Hydroxy Minerals - The Newest Development in Mineral Nutrition

By Jeff Cohen and F. A. Steward

For at least 30 years nutritional sources of essential trace minerals such as iron, zinc, copper and manganese have been commonly described as being either organic or inorganic products. However, recent and more intensive research studies have shown that this distinction is of little value in revealing how a given metal source will perform in a biological system. Similarly, for most of the last 60 years, comparisons of relative bioavailability have been the primary focus when evaluating alternative sources of minerals. By comparison, newer published studies make it clear that the picture is more complex than previously believed. In addition to differences in efficiency of absorption of the target metal into the bloodstream, different sources can affect nutrition and animal performance in at least four other important ways: (1) destruction of nutrients, including vitamins, in a feed mixture, (2) interactions with other nutrients in the digestive tract, (3) direct influence of gut microbial ecology; and (4) effects on the animal’s natural immune functions. The common thread which links the mechanisms in all of these performance criteria is the speed with which the target metal is released in the feed mixture or in the gut. There are many possible chemical and biochemical reactions which are constantly competing for the supplemented metal. The main thing that differentiates how different mineral products perform is the strength of the bonds holding them in the source compound.

Early History

After copper and zinc were found to be essential nutrients in the 1920’s and 1930’s, various low-cost sources of these metals, such as industrial by-products and wastes were added to animal diets to provide the metals. However, a proliferation of university studies after World War II led to the generally accepted view that only water-soluble metal salts could be easily absorbed from the gut. This led to a progressive shift in the animal feed industry away from metal oxides and toward the use of highly-soluble metal sulfates, which were arbitrarily assigned a value of 100% relative bioavailability (RBV).

Organics

Starting in the 1980’s, there was a new trend toward the use organo-metallic complexes of essential trace minerals in animal nutrition. Initially this trend was based on the notion that such complexes would be more efficiently absorbed since they were felt to approximate natural biological complexes of metals. Later, a number of studies revealed that an animal deploys specific ligands to escort essential metals through epithelial tissues, so it then appeared that the
main value of the manufactured organo-metallics was to “protect” the ingested metal from becoming entangled in parasitic reactions which compete with absorption. In fact, under certain conditions, the best of the organo-metallic products can have somewhat better bioavailability than metal sulfates (>100% RBV). This occurs because the higher strength of the bonds holding the metal impedes side, or parasitic, reactions. This can be thought of as a form of controlled release over time, thus increasing the probability that the metal will be successfully presented to the natural absorption mechanism at the epithelium.

Hydroxy Minerals
The most recent trend in mineral nutrition has been toward metal salts that have been partially reacted with an alkali to produce hydrolyzed inorganic metal complexes. The first such commercial product, dicopper chloride trihydroxide (basic copper chloride or IntelliBond® C), was introduced in 1995. This compound was chosen because it naturally forms a well-defined three-dimensional crystal lattice structure with unusual stability. That structure is desirable because growth of a crystal lattice is a natural purification step that excludes impurities and because it utilizes the same type of chemical bonds (covalent) that allow the good organo-metallic products to outperform metal sulfates, which have weak ionic bonds to the metal. These covalent bonds with the metal are strong enough to limit parasitic reactions, but weak enough to readily hand off the metal to the escort ligands deployed by an organism to facilitate absorption. Thus, these hydroxy compounds result in RBV values greater than 100%, while avoiding the higher manufacturing cost and environmental impact involved in manufacturing organo-metallic compounds. They also improve the stability of feed mixtures, thus reducing losses of other valuable nutrients, such as vitamins, and enzymes. Finally, due to the stability of the crystal structure, these products hold the target metal tight enough that it is still being slowly released in the later sections of the intestine where the majority of pathogen challenges occur and where the immune tissues are concentrated.

Stages in the Evolution of Mineral Nutrition For Animals

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<thead>
<tr>
<th>Stage</th>
<th>Approx. Dates</th>
<th>Description</th>
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<tbody>
<tr>
<td>1st Generation</td>
<td>1930’s thru 1950’s</td>
<td>Metal oxides &amp; industrial by-products</td>
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<tr>
<td>2nd Generation</td>
<td>1950’s thru 1980’s</td>
<td>Shift to metal salts of sulfuric acid for higher</td>
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<tr>
<td>RBV</td>
<td></td>
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<tr>
<td>3rd Generation</td>
<td>1980’s thru current</td>
<td>Metal salts of organic acids</td>
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<tr>
<td>4th Generation</td>
<td>1990’s thru current</td>
<td>Basic metal salts of low-cost mineral acids</td>
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An illustration of Comparative Bond Strengths
Samples of various copper sources were stirred in a moderately aggressive solvent to illustrate the comparative rate at which they would release the metal. This test does not make any attempt to simulate conditions in an animal’s gut which are very complex and variable over time and location. It simply shows the variability of bond strengths in different source compounds.
**Minerals In The Gastrointestinal Tract**

Recent studies in Dr. Kirk Klasing’s lab at the University of California Davis have provided a clearer picture of the relationship between bond strength and mineral function in the gastrointestinal tract. In work from 2010, luminal contents from broiler chicks fed either basic copper chloride (IntelliBond C) or copper sulfate were analyzed to determine the form of the copper in various portions of the intestinal tract. The results indicated that as the digesta moved further along the small intestines, more copper was bound and unextractable (or unavailable) when copper sulfate was the source. This is likely due to more participation in antagonistic side reactions. This work confirmed the chemical mechanism by which basic copper chloride demonstrates higher relative bioavailability as well as its increased opportunity to interact with the micro flora in an animal’s gut.

*Within a tissue and Cu type, means are different (p<0.05).*
In a follow up study using a similar protocol, the two copper sources were again fed to chicks for seven days. Luminal content was collected and 500 colony forming units of E. coli were introduced to determine the effects of the copper on bacteriostatic activity. Results indicated a significantly greater reduction in E. coli growth with the luminal contents from chicks fed basic copper chloride.

A third trial consisted of two parts. The initial experiment demonstrated that basic copper chloride has a lower minimal inhibitory concentration (MIC) than copper sulfate. Surprisingly, copper sulfate’s higher solubility and reactivity did not result in greater bactericidal effects. The second part again looked at the effects of the luminal contents, but this time included *E. coli, Clostridia perfringens, Salmonella gallinarum, Salmonella enteritidis* and *Eimeria*. In addition, the copper sources included a copper amino acid complex. As the following chart shows, basic copper chloride and the copper amino acid complex were both better than copper sulfate at reducing E. coli numbers in ileal contents*. 

![Graph showing E. coli growth](image)

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**Immune Function And Intestinal Microbes**

The billions of bacteria present in the intestinal tract (commensals) have the dual role of aiding digestion while also forming a barrier to protect the animal from pathogenic organisms. Minerals are thought to play a key role in regulating these bacteria populations. The balance between the...
commensal population and the immune system controlling them is essential. The work described earlier revealed that the hydroxy mineral form of copper (IntelliBond C) - as a result of the ideal strength of its bonds – acts throughout the intestinal tract. Thus these minerals are able to assist in maintaining a more stable balance of micro flora and to allow nutrients to be used for growth rather than for battling challenges.

In an attempt to explore the differences that various mineral forms might have on the innate immune system, work from Dr. Liz Koutsos’s lab at California Polytechnic State University, San Luis Obispo in 2005 revealed a lower inflammatory response between broilers fed basic copper chloride compared to those fed either copper sulfate or no additional copper. The in vitro work showed that plasma from chicks fed basic copper chloride, as compared to those with no supplemental copper, had a lower inflammatory profile based on its ability to dampen nitric oxide production by macrophages in response to lipopolysaccharide (LPS). The anti-inflammatory impact of basic copper chloride was dose-dependent, as higher levels of copper chloride plasma resulted in more dampened NO responses.

![Graph showing nitric oxide production with percentage of plasma from TBCC-fed chicks in cell culture media](image1)

In vivo work involved using plasma from LPS-challenged chicks fed basic copper chloride, resulting in lower NO responses by HD11 macrophages as compared to plasma from LPS-challenged chicks fed no supplemental copper.

![Graph showing nitric oxide production with percentage of plasma from TBCC-fed chicks in cell culture media](image2)
The researchers theorized that chicks fed hydroxy copper released less inflammatory cytokines into their blood, presumably due to fewer or less severe pathogen challenges in the intestines. This may indicate that copper chloride’s better performance has a systemic component and ongoing research will determine if this effect is related to a shift in microbial ecology or if it is due to a direct effect on leucocytes.

Summary
As in all fields of scientific inquiry, mankind’s understanding of mineral nutrition continues to evolve. The immense importance of the huge and complex colony of commensal organisms in the lower gut, and the interactions between that colony and the host’s immune reactions is only starting to be understood and explored. Some of the most recent work with essential trace minerals shows that, in addition to supporting well known systemic functions, minerals play a number of different roles in affecting intestinal health in animal husbandry.

References


