A RESEARCH REVIEW™
PRODUCT REVIEW

Multimin® for Supplementation of Trace Minerals in Dairy Cows

Making Education Easy **2021**

About the Expert

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Hamish Newton graduated from Massey University with a BVSc in 1998 and started working in mixed practice at the Veterinary Centre – Oamaru. He then worked in mixed practice in the UK before starting a PhD at Bristol University examining factors that influence the cure of intramammary infections in the involuting mammary gland. Upon completing his PhD in 2007 he returned to the Veterinary Centre – Oamaru and became a partner in 2008. He now spends most of his working time dealing with dairy cows.

This review is intended as an educational resource for veterinary health professionals and dairy farmers. It is a summary of the role of trace minerals supplementation in supporting dairy cow health and reproductive efficiency, with a focus on the injectable trace minerals supplement, Multimin®, and its strategic use in dairy herds during times of high trace mineral demand. This review is funded by Virbac NZ.

Trace minerals

Inorganic elements are required in animals for optimal growth, reproduction, and resistance to infectious disease.[1-3] Elements required in milligram or microgram amounts are referred to as trace minerals and include cobalt, copper, iron, manganese, molybdenum, selenium, and zinc.[1,2] Trace minerals often serve as components of metalloenzymes, enzyme cofactors, and hormones, contributing to normal cellular and tissue processes and immune system competency.[1,3]

Physiological stress and trace minerals

Metabolic demands associated with late pregnancy, parturition, and lactation are thought to increase the production of reactive oxygen species (ROS).[4,5] When production of ROS exceeds antioxidant defence mechanisms, oxidative stress ensues. ROS initiate lipid peroxidation leading to cell and tissue damage as well as immune system dysregulation.[4] Impaired immune cell function prior to parturition has been associated with health disorders such as retained placenta, metritis, and mastitis. The stresses of late pregnancy and parturition stimulating release of stress hormones may also contribute to impaired immune response and increased disease susceptibility in periparturient dairy cows.[4]

Based on the importance of trace minerals to animal health, the practice of supplementing animals with trace minerals attempts to mitigate the harmful effects of physiological stress, improving health status, and reducing disease incidence.[3,5] For example, studies in dairy cows have demonstrated favourable responses to chromium supplementation, including improved humoral immune response and increased feed intake and milk production, especially if the animals are under some form of physiological stress.[1,4] Supplementation with selenium has been associated with reduced prevalence of retained placenta in dairy cows in numerous studies, as well as reduced prevalence and severity of mastitis and improvements in metritis, cystic ovaries, and udder oedema.

Timing of trace mineral supplementation

Given that periods of physiological stress and disease can result in increased demand for trace minerals, it has been suggested that the timing of trace mineral supplementation (TMS) to grazing animals should focus on vulnerable phases of the lifecycle rather than year-round supplementation, particularly reproductive performance of dams and the growth of young animals.[6]

Dairy cows are vulnerable to health disorders during the transition period, traditionally the 21 days before and the first 21 days after calving,[4,5] which is a stressful time for dairy cows.[4] However, it has been proposed that the transition actually starts 60 days prior to calving and extends to 30 days post-calving.[7] Irrespective of the definition of the transition period, adequate adaptation to the physiological demands of this period is important, in particular noting that:

- Dairy cows experience physiologic and metabolic stress during the transition into early lactation, which is when body reserves are used for milk production.[8] These stressors can promote oxidative stress, inflammation, and immune dysfunction.
- During the dry period, energy intake being lower than energy requirements can lead to inflammatory and metabolic changes and increased risk of metabolic disorders.[9,10]
- Calving is a stressful life event for both the dam and newborn.[11] Stress during the perinatal period can leave the neonatal calves susceptible to infections and diarrhoea.

Weaning can also be a stressful time for calves due to their main source of nutrients being switched from liquid to solids and having to adapt to a new environment with a high pathogen load.[11,12] Changes in housing, competition in new groups, and general husbandry practices also induce stress.[12]

Additionally, multiple stressors that cattle experience during transportation can induce inflammation and immunosuppression and increase the risk of respiratory disease.[13,14]

Role of trace minerals (Cu, Mn, Se, and Zn) in animal health

Deficiency of copper (Cu), manganese (Mn), selenium (Se), or zinc (Zn) can lead to a reduction in production, which is more likely to occur when the deficiency corresponds to phases of animal growth, reproduction, or lactation.[15] The roles of copper, manganese, selenium, and zinc in dairy cow health are summarised in **Table 1**.[1,4,16-18]

Copper is a component of enzyme systems that are essential for collagen formation and the absorption and transport of iron necessary for haemoglobin synthesis.[1,4] As a component of superoxide dismutase and ceruloplasmin, copper is involved in the antioxidant system.[1,4] Additionally, copper helps to maintain immune function through optimal phagocyte function and neutrophil chemotaxis. Signs of copper deficiency include reduced fertility, poor growth, supressed immunity, and most distinctively loss of coat pigment.[1] Anaemia and fragile bones are also observed in copper deficiency.

Manganese is required for normal reproduction (fertility) and growth (bone and connective tissue).[1] Playing a role in steroid and cholesterol synthesis may explain the influence of manganese on reproductive function.[17] In combination with anti-oxidants, manganese helps to minimise ROS accumulation.[1]

Selenium deficiency causes white muscle disease in newborn calves.[1,18] It is also a cause of leg weakness in calves at birth and increases their susceptibility to calfhood diseases such as scours. Selenium is a component of many enzymes and plays an important role in the antioxidant system.[1,4,18] It plays a role in the synthesis of the thyroid hormone and influences overall body metabolism.[18] Selenium influences reproductive tissues via its antioxidant role and a potential role in prostaglandin synthesis.[17] Higher rates of retained placentas and poor reproductive performance are often seen in cows with selenium deficiencies.[1,18] A higher rate of mastitis in dairy cows is also associated with selenium deficiency.

Zinc is a component of many metalloenzymes involved in metabolism and the antioxidant system and is a component of thymosin, which is a hormone involved in regulating immunity.[1,4] Zinc also influences prostaglandin and testosterone synthesis, which may affect reproductive function.[17] Cows deficient in zinc demonstrate reduced feed intake and growth rate, impaired growth of testes, and poor skin and hoof health.[1,17]

		Physiological roles:	Role in normal body function:
Copper	Cu[29]	Antioxidant system Enzyme function Bone and connective tissue formation Haemoglobin synthesis Neutrophil/phagocytic cell function	Protects against cell and tissue damage, supports growth and development, facilitates immune response
Manganese	Mn[25]	Bone and cartilage formation Antioxidant system Steroid and sex hormone synthesis	Supports growth and development, supports reproductive performance
Selenium	Se[34]	Antioxidant system Enzyme function Thyroid hormone synthesis and metabolism Neutrophil/natural killer cell function, cell-mediated immunity	Protects against cell and tissue damage, supports growth and development, supports reproductive performance, facilitates immune response
Zinc	Zn[30]	Antioxidant system Enzyme and hormone function Prostaglandin and testosterone synthesis Spermatogenesis Hormone function	Supports growth and development, supports reproductive performance, facilitates immune response

Table 1. Summary of the of role of trace minerals in animal health.[1,4,16-18]

Product profile: Multimin

Multimin is an injectable trace minerals supplement containing copper, manganese, selenium, and zinc for use in cattle in good health.[19] Copper, manganese, and zinc are present in a chelated form.

Formulation

Active constituents in Multimin are:[19]

	Concentration	Form
Copper	15 mg/mL	Copper disodium EDTA
Manganese	10 mg/mL	Disodium manganese EDTA
Selenium	5 mg/mL	Sodium selenite
Zinc	40 mg/mL	Disodium zinc EDTA

Dosage and administration

Multimin is administered as a subcutaneous injection and according to the following dosage recommendations:[19]

	Age	Dose
Calves	Up to 1 year	1 mL/50 kg
Cattle (yearlings)	1–2 years	1 mL/75 kg
Cattle (adult)	Over 2 years	1 mL/100kg
	Timing of administration	
Calves	• At day 1 and weaning	
Cows	• 3-4 weeks before calving, mating, and drying off	
Heifers	• Every 3 months, especially 3-4 weeks before mating	
Additional	• Every 2 months in wet conditions	

Multimin doses >7 mL should be administered in separate sites.[19] Multimin should be administered on the opposite side of the neck to any other products or, where this is not possible, ≥10 cm from any other injection sites.

Withholding period

No withholding period is required when Multimin is used as directed.[19]

Contraindications

Multimin should not be administered:[19]

- Concurrently with any other form of copper supplementation.
- At the same time as any other selenised fertiliser, prill, or product without consulting a veterinarian.
- To animals that have liver disease, fascioliasis, or that have been grazing on plants that may cause liver disease.
- To emaciated animals of body condition score less than 3/10.
- At a dose that exceeds the stated dose.

Effects on immunity and morbidity and mortality

Evidence from four pharmacological studies in dairy (n=3) and beef calves (n=1) indicate that parenteral TMS with Multimin at anticipated periods of stress has beneficial effects on indicators of animals' immune response,[20-23] and can lead to a reduction in morbidity and mortality according to three clinical studies in dairy cows and calves (see **Key Study Summary**).[20,24,25]

KEY STUDY SUMMARY

Reduction in morbidity and mortality of dairy calves from an injectable trace mineral supplement[24]

Authors: Bates A et al.

Aim: To evaluate the effect of TMS with Multimin at and after birth on the health and growth of Friesian-Jersey cross heifer calves during the preweaning period under a pastoral rearing system.

Methods: A total of 971 calves enrolled from four seasonally-calving pasture-based dairy farms in Canterbury NZ were randomly assigned to receive Multimin (n=435) at birth and/or day 35 and/or day 70, or an untreated control group (n=536). Comparisons between treatment and no treatment and between the different options of timing were possible. Morbidity, mortality from natural challenge and growth rates were recorded for 140 days.

Results: Although no significant differences in cumulative perinatal morbidity and mortality were observed within 48 hours of birth for treated calves compared with controls, both were significantly lower from 3 to 35 days period. Morbidity for Multimin calves was 7.5% (32/427) compared with 15.6% (81/519) for control calves (RR 0.48; 95% CI: 0.33–0.71). In the Multimin group, 4.9% (21/427) calves were recorded as having diarrhoea compared with 10.6% (55/519) in the control group (RR 0.46; 95% CI: 0.29–0.75). Adjusted OR of Multimin calves scouring between 3 and 35 days was 0.44 (95% CI: 0.24–0.82, p=0.009). Mortality from 3 to 35 days was 4.4% (19/427) for Multimin calves versus 10.4% (54/519) for control calves (RR 0.43; 95% CI: 0.26–0.71). From birth to 140 days of life, Multimin approximately halved the probability of morbidity and mortality (p<0.001) [**Figure 1**]. Average rate of weight gain was 0.67 kg/day (95% CI: 0.66–0.67) but no association between Multimin and weight gain was demonstrated (p=0.605).

Expert comments: This paper looks at TMS at varying time points, but I will concentrate solely on the results of the calves that got Multimin within 24 hours of birth or not. Mainly because it keeps life simple and that seems to be where the biggest effects are. The administration of Multimin as calves entered the shed did not result in lower perinatal mortality (death within 48 hours of birth). This seems to make sense as other studies cited in this paper found increased cellular and humoral immune response detectable in calves injected with Multimin "within seven days" but presumably not immediately. If a farmer has an issue with perinatal mortality, I doubt Multimin is going to plaster over the underlying issue, it may help, but something else will need to change. The biggest effect was on calf morbidity (calves affected with diarrhoea and or omphalitis). The calves that received Multimin had half the risk of being afflicted with either diarrhoea or a navel infection. What is important to note is that although the mortality rate from day 3 to 35 was roughly halved in the Multimin-treated calves this was due to the reduced number of calves affected. The case-fatality risk (of the calves that got diarrhoea, the number that died) was not significantly different if you got Multimin or not. This suggests that if there is an outbreak of diarrhoea then giving Multimin probably will not reduce the number of calves with diarrhoea that die. This paper supports the use of Multimin as a preventative measure but do not forget or neglect colostrum management and hygiene. I think this paper strongly supports the use of Multimin given to calves as they enter the calf shed, but only as an addition to good colostrum management and hygiene practices.

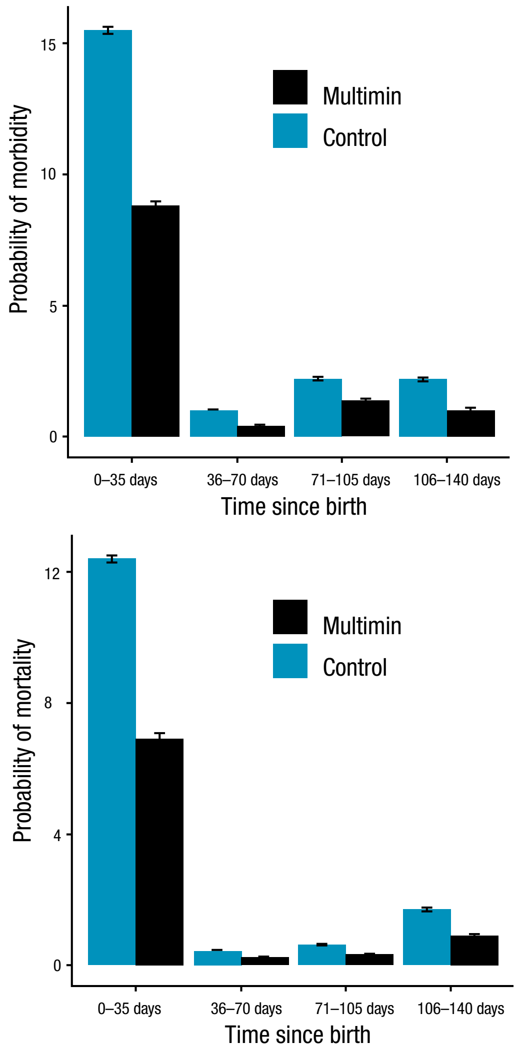

Figure 1. Model predicted average (±SEM) marginal probability of farmer-diagnosed morbidity and mortality from birth to 140 days for 971 calves treated with Multimin (n=435) or control (n=536).[24]

Effects on reproductive health traits and reproduction

Parenteral TMS with Multimin during gestation and post partum in dairy cows has been demonstrated to improve udder health, endometritis, and incidence of stillbirth in a US study (**Key Study Summary**),[25] and its administration in dairy cows prior to calving and mating has been associated with statistically significant increase in overall in-calf rate in an NZ study conducted by David Hawkins.[26]

The NZ study was conducted in 2,168 cows from six herds across the country under typical NZ pasture-based conditions.[26] Cows that received TMS with Multimin had a 3.3% higher overall in-calf rate versus the control group (p=0.035). The mechanism of this effect was presumed to be via improved conception and reduced embryonic mortality. Median conception day relative to planned start of mating was 22.9 days for the Multimin group versus 26.3 days for the control group. Multimin was not associated with a significant reduction in the incidence of clinical mastitis versus control. A cost-benefit analysis, which was part of the NZ study, indicated that TMS with Multimin was associated with either a 3.47 or 4.11 return on investment (depending on estimations of extra days in milk).

KEY STUDY SUMMARY

Effect of an injectable trace mineral supplement containing selenium, copper, zinc, and manganese on the health and production of lactating Holstein cows[25]

Author: Machado VS et al.

Aim: To evaluate the effect of TMS with Multimin on health traits, milk production, and reproductive performance of lactating Holstein cows.

Methods: This field trial was conducted on three large commercial dairy farms in the US, with 1,416 cows enrolled. The cows were housed and fed a total mixed ration consisting of approximately 55% forage and 45% concentrate on a dry matter basis of the diet, which supplied trace mineral concentrations that were 2- to 6-fold above National Research Council requirements. Dry cows and pregnant heifers were blocked by parity and randomly assigned to receive Multimin or control at 230 and 260 days of gestation and at 35 days post partum.

Results: The effect of TMS on somatic cell count (SCC) increased as parity increased. The decrease in SCC with TMS relative to control was small in primiparous cows compared with SCC reductions in multiparous cows, particularly in Multimin-treated parity three or greater cows whose SCC were significantly ($p<0.05$) lower versus control cows. The frequency of subclinical mastitis was significantly lower in Multimin compared with control cows (8% vs 10.4%; p=0.005). The effect of treatment on clinical mastitis was not significant but the interaction of treatment and parity was significant: for primiparous cows, the frequency of clinical mastitis was 11.8% in Multimin versus 15.6% in control cows (p=0.33); for multiparous cows, the frequency of clinical mastitis was 19.7% in Multimin versus 25.4% in control cows (p=0.03). Although no significant difference in reproductive performance between Multimin and control cows was observed, control cows had increased odds of stillbirth and endometritis (OR 1.69 and 1.30, respectively). Indeed, the rate of endometritis was significantly lower in Multimin cows versus control cows (28.6% vs 34.2%; p=0.039). Treatment with Multimin did not appear to affect milk production or other health traits.

Expert comment: This paper exposed to me what I do not know about TMS. The cows in this study were fed well above the NMR recommendations for trace minerals, so presumably they were not deficient, but the actual trace mineral status of the cows was not reported. It may be that inclusion of trace minerals in the diet does not ensure absorption. It surprised me that the effect of Multimin supplementation on intramammary infections was greater in older cows. With my NZ-centric view, I thought it would be the other way around. Contrary to what I am used to seeing, multiparous cows in this study had more mastitis than primiparous cows. The responses that were reported are not attributable to a specific mineral but there is supporting evidence for selenium supplementation being important for udder health and some papers have shown no effect of selenium supplementation on udder health and David Hawkins in his NZ Multimin trial[26] did not find a reduction in clinical mastitis. It could be that the effect of supplementation was detectable in multiparous cows because they faced challenges or risks for acquiring infections that were related to trace minerals but primiparous cows had other challenges, at least in the environment this study was conducted in.

Still births (death of the calf within 48 hours of parturition) was reduced in supplemented cows but this did not flow on to increased reproductive performance. It seems hard to believe that calves were born so deficient in trace minerals that they died within 48 hours of birth. What effect the Multimin had on either the dam or the calf that resulted in fewer still births is unclear, it may be as simple as parturition was quicker. The other effect found was less endometritis in the Multimin-treated cows. This also did not result in better reproduction in this study, but as endometritis delays conception, in a system where the time between calving and conception is critical (a seasonal-calving system), it may well be clinically important here in NZ. The other reason that may have resulted in no reported change in reproductive performance was the timing of the last injection of Multimin at 35 days in milk. It is unclear to me when this injection occurred relative to start of mating for the cows in this study, perhaps it was not close enough to mating for an effect, if there is one, to be detected. David Hawkins reported a positive effect on in-calf rate when Multimin was given 4 weeks prior to the planned start of mating.[26] This study highlights possible benefits of giving Multimin to adult cows but due to our different patterns of mastitis and mating timings the results reported here may under, or over, estimate any effects.

EXPERT'S CONCLUDING COMMENTS

There seems to be good evidence that the supplementation of calves with Multimin perinatally in a NZ context will result in less morbidity due to diarrhoea and navel ill, which resulted in less mortality. I would love to have some research into the actual effects of supplementing adult dairy cows with Multimin in a seasonally-calving, pasture-based system. The international data seems to show effects that may be clinically important in our systems where we attempt to have an inter-calving interval of 365 days. Additionally, our patterns and causes of mastitis are different to those reported in the studies done to date, so it would be great to have some more data from NZ that examines the effect of Multimin on mastitis incidence in NZ.

TAKE HOME MESSAGES

- Physiological stress in dairy cows is associated with increased trace mineral demand.
- Trace mineral deficiency can result in reduced milk production, more disease, and reduced reproductive performance.
- Periods of physiological stress include early lactation, drying off, calving, weaning, and livestock transport.
- Supplementation with trace minerals attempts to mitigate the effects of physiologic stress and its sequelae in dairy cows.
- Copper, manganese, selenium, and zinc are trace minerals that variously play important roles in the maintenance of normal animal immunity, growth and development, and reproduction.
- Multimin is an injectable trace minerals supplement containing copper, manganese, selenium, and zinc.
- In immunity and morbidity and mortality studies:
  - TMS with Multimin was associated with beneficial effects on indicators of dairy calves' immune response.
  - Dairy calves that received TMS with Multimin at birth had a 52% reduction in disease and 58% reduction in death versus control.
- In reproductive health and performance studies:
  - Lactating dairy cows that received TMS with Multimin had improvements in udder health, endometritis, and incidence of stillbirth.
  - Dairy cows that received TMS with Multimin prior to calving and mating achieved in-calf status 3.4 days earlier versus controls and a 3.3% higher final in-calf rate.

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