological features of NEC are local ischemic necrosis of the small and large intestine [28]. Though premature delivery is the main dangerous factor for NEC, breast-feed has been proved to be the key protection strategy for preventing NEC [29]. Yazji *et al.* demonstrated in the study of mouse NEC model that adding sodium nitrate and nitrite to infant formula can reduce NEC is very outstanding [30]. This study explains the role of breast milk in reducing the morbidity of asthma, allergy, leukemia and cardiovascular disease in infants [31, 33].

### Conclusion

Breast milk is the most complete food in nature and contains nutrients that are critical to the health and development processes of infants. In addition, the American Academy of Pediatrics also recommends that the mother start breastfeeding the baby from the first year and continue breastfeeding until she feels that she can stop breastfeeding. Some studies have shown that breastfeeding has many important health benefits. The fact that breast milk contains

nitrate and nitrite indicates that they have significant physiological action for the growth and development processes of newborns. It has many health benefits from birth to your entire life.

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