Selenium Toxicity for Ruminants - Paranoia or Precaution?

L.R. McDowell[1], P.A. Davis, L.A. Cristaldi, N.S. Wilkinson,
C.D. Buergelt and R. Van Alstyne
Department of Animal Sciences
University of Florida, Gainesville

Introduction

Selenium (Se) is an important nutrient in animal and human nutrition. Before we go further let us check the definition of Se in a medical dictionary (Merriam-Webster, 1996).

> **Selenium**-a nonmetallic element that resembles sulfur and tellurium chemically, causes poisoning in range animals when ingested by eating some plants growing in soils in which it occurs in quantity, and occurs in allotropic forms of which a gray stable form varies in electrical conductivity with the intensity of its illumination and is used in electronic devices-symbol Se.

Obviously all of us at this meeting are appalled at this definition, which notes only toxicity and no mention of deficiency. Since 1957, the essential nature of Se has become the center of attention, and this element is known to be required by laboratory animals, food animals, and humans. Research has established that areas of the world affected by Se deficiency are far greater and the consequences are more economically important than those afflicted with Se excess (McDowell, 1997; 2003; Oldfield, 1999). To add more insult to injury this dictionary in defining "white muscle disease", notes that it is due only to an inadequate intake of vitamin E (versus also Se).

Previously, the U.S. Food and Drug Administration (FDA) prohibited the addition of supplemental Se to livestock feeds. However, from the time period of 1974-1980, this regulatory agency gradually allowed Se supplementation for various classes of livestock. Presently, the FDA is allowing Se supplementation to equal an upper limit of 0.3 ppm for livestock diets. Selenium is regulated by the FDA because it originally (1943) was thought to cause cancer in rats and because of its perceived toxicity. The suggestion has often been made that "the range between optimal and toxic levels of Se is narrow". This paper will update the tolerance of Se for ruminants and point out that "the range between optimal and toxic levels of Se is wider than for most minerals".

[1]Contact at: P. O. Box 110910, Department of Animal Sciences, University of Florida, Gainesville, FL 32611; Tel: (352)392-7561-Office; Fax: (352)392-7652; mcdowell@animal.ufl.edu

Maximum Tolerable Selenium Concentrations

Selenium tolerance by domestic livestock varies with chemical form of the ingested element, duration and continuity of intake, criterion of tolerance that is applied, and nature of the whole diet. Maximum tolerable levels for livestock species have been estimated (NRC, 1980; Table 1). In Table 1 the tolerance levels for sheep, cattle, horses and rabbits are in parentheses at (2 ppm), indicating they were derived from extrapolation versus reliable data. This committee of the NRC has noted that signs of toxicosis have been seen in some animal species when 5 ppm Se was fed in relatively short-term studies and 4 ppm for rats fed semipurified diets. However, 2 ppm Se has produced no unequivocally toxic signs, and this dietary concentration is suggested as a maximum tolerable level for all species (NRC, 1980).

Table 1. Maximum Tolerable Se (ppm) for Domestic animals[a]

Cattle	Sheep	Swine	Poultry	Horse	Rabbit
(2)[b]	(2)	2	2	(2)	(2)

[a]NRC (1980)
[b]Levels in parenthesis derived by extrapolation

Is 2 ppm the maximum tolerable level for swine? Recent research from Ohio would suggest otherwise (Kim and Mahan, 200la, b, c). Kim and Mahan (2001c) fed Se-yeast and sodium selenite at Se levels of 0.3, 3, 7 and 10 ppm from 25 kg through one parity; toxicity (selenosis) occurred with both Se sources when fed at 7 to 10 ppm. Selenite was found to be more detrimental during lactation and Se-yeast more on reproductive performance. Kim and Mahan (2001b) fed 0.3, 1, 3, 5, 7 and 10 ppm Se for 12 wks to growing-finishing pigs. Selenosis was produced from diets containing 5 to 7 ppm of both sources, affecting weight gains, feed intake, hair loss and hoof lesions. Separation of the hoof at the coronary band site occurred at ≥ 10 ppm for selenite but at ≥ 15 ppm with organic Se (Kim and Mahan, 2001a). In concluding that > 5 ppm dietary Se, regardless of source, did produce signs of Se toxicity in growing swine, those authors postulated that the greater tissue retention of organic Se may reduce the incidence of Se toxicity.

This maximum safe Se level for ruminants of 2 ppm as suggested by NRC (1980) is controversial. Harr et al. (1967) noted that rats fed commercial diets showed 2 to 3 times greater resistance to Se toxicosis than when fed a semipurified diet. Unfortunately, this NRC estimate was based on data from monogastric animals and failed to sufficiently evaluate ruminant Se toxicosis studies from natural diets or to take into account that monogastric animals absorb much more Se than ruminants from their diets. This NRC estimate fails to consider that ruminal microorganisms may reduce Se to selenide or other compounds (Butler and Peterson, 1961; Peterson and Spedding, 1963; Hidiroglou et al., 1968), which are insoluble. Peterson and Spedding (1963) showed a reduction of orally administered selenite to insoluble or unavailable forms of Se by rumen microorganisms, illustrated in insoluble fecal Se.

It has been proven that Se is less available to ruminants than monogastrics (Wright and Bell, 1966). These researchers administered radio-labeled selenium (Se^{75}) in oral and intravenous doses to sheep and swine. Retention of oral Se^{75} after 120 hours was 77% in swine compared to 29% in sheep. In relation to net absorption, it was 36% for sheep and 86% for swine. We could speculate that since sheep only absorb 40% as much as pigs; sheep could potentially have a Se tolerance of 2.5 times higher than pigs.

Selenium Maximum Tolerance Studies in Sheep

At the University of Florida, three experiments with sheep were conducted to determine the maximum tolerable level of Se for ruminants.

Experiment 1- One year study in wether sheep (Cristaldi et al., 2005)

Thirty-nine crossbred wether lambs initially weighing 22.8±3.3 kg were randomly allotted to one of six treatments. Sodium selenite was added to provide 0.2 (control) 2, 4, 6, 8, and 10 ppm Se to a basal diet based on corn, cottonseed hulls and soybean meal for a 1 year trial. Serum and whole blood, wool, hooves, bile and five tissues were analyzed for Se concentrations. Five tissues at experiment termination were microscopically evaluated for tissue breakdown due to Se toxicosis. Also, five enzyme activities (alkaline phophatase, alanine transaminase, aspartate transaminase, creatinine phosphokinase and gamma glutamyl transferase) and albumin were determined.

Lamb body weights were not influenced by dietary Se concentrations ($P > 0.15$). Both serum (Table 2) and whole blood Se concentrations increased at each collection period as dietary Se level increased ($P < 0.01$). There was a strong positive correlation ($r = 0.92$) between serum and whole blood Se concentration.

Table 2. Effect of dietary Se level on serum Se concentration of wethers[a,b]

Serum Se	Added Se (ppm)					
(µg/mL)	0.2	2	4	6	8	10
Initial	0.09[d]	0.09[d]	0.09[d]	0.10[d]	0.09[d]	0.10[d]
12 wk	0.10[d]	0.19[d,e]	0.26[e,f]	0.31[f,g]	0.37[f,g]	0.39[h]
24 wk	0.13[d]	0.23[e]	0.31[e,f]	0.38[f,g]	0.40[f,g]	0.66[h]
40 wk	0.12[d]	0.27[e]	0.36[e,f]	0.50[g]	0.31[e,f]	0.83[h]
52 wk	0.12[d]	0.19[d]	0.29[e]	0.41[f]	0.49[f]	0.87[g]

[a]Dietary Se level response ($P<0.01$); time response ($P<0.01$); dietary Se level x time interaction ($P<0.01$).
[b]S.E.M. is 0.36 for treatments 0.2, 2 and 4 ppm added Se, 0.033-0.35 for 6 ppm Se, 0.033-0.054 for 8 ppm Se, and 0.033 for 10 ppm Se.

Increased dietary Se elevated wool Se concentrations ($P < 0.01$; Fig. 1). For the wool, there was a linear trend ($P < 0.001$) for all treatments. As with the serum, the

wool Se concentration reflected dietary Se level as did the hair in cattle of other reported research.

At termination of the study, all tissues, hoof, and bile Se concentrations increased as dietary Se level increased ($P<0.01$; Fig.2). Liver had the highest Se concentration followed by the kidney in all but the lowest dietary treatment of 0.2 ppm. Both gross and microscopic evaluation of tissues revealed no significant lesions for any treatment groups. There was no apparent pathological evidence of selenosis based on tissue evaluation. Albumin and serum enzyme levels suggestive of tissue breakdown as a result of selenosis did not vary ($P > 0.15$) among treatments, and enzymes were within their respective normal ranges

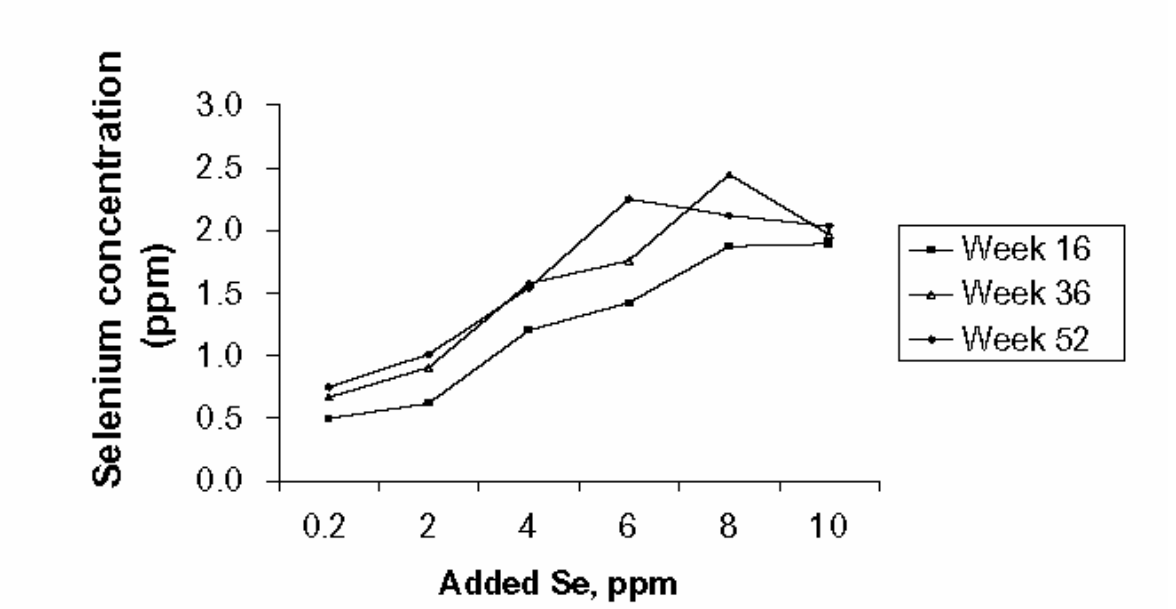

Figure 1. Effect of dietary Se level on wool Se concentration of wethers fed various levels of Se (selenite). S.E.M. is 0.25, 0.23–0.25, 0.23–0.31, 0.23 for 0.2, 2, and 4 ppm added Se, 6, 8, and 10 ppm, respectively.

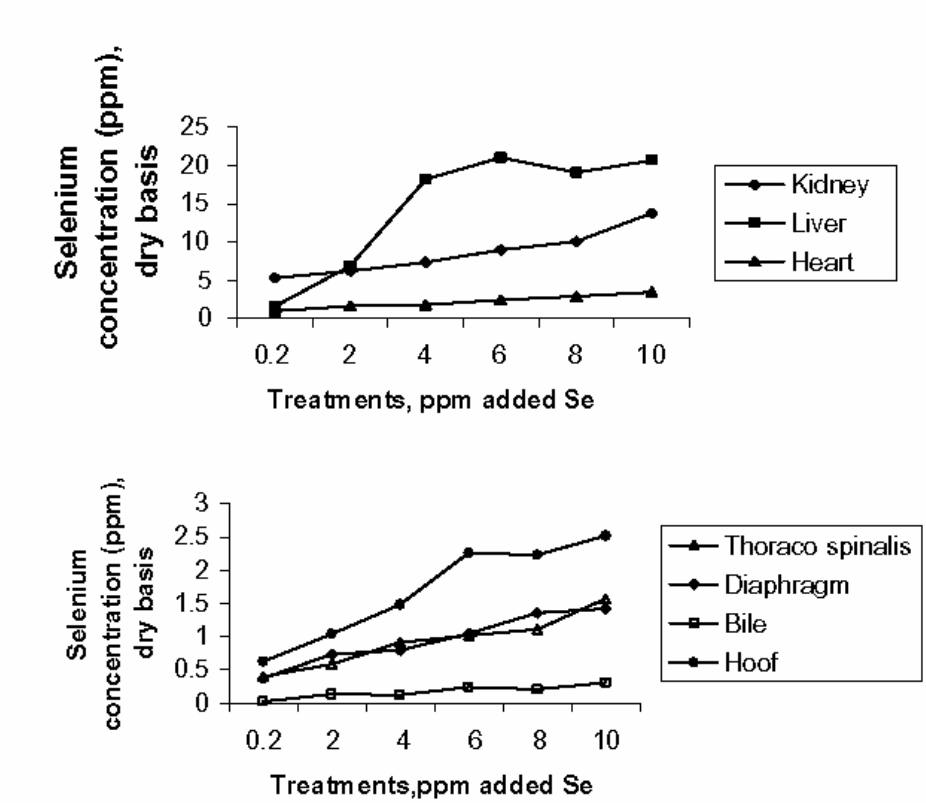

Figure 2. Effect of dietary Se level on tissue Se content. S.E.M. is 0.63–0.83, 3.58–4.73, 0.29–0.32, 0.13–0.17, 0.09–0.12, 0.05–0.06, 0.22–0.29 for kidney, liver, heart, thoraco spinalis, diaphragm, bile, and hoof, respectively.

These results suggest that ≥10 ppm dietary Se as selenite is not toxic to wether lambs when fed for 1 year. It seems plausible, therefore, to consider the maximum tolerable level of Se as selenite for sheep to be considerably higher than 2 ppm as previously suggested.

Experiment 2- 72 week study in gestating-lactating ewes (Davis et al., 2005a)

Forty-one range-type ewes were used in a completely randomized design with six dietary treatments. Sodium selenite was added to a corn-soybean meal basal diet to provide 0.2 (control), 4, 8, 12, 16, and 20 ppm dietary Se to ewes during lamb production. Serum Se and ewe body weights measured at 4-wk intervals, whole blood Se and wool Se were measured every 12 wk, and samples of brain, diaphragm, heart, hoof, kidney, liver, and psoas major muscle were collected at the termination of the experiment. Sections of liver, heart, kidney, diaphragm, and psoas major muscle were microscopically evaluated for possible Se toxicosis. Albumin and five enzymes were measured for the purpose of detecting tissue breakdown due to Se toxicosis as follows: alkaline phosphatase, alanine transaminase, aspartate transaminase, creatinine phosphokinase, and gamma glutamyl transferase.

Dietary Se did not affect ewe body weights in or during the study (P = 0.69). Both serum (Table 3) and whole blood Se increased linearly as dietary Se level increased (P < 0.001). Wool Se also increased linearly (P<0.001) as dietary Se increased. Brain, diaphragm, heart, and psoas major Se increased linearly as Se in the diet increased, liver Se responded quadratically, and hoof and kidney Se responded cubically (P ≤ 0.05) to treatment (Fig. 3, 4, 5).

Table 3. Effect of dietary inorganic Se level on serum Se concentration of mature ewes at various stages of lamb production[a]

	Dietary Se, mg/kg					
Stage of Production	0.2	4	8	12	16	20
	Serum Se, μg/L					
Late Gestation, yr 1[b]	149^{g} ± 67	242^{gh} ± 67	354^{hi} ± 79	414^{hi} ± 79	463^{i} ± 79	707^{j} ± 81
Lactation, yr 1[c]	151^{g} ± 56	272^{g} ± 54	486^{h} ± 63	623^{hi} ± 63	718^{ij} ± 63	811^{j} ± 66
Dry, rebreeding[d]	162^{g} ± 110	298^{gh} ± 95	458^{hi} ± 100	604^{i} ± 99	1205^{j} ± 106	1084^{j} ± 113
Late Gestation, yr 2[e]	140^{g} ± 137	313^{gh} ± 124	446^{gh} ± 142	596^{hi} ± 142	986^{ij} ± 158	1072^{j} ± 149
Lactation, yr 2[f]	127^{g} ± 114	325^{gh} ± 103	536^{hi} ± 114	718^{i} ± 114	769^{i} ± 136	1355^{j} ± 121

[a]Data represent least squares means ± SE.
[b]Late gestation, yr 1, defined as 56 d prepartum and includes serum Se concentrations for wk 4, 8, and 12.
[c]Lactation, yr 1, defined as 84 d postpartum and includes serum Se concentrations for wk 12, 16, 20, and 24.
[d]Dry, rebreeding period, 168 d, includes serum Se concentrations for wk 28, 32, 36, 40, 44, and 48.
[e]Late gestation, yr 2, defined as 56 d prepartum and includes serum Se concentrations for wk 52, 56, and 60.
[f]Lactation, yr 2, defined as 84 d postpartum and includes serum Se concentrations for wk 60, 64, 68, and 72.
[g,h,i,j]Means within rows lacking a common superscript differ ($P < 0.05$).

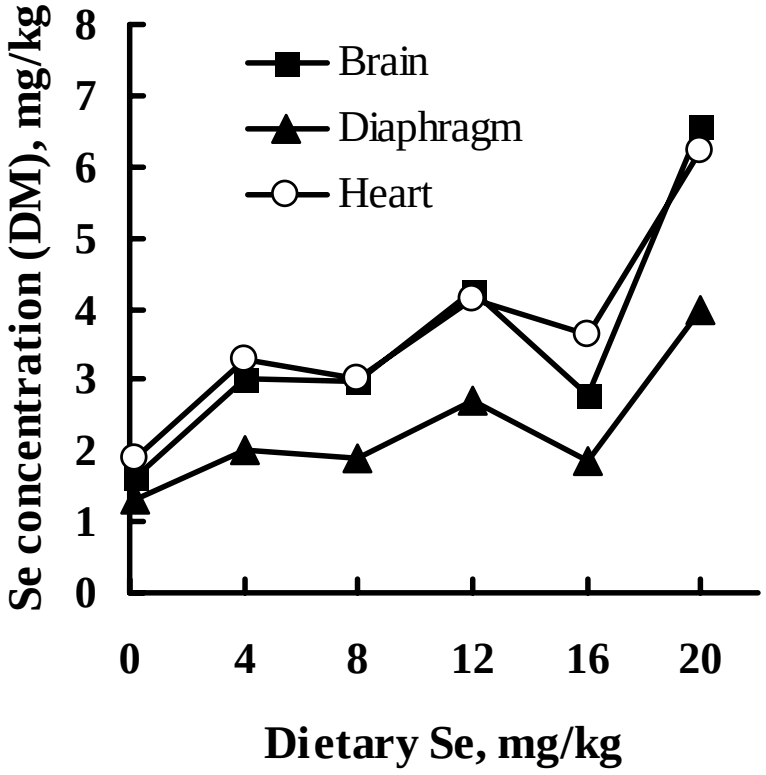

Figure 3. Effect of dietary inorganic Se level on Se concentrations in brain, diaphragm, and heart of ewes; SE = 0.6 to 0.9, 0.3 to 0.4, and 0.4 to 0.6 for brain, diaphragm, and heart, respectively.

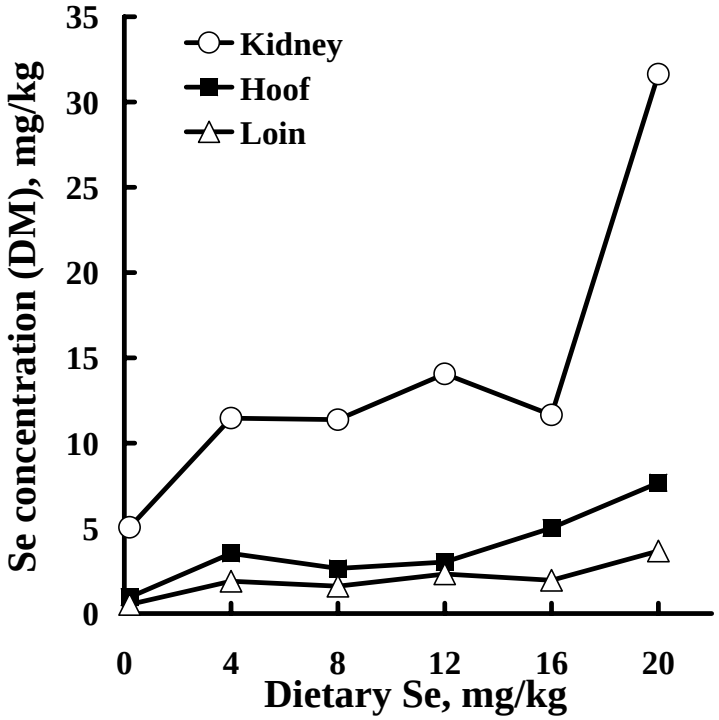

Figure 4. Effect of dietary inorganic Se level on Se concentrations in kidney, hoof, and loin (psoas major) of ewes; SE = 3.0 to 3.3, 0.8 to 1.1, and 0.3 to 0.5 for kidney, hoof, and loin, respectively.

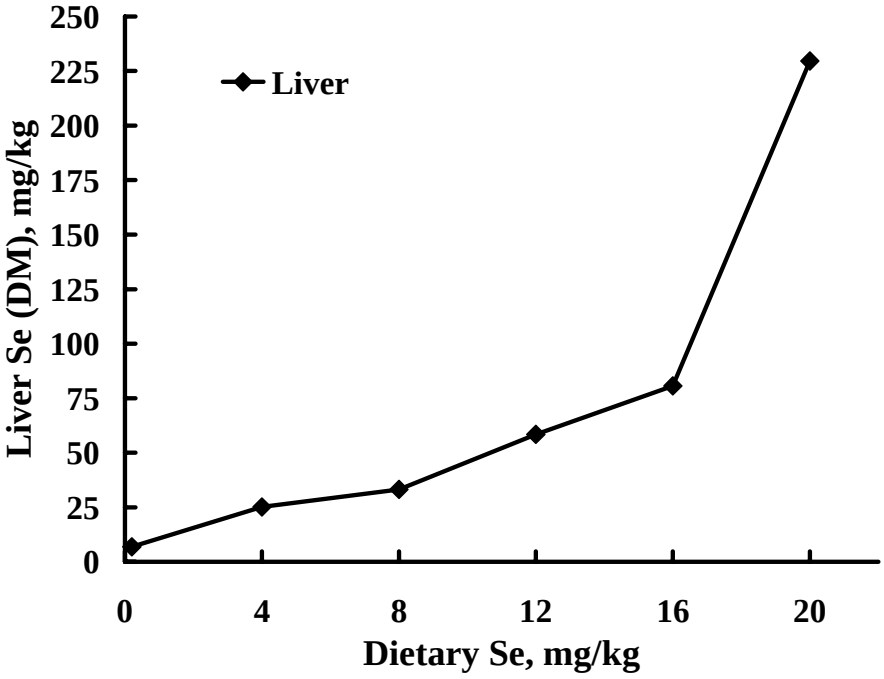

Figure 5. Effect of dietary inorganic Se level on liver Se concentration in ewes; SE = 27.5, 25.4, 24.5, 24.5, 34.6, and 26.9 for 0.2, 4, 8, 12, 16, and 20 mg/kg dietary Se, respectively.

Though serum, whole blood, and wool Se concentrations were elevated in ewes receiving increased dietary Se, at no time did serum, whole blood, or wool Se concentrations reach levels previously reported as toxic and a pattern of clinical signs of Se toxicosis was not observed. Histopathological microscopic evaluation of liver, kidney, diaphragm, heart, and psoas major muscle did not reveal evidence of Se toxicosis in ewes on any dietary Se level. Also, there was no evidence of tissue breakdown as albumin and serum enzymes were within their normal ranges.

Ewes under these experimental conditions and during the stresses of production were able to tolerate up to 20 ppm dietary Se as sodium selenite for 72 wk. These findings, likewise, suggest that the maximum tolerable level of inorganic Se for sheep to be much higher than 2 ppm as was suggested previously.

Experiment 3- Tolerance in wethers comparing selenite and Se yeast

Twenty-eight, 2-yr-old, Rambouillet-crossbred wethers (62.3 ± 8.5 kg initial BW) were utilized in a 2 x 4 factorial experiment 0.2, 20, 30, and 40 ppm dietary Se (as-fed) from sodium selenite or Se yeast added to a corn-soybean meal basal diet for 60 weeks (Davis et al., 2005b). Serum Se, whole blood Se, and wool Se were measured every 12 wk, and samples of brain, diaphragm, heart, hoof, kidney, liver, and loin muscle and serum samples for evaluation of albumin and enzyme activities (previously mentioned) were collected at the termination of the experiment.

Serum Se, whole blood Se, and wool Se concentrations increased ($P < 0.05$) as dietary level of Se increased. Serum Se, whole blood Se, and wool Se concentrations from wethers receiving organic Se were higher ($P < 0.001$) than those from wethers receiving inorganic Se. Selenium concentrations in brain, diaphragm, heart, hoof, kidney, liver, and loin muscle were affected ($P < 0.05$) by dietary Se level, with higher Se concentrations generally observed in tissues from wethers receiving organic Se (Table 4). Though Se concentrations in serum, blood, wool, and major organs at most times exceeded concentrations previously reported in livestock suffering from Se toxicosis, a pattern of clinical signs of Se toxicosis was not observed in this experiment. Histopathological evaluation, as well as normal serum concentrations of albumin and enzyme activities, microscopic evaluation of liver, kidney, diaphragm, heart, and psoas major muscle did not reveal evidence of Se toxicosis in wethers on any dietary Se treatment. Wethers under these experimental conditions tolerated up to 40 ppm dietary Se for 60 wk, though differences in Se source were observed.

Table 4. Effects of four dietary levels of Se as sodium selenite or Se yeast on tissue Se of wethers[a]

	Se source								
	Sodium selenite				Se yeast				
	Dietary Se level, mg/kg								
Tissue	0.2	20	30	40	0.2	20	30	40	SEM
	Se concentration, mg/kg								
Brain	1.28	4.22	4.74	6.87	6.12	21.90	32.30	18.71	0.99[bcd]
Diaphragm	0.82	4.74	3.33	7.81	5.28	10.30	26.34	20.71	2.69[bcde]
Heart	1.59	3.80	5.13	6.23	6.35	23.77	28.71	33.93	2.43[bcd]
Hoof	3.44	8.79	9.68	13.78	6.26	12.53	29.20	23.66	5.52[ce]
Kidney	8.43	19.94	27.93	27.89	22.26	33.96	77.61	36.28	6.87[bcde]
Liver	2.66	31.72	41.42	78.18	15.67	23.42	132.73	41.24	18.17[bde]
Loin	0.71	3.13	4.41	5.13	5.73	14.69	23.51	26.87	1.05[bcd]

[a]Data represent least squares means and pooled SE.
[b]Dietary Se level response ($P < 0.05$).
[c]Selenium source response ($P < 0.05$).
[d]Dietary Se level × Se source interaction ($P < 0.05$).
[e]Dietary Se level linear response ($P < 0.10$).

Selenium Tolerance in Relation to Other Trace Elements

In relation to toxicity, is Se the most dangerous supplemental element for ruminants? We often hear the statement that "the range between optimal and toxic levels of Se is narrow". At best there could be very limited validity to that statement if the maximum tolerance of Se for all livestock was 2 ppm (NRC, 1980). However, even for swine it is suggested that 5 ppm is a more logical tolerance level (Kim and Mahan, 2001 a, b, c). Older research has shown that ruminants metabolize Se differently than monogastric animals (Peterson and Spedding, 1963; Hidiroglou et al., 1963). As previously mentioned, Wright and Bell (1966) noted that swine have retained 2.7 times more Se than sheep. Recent data from the University of Florida (Cristaldi et al., 2005; Davis et al., 2005a,b) have shown that sheep tolerated over 10 ppm Se for relatively long periods of time.

Using 10 ppm as a suggested tolerance level, Table 5 illustrates the range between optimal and toxic levels of Se in relation to other trace minerals for beef cattle. It is apparent that Co, Cu, Fe, Mn and Zn have a narrower optimal to toxic level than Se. Both Se and I have the widest ratio of requirement to toxicity of 100. Most macro minerals have even a less favorable requirement to tolerance ratio. As an example, ratio of tolerance to requirement is only 2:1 for Mg, 4.2:1 for K and 2.6:1 for S.

Table 5. The ratio of required to maximum tolerable level of trace minerals (ppm) for beef cattle.

Trace Mineral	Requirement[a]	Maximum Tolerable Level[b]	Requirement to Tolerable level
Cobalt	0.2[c]	10	50
Copper	10	100	10
Iodine	0.50	50	100
Iron	50	1000	20
Manganese	20	1000	50
Selenium	0.1	10	100
Zinc	30	500	16.7

[a] NRC (1996)-Requirements are for gestating and early lactating beef cows.
[b] NRC (1980)
[c] Stangl et al (2000)-Requirement suggested to be 0.2-0.3 ppm

Summary and Implications

Three experiments were carried out with sheep to determine maximum tolerance level of Se. The shortest duration of the experiments was one year. Each experiment examined wool, hooves, blood, tissue levels, tissue pathology, albumin and serum enzymes suggestive of tissue breakdown. Selenium toxicosis was not found in any experiment and, therefore it is suggested that sheep (and likely other ruminants) can tolerate over 10 ppm for relatively long periods of time. Organic sources of Se result in higher tissue concentrations of Se than selenite Se. However the organic sources may be less toxic. Experiments which are longer in duration and use different Se sources are necessary to clearly define the maximum tolerable level of Se. Nevertheless, the maximum tolerable level of Se, regardless of source, is much higher than the current estimate of 2 ppm. In relation to most other minerals Se has a wider optimal requirement to toxic level.

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