Calcium citrate malate as source for calcium for use in foods for Particular Nutritional Uses and in foods for the general population (including food supplements)\(^1\)

Scientific Opinion of the Panel on Food Additives, Flavourings, Processing aids and Materials in Contact with food (AFC)

(Question No EFSA Q-2006-201, Q-2006-205, Q-2006-206, Q-2007-052)

Adopted on 27 November 2007

Panel Members


Summary

Following a request from the Commission, the Panel on Food Additives, Flavourings, Processing aids and Materials in Contact with Food (AFC) was asked to give a scientific opinion on the safety and bioavailability of calcium citrate malate as a source for calcium intended for use in foods for Particular Nutritional Uses (PARNUTS) and foods intended for the general population (including food supplements).

The present opinion deals only with the safety and bioavailability of a particular source of calcium. The safety of calcium itself, in terms of amounts that may be consumed, is outside the remit of this Panel.

The available data provide information to conclude that calcium is bioavailable from calcium citrate malate. The safety evaluation of calcium citrate malate was based on specific toxicity studies and extensive information on calcium supplementation trials in humans as well as existing safety evaluations of its individual component substances, citric acid and malic acid.

\(^1\) For citation purposes: Scientific Opinion of the Panel on Food additives, Flavourings, Processing aids and Materials in Contact with food (AFC) on a request from the Commission on Calcium citrate malate as source for calcium intended for use in foods for Particular Nutritional Uses (PARNUTS) and in foods for the general population (including food supplements). The EFSA Journal (2007) 612, 1-24.
On this basis, the Panel concluded that the use of calcium citrate malate as source for calcium intended for use in foods for Particular Nutritional Uses (PARNUTS) and foods for the general population (including food supplements) is of no safety concern at the maximum levels estimated in this opinion.

**Key words:**

PARNUTS, Food supplements, foods intended for the general population, calcium citrate malate, CAS Registry Numbers 120250-12-6, 142606-53-9.
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BACKGROUND AS PROVIDED BY THE COMMISSION

The European Community legislation lists nutritional substances that may be used for nutritional purposes in certain categories of foods as sources of certain nutrients.

The Commission has received a request for the evaluation of Calcium Citrate Malate added for nutritional purposes to foodstuffs. The relevant Community legislative measures are:

- Commission Directive 2001/15/EC of 15 February 2001 on substances that may be added for specific nutritional purposes in foods for Particular Nutritional Uses;

TERMS OF REFERENCE AS PROVIDED BY THE COMMISSION

In accordance with Article 29 (1) (a) of Regulation (EC) No 178/2002, the European Commission asks the European Food Safety Authority to provide a scientific opinion, based on its consideration of the safety and bioavailability of calcium citrate malate for nutritional purposes in foods for Particular Nutritional Uses, and foods (including food supplements) intended for the general population (EC 2002a, 2002b).

ACKNOWLEDGEMENTS

The European Food Safety Authority wishes to thank the members of the Additives Working Group for the preparation of this opinion:

ASSESSMENT

The present opinion deals only with the safety and bioavailability of a particular source of calcium intended for foods for Particular Nutritional Uses (PARNUTS), food supplements and foods intended for the general population. The safety of calcium itself, in terms of the amounts that may be consumed, is outside the remit of this Panel.

1. Technical data

1.1. Description

Calcium citrate malate is described as a metastable complex of calcium, citrate and malate or as a mixture of calcium salts comprising the calcium salt of citric acid and malic acid. It may consist of a mixture of calcium citrate and calcium malate, a complex of calcium containing citrate and malate ligands, a mixture of calcium salt with citric acid and malic acid and combinations thereof.

Metastable means that the material is not at equilibrium and it is a mixture of various crystalline and non-crystalline forms and solid solutions of the calcium ions, citrate anions and malate ions as well as salts of these materials. The exact structure of the material is not known. The X-ray diffraction pattern indicates only that the complex salt is different from pure calcium citrate or pure calcium malate and that it may be crystalline or micro crystalline, but may also contain calcium, citrate and malate ions.

Calcium citrate malate can exist in several states of hydration. The metastable materials have more than one crystalline state, reflected by the presence of multiple hydration states. In addition, there are likely to be significantly different arrangements of the citrate and malate within the material. The physical and chemical data of these salts are consistent with the theory that there are non-crystalline regions within the powdered material which can hydrate to the point of behaving like a solution. It is important for the solubility characteristics of the calcium citrate malate that the apparent metastable structure be achieved.

CAS Number

There are many different calcium citrate malate complexes or mixtures. To the salt that has a molecular ratio calcium:citrate:malate of 6:2:3 (MW 1014), two CAS numbers 120250-12-6 and 142606-53-9 have been assigned.

Compositions and calculated (apparent) molecular weights

There are many different calcium citrate malate salts with different compositions, solubility and levels of hydration for which various molecular weights have been calculated. The molecular ratios proposed by four petitioners and the calculated molecular weights are given below:

<table>
<thead>
<tr>
<th>Formula</th>
<th>Molecular Weight (MW)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ca₆(C₆H₅O₇)₂(C₄H₄O₅)₃</td>
<td>1014</td>
</tr>
<tr>
<td>Ca₆(C₆H₅O₇)₂(C₄H₄O₅)₃.5H₂O</td>
<td>1105.06</td>
</tr>
<tr>
<td>Ca₁₂(C₄H₂O₇)₆(C₄H₄O₅)₃</td>
<td>2011.79</td>
</tr>
<tr>
<td>Ca₃(C₆H₅O₇)₂(C₄H₄O₅)₂</td>
<td>842.75</td>
</tr>
</tbody>
</table>

The EFSA Journal (2007) 612, 5-24
1.2. Specifications

On the basis of the properties of the calcium citrate malate materials in this opinion, the following general specifications apply: white powder or granules, slightly soluble in water and soluble in dilute acids containing not less than 98 % on a dry basis (one petitioner proposes 95 %) and showing a loss on drying not more than 10 %. Calcium citrate malate is described as containing between 20 – 24 % of calcium on a dry basis having a pH 4.0 – 8.0. Heavy metal levels of less than 20 mg/kg are proposed, for lead two petitioners propose a maximum level of 2 mg/kg and two others propose a maximum of 10 mg/kg. For arsenic a level of less than 3 mg/kg is proposed, for fluoride three petitioners propose a level of less than 30 mg/kg whereas one petitioner proposed a maximum of 500 mg/kg.

1.3. Case of need and intended use levels

According to the petitioners, calcium citrate malate allows the calcium salt to be added to neutral as well as to acid foods in a soluble form. According to the petitioners, this mixed salt is a better source of calcium as it is more readily soluble compared to calcium citrate and calcium malate, which are poorly soluble in water and hydrate when stored.

No specific information was provided on intended use levels and/or expected calcium exposure arising from the use of calcium citrate malate in PARNUTS and/or fortified foods. It was only stated that typically the addition level will not exceed a Recommended Daily Allowance for calcium (no levels given) but that in some cases may be higher, subject to conditions in the relevant directives. It is stated that calcium citrate malate levels will be controlled by the limits and recommendations set in the relevant specific directives.

1.4. Manufacturing process

The manufacturing processes have been adequately described. The salt is prepared by the reaction of calcium carbonate, calcium hydroxide or calcium oxide with citric and malic acids in aqueous solution. The reaction mixture is dried at a temperature of less than 100 °C, and the resultant solid is a metastable solid. The solid can be ground to reduce the particle size for easier tabletting or adding to foods and beverages.

1.5. Methods of analysis in food

Information on analysis in food was not provided. Analytical methods for the determination of calcium in food supplements are given by two petitioners (calcium citrate malate MW 842.75 and 1014) (Technical dossier, 2006). Quantitative determination of calcium present in tablets can be performed using standard assays described by AOAC (Technical dossier, 2005b; Technical dossier, 2006).

1.6. Reaction and fate in foods to which the source is added

Powdered calcium citrate malate samples (MW 1105.06) have been shown by one petitioner to be stable during storage for 6 months at 25 and 40 °C, under 2 and 75 % relative humidity, respectively (Technical dossier, 2005c). Stability of calcium citrate malate in food supplements is not given.
Results of a 24-month long term stability study performed with a typical multi-vitamin and multi-mineral product (film-coated tablet) showed no changes in calcium levels (Technical dossier, 2005b).

Lots of 250 mg calcium citrate malate capsules, swallowable tablets and chewable tablets were subjected to stability testing at 23 °C and 50% relative humidity for up to 27 months (Technical dossier, 2006). It was reported that the calcium content did not change significantly under these conditions. In swallowable tablets and chewable tablets stored for one year at 38°C under 80% relative humidity, 1.5% and ~8% lower calcium concentrations were reported, respectively (Technical dossier, 2006).

1.7. Exposure

According to one petitioner, the exposure to calcium citrate malate (MW 2011.79) from its use in food supplements can be estimated to be from 400 mg (approximately 100 mg of calcium, 225 mg of citrate, and 80 mg of malate) to 4200 mg (approximately 1000 mg of calcium, 2350 mg of citrate, and 840 mg of malate) per person per day (Technical dossier, 2005a). A worst case exposure scenario estimated by this petitioner, taking into consideration individuals consuming 1000 mg calcium from food supplements and a multivitamin tablet with 800 mg calcium, resulting in a total amount of calcium of 1800 mg per day, would correspond to a daily exposure of 7500 mg calcium citrate malate. This estimation would amount to a daily exposure of 4230 mg citrate ion and 1480 mg malate ion per person. It is further indicated that calcium tablets supply up to 1000 mg calcium/day, which in terms of calcium citrate malate would amount to approximately 4200 mg/day (Technical dossier, 2005a).

A second petitioner estimated the exposure to calcium citrate malate (MW 842.75) arising from food supplements on the basis of the annual product sales, apparently in Hungary (Technical dossier 2005b). In 2004 about 3,000,000 tablets were sold having an average calcium citrate malate content of 435 mg which, according to the petitioner, would correspond to 100 mg calcium/tablet. The typical dosage of the products is 1-2 tablets per day, therefore the population calcium exposure arising from food supplements can be calculated as 200 mg calcium/day (Technical dossier, 2005b). However, estimation of the proportion of food supplement consumers in the population was not taken into account.

The Panel estimated the exposure of calcium citrate malate from its only reported current use in food supplements in Europe, 100 mg calcium/tablet and a calcium content of 24%. Data from the UK Food Standards Agency survey on the consumption of food supplements indicate that 24% of adults (Henderson et al., 2002), 14% of young people (Gregory, 2000) and 17% of toddlers consumed food supplements (Gregory, 1995). The use among high consumers (97.5th percentile) ranged from 2 units per day (data do not discriminate between tablets or capsules) in young people to 7 units per day in adults, resulting in 200 – 700 mg calcium per day for high consumers, respectively. According to data supplied by one petitioner, these values would correspond to an exposure to 833 – 2917 mg of calcium citrate malate per day (14 – 49 mg/kg bw/day for a 60 kg individual), 167-583 mg of malate per day (2.8 – 9.7 mg/kg bw/day), 468-1641 mg of citrate per day (7.8 – 27 mg/kg bw/day).

Based on a potential exposure from all these sources (foods for Particular Nutritional Uses (PARNUTS), food supplements and foods intended for the general population), matching the tolerable upper intake level for calcium of 2500 mg calcium/day (SCF 2003), the equivalent exposure to citric acid would be around 1400 mg/day and the malic acid exposure would be around 500 mg/day.
1.8. Existing authorisations and evaluations

One petitioner stated, without further details, that calcium citrate malate is accepted for use in dietary supplements in Denmark (Technical dossier, 2005a).

Calcium citrate and calcium malate identified as E 333 and E 352 respectively, are authorised food additives in the European Union and both compounds may be added to foods following the quantum satis principle (EC, 1995). Furthermore, calcium salts of citric acid are allowed to be used as food supplements in the EU (EC, 2002).

The Scientific Committee on Food of the European Commission (SCF) evaluated the safety of use of calcium citrate and calcium malate as a food additive in 1990 (SCF, 1990). Calcium cations were allocated an Acceptable Daily Intake (ADI) not specified and the Committee concluded that no safety problems are likely to arise, provided the contributions from food intake do not disturb the homeostatic mechanisms controlling the electrolyte balance of the body. Citrate anions were allocated an ADI not specified, the Committee placing emphasis on the well-established role of citrate as an intermediate metabolite in the citric acid cycle and as a natural component of food. Malate anions were also allocated an ADI not specified, the Committee placing emphasis on the well-established metabolic pathway of this anion and the daily consumption of malate-containing food. The available evidence shows that D(+)-malate is metabolised without difficulty and there is no clear evidence for a need to distinguish between the enantiomers when malate is used in food.

The Scientific Panel on Food Additives, Flavourings, Processing Aids and Materials in Contact with Food (AFC) evaluated calcium malate and magnesium potassium citrate added to foods for Particular Nutritional Uses, food supplements and foods intended for the general population (EFSA, 2006a, 2006b). The AFC Panel concluded that the use of malates as sources for calcium, and magnesium potassium citrate as a source for magnesium and potassium were of no safety concern. However it was stressed that for infants and young children, only L-malates should be used.

The Joint FAO/WHO Expert Committee on Food Additives (JECFA) evaluated individually calcium citrate and calcium malate. For calcium citrate an ADI not specified was allocated together with the sodium and potassium salts of citric acid (WHO, 1974). For malic acid an ADI not limited was set for the L(+) isomer, on the basis of its well-established metabolic pathway and the daily consumption of malic acid-containing food. An ADI of 0-100 mg/kg bw was allocated for the D(-) isomer by JECFA for adults, with the limitation that neither D(-) nor DL-malic acid should be added to food for very young infants except for therapeutic purposes (FAO, 1967). Calcium DL-malate was evaluated by JECFA in 1979 and a group ADI not specified was allocated to this compound, together with malic acid and sodium and potassium malates (WHO, 1980).

In the USA, calcium citrate is an ingredient used in food with no limitation other than current good manufacturing practices and may also be used in infant formula (CFR, 2004).
2. Biological and toxicological data

2.1. Bioavailability of calcium from the source

A number of studies with animals and healthy persons (children, adolescents, adults) showed that calcium is absorbed and is bioavailable after ingestion of calcium citrate malate. Some results from these studies are summarized as follows:

Absorption of calcium from calcium citrate malate in rats and humans was compared to calcium absorption from calcium carbonate (CaCO$_3$) and milk (Smith et al., 1987). Relative calcium absorption from calcium citrate malate was measured as whole body retention of $^{47}$Ca administered by gavage in a trial test with four groups of 7 and 13 Sprague-Dawley male rats, six days after dosing. Calcium citrate malate showed higher values than calcium from milk but similar retention values when compared to CaCO$_3$. In humans, absolute calcium absorption from calcium citrate malate was estimated in four groups of 10 and 12 women, 21-30 years of age, using the double isotope technique ($^{45}$Ca and $^{47}$Ca). In the human subjects, calcium citrate malate administered either as tablet or in an orange juice beverage showed higher absorption values (8 %) than calcium from CaCO$_3$ or milk.

The effect of calcium supplementation on skeletal development in four groups of 14 C/D female rats administered for 4 or 12 weeks as calcium citrate malate, measured as cortical and trabecular$^2$ bone formation, was compared with administration of CaCO$_3$ (Kochanowski, 1990). Animals fed calcium citrate malate showed significantly more trabecular bone formation after 4 weeks (44 to 47% more) and 12 weeks of treatment (23-25% more) than rats fed CaCO$_3$. Similarly, longitudinal bone growth was significantly increased after 4 weeks of treatment with calcium citrate malate compared to that in rats fed CaCO$_3$, but remain unchanged after 12 weeks of treatment. Neither treatment affected cortical bone formation in rats. Based on these results, calcium from calcium citrate malate is more bioavailable than calcium from calcium carbonate.

Calcium bioavailability was measured as whole body $^{47}$Ca retention in groups of 5-6 male Sprague-Dawley rats at ages of 8, 16, 20 and 32 weeks gavaged with intrinsically labelled $^{47}$Ca calcium citrate malate, calcium carbonate or hydroxyapatite (Ca$_{10}$[PO$_4$]$_6$[OH]$_2$) (Andon et al., 1993). After five days of treatment, the percentage of whole body $^{47}$Ca retention was higher in animals administered calcium citrate malate than in animals administered CaCO$_3$ or hydroxyapatite. Overall $^{47}$Ca retention from all three sources decreased with the animal age.

Comparison of femur calcium uptake from calcium fumarate, calcium malate fumarate, calcium citrate malate and calcium carbonate, intrinsically labelled with $^{48}$Ca, administered by gavage to 6 groups of 15 Sprague-Dawley male rats, showed no statically significant differences (P> 0.05) among tested calcium salts 48 hours after treatment (Weaver et al., 2002). Calcium absorption from all sources was estimated to be about 30%.

Comparison of calcium absorption in young growing chickens (calculated by using the slope-ratio methodology) receiving 0.50, 0.55, 0.60, 0.65 or 0.70 % calcium from calcium citrate malate and a commercial-grade limestone (largely composed of CaCO$_3$) for up to 18 days, showed that calcium bioavailability was equivalent between these two sources (Henry and Pesti, 2002). Calcium citrate malate administration was however, associated with an increase in body weight gain and feed efficacy in chickens as well as with a tendency to lower the

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$^2$ spongy, osseous tissue that fills inner cavity of long bones
incidence of tibial dyschondroplasia in male chickens, a major skeletal problem associated with calcium and phosphorus deficiency and imbalance.

Calcium absorption from calcium citrate malate and calcium carbonate as tablets was measured in a two-period crossover study with 12 healthy adolescents (6 boys, 6 girls), ages 10-17 years, given 114.6 mg of elemental calcium enriched with 10.4 mg $^{44}$Ca as both salts (Miller et al., 1988). Thirty minutes after ingestion, subjects received 3.6 mg $^{42}$Ca intravenously. Calcium absorption was calculated from the ratio of the tracer isotopes in 24-hr urine samples compared to the dose before tracer administration. Results showed that calcium absorption from calcium citrate malate was significantly higher in these adolescents ($p< 0.03$) compared to calcium absorption from CaCO$_3$. The average absorption from CaCO$_3$ was approximately 27% (13 to 40%), whereas that from calcium citrate malate was approximately 36% (27 to 53%). The average difference in absorption was approximately 10% between these two sources of calcium.

Calcium absorption from calcium citrate malate given as chewable tablets enriched with $^{44}$Ca (14% of total calcium) and from CaCO$_3$ given as powder containing $^{42}$Ca (93.77%), were measured with the double-radioisotope technique in 6 healthy children 11–17 years old (Miller et al., 1989). Results confirmed previous results (Miller et al., 1988) suggesting that calcium absorption from calcium citrate malate was significantly higher in these children ($P= 0.094$) compared to calcium absorption from CaCO$_3$. Comparison of these results with those from an early study by the same authors, using calcium citrate malate in a swallowable form, suggest that both calcium citrate malate forms give equivalent absorption values. The average absorption from CaCO$_3$ was approximately 27% (19 to 40%), whereas that from calcium citrate malate in chewable form was approximately 42% (28 to 51%). The average difference in absorption was approximately 15% between these two sources of calcium.

In a two-year double-blind, placebo-controlled, randomised trial to determine the effect of calcium on bone loss in 301 healthy postmenopausal women, 40 - 70 year of age, receiving either calcium carbonate or calcium citrate malate (500 mg of calcium per day), calcium citrate malate supplementation was more effective in preventing bone losses than supplementation with calcium carbonate (Dawson-Hughes et al., 1990). After two years of treatment, Bone-Mineral areal Density (BMD) measurements showed that women who took calcium citrate malate had higher femoral neck and radius bone-mineral densities and a slower loss of spine bone-mineral density than those taking CaCO$_3$ or the placebo group. Some of these results were already noticeable after one year of administration in this group. In women who had undergone earlier menopause, five or less years early, the two sources of calcium supplementation did not show marked effects on BMD and spine bone-mineral losses.

A three year, double-blind, placebo controlled trial studied calcium and vitamin D supplementation on BMD, bone metabolism and incidence of nonvertebral fractures in 176 men and 213 women, 65 years of age or older (Dawson-Hugues et al., 1997). Subjects were randomly assigned to two cohorts, either a group given 500 mg calcium/day as calcium citrate malate plus 700 IU of vitamin D$_3$ as pills or a placebo group. BMD analysis of the hip, spine and total body as well as biochemical assays and other measurements were done every 6 months. Calcium citrate malate and vitamin D supplementation moderately reduced total-bone loss in men and women already after 1 year of treatment, lasting until the end of the study. According to the authors, after three years supplementation, biochemical parameters indicated that calcium supplementation led to a reduction in the rate of bone modelling (turnover) which could explain the observed reduction in the incidence of nonvertebral fractures in the calcium citrate malate and vitamin D supplementation group. However, the authors pointed out that these results should be interpreted with caution because of the small number of study subjects.
Calcium citrate malate as source for calcium

Calcium availability from calcium citrate malate, skim milk and a calcium carbonate supplement in 12 subjects (9 women and 3 men, mean ages 70 and 76 years, respectively) consuming a low-calcium complex (300 mg/day) or a high-calcium diet (1300 mg/day) for three one-week periods each, during a 6-week crossover study, did not differ between the tested sources when measured as a suppression of serum parathyroid hormone (PTH) (Martini and Wood, 2002). A complex meal was used in this study (wheat bread, jelly, butter, eggs, mushrooms, green peppers, soybean oil, seasoning and beverage) (Wood and Martini, 2003).

Calcium bioavailability from calcium citrate malate was compared to the bioavailability from a mixture of tricalcium phosphate and calcium lactate (tricalcium phosphate/calcium lactate) administered in orange juice to provide 500 mg calcium, in a randomised crossover-within-subject study in 25 healthy premenopausal women, 21-45 years of age (Heaney et al., 2005). Calcium bioavailability was derived from the area under the curve (AUC) of serum calcium levels measured after 1, 2, 4, 6, 8, and 9 hours of administration, although only the increment above the baseline value was used rather than total serum calcium values to calculated AUC, on the basis that it would better reflect calcium absorption. Mean serum values of 25OH vitamin D were similar amongst groups and laboratory reference ranges and no significant correlation was found between baseline vitamin D value and AUC. Results showed that at any time-point measured serum calcium was significantly (P<0.001) higher in the calcium citrate malate group than in the tricalcium phosphate/calcium lactate group, indicating according to the authors that the calcium citrate malate source was 48% more absorbable.

A four year randomised, placebo-controlled, double-blind trial evaluated the effect of calcium tablets or 25-hydroxy vitamin D capsules supplementation on bone mass and structure at the hip and on bone turnover (Peacock et al., 2000). Three cohorts were studied, 316 women (mean age 73.7 years) and 122 men (mean age 75.9 years) randomly assigned to receive either 750 mg calcium/day as calcium citrate malate, 15 µg 25OH vitamin D3/day, or placebo. BMD of the hip, spine and total body were measured every 6 months and radiographs of the lower pelvis/upper femurs were examined every 12 months. Blood and urine biochemistry was also measured at each visit. Results showed that the calcium citrate malate supplementation group showed reduced bone loss, reduced secondary hyperthyroidism and reduced bone turnover compared with that of the other two groups. In subjects with calcium exposures less than the median in the study (716 mg/day), a positive relationship was found between serum 25-OH vitamin D3 and changes in total hip BMD. This was not found in subjects with higher than the median calcium exposures. The authors concluded that calcium citrate malate supplementation prevents loss of BMD, reduces medullary expansion, secondary hyperparathyroidism, and bone turnover. Supplementation with 25OH vitamin D3 was related to a beneficial effect in reversing calcium insufficiency, although effects were only noticed at low calcium exposures.

A seven-year study evaluated the efficacy of calcium supplementation on BMD of the hip and spine and on bone geometry and mineral areal density of the forearm in adolescent girls aged ~11 years at start (Matkovic et al., 2004). Three cohorts were studied: 79 girls supplemented with pills containing calcium citrate malate and 100 girls supplemented with placebo pills participated in a double-blind placebo-controlled trial. Eighty-five girls consuming higher amounts of dietary calcium from dairy products participated in an observational study. BMD of the hip and spine were measured during the last 3 years whereas forearm bone mineral areal density was measured at the end of the study. Total body, forearm bone mineral areal density and metacarpal radiogrammetry were measured over the 7-year period. According to reported compliance, the calcium citrate malate supplemented cohort had an average calcium intake of 1586 mg/day, the placebo group 785 mg/day and the high dairy group 1213 mg/day. Results showed that the high dairy group girls remained significantly taller and showed higher BMD of
the spine than the supplemented and placebo groups. BMD of the anterior posterior spine increased in all three groups. High dairy calcium group had higher bone mineral density of the spine. Calcium citrate malate supplemented group had significantly higher BMD of the femur trochanter (p = 0.0024). BMD of the hip was similar amongst high dairy and the supplemented groups. The authors concluded that calcium effects on bone mass acquisition are relatively weak.

### 2.2. Metabolic fate of the source and biological distribution

The known metabolic fate of calcium is described by petitioners but no details were provided on the metabolic fate of the calcium citrate malate substance. Malate and citrate are expected to be dissociated from calcium in the gastrointestinal tract. It is assumed in this opinion that citrates and malates are available for absorption as calcium citrate and calcium malate salts in the intestinal tract.

Citric acid and D(+) malate are metabolised without difficulty as intermediates in the tricarboxylic acid cycle (WHO, 1974). For malates there is no clear evidence for a need to distinguish between the enantiomers when malate is used in food (SCF, 1990).

### 2.3. Toxicity data

Unpublished results from short term and subchronic toxicity studies in two animal species, rats and dogs, carried out with calcium citrate malate and calcium carbonate, were summarized by one petitioner (Technical dossier, 2006). It is stated that the studies were conducted in compliance with US Good Laboratory Practices.

#### Rats:

A 28-day feeding study conducted in Sprague-Dawley rats compared the effects of calcium carbonate to calcium citrate malate (Technical dossier, 2006). One hundred (50 male and 50 female) rats divided into 5 treatment groups were fed a semi-purified diet. Three groups were fed calcium sources to deliver 0.5% calcium in the diet (equivalent to ~250 mg calcium/kg bw/day): a calcium carbonate group (group 1), a calcium carbonate plus citric and malic acids group (group 2) receiving the same levels the individual acids as group 3, and a calcium citrate malate group (group 3). Two more groups were fed calcium sources to deliver 1.0% calcium in the diet (equivalent to ~500 mg/kg bw/day): a calcium carbonate plus calcium citrate malate group (group 4) and a calcium carbonate group (group 5). The treatment protocol is summarised in the following table.

<table>
<thead>
<tr>
<th>Calcium content in the diet</th>
<th>Group 1</th>
<th>Group 2</th>
<th>Group 3</th>
<th>Group 4</th>
<th>Group 5</th>
</tr>
</thead>
<tbody>
<tr>
<td>0.5 %</td>
<td>Calcium carbonate</td>
<td>Calcium carbonate + citric and malic acids</td>
<td>Calcium citrate malate</td>
<td>Calcium carbonate + calcium citrate malate</td>
<td>Calcium carbonate</td>
</tr>
<tr>
<td>1.0%</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Table 1. Protocol treatments in the rat and dog toxicity studies with calcium citrate malate
Parameters evaluated included body weight and food consumption, in-life and gross necropsy observations, clinical chemistry, haematology, and urinalysis, kidney calcium content, selected organ weights, and histology of kidney, stomach, and aorta.

Daily and weekly observations revealed no treatment-related effects. Abnormal conditions such as oily coat and scabbing occurred sporadically and randomly across groups, and were not considered to be treatment-related.

No statistically significant differences in food consumption, weekly body weight, or body weight change were reported in rats of either sex supplemented with calcium citrate malate as compared to the other groups. No statistically significant differences in mean corpuscular volume, haemoglobin, white blood cells or serum chemistry were reported.

Male rats supplemented with calcium citrate malate were reported to have significantly higher 24-hour excretion of calcium compared to male rats supplemented with low calcium carbonate (group 1). The same results were found in animals supplemented with calcium carbonate plus citric and malic acids (group 2). The reason for the increased total calcium excretion is not known but a similar effect was not observed in females, nor was a parallel trend evident in the kidney calcium values of males.

There were scattered statistically significant differences in absolute and relative (to body weight) organ weights in group 3 and 4 rats when compared to their respective groups 1 and 5, however, none of these were considered biologically significant.

The histopathological evaluation of kidneys revealed nephrocalcinosis in all females at an incidence of 80-90% in males of groups 4 and 5 (fed ~500 mg/kg bw/day) and 10 – 30% in males of groups 1, 2 and 3 (fed ~250 mg/kg bw/day). All females in all groups were affected, with predominantly grade 3 and 4 lesions (on a scale of 1 – 5). Among males, incidence and severity were greater in groups 4 and 5 compared to groups 1 and 3. The lesion was characterized by mineralised tubular casts in the outer stripe of the medulla. The serum chemistry changes, increased kidney weights, and kidney calcium levels were correlated with the microscopic diagnosis.

It is reported that the microscopic examination of stomachs and aortas, common sites of metastatic calcification, showed no evidence of either a treatment-related effect or calcium deposition in any group.

There were no statistically significant differences in levels of calcium in the kidney in animals supplemented with calcium citrate malate of either sex when compared to animals supplemented with calcium carbonate (group 1).

A 91-day feeding study was conducted in Sprague-Dawley rats to compare the effects of calcium carbonate and calcium citrate malate. Two hundred (100 male and 100 female) rats were fed a semi-purified diet and divided into the same treatment groups as in the previous study.

Parameters evaluated included body weight and food consumption, in-life and gross necropsy observations, clinical chemistry, haematology, and urinalysis, kidney calcium content; spleen and liver iron content, fat-free dry weight, ash, and magnesium and phosphorus content of the left femur; selected organ weights, and histology of kidneys, thyroid glands, parathyroid glands, and left tibia. As an investigational part of the study, non-decalcified bone histology of the right tibia was performed on samples from selected group 1 and 3 animals, and 24-hour faecal samples were collected from one hundred animals for calcium content analysis.
It was reported by the petitioner that the calcium concentration of the diets in groups 2 to 4 were somewhat lower than the targeted levels but this was not considered to affect the interpretation of the results, or to lessen the impact of the study. The reason for the difference was attributed to lower than expected calcium content of the prepared test material and to hydration of the diets during shipment and storage.

During the study, daily and weekly observations revealed most animals to be healthy and normal. Abnormal conditions such as oily coat and scabbing occurred sporadically and randomly across groups, and as before were not considered to be attributable to the administration of test substances.

Problems with incisors (such as malalignment, large gaps, chipped teeth, and tooth loss) were reported in 7 males and 3 females from groups supplemented with calcium citrate malate or with calcium carbonate plus citric and malic acids. The petitioner considered these effects not related to citrate or malate exposure since dental abnormalities, particularly malocclusion and tooth overgrowth, occur spontaneously in rodents but a potential link could not be ruled out completely in this study.

No statistically significant difference in weekly consumption, body weight, body weight change, and feed efficiency was reported in rats supplemented with calcium citrate malate (group 3) as compared to the low calcium carbonate group (group 1). Statistically significant changes were also not reported in rats supplemented with calcium carbonate plus calcium citrate malate (group 4) and high calcium carbonate (group 5). Male and female rats in group 4 and female rats in group 5 showed differences in feed consumption compared to group 1 animals. These were attributed to differences in utilisation efficiency of the diets since increased feed consumption was not associated with an increase in body weight. According to the petitioner, the diets of groups 4 and 5 were somewhat different to group 1 in that they contained, instead of sucrose, high-fructose corn syrup solids and increased amounts of KHPO₄, resulting in a diet with slightly lower caloric density. Lower body weights in male rats fed calcium carbonate plus citric and malic acids (group 2) compared to group 1 rats were also reported, but these were attributed to palatability problems arising from free citric and malic acids in their diet.

Statistically significant higher red blood cell counts, haemoglobin and haematocrit levels and average absolute lymphocytes were reported in female rats supplemented with calcium citrate malate compared to the low calcium carbonate (group 1). However, according to the petitioner these increases were primarily the result of the group 1 values being lower than those for all other groups. Male rats supplemented with calcium carbonate plus calcium citrate malate (group 4) had a decreased red blood cell count and mean corpuscular haemoglobin concentrations, and an increased mean corpuscular volume when compared to rats supplemented with high calcium carbonate (group 5). No statistical differences were reported to occur within females. The differences noted in haematology parameters of group 4 males relative to group 5 were attributed by the petitioner primarily to group 5 having a slightly decreased mean corpuscular volume with a compensatory increase in red cell numbers.

In females, rats supplemented with calcium carbonate plus calcium citrate malate (group 4) had decreased total protein, globulin, calcium and phosphorus levels and an increased albumin/globulin ratio as compared to those in group 5. According to the petitioner these differences were not seen neither in males nor in rats supplemented with calcium citrate malate (group 3) and therefore were not considered treatment related. No significant differences were reported for either sex in urinalysis parameters of all groups.
No significant differences in the body and organ weight data were reported to occur in either sex of rats supplemented with calcium citrate malate. The average absolute brain weight of male rats supplemented with calcium carbonate plus calcium citrate malate was statistically lower than that of male rats in group 5. Female rats in the same group had statistically lower absolute liver weights relative to the group 5 females. Females had higher levels of iron in their livers and spleens than males for any given group. No significant difference in these parameters was seen in either sex of rats supplemented with calcium citrate malate.

In male rats supplemented with calcium carbonate plus calcium citrate malate (group 4) spleen and liver iron contents were reported to be statistically higher than those in high calcium carbonate group (group 5), whereas in females only liver iron content was statistically higher. According to the petitioner, this was due to the presence of lower iron levels in group 5 relative to the group 4. In animals supplemented with calcium citrate malate or calcium carbonate plus citric and malic, the iron content of both liver and spleen of males and females was reported to be generally higher, although not statistically significant, compared to the low calcium carbonate group. According to the petitioner, this suggests that the inhibitory effect of calcium on iron absorption was decreased in the presence of citric and malic acid or their calcium salts.

Ash content of femurs in male and female rats supplemented with calcium citrate malate and calcium carbonate plus calcium citrate malate (group 4) was reported to be statistically significant higher for males compared to high calcium carbonate males. Calcium, magnesium and phosphorus content of bones in male rats supplemented with calcium citrate malate or calcium carbonate plus calcium citrate malate were reported to be statistically higher. In female rats supplemented with calcium carbonate plus calcium citrate malate phosphorus content of femurs was significantly higher. The biological significance of the decreased ash weights of femurs in animals supplemented with calcium citrate malate was questioned by the petitioner, based on the fact that the increased calcium, magnesium and phosphorus contents were only significant in males.

As reported previously for the 28-day study, in this 91-day study nephrocalcinosis was observed in all groups for both sexes. In males, this condition was less severe in groups 1, 2, and 3 (fed ~250 mg/kg bw/day) compared to groups 4 and 5 (fed ~500 mg/kg bw/day). The incidence of tubular casts in males was 15% for group 1, 40% for groups 2 and 3, 85% for group 4 and 50% for group 5. Although the relative incidence was greater in males treated with calcium citrate malate, it was reported that the severity was similar in rats receiving calcium carbonate, with a mean severity grade ranging from 1.3 to 2.3 (on a scale of 1 to 5). Nephrocalcinosis was observed in all females except one animal in group 3 and was more severe than that of the males in the corresponding treatment groups. It was reported that the mean severity for females ranged from 3.2 to 4.0. The high background incidence of nephrocalcinosis (95 – 100%) was reported to limit conclusions regarding the comparative effect between calcium citrate malate and calcium carbonate in females. However, according to the petitioner, the higher incidence of nephrocalcinosis in the males in groups 3 and 4 suggests an effect related to the consumption of calcium citrate malate at these doses.

The incidence of nephrocalcinosis in both sexes was not correlated with the group mean calcium levels; however individual animals with nephrocalcinosis generally had higher kidney calcium levels within each group.

Females had much higher levels of calcium in their kidneys than males for any given group. Females supplemented with high calcium diets (groups 4 and 5) showed higher kidney calcium levels than those supplemented with low calcium diets (groups 1 to 3). No statistically
significant differences were related to rats supplemented with calcium citrate malate or its salts in either sex.

**Dogs:**
A 91-day feeding study was conducted in Beagle dogs to compare the effects of calcium carbonate and calcium citrate malate. Forty dogs (20 male and 20 female) divided into 5 treatment groups were fed a semi-purified diet as in the rat studies. Calcium sources were adjusted to deliver 1.0% and 2.0% calcium in the diet (equivalent to ~250 and 500 mg calcium/kg bw/day, respectively).

Parameters evaluated included body weight and food consumption, in-life and gross necropsy observations, clinical chemistry, haematology, urinalysis, and faecal analysis, selected organ weights; iron content of liver and spleen, calcium content of kidneys, histology of kidneys, thyroid gland, and right tibia, left femur for length and width, fat-free dry weight, ash, calcium, magnesium and phosphorus.

Diet analyses revealed that the calcium concentration of the diets was lower than the targeted levels of ~1.0% for groups 1 to 3 and ~2.0% for groups 4 and 5. The reason for the difference was attributed to lower than theoretical calcium content of the prepared test material (which was reported to remain inadvertently uncorrected until week 9) and to hydration of the calcium citrate malate during shipment and storage. As well, iron content in the diet was reported to be ~1500 mg/kg, while the expected level was 3000 mg/kg.

Poor general health status was noticed in the group 1 males and females throughout the entire study. Both males and females in this group experienced vomiting and/or diarrhoea sporadically throughout the study. The reason for this could not be explained by the petitioner, but was attributed to lack of acclimation of animals to the diet. For this reason, results summarised by the petitioner on group 1 animals were not included in this opinion. One male from group 2 became moribund during the study and was sacrificed on day 45. Upon necropsy it was reported that the animal had pneumonia and haematological analysis showed it to be anaemic.

No statistically significant differences in body weight or food consumption (and in the associated calculations of body weight gain and feed efficiency) were reported in dogs supplemented with calcium citrate malate or its salts.

It was reported that all animals had iron deficiency anaemia characterized by depressed biochemical parameters (protein, globulin, A/G ratio, ALAT, sodium, potassium, calcium, bilirubin, phosphorus, cholesterol and triglycerides), microcytic and hypochromic red cells, increased platelet counts, and low serum iron with elevated total iron binding capacity (TIBC) at the end of the study as compared to baseline at the beginning of the study. The most severely affected groups were those receiving calcium carbonate alone (group 5). These findings were attributed by the petitioner to secondary effects of the semi-purified diet having slightly lower than expected iron content and/or to the fact that most of the haematological parameters measured at baseline were low when compared to published values for the normal range. No statistically significant changes were reported for the mean iron content of the liver or for the mean kidney calcium content. In females, total calcium levels were statistically significantly

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3 assuming a dry chow diet.
higher in group 4 compared to group 5, whereas no differences were reported to be seen in males.

No significant difference in urine parameters was reported amongst groups 2 to 5.

Group 4 males had a significantly higher dry weight and magnesium femur content than group 5 males. The remaining differences in percent ash and calcium among females, and in percent magnesium in males were, for the most part, isolated, and were considered to have no biological significance.

Contrary to findings in the rat studies, it was reported that there were no apparent treatment-related histopathological lesions (e.g. kidney) and that any pathology seen was either of low incidence or present across all groups equally.

A decreased relative liver weight in group 4 females when compared to group 5 was reported. Gross observations at necropsy revealed no abnormalities, however the study pathologist concluded that the decreased relative weight could be treatment-related but its biological significance was questionable. No corresponding significant differences in the absolute liver weights of group 4 females compared to their control group (group 5) were reported and no significant differences in absolute liver weights were seen among the males, nor were any statistically significant differences in the relevant serum chemistry parameters reported.

Lower relative kidney weights in females of all groups and lower relative brain, kidney, liver and testes weights in males of groups 3 to 5 or 2 to 5 were reported. Organ to body weight ratio changes in these groups were not accompanied by differences in absolute weights.

**Human studies:**

A number of published long-term human studies on bone metabolism, although not specifically designed to evaluate toxicological end-points, suggest that calcium citrate malate supplementation is well tolerated.

Some of these studies were carried out on up to 148 volunteers (Dawson-Hugues et al., 1997), for supplementation periods lasting up to seven-years (Matkovic et al., 2004), at doses of calcium citrate malate providing up to 500 mg calcium per day (equivalent to 2083 mg calcium citrate malate/day4 or 35 mg/kg bw/day for a 60-kg individual) (Dawson-Hugues et al., 2002; Lloyd et al., 1993). No adverse effect due to calcium citrate malate exposure was reported in these studies. One case of kidney stone, one case of development of parathyroidism, two cases of hypercalcaemia (one in the placebo group) and some cases of epigastric distress and constipation were reported (Peacock et al., 2000; Dawson-Hugues et al., 1997).

In an open crossover 11 weeks study in idiopathic hypercalciuric individuals (non-stone forming), consumption of calcium citrate malate providing 600 mg calcium/day (~ 2500 mg calcium citrate malate/day4) did not alter significantly urinary chemistry nor significantly modify crystallization profiles (Coe et al., 1992). Calcium citrate malate supplementation increased significantly pH, citrate and calcium carbonate concentrations in urine of both sexes. However, the first two changes were related rather to a protective effect against oxalate stone formation whereas for the latter, similar results were found in individuals consuming another source of calcium (milk).

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4 assuming a content of 24 % calcium on dry weight basis
Calcium citrate malate as source for calcium

In an unpublished, 28-day, single-blind placebo-controlled parallel study carried-out in 59 post-menopausal women, consumption of calcium citrate malate providing 1000 mg calcium/day (~4160 mg calcium citrate malate/day) was reported as not causing hypercalcaemia or hypercalcuria nor did it appear to interfere with body iron status (Technical dossier, 2006). Parameters measured in this study were serum calcium, ionised calcium, serum and urinary creatinine, urinary calcium, serum iron, TIBC, bilirubin, haematocrit, ferritin and haemoglobin.

In a double-blind, placebo controlled 3 years supplementation trial with 500 mg calcium (equivalent to 2083 mg calcium citrate malate) and 700 IU of vitamin D per day on 145 subjects, followed by 2 years without supplementation, calcium and vitamin D supplementation was reported to have a beneficial effect on tooth retention (Krall et al., 2001).

3. Discussion

Overall, results from human and animal studies show that calcium from calcium citrate malate is slightly more bioavailable (8–15%) than calcium from some other calcium sources mentioned in this opinion. However, this will not affect its safety of use since human studies using calcium citrate malate have been taken into account for the derivation of the tolerable upper intake level of calcium by the SCF (2003).

The metabolism of citric acid and L(+) malic acid are well understood and it has been considered previously that their role in the citric acid cycle does not give rise to any concern (EFSA, 2006a; OECD SIDS, 2001). Citrates occur in many foods and are normal metabolites in the body and are therefore considered as of no safety concern (EFSA, 2006b). An exposure to citric acid from foods for Particular Nutritional Uses (PARNUTS), food supplements and foods intended for the general population, as magnesium potassium citrate, adding up to around 600 mg citric acid was considered of no safety concern (EFSA, 2006b).

Toxicity studies in rats with calcium citrate malate at dietary concentrations providing 0.5% and 1.0 % calcium in the diet (equivalent to about 250 and 500 mg calcium/kg bw/day) reported nephrocalcinosis in animals of both sexes. These dietary doses would correspond to approximately 1040 mg calcium citrate malate/kg bw/day, assuming a content of 24% calcium on dry weight basis. The Panel considered however that the nephrocalcinosis finding in rats is not relevant for human safety assessment because the rat is a species known to be particularly sensitive to mineralisation of the renal tubule epithelium due to dietary alteration of the calcium and phosphorus homeostasis (Ritskes-Hoitinga et al., 1989, 1991, 1992). Females are more sensitive than males to this effect, partially due to an oestrogen-induced renal mineralization (Latendresse et al., 2001). Nephrocalcinosis in rats can be observed early during experimentation, already after 2 weeks under a diet-induced calcium: phosphorus imbalance (Cockell and Belonje, 2004).

Results from a 91-day toxicity study in Beagle dogs fed calcium citrate malate at doses to achieve equivalent calcium levels in the diet as in the rats studies (~ 250 and 500 mg calcium/kg bw/day) did not report any signs of nephrocalcinosis. Furthermore, long-term human calcium citrate malate supplementation studies, providing calcium doses up to 500 mg calcium/day, did not report induction of nephrocalcinosis or other adverse effects attributed to this supplementation.

Long-term human supplementation trials, although not specifically designed to evaluate toxicological end-points, suggest that calcium citrate malate supplementation is well tolerated.
Based on a hypothetical calcium exposure, arising from calcium citrate malate jointly from all sources concerned by this opinion (PARNUTS, food supplements and foods intended for the general population), at the tolerable upper intake level for calcium of 2500 mg calcium/day, the equivalent exposures of malic acid and citric acid, would be around 500 mg/day and 1400 mg/day, respectively. Malates and citrates used as food additives have been previously evaluated. The natural occurrence of malic acid in fruits (1990 mg/100g) and the reported daily consumption of malic acid from vegetables, fruits and their juices (1500 to 3000 mg/day) (FAO, 1967), indicate that malate exposure from calcium citrate malate at the levels mentioned in this opinion would be of no safety concern.

CONCLUSIONS

The available data provide information to conclude that calcium is bioavailable from calcium citrate malate.

The exposure to citrate and malate resulting from the use of calcium citrate malate as source of calcium intended for use in foods for Particular Nutritional Uses (PARNUTS), food supplements and foods intended for the general population is of no safety concern, at the maximum levels estimated in this opinion.

The present opinion deals only with the safety and bioavailability of calcium citrate malate as a source of calcium intended for use in foods for Particular Nutritional Uses (PARNUTS), food supplements and foods intended for the general population. The safety of calcium itself, in terms of amounts that may be consumed, is outside the remit of this Panel.

The Panel notes that there are different proposals for the specifications for fluoride from the different petitioners and recommends that the lowest figure is retained in the European specifications.
Calcium citrate malate as source for calcium

DOCUMENTATION PROVIDED TO EFSA


REFERENCES


EFSA, 2006a. Opinion of the Scientific Panel on Food Additives, Flavourings, Processing Aids and Materials in Contact with Food related to Calcium, Magnesium and Zinc Malate added for nutritional purposes to food supplements as sources for Calcium, Magnesium and Zinc and to Calcium Malate added for nutritional purposes to foods for Particular Nutritional Uses and foods intended for the general population as source for Calcium. The EFSA Journal 391a, b, c, d, 1-6.


Calcium citrate malate as source for calcium


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## Glossary / Abbreviations

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<tr>
<th>Abbreviation</th>
<th>Definition</th>
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<tr>
<td>ADI</td>
<td>Acceptable Daily Intake</td>
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<tr>
<td>AFC</td>
<td>Scientific Panel on Food Additive, Flavourings, Processing Aids and Materials in Contact with Food</td>
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<td>A/G ratio</td>
<td>Albumin/globulin ratio</td>
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<td>ALAT</td>
<td>Alanine Aminotransferase</td>
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<td>AOAC</td>
<td>Association of Official Analytical Chemists</td>
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<td>BMD</td>
<td>Bone Mineral Density</td>
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<td>CAS</td>
<td>Chemical Abstract Service</td>
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<td>JECFA</td>
<td>Joint FAO/WHO Expert Committee on Food Additives</td>
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<td>PARNUTS</td>
<td>Foods for Particular Nutritional Uses</td>
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<td>PTH</td>
<td>Parathyroid hormone</td>
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<tr>
<td>SCF</td>
<td>Scientific Committee for Food</td>
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<tr>
<td>TIBC</td>
<td>Total Iron Binding Capacity</td>
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<td>WHO</td>
<td>World Health Organisation</td>
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