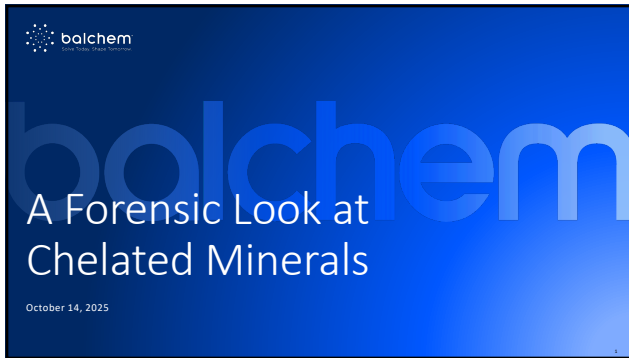




1

Background and Disclosure

- Officially, I have been in the OTM manufacturing business for 40+ years.
- Started my career at Albion Laboratories and formulated their MAAC product line before it was sold to Novus in 2010
- I am the primary formulator for Metalosate® (Plant Nutrition) and initial formulator for Albion Minerals (Human Nutrition)
- In 2016, Albion was acquired by Balchem Corporation.
- My current job function with Balchem still remains in their R&D department with continued primary responsibility for the Metalosate® and primary responsibility for the KeyShure® and KeyShure Plus® product lines.

AlbionMinerals

Metalosate
Powered by Albion Technology

KeyShure
Chelated Minerals

KeyShure Plus
Amino Acid Chelated Minerals

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2

Periodic Table

- There are currently 118 elements that are discovered.
- Twenty five elements are considered necessary to the processes of life.
- Of the 25 elements necessary for life, carbon, nitrogen, oxygen, and hydrogen are approximately 95% of life composition.
- Life cannot synthesize metals: they must come from feeding or the diet

Minerals are essential components of life

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3

Mineral classifications

Inorganic minerals

- Consist of a cation charge balanced with an anion
- Anion typically does not have carbon as an element
- Typically these are considered salts
- Examples include sulfate, oxides, hydroxides, phosphate, carbonates (exception to the carbon generality), etc.
- Hydroxy chlorides (intellibond products) are inorganic salts.

Organic minerals

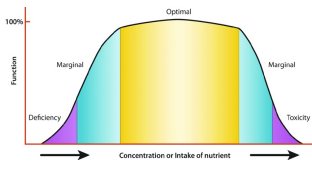
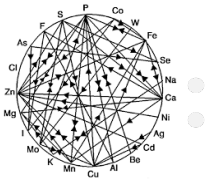
- Consist of cation balanced with an anion, but anion is typically much larger
- Anion includes carbon as major component of the molecule
- These can be salts, complexes or chelates
- Examples include acetates, citrates, propionates, amino acid complexes/chelates, proteinates.

Inorganic vs Organic

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4

Duality of Minerals

Minerals must be optimally fed and in balance.

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5

What is an Antagonist?

- Antagonists can be other minerals or organic compounds in the diet
- Excess intake of a single element can decrease the intestinal absorption of another element.
- Other dietary ingredients can bind up the mineral and prevent absorption

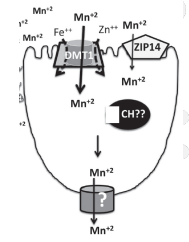
- Antagonists affect the absorption of the mineral into the enterocyte. Once absorbed into the enterocyte, the mineral is subject to normal regulatory pathways and is bioavailable.

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6

Mineral-Mineral Interaction: Competing Absorption

- Divalent Metal Transporter 1 (DMT1) is a general metal transporter across the apical membrane.
- It can transport manganese, iron and zinc.
- Copper has a primary absorption pathway using CTR1, but can also be absorbed using DMT1.
- Zinc Importer Proteins (ZIP family) can also transport manganese across the membrane.
- A diet high in a particular mineral can impact the absorption of other minerals that use the same transport proteins.
- In Wilson's disease (a defect in ATP7A) medical treatment includes high levels of zinc ingestion to limit the amount of copper that is absorbed.



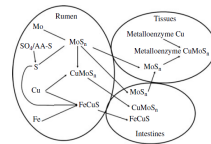
• Goff JP. J Dairy Sci 2018;101:2763-2813

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Mineral-Mineral Interactions: Decreased Bioavailability

- Copper, molybdenum, and sulfur can form copper thiomolybdates.
- There are several chemical species of Cu thiomolybdates, but the tetra-thiomolybdate is the first formed.
- Copper tetra-thiomolybdates are very chemically stable, and effectively eliminate the biological activity of the copper
- The major sources of thiomolybdates can be the drinking water, and soil consumption.
- Forage can also be a significant source when the forage has been grown under certain conditions such as wet conditions or liming of soils



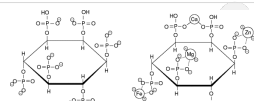
• Gould L and Kendall NR. Nutr Res Rev 2011;24:176-182

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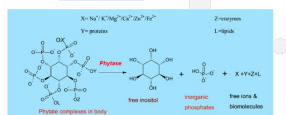
8

Mineral-Dietary Ingredient Interactions

- Phytic acid is a common organic dietary ingredient found in most grains.
- Phytic acid consists of phosphate groups that bind mineral cations
 - Calcium can cross link
 - Other minerals bind to the phosphate moieties
- Inositol-6-phosphate (IP6) and inositol-5-phosphate demonstrate the strongest antagonistic effects.
- Phytase (a phosphatase) can help neutralize the effects of phytic acid



• A. Zifferman, in *Encyclopedia of Food Science and Nutrition* (Second Edition) 2003



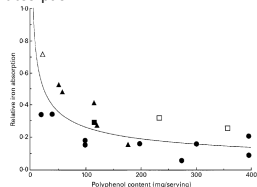
• Bajaj P, in *Development and Applications of Enzymes from Thermophilic Microorganisms* 2023

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9

Iron Absorption in Human Nutrition.

- Cholinergic acid (polyphenol) is a commonly consumed dietary ingredient is a potent antagonist to iron absorption.



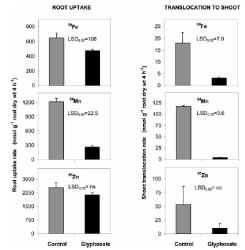
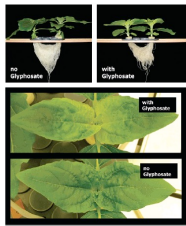
- Murrell RJ, et al. Brit J Nutr 1999;81:289-295



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Glyphosate Induced Manganese Deficiency



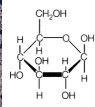
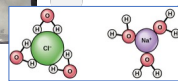
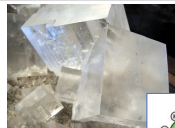
- Ecker S, et al. J Ag Food Chem. doi:10.1021/jf0625196

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Types of Binding

- Physical binding (slow release)
- Chemical binding
 - Ionic
 - Covalent
 - Coordination



Chelates and complexes have covalent and coordination bonding

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12

Organic Trace Minerals Approved by AAFCO

- 57.150 – Metal Amino Acid Complex
 - Zinpro Availamins
- 57.151 – Metal (Specific amino acid) Complex
 - Zinpro methionates
 - Some glycines such as Traxmins
- 57.142 – Metal Amino Acid Chelate
 - Balchem KeyShure Plus
- 57.28 – Metal Methionine Hydroxy Analogue Chelate
 - Mintrex products
- 57.29 – Metal Polysaccharide Complex
 - Qualitech products
- 57.23 – Metal Proteinate
 - Balchem, Trouw, JH Biotech, Buffermin, and others.

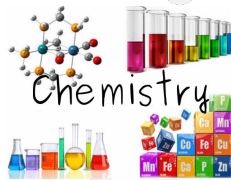
General forms of OTM approved for use in feeds



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Chemical Requirements for Metal Chelation

- The ligand must contain two atoms that can bond to the same metal.
- The ligand must form a heterocyclic ring with the metal as the closing member.
- It must be sterically possible to chelate the metal.
- Must have a metal:ligand molar ratio that is a minimum of 1:1.



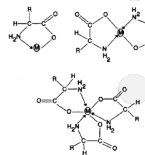
Minimal requirements



14

Must Have a Metal:Ligand Molar Ratio that is a Minimal 1:1

- This necessitates knowing the molecular weight and moles of the ligand.
- Since chelation is a reaction, it must be chemically balanced.
- If it is less than a 1:1 ratio, it cannot be fully chelated.



Most commonly ignored requirement in OTM's



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Levels of Chelation Protection



Inorganic or no chelation protection



1:1 Chelate protection is most common and provides good antagonist protection



2:1 Chelate protection provides maximum protection against antagonists

Different ligands offer differing levels of protection



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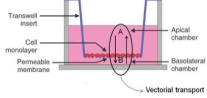
Using a Cell Culture Antagonist Model to Evaluate Zinc Absorption from Organic and Inorganic Trace Minerals

IPPE 2021
Shane C. Morgan, Zachary S. Lowman, Kenneth Sanderson, and Kari A. Estes
 Balchem Corporation, New Hampton, New York, United States



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Experimental Design



Zinc Solution Preparation

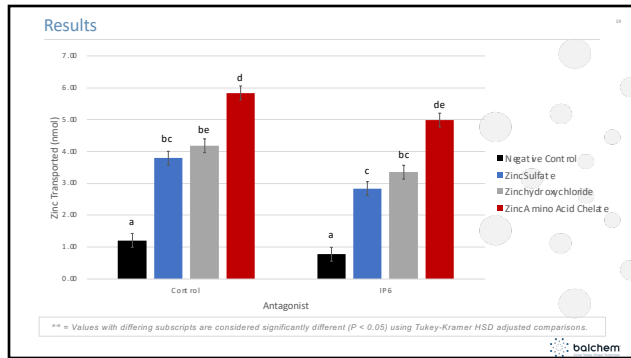
- 5mM of Zn stock solution (Zn source = 0.1N HCl)
- TRT 1: Control** (No antagonist added)
- TRT 2: Phytate** (Phytate added (100 μ L of 10 mg/mL phytate))
- Incubate for 1 hr at 37°C
- Adjust to pH 7.0 with 2.5 mL of 0.2N NaOH
- Bring up to 10 mL with ultra-pure H₂O

Transport Assay

- 25 μ L of prepared Zn solution is added into a well with 300 μ L of media + antagonist Zn solution (performed in duplicate)
- Treated cultures are incubated at 37°C and 5% CO₂ for 4 hrs
- Basal fluid is collected from each well for Zn analysis via colorimetric Zn assay kit (Bio Vision, K387-100)



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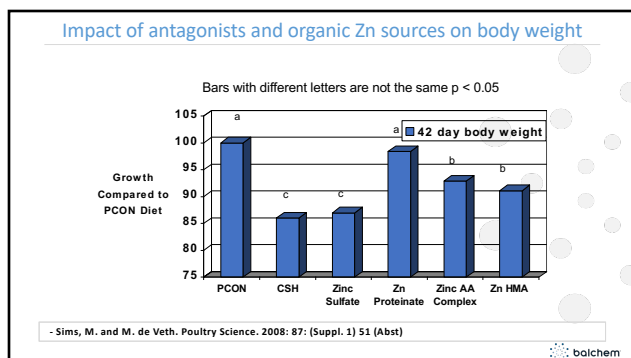
Deposition of and performance responses to Zn from three organic sources fed to broiler chickens in the presence of cottonseed hull diets containing gossypol

- 1200 CobbXRoss broilers were fed different zinc sources from day 1-42.
- Basal Diets were 1400 kcal/ME, Corn/Soy with 20% protein. They were all Naturally adequate for all mineral, except Mn and I which were added.
- Treatments included:
 - Positive control diet (40 ppm Zn Sulfate, no antagonist)
 - Control (no added Zn, with antagonist)
 - Zn Proteinates (40 ppm Zn with antagonist)
 - Zn Amino Acid Complex (40 ppm Zn with antagonist)
 - Zn 2-hydroxy-4-(methylthio) butanoic acid (HMA) (40 ppm Zn with Antagonist)
- Growth as a indicator of Zn bioavailability was measured



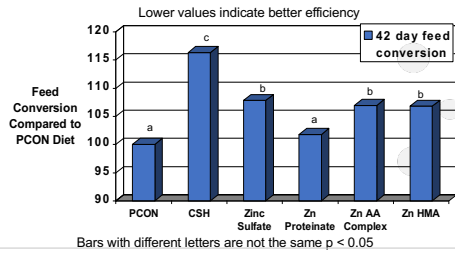
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Impact of antagonists and chelated Zn sources on 42 day feed conversion



- Sims, M. and M. de Veth. Poultry Science. 2008; 87: (Suppl. 1) 51 (Abst)



22

Bioavailability of copper from copper glycinate in steers fed high dietary sulfur and molybdenum

- Sixty Angus and Angus X Simmental steers age 9 months and approximately 277 Kg BW were stratified by BW and randomly assigned to 1 of 5 treatments.
- Basal diet included 2 mg Mo/Kg DM and 0.15% S and was fed for 120 days (Phase 1).
- After 120 days, Mo was increased to 6 mg Mo/Kg DM for another 28 days (Phase 2)
- Treatments included:
 - Control (basal diet)
 - 5 mg Cu/Kg DM from Cu sulfate
 - 10 mg Cu/Kg DM from Cu sulfate
 - 5 mg Cu/Kg DM from Cu glycinate
 - 10 mg Cu/Kg DM from Cu glycinate
- Plasma Cu, ceruloplasmin and liver Cu was determined for each phase.

- Hansen SL et al. J Anim Sci 2008;86:173-179



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Table 4. Estimated relative bioavailability of Cu sources in steers fed diets high in Mo and S, based on multiple linear regression of Cu indices on total supplemental Cu intake (g)¹

Cu indices	Cu source	Slope ± SE	P-value ²	Relative bioavailability, %
Phase 1 ³				
Plasma Cu ⁴	Sulfate	0.017 ± 0.009	0.10	100
	Glycinate	0.024 ± 0.011		140
Plasma ceruloplasmin	Sulfate	0.862 ± 0.218	0.01	100
	Glycinate	1.338 ± 0.255		140
Liver Cu ^{4,5}	Sulfate	0.051 ± 0.010	0.12	100
	Glycinate	0.067 ± 0.012		131
Phase 2 ⁶				
Plasma Cu ⁴	Sulfate	0.020 ± 0.006	0.01	100
	Glycinate	0.029 ± 0.008		144
Plasma ceruloplasmin	Sulfate	0.646 ± 0.135	0.01	100
	Glycinate	1.014 ± 0.158		157
Liver Cu ^{4,5}	Sulfate	0.033 ± 0.009	0.01	100
	Glycinate	0.050 ± 0.010		150

¹Based on regression of Cu indices (plasma Cu in mg/L, ceruloplasmin activity in mg/L, liver Cu in mg/kg of DM) on total supplemental Cu intake (g) of steers over the 120 d (phase 1) or 148 d (phase 2) period.

²P-values for slope differences between Cu sources.

³Regression based on final measurements following 2 mg of Mo/kg of DM supplementation.

⁴Day 0 values used as a covariant.

⁵Data log_e transformed before regression analysis.

⁶Regression based on final measurements following 6 mg of Mo/kg of DM supplementation.

- Hansen SL et al. J Anim Sci 2008;86:173-179



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Bioavailability of Copper Proteinate and Copper Carbonate Relative to Copper Sulfate in Cattle

- 40 heifers were fed diets containing additions of 0.15% S and 5 mg Mo/Kg DM.
- They were randomly assigned one of 4 treatments:
 - Control (no added Cu)
 - Copper Sulfate 5 mg Cu/Kg DM
 - Cu Carbonate 5 mg Cu/Kg DM
 - Cu propeinate 5 mg Cu/Kg DM
- Treatments were fed for 54 days
- Plasma samples were taken and analyzed for Cu content on day 0,10,28, and 54.

- Ward JD et al. J Dairy Sci 1996;79:127-132



25

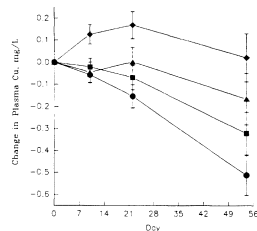


Figure 3. Effect of different Cu sources on concentrations of Cu in plasma when heifers were fed 5 mg of added Mo/Kg of DM (Experiment 2). Sources: control (●), CuSO₄ (■), CuCO₃ (▲), and Cu propeinate A (◆). Bars represent standard errors.

- Ward JD et al. J Dairy Sci 1996;79:127-132



26

HIGH IRON INTAKE DEPRESSES HEPATIC COPPERCONTENT IN GOATS

- In a 56 X 56 day cross over trial design, non pregnant goats were fed either 269 or 2380 mg Fe/Kg DM.
- Plasma Cu, ceruloplasmin activity and hepatic copper were measured at the outset and completion of treatment.

Measure	Experimental ration				
	Low iron		High iron		p value
	Mean	SE	Mean	SE	
Plasma copper (µmol/l)	17.6	0.95	14.4	2.11	0.117
Plasma ceruloplasmin activity (absorbance units) ²	314.8	56.54	272.7	63.76	0.276
Hepatic copper (µmol/g dry matter)	4.0	0.29	2.9	0.55	0.0497

¹ Values are for six animals.

² Ceruloplasmin oxidase activity is expressed as absorbance change due to formation of the coloured oxidation product of p-phenylenediamine at 530 nm (Absorbance/min.L).

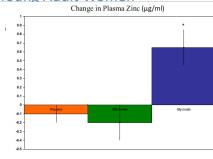
- Schonewille JTh, et al. Vet Quar 1995;17:14-17



27

Moderately High Dose Zinc Gluconate or Zinc Glycinate: Effects on Plasma Zinc and Erythrocyte Superoxide Dismutase Activities in Young Adult Women

- Thirty females were randomly assigned to placebo, zinc gluconate, or zinc glycinate treatments.
- Zinc treatments consisted of 60 mg Zn/day for 6 weeks.
- Plasma Zn levels and erythrocyte SOD (measure of copper status) were evaluated.
- The Zn Glycinate increased blood plasma levels, but had no impact on SOD activities.
- Authors suggested that perhaps the zinc glycinate was absorbed differently



Group	Pre-treatment	Post-treatment
Placebo	3361±1402	3380±420
Zinc gluconate	3348±383	3301±489
Zinc glycinate	3423±952	3489±622

Means in each post-treatment period differ (SD). No significant change in any group between pre- and post-treatment (paired t test, p>0.05).

- DiSilvestro RA, et al. Biol Trace Elem Res 2015; DOI 10.1007/s12011-015-0334-3



28

Conclusions

- Antagonists are going to be present in the feed/water intake streams.
- Organic trace minerals (OTM) if properly protected as a chelate can help overcome deleterious effects of antagonists.
- Perhaps the increased bioavailability seen with OTMs is due to less interaction with dietary antagonists when compared to inorganics.
- OTMs represent the best "insurance policy" to maximize mineral nutrition in the animal which will result in a healthier animal.



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Thank You!

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