An Overview of the Micronutrients Pre-conference Session at the 2019 Cornell Nutrition Conference

-No Guts No Glory-

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The annual Cornell Nutrition Conference (CNC) is designed to provide leading research and information to feed industry professionals and nutritional consultants. The pre-conference session was hosted by Micronutrients, a Nutreco company, which is responsible for the development of the **Intellibond® (IB) hydroxy trace minerals (HTM)**. Following the development of organic trace minerals (OT) in the 70's, IB Zn, Cu and Mn which was developed in the 1990's, is the most recent and cost-effective technology in trace mineral nutrition.

The theme of the pre-conference was "no guts no glory" focusing on strategies supporting a healthy digestive system. This theme pulled through the whole conference with topics focusing on gastrointestinal health and function and possible mitigating strategies to counter for inflammation and oxidative stress caused by heat stress, low feed intake, acidosis and especially during the transition period. Strategies such as the feeding of specific TM and additives, which support gastrointestinal function and helps accelerate recovery after a challenge, was addressed.

Dr Sara Kvidera (Ruminal Technical Manager at Micronutrients, USA LLC, Indianapolis, IN) presented an excellent summary on the knowledge gained since the 90's through research on IB HTM's. The question is whether your TM program is doing more harm than good? The differences in TM sources and their effectiveness depends a lot on the type of chemical bond that binds the metal to its ligand (Figure 1). Sulfate trace minerals (STM) contain a metal ion, bound to a sulfate ion, via an ionic bond. This ionic bond breaks apart easily in an aqueous environment, releasing a free metal ion which can at liberty interact with other nutrients or microbes in the rumen. Organic and IB TM's contain stronger covalent bonds that protect the metal from being released too early in the premix, the feed manufactured at a factory, the total mixed ration (TMR, normally with added water) or in the digestive tract. This gives IB TM's an advantage in **diet stability, palatability, bioavailability and digestibility, over sulfate trace minerals**.

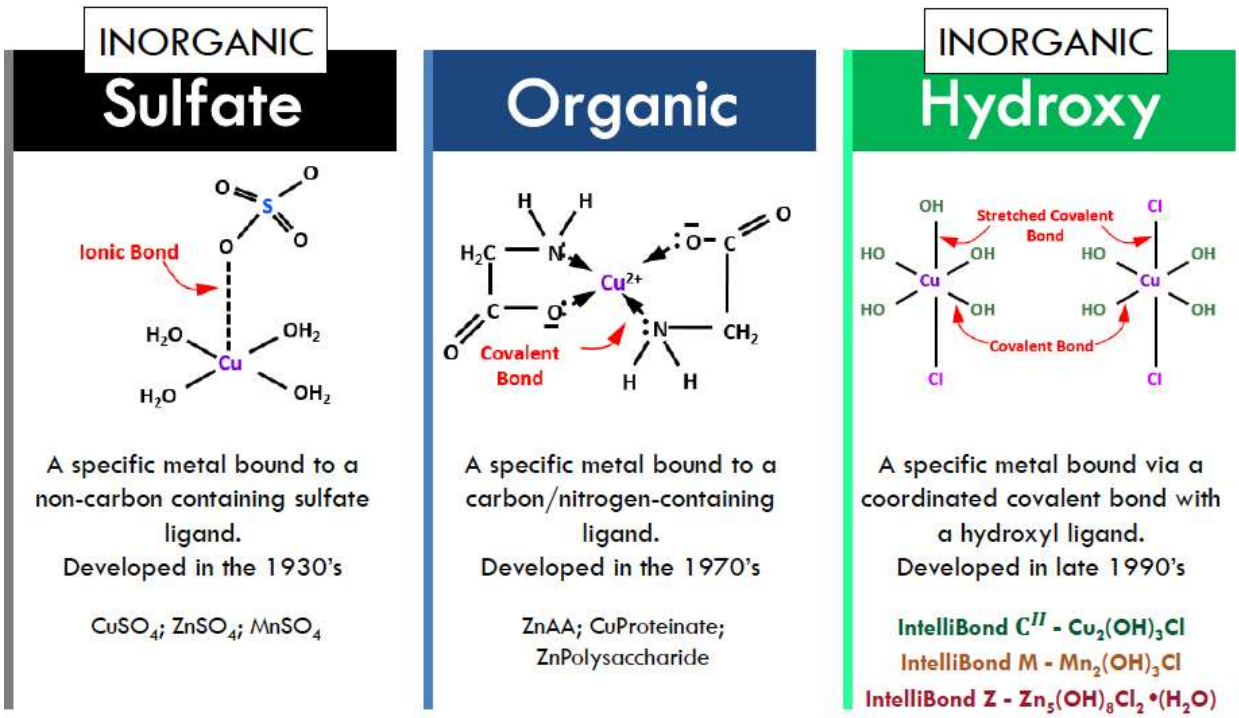

Figure 1. Chemical characteristics of different trace mineral sources.

Stability of some nutrients and additives included in a TMR may be compromised because they are susceptible to oxidative free metals released by sulfate trace minerals. Vitamins, lipids and enzymes are especially sensitive to its environment because it is vulnerable to oxidation and its stability is often compromised when TM's are included in the premix. Furthermore, the stability of vitamins A, E, and K were decreased to a greater extent with sulfate or free metals in a premix compared to organic or oxide TM's, indicating that TM source impacted vitamin availability. Several studies showed a better vitamin, lipid and enzyme stability/retention with IB Cu versus Cu sulfate after storage. IB Cu in the premix also resulted in higher liver and plasma vitamin E levels when these diets were fed to chicks. It was also reported that feeding poultry diets containing IB Cu vs Cu sulfate resulted in 17-35% less primary lipid oxidation and 7-45% less secondary lipid oxidation. Enzymes added to the diet are also susceptible to degradation by free metals. Phytase fed to improve phosphorus availability in poultry diets showed 16% greater retention in feed when formulated with IB Cu compared to Cu sulfate, indicating a prevention of phytase degradation during feed storage. Using a less reactive TM source appears to protect vitamins, lipids, and enzymes in feed, ensuring the nutrients formulated retain their optimum quantity and quality.

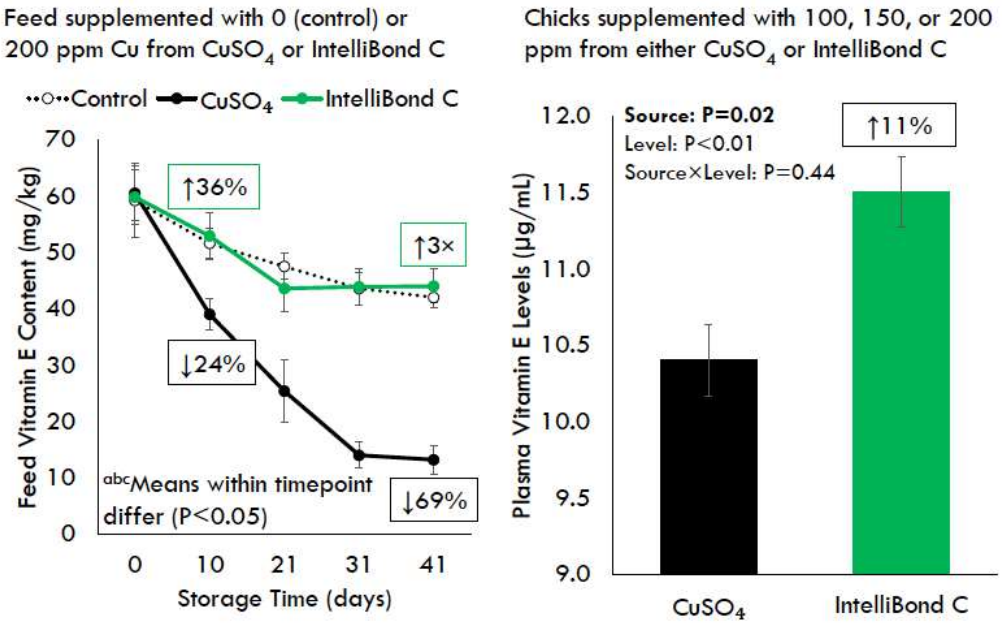

Figure 2. Feed vitamin E content over time in a poultry diet containing no added Cu (Control) or 200 ppm Cu from either Cu sulfate (CuSO4) or IB Cu (Lu et al., 2010).

Palatability studies across a variety of species have shown that, when given the choice, animals prefer to consume IB TM's rather than sulfate sources. The reason behind increased palatability may be related to the high reactivity of STM's due to their weak ionic bond and release of free metal stimulating an averse metallic taste.

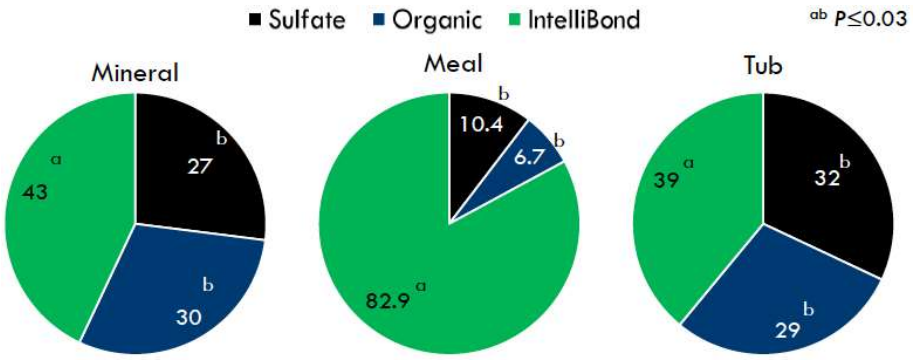

Figure 3. Preferential intake of beef calves as a percentage of total intake when fed a creep-feed mineral (left; Wiebusch et al., 2015), meal supplement (center; Caramalac et al., 2017), or a cooked molasses block (right, Ranches et al., 2018) formulated with minerals from sulfate, organic, or IntelliBond sources of Zn, Cu, and Mn.

A high level of **bioavailability** is one of the goals in TM supplementation and to ensure TM's are available to the animal during the different situations that might affect its bioavailability. Several dietary antagonists and imbalances have the potential to affect absorption of different TM's and most of these antagonistic reactions occur in the rumen. When dosed in the rumen, sulfate sources of Cu, Zn, and Mn were shown to be significantly more soluble than the IB TM's because Cu, Zn, and Mn sulfate are ionic bonds. Studies also shown that the marked increase in rumen soluble minerals from sulfates resulted in the metal becoming very tightly bound to antagonistic complexes which renders it unavailable. IB HTM's begin to solubilize in acidic conditions such as the abomasum and gradually throughout the intestinal tract. The data indicates that IB sources avoid antagonistic interactions early in the digestive tract (mouth up to abomasum), ensuring trace minerals reach their site of absorption in an available form with as little interference as possible.

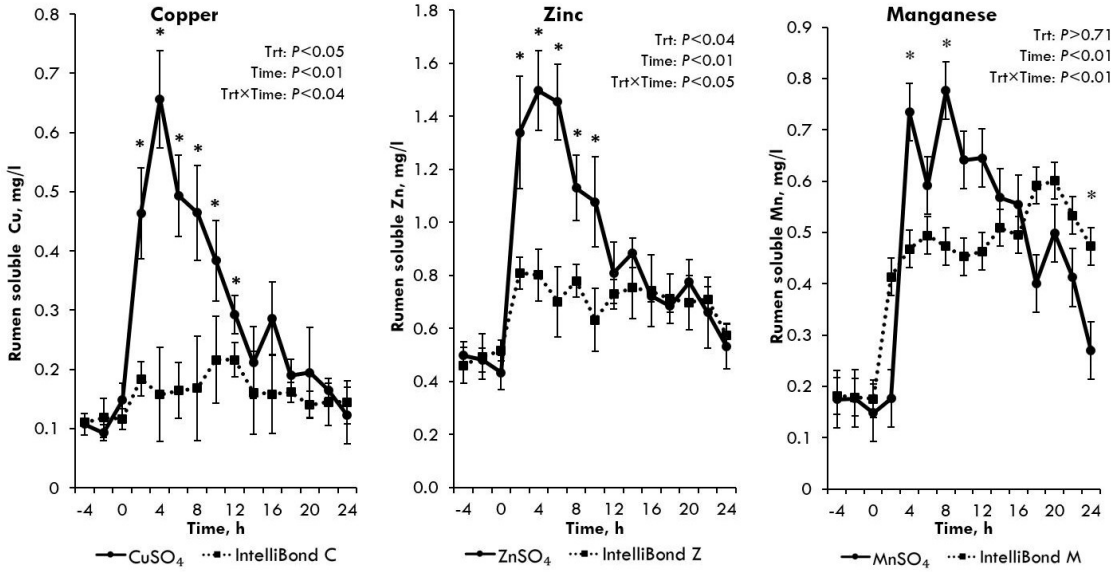

Figure 4. Influence of trace mineral source on rumen soluble Cu, Zn, and Mn concentrations (Caldera et.al., 2019).

Bioavailability of IB Cu was 1.96x and 1.12x higher compared to Cu sulfate based on liver Cu concentrations when S and Mo (Cu antagonists) were fed to Cu-depleted steers. Additionally, when steers were depleted and then fed 25 ppm Zn from either Zn sulfate or IB zinc, the bioavailability of IB Zn was 2.04x compared to Zn sulfate based on retained zinc as measured via total fecal and urine collection.

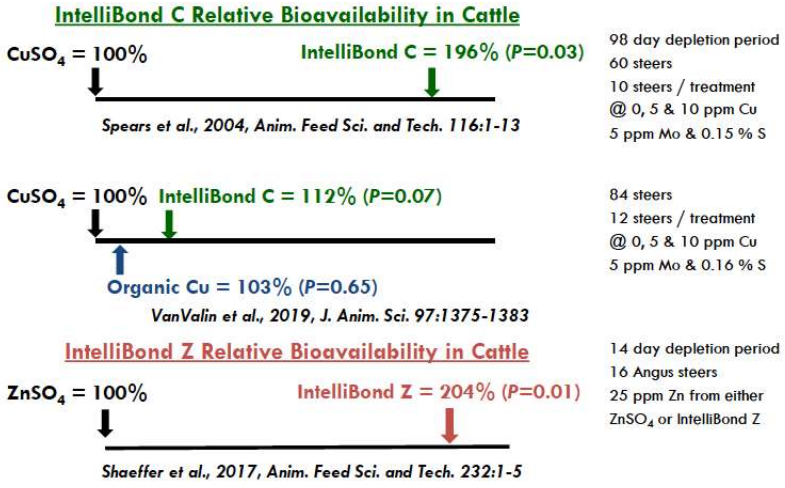

Figure 5. Bioavailability of IB Cu during a Mo and S antagonist challenge (Spears et al., 2004; VanValin et al., 2019) or IB Zn following a Zn depletion period (Shaeffer et al., 2017) expressed relative to respective sulfate sources.

Neutral detergent fiber **digestibility** (NDFd), which is fundamental to the production of volatile fatty acids as an important energy source for the ruminant, depends on healthy microbial activity in the rumen. Metals such as Cu, Zn and Ag have known antimicrobial properties that are utilized as antimicrobial agents and antibiotic alternatives in other industries. Therefore, reactive trace mineral sources are counterproductive because, once broken down in the rumen, the metal ion (Zn or Cu) originally linked within the sulfate ligand now possesses these antimicrobial properties. Consequently, these free metal ions can potentially harm the beneficial fibrolytic bacteria. Several in vitro studies have indicated that even very low amounts of added Cu are highly toxic to cellulolytic bacteria. Also, that there is a recognized but quite low rumen microorganism requirement for Zn.

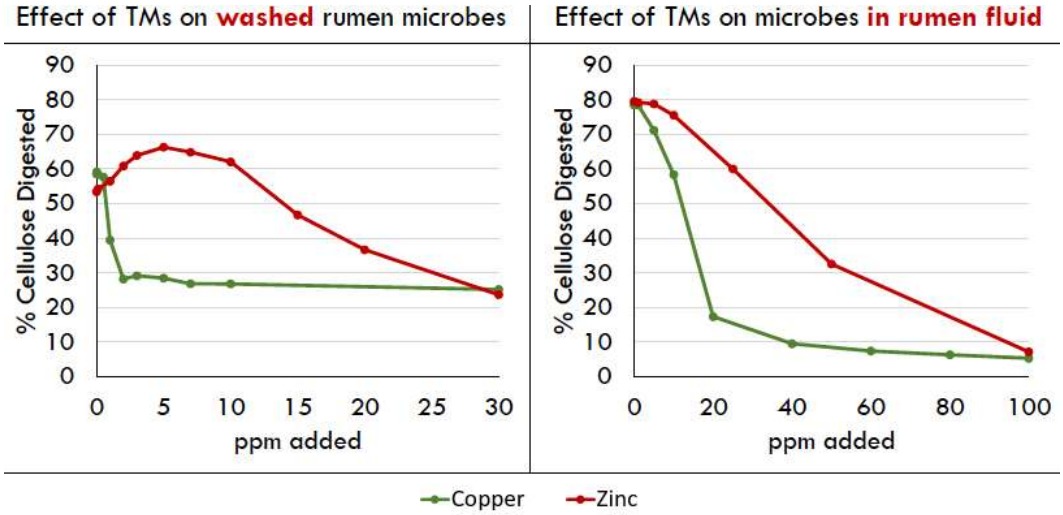

Figure 6. Trace minerals impact rumen microbial function (Martinez and Church, 1970; Sala, 1957).

In a wide range of studies comparing how STM's affect NDFd relative to IB HTM's, research has found an improvement in NDFd ranging from 1.1 to 4.6 points with IB trace minerals relative to sulfate sources (Figure 6). As Oba and Allen (1999) suggest, a one-point change in NDFd can translate to a 0.17 kg increase in dry matter intake and a 0.25 kg increase in 4% fat-corrected milk.

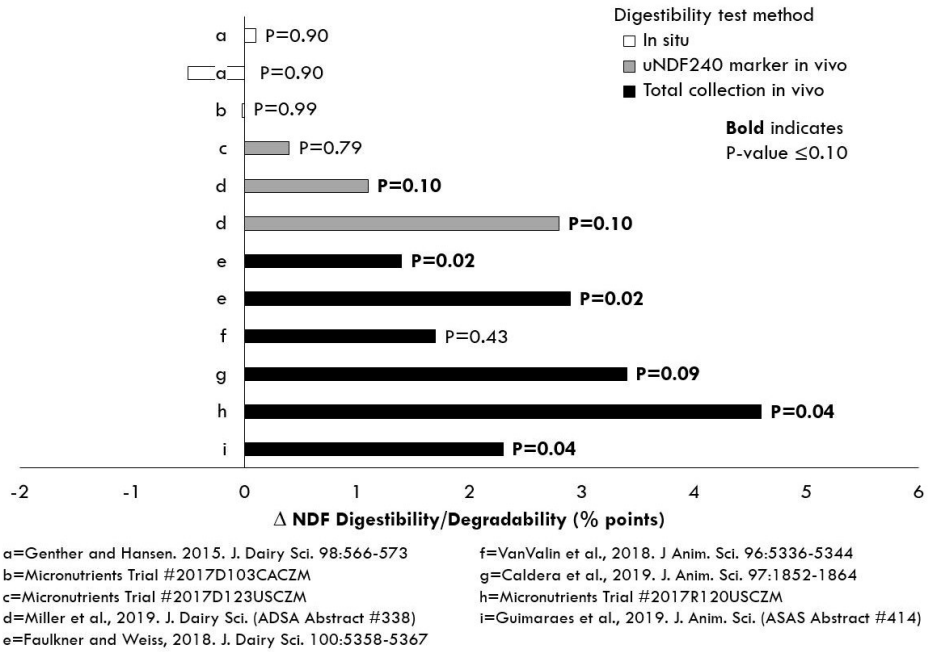

Figure 6. Change in neutral detergent fiber (NDF) digestibility relative to sulfate sources of trace minerals in various studies.

A study by by Michael Miller (Ph.D. candidate at the William H. Miner Agric Research Institute, Chazy, NY) looked at fiber digestion with a focus on forage and TM source. He evaluated the effect of source of corn silage and TM's on fiber digestibility and lactation performance. Cows fed the brown midrib gene mutation (BM3) corn silage diets had higher DMI and ECM than cows fed the conventional corn silage control diets (CON). Source of TM's had an effect on DMI with the cows fed the HTM diets having higher DMI than the cows fed the STM diets. This DMI difference between the HTM and STM diets can be accounted for by the difference in total tract digestibility of aNDFom. The effect was greater for the cows fed the BM3 diets compared to the cows fed the CON diets. Source of trace minerals influences DMI and total tract digestibility of aNDFom and should be taken into consideration when formulating diets for high-producing dairy cows.

The primary goals of TM supplementation are to meet the nutritional demands of today's high producing animals and to provide a bioavailable mineral source that does its job without negatively interacting with other components of the diet. Providing a high-quality improved TM source as a replacement for STM's ensures proper TM nutrition without the negative side-interactions sulfate minerals may have on diet stability, palatability, bioavailability, and digestibility that may do more harm than good.

Dr Greg Penner, Department of Animal and Poultry Science, University of Saskatchewan lectured on the effects of low feed intake (LFI) on gastrointestinal function and summarized that LFI negatively affects absorptive and barrier functions of the gastrointestinal tract and predisposes cattle to ruminal acidosis. Feeding a diet with a greater energy density prior to low feed intake can help accelerate the recovery response as can feeding a diet with a high forage content after a period of low feed intake. In a finishing scenario, this can be accomplished simply by increasing the proportion of forage in the diet by approximately 11% units.

He also reported that feeding additives which support gastrointestinal function (e.g. betaine, superoxide dismutase, and butyrate), can help accelerate the recovery response for the gastrointestinal tract. Betaine has been reported to help support GIT function during coccidia challenges (Kettunen et al., 2001; Fetterer et al., 2003), and superoxide dismutase has been reported to improve GIT function in mice (Vouldoukis et al. 2004). Moreover, there is evidence that the ruminal epithelia may experience hypoxic conditions (Dengler et al., 2015) supporting that antioxidants may have a beneficial role in the ruminant GIT. Finally, butyrate has been shown to induce positive effects at a low dose. (Gorka et al., 2007; Kowalski et al., 2015).

Dr Lance Baumgard, Department of Animal Science, Iowa State University lectured on the causes and metabolic consequences of leaky gut. There are a variety of circumstances in a cow's life which result in hindered productivity

including heat stress, ketosis, rumen and hindgut acidosis, feed restriction, and psychological stress associated with normal animal management practices. Although these insults have different origins, a commonality among them is increased production of inflammatory biomarkers and markedly altered nutrient partitioning. Researchers have generated convincing data strongly implicating intestinally derived lipopolysaccharide (LPS) as sometimes being the culprit in these situations. Immune activation in response to LPS markedly alters nutrient partitioning as a means of fueling the immune response.

LPS-induced inflammation has an energetic cost which redirects nutrients away from anabolic processes that support milk and muscle synthesis and thus compromises productivity. Upon activation, most immune cells become obligate glucose utilizers via a metabolic shift from oxidative phosphorylation to aerobic glycolysis (not anaerobic glycolysis typically learned about in biochemistry classes), a process known as the Warburg effect. Previously it was believed that the energetic cost was due to elevated muscle requirement during heat stress.
More research is still needed to understand the mechanisms and consequences of intestinal permeability and associated inflammation in order to provide foundational information for developing strategies aimed at maintaining productivity.

Potential dietary mitigation strategies aimed at improving gut health are currently of great interest, especially considering the numerous stressors (i.e., heat stress, feed restriction, acidosis) that potentially impact intestinal permeability. Zinc is an essential nutrient which is crucial for maintaining epithelial integrity (i.e., mammary, uterine, intestinal) and regulating the renewal of damaged epithelium. Zinc was first demonstrated to improve intestinal "health" in human leaky gut models. This were extended to improved metrics of intestinal permeability in a variety of farm animal stress models including heat stress and feed restriction using Zn hydroxychloride as Zn source. Additionally, altered febrile, cytokine, and acute phase protein responses were observed during heat stress and in response to LPS administration with dietary Zn supplementation. Presumably the aforementioned changes in inflammatory variables are indicative of a blunted immune response (because of improved intestinal barrier function). Therefore, Zn as a dietary supplement appears to be a promising avenue to improve gut health and to ameliorate alimentary canal associated inflammation.

Effects of zinc hydroxychloride on production and metabolism during 5 days of feed restriction. E. A. Horst*1, E. J. Mayorga1, M. Al-Qaisi1, S. Rodriguez-Jimenez1, B. M. Goetz1, M. A. Abeyta1, R. S. Fry2, S. K. Kvidera2, and L. H. Baumgard1, 1Department of Animal Science, Iowa State University, Ames, IA, 2Micronutrients LLC, Indianapolis, IN (2019 ADSA Abstract).
Objectives were to evaluate effects of supplemental zinc hydroxychloride (HYD; Micronutrients, Indianapolis, IN) on production parameters and metabolism during feed restriction (FR) in midlactation Holstein cows. Twenty-four cows were randomly assigned to 1 of 4 treatments:
1) ad libitum-fed and control diet (ALCON; 75 ppm zinc [Zn] from Zn sulfate; n = 6),
2) ad libitum-fed and HYD diet (ALHYD; 75 ppm Zn from HYD; n = 6),
3) 40% of ad libitum feed intake and control diet (AL40CON; n = 6), or
4) 40% of ad libitum feed intake and HYD diet (AL40HYD; n = 6).

In summary, HYD supplementation tended to increase DMI and milk yield during both periods, tended to increase BHB during P2, but did not influence the other parameters during an intense FR.

This is an overview of the Micronutrients pre-conference session and all proceedings and references are available on request. For more information, contact the author at heinri@westside.co.za