Dairy cows and the copper conundrum

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Copper's double-edge sword

Hao Wie, Linus Pauling Institute, Oregon State U, 2009

The Good

- Most abundant trace mineral in the body involved in many biochemical reactions.
- Copper is a cofactor in enzymes involved in cellular energy production, free-radical detoxification, connective tissue production, iron mobilization, neurotransmission.
- Required for angiogenesis & bone development.

The Bad

- Copper can accept and donate electrons generating reactive oxygen species (ROS) such as superoxides and hydrogen peroxide causing oxidative damage.
- High copper levels can displace other essential metals from their natural ligands
  - The replacement of zinc by copper in the human estrogen receptor renders the protein defective, altering hormone dependent cell signaling.
- Well described toxicity causing hemolysis, hemoglobinunic nephropathy, hepatic necrosis & icterus

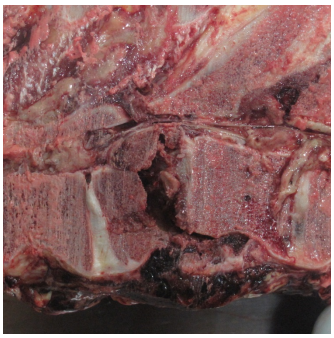
Beef feedlot steers:

Spontaneous fractured of lumbar spinal columns.

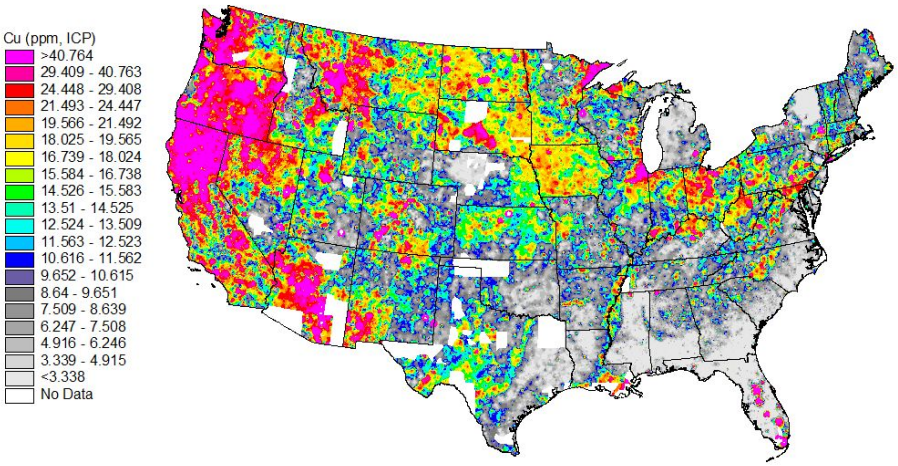
Liver coppers were deficient at 13, 26 and 27 mg/kg DM

(reference range 50-300 mg/kg)

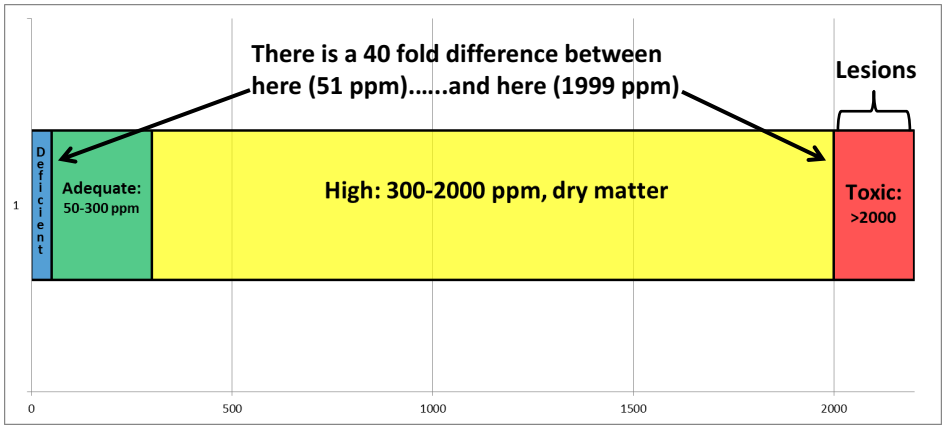
They had been injected with an injectable mineral product



Soil copper



Bovine Liver Copper Ranges
(dry matter)



Goals

- Learn a clinical skill:
  - Observe and practice collecting liver biopsies from mature cows
- Learn a diagnostic skill:
  - Collect blood and examine serum chemistries in cows that are otherwise healthy.
- Collection of liver biopsies and serum chemistry results are NOT commonly done by practitioners, but I believe they can add value.

Copper conundrums

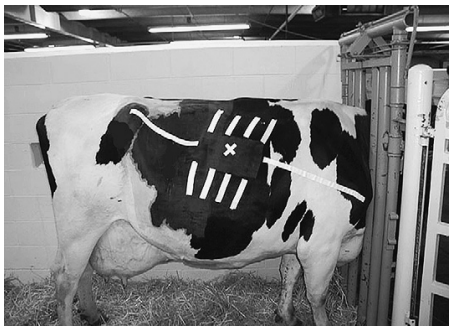
- Many dairy cow livers test “high” but they do not have lesions of copper toxicity.
  - Are they still OK?
- If there are no gross or microscopic lesions, should we care?
- Can we find any consequences of high copper?
- Should copper be monitored and what methods should be used?

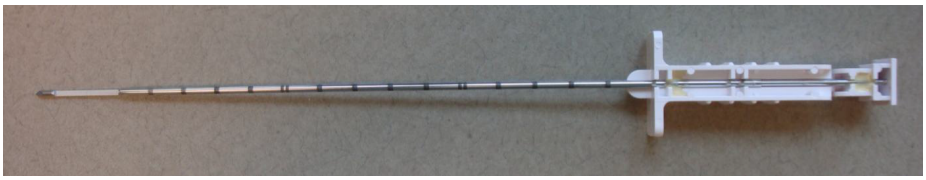
Copper conundrums

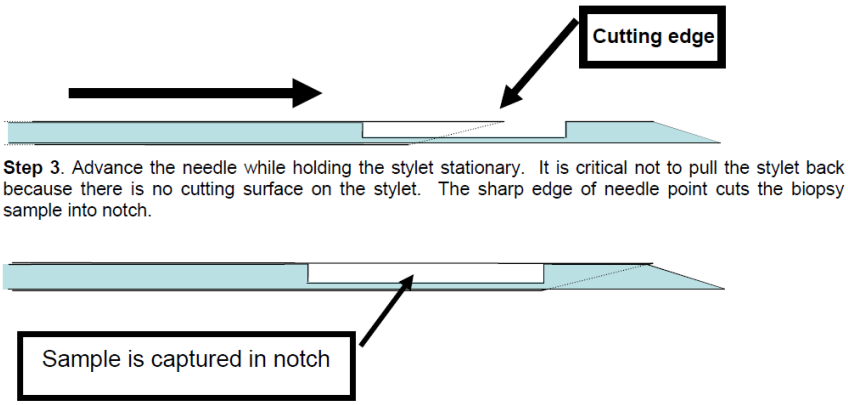
- What about Copper and it’s interactions
  - Molybdenum
  - Sulfur
  - Iron
  - Selenium
- Copper feeding rates are based on dry matter intake. The current NRC feeding rate is 12 -16 mg / kg of dry matter. The more a cow eats, the more copper she consumes, but does she need it?

Liver biopsy – Key details

- LOCATION, LOCATION, LOCATION
  - The 10/11 rib space is critical.
  - A line from the "hook" to shoulder
  - Understand the mechanics and familiarize yourself with the tool.







Step 3. Advance the needle while holding the stylet stationary. It is critical not to pull the stylet back because there is no cutting surface on the stylet. The sharp edge of needle point cuts the biopsy sample into notch.

Step 4. Advance the needle all the way over the stylet. This captures the sample and the instrument may be withdrawn from the animal.

Swenson Herd

- High producing, well-managed “robot” herd in central Minnesota
- There were no previous findings, or suspicions, to prompt liver biopsies.
- The goal of sampling cows was to investigate if there was evidence of sub-clinical disease, specifically liver damage.
  - The liver is the power-house and if we expect high health and production, we need optimal liver health.

Cow selection

- This approach was a paradigm shift ***away* from** sick, or “broken” cows.
- I wanted to select cows that were eating and milking well and avoid cows with other confounding health problems.
- 7 high producing cows were bled, the blood was allowed to clot and serum was collected on farm
- At least 15 mg of liver (two biopsies) were collected

Serum Chemistry Results

	Scipio	Cow 2310	Cow 2283	Cow 2170	Cow 2128	Cow 2113	Cow 2070	Reference Range
GLDH	36	306 High	99 High	54 High	158 High	68 High	112 High	0-50
SDH	20.6	56 High	39 High	27	132 High	36	60 High	6.6-37.8
GGT	35	22	28	21	31	28	38	4-41
Total Bili	0.1	0.1	0.1	0.1	0.2	0.1	0.1	0.0-0.2
Albumin	3.1	3.9	3.1	3.7	3.4	3.2	3.7	3.1-4.3
Total Protein	7.2	6.9	6.5	7.3	7.1	8.2 High	7.3	5.6-7.8
Globulin	4.1 High	3	3.4	3.6	3.7	5 High	3.6	2.0-4.0
Calcium	9.5	9.3	10.4	10.1	10	9.6	10.2	7.9-10.5
Phosphorous	4 Low	6.1	5.9	6.4	8.8 High	6.5	5.2	4.1-8.3
Sodium	137	139	138	141	142	136	140	135-145
Potassium	4.5	4.7	4.8	5.2	4.1	4.3	5.1	3.7-5.6
Chloride	94 Low	98	98	98	88 low	98	96 low	98-109
								22-29
CK	342 High	97	95	110	5448 High	98	169	50-271
AST (GOT)	110	128	104	87	228 High	95	144	48-204
Bicarbonate	31 High	28	28	28	37 High	26	29	
Anion Gap	17	18	17	20	21	16	20	17
Glucose	49	55	70	65	87 High	70	70	44-75
BUN	15	16	10	16	10	11	12	8-22
Creatinine	0.7	0.6	0.6	0.6	0.7	0.6	0.6	0.3-0.8
Cholesterol	338 High	309	225	220	264	228	260	112-331

Liver biopsy results and Means

	Scipio	Cow 2310	Cow 2283	Cow 2170	Cow 2128	Cow 2113	Cow 2070	
Copper	131	284	601 High	367 High	1106 High	648 High	210	50-300
Iron	217	205	206	283	214	282	194 Low	200-450
Manganese	13.9 High	19 High	11.4 High	14.7 High	10.2 High	18.9 High	13.1 High	5-9
Molybdenum	3.5 High	3.7 High	5.1 High	4.1 High	3.7 High	3.8 High	3.3 High	1.5-3.0
Selenium	3.3 High	5.8 High	4.5 High	3.8 High	6.8 High	3.7 High	3.3 High	0.7-2.5
Zinc	111	102	152	108	413 High	97 Low	81 Low	100-300

	Mean	Range
GLDH	**119.00**	0-50
SDH	**52.00**	6.6-37.8
Copper	**478.00**	50-300
Selenium	**4.45**	0.7-2.5

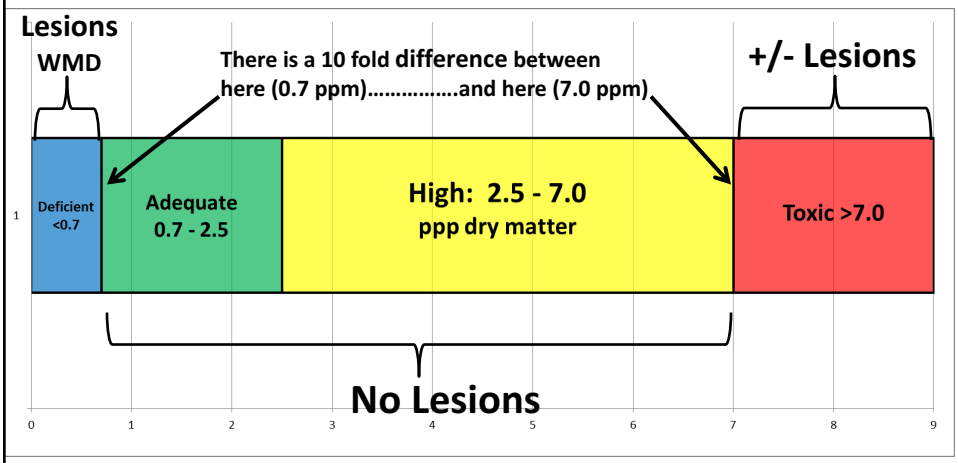
Why?

- High producing cows eat a lot.
- The copper feeding rate is..
  …..12 mg/kg of Dry Matter consumed
- The more a cow eats, the more copper she gets…but does she need it?
- Comparison of two cows: Scipio and 2283
  - Scipio was the Brown Swiss and if I back calculate from milk production, she was eating 20 kg of dry matter, or about 240 mg of copper
  - 2283 was a high producing Holstein and we estimate she was eating 27 kg of dry matter, or 325 mg of copper.

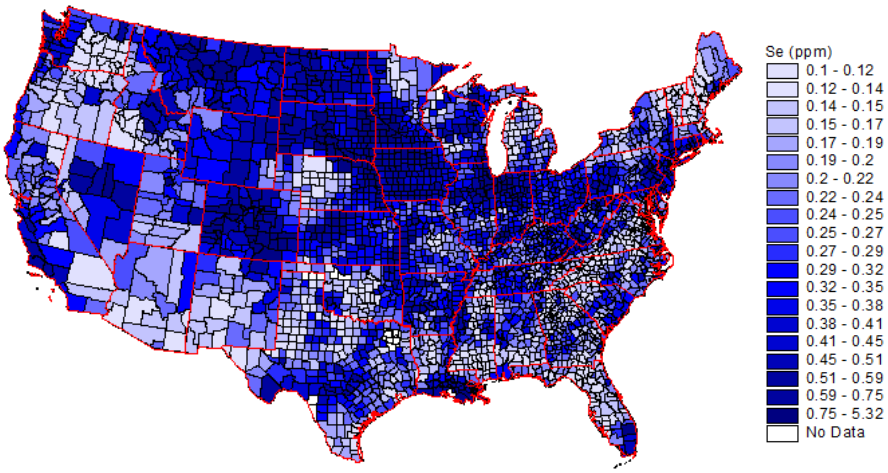
Selenium

- The legal limit of selenium is 0.3 mg/kg of dry matter, but do some farms feed more? Do all farms need the legal limit?
- Recognize an important interaction between selenium and copper!
  - Selenate or selenite supplementation causes drop in serum ceruloplasmin, primary Cu transport protein, resulting in lower serum and increased liver Cu.

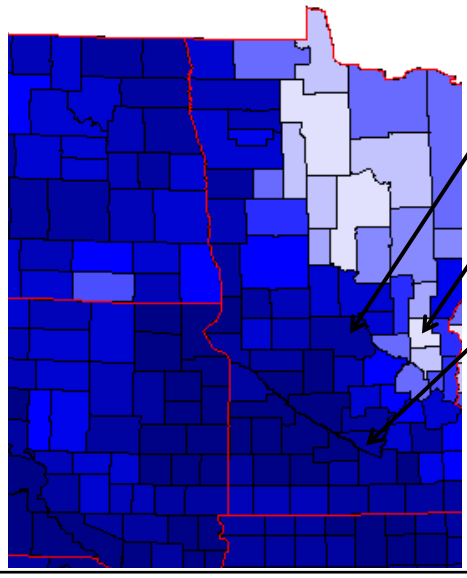
Bovine Liver Selenium Ranges



Soil Selenium



Midwest Soil Selenium



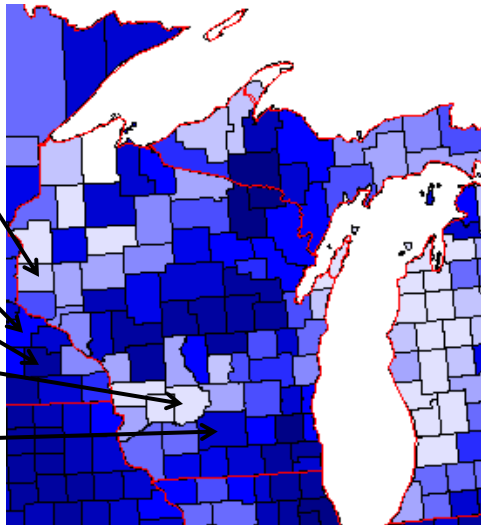
Stearns County:
0.70 +/- 0.30

Isanti County:
0.12 +/- 0.12

Nicollet County:
0.63 +/- 0.29

Midwest Soil Selenium

- St. Croix County WI 0.17 +/- 0.07
- Goodhue County 0.34 +/- 0.11
- Olmsted County 0.52 +/- 0.33
- Sauk County WI 0.13 +/- 0.03
- Dane County WI 0.41 +/- 0.13

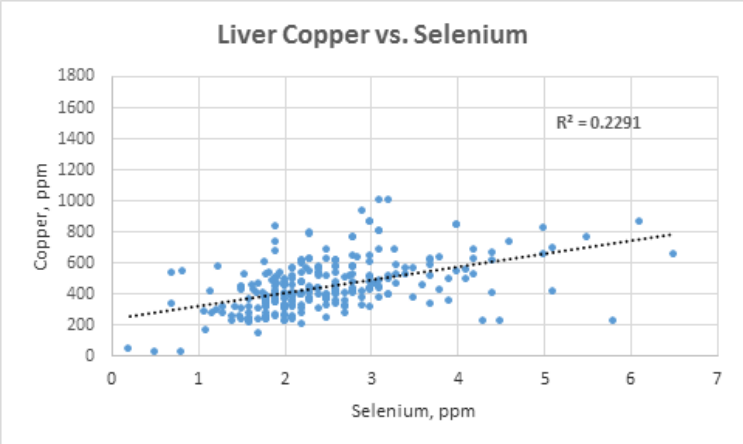


Selenium in Feed

http://www.ansci.cornell.edu/plants/toxicagents/selenium.html

- Sunflower meal 2.13, Fish meal 1.4-2.4 mg/kg
- Alfalfa 0.32 – 0.37 mg/kg
- Corn
  - Gluten meal 1.11 mg/kg
  - Distillers 0.48 mg/kg
  - Grain 0.08 mg/kg

For every 2 point drop in liver selenium we should expect a 200 point drop in liver copper



Copper and selenium

- How significant is the copper, serum ceruloplasmin and selenium interaction?
- Are the high selenium cows they same high copper cows that ate the most feed?
- Could selenium be high for the same reason the copper is high…those cows just eat more?

What should be done? Suggestions?

- It would be very difficult to convince anyone to reduce the copper feeding levels below the NRC requirement of 12 mg/kg of DM and drop the selenium level below 0.3 ppm.
- Current suggestion for Swenson herd: Do not add minerals to the grain offered in the robot feeders. High producing cows need the protein and energy to maintain production but I doubt they require additional copper and selenium.

Schwinghammer Herd

- Producer and veterinarian complaints.
  - One aborted fetus had a liver selenium level of 6 (reference range 0.7 to 2.5). Toxic >7.
  - Foot health is poor and has gotten worse because copper sulfate foot baths have been discontinued.
  - The farm stopped foot baths because he saw cows drinking from them.

Schwinghammer - Serum Chemistry

	Cow 716		Cow 712		Cow 671		Cow 527 (big leg)	Cow 419		Cow 789		Reference Range	Mean
GLDH	28		61	High	27		22	58	High	32		0-50	38
SDH	29.1		36.2		22.9		19.4	33.3		24.1		6.6-37.8	27.5
GGT	28		39		28		15	28		22		4-41	27
Total Bili	0.1		0.1		0.2		0.1	0.1		0.1		0.0-0.2	0.12
Albumin	3.8		3.4		3.3		3.6	3.4		3.8		3.1-4.3	3.55
Total Protein	7.1		7.8		9.6	High	7.4	6.9		7.3		5.6-7.8	
Globulin	3.3		4.4		6.3	High	3.8	3.5		3.5		2.0-4.0	
Calcium	9.1		9.7		9		9.7	9.4		9.9		7.9-10.5	
Phosphorous	5		5.5		3.8		5.5	5.3		7		4.1-8.3	
Sodium	137		136		130	Low	140	138		138		135-145	
Potassium	4.6		4.4		4.8		4.4	4.6		4.2		3.7-5.6	
Chloride	97	Low	97	Low	100		99	101		96	Low	98-109	
												22-29	
CK	118		92		215		527	71		175		50-271	
AST (GOT)	69		102		82		73	70		58		48-204	
Bicarbonate	29		27		22		25	26		27			
Anion Gap	16		16		13		20	16		19		17	
Glucose	57		58		74		66	63		61		44-75	
BUN	15		14		20		16	15		16		8-22	
Creatinine	0.6		0.7		0.7		0.6	0.7		0.8		0.3-0.8	
Cholesterol	211		258		273		269	224		218		112-331	

Schwinghammer – Liver biopsy

	Cow 716		Cow 712		Cow 671		Cow 527 (big leg)		Cow 419		Cow 789			Mean
Copper	523	High	478	High	511	High	164		677	High	178		50-300	421
Iron	258		162	Low	274		285		277		201		200-450	
Manganese	NA		NA		NA		NA		NA		NA		5-9	
Molybdenum	4.1	High	4.2	High	4.3	High	4.1	High	4.2	High	4.1	High	1.5-3.0	4.17
Selenium	3.7	High	3.7	High	4.3	High	3.9	High	4.1	High	4.6	High	0.7-2.5	4.05
Zinc	133		132		185		132		165		117		100-300	

Schwinghammer – Suggestions?

- Why do cows drink from copper sulfate foot bath?
  - Are they thristy after milking?…set out a stock tank
  - Are they craving salt?....set out a salt feeder
- Could high selenium be playing a role in health and should the Se feeding rate be lowered?
- If lowered below NRC, how should copper and selenium be monitored?

Ongoing monitoring

- Additional liver biopsies, on the same cows, would be the gold standard, but might be interpreted as costly.
- Serum GLDH is $7.50 per cow. If cows are above 50, then elevated copper **might be** causing a problem. Liver biopsies are needed to confirm high copper. Molds and mycotoxins can drive GLDH high.
- High selenium does not appear to produce significant changes on a chemistry profile. Whole blood collected in a purple-topped tube is a non-invasive sample for assessing selenium levels.

Comparison

	Swenson	Schwinghammer	Ref Range
GLDH	119	38	0-50
SDH	52	27	6.6-37.8
Copper	478	421	50-300
Selenium	4.45	4.05	0.7-2.5

Herd 3: High copper (30 ppm): Before and 6 month after copper was dropped

	Maztaz	Bumble	Twyla	Utah	Essence	Ollie	Mean	Reference Range
GLDH	29	84	94	71	119	424	136	0-50
SDH	28.8	69.8	58	63.7	80.7	105.9	68	6.6-37.8
GGT	15	20	21	37	31	54	30	4-41
Copper	600	580	850	290	770	1000	681	50-300
Selenium	3.8	4.5	4.4	3	4.7	4.2	4.10	0.7-2.5

22 of 30 above reference range

	Maztaz	Bumble	Twyla	Utah	Essence	Ollie	Mean	Reference Range	% drop	
GLDH	17	38	33	15	7	130	40	0-50	71%	GLDH
SDH	17.1	15	24	14	18	53	24	6.6-37.8	65%	SDH
GGT	13	16	17	27	20	29	20	4-41	31%	GGT
Copper	253	395	329	89	318	145	254	50-300	63%	Copper
Selenium	2.72	3.5	2.81	0.8	2.62	1.2	2.28	0.7-2.5	45%	Selenium

Summary

- Collecting liver biopsies and serum for chemistries appears to have value.
- Veterinarians are uniquely qualified to do these things.
- A “cheap” herd “dipstick” test would be testing GLDH only ($7.50 per sample). If cows are testing high GLDH, a full chemistry profile ($15 per sample) and liver biopsies ($40 per sample) could be attempted to determine a trace mineral role.