Interpretation of the Results of EFSA1) -Report 1187 (2009)

1. Function and Natural Occurrence of Orotic Acid

Orotic Acid is a biological precursor of pyrimidine nucleotides and thus of pivotal importance for the biosynthesis of proteins, the formation of phospholipids and the energy metabolism of cells. Orotic Acid can improve cardiac performance by inducing the ATP production and by optimizing the energy metabolism of the myocardial cells.

Orotic Acid was first isolated from whey and can be found abundantly in dairy products. Cow’s milk contains approx. 50-100mg/l, goat’s milk 60-300 mg/l and sheep’s milk approx. 325 mg/l (Gröber 2000)-400 mg/l. Based on these data, the Orotic Acid concentration of cheese is calculated to be 500-1000 mg/kg cheese for cheese made from cow’s milk, 600-3000 mg/kg goat cheese and 1600-2250 mg/kg sheep cheese assumed that the production of 1 kg cheese requires 10l cow’s and goat’s milk and only 5l sheep’s milk because of the higher yield of sheep’s milk. Consequently, every human daily takes in a certain amount of Orotic Acid by consuming milk or dairy products. Different agricultural / nutritional scientific publications propagate the prophylactic effect especially of goat’s and sheep’s milk against cancer, amongst others because of its Orotic Acid content.

2. Indications for Orotic Acid or Orotates

Orotic Acid can be found in different medicaments as anion, though generally functioning as organic anion – comparable for example with citrate – and with the cation, e.g. Zinc, as the pharmacologically active component. As a consequence, there is a multitude of indications, e.g. for

Zinc Orotate: treatment of Zinc deficiencies as far as these cannot be remedied by regular food intake

Magnesium Orotate: this substance is special as it combines the cardioprotective properties of Magnesium and the cardioprotective properties of orotic acid. Even if the indication is primarily determined by the cation, Orotic Acid can provide an additional advantage, e.g. in case of cardiovascular diseases as it improves the energy supply of the cardiac muscle.

1) EFSA (European Food Safety Authority)
3. Tumor Potential of Orotic Acid and of Magnesium Orotate

Animal testing in the 1980s found that Orotic Acid stimulates the growth of tumors in the liver of rats if tumors had before been induced by very strong carcinogens (Rao et al. 1984). Obviously, the growth-stimulating effect of Orotic Acid on tumors is species-dependent as it was only observed on induced tumours of rats, but not on the mouse model (Laconi et al. 1990). The stimulating effect of Orotic Acid on the growth of tumors in rat livers discovered in animal testing

→ is a peculiarity of the rat metabolism.

Up to now, there is no hint of a clinical relevance of these results with regard to nutrition and therapy of humans with preparations containing Orotic Acid.

EFSA itself thinks, that up to 1% of the daily consumation of Orotic Acid does not cause any accumulation of fatty acid and this is approved by all tested different animal species beside rats. (In repeated dose Orotic Acid induces fatty livers in the rat, but not in other species tested, EFSA journal 1187,2-25) Also the rhesus monkey did not show fatty liver after being fed 10 weeks with basal diet containing 1% orotic aci (EFSA journal 1187,11-25 – in Korycka-Dahl et al. 1979: Absence of fatty livers in rhesus monkeys fed with Orotic Acid, J.Dairy Sci. 62(11), 1801-3)

EFSA cannot determine a « tumor promoting » effect for rats with a ratio of 0,1% Orotic Acid (The usual concentration to promote tumors has been 1% in the diet, but also 0,5 and 0,2% in the diet has been shown to have promoting effect, while 0,1% in the diet did not have effect within the time span tested (up to 20 weeks), EFSA journal, 1187,2-25).

In animal testing, 0,5-1% Orotic Acid is normally added to the animal food after tumor induction to stimulate tumor growth.

→ Orotic Acid alone did not have any carcinogenic effect even at a concentration as high as 4% (Laconi et al. 1993).

For humans with a daily food intake of 1,5 kg, a concentration of 1% Orotic Acid in food corresponds to approx. 15 g. A daily dose of Magnesium Orotate with 2-3 tablets makes up only 1-1,5g (including the Magnesium content!) and thus amounts to

→ only 10% of the quantity added to the food in animal testing.

50 mg/kg and day of Orotic Acid is the related dose without any side-effects. This is equivalent to a daily intake of 3,5g of Orotica acid of an adult of 50kg, which is a comon dose. (This is equivalent to 50 mg/kg bw/day, which may be considered as the highest no observed level (NOEL) for this effect under these conditions, EFSA journal, 1187,12-25).
Contrariwise some reports keep record about a protective impact of Orotic Acid. (Anti-tumor effects were seen in rats treated with ethionine (Sidransky et al, 1970) and in mice it was shown that Orotic Acid reduced the carcinogenic effects of methylcholanthrene (Rogers, 1957a: Inhibitory influence of a normally occurring pyrimidine precursor upon methylcholanthrene. Carcinogenesis. Proc.Soc.expBiol. med 96, 464-465, in EFSA report (2009), 1187,12-25 mentioned).

Above that, any discussion on the possible tumor potential of Magnesium Orotate has to consider that Magnesium Orotate contains Magnesium as active cation. For Magnesium, it was shown that tumor deaths could be reduced by high Magnesium levels (Leone et al. 2006). Conversely, Magnesium deficiencies can stimulate tumor growth as they reduce the cell-membrane stability and consequently make the cell membrane more vulnerable (Quintero et al. 2006). Magnesium-rich nutrition seems to reduce the risk of colon cancer for women (Folsom and Hong 2006). Thus it may be assumed that for certain tumors raising the Magnesium level can have tumor-inhibiting effects.

Above that, improving the physical capacities in tumor patients by administering Magnesium Orotate may lead to an improved general condition and may thus be desired.

In view of the extremely different tumor biology depending on the type of the tumor it is currently not possible to make general conclusions. In summary, it has to be noted that up to now no report on tumor-stimulating effects of Magnesium Orotate on humans exist.

Orotates are sold since over 40 years without any single case of causing cancer.

Not every single lab test with rats is of importance for human beings. As example the well known Aspirin is strong carcinogen for rats.