FUNCTIONAL MEDICINE
Continuing Education

Case Based Approach to Detoxification with a Focus on Heavy Metals

Lyn Patrick ND

Disclosures

- I have no disclosures and no financial interests in products or services for patient care related to this presentation.

Learning Objectives

1. Identify the signs, symptoms and lab markers for toxic metals exposure for aluminum, mercury, arsenic, lead and cadmium.
2. Choose appropriate protocols for the indicated chelation of arsenic, lead, cadmium, and mercury.
3. Identify sources of exposure for aluminum, mercury, arsenic, lead and cadmium.

Agency for Toxic Substances and Disease Registry Priority List

2019 Rank	Substance Name	Total Points	CAS RN
1	ARSENIC	1676	7440-38-2
2	LEAD	1531	7439-92-1
3	MERCURY	1458	7439-97-6
4	VINYL CHLORIDE	1356	75-01-4
5	POLYCHLORINATED BIPHENYLS	1345	1336-36-3
6	BENZENE	1327	71-43-2
7	CADMIUM	1318	7440-43-9
8	BENZO(A)PYRENE	1307	50-32-8
9	POLYCYCLIC AROMATIC HYDROCARBONS	1278	130498-29-2
10	BENZO(B)FLUORANTHENE	1253	205-99-2

Substance Priority List | ATSDR (cdc.gov) Accessed 2021-10

Which Metals are Clinically Relevant?

- Arsenic
- Lead
- Mercury
- Cadmium
- Hexavalent chromium (Cr+6)
- New Toxics: Gadolinium, Cobalt, Thallium, Cesium
- You will see Al, Ni, Pd, Pt, Sb, Sn, Ti in urine: vaccines, antacids (Al) implants and dental materials.
- Delayed hypersensitivity/autoimmunity resulting from metal exposure: Ni, Hg, Au, Al, Ti, Cr, Co, Pd

Environmental Research 2018;161:573–579.
Inflamm Allergy Drug Targets 2008; 7 (3): 145-62.

Random urine levels in total population adults 20+yrs from CDC NHANES Updated Tables Volume 1 2019

units: mcg/g of creatinine

METAL	MEAN	50th%	75th%	90th%	95th%	Sample Size	Data Year
Antimony	0.049	0.046	0.07	0.113	0.151	1792	2015-2016
Arsenic (total)	6.92	5.62	11	28.1	56.2	1792	2015-2016
Barium	1.21	1.24	2.12	3.57	4.83	1792	2015-2016
Beryllium	less than the limit of detection					2019	2009-2010
Cadmium	0.19	0.188	0.346	0.623	0.882	1792	2015-2016
Cesium	4.31	4.22	6.02	8.47	10.4	1792	2015-2016
Lead	0.331	0.315	0.541	0.9	1.14	1792	2015-2016
Mercury	not calculated	0.198	0.391	0.776	1.15	1800	2015-2016
Platinum	less than the limit of detection			0.023	0.035	2018	2009-2010
Thallium	0.163	0.159	0.231	0.323	0.4	1792	2015-2016
Tin	0.493	0.431	0.885	1.69	3.06	1791	2015-2016
Tungsten	0.064	0.061	0.103	0.177	0.279	1791	2015-2016
Uranium	0.006	0.005	0.009	0.016	0.026	1792	2015-2016

The CDC recognizes the 95th values as “values of concern” but they cannot be used for diagnostic purposes

Source: National Report on Human Exposure to Environmental Chemicals: https://www.cdc.gov/exposurereport/index.html

Whole blood levels:

units: mcg/L except lead is mcg/dL

METAL	MEAN	50th%	75th%	90th%	95th%	Sample Size	Data Year
Chromium	not calculated	not detected	not detected	0.7	1.08	3442	2015-2016
Cobalt	0.151	0.13	0.17	0.28	0.4	3454	2015-2016
Blood Lead	0.92	0.88	1.46	2.3	2.89	2610	2015-2016
Blood Mercury	0.81	0.74	1.47	2.86	4.66	2610	2015-2016
Blood Cadmium	0.295	0.27	0.48	0.94	1.35	2610	2015-2016
Serum Copper	115	113	132	156	172	1744	2015-2016
Blood Manganese	9.34	9.2	11.6	14.7	16.1	2609	2015-2016

In general blood levels reflect current exposure with the EXCEPTION of lead.

Source: National Report on Human Exposure to Environmental Chemicals: https://www.cdc.gov/exposurereport/index.html

CDC WHOLE BLOOD METALS mcg/dL 2015-2016

Metal	Age Range	50th	75th	90th	95th
LEAD	1-5	.69	1.10	1.86	2.76
	6-11	.55	.78	1.18	1.59
	12-19	.45	.68	.93	1.17
	20 plus	.880	1.46	2.30	2.89
MERCURY	1-5	<LOD	.38	.69	1.06
	20 plus	.740	1.47	2.86	4.66
MERCURY ASIANS	20 plus	2.03	4.21	7.66	11.3

Data from: from CDC National Report on Human Exposure to Environmental Chemicals 2017
https://www.cdc.gov/exposurereport/index.html

How to measure toxic metals

Diagnosis of toxic metals exposure-

- Urine, blood, fecal metals (infants)
- Whole blood: lead, mercury, cobalt (cobalt can also be measured in serum)
- RBC: chromium (Cr+3)
- Spot urine: cadmium, arsenic, gadolinium, thallium, aluminum, antimony, barium, cesium, mercury, platinum, tin, tungsten, uranium
- Provocation urine testing using EDTA/DMSA/DMPS- indicates a body burden measures kidney stores, useful for assessing mercury, lead body burden

Why Test for Toxic Metals?

- What is the prevalence of exposure?
- What relationship does exposure have to disease?
- How do we assess and treat exposure and retention?

Table 1. Toxin Load and Disease Risk

Toxin	Disease	Risk	Reference
Arsenic	Diabetes	3.6	Navas-Acien et al[8] (2008)
	Lung cancer	3.0-5.0	Heck et al[9] (2009)
Cadmium	Myocardial infarction	1.8	Everett et al[10] (2008)
	Osteoporosis	1.4	Gallagher et al[11] (2008)
	Obstructive lung disease	2.52 (top decile)	Yoon et al[12] (2014)
Lead	Gout	3.6	Krishnan et al[13] (2012)
	Obstructive lung disease	2.37 (top decile)	Rokadia et al[14] (2013)
Organochlorine pesticides	Diabetes	9.1	Kim et al[15] (2014)
	Rheumatoid arthritis	3.5	Lee et al[16] (2007)
	Hyperuricemia	2.5	Lee et al[17] (2013)
Organophosphate pesticides	IQ in children according to OPs in mother	7.1 point decrease in IQ	Bouchard et al[18] (2010)
	ADHD	2.0	Bouchard et al[19] (2011)
PCBs	ADHD	>3.0	Boersma et al[20] (2000)
	Rheumatoid arthritis	8.5	Lee et al[16] (2007)
Bisphenol A	Prediabetes	1.34 (top tertial)	Sabanayagam et al[21] (2013)
	Metabolic syndrome	1.51	Tepalla et al[22] (2012)
	Obesity (children)	2.55	Bhandari et al[23] (2013)
Polybrominated diphenyl ethers	Diabetes	2.0-3.0	Lim et al[24] (2008)
Phthalates	Osteoporosis	14.1 fold (MCPP) 5.9 (MCOP) 5.9 (MBzP)	Min et al[25] (2014)
	Obesity	1.62 (DEHP, adults) 1.77 (HMW, adults) 2.84 (LMW, children) 4.29 (MiBP, male children)	Buser et al[26] (2014)

A direct quote from the National Academy of Sciences

"The combination of three environmental chemical exposures:

- lead
- organophosphate pesticides
- and methylmercury

are responsible for greater IQ loss

than medical conditions such as preterm birth, neurodevelopmental disorders such as autism and ADHD, and socioeconomic and nutrition-related factors such as iron deficiency and non-organic failure to thrive."
– David Bellinger

Why did they quote Bellinger?

- David Bellinger* and colleagues estimated the contribution of these risk factors to significant IQ loss in a population of 25.5 million children and found that lead, methylmercury and organophosphate pesticides were responsible for the majority of IQ loss.

* Professor of neurology, psychology, and environmental health at Boston Children's Hospital, Harvard Medical School, and the Harvard T.H. Chan School of Public Health

PMID: 23515885

Low level chronic exposure vs. acute occupational exposure

- A patient with significant metal toxicity typically has general symptoms: malaise, headache, weakness, mild or moderate hypertension, tinnitus, mood disorder, etc.
- However, [renal and neurological] damage can also happen in those who have metal toxicity and are asymptomatic.
- "This makes the diagnosis of metals toxicity in a clinical setting very difficult unless a clinician has the knowledge and training to suspect the diagnosis and is able to order the correct diagnostic test."

H2I *"+(H- (, J (, 8H((
(; 2"0 $"(! ##2' &F$(J&$' F2"=(F1$(H*"K*"+(L MHO(N%K&2%0 $%F*3O' &$% $#(/ $%F$"=(
H*"K*"+((O' 1223(2F8- : 3&(H$*3F1=(F2- %+&%6(, $+&*3N+&F2"(N%K&2%0 $%F*3H$*3F1(
8$"#7$' F&K$#=(- ""$%F3 ((L O; (M%F$"%*F&2%*3J $7F(/ 1*&=(N%K&2%0 $%F*3H$*3F1(O' &$% $#(
(Q(, &1&6*%((O' 1223(8- : 3&(H$*3F1(

https://keck.usc.edu/faculty-search/howard-hu/

Lead

Lead in Wine

Domestic wines: 1 - 521 ppb

Imported wines: 4 - 673 ppb

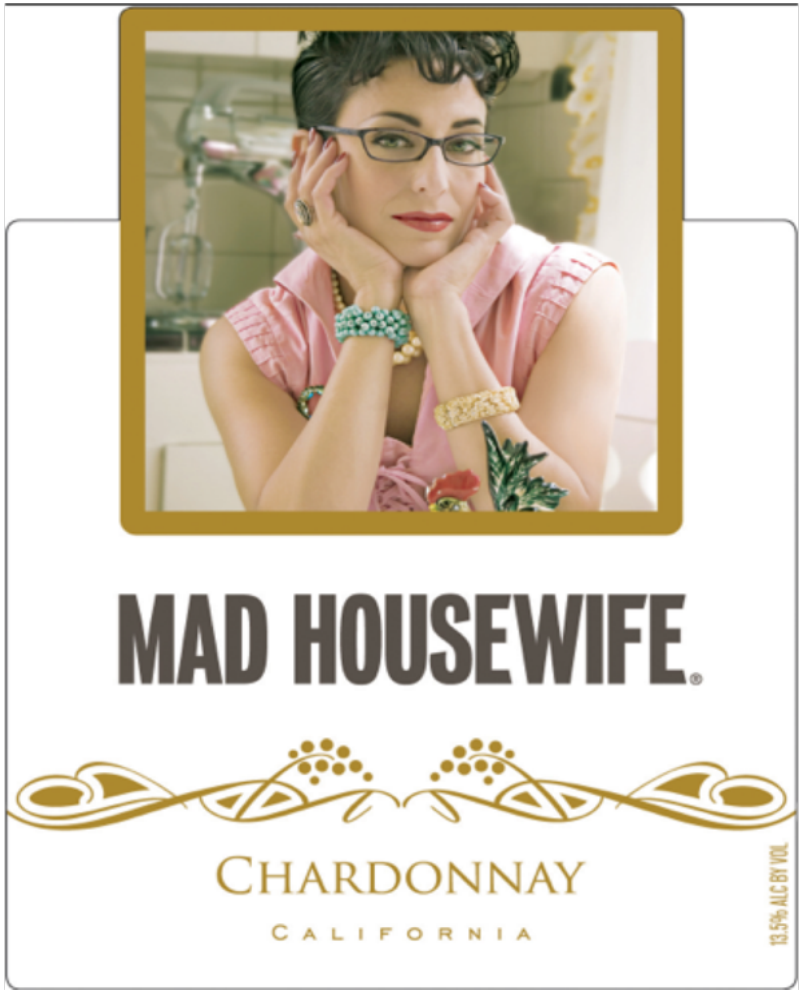
When the wine was poured:

Domestic wines: 3 - 720 ppb

Imports from 13 - 1,980 ppb

The EPA limit for lead in drinking water is 50 ppb.

Blood lead levels of heavy drinkers were 2-3x that of non-drinkers



Food Addit Contam. 2003 Feb;20(2):141-8/Pharmacol Res. 2002 Jan;45(1):47-50./Food Addit Contam. 1998 May-Jun;15(4):437-45/Food Addit Contam. 1990 Jan-Feb;7(1):93-9

Heavy Metal Content of Ayurvedic Herbal Medicine Products
JAMA. 2004;292:2868-2873.

containing HMPs recommended for adults and children. All 10 HMPs containing lead and recommended for adults could result in ingestions higher than the comparable *USP* standard. Six HMPs were orders of magnitude higher. mercury-containing HMPs recommended for children have estimated ranges of daily mercury intake of 2 to 3 orders of magnitude higher than the EPA reference dose for a 10-kg child. Four of 5 arsenic-containing HMPs testing. For the HMPs unavailable for repurchase, we performed split-sample retesting using the original HMPs. All 10 repurchased HMPs had heavy metal concentrations similar to the original samples: lead, average of

Table 1. Heavy Metal Concentrations in Ayurvedic Herbal Medicine Products (N=70)*

	Metal							
	Lead	Mercury	Arsenic	Tin	Silver	Gold	Cadmium	Any Metal*
No. of HMPs with detectable levels of the metal (% of total No. of HMPs)	13 (19)	6 (9)	6 (9)	5 (7)	4 (6)	3 (4)	0	14 (20)
Median concentration among those HMPs with detectable levels of the metal (IQR), µg/g	40 (8-300)	20 225 (4380-72 100)	430 (54-2800)	22 800 (3940-23 500)	14 310 (2475-26 575)	†	NA	
Range, µg/g	5-37 000	28-104 000	37-8130	150-26 400	230-29 250	†	NA	

Abbreviations: HMPs, herbal medicine products; IQR, interquartile range; NA, not applicable.
*A total of 14 (20%) of 70 HMPs (95% confidence interval, 11%-31%) contained lead, mercury, and/or arsenic.
†Presence of gold detected qualitatively only.

URINE TOXIC METALS

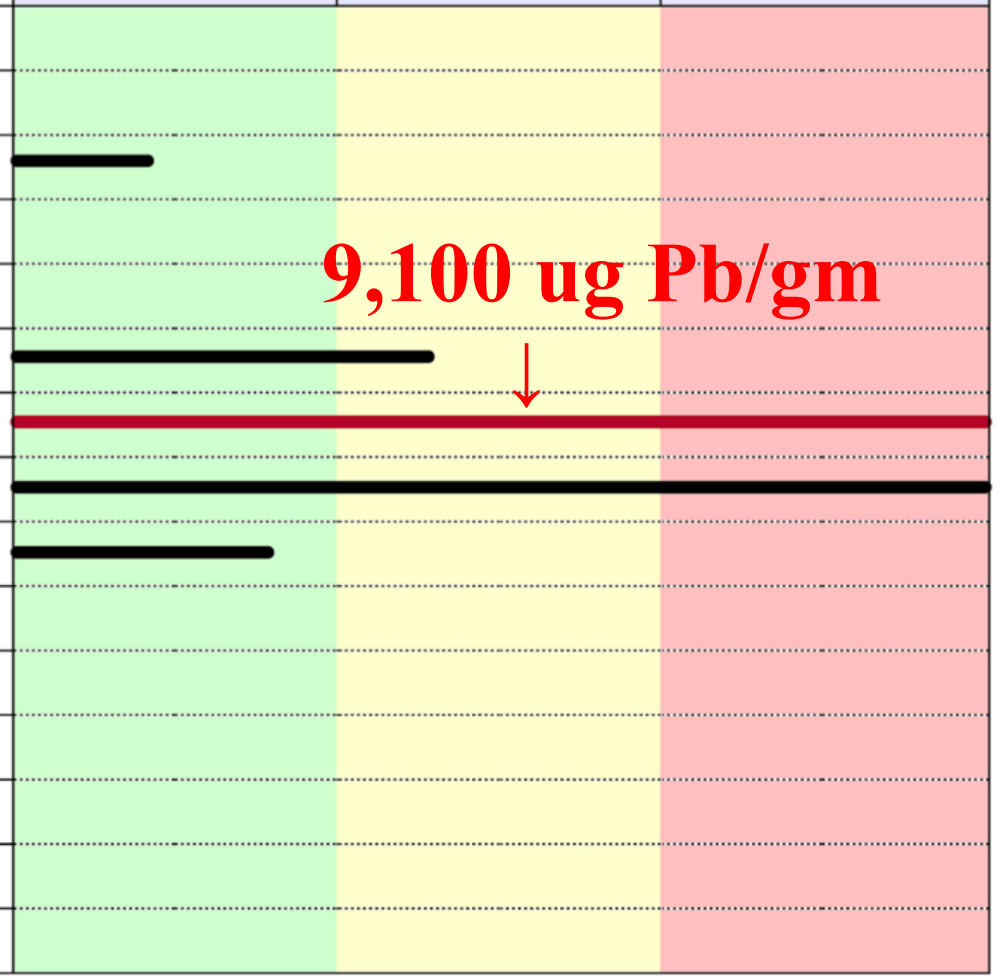
DOCTOR'S DATA INC

LAB#: U000000-0000-0
PATIENT: Herbman/DMSA
SEX: Male
AGE: 55

CLIENT#:
DOCTOR:

POTENTIALLY TOXIC METALS

METALS	RESULT µg/g CREAT	REFERENCE RANGE
Aluminum	< dl	< 25
Antimony	< dl	< 0.6
Arsenic	50	< 120
Beryllium	< dl	< 0.5
Bismuth	< dl	< 10
Cadmium	2.6	< 2
Lead	9100	< 15
Mercury	39	< 3
Nickel	8	< 10
Platinum	< dl	< 1
Thallium	< dl	< 0.7
Thorium	< dl	< 0.3
Tin	< dl	< 9
Tungsten	< dl	< 0.7
Uranium	< dl	< 0.1



CTIONAL
ICINE
ducation

Where ELSE does it come from?

- Soft vinyl lunchboxes- found to contain more than 90 times legal limit
- Candy imported from Mexico
- Imported children's jewelry
- Vinyl Mini blinds before 1997 from China, Indonesia, Taiwan and Mexico.
- Leaded gasoline- currently used in farm machinery, boats, racing cars, small aircraft

http://www.cpsc.gov/en/Business--Manufacturing/Business-Education/Lead/

NO Safe Level of Lead

- No safe level of lead exposure in the blood of children has been identified (the CDC, EPA, and American Academy of Pediatrics agree)
- The current CDC safe level of lead:
  - children: <3.5 mcg/dL
  - adults: <5.0 mcg/dL
- By the way, the same is true for drinking water. (15 ppb is simply a level that industry and municipal water providers were willing to accept.)
- LOD in the blood should be 1.0 µg/dL

Symptoms: LEAD

acute

- normocytic or microcytic anemia
- abdominal pain and constipation (“lead colic”)
- arthralgias and myalgias
- headache
- mood disorder
- encephalopathy within weeks post exposure

chronic

- decreased libido
- impotence and infertility
- anorexia, abdominal pain, weight loss, change in bowel habits
- muscle weakness (abductor mm hand) and pain
- fatigue, depression, irritability
- insomnia
- paresthesias
- headache
- anxiety

PMID: 24083830

Lowest Exposure Dose Signs and Symptoms: Impaired Abilities (patient may appear asymptomatic)

- Decreased learning and memory
- Lowered IQ
- Decreased verbal ability
- Impaired speech and hearing functions
- Early signs of hyperactivity or ADHD

Low Exposure Dose Signs and Symptoms

- Myalgia or paresthesia
- Mild fatigue
- Irritability
- Lethargy
- Occasional abdominal discomfort

Moderate Exposure Dose Signs and Symptoms

- Arthralgia
- General fatigue
- Difficulty concentrating/Muscular exhaustibility
- Tremor
- Headache
- Diffuse abdominal pain
- Vomiting
- Weight loss
- Constipation

High Exposure Dose Signs and Symptoms

- Paresis or paralysis
- Encephalopathy—may abruptly lead to seizures, changes in consciousness, coma, and death
- Lead line (blue-black) on gingival tissue
- Colic (intermittent, severe abdominal cramps)

Signs: LEAD

- normocytic or microcytic anemia
- renal damage including interstitial nephritis
- elevated blood pressure
- Zinc protoporphyrin
- ALAD

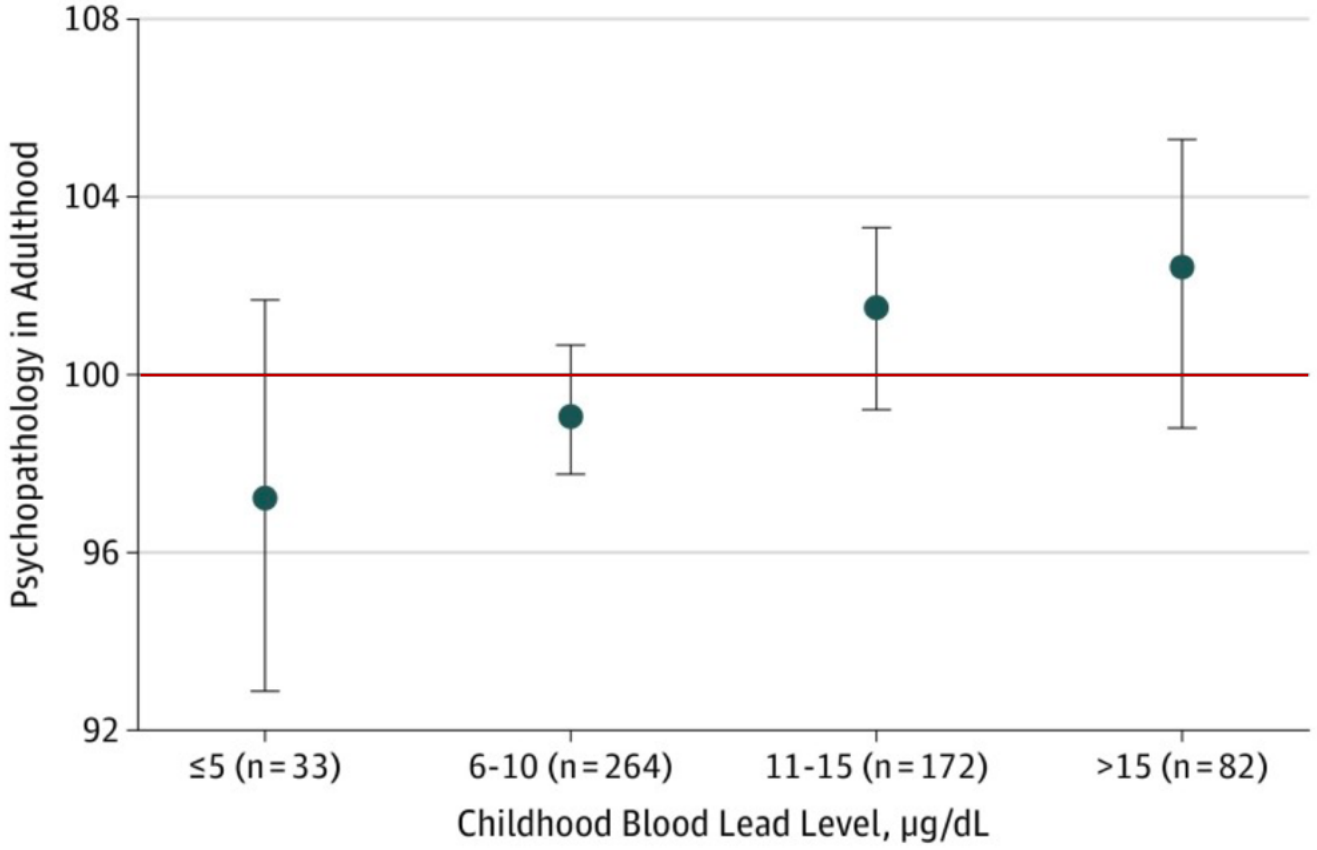
PMID: 24083830

LEAD AND BRAIN

- Adults with BLL **>1.7 ug/dL** (current CDC 50th percentile) more likely to have depression and panic
- BLL of 3.0 ug/dL risk of depression (OR 2.3), panic (OR 4.0)
- Nurses study BLL associated with depression and phobic anxiety

PMID: 26624239, 19996036, 22538241

579 New Zealand children followed up for more than 30 years- Figure below is blood lead level at age 11 y.o. correlated with adult general psychopathology at 38 y.o.



PMID: 30673063 (JAMA 2019)

Lead Exposure in Childhood and Episodes of psychosis at ages 30-35

- A US study that used linked health records and clinical interviews to identify cases of psychosis in 2 lead-tested child cohorts born in the late 1960s (N = 200; age range, 30-35 years at follow-up) reported a 2-fold increased risk of schizophrenia spectrum disorder in adulthood for individuals with high blood lead levels as children: >15 µg/dL.

PMID: 19057716

Lead and Bad Behavior

- High bone lead levels in boys at 11 yo were associated with an increased risk of exceeding the clinical score (T>70) for attention, aggression, and delinquency.
- Multiple studies conclude that childhood lead exposure is strongly linked with conduct disorder, juvenile delinquency, drug use and incarceration.
- Levels of risk started in one Korean study of 1,178 elementary school kids risk for ADH was almost double (1.78) if they had blood lead levels >3.5 µg/dL compared to those with <1.0 µg/dL.

PMID: 8569015, 1415859, 12460653, 11792521, 17185283, 18413435, 17868654, 18941585, 19100765
National Research Council. Measuring lead exposure in infants, children, and other sensitive populations. Washington DC: National Academy Press; 1993.

Lamphear et al, 2018

Low-level lead exposure and mortality in US adults: a population-based cohort study

Bruce P Lanphear, Stephen Rauch, Peggy Auinger, Ryan W Allen, Richard W Hornung

Summary

Background Lead exposure is a risk factor for cardiovascular disease mortality, but the number of deaths in the USA attributable to lead exposure is poorly defined. We aimed to quantify the relative contribution of environmental lead exposure to all-cause mortality, cardiovascular disease mortality, and ischaemic heart disease mortality.

Lancet Public Health 2018; 3: e177–84

Published Online March 12, 2018

Comparing those with blood lead 1·0 µg/dL (10th percentile) to 6·7 µg/dL (90th percentile) was associated with increased all-cause mortality, cardiovascular disease mortality, and ischaemic heart disease mortality.

Lead and Cardiovascular Disease

- Those in the highest tertile of blood lead:
  (3.63-10.0 µg/dL)

- **2.5** times risk for stroke mortality
- **1.89** times risk for myocardial infarction mortality
- **1.70** times risk for cardiovascular disease mortality

"Blood lead is a much more significant risk factor for CVD and stroke than blood lipids."

Circulation 2006;114:1347-1349.

BLOOD LEAD AND MORTALITY FROM ISCHAEMIC HEART DISEASE

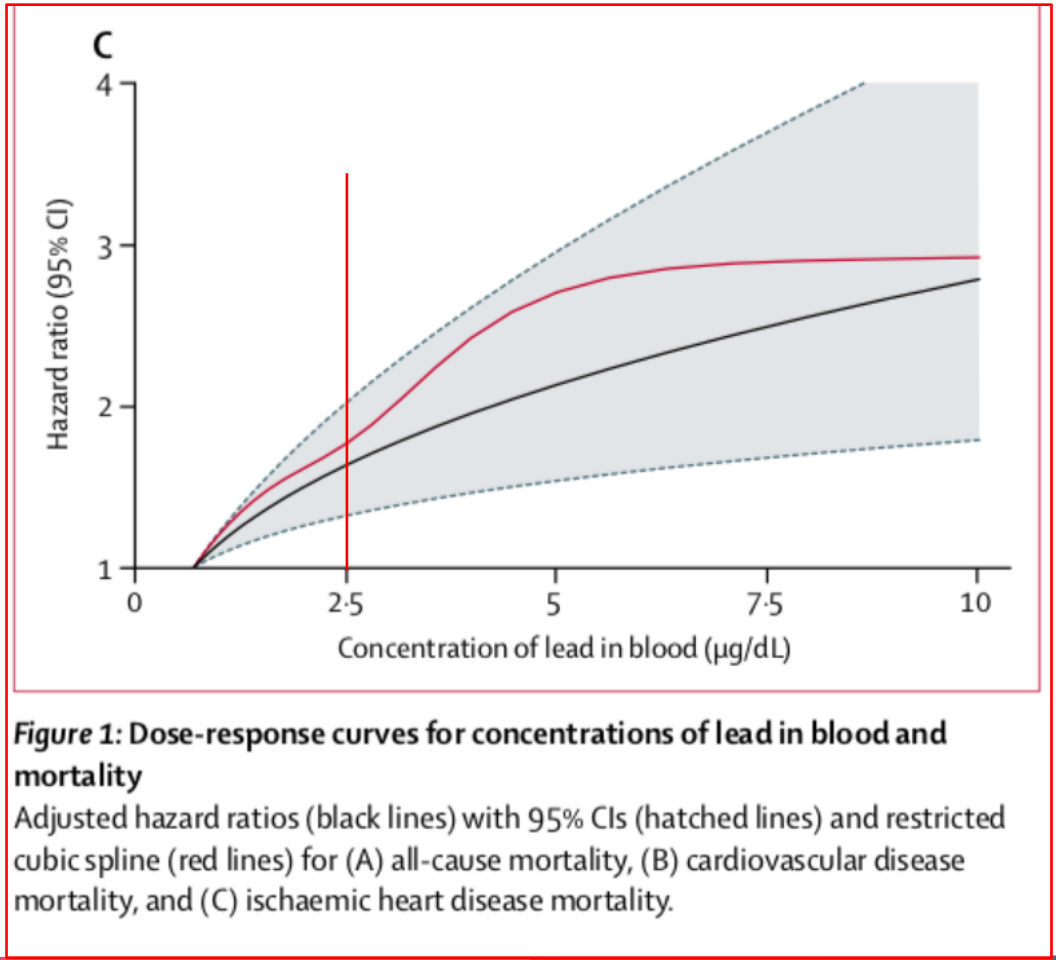


Figure 1: **Dose-response curves for concentrations of lead in blood and mortality**

Adjusted hazard ratios (black lines) with 95% CIs (hatched lines) and restricted cubic spline (red lines) for (A) all-cause mortality, (B) cardiovascular disease mortality, and (C) ischaemic heart disease mortality.

Circulation 2006;114:1347-1349.

Do You Check Whole Blood Lead in Patients at Risk for CVD?

- >3.63 mcg/dL would indicate significant increased risk but risk starts as low as 2.5 mcg/dL

NHANES EXTENSION STUDY 2018 (same population from 2006 Circulation article)

NHANES III COHORT from 1988-94 followed out to 2011

	HR/Adj HR	POPULATION ATTRIBUTABLE (fx)	AVOIDABLE DEATHS
All cause mortality	3.79/1.37	18.0%	412,000
CV mortality	4.44/1.70	28.7%	256,000
Ischemic mortality	5.31/2.08	37.4%	185,000

19.3 yr follow up of 14,289 people in US from NHANES CDC database
4,422 people died of CVD,
The population attributed fraction for all cause mortality for lead was 18%
= 412,000 “all cause” deaths from lead in the US every year.

Lanphear,Bruce March 12, 2018 DOI:https://doi.org/10.1016/S2468-2667(18)30025-2

FUNCTIONAL MEDICINE
Continuing Education

Lead toxicity case

The Case of the Lawyer who was Losing His Mind

- A 69 year old Caucasian male retired lawyer presented for evaluation of lethargy, fatigue, memory impairment, generalized weakness, severe constipation, anorexia, and weight loss of 18 kg over the preceding eight months.

Breeher et al.: A case report of adult lead toxicity following use of Ayurvedic herbal medication. Journal of Occupational Medicine and Toxicology 2013 8:26.

- Approximately six weeks before the onset of his symptoms, he began using an Ayurvedic herbal medication, “Bhasma”, which he obtained while traveling in India.
- The medication was used to treat partial aphasia, cognitive impairment, and right-sided motor weakness resulting from a spontaneous left temporoparietal hemorrhagic stroke experienced two years previously.

Hallmark of Lead Toxicity

- hemoglobin level of 6.4 gm/dL (reference range: 13.2 gm/dL – 17.7 gm/dL).
- CT scan of the abdomen and pelvis, upper endoscopy and colonoscopy revealed no etiology for his anemia at that hospital.

Always ask patients about this!

- a blood lead level (BLL) of 94 µg/dL (reference range: 0.0-4.9 µg/dL) was obtained. After the family suggested the Ayurvedic “Bhasma” medication could be the cause, it was analyzed for heavy metals and found to contain 19,400 mg/kg of lead and 1,430 mg/ kg of arsenic.
- At the recommendation of the Iowa Poison Control Center, he was admitted to the medical intensive care unit for monitoring, given intramuscular chelation with Dimercaprol (BAL) at a dose of 5 mg/kg q4 hrs for three days, and given intravenous chelation with calcium disodium EDTA at a dose of 1500 mg/m2/day as a continuous infusion for five days beginning after the second dose of BAL

Blood lead rebound should be expected

- blood lead level following two days of chelation with BAL and EDTA as described above had dropped to 27.1 µg/dL
- blood lead level on discharge was 25.5 µg/dL and he was instructed to complete a nineteen day course of oral chelation with dimercaptosuccinic acid (DMSA), 10 mg/kg three times daily for five days, then 10 mg/kg twice daily for fourteen days.
- After completion of the nineteen day course of DMSA,the patient's BLL had decreased to 23 µg/dL and he reported feeling much more energetic. Over the next six weeks his BLL rose to 38 µg/dL and the patient reported a coincident decline in speech fluency and memory.
- **As expected**, his blood lead levels decreased immediately following chelation therapy and showed some rebound after completion of treatment suggesting re-distribution from bone.

- Additional chelation was recommended and he was treated with another course of oral DMSA which reduced his BLL to 20 µg/dL. The patient again reported that his mood was much improved and he then discontinued use of antidepressant medication without recurrence of depressed mood.
- Three months later, he received an alternative treatment at an Ayurvedic Health Clinic due to continued symptoms of cognitive impairment. The alternative treatment consisted of thirteen days of “Bastis” (enemas) and oil massages which were intended to rid his body of lead.

Outdated Guidance

- Repeat BLL was 29 µg/dL at that time.
- **Although not typically offered to patients with a BLL below 40 µg/dL**, a third nineteen day course of oral DMSA chelation therapy was administered in an effort to treat the patient's cognitive symptoms.
- His blood lead level following the third course of chelation with DMSA was 7 µg/dL. Neuropsychological testing was performed both before and immediately following completion of the third course of DMSA to assist in distinguishing reversible neurocognitive effects of lead from fixed residual effects of his prior stroke.

Benefits of Chelation?

- Despite significant deficits in aspects of language, working memory/executive functions, and right-sided fine motor dexterity-
- performance on the Controlled Oral Word Association Test revealed a doubling of his raw score from 11 to 22 reflecting a significant improvement in semantic and phonetic verbal fluency.
- “modest performance gains across various tests of attention and cognitive efficiency”.

“Chelation is usually reserved for BLL over 30”

- In this setting of uncertainty, we elected to chelate the case patient when his BLL was 29 µg/dL in an effort to more fully control his neurocognitive and affective symptoms.

Cadmium

Cadmium

- Vasculotoxic
- Renaltoxic
- Osteotoxic
- Immunotoxic: increased risk for prostate CA
- Sources: vegetables grown in cadmium-containing fertilizer or near point source pollution, shellfish, liver, kidneys, smoking (1-3mcg. per pack), tap water (2-4 mcg/day).
- GI absorption increased in Fe, Ca, Zn, protein- deficient diets

ATSDR Cases Studies in Environmental Medicine: Cadmium
http://www.atsdr.cdc.gov/csem/csem.asp?csem=6&po=9

Table 1. Toxin Load and Disease Risk

Toxin	Disease	Risk	Reference
Arsenic	Diabetes	3.6	Navas-Acien et al[8] (2008)
	Lung cancer	3.0-5.0	Heck et al[9] (2009)
Cadmium	Myocardial infarction	1.8	Everett et al[10] (2008)
	Osteoporosis	1.4	Gallagher et al[11] (2008)
	Obstructive lung disease	2.52 (top decile)	Yoon et al[12] (2014)
Lead	Gout	3.6	Krishnan et al[13] (2012)
	Obstructive lung disease	2.37 (top decile)	Rokadia et al[14] (2013)
Organochlorine pesticides	Diabetes	9.1	Kim et al[15] (2014)
	Rheumatoid arthritis	3.5	Lee et al[16] (2007)
	Hyperuricemia	2.5	Lee et al[17] (2013)
Organophosphate pesticides	IQ in children according to OPs in mother	7.1 point decrease in IQ	Bouchard et al[18] (2010)
	ADHD	2.0	Bouchard et al[19] (2011)
PCBs	ADHD	>3.0	Boersma et al[20] (2000)
	Rheumatoid arthritis	8.5	Lee et al[16] (2007)
Bisphenol A	Prediabetes	1.34 (top tertial)	Sabanayagam et al[21] (2013)
	Metabolic syndrome	1.51	Tepalla et al[22] (2012)
	Obesity (children)	2.55	Bhandari et al[23] (2013)
Polybrominated diphenyl ethers	Diabetes	2.0-3.0	Lim et al[24] (2008)
Phthalates	Osteoporosis	14.1 fold (MCPP) 5.9 (MCOP) 5.9 (MBzP)	Min et al[25] (2014)
	Obesity	1.62 (DEHP, adults) 1.77 (HMW, adults) 2.84 (LMW, children) 4.29 (MiBP, male children)	Buser et al[26] (2014)

Pizzorno J. Editorial. IMCJ 2015;14:8-14

Slide elements Courtesy Joseph Pizzorno ND

FUNCTIONAL MEDICINE
Continuing Education

Ferraro *et al. BMC Public Health* 2010, **10**:304
http://www.biomedcentral.com/1471-2458/10/304

BMC Public Health

RESEARCH ARTICLE Open Access

Low level exposure to cadmium increases the risk of chronic kidney disease: analysis of the NHANES 1999-2006

Pietro Manuel Ferraro, Stefano Costanzi, Alessandro Naticchia, Antonio Sturniolo and Giovanni Gambaro*

> 1.0 mcg/g creatinine in urine associated with albuminuria and chronic kidney disease

Abstract

Background: Environmental factors have been associated with the outbreak of chronic kidney disease (CKD). We evaluated the association of Cadmium (Cd) exposure with the risk of CKD in U.S. adults who participated in the 1999-2006 National Health and Nutrition Examination Surveys (NHANES).

Methods: 5426 subjects ≥ 20 years were stratified for values of urinary and blood Cd and a multivariate logistic regression was performed to test the association between blood and urinary Cd, CKD and albuminuria (ALB) after adjustment for age, gender, race/ethnicity, body mass index and smoking habits.

Results: Subjects with urinary Cd > 1 mcg/g and subjects with blood Cd > 1 mcg/L showed a higher association with ALB (OR 1.63, 95% CI 1.23, 2.16; $P = 0.001$). Subjects with blood Cd > 1 mcg/L showed a higher association with both CKD (OR 1.48, 95% CI 1.01, 2.17; $P = 0.046$) and ALB (OR 1.41, 95% CI 1.10, 1.82; $P = 0.007$). An interaction effect on ALB was found for high levels of urinary and blood Cd ($P = 0.014$).

Conclusions: Moderately high levels of urinary and blood Cd are associated with a higher proportion of CKD and ALB in the United States population.

Cadmium and Risk for Osteoporosis in 2688 Women in Sweden

Women with urinary Cd of ≥ 0.75 µg/g of cr vs. women < 0.50 µg/g :

- 2.5 times more likely to have osteoporosis in femoral neck
- 2.0 times more likely to have it in lumbar spine.
- Among those women who had never smoked the odds were higher:
- 3.5 increased risk for fracture of femoral neck and 3.26 X higher for lumbar spine.
- The odds of any first fracture were greater in those with U-Cd ≥ 0.50 µg/g creatinine

J Bone Miner Res. 2011 Mar;26(3):486-95.

Toxic Metals; Urine 24 hour

Non-provocation 24 hr urine

TOXIC METALS PER CREATININE					TOXIC METALS PER 24 HOURS		
		RESULT µg/g creat	REFERENCE INTERVAL		RESULT µg/24 HOUR	REFERENCE INTERVAL	WITHIN REFERENCE / OUTSIDE REFERENCE
Aluminum	(Al)	4.4	<	35	6.4	< 30	
Antimony	(Sb)	< dl	<	0.2	< dl	< 0.2	
Arsenic	(As)	15	<	80	22	< 90	
Barium	(Ba)	3.3	<	7	4.7	< 7	
Beryllium	(Be)	< dl	<	1	< dl	< 1	
Bismuth	(Bi)	< dl	<	4	< dl	< 3	
Cadmium	(Cd)	1.2	<	1	1.8	< 1.2	
Lead	(Pb)	0.3	<	2	0.5	< 2	
Mercury	(Hg)	< dl	<	4	< dl	< 5	
Nickel	(Ni)	10	<	10	15	< 13	
Palladium	(Pd)	< dl	<	0.3	< dl	< 0.3	
Platinum	(Pt)	< dl	<	0.1	< dl	< 0.2	
Tellurium	(Te)	< dl	<	0.5	< dl	< 0.5	
Thallium	(Tl)	0.5	<	0.5	0.7	< 0.5	
Thorium	(Th)	< dl	<	0.03	< dl	< 0.03	
Tin	(Sn)	0.1	<	5	0.2	< 4	
Tungsten	(W)	0.1	<	0.4	0.2	< 0.4	
Uranium	(U)	< dl	<	0.04	< dl	< 0.04	

DXA -2.7 lumbar spine/-2.1 femur

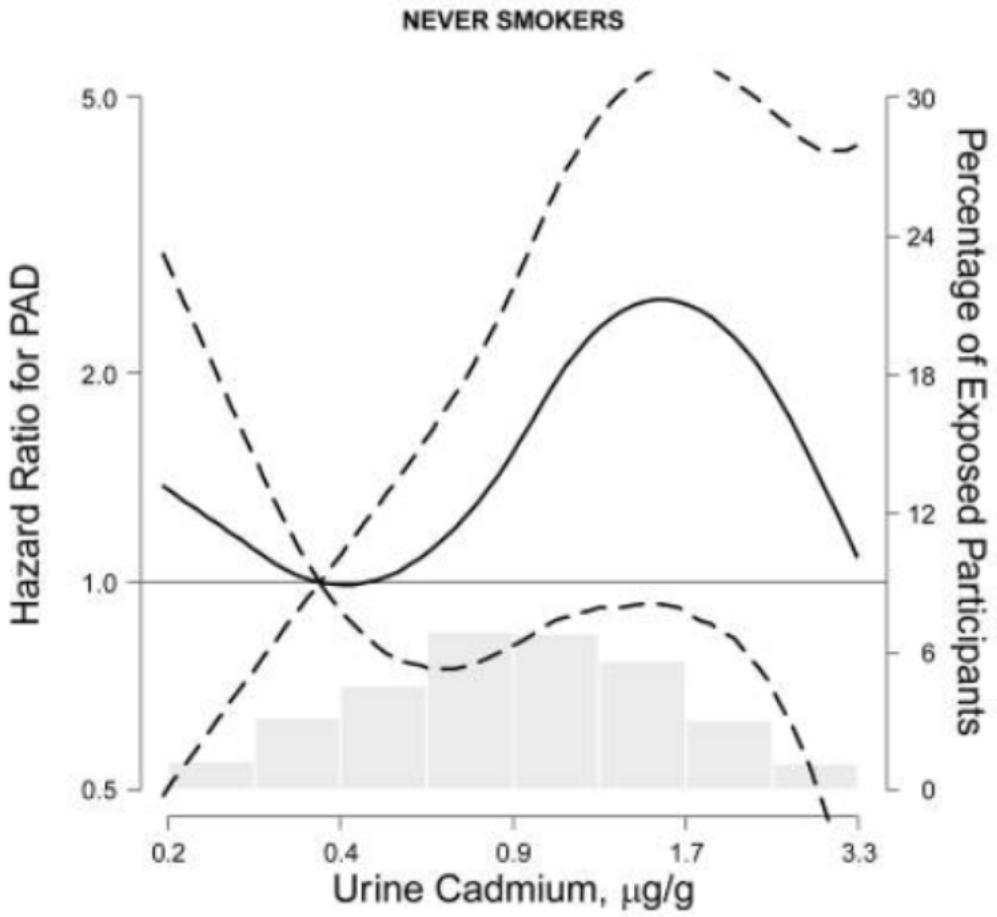
FUNCTIONAL MEDICINE
Continuing Education

Cadmium: CVD and Cancer

- 14,000 adults:
  - Risk for all cause mortality and mortality from CVD is significantly increased at .80 mcg/gm urinary creatinine in both men and women
  - Increased risk for cancer mortality at .80 mcg/gm urinary creatinine: 55% increase
- Strong Heart Study
  - Increased risk for prostate cancer, lung cancer, total cancer: 1.6 mcg./gm creatinine
- South Louisiana
  - Increased risk for pancreatic cancer: .5 mcg/g cr. (not corrected for co-exposure to other metals and solvents)

Environ Health Perspect 2013;120:1017–1022.
Environ Health Perspect 2014;122: 363-370.
J Environ Pub Health 2012;180186. PMID:23319964

Cadmium and Peripheral Arterial Disease- Strong Heart Study



Circ Cardiovasc Qual Outcomes. 2013;6(6): 626–633.

FUNCTIONAL MEDICINE
Continuing Education

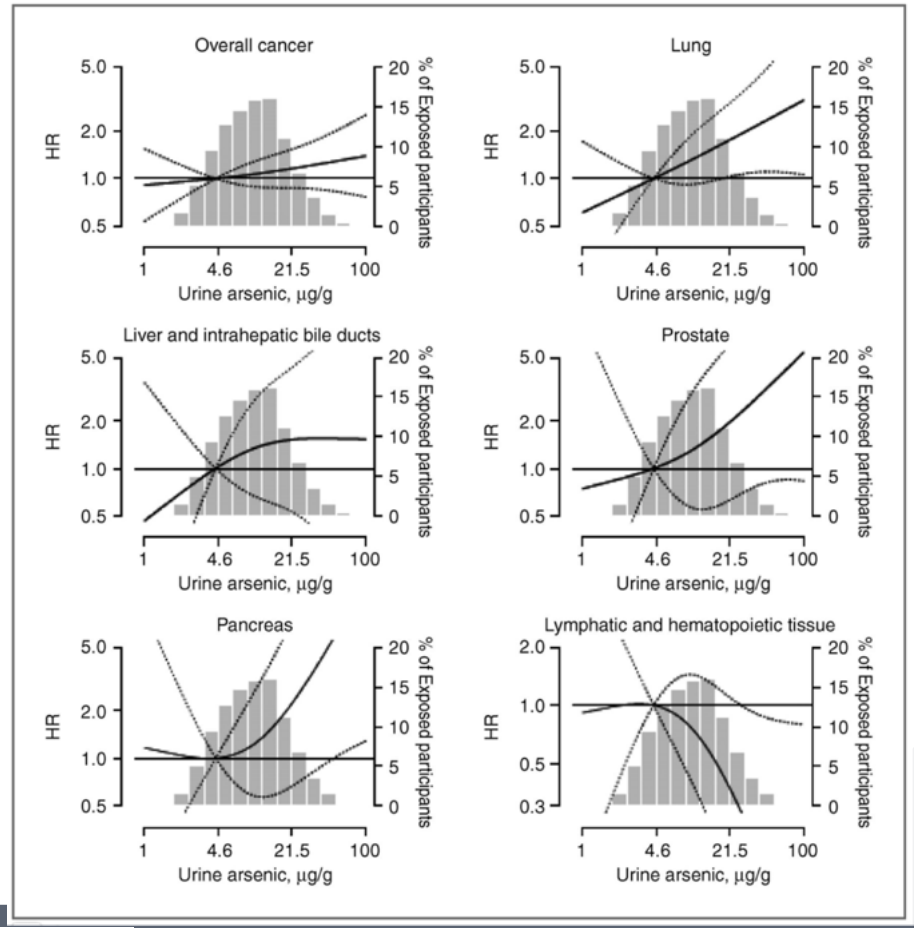
Arsenic

Arsenic and Disease

Disease	Threshold	% Above Threshold	Odds Ratio	% of Disease	Example PMID
Gout	12.5 ug/L	25%	5.5	52%	25499256
Cancer, prostate	13.3 ug/g	20%	3.3	32%	23800676
Cancer, pancreatic	13.3 ug/g	20%	2.5	23%	23800676
Diabetes	16.5 ug/L	20%	2.1	18%	18714061
Cancer, bladder	10.0 ug/L	10%	2.7	14%	24889821

Arsenic Major Factor in Many Cancers

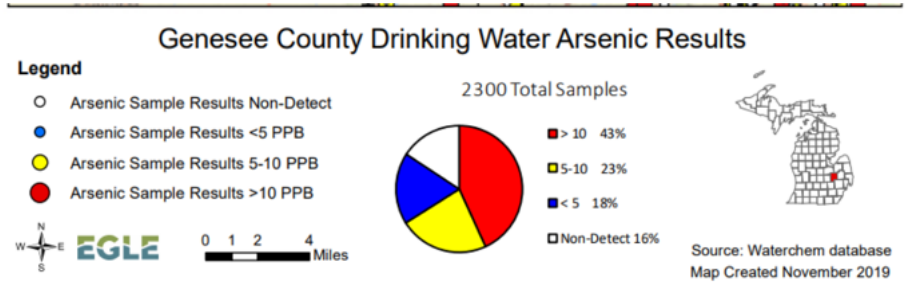
- Dose-dependent carcinogen
- 3,932 American Indians
- Arsenic not associated with cancers of esophagus, stomach, colon, rectum, and breast
- Protective for blood cancers?
- Adjusted for age, sex, smoking status, BMI (kg/m2)



García-Esquinas E, Pollán M, Umans JG, et al. Arsenic exposure and cancer mortality in a US-based prospective cohort: the strong heart study. Cancer Epidemiol Biomarkers Prev. 2013 Nov;22(11):1944-53

Arsenic in Flint Drinking Water

- 43% > 10 ug/L!



Prostate cancer in 48 yo Male

- born and raised in Phillipines
- works as executive no occupational hx exposure
- Onset urinary frequency, nocturia, urgency, decreased urinary volume w back pain x 12 mos.
- Experiences occasional night sweats where he soaks his shirt.
- Originally dx prostatitis and tx w botanical medicine, no improvement

Relevant History

- “He has an anxiety disorder which he self medicated with prior extensive use of recreational drugs.
- His diet consists mainly of fish, chicken, vegetables, rice and fruit.”

Prostate carcinoma

- PSA 14, biopsy positive
- Dx acinar adenocarcinoma of the prostate, no nodes, low Gleason score, opted for watch and wait approach

Patient Case- Notes from Treating Doc

- ELISA/ACT: LEAD reactivity
- “Had amalgams removed in 2000. Multiple rounds of IV and oral chelation have not succeeded in reducing his mercury levels, since 2005.”
- 2005 and annually: Heavy metal testing. He was found to have high levels of mercury, as early as 2005, and this has remained static and unresponsive to chelation therapy. This may have been due to extensive tuna exposure growing up in the Philippines with a lot of sushi and sashimi. “Of note that he has been on a detox regiment since March 2012, and is still currently on a detox regimen.”

Nutrient & Toxic Elements Profile - Blood

Methodology: Inductively Coupled Plasma/Mass Spectroscopy

	Results	Quintile Ranking (1st 2nd 3rd 4th 5th)	95% Reference Range	
Nutrient Elements				
Erythrocytes (packed cells)				
1. Potassium	2952	2672	2303-3374	ppm
2. Magnesium	45	44	34-63	ppm
3. Calcium*	44	44	24-65	ppm
Plasma				
4. Zinc	816	815	643-1594	ppb
5. Copper	1233	929	753-1920	ppb
Whole Blood				
6. Selenium	0.17	0.16	0.13-0.32	ppm
Toxic Elements				
Whole Blood				
7. Aluminum	28	45	<= 140	ppb
8. Arsenic	8.8	5.1	<= 13.7	ppb
9. Cadmium	0.37	0.60	<= 1.50	ppb
10. Lead	13	18	<= 36	ppb
11. Mercury	8.3	4.3	<= 13.8	ppb

Nutrient & Toxic Elements Profile - Blood

Methodology: Inductively Coupled Plasma/Mass Spectroscopy

	Results	Quintile Ranking (1st 2nd 3rd 4th 5th)	95% Reference Range	
Nutrient Elements				
Erythrocytes (packed cells)				
1. Potassium	2952	2672	2303-3374	ppm
2. Magnesium	45	44	34-63	ppm
3. Calcium*	44	44	24-65	ppm
Plasma				
4. Zinc	816	815	643-1594	ppb
5. Copper	1233	929	753-1920	ppb
Whole Blood				
6. Selenium	0.17	0.16	0.13-0.32	ppm
Toxic Elements				
Whole Blood				
7. Aluminum	28	45	<= 140	ppb
8. Arsenic	8.8	5.1	<= 13.7	ppb
9. Cadmium	0.37	0.60	<= 1.50	ppb
10. Lead	13	18	<= 36	ppb
11. Mercury	8.3	4.3	<= 13.8	ppb

How Much is Too Much?

Mercury

EPA levels of whole blood mercury:

<5.8 mcg/L for adults and children

<3.5 mcg/L for pregnant women

Mayo Clinic: “normal whole blood mercury is usually below 10.0 ng/ml”

Arsenic

Mayo Clinic: inorganic arsenic

- 0-17 years: Not established
- > or =18 years: <24 mcg/g creatinine
- ATSDR: 50 mcg. urinary inorganic arsenic indicates acute toxicity

ATSDR

- The half-life of inorganic arsenic in blood is 4 to 6 hours, and the half-life of the methylated metabolites is 20 to 30 hours.
- Abnormal blood arsenic concentrations (>12 ng/mL) indicate significant exposure, but will only be detected immediately after exposure.

ATSDR

- Arsenic is not likely to be detected in blood specimens drawn more than 2 days after exposure because it has become integrated into nonvascular tissues.
- Consequently, blood is not a good specimen to screen for arsenic, although periodic blood levels can be determined to follow the effectiveness of therapy.
- Urine is the preferred specimen for assessment of arsenic exposure.

Toxic Metals; Urine

TOXIC METALS		RESULT µg/g creat	REFERENCE INTERVAL	WITHIN REFERENCE / OUTSIDE REFERENCE
Aluminum	(Al)	**4.5**	< 35	
Antimony	(Sb)	**0.3**	< 0.2	
Arsenic	(As)	**160**	< 80	
Barium	(Ba)	**3.8**	< 7	
Beryllium	(Be)	**< dl**	< 1	
Bismuth	(Bi)	**< dl**	< 4	
Cadmium	(Cd)	**0.2**	< 1	
Cesium	(Cs)	**8.1**	< 10	
Gadolinium	(Gd)	**4.9**	< 0.8	
Lead	(Pb)	**0.4**	< 2	
Mercury	(Hg)	**2.2**	< 4	
Nickel	(Ni)	**6.4**	< 10	
Palladium	(Pd)	**< dl**	< 0.3	
Platinum	(Pt)	**33**	< 0.1	
Tellurium	(Te)	**< dl**	< 0.5	
Thallium	(Tl)	**0.3**	< 0.5	
Thorium	(Th)	**< dl**	< 0.03	
Tin	(Sn)	**0.7**	< 5	
Tungsten	(W)	**< dl**	< 0.4	
Uranium	(U)	**< dl**	< 0.04	

URINE CREATININE	RESULT mg/dL	REFERENCE INTERVAL	-2SD -1SD MEAN +1SD +2SD
Creatinine	**54.9**	30- 225	

Toxic Metals; Urine

TOXIC METALS		RESULT µg/g creat	REFERENCE INTERVAL	WITHIN REFERENCE / OUTSIDE REFERENCE
Aluminum	(Al)	13	< 35	
Antimony	(Sb)	0.4	< 0.2	
Arsenic	(As)	76	< 80	
Barium	(Ba)	2.4	< 7	
Beryllium	(Be)	< dl	< 1	
Bismuth	(Bi)	1	< 4	
Cadmium	(Cd)	2.3	< 1	
Cesium	(Cs)	7.3	< 10	
Gadolinium	(Gd)	12	< 0.8	
Lead	(Pb)	10	< 2	
Mercury	(Hg)	13	< 4	
Nickel	(Ni)	15	< 10	
Palladium	(Pd)	< dl	< 0.3	
Platinum	(Pt)	20	< 0.1	
Tellurium	(Te)	< dl	< 0.5	
Thallium	(Tl)	0.2	< 0.5	
Thorium	(Th)	< dl	< 0.03	
Tin	(Sn)	1.4	< 5	
Tungsten	(W)	0.08	< 0.4	
Uranium	(U)	< dl	< 0.04	

URINE CREATININE		RESULT mg/dL	REFERENCE INTERVAL	-2SD -1SD MEAN +1SD +2SD
Creatinine		39.5	30– 225	

CDC- Blood Total Mercury (2003 - 2010)

Geometric mean and selected percentiles of blood concentrations (in µg/L) for the U.S. population from the National Health and Nutrition Examination Survey.

Demographic Categories	Survey (Years)	Geometric Mean (95% CI)	50th Percentile (95% CI)	75th Percentile (95% CI)	90th Percentile (95% CI)	95th Percentile (95% CI)	Sample Size
Total population	03-04	.797 (.703-.903)	.800 (.700-.900)	1.70 (1.50-1.90)	3.30 (2.90-3.90)	4.90 (4.30-5.50)	8373
Total population	05-06	.863 (.787-.946)	.830 (.760-.920)	1.66 (1.48-1.93)	3.20 (2.87-3.54)	4.64 (4.17-5.25)	8407
Total population	07-08	.769 (.689-.859)	.740 (.660-.830)	1.48 (1.29-1.69)	2.95 (2.46-3.59)	4.64 (3.74-5.79)	8266
Total population	09-10	.863 (.792-.941)	.790 (.730-.880)	1.68 (1.49-1.91)	3.43 (3.07-3.84)	5.13 (4.57-5.67)	8793

https://www.cdc.gov/exposurereport/data_tables.html?NER_SectionItem=NHANES

CDC- Urinary Inorganic-related Arsenic Species; creatinine corrected (2003 - 2010)

Demographic Categories	Survey (Years)	Geometric Mean (95% CI)	50th Percentile (95% CI)	75th Percentile (95% CI)	90th Percentile (95% CI)	95th Percentile (95% CI)	Sample Size
Total population	03-04	6.47 (5.84-7.16)	5.95 (5.40-6.62)	9.64 (8.25-11.4)	15.7 (13.3-18.5)	20.0 (17.4-23.9)	2569
Total population	05-06	6.72 (6.30-7.17)	6.21 (5.81-6.58)	9.75 (8.81-11.0)	16.2 (14.2-18.0)	21.3 (18.7-24.3)	2588
Total population	07-08	6.75 (6.41-7.12)	6.42 (5.97-6.88)	9.77 (9.03-10.6)	15.5 (14.2-17.0)	21.2 (18.1-23.3)	2576
Total population	09-10	6.94 (6.55-7.36)	6.55 (6.04-7.00)	10.3 (9.58-11.0)	16.4 (14.9-17.9)	22.5 (19.0-26.5)	2851

https://www.cdc.gov/exposurereport/data_tables.html?NER_SectionItem=NHANES

Sources?

- Acute exposure (this is what whole blood reflects) are evident for: mercury and arsenic
- Where are these metals coming from?
- Air?
- Water?(risk for highest exposure levels)
- Soil? (pediatric exposure source for As)
- Food? Fish (Hg), rice, apple juice, chicken, grape juice, shellfish (As)

Relevence of Labs to Dx?

- Is mercury exposure related to prostate CA?
- Is arsenic?
- Are the blood/urine levels relevant?

Mercury

- Generates high levels of reactive oxygen species(ROS) and oxidative stress, depletes glutathione and thiols causing increased neurotoxicity from interactions of ROS, glutamate, and dopamine.
- Immunotoxic (damages and inhibits immune T-cells, B-cells, neutrophil function, etc.)

Mercury

- Nephrotoxic
- Endocrine system-disrupting chemical- accumulates in pituitary gland and damages or inhibits pituitary gland's hormonal functions at very low levels
- Adrenal gland function, thyroid gland function, and disrupts enzyme production processes at very low levels of exposure

Mercury and Prostate

- Evidence for storage in prostate gland in one human subject in entire medical literature
- Evidence in animal models using injected mercury

European Radiology 11.8 (2001): 1351-1354.
Archives of Environmental Health: An International Journal 6.5 (1963): 589-601.

Arsenic and Prostate CA

- Utah exposure to moderate arsenic levels in drinking water, the SMR for prostate cancer compared to the overall US population was 1.48 (95%CI: 1.07–1.91)
- Strong association w urinary levels As in Taiwan.
- Strong Heart Study: 3,935 participants followed for 19 years. Association with lung, liver, prostate and kidney cancer.”

PMID: 23800676/ 10210691

Strong Heart Study:
Comparing the 80th (top 20% -21.0 mcg/gm creatinine) vs. 20th percentile (bottom 20% 4.6 mcg/gm creatinine) of urine arsenic concentrations:

- 1.14 (0.92–1.41) for overall cancer
- **1.56 (1.02–2.39) for lung cancer**
- **1.34 (0.66, 2.72) for liver cancer**
- **3.30 (1.28–8.48) for prostate cancer**
- 0.44 (0.14, 1.14) for kidney cancer.
- **2.46 (1.09–5.58) for pancreatic cancer**

CDC- Urinary Inorganic-related Arsenic Species; creatinine corrected (2003 - 2010)

https://www.cdc.gov/exposurereport/data_tables.html?NER_SectionItem=NHANES

Demographic Categories	Survey (Years)	Geometric Mean (95% CI)	50th Percentile (95% CI)	75th Percentile (95% CI)	90th Percentile (95% CI)	95th Percentile (95% CI)	Sample Size
Total population	03-04	6.47 (5.84-7.16)	5.95 (5.40-6.62)	9.64 (8.25-11.4)	15.7 (13.3-18.5)	20.0 (17.4-23.9)	2569
Total population	05-06	6.72 (6.30-7.17)	6.21 (5.81-6.58)	9.75 (8.81-11.0)	16.2 (14.2-18.0)	21.3 (18.7-24.3)	2588
Total population	07-08	6.75 (6.41-7.12)	6.42 (5.97-6.88)	9.77 (9.03-10.6)	15.5 (14.2-17.0)	21.2 (18.1-23.3)	2576
Total population	09-10	6.94 (6.55-7.36)	6.55 (6.04-7.00)	10.3 (9.58-11.0)	16.4 (14.9-17.9)	22.5 (19.0-26.5)	2851

Where did arsenic exposure come from?

Public drinking water systems for the study:

- Arizona <10 - 61 µg/L
- North and South Dakota <10 - 21 µg/ L
- Levels in private wells are not known but given arsenic levels in groundwater they could exceed 10 - 50 µg/L.

NIH/NIEHS

- CONCLUSION: Available evidence in human populations and human cells *in vitro* indicates that the prostate is a target for inorganic arsenic carcinogenesis. A role for this common environmental contaminant in human prostate cancer initiation and/or progression would be very important.

Mercury

Mercury – a review important for cases coming up

- Organic mercury (methylmercury): fish, vaccines, intestinal bacteria can methylate small amounts of elemental mercury; organic mercury can also be demethylated to inorganic mercury; organic mercury is excreted in hair and feces OR stored in CNS

- Elemental mercury: mercury vapor, amalgams, air pollution ALL elemental mercury is oxidized to inorganic mercury and eliminated through urine OR stored in body organs (primarily the kidneys) and other tissues (including fat)

- Inorganic mercury: skin-lightening creams, pharmaceuticals, high fructose corn syrup, eliminated through urine OR stored in body organs (primarily kidneys) and other tissues (including fat)

Neurotoxicants Targeted: Mercury

- Approximately 15% of women of childbearing age in U.S. have blood mercury levels high enough to cause risk for neurodevelopmental damage to the fetus.

PMID: 16555611

Biomarkers of mercury: a review

- RBC mercury = organic mercury (>90% of methylmercury in blood is bound to RBC) small amount of inorganic mercury
- Whole blood = organic mercury/inorganic mercury
- Plasma mercury = inorganic mercury (amalgams)
- Fecal Hg = organic mercury elimination - 90% of elimination is through bile to intestines, 10% is eliminated in urine as inorganic Hg (demethylated)
- Urine Hg = inorganic Hg (amalgams)

PMID: 16202128

Mercury Testing

1. An upper limit of whole blood mercury of less than 5.8 mcg/L (EPA, NAS and many labs use 5.0 mcg/L based on a 3.5 mcg/L upper limit for the fetus.
2. Upper limit of urine mercury 50 mcg/gm creatinine (CDC) but levels >20 are reportable in NY and CO. Neurological signs can be seen at levels as low as 5-10 mcg/L.
3. A hair mercury of less than 1.0 mcg/g (CDC)
4. Exposure to more than .1 mcg/kg body weight/day from food (called a Reference Dose or RfD) will exceed these levels. (EPA)

Pediatrics 2001; 108:197–205./Curr Probl Pediatr Adolesc Health Care . 2010 September ; 40(8): 186–215

Mercury Exposure Sources

Mercury toxicity is either acute (fish/airborne/amalgam)

or chronic (long-term low-level exposure:ex. amalgam fillings)

Elevated blood levels will tell you that your patient has exposure from diet/vaccines (fish/thimerosal/high-fructose corn syrup)

Elevated urine levels (95^{th} %) may indicate elevated inorganic mercury exposure (amalgams, airborne exposure)

However, normal blood and urine levels will not rule out chronic low-level exposure.... Only a brain and kidney biopsy would do that!

Mechanisms of Mercury Cardiotoxicity

International Journal of
Environmental Research and Public Health

MDPI

Review

Mercury Exposure and Heart Diseases

Giuseppe Genchi [1], Maria Stefania Sinicropi [1,*], Alessia Carocci [2,*], Graziantonio Lauria [1] and Alessia Catalano [2]

Recent studies suggest that chronic exposure, even to low concentration levels of mercury, can cause cardiovascular, reproductive, and developmental toxicity, neurotoxicity, nephrotoxicity, immunotoxicity, and carcinogenicity. Mercury exposure could have a long-lasting effect on cardiac parasympathetic activity and some evidence has shown that mercury exposure might affect heart rate variability, particularly early exposures in children. The mechanism by which mercury produces toxic effects on the cardiovascular system is not fully elucidated, but this mechanism is believed to involve an increase in oxidative stress. The exposure to mercury increases the production of free radicals, potentially because of the role of mercury in the Fenton reaction and a reduction in the activity of antioxidant enzymes, such as glutathione peroxidase.

Int. J. Environ. Res. Public Health **2017**;*14*:74.

SUMMARY OF VASCULAR EFFECT OF MERCURY

1. Oxidative Stress: catalyst in Fenton-Type Reactions leading to increased ROS and superoxide anion (O_2^-).
2. Inflammation
3. Thrombosis
4. Vascular Smooth Muscle (VMS) proliferation and migration
5. Endothelial Dysfunction and reduced NO
6. Dyslipidemia (OxHDL and Paroxonase)
7. Immune Dysfunction
8. Mitochondrial Dysfunction

Houston MC: The Role of Mercury and Cadmium Heavy Metals in Vascular Disease, Hypertension, Coronary Heart Disease and Myocardial Infarction: Alternative Therapies in Health and Medicine 2007;13: S 128-S133

CLINICAL VASCULAR CONSEQUENCES OF MERCURY TOXICITY

1. Hypertension
2. Coronary Heart Disease
3. Myocardial Infarction
4. Carotid IMT and Obstruction
5. Generalized Atherosclerosis
6. Renal Dysfunction and Proteinuria
7. CVA
8. Total Mortality Increased

Altern Therap Health Med 2007;13: S 128-S133.

MERCURY AND CORONARY HEART DISEASE

- 684 men with first MI, case control study in nine countries
- Association of toenail Hg^{++}, adipose tissue DHA and first MI
  - 15% higher Hg^{++} toenail content (95% CI; 5-25%)
  - OR risk adjusted for MI – 2.16 in highest vs. lowest quintile ($p = 0.006$) (95 CI; 1.09 – 4.29)
  - DHA proportional to Hg^{++} ($p < 0.001$)
  - DHA inversely correlated to MI
    OR = .59 in highest vs. lowest quintile
    $p = 0.02$, 95% CI; .30 – 1.19
  - Toenail Hg^{++} measured by Neutron Activation Analysis (NAA)

NEJM 2002; 347:1747-1754.

MERCURY AND CORONARY HEART DISEASE

- Conclusion
  - Positive, monotonic increase in risk of MI with Hg^{++} levels above 0.25 ug / gram. Steeper if adjusted for DHA levels
  - Hg diminishes CV protection of fish intake

NEJM 2002; 347:1747-1754

CAROTID ATHEROSCLEROSIS AND MERCURY

High hair mercury content increases carotid IMT and atherosclerosis

- 1,014 men ages 42 – 60 years
- Increase in mean IMT in 4 years ($p = 0.0007$)
- Each increase in one ug / gm in hair content equals 8 um in carotid IMT (7.3% of mean)

Atherosclerosis 2000; 148:265-273.

CAROTID ATHEROSCLEROSIS AND MERCURY

- 0.034 mm / 4 years – 32% greater in highest quintile vs. lowest ($p < 0.05$)
- Mercury content proportional to:
  - Blood Pressure $p = 0.0002$
  - Fibrinogen $p = 0.0002$
  - WHR $p = 0.0002$
  - Low HDL $p = 0.0002$

Atherosclerosis 2000; 148:265-273.

MERCURY AND CORONARY HEART DISEASE

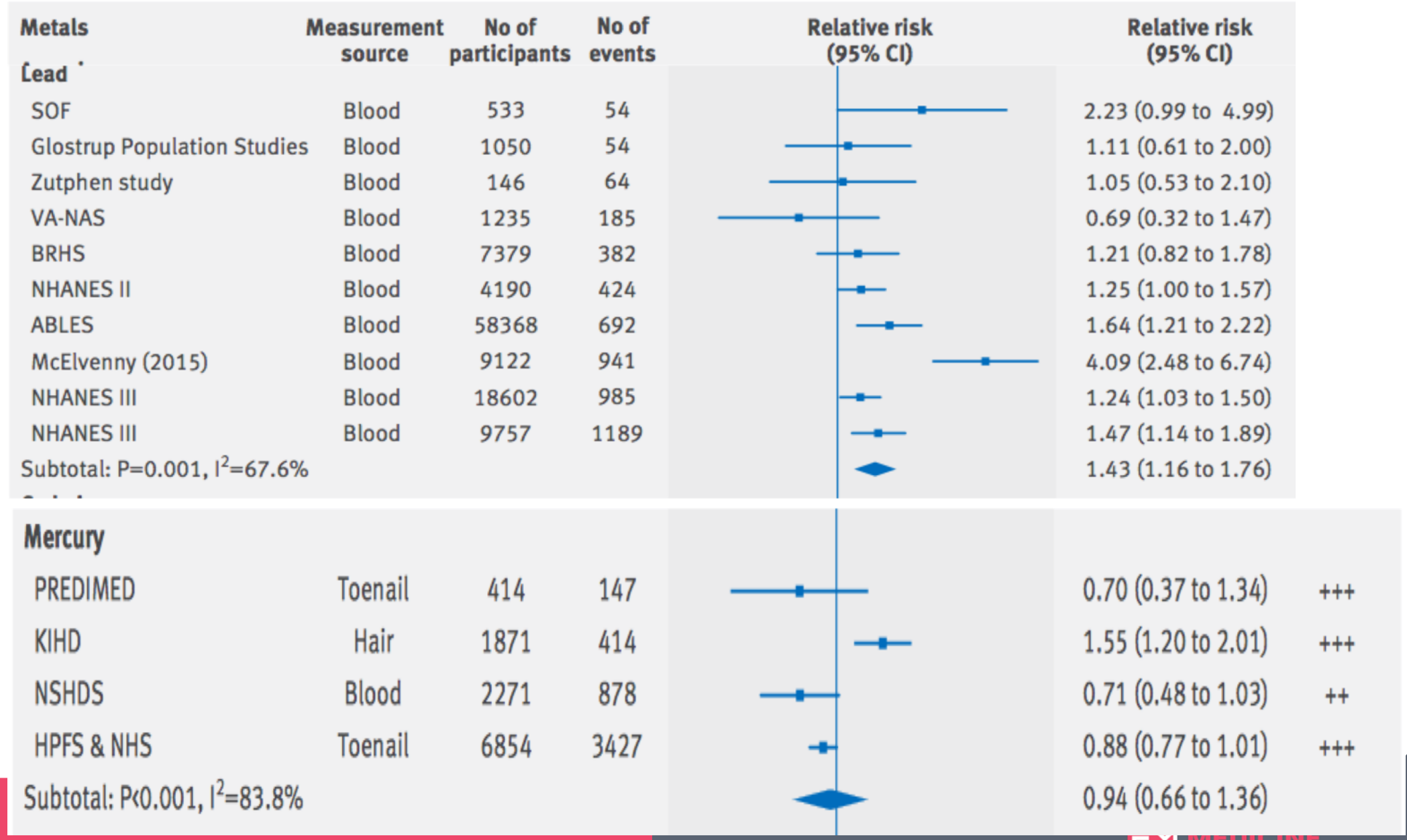
Finnish Study

- Hair Hg highest tertile > 2.0 ug / gm
- 24 hour urine Hg
  - CHD / MI increased 2 x (p = 0.005)
  - CV death increased 2.9x (p = 0.014)
  - Increased OxLDL and immune complexes

Gothenburg Study

- Serum Hg α to number amalgam fillings
- No correlation to CHD / MI

Circulation. 1995;91(3):645-655/*Atherosclerosis.* 2000;148(2):265-273./*Acta Odontol Scand.* 1999;57(3):168-174.



Metals	Measurement source	No of participants	No of events	Relative risk (95% CI)		Relative risk (95% CI)	
Lead							
SOF	Blood	533	54			2.23 (0.99 to 4.99)	
Glostrup Population Studies	Blood	1050	54			1.11 (0.61 to 2.00)	
Zutphen study	Blood	146	64			1.05 (0.53 to 2.10)	
VA-NAS	Blood	1235	185			0.69 (0.32 to 1.47)	
BRHS	Blood	7379	382			1.21 (0.82 to 1.78)	
NHANES II	Blood	4190	424			1.25 (1.00 to 1.57)	
ABLES	Blood	58368	692			1.64 (1.21 to 2.22)	
McElvenny (2015)	Blood	9122	941			4.09 (2.48 to 6.74)	
NHANES III	Blood	18602	985			1.24 (1.03 to 1.50)	
NHANES III	Blood	9757	1189			1.47 (1.14 to 1.89)	
Subtotal: P=0.001, I^2=67.6%						1.43 (1.16 to 1.76)	
Mercury							
PREDIMED	Toenail	414	147			0.70 (0.37 to 1.34)	+++
KIHD	Hair	1871	414			1.55 (1.20 to 2.01)	+++
NSHDS	Blood	2271	878			0.71 (0.48 to 1.03)	++
HPFS & NHS	Toenail	6854	3427			0.88 (0.77 to 1.01)	+++
Subtotal: P<0.001, I^2=83.8%						0.94 (0.66 to 1.36)	

BMJ 2018;362:k3310 | doi: 10.1136/bmj.k3310

Mercury toxicity-Patient case 1

- 54 y o woman
- Onset of dementia, epilepsy, peripheral neuropathy at age 49 in 2010
- Prescribed oxcarbezapine for seizures at that time and currently on it
- Neuropsychological testing was conducted in 2013 showing severe dementia
- In 2013 she was diagnosed with mercury toxicity (blood mercury of 90 µg/L) and DMPS treatment was initiated.
- Since the patient part of the year in Morocco and part-time in Germany, a probable source of mercury exposure was assumed to be fish or residence near a copper mine in Morocco.
- She continued DMPS therapy until Jan 2015 when a significant side effect (skin rash) prevented her from continuing.

BMJ Case Reports PMID: 27793866

HOSPITAL ADMISSION

- MAY 2015
- She was seen in hospital in Munich Germany with mercury-specific skin lesions on shins and calves (charted previously in 2013). A neurological examination revealed pain in all extremities without paraesthesia and paresis. She also suffered from headaches and had pain “in her whole body” .
- MRI of the brain ruled out stroke

Figure 2 Skin lightening creams containing exorbitantly high mercury concentrations. Left: Shirley Beauty Cream, Taiwan (photographed). Right: ideal cream, Lebanon (source: http://www.saudi.souq.com).

May 2015 FINALLY speciated blood mercury was run and methylmercury levels in whole blood found to be normal so VIRTUALLY ALL the blood mercury was inorganic mercury from:
A daily application of skin lightening creams (Shirley Beauty Cream, Taiwan and IDEAL cream, Lebanon) over the previous 6 years.
Positive laboratory tests for mercury in cream samples with **420 and 20,000 mg/kg,** respectively, confirmed this hypothesis and exposure was stopped immediately.)
By this point she had severe dementia, microhematuria, proteinuria.

Follow-up DMSA initiated

- 200 mg oral DMSA three times a day was started and well tolerated. After 5 days of treatment, the blood mercury level had fallen from 13.3 to 5.2 µg/L .
- The patient was discharged with a DMSA prescription for the next 4 weeks.
- After 4 weeks of DMSA-therapy :
- Labs run 2 months post end of DMSA therapy: Blood Hg 2.8 (<2) Urine Hg 3.7 (<1)
- qualitative improvement of her dementia

Here in the U.S.-WORD OF WARNING

NYC Post-9/11 NHANES STUDY-

Mean urine mercury concentration in NYC was higher for Caribbean-born blacks (1.39 µg/L) and Dominicans (1.04 µg/L) than for non-Hispanic whites (0.67 µg/L) or other racial/ethnic groups tested.

95th percentile of exposure among Dominican women was 21.18 µg/L.

Mercury-containing skin-lightening creams were a source of exposure among those most highly exposed, and subsequently identified 12 imported products containing illegal levels of mercury in NYC stores.

PMID: 20923743

MERCURY TOXICITY- CASE #2

The Journal of Emergency Medicine, Vol. ■, No. ■, pp. 1–4, 2019

0736-4679/$ - see front matter

https://doi.org/10.1016/j.jemermed.2018.12.039

Selected Topics: Toxicology

A CASE OF ACCIDENTAL MERCURY INTOXICATION

Olivia L. Kamensky, BSA,*† Destiny Horton, BSA,*† Donald P. Kingsley, DO,† and Christy C. Bridges, PHD*

*Department of Biomedical Sciences, Mercer University School of Medicine, Macon, Georgia and †Department of Internal Medicine, Navicent Health, Macon, Georgia

Reprint Address: Christy C. Bridges, PHD, Mercer University School of Medicine, 1501 Mercer University Dr., Macon, GA 31207

PMID: 30718027

FUNCTIONAL MEDICINE
Continuing Education

Mercury toxicity-Patient case 2

- A 32-year old white woman had a known exposure to elemental mercury.
- Her 15-year-old daughter brought home a vial of elemental mercury from the home of a friend. (the friend's home was a rental house owned by a dentist who was storing elemental mercury in the basement for use in dental amalgams.)
- They were playing with the liquid and they accidentally spilled it onto the carpet. The spill was cleaned by vacuuming the mercury with the household vacuum cleaner.

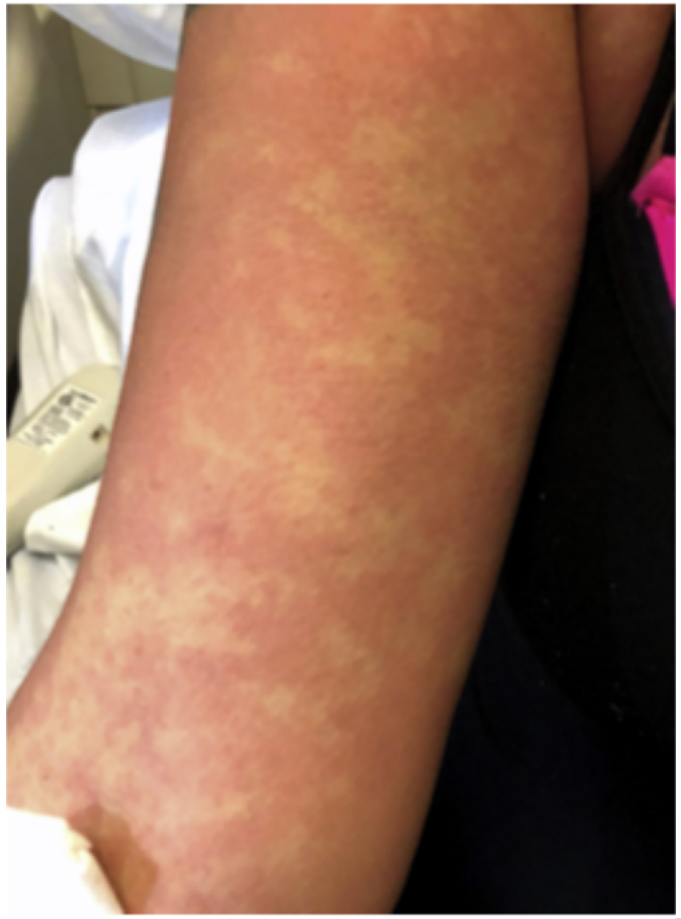
Mercury toxicity-Patient case 2

- The mother then unknowingly used the same vacuum cleaner to vacuum the floors throughout the rest of the house.
- Both mother and daughter had immediate onset of fever, headache, myalgias, dyspnea, and rash. They initially visited a local hospital but they were discharged with a diagnosis of a viral illness. Approximately 6 days after the exposure occurred, the patient learned that mercury had been brought into the home and returned to the hospital.

Mercury toxicity-Patient case 2

- She was febrile, with a temperature of 102 F
- pulse rate of 122 beats/min;
- respiratory rate of 22 breaths/min.
- She had a flat, erythematous, blanching confluent rash covering her arms and legs bilaterally, as well as her chest, abdomen, and back.
- She complained of a headache, myalgias, peripheral neuropathy, oral paresthesia, and tender, posterior cervical lymphadenopathy.
- The patient's 24-h urine mercury level was 91.4 mg/L. Her whole blood mercury level was 170 ng/mL (mcg/L).
- The home of the patient was found to be contaminated heavily with mercury and the CDC sealed the home for decontamination.

Acute mercury toxicity



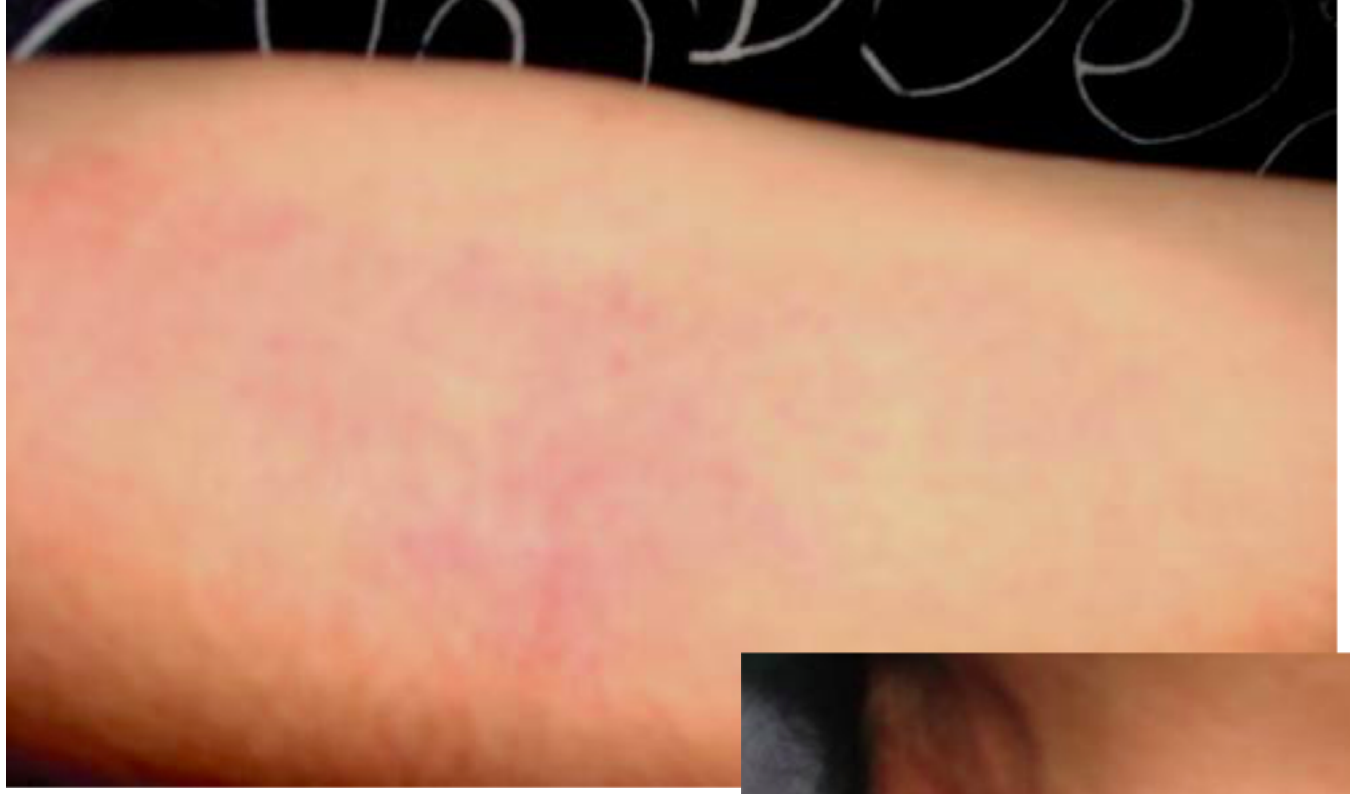
TREATMENT

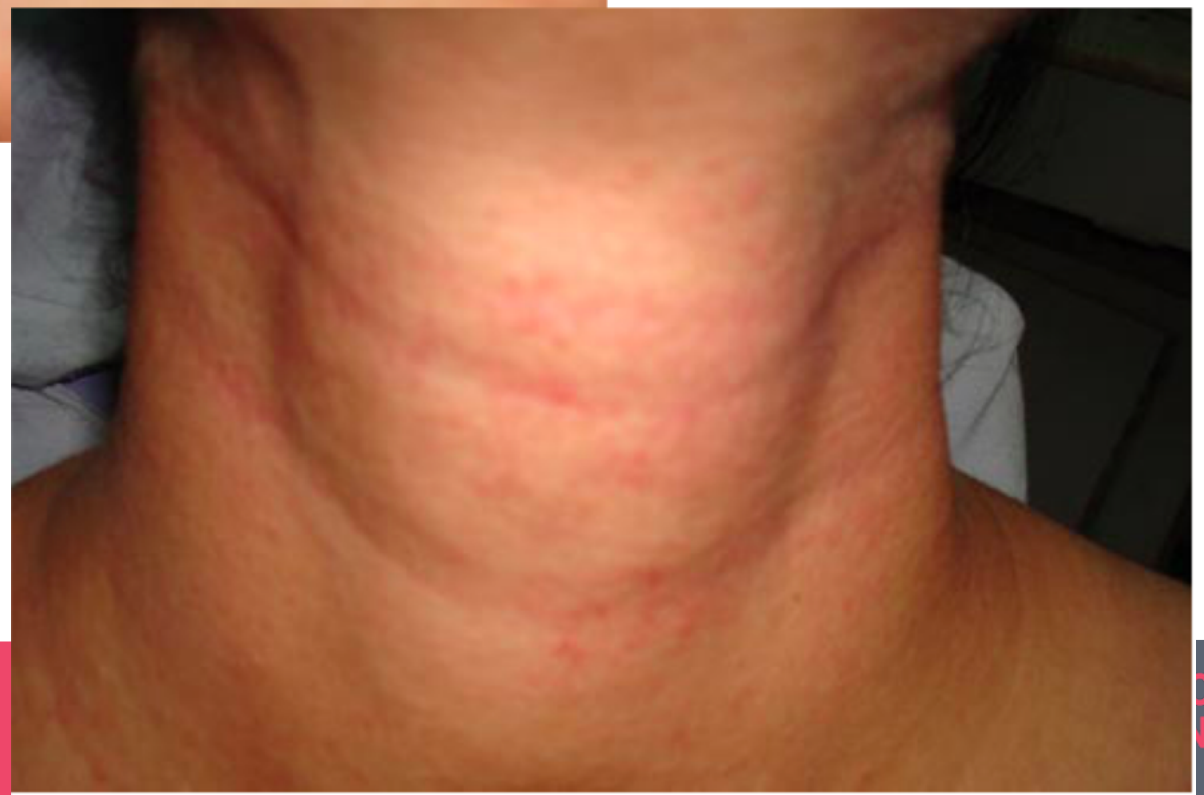
- standard hospital protocol: succimer (DMSA)10 mg/kg by p.o. t.i.d. for 5 days, followed by succimer (10 mg/kg p.o. b.i.d.) for 14 days.
- Post tx (the hospital used BAL instead as they were “out of” succimer- they had used it with her daughters, blood mercury came down from 170 to 127 and continued treatment with BAL but was lost to follow-up. (BAL is an injection and known to be very painful).

Mercury toxicity-Patient case 3

- 23 year old female dental student reports a rash that has developed with itching and redness on her face, neck and flexor surface of her arm within 24-48 hours after coming into contact with mercury vapor while performing amalgam placement on patients.
- She did not have any amalgam fillings herself but had previous reactions to mercury when exposed: prior hx of exposure to broken thermometer with swelling of her face and neck, itching and redness extending to the axilla. This reaction subsided within a week.

PMID: 18849934





ONAL
NE

What her provider prescribed

- Allopathic standard of care for mercury sensitivity: Dermashield (activated dimethisone) and Clonate Lotion (0.05% clobetasol propionate)

what's missing from this picture?

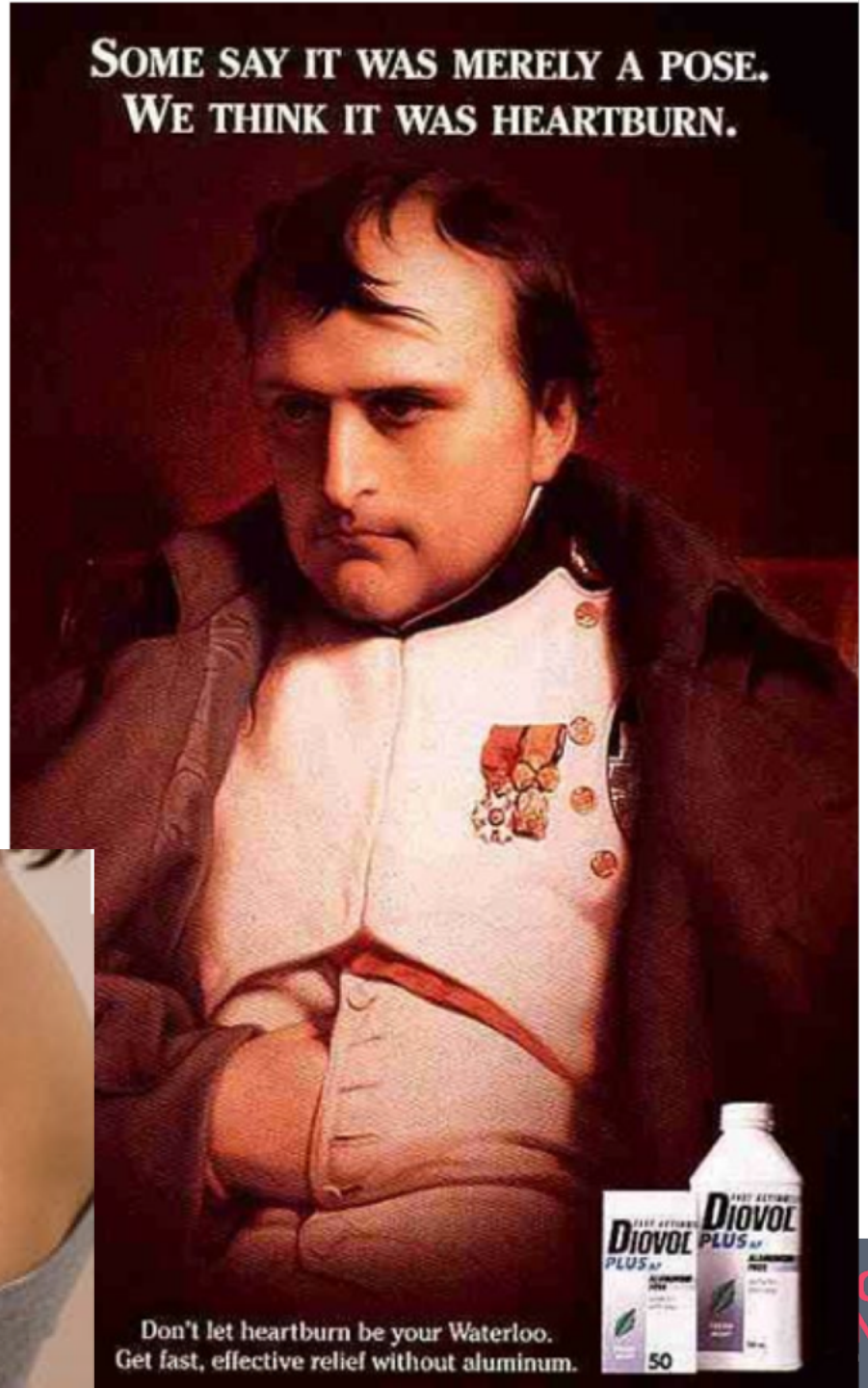
- there is a documented increase in the development of hypersensitivity to mercury as students progress through dental school
- exposure to mercury during the preparation of silver amalgam definitely presents an additional occupational hazard as an allergen for dentists.
- mean blood mercury levels for a large cohort of dentists have been shown to be approx. 8.2 mcg/L
- any other exposures? Mercury-containing fish? Skin-lightening cream? Cosmetics? (mascara, eyeliner, eye shadow and eye pencils), red tattoos, broken thermometers?

CLINICAL PEARLS

- On your intake form: please add the following-
- Do you eat fish? What kind? How often?
- Do you or have you had amalgam (silver fillings) in your mouth? How many and if you had them taken out how long ago?
- Do you use any imported beauty products to lighten your skin?

Aluminum


Wahaya


SOME SAY IT WAS MERELY A POSE.
WE THINK IT WAS HEARTBURN.
Don't let heartburn be your Waterloo.
Get fast, effective relief without aluminum.
DIOVOL
PLUS
50

Aluminum exposure sources

Sources of exposure:

Oral:

- Tap water (historically used in dialysis caused dialysis encephalopathy due to inability to clear aluminum through a compromised renal system)
- Concentrations of aluminum are highly variable in drinking water, ranging from <0.001 to 1.029 mg/L (Schenk et al. 1989). The use of alum (aluminum sulfate) as a flocculent in water treatment facilities typically leads to high aluminum concentrations in municipal water supplies.
- The aluminum content of human breast milk generally ranged from 9.2 to 49 Ig/L Soy-based infant formulas contain higher concentrations of aluminum compared to milk-based infant formulas or breast milk.

PMID: 30871123 (2019)

Aluminum exposure sources

- Processed food in aluminum cans or aluminum-based foil containers (foil Tetra-Pak)
- General population oral intake: 1 mg/kg/wk

Dermal/Intradermal :

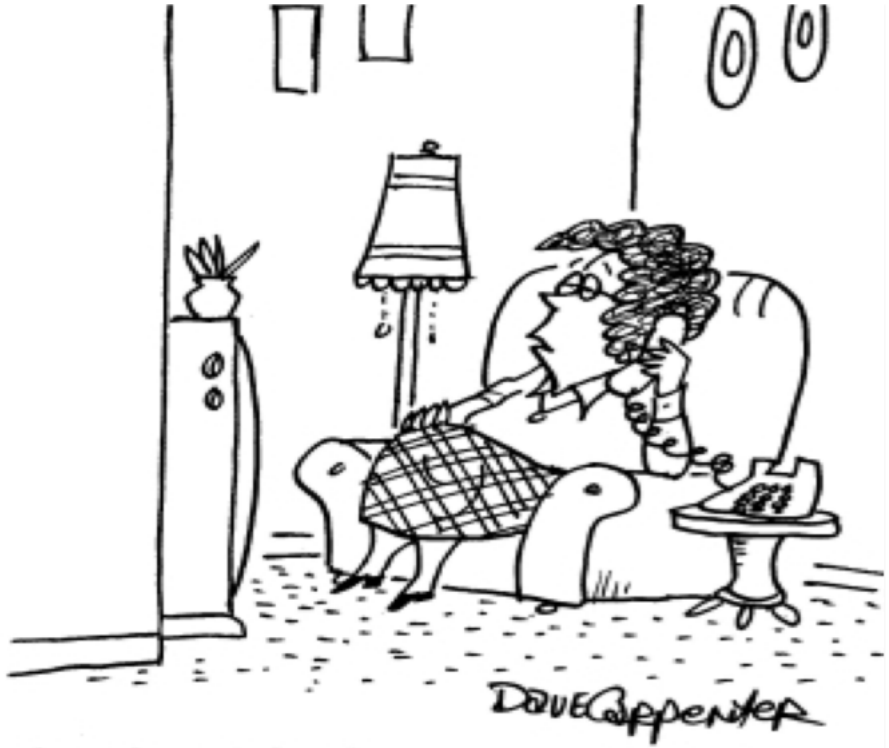
- Personal Care Products containing aluminum chlorhydrate (antiperspirant)

Injections:

- Injection Fluids: 10 mcg./L (US Assoc. for Advancement of Medical Instrumentation)
- Aluminum adjuvant-containing vaccines (multi-dose flu vaccines)

Aluminum in Pharmaceuticals

- Antacid use: 840-5000 mg/day
- Buffered aspirin: 130-730 mg/day
- Anti-ulcerative medication: 830 mg/day
- Anti-diarrheal agents: 1450 mg/dose



"Today, I watched so many food shows, I had to take an antacid tablet."

J Toxicol Environ Health B Crit Rev. 2007; 10(Suppl 1): 1–269.

Aluminum toxicokinetics

- Trivalent Al (+3), the form found in the human body when the salt dissociates- generates oxygen radicals and damages target organs.
- Al can be absorbed from the gut or the lungs into the systemic circulation and is distributed widely to the lung, liver, bone, muscle and brain, with highest levels found in lung tissue.
- It can accumulate with long-term exposure and the body's burden of Al may remain elevated for many years following cessation of occupational or other exposure.
- It is present in breastmilk and is found in the placenta and fetus.
- Urine is the main route of elimination and the elimination half-life of Al depends on kidney function and level of exposure: following acute exposure, it is in the order of days, but may be as long as three years in chronic exposure. Half-life in the brain is 7 years.
- Aluminum is excreted in sweat and feces and significant amounts of aluminum were found in sweat of individuals participating in sauna therapy.

PMID: 18085482 21057782

Aluminum- who is at risk?

- Individuals with impaired renal function do not clear aluminum as effectively as healthy individuals.
- This population can also be exposed to extremely high levels of aluminum that are administered inadvertently via their intravenous feeds.
- This route of exposure may be particularly significant because it bypasses the barrier imposed by GI absorption characteristics.
- Infants, especially those born pre-term, are also vulnerable to aluminum exposure due to immaturity of the GI wall, the BBB, and the renal system.
- Pediatric parenteral solutions pose risk for Al exposure.

PMID: 18085482 21057782

Aluminum Effects

- Impairing cognitive and motor function
- Altering of DNA, chromatin RNA structure
- Inducing autoimmunity (ASIA)
- Blocking neuronal signaling
- Inhibiting antioxidant enzyme action
- Interfering with synaptic transmission and disrupting mitochondria
- Endocrine disruption in brain
- Brain: genotoxic. pro-inflammatory, immunotoxic
- Carcinogen: application dermally (underarm deodorant) has been shown to correlate with increased breast cancer risk

PMID: 22108899 PMID: 26275795

Aluminum effects in dialysis patients

- Osteomalacia- associated with dialysis encephalopathy. A 10-fold increase in aluminum concentrations was reported in patients with aluminum intoxication through the use of hemodialysis solutions with high levels of aluminum.
- Anemia (microcytic) through decreased heme synthesis, decreased globulin synthesis, and increased hemolysis. Aluminum displaces iron binding to transferrin.
- Patients with anemia from aluminum toxicity often have increased reticulocyte counts, decreased mean corpuscular volume, and mean corpuscular hemoglobin.

PMID: 22108899, 26275795

Aluminum effects

- High aluminum concentrations have been found in postmortem brain specimens of patients with Parkinson's disease and in animal models where administration of aluminum caused a strong decrease in dopamine content of the striatum.
- Vaccine-associated macrophagic myofasciitis and chronic fatigue syndrome.
- Evidence from brain biopsies finding elevated aluminum levels in Alzheimer's and Parkinson's disease, multiple sclerosis, autism.
- Cases of adult-onset seizure disorder have been found in non-occupationally aluminum-exposed individuals.

PMID: 22108899, 26275795

Assessing Exposure

- Urine aluminum: Daily excretion >50 mcg/L indicates exposure to excessive amounts of aluminum. Normal values have not been determined for random specimens.
- Serum aluminum reference ranges: 0-6 ng/mL (all ages) and <60 ng/mL in dialysis patients-all ages.
- Serum levels in healthy individuals range from 1 to 3 µg/L.

Provocation testing with orthosilicic acid has been demonstrated in Chris Exley's lab: collect 24 hr baseline urine have patient drink 1.5 L silicon-rich mineral water (≥30 mg/L silica) and then collect second 24 hr urine.

MayoMedical Labs Interpretive Guide accessed 4/6/12
Exley C. Imagine You Are an Aluminum Atom. Conversations with Mr. Aluminum Skyhorse Pub. 2020 p. 23

Treatment using orthosilicic acid from silica-rich mineral water

Controlled Clinical Trial > J Alzheimers Dis. 2013;33(2):423-30.
doi: 10.3233/JAD-2012-121231.

Silicon-rich mineral water as a non-invasive test of the 'aluminum hypothesis' in Alzheimer's disease

Samantha Davenward [1], Peter Bentham, Jan Wright, Peter Crome, Deborah Job, Anthony Polwart, Christopher Exley

Affiliations + expand

PMID: 22976072 DOI: 10.3233/JAD-2012-121231

We have shown that drinking up to 1 L of a silicon-rich mineral water each day for 12 weeks facilitated the removal of aluminum via the urine in both patient and control groups

Preliminary evidence that over 12 weeks of silicon-rich mineral water therapy the body burden of aluminum fell in individuals with Alzheimer's disease and, concomitantly, cognitive performance showed clinically relevant improvements in at least 3 out of 15 individuals.

Case report: Aluminum Chlorohydrate in Antiperspirant

- A woman who applied ~ 1 g of aluminum chlorohydrate-containing antiperspirant to each regularly-shaved underarm daily for 4 years was reported to have experienced bone pain and fatigue. Serum aluminum was 105 mcg/L and 24 hr urinary aluminum was 47 mcg.
- After discontinuation of antiperspirant use, urine and serum aluminum concentrations decreased over 7 months, her bone pain disappeared and her fatigue improved.

Am J Med. 2004 Dec 15;117(12):956-9.

Treatment

- Avoidance:
  - Hg: big fish, amalgam removal if indicated, high fructose corn syrup, imported skin lightening creams, thimerosal
  - Cd: tobacco smoke, shellfish
  - As: unfiltered drinking water, rice
  - Pb: unfiltered drinking water, red lipstick, imported candy, home renovation using protection

DMPS/DMSA

- They both bind to arsenic, lead, mercury, etc. in the proximal tubular epithelium, not in other organs or the bloodstream.
- However animal data shows both agents can decrease metal levels in the brain and other organs
- DMSA is more gentle chelator, not used IV only orally
- DMPS has higher risk for more severe ADR but has higher binding capacity for arsenic and mercury compared to DMSA
- DMSA has higher binding capacity for lead and can be used in conjunction with EDTA where DMSA mobilizes lead from soft tissue (kidneys) and DMSA mobilizes lead from trabecular bone.
- A combination of both EDTA and DMSA may be more effective in chelating lead in lead-exposed workers than either alone.

Chem Res Toxicol 2012:25(9):1825-1838./PMID: 19852620, 7697134

DMPS (Unithiol)

- Indications: Developed in 1951 by Heyl in Germany, used in Russia and China in acute and chronic poisoning with metallic, inorganic and organic mercury as well as mercury vapor and **arsenic**, and to a lesser degree—copper, antimony, chromium, cobalt. It may also increase urine zinc, selenium, magnesium.

PMID: 8113976/11192456

DMPS

- Pharmacology
- 39% bioavailable orally
- ½ life of intravenous administration: 20 hrs, peak urinary concentration occurs 2-3 hours after administration.
- ~50% of orally administered DMPS is absorbed and excreted via the kidneys. The peak urinary concentration occurs 2-3 hours after administration
- Intravenously:
    - 50% excreted via the kidneys in 1 hour, more than 90% at 24 hours. Also excreted to a lesser extent via the bowel.
    - Does not cross the blood brain barrier
    - Strongly binds to divalent cations: Hg, Pb, Cr, As, Sb,

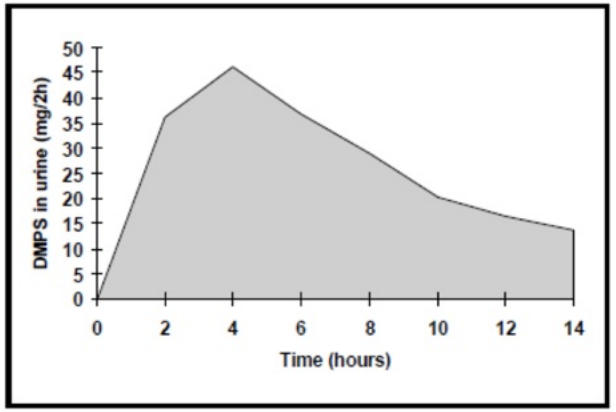
DMPS Monograph Heyl Pharmaceuticals

DMPS Not FDA approved as a drug- only legally used as a compounding agent.

- Explanation of non-FDA approved status:
  - Classified as safe by the FDA as a bulk ingredient in compounding.
  - Please see complete legal opinion written for College Pharmacy by Howard Hoffman of Duane Morris, LLP
  - (leading authority on FDA law and pharmacy compounding).
  - Ref. Compliance Policy Guide Sec.460.200 Pharmacy Compounding
- If DMPS is used, have patient sign an informed consent.

DMPS

- Pharmacokinetics



Renal excretion of DMPS after oral administration of 400 mg to 6 volunteers<882>

882.Stephan W; Pharmacokinetics of uroprotective sulfhydryl groups in urine of normal test persons after oral admission of Na-mercatoethanesulfonate (Uromitexan) and Na-Dimercaptopropansulfonate (Dimaval); Dissertation, Universität Bern 1989

Parameter		Dimension	Plasma (oral)	Blood (oral)	Plasma (i.v.)	Blood (i.v.)
Elimination half-life	$t_{½}\alpha$	Hours	9.9	9.1	1.1	0.9
	$t_{½}ß$				27.6	19.0
AUC		µmol/l	318	148	426	242
Plasma clearance		ml/min			37.8	67.4
Distribution volume		l			39	13
Mean steady-state concentration		µmol/l			17.7	10.1
Concentration peak	c_{max}	µmol/l	25.3	11.9		
	t_{max}	Hours	3.4	3.7		

Pharmacokinetic parameters for DMPS in humans (300 mg DMPS orally, 10 volunteers<603> *or 3 mg DMPS/kg i.v., 5 volunteers*<285,409>*)*

Heyl Monograph

603.Maiorino RM, Dart RC, Carter DE, Aposhian HV; Determination and metabolism of dithiol chelating agents. XII Metabolism and pharmacokinetics of sodium 2,3-dimercaptopropane-1-sulfonate in humans; J. Pharmacol. Exp. Ther. 259(2) 808-814 (1991)

285.Eybl V, Sykora J, Drobnik J, Mertl F, Svec F, Benes M, Stamberg J, Peska J; Influence of metal-complexing polymers on the retention and distribution of cadmium and mercury in mice; Plzen. Lek. Sborn 49(Suppl.) 169-172 (1985)

409.HEYL; Unveröffentlichte Studien zu Dimaval®(DMPS) und DMPS-Heyl® (1992/1993)

DMPS DOSING

- Adult Dosing: IV- 3 mg/kg (max dose: 250 mg)
- p.o. : 10 mg/kg in 3 divided doses for 3 days, then 11 days off
- p.r. : 10 mg/kg, 1x/day x 3 days, 11 days off

- Administration of IV DMPS necessitates understanding of patient's sensitivity, if possible pretest w intradermal testing or oral administration w small dose.

DMPS

- Adverse Reactions:
  - General—nausea, headaches, fever, odor of rotten eggs in body excretions.
  - Skin—itching, exanthema or rashes, severe allergic skin reactions have been reported rarely (IM/IV B12 can often reverse some rashes)
  - Cardiovascular—If IV administered too quickly (less than : Hypotension, dizziness, weakness, palpitation.

Treating acute arsenic toxicity with DMPS

- The ½ life of arsenic in the body is hours to 2-4 days.
- Most of the arsenic elevations you will see result from food or drinking water contamination and will not qualify as ACUTE arsenic toxicity (acute toxicity >50 mcg arsenic/gm creatinine)
- ACUTE arsenic toxicity necessitates immediate chelation preferably with IV DMPS
- The appropriate and first action for elevations in blood or urine arsenic is to identify and remove the source of exposure. LOE:A

DMPS-mercury

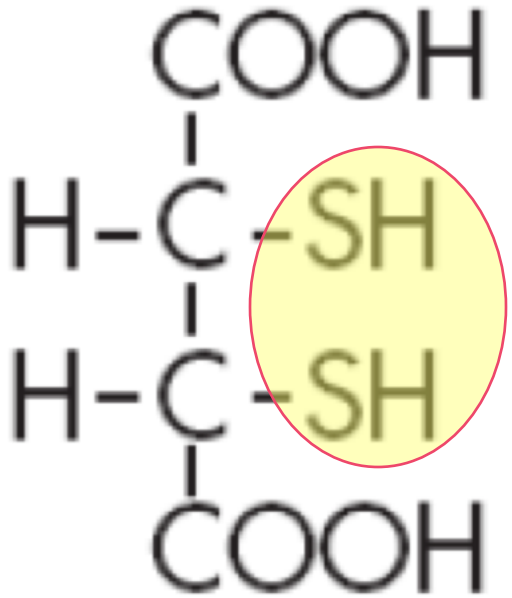
- **Dosage and Administration:**
  - IV 3mg/kg not to exceed 250 mg. per IV LOE:C
  - Administered no more than once weekly
  - *IV administration time should not be less than 10 minutes!

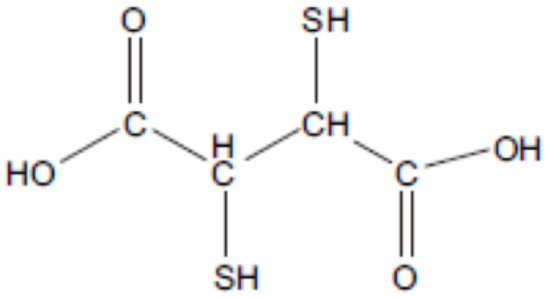
Oral Use:

- 10 mg/kg in 3 divided doses (100 mg-200 mg PO TID) LOE:C
- In sensitive patients: 50 mg PO q 6 hr

DMSA

- meso-2,3-Dimercaptosuccinic acid
- Synonyms: Succimer; Chemet





Because of the two neighboring SH groups, it has a high affinity for many heavy metals that have an affinity for sulfur and forms stable complexes with them.

DMSA

- **Indications:** FDA approved in 1991 for the treatment of lead poisoning in pediatric patients with blood lead levels above 45 µg/dL (2.17 µmol/L)*
- **Contraindications:** Chemet should not be administered to patient with a history of allergy to the drug
- **Warnings:** Mild neutropenia has been reported in some patients receiving DMSA
  - Check CBC with differential prior to starting treatment

*U.S Department of Health and Human Services. Succimer approved for severe lead poisoning. FDA Medical Bulletin 1991; 21:5

Chemet/Succimer (DMSA)

Manufacturers directions:

For treatment of acute lead toxicity

- Pediatric use: 1 year or older: Blood lead levels above 45 mcg/dL, 10 mg/kg or 350 mg/sq.meter q8hr for 5 days, then 10 mg/kg or 350 mg/sq.meter q12hr for 14 days
- Pediatric suppositories: 25 mg/kg, 1x/day for 3 days on, 11 days off. LOE:C
- Research Protocol Johns Hopkins pediatric protocol : 1050 mg/m2/d in 3 oral doses for the first 5 days, at which point the dosage was reduced to 700 mg/m2/d and divided into 2 doses over the next 21–23 days. LOE:B
- Adult use: 10 mg/kg PO q8hr for 5 days; follow by 10 mg/kg/dose q12hr for 14 days; not to exceed 500 mg/dose or 2300 mg total daily dose. LOE:C

Clin Toxicol 2000;38(4), 365–375.

Alternative protocol

- Integrative medical clinics have used 250 mg every 3rd evening for longer periods of time to prevent ADR and increase compliance. LOE:C
- 10 mg/kg tid x 2 days w 5 day wash-out LOE:C
- 10 mg/kg tid x 5 days w 9 day wash-out LOE:C
- 10 mg/kg/dose, max 500 mg./dose tid- 3-5 days on, 11 days off. No more than 2300 mg. per 24 hrs. LOE:C

Crinnion W, Pizzorno J. Clinical Environmental Medicine Elsevier 2019 p.798

DMSA

- **Precautions:** Ensure adequate hydration during treatment
- Transient mild elevations of serum transaminases have been observed in <10% of patients.
    - **Check AST. ALT prior to starting treatment**
- **Drug Interactions:** None
- **Pregnancy:** Category C
- **Nursing mothers:** If treatment is necessary, mothers should be discouraged from nursing
- **Pediatric Use:** Safety in patients <1 yr has not been established

DMSA

- **Adverse Reactions:**
  - GI side effects—nausea, vomiting, diarrhea, metallic taste in mouth <10%. Most common: gas/bloating (Peppermint/ginger tea and peppermint tablets often can alleviate GI side effects)
  - Skin—mucocutaneous eruption, pruritus, uriticarial rash, erythematous rash
  - Neutropenia
  - Metabolic—elevated transaminases (ALT, AST), Alkaline Phosphatase, Cholesterol <10%

DMSA

- **Adverse Reactions:**

Study	N	Adverse Effects
Besunder JB, Anderson RL, Super DM. Short-term efficacy of oral dimercaptosuccinic acid in children with low to moderate lead intoxication. Pediatrics 1995; 96:683-687	46 treated, 18 excluded, N=28	Neutropenia (N=1)
Bradberry SM. The Role of Succimer (DMSA) in the Treatment of Inorganic Lead Poisoning. Birmingham, UK: University of Brimingham; 2009	N=1	Mucocuntaneous eruption
Chisolm JJ. Safety and efficacy of meso-2,3-dimercaptosuccinic acid (DMSA) in children with elevated blood lead concentrations. J Toxicol Clin Toxicol 2000; 38:365-375	N=59	Elevated alkaline phosphate levels (N=2), eosinophilia (N=1)
Gerr F, Frumkin H, Hodgins P. Hemolytic anemia following succimer administration in a glucose-6-phosphate dehydrogenase deficient patient. J Toxicol Clin Toxicol 1994; 32:569-575	N=1	Hemolytic anemia d/t G6PD

DMSA

- **Adverse Reactions:**

Bradberry et al.[55] also reported the development of a mucocutaneous reaction in one patient 2 days after commencement of DMSA. The patient who had no history of atopy or allergy complained initially of pruritus affecting the neck. A semi-confluent erythematous rash then developed over the neck and forearms, which was associated with a mild fever (37.9°C). There was no wheeze or other systemic effect and the white cell count was normal. Further DMSA was withheld. The following morning (~24 h after the second dose) the patient was apyrexial but had developed ulcers in the oropharynx that settled over 4 days with conservative treatment (Fig. 4). This patient had received five previous courses of DMSA without a skin reaction developing.

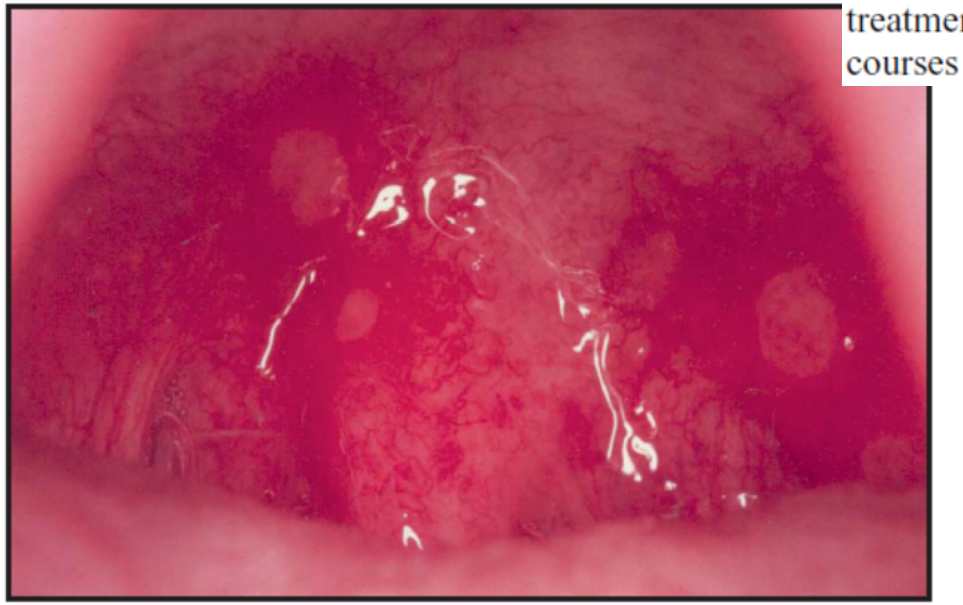


Fig. 4. Ulcers in the oropharynx following oral DMSA.[95]

Bradberry SM. The Role of Succimer (DMSA) in the Treatment of Inorganic Lead Poisoning. Birmingham, UK: University of Birmingham; 2009.

Clinical Toxicology (2009) 47, 617-631

FUNCTIONAL MEDICINE
Continuing Education

References for provocation specific dosages and implications

EDTA provocation studies

1. Multiple studies with mild-moderate renal disease adult patients: those with post-EDTA challenge using 1 gram Ca2NaEDTA yielding less than <60 mcg/g creatinine Pb would not benefit from chelation therapy but >80 mcg/gm Pb post-provocation would benefit from chelation. This effect was applicable up to 600 mcg/gm creatinine Pb (PMID 22721929/ PMID 12540640)

2. The Centers for Disease Control and Prevention (CDC) recommends that the calcium disodium edetate ($CaNa_2EDTA$) challenge test be considered for children who have blood lead levels of 1.21-2.12 µmol/L (25-44 µg/dL) to determine whether chelation is indicated. This recommendation is historical and is no longer considered necessary for the initiation of chelation therapy, as blood levels alone are sufficient.

References for provocation specific dosages and implications

- DMSA

A Belgian study comparing occupational exposure to non-exposed group of adults given 1 gram of DMSA with a 4 hour urine collection proposed that any sample yielding over 22 mcg Pb (total) would be considered an excessive level of lead. (PMID: 16239340.)

Metal provocation testing

- CANNOT be used for diagnostic purposes
- “No randomized, controlled studies comparing use of a challenge test in subjects with ***metal poisoning*** to those *without metal poisoning”**
- Provocation is almost always a reflection of stored metal accumulation in the kidneys (lead, cadmium, mercury).

J Med Toxicol. 2013 Dec; 9(4): 298–300./ J Med Toxicol. 2013 Dec; 9(4): 318–325.

Children's Reactions to Lead (micrograms per deci-liter)

Blood Lead Level	Possible Health Effects
10 ug/dL	Slight loss in IQ; hearing and growth problems
20 ug/dL	Moderate loss in IQ; hyperactivity; poor attention span; difficulty learning; language and speech problems; slower reflexes
40 ug dL	Poor bone and muscle development; clumsiness; lack of coordination; early anemia; fewer red blood cells to carry oxygen and iron; tiredness; drowsiness
50 ug/dL	Stomach aches and cramps; anemia; destruction of red blood cells; brain damage
100 ug/dL & above	Swelling of the brain; seizures; coma; death

Not OK to chelate

OK to chelate

Adult Reactions to Lead (micrograms per deci-liter)

Blood Lead Level	Possible Health Effects
15 ug/dL	Increase in blood pressure; harmful effects on fetus; joint and muscle aches
25 ug/dL	Reproductive problems
40 ug/dL	Kidney damage; damage to blood formation
60 ug/dL	Anemia; nerve damage; constipation; stomach pains; irritability and fatigue; memory and concentration problems; clumsiness; drowsiness and sleep problems
80 ug/dL & above	Blue line on gums; uncontrollable shaking of hands; wrist and foot drop; hallucinations; brain damage; coma; death

Source: ATSDR; California Health Dept 1993

Not OK to chelate

OK to chelate

DMSA protocols

- Initial clinical studies with DMSA involved the administration of a 5-day course of treatment. Subsequently, a 19- to 26-day regimen was introduced with the intent of preventing or at least blunting a rebound in the blood lead concentration.
- Studies suggest, however, that repeated courses of DMSA 30 mg/kg/day for at least 5 days are equally efficacious if a treatment-free period of at least 1 week between courses is included to allow redistribution of lead from bone to soft tissues and blood. There is also evidence that in more severely poisoned patients DMSA 30 mg/kg/day can be given for more than 5 days with benefit.

Clin Toxicol (Phila). 2009 Aug;47(7):617-31. doi: 10.1080/15563650903174828.

Guidelines for Chelation

- “Chelation therapy during pregnancy or early infancy may be warranted in certain circumstances where the maternal or neonatal blood lead exceeds ≥45 µg/dL and in consultation with an expert in lead poisoning. Insufficient data exist regarding the advisability of chelation for pregnant women with BLL <45 µg/dL.

http://www.cdc.gov/nceh/lead/publications/leadandpregnancy2010.pdf

REMAINING QUESTIONS for oral agents

- Malabsorption of oral chelating agents will lead to false negative post-provocation testing results and insignificant drops in BLL on treatment- we need more data on pre and post provocation differences. Question insignificant rises in post-provocation challenges if pre-provocation levels are concerning.
- Anti-gliadin antibody positive adults show signs of DMSA malabsorption (pers observation)
- 67% of adults on PPIs have SIBO- do they malabsorb DMSA? Data is needed.
- Glutathione deficiency (acetominophen, alcohol) prevents metal excretion
- Urine acidity supports tubular reabsorption of metals (weak acid complexes with glutathione)
- There are no existing reference ranges for post-provocation urine assays.

EDTA

- Available as 2NaEDTA or Ca2NaEDTA since 1950s
- Disodium EDTA First published in 1956 (Clark et al) for use in angina, also used in PVD
- Ca2NaEDTA FDA approved for lead and other metals toxicity 2NaEDTA approved for hypercalcemia and ventricular arrhythmias associated with digitalis toxicity
- 2NaEDTA administered slowly and w magnesium to prevent hypocalcemia.
- Found to be safe in renal disease, if no more than 50mg/kg with 3 gr upper limit given at 16.6mg/min.

Cranton E. Textbook on EDTA Chelation Therapy 2nd Edition Hampton Roads Pub. 2001. pg. 345, 361.

EDTA- pharmacokinetics

- Non-metabolized excreted in urine unchanged
- 95% excreted within 24 hrs. the majority in 9 hrs
- Non-toxic- an equivalent of 45 grams for a 60 kg person to equate to animal toxicity dose.

PMID: 12396676

Edta Metal binding

Metal	Formation constant ($log_{10}K_1$)
Fe3+	25.10
Hg2+	21.70
Cu2+	18.80
Pb2+	18.04
Zn2+	16.50
Cd2+	16.40
Al3+	16.30
Fe2+	14.32
Ca2+	10.69
Mg2+	8.79
Na+	1.66

mercury binds tightly to sulfhydryl groups in proteins and does not bind to EDTA in vivo so this binding constant doesn't apply in chelation therapy

PMID: 10532851

EDTA in lead toxicity

- CaNa2EDTA is administered at a dose of 500 mg/m2 (pediatric) 50mg/kg (adult) at rate of 1 gm/hour.
- With high lead levels, at the end of each treatment cycle, the blood lead concentration usually declines.
- Within a few days, however, re-equilibration among body lead compartments takes place and may result in a rebound; thus, the blood lead level must be rechecked 7 to 21 days after treatment to determine whether retreatment is necessary.

QUESTIONS?

- info.emei.emcourses@gmail.com

FUNCTIONAL MEDICINE
Continuing Education

Take-Aways

1. Measuring metals in blood (lead, mercury) and urine (arsenic, cadmium, aluminum) is most useful if you use CDC database and ATSDR guidelines for interpreting results-

NOT lab reference range (unless they include NHANES data).

Take-Aways

2. High risk patients for metals exposure based on condition:

-cardiovascular disease

-DM II

-renal disease

-osteoporosis

-autoimmune thyroiditis

Take-Aways

3. Prioritize the cardinal rule of toxicology: AVOIDANCE

This necessitates understanding the patient's exposome:

-age of home (lead, chlordane), toxicants in drinking water (lead, arsenic), diet (fish, high fructose corn syrup), proximity to point sources (municipal waste cites, manufacturing, crematorium, airports)