Effects of dietary potassium citrate supplementation on urine pH and urinary relative supersaturation of calcium oxalate and struvite in healthy dogs

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Objective—To assess the effect of dietary potassium citrate supplementation on the urinary pH, relative supersaturation of calcium oxalate and struvite (defined as the activity product/solubility product of the substance), and concentrations of magnesium, ammonium, phosphate, citrate, calcium, and oxalate in dogs.

Animals—12 healthy adult dogs.

Procedure—Canned dog food was fed to dogs for 37 days. Dogs were randomly allocated to 3 groups and fed test diets for a period of 8 days. Study periods were separated by 6-day intervals. During each study period the dogs were fed either standard diet solus (control) or standard diet plus 1 of 2 types of potassium citrate supplements (150 mg potassium citrate/kg of body weight/d) twice daily. Urinary pH, volume and specific gravity, relative supersaturation of calcium oxalate and struvite, and concentrations of magnesium, ammonium, phosphate, calcium, oxalate, and citrate were assessed for each treatment.

Results—Mean urine pH was not significantly affected by dietary potassium citrate supplementation, although urine pH did increase by 0.2 pH units with supplementation. Diets containing potassium citrate maintained a higher urine pH for a longer part of the day than control diet. Three Miniature Schnauzers had a significantly lower urinary relative calcium oxalate supersaturation when fed a diet supplemented with potassium citrate, compared with control diet.

Conclusions and Clinical Relevance—Dietary potassium citrate supplementation has limited effects on urinary variables in most healthy dogs, although supplementation results in maintenance of a higher urine pH later in the day. Consequently, if supplementation is introduced, dogs should be fed twice daily and potassium citrate should be given with both meals or with the evening meal only. (Am J Vet Res 2000;61:430–435)

Currently, a recognized treatment for the medical dissolution of calcium oxalate uroliths in situ does not exist. However, dietary potassium citrate supplementation ($K_3C_6H_5O_7 \bullet H_20$) has been used for the past decade in humans to help prevent recurrence of calcium oxalate stones in the kidney.[1] The beneficial effects are thought to be caused primarily by the alkalinizing properties of citrate, although they may be partially attributable to concurrent advice for the patient to increase fluid intake.[1]

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In humans, oral intake of potassium citrate does not directly affect the amount of citrate excreted in the urine, because most citrate that is absorbed from the gastrointestinal tract is metabolized to bicarbonate.[2] This creates an alkaline tide and a resultant increase in urinary excretion of citrate caused by an increase in production of citrate within the mitochondria of renal cells[1] or a decrease in tubular reabsorption of citrate in the proximal tubular cells.[3] Metabolic alkalosis results in an increase in urine pH and an increase in reabsorption of calcium in the distal tubule.[3] As much as 60% of filtered citrate may also appear in human urine during alkalosis.[4] Together, these factors help to decrease urinary calcium oxalate crystallization in humans in a number of ways. Total urinary calcium excretion decreases and the availability of ionized calcium decreases further in alkalized urine by an increase in the amount and strength of binding to form soluble citrate and phosphate salts.[1,3] Certain inhibitors of the growth and precipitation of calcium oxalate crystals found in the urine of humans, such as citrate and pyrophosphate, are also activated with an increase in urine pH.[1] Indirectly, the amount of citrate excreted in the urine may also increase.[4] The cumulative effect is one of a decrease in urinary calcium oxalate supersaturation.[3] Thus, the overall beneficial effect of dietary potassium citrate supplementation is far more complex and controversial than a simple increase in urinary excretion of citrate.

Dietary potassium citrate supplementation as a wax matrix tablet, launched in the United States in 1996, is commonly prescribed in humans with recurrent calcium oxalate stone formation. The manufacturers claim that this form of potassium citrate will inhibit stone formation rate in > 90% of human patients by decreasing urinary saturation of calcium oxalate and inhibiting crystallization. The wax matrix also permits delayed absorption and excretion of citrate throughout the day.[5]

Dietary potassium citrate supplementation has also been advocated in the prevention of recurrence of calcium oxalate uroliths in dogs.[5-8] Potassium citrate has been permitted as a food preservative for all species, including dogs, since 1991 and has been authorized for use as a urinary modifying substance in pet food since 1994 in Europe.[9,a] In the United States, potassium citrate is listed as an acceptable mineral supplement in the *American Association of Feed Control Officials Handbook*, although no similar directives exist. Inclusion amounts of 0.2 to 0.5% in canned food and 1 to 2% in dry food have been recommended for

modifying urine pH.[9] This amount of potassium citrate corresponds to approximately 150 mg/kg/d and, in dogs, has been reported to cause an increase in urine pH, although no consistent increase in citrate excretion was found.[6-8] On the basis of this information, potassium citrate has been included in a commercially available diet designed to help prevent recurrence of calcium oxalate uroliths in dogs.[7]

Nevertheless, evidence to support the inclusion of potassium citrate in such diets is inconclusive. To our knowledge, the effect of dietary potassium citrate supplementation on urinary calcium oxalate supersaturation in dogs has not been established. Furthermore, dietary use of potassium citrate in the form of wax matrix tablets has not been studied in dogs, although recommendations for their use do exist in the literature.[5,6]

The purposes of the study reported here were to assess the effects of dietary potassium citrate supplementation on the urine pH, urinary **relative supersaturation (RSS)** of calcium oxalate and struvite (defined as the activity product/solubility product of each substance [values are calculated relative to the equilibrium saturation value]), and urinary concentrations of magnesium, ammonium, phosphate, citrate, calcium, and oxalate in healthy adult dogs.

Materials and Methods

Dogs—Twelve healthy adult dogs consisting of 6 Miniature Schnauzers, (1 sexually intact male, 2 castrated males, and 3 sexually intact females; mean age 5.5 ± 1.3 years), 4 Beagles, (3 spayed females and 1 sexually intact female; mean age 4.5 ± 0.6 years), 2 Labrador Retrievers, (sexually intact females; mean age 4.9 ± 2.3 years) were fed a commercially prepared canned dog food[b] (**Appendix 1**) twice daily at 8:30 AM and 3:30 PM for 37 days. Food allowances were calculated according to adult maintenance energy requirements (110 $W^{0.75}$ kcal/d, where W is body weight expressed in kg)[c] and adjusted during the study to ensure body weight maintenance within ± 0.5% of original weight. All dietary nutrients, with the exception of protein, were measured using modified standard methods.[10] Protein was analyzed by a modified method based on the Duma principle, using a nitrogen analyzer.[11,d] Water was provided ad libitum.

Study design—The dogs were randomly allocated to 3 feeding groups and fed the test diets for a period of 8 days, according to a Latin Square design. Each study period was separated by a 6-day interval. During each study period the dogs were fed either the standard diet solus (control) or the standard diet plus 1 of 2 types of potassium citrate supplement mixed with the food twice daily. Supplements were either tri-potassium citrate[e] or wax matrix tablets[f] and were administered at a dosage of 150 mg of potassium citrate/kg/d. Each dog was weighed once weekly to ensure an accurate dosage was administered throughout the study.

Housing details—Dogs were housed separately, as described by Stevenson et al[12] for two 48-hour periods (days 3 to 4 and 7 to 8). During the remaining 4 days, and during the interval phases, dogs were housed in pairs. During this time all dogs were walked once daily for approximately 15 minutes and group exercised in grass paddock areas for 1 to 2 hours.

Urinary measurements—Urine pH was continuously measured using the noninvasive automated urine pH measuring system,[12,13] and specific gravity and urine volume were measured during days 3 and 4 of every treatment. During days 7 and 8, a 48-hour urine sample was collected from each dog and immediately frozen, as described by Stevenson et al.[12]

Urinalysis—Frozen urine samples were defrosted after 48 hours, titrated to pH 2.0 with a 37% solution of hydrochloric acid,[c] refrozen, and stored at –20 C. Samples were prepared and analyzed by described methods.[14] A lyophilized human urine control standard[g] with certified assay data was used to verify the reliability of this procedure. Urinalysis data were then entered into a computer program[15] that calculated RSS values for calcium oxalate and struvite.

Statistical analyses—Analysis of variance and multiple range tests (**Neuman-Keuls [NK]**) were used to test the significance of dietary potassium citrate supplementation on urine volume, specific gravity and pH, urinary RSS of calcium oxalate and struvite, and urinary concentrations of magnesium, ammonium, phosphate, calcium, oxalate, and citrate. Level of significance was set at $P < 0.05$.

Results

Food intake and body weight maintenance—All food offered to dogs was consumed every day, ensuring that the dogs always received the correct amount of potassium citrate. Body weight remained constant throughout the trial with an overall weight change of 0.4%.

Urine measurements—Dietary potassium citrate supplementation (in either form) did not have an effect on urine volume or specific gravity (**Table 1**). Results of mean diurnal urine pH profiles (**Fig 1**) indicate that

Table 1—Mean (± SD) daily urine volume, urine specific gravity, urine pH, and urinary relative supersaturation* of calcium oxalate and struvite in 12 healthy dogs fed a commercially prepared dog food[b] solus (control diet) or the same diet supplemented with potassium citrate[e,f] at a dosage of 150 mg/kg of body weight/d

Diet	Urine volume (ml/d)	Specific gravity	Relative supersaturation CaOx	Relative supersaturation Struvite
Control diet[b]	436 ± 312	1.027 ± 0.008	1.42 ± 0.63	2.59 ± 1.40
Diet + TCP[e]	463 ± 408	1.026 ± 0.007	1.68 ± 0.83	3.55 ± 3.43
Diet + WMT[f]	479 ± 347	1.028 ± 0.006	1.24 ± 0.53	3.44 ± 2.63

*Urinary relative supersaturation for calcium oxalate and struvite is calculated as activity product/solubility product for each substance.

CaOx = Calcium oxalate. TCP = Potassium citrate supplemented as tri-potassium citrate powder.[e] WMT = Potassium citrate supplemented as wax matrix tablets.[f]

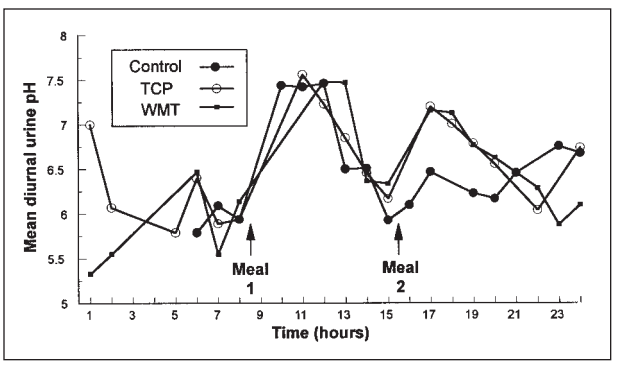

Figure 1—Mean diurnal urine pH profiles for 12 healthy dogs fed a commercially prepared dog food[b] solus (control) or treated with 2 forms of potassium citrate supplement (powder [TCP] or tablet [WMT])[e,f] at 150 mg/kg of body weight/d.

Table 2—Mean (± SD) urinary concentration of magnesium, ammonium, phosphate, calcium, oxalate, and citrate in 12 healthy dogs fed a commercially prepared dog food[b] solus (control diet) or the same diet supplemented with potassium citrate[e,f] at a dosage of 150 mg/kg of body weight/d

	Urinary concentration (mmol/L)					
Diet	**Magnesium**	**Ammonium**	**Phosphate**	**Calcium**	**Oxalate**	**Citrate**
Control diet[b]	1.25 ± 0.84	72.70 ± 18.42	52.28 ± 16.47	0.51 ± 0.16	0.33 ± 0.06	0.10 ± 0.06
Diet + TCP[e]	0.95 ± 0.35	59.37 ± 15.10	48.13 ± 15.81	0.56 ± 0.43	0.31 ± 0.11	2.81 ± 8.97
Diet + WMT[f]	1.13 ± 0.70	72.28 ± 37.87	49.11 ± 12.88	0.48 ± 0.18	0.31 ± 0.08	0.23 ± 0.20

See Table 1 for key.

all 3 diets resulted in an increase in urine pH between 8:00 AM and 12:00 PM. Diets containing potassium citrate maintained a higher urine pH than the control diet from 3:00 PM to 9:00 PM. Consequently, compared with control diet, mean urine pH was higher in diets supplemented with potassium citrate by approximately 0.2 pH units (control diet, pH 6.75 ± 0.34; diet with wax matrix tablet, pH 6.97 ± 0.56), although this difference was not significant ($P = 0.34$).

Urinary RRS—Dietary potassium citrate supplementation in either form did not influence mean urinary RSS of calcium oxalate or struvite (Table 1). On examination of RSS data, a significant decrease in calcium oxalate RSS ($P = 0.049$) was found in 3 dogs (1 sexually intact male and 2 sexually intact female Miniature Schnauzers) fed diets supplemented with potassium citrate, compared with control diet.

Urinary concentrations—Dietary potassium citrate supplementation did not have an effect on urinary concentrations of magnesium, calcium, oxalate, and citrate (**Table 2**). However, when examining data from each dog, the 3 Miniature Schnauzers with significantly decreased calcium oxalate RSS also excreted greater amounts of citrate, although this difference was not significant. None of the other urinary concentrations were influenced by the potassium citrate supplemented diets.

Discussion

Results of many studies within the field of human medicine indicate that dietary potassium citrate supplementation significantly increases urine pH and citrate excretion while decreasing urinary calcium oxalate supersaturation.[16-20] Hypocitraturia may be a risk factor for calcium oxalate stone formation in humans, with reports of 15 to 50% of affected individuals having low amounts of citrate excretion.[2] In healthy humans, citrate chelates calcium in the urine, helping to prevent precipitation of calcium salts, particularly in alkaline urine.[4] Under usual conditions, as much as 70% of urinary calcium may be bound to citrate.[4] When citrate excretion decreases, less calcium is chelated, and calcium urolithiasis is promoted.[4] The reference range of urinary citrate concentration in humans is 2 to 5 mmol/L and hypocitraturia is defined as < 1.5 mmol/L.[3] In a study conducted by Whalley et al,[21] giving hypocitraturic human subjects 31 mmol of potassium citrate/d (approx 100 mg of potassium citrate/kg) resulted in an increase in urinary citrate concentration to within reference range. Consequently, the rate of stone formation was decreased by > 80%. There are many other published examples of dietary potassium citrate supplementation increasing urinary citrate concentrations in humans.[2,19,22] However, despite a tendency to hypocitraturia, there is no relationship between mean excretion of citrate and severity of disease in people that form oxalate stones.[1] Contrastingly, studies have also been conducted in which dietary citrate supplementation has had no effect on citrate excretion in humans.[h] It is possible that dietary potassium citrate supplementation is of benefit to people with hypocitraturia but may be of limited use when the amount of citrate excretion is within reference range prior to treatment. In view of the complex nature of the biochemical response to dietary potassium citrate supplementation, conclusions have not been drawn as to the importance of high citrate excretion in the prevention of calcium oxalate stone formation in humans.[1]

It is not known whether hypocitraturia is a risk factor for calcium oxalate stone formation in dogs. Results of a study comparing urine excretion of citrate in 6 Miniature Schnauzers that formed oxalate stones with that of healthy Beagles reveal that there is no difference in citrate excretion, indicating that hypocitraturia may not be an important contributing factor for calcium oxalate formation in dogs.[23] Results of another study on healthy dogs indicate that administration of up to 150 mg of potassium citrate/kg/d is not associated with a consistent increase in urinary citrate excretion (as it is in humans), although there is a dose-dependent increase in urine pH.[5] One explanation for this difference between people and dogs may be that although humans excrete 10 to 35% of filtered citrate in urine, only 1 to 3% of filtered citrate is excreted by dogs.[4] This is further clarified by comparing urinary citrate concentration in healthy dogs in our study with healthy people.[24] Our dogs excreted far less citrate (0.1 mmol/L of urine) than reported for humans (2.5 mmol/L of urine).[24]

In our study, a consistent increase in citrate excretion was not seen with dietary potassium citrate supplementation. However, 3 Miniature Schnauzers did excrete larger amounts of citrate when fed the supplemented diets. This finding is consistent with that found from the same dogs in a separate dose-response study that used potassium citrate powder.[i] In another study involving 5 healthy dogs, supplementation of the diet with 100 mg of potassium citrate/kg/d, resulted in a mean increase in urine pH of 0.2 pH units from 7.34 to 7.55 (increase not significant).[9] This increase in urine pH is comparable with the increase in mean urine pH in our study. Results of studies of humans that form oxalate stones indicate a far more pronounced effect of citrate

treatment on daily urine pH (increases in pH from 5.92 to 6.22 when potassium citrate dosage is approx 30 mEq/d [approx 100 mg of potassium citrate/kg], and from 5.62 to 6.55 when potassium citrate dosage ranges from 30 to 100 mEq of potassium citrate/d with a mean of 60 mEq/d [approx 200 mg of potassium citrate/kg]).[19]

Urinary pH is not a constant and has marked fluctuation during a 24-hour period. Factors including exercise, pulmonary ventilation, dietary habits, and emotional status are all known to influence urine pH in humans and, as a result of these diurnal variations, pH is usually lowest through the night and highest during the day.[25] Humans were found to be at greater risk of calcium oxalate crystallization overnight when urine pH is at its lowest.[26] At night the urine volume decreases and body temperature is also at its lowest, facilitating an increase in urine supersaturation; hence, increasing the potential for crystallization and stone formation in susceptible humans.[27] It is likely that the diurnal urine pH profile in dogs is affected by similar factors. In dogs in our study, urine pH peaked between 1 and 4 hours after the first meal, and the amount of response was similar in all feeding groups (Fig 1). This effect was thought to be partly attributable to a postprandial alkaline tide effect and partly to an increase in activity. A second smaller peak in urine pH was observed between 1 and 4 hours after the second meal, and this effect was greater in the potassium citrate-supplemented dogs. A higher urine pH was maintained during a longer period when the diet was supplemented with potassium citrate. This may shorten the period of greatest risk for calcium oxalate formation in susceptible dogs.

Compared with our study, a substantially higher postprandial urine pH has been described for dogs fed a potassium citrate supplemented diet,[9] but dogs in that study were fed only once daily, in the morning. The apparent benefit of this postprandial pH response is debatable. Results of our study indicate that a postprandial increase in urine pH develops after feeding in the morning, even without potassium citrate supplementation, and a further increase in urine pH may not be of any additional clinical benefit. Furthermore, the response time is limited when dietary supplementation is given only once daily and may not coincide with the period of greatest risk for stone formation. For dogs fed twice daily, however, a single dose of potassium citrate may be more beneficial if given with the evening meal, because this would add to the initial postprandial pH effect and increase the magnitude of the second increase in urine pH at a time when the potential for crystallization may be highest. Results of a study conducted in healthy humans reveal that administration of potassium citrate at approximately 62 mg/kg/d in a single evening dose increases urine pH to a peak at 2 hours after administration.[20] This increase in urine pH is maintained until the next morning, although excretion of calcium and citrate are unaffected.[20] In that study, the response to potassium citrate administration in healthy humans was compared with that of humans who form oxalate stones. These results indicate that in humans a single dose of potassium citrate in the evening has a more favorable effect, decreasing urinary calcium oxalate supersaturation in addition to increasing urine pH, during the overnight risk period.[20] It can also be postulated that dogs that form stones may have a more favorable response than healthy dogs when supplemented with potassium citrate in a single evening dose.

The clinical importance of increasing urine pH for the management of calcium oxalate urolithiasis in dogs has not been investigated. Determination of urinary calcium oxalate RSS is a well established method for assessing the effect of prophylactic measures on the calcium oxalate forming potential of the urine in humans,[28] although similar studies in dogs that form stones have not, to our knowledge, been published. In our study, the increase in urine pH had no effect on urinary calcium oxalate RSS in most healthy dogs, although the increase in urine pH was minimal. Nevertheless, dietary potassium citrate supplementation significantly reduced urinary calcium oxalate RSS in 3 dogs, all Miniature Schnauzers, and in these dogs there was also an increase urinary citrate excretion, although this increase was not significant. Miniature Schnauzers are known to be susceptible to calcium oxalate formation.[29] Results of one study indicate that Miniature Schnauzers that form calcium oxalate stones differ from control dogs (healthy Beagles) in terms of urinary variables.[23] Compared with healthy dogs, affected Miniature Schnauzers have a higher calcium excretion and a lower oxalate excretion than the control dogs, whereas citrate excretion is unchanged.[23]

To compare urinary excretion values from healthy dogs of our study with those of dogs that form stones of other studies, our urinary data were converted from millimoles per liter of urine to milligrams per kilogram per day. Calcium and oxalate excretion remained unchanged throughout our study; overall mean values were used for comparison with published data.[23] Calcium excretion in our dogs (0.65 ± 0.29 mg/kg/d) was comparable to values from healthy Beagles (0.51 ± 0.28 mg/kg/d)[23] and lower than values from Miniature Schnauzers that form stones (2.54 ± 1.20 mg/kg/d).[23] Oxalate excretion in our dogs (0.90 ± 0.35 mg/kg/d) was comparable with that of Miniature Schnauzers (0.89 ± 0.85 mg/kg/d)[23] and lower than that of healthy Beagles (1.74 ± 0.90 mg/kg/d).[23] Citrate excretion in the dogs of our study (0.57 ± 0.32 mg/kg/d [control diet] to 1.55 ± 1.00 mg/kg/d [diet with wax matrix tablet]) was lower than reported for Miniature Schnauzers that formed stones (6.68 ± 7.7 mg/kg/d)[23] or healthy Beagles (2.57 ± 2.31 mg/kg/d).[23] Differences between studies in citrate and oxalate excretion values may be the result of different procedures for analysis or differences in dietary content of oxalate and citrate.

Another proposed benefit of dietary potassium citrate supplementation is that the induced urinary alkalization increases renal tubular reabsorption of calcium, thereby decreasing its excretion in urine. In a study in humans, intake of 10 g (approx 142 mg/kg) of potassium citrate caused a 30% mean decrease in urinary calcium excretion.[3] However, there are also the results of many other studies in humans that indicate that citrate treatment had no effect on calcium excretion.[19,21,22,h] It has been suggested that this effect may also be beneficial in dogs even without an associated increase in urinary

citrate excretion.[5,7,8] In our study, a reduction in calcium excretion was not seen when dogs were given a diet supplemented with potassium citrate ($P = 0.67$, NK).

Although dietary potassium citrate supplementation in the form of wax matrix tablets[f] has been recommended for management of canine calcium oxalate urolithiasis,[5,6] we know of no published data to support this recommendation. Results of a study in humans, in which people that formed stones were treated with potassium citrate as a wax matrix tablet, indicates that potassium citrate supplementation significantly increases urine pH and citrate excretion.[18] Although it has been suggested that the wax matrix formulation may delay gastrointestinal tract absorption and subsequent urinary excretion of citrate, there is no evidence currently available to support this claim in dogs. In our study of healthy dogs, no differences in citrate excretion or urine pH response were found between wax matrix and powder supplements.

[a]Council directive 93/74EEC, commission directive 94/39EC, The Pet Food Manufacturers' Association, London, UK.
[b]Cesar (chicken variety), Pedigree Petfoods, Waltham on the Wolds, Leicestershire, UK.
[c]Burger I. Updated feeding recommendations for the canine diet (abstr). *Waltham Focus* 1995;5:3, 32.
[d]LECO, Cheshire, UK.
[e]BDH Laboratory Supplies, Poole, UK.
[f]Urocit-K, Mission Pharmacal, San Antonio, Tex.
[g]Sigma, Sigma-Aldrich Chemical Co Ltd, Poole, Dorset, UK.
[h]Thomas NE, Moorthy HK, Vathsala RK, et al. Urinary citrate in relation to dietary citrate. *Urolithiasis 2*. New York: Plenum Press, 1994:427.
[i]Stevenson AE, Smith BHE, Markwell, PJ. The effect of potassium citrate supplementation on urine pH and urinary relative supersaturations of the dog (abstr). *BSAVA Proceedings*, 1998;305.

Appendix 1

Nutrient content of the commercially prepared dog food[b]

Nutrient	Amount/100 kcal
Moisture (g)	109.30
Protein (g)	10.41
Fat (g)	7.16
Ash (g)	2.47
Linoleic acid (g)	0.64
Linolenic acid (g)	0.10
Linoleic acid + arachidonic acid (g)	0.04
Calcium (g)	0.36
Phosphorus (g)	0.41
Calcium-to-phosphorus ratio	0.87
Sodium (g)	0.16
Magnesium (g)	0.02
Iron (mg)	5.46
Copper (mg)	0.61
Manganese (mg)	0.39
Zinc (mg)	2.98
Vitamin A (U)	2,134.03
Vitamin E (mg)	3.15
Thiamin (mg)	0.31
Riboflavin (mg)	0.75
Niacin (mg)	3.12
Pyridoxine (mg)	0.16
Pantothenic acid (mg)	1.43
Folic acid (mg)	14.31
Vitamin B12 (mg)	7.55
Choline (mg)	96.29
Methionine (g)	0.16
Methionine and cystine (g)	0.27

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