

Statement on the guidance levels for the fortificants in the Bread and Flour Regulations

# **Toxicity - Statement on the guidance levels for the fortificants in the Bread and Flour Regulations**

## **In this guide**

### [In this guide](#)

1. [Introduction - Statement on the guidance levels for the fortificants in the Bread and Flour Regulations](#)
2. [Background - Statement on the guidance levels for the fortificants in the Bread and Flour Regulations](#)
3. [Toxicity - Statement on the guidance levels for the fortificants in the Bread and Flour Regulations](#)
4. [Health based guidance values - Statement on the guidance levels for the fortificants in the Bread and Flour Regulations](#)
5. [Exposure assessment - Statement on the guidance levels for the fortificants in the Bread and Flour Regulations](#)
6. [Risk characterisation - Statement on the guidance levels for the fortificants in the Bread and Flour Regulations](#)
7. [Conclusion - Statement on the guidance levels for the fortificants in the Bread and Flour Regulations](#)
8. [List of Abbreviations and Technical terms- Statement on the guidance levels for the fortificants in the Bread and Flour Regulations](#)
9. [References - Statement on the guidance levels for the fortificants in the Bread and Flour Regulations](#)
10. [Annex A - Review of the guidance levels for fortificants in the bread and flour regulations \(BFR\)](#)

## **Calcium**

5. High intakes of calcium carbonate of around 4,000 mg/day (equivalent to 1,600 mg calcium) can result in a condition called milk-alkali syndrome in people with underlying medical conditions such as peptic ulcers (EFSA, 2006). This condition is characterised by hypercalcaemia, alkalosis and renal impairment, which is associated with hypertension, neurological problems, abdominal pain and tissue calcification (EVM, 2003).

6. Calcium supplements have been administered to people with colonic polyps or people who are at risk of colonic polyps. Gastrointestinal (GI) effects were reported in a small number of patients receiving 1,600 or 2,000 mg/day of calcium (EVM, 2003).

7. High calcium diets can affect the bioavailability of other minerals such as iron, zinc, magnesium and phosphorous by inhibiting the absorption of iron salts, haem-iron and zinc, reducing magnesium absorption and excretion, and the binding of calcium acetate and calcium carbonate to phosphate in the intestinal lumen (EFSA, 2006).

## **Iron**

8. Iron toxicity is particularly hazardous in children and most poisoning cases are reported in children consuming iron supplements intended for adults. Symptoms in infants include GI irritation at acute doses of around 20 mg/kg bw and systemic effects which occur at doses >60 mg/kg bw. The lethal dose in children is between 200-300 mg/kg bw (EVM, 2003).

9. In adults, GI effects such as constipation, nausea, vomiting and diarrhoea have been reported at therapeutic doses of 50-220 mg/person/day (EFSA, 2006). Iron toxicity can lead to inflammation and perforation of the GI tract and iron disrupts cellular metabolism in the central nervous system, liver and heart. Free iron in the serum enters and concentrates in the mitochondria where it forms free radicals, which can impair energy metabolism and can eventually lead to cell death (Baranwal and Singhi, 2003; Yuen and Becker, 2022). However, iron poisoning (where iron is in its free form) in adults is rare, Individual case reports suggest a lethal dose of 1,400 mg/kg bw (EVM, 2003).

## **Niacin (vitamin B3)**

10. Symptoms of acute toxicity from niacin include flushing, itchy skin, nausea, vomiting and GI issues (such as diarrhoea and constipation). Long term intakes of 3,000 mg/day of niacin have been reported to cause jaundice, hyperglycaemia

and abdominal pain. In addition to elevated serum bilirubin, increased alkaline phosphatase and aminotransferase levels, indicative of effects on the liver, have been reported in a small number of cases. Anorexia, ophthalmological effects, skin hyperpigmentation and precipitation of incipient psychosis have also been reported as side effects of niacin therapy (EVM, 2003).

11. Patients with hypercholesterolaemia that have been treated with niacin at 3-9 g/day over a period of months to years showed symptoms of severe liver dysfunction, which has the potential to be life threatening and may require liver transplantation (EFSA, 2006).

## **Thiamin (Vitamin B1)**

12. Thiamin is considered to be of very low toxicity, with symptoms such as headache, nausea, irritability, insomnia, rapid pulse and weakness being seen at high oral doses of  $\geq 7,000$  mg thiamin hydrochloride (EVM, 2003).

13. However, a small number of case reports have shown association with adverse effects such as muscle tremors, rapid pulse and nerve hyperirritability at daily doses as low as 17 mg/day of thiamin hydrochloride. In one case, a patient consuming thiamin at 100 mg/day for a period of 15 days, 2 months prior to consumption of a single oral dose of thiamin of 100 mg, experienced an anaphylactic reaction followed by death. In another case, a patient experienced exacerbated eczema after receiving an oral dose of 200 mg of thiamin in an experimental provocation (EVM, 2003). In a 2018 report, a few patients with Parkinson's disease treated with 2-3 intramuscular doses of 100 mg of thiamin/week experienced adverse effects of discomfort, unrest and an overall worsening of symptoms of Parkinson's disease, and a medium intensity migraine (Costantini and Fancellu, 2018).

14. The COT noted that alcohol consumption may be a confounding factor in some of the case reports. Most cases of thiamin deficiency were associated with chronic alcoholism, where absorption and utilisation of thiamin are impaired (EVM, 2003).