

Selenium nutrition of dairy cows: comparing responses to organic and inorganic selenium forms

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Introduction

Research regarding the nutritional importance of selenium (Se) has changed markedly over the last 75 years. In the 1930s selenium was identified as the toxic agent causing alkali disease in animals. In the 1940s and early 1950s research was conducted to identify the specific seleno-compounds causing toxicity and to develop prophylactic and treatment schemes for selenium toxicity. Selenium research changed completely after Schwarz and Folz (1957) reported that selenium was an essential nutrient for laboratory animals. Research quickly focused on domestic animals and selenium deficiency was identified as a cause of white muscle disease (Muth *et al.*, 1958). In 1979, after years of research showing many beneficial effects of selenium supplementation of domestic animals, the US Food and Drug Administration published regulations that legalized selenium supplementation of diets for dairy cattle. The current (February 2003) US FDA regulation was published 1987 and allows ruminant diets to be supplemented with 0.3 ppm selenium from either sodium selenite or selenate. However, we can expect this to be amended soon to allow supplementation with selenium yeast.

Selenium absorption and metabolism

SELENIUM ABSORPTION FROM THE GUT

The most prevalent forms of selenium consumed by ruminants are selenomethionine (SeMet), selenocysteine (SeCys), selenite, and selenate. Basal feedstuffs and selenized yeast (selenium yeast) provide mostly selenoamino acids and inorganic supplements provide selenite and selenate.

The selenoamino acids are identical to their counterparts (i.e., methionine and cysteine) except that a selenium molecule replaces the sulfur. Limited data are available on ruminal metabolism of selenium compounds and essentially no information is available on selenium absorption mechanisms in ruminants. Selenium speciation studies have not been conducted to determine the specific selenium compounds that are produced in the rumen. Most of the selenate that is consumed is probably reduced to selenite in the rumen (Paulson *et al.*, 1968). Some of the selenite (either consumed or produced from selenate) may be converted to low molecular weight insoluble compounds and some of the selenium from selenite is found in bacterial proteins (Paulson *et al.*, 1968; Whanger *et al.*, 1968). The insoluble low molecular weight compounds formed in the rumen probably have low digestibility. Selenium from SeMet appears to undergo fewer alterations in rumen contents than selenite (Whanger *et al.*, 1968). Absorption of selenium compounds occurs in the small intestine and differences between SeMet, selenite, and selenate have been observed with laboratory animals. Absorption of selenate and SeMet from ligated intestinal loops of rats was about 80% of dose but only 35% for selenite (Vendeland *et al.*, 1992). SeMet is probably absorbed from the intestine via the methionine transporter system. Selenate appears to have an active transport system and absorption of selenite appears to be mainly by passive diffusion.

The apparent digestibility of selenium [i.e., (Se intake - fecal Se)/Se intake] has been measured in ruminants but the data must be interpreted carefully. A certain portion of fecal selenium is endogenous, therefore apparent digestibility underestimates true

digestibility The underestimation is greater at low selenium intakes. Endogenous fecal selenium can be measured by dosing labeled selenium into the blood and measuring fecal appearance of the label. It also can be estimated by regressing selenium intake on intake of apparently digested selenium (the intercept is an estimate of endogenous fecal selenium). Koenig *et al.* (1991) proposed a method to estimate endogenous fecal selenium by dividing tracer enrichment in feces by tracer enrichment of certain tissues and multiplying by fecal selenium excretion. The accuracy of that method has not been confirmed. Using the first two methods, true digestibility of selenium from selenate or selenite was 51.5% in dry dairy cows (Harrison and Conrad, 1984a; 1984b), 51% in lactating dairy cows fed diets with normal sulfur concentrations (Ivancic and Weiss, 2001), and 37 to 64% in lactating goats (Aspila, 1991). Koenig *et al.* (1991) using the method outlined above reported true digestibility values of 9 to 11% in dry cows. Data on the true digestibility of selenium from SeMet (or other organic sources) is extremely limited for ruminants. Aspila (1991) reported that selenium from SeMet had a true absorption of 65% in lactating goats. A study with sheep using an oral dose of labeled selenium reported that apparent digestibility of selenium from selenite was slightly higher than that for SeMet (42.7 vs. 38.4%) (Koenig *et al.*, 1997). The limited data that are available suggest that under normal dietary conditions (no antagonists) absorption of selenium from selenite (or selenate) or SeMet is similar in ruminants.

SELENIUM METABOLISM

When inorganic selenium (selenite or selenate) is consumed, selenate is probably reduced to selenite, which is then absorbed. Once absorbed, selenite is reduced to selenide via a series of reactions. The selenide can then be used in the synthesis of SeCys (Figure 1). When SeMet is consumed, the selenium moiety can be removed, reduced to selenide, and used for synthesis of SeCys. Alternatively, SeMet can remain intact and be used in protein synthesis. A specific tRNA has not been identified for SeMet and it appears that no discrimination occurs between methionine and SeMet during protein synthesis.

The active form of selenium in selenoenzymes is SeCys, however dietary SeCys is not incorporated directly into the active site of selenoenzymes (Sunde and Hoekstra, 1980; Sunde and Evenson, 1987). The SeCys used in the active site of selenoenzymes is produced during protein translation. The hydroxyl group of a serine molecule that is linked to a specific tRNA (UGA codon) is replaced with a selenol moiety (forming SeCys-tRNA), which is then inserted during the synthesis of selenoenzymes. Dietary selenium, regardless of the form consumed, must first be converted to inorganic selenide, which is then used to synthesize 'bioactive' SeCys.

Cattle responses to selenium supplementation

The soils in the major dairy areas of the US (east

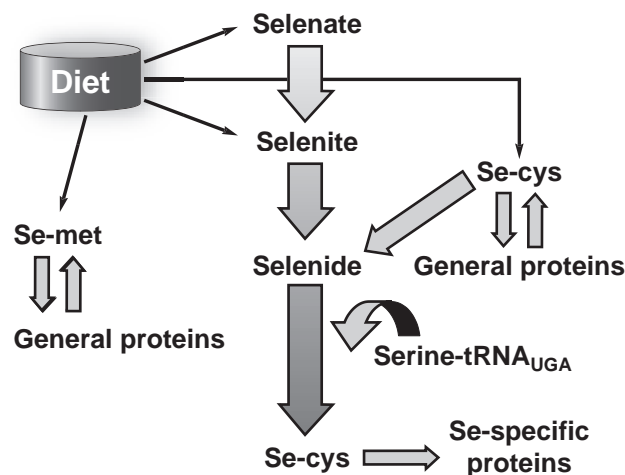


Figure 1. Basic pathways for selenium metabolism in animals.

of the Mississippi and west of the Rocky Mountains) are low in selenium, therefore, feeds produced in those areas also are low in the element. Most diets in these areas that are not supplemented with selenium would be considered Se-deficient. An important factor common to all the clinical and immunological experiments is that most control diets would be considered deficient in selenium and treatment diets generally contained either 0.1 or 0.3 ppm supplemental selenium. Supplementation of selenium to deficient diets often elicits a positive response; additional supplementation of Se-adequate diets should not be expected to produce additional clinical benefits.

Growth responses to selenium supplementation have generally been non-significant or slightly positive for beef cattle. Likewise, milk production rarely increases when Se-deficient animals are supplemented. Although substantial production responses are rarely observed when selenium is supplemented, supplementation can improve animal health. Research studies with dairy and beef cattle have found the following clinical responses to selenium supplementation of Se-deficient diets: 1) reduced prevalence of retained fetal membranes (Harrison *et al.*, 1984), 2) reduced severity and prevalence of clinical mastitis (Smith *et al.*, 1997), 3) reduced milk somatic cell counts (Weiss *et al.*, 1990), and 4) reduced calf mortality (Spears *et al.*, 1986).

RETAINED FETAL MEMBRANES (RETAINED PLACENTA)

A survey of high producing herds in the US found that about 9% of all calvings resulted in retained fetal membranes (RFM) (Kellogg *et al.*, 2001). The estimated total cost associated with RFM ranges from about \$100 to \$280/case (Joosten *et al.*, 1988; Kelton *et al.*, 1998). Selenium supplementation (dietary and/or injected) reduced the incidence of RFM in about 80% of the studies (Harrison and Hancock, 1999). The incidence of RFM for cows that have low vitamin E status often is not influenced by selenium supplementation (Harrison *et al.*, 1984). Kimura *et al.* (2002) reported that neutrophils from cows with RFM had significantly less killing ability than neutrophils from cows without RFM (this difference was observed about two weeks before calving). Neutrophils from Se-deficient cows have lower killing ability than neutrophils from Se-

adequate cows (Hogan *et al.*, 1990). The effect of selenium on neutrophils may explain why selenium supplementation reduced RFM.

MASTITIS

Mastitis is an extremely prevalent and expensive problem for dairy farmers. On well-managed farms, approximately 50 cases of clinical mastitis can be expected per 100 cow-years (assuming 305 day lactation). The total costs associated with clinical mastitis range from about \$100 to \$140 per case (Hoblet *et al.*, 1991). Compared with cows receiving no supplemental selenium, dietary supplementation or injections of selenium has reduced the prevalence and severity of clinical mastitis from natural infections and experimental *E. coli* challenge (Smith *et al.*, 1984; Erskine *et al.*, 1989; Malbe *et al.*, 1995). Selenium supplementation did not affect the response to *Staphylococcus aureus* challenge (Erskine *et al.*, 1990). The positive effect of selenium supplementation on clinical mastitis is probably mediated via effects of selenium on neutrophils and other immune cells. In the US, studies have found a negative correlation between somatic cell count and selenium status (Erskine *et al.*, 1987; Weiss *et al.*, 1990), but no relationship was observed in a study from New Zealand (Grace *et al.*, 1997). One likely difference between the US and New Zealand studies is the vitamin E status of the cows. Cows on the New Zealand study grazed high quality pasture (expected to have very high intakes of vitamin E); cows in the US studies were in confinement and vitamin E intakes probably were much lower.

Immunological responses to selenium

Immune function is an extremely broad term used to describe changes in immune cell population, changes in function of different immune cells, changes in antibody production or titers, and changes in concentrations or production of immunologically active compounds. Nutritional effects on immune response are studied using both *in vitro* and *in vivo* models. *In vitro* immune response studies involve collecting different types of immune cells from animals fed diets with different concentrations of the nutrient of interest and/or incubating cells in

media containing different concentrations of the nutrient of interest and measuring responses. *In vivo* studies involve animals fed different diets that are then experimentally challenged or vaccinated and measuring immune responses. Although both types of studies provide equivocal data regarding clinical response, results from these studies provide useful supporting information to clinical studies and provide information regarding potential modes of action. The preponderance of studies using cattle (beef and dairy) or sheep have reported positive immune function responses with supplemental selenium (Table 1).

Comparing selenium sources

The amount of selenium that can be supplemented in the US is regulated and set at 0.3 mg/kg of diet and most diets in the US should be supplemented with the maximum legal amount. Essentially no data are available suggesting that additional selenium above 0.3 mg/kg of diet produces any beneficial effects when dietary antagonists are not present. At the current time, only sodium selenite and sodium selenate can be used as sources of supplemental selenium for dairy and beef cattle in the US. In many other countries, selenium yeast is approved

and can be included in diets. In recent years several comparisons between inorganic selenium (selenite or selenate) and Sel-Plex™ selenium yeast have been made using dairy cattle. Selenium supplementation is unlikely to produce significant growth and milk yield responses; therefore production studies are unlikely to differentiate between selenium sources. Clinical studies (e.g., effects of selenium source on RFM) are the best way to compare sources but these experiments are extremely expensive (large number of cows and long duration). In lieu of clinical studies, common methods to compare selenium sources include measuring selenium concentrations in whole blood, plasma, milk, and various tissues, or measuring the activity of the selenoenzyme, glutathione peroxidase (GSH-Px) in whole blood. Any differences in those measures may or may not relate to different clinical responses.

INORGANIC SELENIUM SOURCES

One study using sheep fed high amounts of selenium found that selenium from sodium selenate increased tissue concentrations of selenium about 30% more than the same amount of selenium from sodium selenite (Henry *et al.*, 1988). However, studies with

Table 1. Immune function responses to supplemental selenium (sometimes with supplemental vitamin E) given to ruminants.

Response	Reference
Positive responses	
Increased IgG titer (steers)	Droke and Loerch (1989)
Increased <i>in vitro</i> lymphocyte killing ability (lambs)	Finch and Turner (1989)
Increased antibody titers (lambs)	Reffitt <i>et al.</i> (1989)
Increased neutrophil kill (dairy cows)	Hogan <i>et al.</i> (1990)
Increased lymphocyte proliferation (heifers)	Stabel <i>et al.</i> (1990)
Increased lymphocyte proliferation (lambs)	Turner and Finch (1990)
Increased lymphocyte proliferation (dairy cows)	Maddox <i>et al.</i> (1991)
Increased IgM production (dairy cows)	Stabel <i>et al.</i> (1991)
Increased lymphocyte proliferation (dairy cows)	Cao <i>et al.</i> (1992)
Increased antibody titers (beef cattle)	Nicholson <i>et al.</i> (1993)
Increased lymphocyte proliferation (calves)	Pollock <i>et al.</i> (1994)
Increased serum and colostrum IgG (beef cows)	Awadeh <i>et al.</i> (1998)
Increased neutrophil activity (ewes)	Morgante <i>et al.</i> (1999)
Increased cell-mediated immunity (lambs)	Lacetera <i>et al.</i> (1999)
Increased antibody titers after vaccination (dairy cows)	Panousis <i>et al.</i> (2001)
No response	
IgG and IgM generally not affected (calves)	Stabel <i>et al.</i> (1989)
No effect on antibody titers after vaccination (sheep)	Ellis <i>et al.</i> (1990)
No effect on antibody titers after vaccination (heifers)	Nemec <i>et al.</i> (1990)
No effect on lymphocyte proliferation (dairy cows)	Sordillo <i>et al.</i> (1993)
No effect on colostrum IgG concentrations (dairy cows)	Lacetera <i>et al.</i> (1996)
No effect on virus titer after vaccination (dairy cows)	Ellis <i>et al.</i> (1997)

dairy cows and heifers using diets with typical selenium concentrations (Ortman *et al.*, 1999; Ortman and Pehrson, 1999) found little difference between selenite and selenate based on GSH-Px activities and selenium concentrations in blood and milk. Overall, differences between sodium selenite and sodium selenate for dairy cows appear to be small or insignificant. Based on selenium metabolism (i.e., selenate is probably converted to selenite in the rumen), few differences should be expected.

SELENIZED YEAST

Eight studies with cows, heifers, or steers were found that made direct statistical comparisons on the effects of selenium from selenite or selenium yeast on whole blood concentrations of selenium, all but one of which were conducted with Alltech's Sel-Plex™. Three studies reported higher ($P < 0.05$) whole blood selenium when selenium yeast was fed (Ortman *et al.*, 1999; Ortman and Pehrson, 1997; 1999). One study reported higher concentrations when 2 mg of selenium from selenium yeast was fed to dairy cows compared with 2 mg of selenium from selenite but no effect of selenium source when 4 mg of selenium were fed (Knowles *et al.*, 1999). Another study reported higher whole blood selenium with selenium yeast than with selenite when fed to growing beef animals but not when fed to dairy heifers (Nicholson *et al.*, 1991). Three studies

reported no overall difference in whole blood selenium when selenium yeast or selenite was fed (Nicholson *et al.*, 1993; Awadeh *et al.*, 1998; Pehrson *et al.*, 1999). In two other studies, direct statistical comparisons were not made but numerically one study reported essentially no difference in whole blood selenium between dairy cows fed selenite or selenium yeast (Fisher *et al.*, 1995), the other study reported substantially higher whole blood selenium when selenium yeast was fed to dairy cows (Malbe *et al.*, 1995). Within each study, relative concentration of whole blood selenium was calculated by dividing selenium concentration obtained when selenium yeast was fed by whole blood selenium when selenite was fed. The median response for the ten studies (12 comparisons) was 1.18 (ie, median whole blood selenium concentration was 1.18 times higher when selenium yeast was fed compared with selenite) (Figure 2). Relative differences between concentrations of selenium in plasma or serum when selenium yeast or selenite are fed are similar to those observed with whole blood (data not shown).

Whole blood GSH-Px activity was statistically higher for dairy heifers fed selenium yeast compared with those fed selenite (Pehrson *et al.*, 1989). Knowles *et al.* (1999) reported significantly higher whole blood GSH-Px activity for dairy cows fed selenium yeast than for those fed selenite when supplemented at 2 mg Se/day, but no difference was

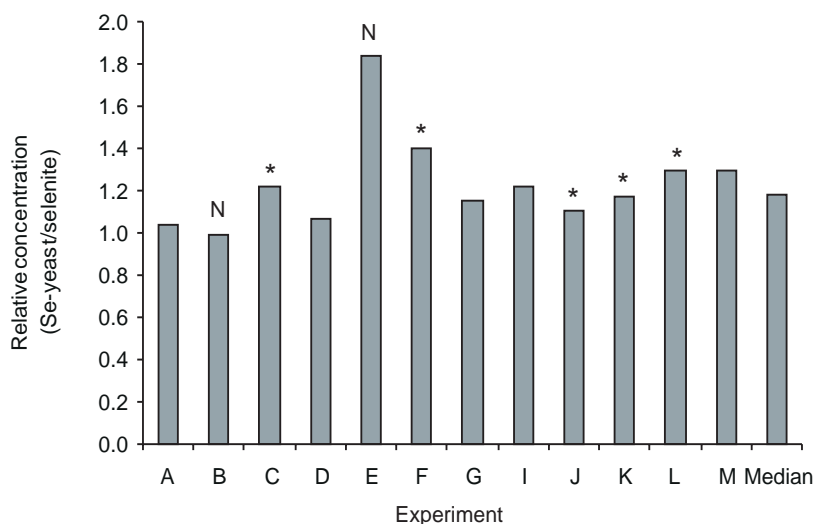


Figure 2. Relative concentrations (i.e., a value of 1.1 indicates response was 1.1 times higher for selenium yeast) of whole blood selenium in cattle fed selenium yeast compared with selenite or selenate (see Table 2 for citation list).

N = not tested statistically; * = $P < 0.05$.

Table 2. Citation list for Figures 2, 3, and 4.

Experiment code on figure				Animal Type	Citation
Figure 2	Figure 3	Figure 4			
A	A	A		Beef cows	Awadeh <i>et al.</i> (1998) ²
B	...	B		Dairy cows	Fisher <i>et al.</i> (1995) ²
C	C	C		Dairy cows	Knowles <i>et al.</i> (1999) (2 mg) ²
D	D	D		Dairy cows	Knowles <i>et al.</i> (1999) (4 mg) ²
E	E	E		Dairy cows	Malbe <i>et al.</i> (1995)
F		Beef heifers+steers	Nicholson <i>et al.</i> (1991)
G		Dairy heifers	Nicholson <i>et al.</i> (1991)
...	H	...		Combined ¹	Nicholson <i>et al.</i> (1991)
I	I	...		Growing beef	Nicholson <i>et al.</i> (1993)
J	J	J		Dairy cows	Ortman and Pehrson (1997) ²
K	K	K		Dairy cows	Ortman and Pehrson (1999)
L	L			Dairy heifers	Ortman <i>et al.</i> (1999)
M	M	M		Beef cows	Pehrson <i>et al.</i> (1999) ²
...	N	...		Dairy heifers	Pehrson <i>et al.</i> (1989)
...	...	O		Dairy cows	Weiss (unpublished) ²

¹GSH-Px data not presented individually for beef animals and dairy heifers. Data are combined results for all animal types (Nicholson *et al.*, 1991).

²Experiments using Sel-Plex™

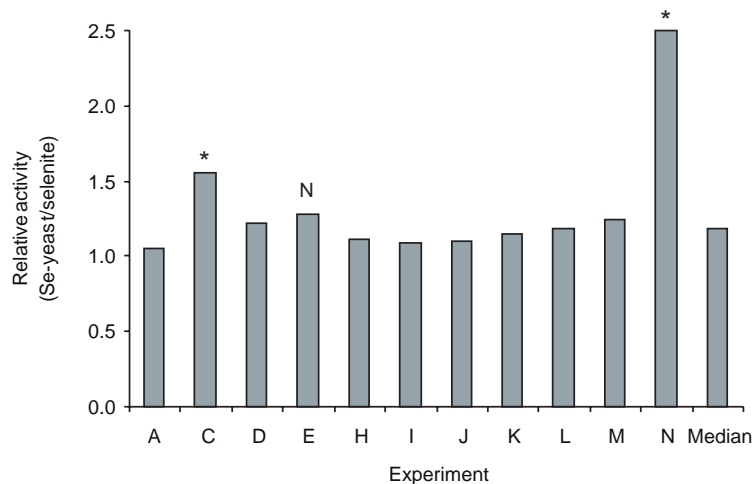


Figure 3. Relative activity (i.e. a value of 1.1 indicates response was 1.1 times higher for selenium yeast) of whole blood GSH-Px in cattle fed selenium yeast compared with selenite or selenate (see Table 2 for citation list). N = not tested statistically; * = P<0.05.

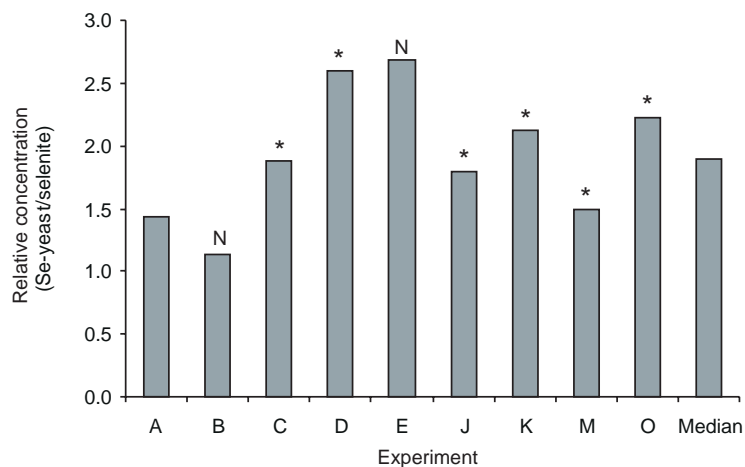


Figure 4. Relative concentrations (i.e., a value of 1.1 indicates response was 1.1 times higher for selenium yeast) of milk selenium from cows fed selenium yeast compared with selenite or selenate (see Table 2 for citation list).

N = not tested statistically; * = P<0.05.

observed when 4 mg Se/d was fed. Eight studies reported no statistical difference in whole blood GSH-Px activity between cattle fed selenium yeast or selenite (Figure 3). Malbe *et al.* (1995) reported higher numerical values for GSH-Px when cows were fed selenium yeast than when fed selenite but statistical analysis could not be conducted. The median relative GSH-Px activity (11 observations) for animals fed selenium yeast was 1.18 times higher than for animals fed selenite (Figure 3).

Five studies reported statistically significant increases in milk selenium concentrations when cows were fed selenium yeast compared with selenite (Figure 4). One study with beef cows reported a non-significant increase. Two studies could not statistically compare treatment effects (one study had a large numerical increase when selenium yeast was fed and the other reported a small difference in milk selenium between cows fed selenium yeast and those fed selenite). The median relative concentration of selenium in milk from cows fed selenium yeast 1.9 times higher than for cows fed selenite (Figure 4).

The way selenium is metabolized explains the different responses in various measures of selenium status when selenite and selenium yeast are compared (i.e., large differences in milk concentrations compared with small differences in whole blood selenium and GSH-Px activity). Activity of whole blood GSH-Px is an index of the available inorganic selenide pool in the body. Whole blood selenium includes the selenium in GSH-Px and other specific selenoproteins, some inorganic Se, and the selenium in SeMet. If SeMet is fed, it would be found in most blood proteins and in the plasma methionine pool as it is transported to tissues. The milk selenium pool consists of specific selenoproteins, probably some inorganic Se, and proteins containing SeMet. When SeMet is absorbed the selenium can enter the methionine pool or the inorganic selenide pool. The SeMet in the methionine pool behaves exactly as methionine and is used to synthesize proteins such as muscle and casein. Ruminants fed selenium yeast almost always have higher milk selenium concentrations and body retention of selenium than animals fed selenite because SeMet is incorporated into all synthesized body proteins. When selenite is fed, the majority of the absorbed selenium enters the inorganic pool and is probably used for SeCys synthesis and is incorporated mainly into specific selenoproteins, not into proteins such as casein. In summary, the small

and usually non-significant increase in GSH-Px activity when selenium yeast is fed indicates that selenium yeast provides equal to slightly higher amounts of selenide for SeCys synthesis compared with selenite. The higher concentration of selenium in whole blood when selenium yeast is fed is probably caused by increases in circulating SeMet (either in a protein or as a free amino acid). Circulating free SeMet would be removed by tissues for protein synthesis. The mammary gland extracts large amounts of methionine to make milk proteins. Milk is a terminal pool for methionine (or SeMet). Once SeMet is incorporated into milk protein it does not re-enter the circulating pool. The large increase in milk selenium concentrations observed when selenium yeast is fed is mostly caused by the continual incorporation of SeMet into casein during milk synthesis.

Dietary factors affecting selenium utilization

Several minerals and vitamins have been shown to affect selenium absorption and utilization, but most of the studies have used laboratory animals. In ruminants, two macrominerals, calcium (Ca) and sulfur (S), have been shown to influence selenium utilization in cattle. In calves, dietary calcium (ranged from 0.17 to 2.35%) had a minor effect on selenium absorption and selenium concentration in tissues (Alfaro *et al.*, 1987). Maximum selenium absorption occurred when diets contained 1.5% Ca. In dry dairy cows, maximum selenium absorption occurred when diets contained 0.9% Ca (ranged from 0.4 to 1.3%) (Harrison and Conrad, 1984a). Selenium absorption was about 40% higher when diets contained 0.9% Ca than when they contained either 0.5 or 1.3% Ca. In sheep, increasing dietary sulfur (sodium sulfate) from 0.05 to 0.24% linearly reduced selenium absorption (Pope *et al.*, 1979). Ivancic and Weiss (2001) also found a linear reduction in selenium digestibility (from selenate) by dairy cows as sulfur (from a mixture of magnesium and calcium sulfate) increased from 0 to 0.4% (Figure 5). Only cows fed no supplemental sulfate and 0.3 ppm Se were in positive selenium balance, and sulfur supplementation reduced plasma selenium concentrations after 112 days. Conversely in an 85 day trial with growing beef cattle (initial weight 210 kg) no differences in whole blood selenium were observed between calves fed no supplemental sulfur or those fed approximately

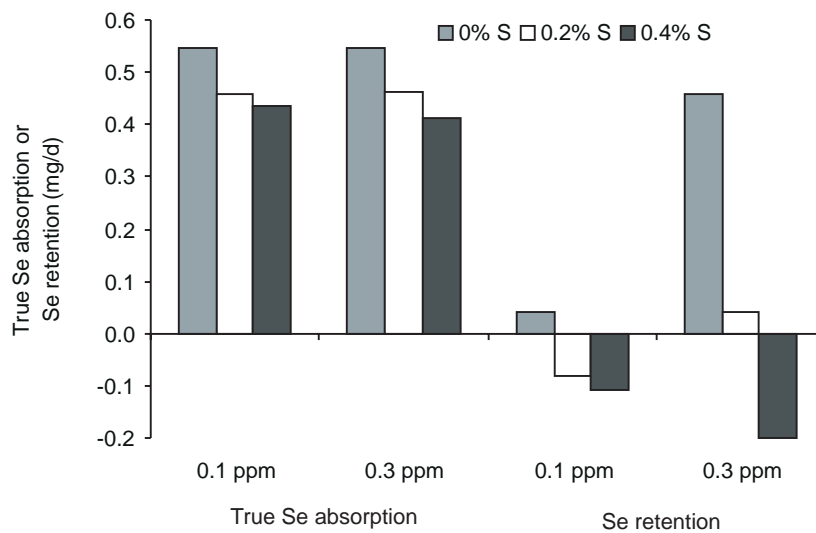


Figure 5. Effect of increasing dietary sulfur via calcium and magnesium sulfate on true digestibility and balance of selenium in lactating dairy cows when fed 0.1 or 0.3 ppm supplemental selenium from selenate (Ivancic and Weiss, 2001).

0.3% added sulfur from calcium sulfate (Khan *et al.*, 1987). Van Ryssen *et al.* (1998) reported that feeding 0.2% added sulfur from sodium sulfate reduced liver selenium but did not affect plasma Se. Gant *et al.* (1998) reported no adverse effects on selenium when dairy cows were fed a diet with 0.4% added sulfur from sulfate for the last 21 days of gestation. Elevated intake of sulfate (from water or feed) for long periods of time (months) appears to reduce selenium status of ruminants fed selenite or selenate. Sulfur reduces uptake of selenium (from selenite) by ruminal bacteria (Van Ryssen *et al.*, 1998). This could change the form of selenium reaching the intestine and reduce its absorption. Sulfur could also interfere with the intestinal selenite transport system. Ruminal metabolism of SeMet is less than that of selenite, and intestinal absorption of SeMet occurs via an amino acid transport system. Those two differences suggest that sulfate would have less effect on the digestibility of selenium from SeMet than from selenite.

Summary and implications

Selenium is needed to maintain good health of cattle. Cows fed inadequate amounts of selenium are at higher risk for retained fetal membranes and mastitis. Many measures of immune function are reduced when ruminants are fed Se-deficient diets. The majority of data suggest that cows need to consume approximately 4 to 10 mg of selenium per

day when selenate or selenite is the primary source of dietary Se. Selenium yeast results in up to 20% higher GSH-Px activity, and selenium blood concentrations compared with similar amounts of selenium from selenite. The research has not been conducted, but differences may be greater between selenium sources when dietary antagonists such as sulfate are consumed. Milk selenium concentrations are approximately twice as high when selenium yeast is fed compared with selenite or selenate. Higher milk selenium concentrations would result in increased intake of selenium by humans consuming dairy products that may have positive human health implications. Increased milk (and colostrum) selenium concentrations when selenium yeast is fed would also increase selenium intake by calves. In addition, calves borne from cows fed selenium yeast generally have higher plasma concentrations of selenium at birth. The higher milk selenium concentrations and increased selenium concentrations in the newborn calf when selenium yeast is fed to the cow may have positive calf health implications.

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