INE INSTITUTE OF NUTRITIONAL ENDOCRINOLOGY

Micronutrients: Molybdenum

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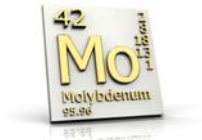
Medical Disclaimer: The information in this presentation is not intended to replace a one-on-one relationship with a qualified health care professional and is not intended as medical advice. It is intended as a sharing of knowledge and information from the research and experience of Dr. Ritamarie Loscalzo, drritamarie.com, and the experts who have contributed. We encourage you to make your own health care decisions based upon your research and in partnership with a qualified health care professional.

Molybdenum (Mb) Basics

- ✓ Essential trace element needed in microgram amounts
- ✓ Functions as a cofactor for a number of enzymes
- ✓ Usually bound to sulfur or oxygen
- ✓ Causes important chemical transformations in carbon, nitrogen, and sulfur cycles
- ✓ The molybdenum content of foods depends on the molybdenum content of soils
- ✓ Esophageal cancer has been linked to the molybdenum content in soils and food

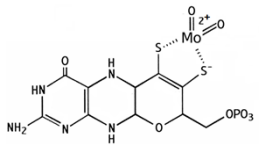


Digestion and Absorption of Molybdenum

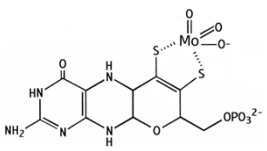
- ✓ Bound to amino acids in foods
- ✓ HCl and pepsin in stomach required to break the bonds
- ✓ Proteolytic enzymes in small intestine hydrolyze to further release bonds
- ✓ Passive diffusion is main mechanism of absorption, but carriers have been identified in animals
- ✓ Transport in blood thought to be as MBO_4^{-2}
- ✓ Highest concentration in liver, kidneys, and bone
- ✓ Small intestine, thyroid, lungs, spleen, brain, muscle, and adrenals also contain molybdenum
- ✓ Usually 50% - 90% is absorbed

Function of Molybdenum

- ✓ Biological form of the molybdenum atom
  - ➢ Organic molecule known as the molybdenum cofactor (Moco)
  - ➢ Present in the active site of Moco-containing enzymes (molybdoenzymes)



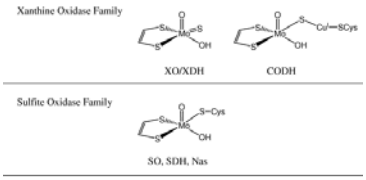
Molybdenum Cofactor (Oxidized)



Molybdenum Cofactor (Reduced)

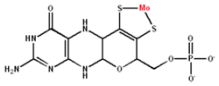
Molybdenum Enzymes

- ➢ Xanthine oxidase
- ➢ Sulfite oxidase
- ➢ Aldehyde oxidase
- ➢ Mitochondrial amidoxime reducing component (mARC)



The 4 Molybdenum Dependent Enzymes #1

1) **Sulfite oxidase**
   - A mitochondrial outermembrane enzyme
   - Mainly found in liver, heart, and kidney
   - Contains 2 molybdopterin and 2 cytochrome residues
   - Causes the transformation of sulfite to sulfate
   - Necessary for the metabolism of sulfur-containing amino acids (methionine and cysteine)

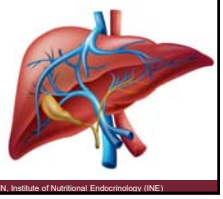


The 4 Molybdenum Dependent Enzymes #2

1) **Sulfite oxidase**
2) **Xanthine oxidase**
   - Iron dependent enzyme
   - Mainly found in thyroid and intestine
   - Causes the breakdown of nucleotides (precursors to DNA and RNA) to form uric acid
   - Contributes to the plasma antioxidant capacity of the blood

The 4 Molybdenum Dependent Enzymes #3

1) **Sulfite oxidase**
2) **Xanthine oxidase**
3) **Aldehyde oxidase**
   - Mostly in the liver
   - Uses molecular oxygen as an electron acceptor
   - Cause hydroxylation reactions that involve a number of different molecules with similar chemical structures
   - Xanthine oxidase and aldehyde oxidase also play a role in the metabolism of drugs and toxins



The 4 Molybdenum Dependent Enzymes #4

1) **Sulfite oxidase**
2) **Xanthine oxidase**
3) **Aldehyde oxidase**
4) **Mitochondrial amidoxime reducing component (mARC)**
   - Forms a three-component enzyme system with cytochrome b5 and NADH cytochrome b5 reductase
   - Causes the detoxification of mutagenic N-hydroxylated bases

Of these enzymes, sulfite oxidase is known to be crucial for human health.

Nutrient Interactions

Tungsten

Major antagonist to molybdenum

Copper

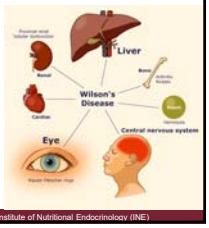
Molybdenum intakes of 500 mcg/day – 1500 mcg/day appears to possibly increase urinary copper excretion

Other possible interactions (mechanisms not clear):

Manganese, zinc, iron, lead, ascorbic acid, methionine, cysteine, protein, silicon

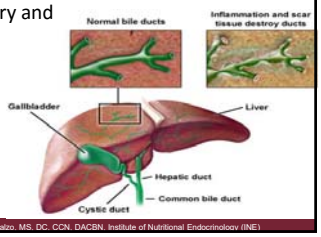
Tetrathiomolybdate

- ✓ Formation of compounds containing sulfur and molybdenum
  - Thiomolybdates
  - Prevents the absorption of copper and can cause fatal copper-dependent disorders
- ✓ Tetrathiomolybdate (TM)
  - Molecule that can form high-affinity complexes with copper
  - Controlling free copper (copper that is not bound to ceruloplasmin)
  - Inhibiting copper chaperones and copper-containing enzymes
- ✓ Used in the treatment of Wilson's disease (copper toxicity disease) – neurologic complications



More on Tetrathiomolybdate as a Therapy for Copper Toxicity

- ✓ TM therapy for kidney cancer, colorectal cancer, and breast cancer
  - ➢ TM stabilized disease or prevented relapse in correlation with copper depletion
- ✓ TM therapy for inflammatory and immune-related diseases
  - ➢ Stabilized and improved survival in those with biliary cirrhosis

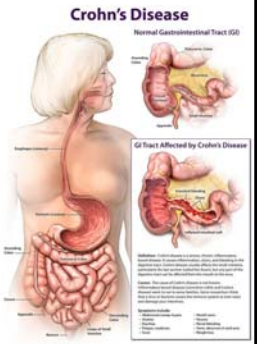


Inherited Molybdenum Cofactor Deficiency

- ✓ Molybdenum functions in the form of the **Moco** (mb co-factor)
- ✓ Disturbance of Moco metabolism can disrupt the function of all molybdoenzymes
- ✓ Moco is synthesized by a multistep metabolic pathway involving four genes: **MOCS1, MOCS2, MOCS3,** and **GPHN**
- ✓ More than 60 mutations affecting mostly MOCS1 and MOCS2 have been identified

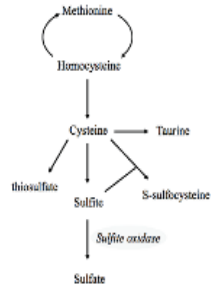
Acquired Molybdenum Deficiency

- ✓ Crohn's disease
  - ➢ Long-term total parenteral nutrition (TPN) without molybdenum added to the TPN solution
  - ➢ Supplement molybdenum in the form of ammonium molybdate (160 mcg/day)
- ✓ Soil deficiency and absorption issues



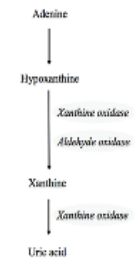
Sulfur Amino Acid Metabolism

Figure 2. Sulfur Amino Acid Metabolism



Uric Acid Production

Figure 3. Uric Acid Production



MOCS1 Mutation

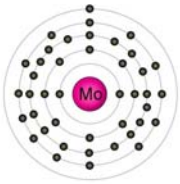
- ✓ The MOCS1 gene
  - ➢ Controls the initial step in the Moco biosynthetic pathway
  - ➢ Causes the conversion of guanosine triphosphate into cPMP
  - ➢ Daily administration of cPMP resolves all metabolic abnormalities associated with defective sulfite oxidase and xanthine pathways
  - ➢ Prevents further signs of neurologic deterioration
- ✓ Cyclic pyranopterin monophosphate (cPMP)
  - ➢ Those with MOCS1 mutations lack cPMP
  - ➢ Successfully used in treatment
- ✓ Early diagnosis and initiation of treatment are essential to ensure success
- ✓ Since cPMP replacement therapy can only benefit MocoD Type A, additional treatment methods are required

Clinical Uses for Molybdenum

- ✓ **Sulfite Sensitivity**: Reduce the risk of sulfite-reactive asthma attacks
- ✓ **Cancer Prevention**: As an anti-cancer agent, it appears to work by playing a role in the detoxification of cancer-causing chemicals
- ✓ **Cavity Prevention**: Molybdenum appears to increase the anti-caries effect of fluoride
- ✓ **Wilson's Disease**: Tetrathiomolybdate forms a complex with copper and blocks its absorption from the intestines or renders blood copper nontoxic
- ✓ **Thyroid Protection:** Cysteine requires Molybdenum as a cofactor in order to be metabolized to glutathione

Molybdenum Toxicity

- ✓Toxicity is rare with intakes up to 1500 mcg
- ✓Gout-like symptoms have been reported in an Armenian population consuming 10 to 15 milligrams (mg) of molybdenum from food daily
- ✓Upper limit set to 2 mg



Recommended Dietary Allowance

1 to 3 years: 17 micrograms per day

4 to 8 years: 22 micrograms per day

9 to 13 years: 34 micrograms per day

14 to 18 years: 43 micrograms per day

19+ years: 45 micrograms per day

Molybdenum Food Sources

- Lentils
- Dried peas
- Lima beans
- Kidney beans
- Soybeans
- Black beans
- Pinto beans
- Garbanzo beans
- Tomatoes
- Romaine lettuce
- Cucumber
- Celery
- Fennel

Molybdenum Food Sources

Adult RDA 45 mcg

Food	Serving Size	Cals	Amount (mcg)	DRI/DV (%)
Lentils	1 cup	229.7	148.50	330
Dried Peas	1 cup	231.3	147.00	327
Lima Beans	1 cup	216.2	141.00	313
Kidney Beans	1 cup	224.8	132.75	295
Soybeans	1 cup	297.6	129.00	287
Black Beans	1 cup	227.0	129.00	287
Pinto Beans	1 cup	244.5	128.25	285
Garbanzo Beans	1 cup	269.0	123.00	273
Oats	0.25 cup	151.7	28.86	64
Tomatoes	1 cup	32.4	9.00	20
Romaine Lettuce	2 cups	16.0	5.64	13
Cucumber	1 cup	15.6	5.20	12
Celery	1 cup	16.2	5.05	11
Barley	0.33 cup	217.1	26.99	60
Eggs	1 each	77.5	8.50	19
Carrots	1 cup	50.0	6.10	14
Bell Peppers	1 cup	28.5	4.60	10
Fennel	1 cup	27.0	4.35	10

http://www.drritamarie.com/go/WHFoodsMolybdenum

Molybdenum Supplementation

- ✓Sodium molybdate
- ✓Ammonium molybdate

Molybdenum Drug Interactions

- Acetaminophen: high doses of molybdenum inhibit metabolism
- No other reported drug interactions

Test for Molybdenum

✓**Blood**

➢For three days prior to testing, do NOT:
1) Eat leafy green vegetables, legumes, or shellfish
2) Take supplements -- specifically minerals
3) Take antacids

✓**Urine**

➢Heavy metals test kit

References

- ✓ *Advanced Nutrition and Human Metabolism*: Gropper, Smith And Groff (suggested textbook for Nutrient part of the course)
- ✓ *Modern Nutrition in Health and Disease*. 10th ed. – Shils, Shike, Ross, Caballero, and Cousins
- ✓ *Metabolic and Molecular Bases of Inherited Disease* – Scriver
- ✓ *PDR for Nutritional Supplements*. 2nd ed. – Hendler and Rorvik
- ✓ Linus Pauling Institute website: http://www.drritamarie.com/go/LPIMolybdenum
- ✓ *Treatment of Metastatic Cancer with Tetrathiomolybdate, an Anticopper, Antiangiogenic Agent*: Phase I Study – Clinical Cancer Research http://www.drritamarie.com/go/CCRTetrathiomolybdate
- ✓ *Molybdenum: An Essential Trace Element* - Nutritional Clinical Practice: http://www.drritamarie.com/go/NCBIMolybdenum