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On supplementing the selenium intake of New Zealanders

1. Short experiments with large doses of selenite or selenomethionine

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1. Urinary and faecal excretion of single oral doses of 1 mg selenium or 0·1 mg Se as selenomethionine (Semet-Se) in solution were studied in two women. Most of the Se was absorbed and little was eliminated in the urine (0·05–0·22 dose).

2. The results have been compared with those from an earlier study (Thomson, 1974) on the same two women after similarly sized doses of sodium selenite (selenite-Se) in solution. Although selenite-Se was almost as well absorbed as Semet-Se more was excreted in the urine (0·41–0·85 dose).

3. Repeated dosing with 1 mg selenite-Se on five consecutive days in one of the women indicated that 1·1 mg had been retained.

4. Twenty patients with muscular complaints from Tapanui (South Otago, New Zealand), a low-Se soil area, ingested 0·5 mg selenite-Se daily for 20 d. Blood Se increased rapidly to almost twice the initial concentration but reached a plateau well below most values reported for residents outside New Zealand. No difference in blood Se concentration was found between those who did or did not report improvement.

5. Spasmodic medication with selenite-Se by some residents near Lincoln (Christchurch, New Zealand) for periods of up to 10 years or more had increased the blood Se somewhat.

In New Zealand where soil selenium concentrations are low and Se deficiencies in animals are well documented (Andrews, Hartley & Grant, 1968), interest has now turned to the possible role of Se in human nutrition. Unusually low urinary excretions and blood concentrations of Se found in New Zealand residents have indicated a low nutritional status for Se (Thomson, 1972; Griffiths & Thomson, 1974; Watkinson, 1974); whereas subjects who had recently arrived from the USA had much greater urinary excretions and blood Se concentrations than New Zealand subjects (Griffiths & Thomson, 1974). The low Se status reflects the low dietary intakes of Se found for New Zealand residents (Thomson, 1972; Griffiths, 1973) and these in turn reflect low Se concentrations in foods (Watkinson, 1974; Robinson, 1976).

These observations suggested that Se deficiencies might occur in New Zealand, and, although it is unlikely that severe deficiencies will be found, marginal deficiencies might occur in vulnerable groups. Low blood Se concentrations have been found in surgical patients during intravenous alimentation (McKenzie, Rea, van Rij & Robinson, 1976). Other groups at risk might include vegetarians consuming no dairy products, infants fed on cow's milk (Watkinson, 1974) and elderly citizens consuming inadequate diets. Hickey (1968) reported alleged benefit and relief from muscular complaints by self-medication with Se amongst residents of low-Se soil areas. These reports of spasmodic dosing with large amounts of Se as sodium selenite in the form of sheep drench or in capsules designed for dogs were of some concern, as little was known about the metabolism of Se in the human body. Recovery of Se from single large doses of 1 mg Se ingested as sodium selenite in solution or as a solid has been investigated in three subjects (Thomson, 1974; Robinson, 1976).

The aim of the present studies was to investigate possible ways of increasing the Se status of the New Zealand population should it become desirable to do so. Response to single-dose supplements of Se as sodium selenite (selenite-Se) or selenomethionine (Semet-Se) and to frequent large doses of selenite-Se are reported in the present paper whereas the response

to long-term supplementation of the diet with physiological amounts of selenite-Se, Semet-Se or Se present in mackerel is reported in the following paper (Robinson, Rea, Friend, Stewart, Snow & Thomson, 1978).

METHODS

Experimental design

Expt 1. Response to single-dose supplements of Se as selenomethionine (1976)

The subjects H and R were two women aged 52 and 29 years, with body-weights of 74 and 56 kg respectively, and who had also participated in a previous study of dosing with selenite-Se (Thomson, 1974). Both subjects had been outside New Zealand for at least 7 months in 1975, travelling in Europe and in North and South America, and this study was carried out 4–5 months after their return.

The procedure was identical to that used in previous trials with selenite-Se (Thomson, 1974). Urinary and faecal excretions were monitored after an oral dose of 1 mg or 0·1 mg Semet-Se (Sigma Chemical Co., St Louis, Missouri, USA) which was prepared in solution and ingested before a continental-type breakfast. Hourly urine samples were collected for 8 h, two-hourly samples for a further 8 h and a final collection made 8 h later. Twenty-four hour urine collections were made by subject H for 6 d during the experimental period and all faeces were collected for 3 d after ingestion of the 1 mg dose. Blood samples were collected every 1 h for 6 h, then every 2 h for a further 4 h and finally for the remaining 12 h. Subsequently blood samples were collected daily for a further 2 d for subject H. Whole blood, erythrocytes and plasma were analysed for Se.

No fish, liver or kidney was eaten by the subjects during the studies.

Expt 2. Response to frequent large doses of selenite-Se

Expt 2A. Five 1 mg doses by subject H. Subject H ingested, immediately after breakfast, 1 mg doses of selenite-Se in solution on each of five consecutive days. A blood sample was taken before dosing, samples were then taken daily during the dosing period (immediately before ingestion of the next dose) and thereafter at frequent intervals. Twenty-four hour urine samples and all stools were collected daily for 3 d before dosing, throughout the dosing period, and for 11 d after dosing ceased. Thereafter, 24 h urine samples and stools were collected periodically around the times that blood samples were collected.

Expt 2B. Tapanui pilot study (1974). Twenty patients suffering from muscular complaints were selected from a general practice in Tapanui, an area in South Otago with a low-Se soil. Each patient ingested each day for 20 d, 0·5 mg selenite-Se prepared in solution. A blood sample was taken from each patient before dosing, at weekly intervals for 3 weeks, and later at 2 weeks and 2 months. Dr P. C. Snow conducted a clinical examination of each patient before and during the dosing period.

Expt 2C. Study of Lincoln 'dosers'. A study was made of blood Se levels of a group of Christchurch residents associated with Lincoln Agricultural College who ingested large doses (1–2 mg selenite-Se) regularly or spasmodically. Blood samples were obtained from eighteen 'dosers' and six controls and 24 h urine collections were made by eight 'dosers' and six controls. Each subject gave information on size and frequency of dose, form of Se ingested, time interval since last dose, reasons for dosing and effects observed.

Techniques

Collection and storage of urine and faeces. Twenty-four hour urine and stool samples were collected and stored as described previously (Robinson, McKenzie, Thomson & van Rij, 1973; Thomson, 1974).

Collection and storage of blood samples. Whole blood (10 ml) was collected into evacuated glass tubes (Becton-Dickinson, Rutherford, New Jersey, USA) containing lithium heparin as anticoagulant. When required, plasma and erythrocytes were separated and the cells washed twice with physiological saline (9 g sodium chloride/l). All samples were stored in a refrigerator.

Analytical method

Se was measured by a modification (Thomson, 1973) of the diaminonaphthalene fluorimetric method of Watkinson (1966). Mean (± SD) concentrations for several determinations on a given urine, faeces or blood sample were respectively: 0·0144 ± 0·0003 μg/ml (*n* 9), 0·402 ± 0·017 μg/g dry matter (*n* 23) and 0·045 ± 0·0014 μg/ml (*n* 9). Mean recovery of Se added to urine, faeces and blood were (%) 101 (*n* 6 estimations), 99 (*n* 7), 100 (*n* 12) respectively.

RESULTS

Expt 1. *Effect of single doses of Se*

Urinary excretion. Table 1 gives the urinary excretion of Se after doses of Semet-Se for subjects H and R. The observed excretion was corrected for baseline excretion as described by Thomson (1974) to give daily excretion of each dose and the proportion of the dose excreted. For comparison the results have been included for studies on the same two subjects after ingestion of comparable doses of selenite-Se (Thomson, 1974).

Fig. 1 shows that peak excretions of Se were obtained at least 1 h sooner after Semet-Se and that during the 1st day the excretion rate after Semet-Se was always less than after selenite-Se, resulting in considerably less of Semet-Se being eliminated. Total cumulative recovery was 0·05–0·22 of the dose compared with 0·41–0·85 of the dose after selenite-Se (Table 1).

Faecal excretion. Faecal excretion was corrected for baseline excretion (Thomson, 1974). After 1 mg Semet-Se, 0·035 of the dose was excreted in the faeces compared with 0·11–0·13 of 1 mg selenite-Se by subject H and 0·06 of 1 mg selenite-Se by subject R.

Intestinal absorption of Se was estimated by the method of Lutwak (1969) as modified by Thomson (1974). Absorption of Semet-Se by subject H was 0·97 of the dose and of selenite-Se were 0·90 and 0·95 of the dose by subjects H and R respectively.

Total recovery of ingested Se. A much smaller proportion of the dose of Semet-Se (0·26) was recovered in the urine and faeces than of the dose of selenite-Se (0·82–0·95), which left 0·74 of the dose of Semet-Se unaccounted for.

Blood Se concentrations. At the time of the dosing trials with Semet-Se, blood Se concentrations of both subjects were still increased after travelling outside New Zealand, and were 0·12 and 0·11 μg Se/ml for subjects H and R respectively.

Fig. 2 shows that for subject H plasma Se increased after each dose of Semet-Se whereas erythrocyte Se remained more or less constant. Plasma Se increased more rapidly and for a longer period after the larger dose of Semet-Se (Figs 2*a*, *b*). For subject R plasma Se increased similarly by 0·01 μg Se/ml after the smaller dose of Semet-Se to reach 0·09 μg Se/ml.

Expt 2. *Frequent large doses of selenite-Se*

Expt 2*A*. Large proportions of the doses were excreted each day in the urine (Fig. 3), with excretions increasing from the 1st to the 4th day of the dosing period. Cumulative urinary excretions had become 0·32 of the total dose of 5 mg selenite-Se at the end of day 8, and 0·36 of the total dose by day 19.

Fig. 4 shows that faecal excretion increased rapidly on day 2 of the dosing period, indicating a 24 h transit time through the gut for subject H. Faecal excretion remained high

Table 1. *Urinary selenium excretion for subjects H and R after a single oral dose of selenomethionine (present study) or sodium selenite (Thomson, 1974)*

(Mean values with ranges in parentheses)

	Dose (mg Se)	Subject	No. of experiments	Period of peak after dose (h)	Peak excretion		24 h excretion on day 1		Total cumulative recovery of dose (proportion of dose)*
					μg Se/h	Proportion of dose*	μg Se/d	Proportion of dose*	
Selenomethionine	1·0	H	1	2	25	0·02	194	0·18	0·22
	0·1	H	1	1	2·5	0·01	23·5	0·11	0·11
		R	1	2	2·3	0·01	18·2	0·05	0·05
Selenite	1·0	H	7	3 (2–4)	114 (83–126)	0·11 (0·10–0·13)	686 (643–720)	0·67 (0·63–0·71)	0·77 (0·69–0·85)
		R	4	4†	98†	0·10†	655 (633–688)	0·64 (0·62–0·67)	0·72 (0·69–0·76)
	0·1	H	1	2	8·2	0·08	40·7	0·29	0·41
		R	1	3	9·5	0·09	59·8	0·46	0·54

* Corrected for baseline urinary excretion, see p. 581.
† Urine samples were collected only at 4 h intervals in these studies of subject R.

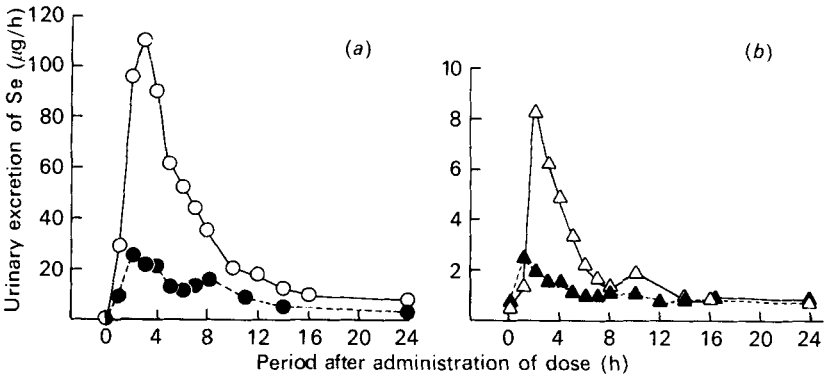

Fig. 1. Expt 1. Urinary excretion of selenium by subject H during 24 h after an oral dose of (*a*) 1 mg Se (○, ●) or (*b*) 0·1 mg Se (△, ▲), given as selenite (○, △) or as selenomethionine (●, ▲). For details of experimental procedures, see p. 580.

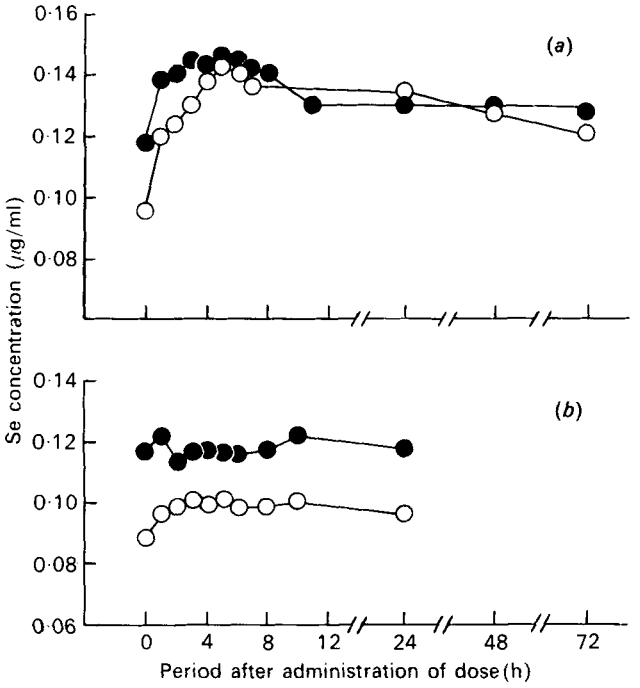

Fig. 2. Expt 1. Selenium concentration in plasma (○) and whole blood (●) of subject H after an oral dose of (*a*) 1 mg Se or (*b*) 0·1 mg Se given as selenomethionine. For details of procedure, see p. 580.

for 3 d after cessation of dosing, when it returned to pre-dosing values. Cumulative faecal excretion was calculated (Thomson, 1974) to be 0·41 of the total dose of 5 mg Se, and intestinal absorption 0·59 of the total dose.

Urinary and faecal excretions together made up 0·78 of the total dose, which left 0·22 of the dose unaccounted for.

Se concentrations in whole blood increased from 0·082 μg Se/ml before dosing to a peak of 0·103 μg Se/ml 4 d after dosing ceased and then decreased gradually to 0·083 μg Se/ml 3 weeks later. Plasma Se concentrations increased rapidly above the whole blood level from

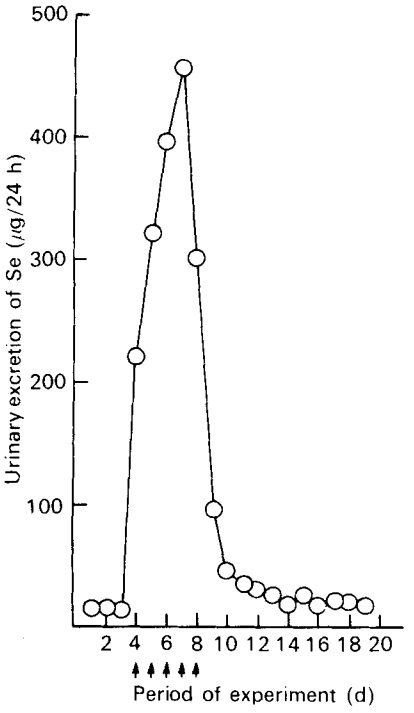

Fig. 3

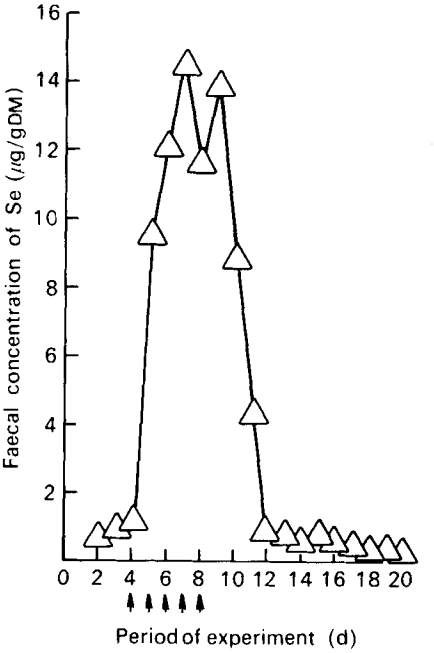

Fig. 4

Fig. 3. Expt 2A. 24 h urinary excretion of selenium by subject H after a daily oral dose (↑) of 1 mg Se as sodium selenite in solution on five consecutive days. For details of procedure, see p. 580.

Fig. 4. Expt 2A. Faecal excretion of selenium expressed as μg/g dry matter (DM) by subject H after a daily oral dose (↑) of 1 mg Se as sodium selenite in solution on five consecutive days. For details of procedure, see p. 580.

0·073 to 0·106 μg Se/ml and decreased slowly to 0·088 μg Se/ml 3 weeks after dosing had ceased, and reached the pre-dosing value at 2 months.

Expt 2B. Tapanui pilot trial (1974). The initial mean (±SD) blood Se concentration of 0·056±0·015 μg Se/ml (Fig. 5) was almost identical with that for twenty-eight blood donors from the adjacent area of Heriot (0·057±0·012 μg Se/ml) (Griffiths & Thomson, 1974). There was an initial rapid increase in blood Se for all subjects during the 1st week to 0·10±0·014 μg Se/ml, almost twice the initial concentration; it remained at this value until it decreased gradually during the last week of the dosing period.

Statistical analysis of the results using both Student's *t* test and analysis of variance, showed a significant difference between blood Se concentrations ($P < 0·01$) at each of the sampling times, except from week 1 to week 2 of dosing period and from 2 months to 4 months of the post-dosing period. Further, 4 months after dosing the whole blood Se was still significantly higher than the pre-dosing value. It was later discovered that during the last 2 months a few of the patients had started to medicate themselves with spasmodic doses of selenite-Se.

Results of the clinical trial indicated that ten patients alleged improvement in their muscular condition while ten claimed no improvement. Analysis of variance failed to indicate any over-all difference between the blood Se of the two groups ($P < 0·05$). These results will be presented and discussed in greater detail elsewhere.

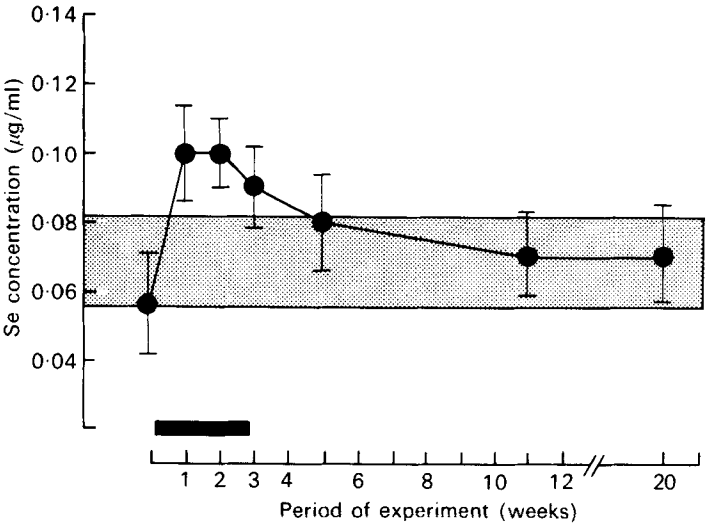

Fig. 5. Expt 2B. Whole blood selenium concentration of twenty patients from Tapanui, South Otago, after a daily oral dose on twenty consecutive days (■) of 0·5 mg Se as sodium selenite in solution. The points are mean values and standard deviations are represented by vertical bars. (▦), range for mean ±SD (0·068±0·013 μg Se/ml) for blood Se for New Zealanders (Griffiths & Thomson, 1974). For details of procedure, see p. 580.

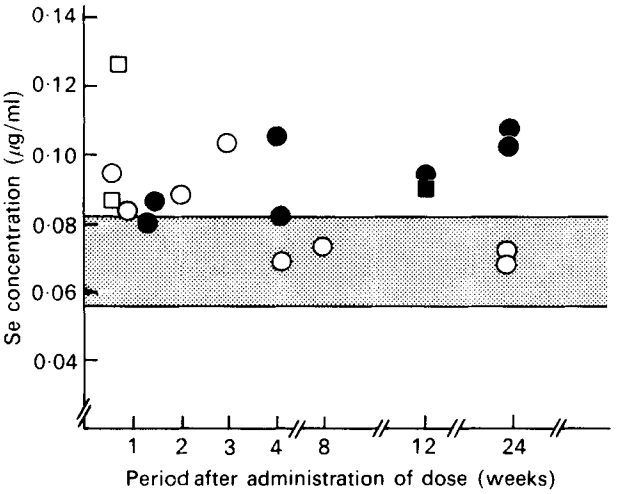

Fig. 6. Expt 2C. Whole blood selenium concentration of residents associated with Lincoln Agricultural College, Christchurch, who had been ingesting spasmodically an oral dose since before 1965 of 1 mg Se (□) or 2 mg Se (■), or more recently 1 mg Se (○) or 2 mg Se (●). (▦), range for mean ±SD (0·068±0·013 μg Se/ml) for blood Se for New Zealanders (Griffiths & Thomson, 1974). For details of procedure, see p. 580.

Expt 2C. Lincoln study. Blood Se concentrations (mean±SD) for the Lincoln 'dosers' (0·089±0·015 μg Se/ml) was just greater ($P < 0·02$) than that for the controls (0·071±0·008 μg Se/ml). In Fig. 6 the plot of blood Se for the 'dosers' *v.* period of time since the last dose shows that many were still within the range for New Zealand residents (Griffiths & Thomson, 1974). Long-term dosing and the larger doses of 2 mg Se had each had little effect on the blood Se.

Twenty-four hour urinary excretions were 13·2–31·4 μg Se/d for the 'dosers', while control values were 10·6–22·3 μg Se/d. There was a significant correlation between whole blood Se concentrations and 24 h urinary excretion for the 'dosers' (r 0·91, $P < 0·001$) and for 'dosers' plus controls (r 0·87, $P < 0·001$).

DISCUSSION

A similar pattern of rapid absorption and initial excretion in urine was observed for both selenite-Se and Semet-Se. However, intestinal absorption of Semet-Se was slightly greater than that of selenite-Se, and a much smaller proportion of Semet-Se was excreted in the urine. These observations are similar to those reported after ingestion of tracer doses of [^{75}Se]selenomethionine and [^{75}Se]selenite (Thomson & Stewart, 1974; Griffiths, Stewart & Robinson, 1976), except that considerably less of the very small doses of Se from [^{75}Se]selenite was excreted in the urine, 7–14 % dose or 14–20 % absorbed dose during the first 2 weeks.

Results from all these studies suggested that the mechanism by which absorbed Se is incorporated into the body pool may not be able to handle the larger doses of Se as efficiently as smaller ones, and that Semet-Se is incorporated more readily than selenite-Se (Griffiths *et al.* 1976). Although there was little retention of infrequent doses of selenite-Se, there might be considerable retention after ingesting large daily doses. Even though blood Se was not measured after single large doses of selenite-Se (Thomson, 1974), spasmodic self-medication by the Lincoln 'dosers' had not increased their blood Se significantly, despite being carried out for a long period of time, nor had regular ingestion of such doses for 20 d increased blood Se concentrations of Tapanui subjects far above the normal New Zealand range. On the other hand, since a large proportion (0·74) of a single dose of Semet-Se was apparently retained in the body, and since plasma Se of subject H was still increased 72 h after ingestion of a dose, Semet-Se might be more effective than selenite as a source of Se.

Burk (1976) has pointed out that, where large quantities of Se are ingested, some of the element is lost in the breath as dimethyl selenide. In the present study no allowance was made for respiratory excretion or dermal output, but it was unlikely that they would have accounted for a significant proportion of the dose, since after ingestion of single large doses of selenite-Se it was observed that respiratory excretion was less than 0·01–0·02 dose (Thomson, 1974). Furthermore, only trace amounts of radioactivity were detected in expired air and dermal losses after ingestion of tracer doses of [^{75}Se]selenite (Thomson & Stewart, 1974) and of [^{75}Se]selenomethionine (Griffiths *et al.* 1976).

These observations on subjects H and R suggest that Semet-Se might be more effective in increasing the blood Se and also the Se status of New Zealanders than ingesting large doses of selenite-Se. However, the possibility that frequent dosing with Semet-Se might result in the retention of toxic amounts of Se requires further investigation before its use is ever contemplated. Further, travelling outside New Zealand and eating foods of higher Se content than in New Zealand might also be more effective in increasing Se status. The effect of increasing daily the dietary intake of Se by 100 μg Se, the amount by which the New Zealand intake is less than most other diets, is reported in the following paper (Robinson *et al.* 1978).

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