

COPPER is an essential

trace element required for the

Copper deficiency in humans can result from:

Inadequate copper intake (e.g., unsupplemented TPN)

Malabsorption (e.g., celiac disease; Menkes syndrome)

Excessive copper excretion (e.g., nephrotic syndrome)

Copper has a higher affinity for metallothionein than zinc

Copper displaces zinc from metallothionein, remains

Left shift in granulocytic and erythroid maturation

Since 2001 copper deficiency in humans has been associated with neurological manifestation

Nations and coworkers (2008) published a study that:

Reported that each patient used large amounts (≥2 tubes/

week) of zinc-containing denture adhesive for years

Vacuolated precursors and ringed sideroblasts in bone marrow

of acquired copper deficiency in humans

in the enterocytes and is lost in the feces

Copper deficiency is a known cause of

Anemia (micro-, macro-, or normocytic)

Neutropenia

hematological abnormalities in humans

Excessive zinc intake is also a well-recognized cause

normal activity of numerous enzymes

Excessive zinc ingestion upregulates metallothionein production in enterocytes

Myelopathy clinically presenting as a spastic gait due to prominent sensory ataxia

Hypothesized that excessive use of zinc-containing denture adhesive resulted in:

Hyperzincemia → Hypocupremia → Hematological/neurological impairment

Presented 4 patients with hematological and neurological abnormalities

Zinc-Containing Denture Adhesives, Toxicity and Causal Inference



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DISCUSSION

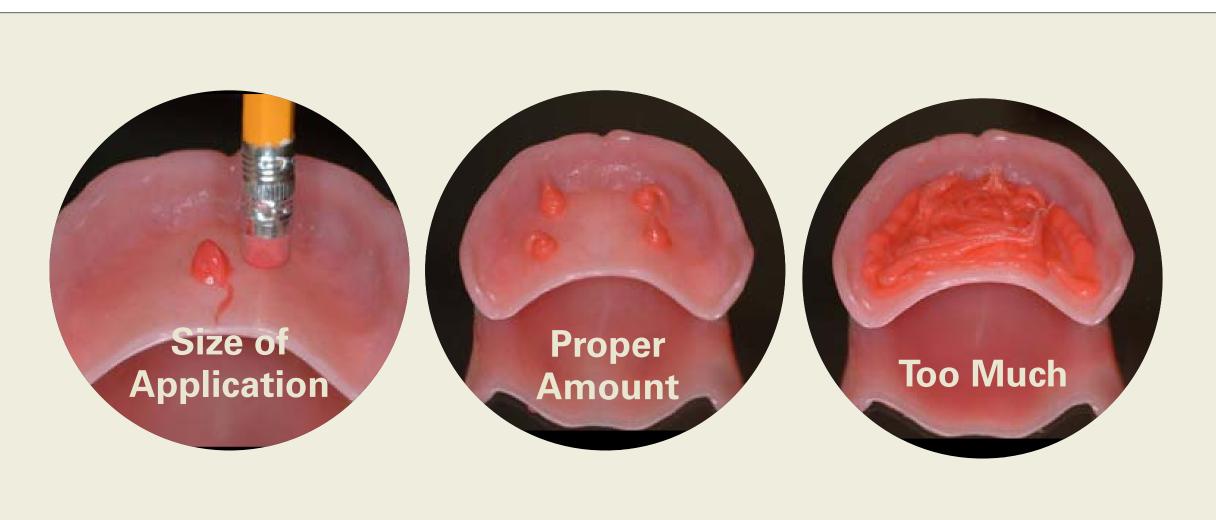
INTRODUCTION

RESULTS



The current body of literature consists of 14 case reports describing 27 patients

Study Number	Authors	Number of Cases	Tubes/Month	Misuse	
1	Willis et al. (2005)	1	28.0	✓	
2	Spinazzi et al. (2007)	1	3.08 • • •	✓	
3	Neerman et al. (2007)	1	use not described	?	
4	Nations et al. (2008)	3*	>8 ••••••		
5	Spain et al. (2009)	1	0.0	?	of 2
6	Hedera et al. (2009)	11	>8 ••••••		
7	Sibley and Maddox (2009)	1	use not described	?	patients
8	Trocello et al. (2010)#	2	use not described	?	excessive
9	Afrin (2010)	1	2.6 ● ● ●		of dentur
10	Doherty et al. (2011)	1	7.1		adhesive
11	Barton et al. (2011)	1	7.1		
12	Summerville and Baloh (2011)	1	use not described	✓	
13	Crown and May (2012)	1	8.0		
14	Shammaa and Rodgers (2012)	1	8.0	✓	
		Normal Usage	1.3		



A 68-gram tube of denture adhesive should last approximately 3-10 weeks with once daily application of 0.5 to 1.5 grams of adhesive per dental unit (Nations et al., 2008)

aboratory Findings

Hypocupremia (n=27) Hyperzincemia (n=25) Low serum ceruloplasmin (n=9)



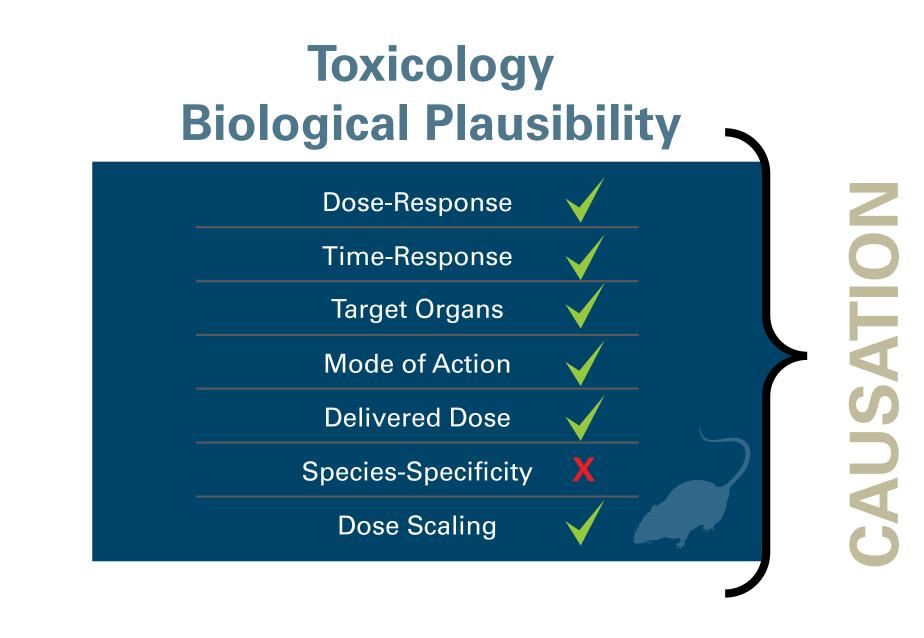
Hematological Findings

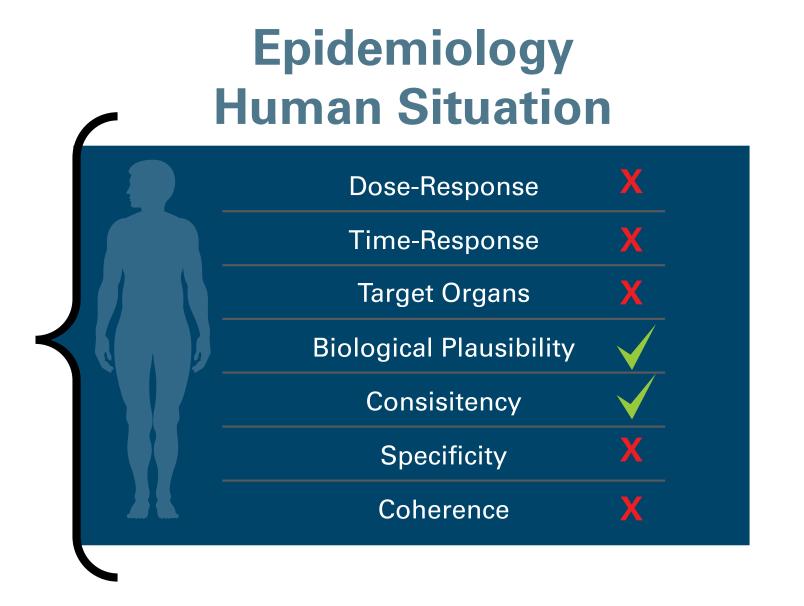
Anemia (n=12) Leukopenia and/or neutropenia (n=8) Pancytopenia (n=11) Myelodysplastic-like syndrome (n=4)

REVERSIBLE

Copper supplementation and discontinuation of zinc

Contribution of toxicological and epidemiological data to causal inference





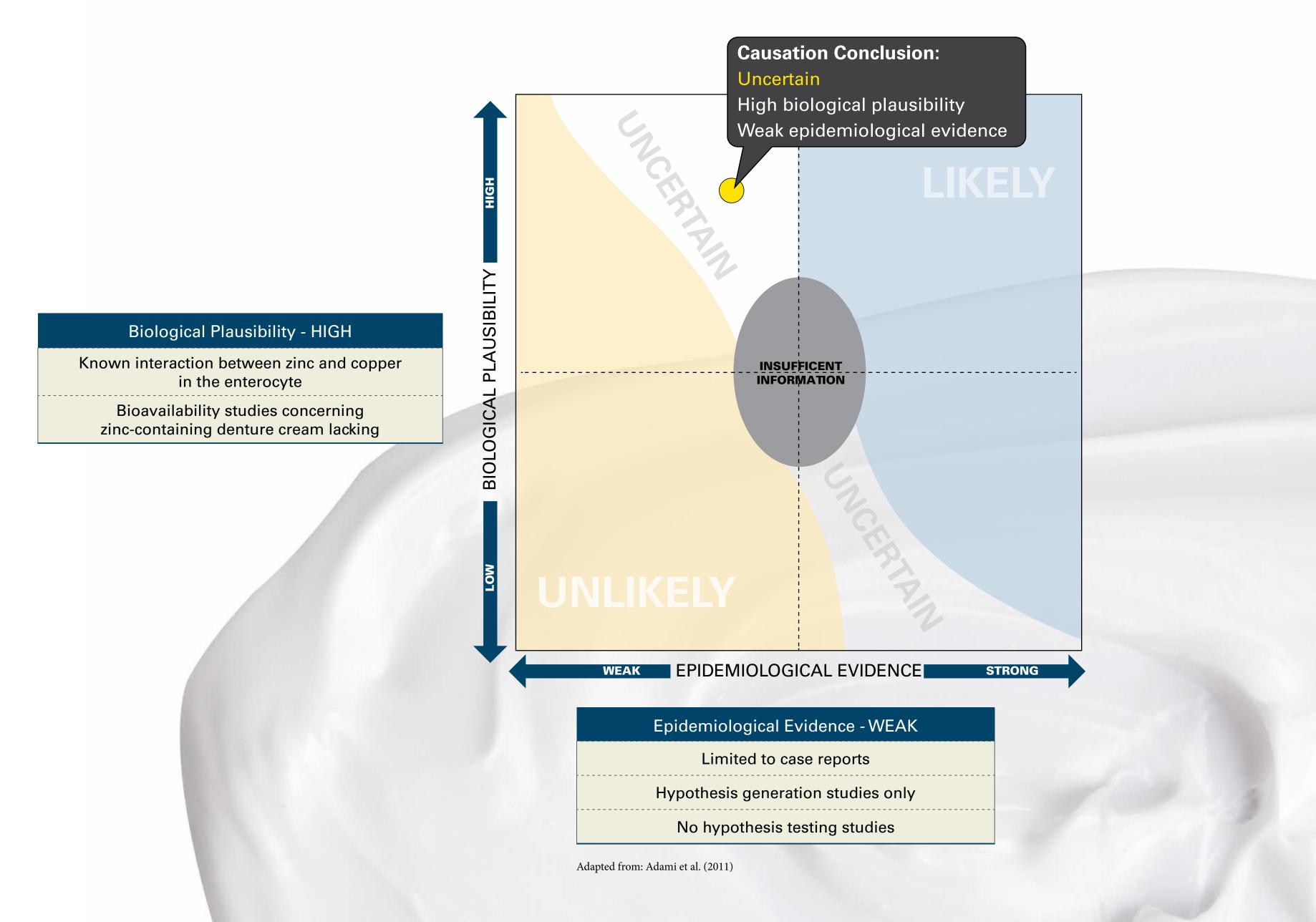
EPID-TOX Graphical Template for establishing a causal relationship between use (misuse) of zinc-containing denture adhesive and neurological impairment

Neurological Findings

27 patients presented with myeloneuropathy generally involving an initial ascending sensory neuropathy followed by ataxia, wide-based gait, loss of balance, and limb weakness (distal greater than proximal). All patients developed difficulty walking.

REVERSIBLE

	Study Numbers													
Reported Neurological Findings		2	3	4	5	6	7	8	9	10	11	12	13	14
Ascending sensory neuropathy lower extremities	✓	✓	✓	✓	√	√			✓	✓	✓	✓	\checkmark	
Sensory neuropathy progressing to upper extremities	\checkmark			\	√	\			\	\checkmark	✓	✓	\	†
Difficult walking/gait ataxia	\checkmark	\	V	\	√	\	\	✓	V	✓	✓	✓	\	\
Wide-based gait		\	\					✓				✓		\
Nerve conduction velocity abnormalities	\checkmark			\	\				\			✓		
Loss of balance	\checkmark				V	\			\	\checkmark	✓	✓		
Positive Romberg sign		\			√						\	✓		†
Brisk tendon reflexes		\								✓		✓		
Extensor plantar reflexes		\	\	\	\					✓				†
EMG abnormalities in upper and/or lower limbs		\		\	\				\					†
Limb weakness distal greater than proximal		\	\		\		\		V	✓	\			\checkmark
Decreased or absent lower limb reflexes					\				\					+
Bowel and/or bladder incontinence		\							V			\		
Objective/subjective improvement in some or all findings after copper supplementation				✓		+	✓	+		✓		✓	✓	✓



SUMMARY

- The current body of literature concerning a possible association between the use (misuse) of zinc-containing denture adhesive and myeloneuropathy consists of 14 case reports describing 27 patients.
- Of the 27 described patients, 22 used excessive amounts of denture cream (use not described in 5).
- All 27 patients had hypocupremia; 25 also had hyperzincemia and 9 had low serum ceruloplasmin
- Myeloneuropathy generally involved an initial ascending sensory neuropathy in the lower extremities followed by ataxia, wide-based gait, loss of balance, and limb weakness (distal greater than proximal). In some, the ascending sensory neuropathy progressed to the upper extremities.
- All patients developed difficulty walking; most required assistance to ambulate and some became wheelchair dependent
- All but one patient presented with concurrent hematological abnormalities.
- Copper supplementation and discontinuation of zinccontaining denture adhesive correct all hematological abnormalities, including myelodysplastic changes.
- Copper supplementation and discontinuation of zinccontaining denture adhesive did not correct the myeloneuropathy in most patients.
 - o For most the myeloneuropathy stabilized but did not improve suggesting permanency
- o Some reported subjective changes not reflected in objective testing

CONCLUSION:

- Although causation is uncertain, patients presenting with myeloneuropathy primarily of the lower extremities should be examined for copper, zinc, and ceruloplasmin
- o Especially if concurrent hematological manifestations
- Similarly, patients presenting with myelodysplastic changes suggestive of myelodysplastic syndrome should also be examined for copper and ceruloplasmin
- o Some of the cases described above were seen in hematological departments for treatment of myelodysplastic syndrome when hypocupremia was first recognized. Copper supplementation reversed the myelodysplastic changes, demonstrating they did not in fact have myelodysplastic syndrome.
- o Hypocupremia from other causes has been previously associated with myelodysplastic syndrome/changes. Despite this, clinicians may not be aware of the association between this hematological condition and hypocupremia.

INVESTIGATION PURPOSE

- Summarize the current epidemiological literature associating use of zinc-containing denture adhesive with hematological and neurological abnormalities
- Analyze this body of evidence using a framework combining toxicological and epidemiological evidence to establish causal inference (Adami et al., 2011)
- Alert physicians and others to possible hematological or neurological abnormalities associated with zinc-containing denture adhesives but masquerading as other maladies

METHODS

PubMed Literature search linking the following terms

- Zinc Copper Hematological abnormalities/toxicity
 - Denture adhesives/creams
- Neurological abnormalities/toxicity