Toxic Metals: Assessment and Detoxification

Dr. Joseph Pizzorno, ND
President Emeritus, Bastyr University
Editor, *Integrative Medicine: A Clinician's Journal*
Chair, Scientific Advisory Board, Bioclinic Naturals
President, SaluGenecists, Inc.

Dr. Joseph E. Pizzorno, N.D.

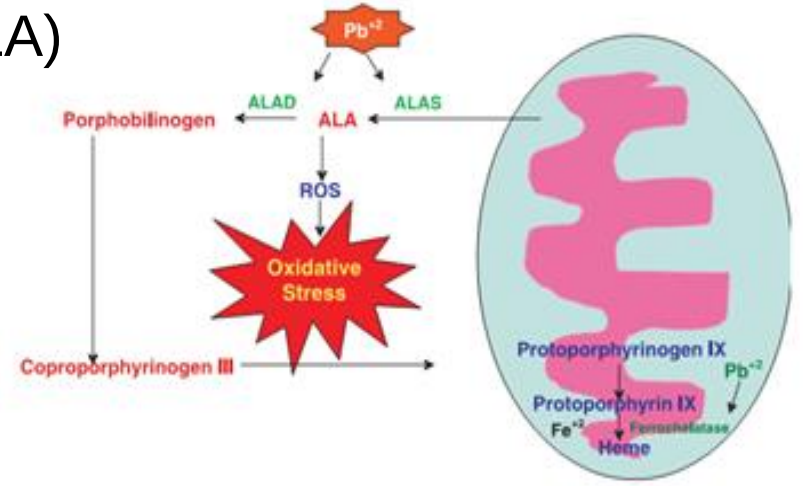
- **Academic**
  - Founding president (1978) of Bastyr University, first accredited, natural medicine university
  - Editor-in-Chief: *Integrative Medicine: A Clinician's Journal*
  - *Textbook of Natural Medicine*, 3nd ed. 2004; 4th edition now in process
- **Policy**
  - Member Medicare Coverage Advisory Committee, 2003-2005
  - Member White House Commission on CAM Policy, 2000-2002
- **Public**
  - *Encyclopedia of Natural Medicine*, 1998 (1,000,000 copies in six languages)
  - *Encyclopedia of Healing Foods*, 2005
- **Example Awards and Recognitions**
  - Juror for Roger's Prize – 2009, 2011
  - Institute for Functional Medicine – Linus Pauling Award, 2004
  - American Holistic Medical Association: *Pioneer in Holistic Medicine*, 2003
  - *Natural Health Magazine*: *Leading health educator in the past 30 years*. 2001
  - Alternative Healthcare Management: *1 of the 4 most influential CAM leaders*, 2000
  - *Seattle Magazine*: *1 of the top 20 national intellectual leaders from Seattle*, 1996

Overview

- Prevalence and Sources of Exposure
  - Lead, mercury, arsenic, and cadmium
- Toxicity/Clinical Relevance
- Assessment
- Intervention

Heavy Metals

- Lead, mercury, arsenic, and cadmium among most toxic and prevalent
- Multiple & overlapping mechanisms of toxicity
  - Increase free radical production
  - Poison enzymes (i.e. lead and ALA)
  - Direct DNA damage
  - Endocrine disruption
  - Mitochondrial or cell wall damage



Flora 2008

Flora SJ Heavy metal induced oxidative stress & its reversal by chelation therapy. Indian J Med Res. 2008

Lead Prevalence

- No threshold for safety –
  - Children who had whole blood lead concentrations of <5 µg/dL (but > zero) associated with decreased IQ
  - 2.4 million children at levels between 5 and 9. ug/dL
  - NHANES III: In 1999-2002, 91.7% of children in US had detectable levels of lead in the blood
  - July 2012: CDC changed recommended level to intervene in children from 10 ug/dL to 5.. Also eliminated term “level of concern”, to avoid giving false sense of safety

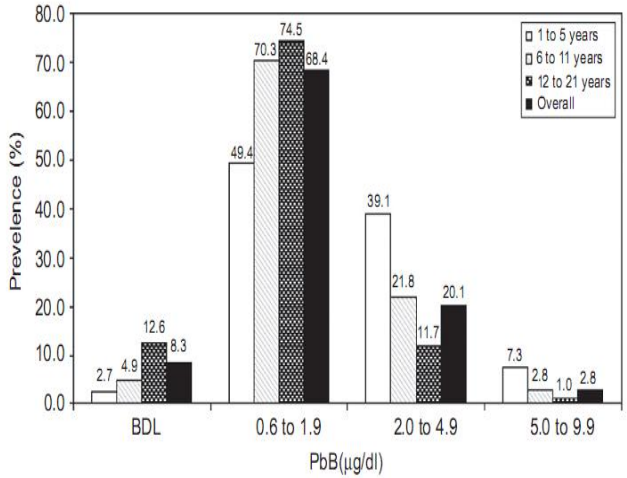


Fig. 1. Blood lead levels below 10 µg/dl among 1–21 years old US population 1999–2002.

Iqbal 2008

Iqbal S, et al. Estimated burden of blood lead levels 5 microg/dl in 1999-2002 and declines from 1988 to 1994. Environ Res. 2008
http://www.cdc.gov/nceh/lead/acclpp/cdc_response_lead_exposure_recs.pdf

Lead in Adults

- 100% of Canadian population had detectable blood lead in national study
- Even among adults, a BLL of 5-9 ug/dL has been associated with an increased risk of death from all causes, cardiovascular disease, and cancer

Bushnik T, et al. Lead and bisphenol A concentrations in the Canadian population. Health Rep. 2010 Sep;21(3):7-18.
Schober SE, Mirel LB, Graubard BI, et al. Blood lead levels and death from all causes, cardiovascular disease, and cancer: results from the NHANES III mortality study. Environ Health Perspect. 2006 Oct;114(10):1538-41.

Mercury

- Children born to women with blood mercury >5.8 ppb have a "higher risk of adverse health effects."
  - 8% of women of child-bearing age tested had "at least" that level of Hg
  - >300,000 born every year in US at increased risk due to mercury toxicity
- Women may have levels 7x higher if frequent consumption of fish/shellfish

Schober SE, et al. Blood mercury levels in US children and women of childbearing age, 1999-2000. JAMA. 2003
Mahaffey KR,et al. Blood organic mercury and dietary mercury intake: National Health and Nutrition Examination Survey, 1999 and 2000. Environ Health Perspect. 2004

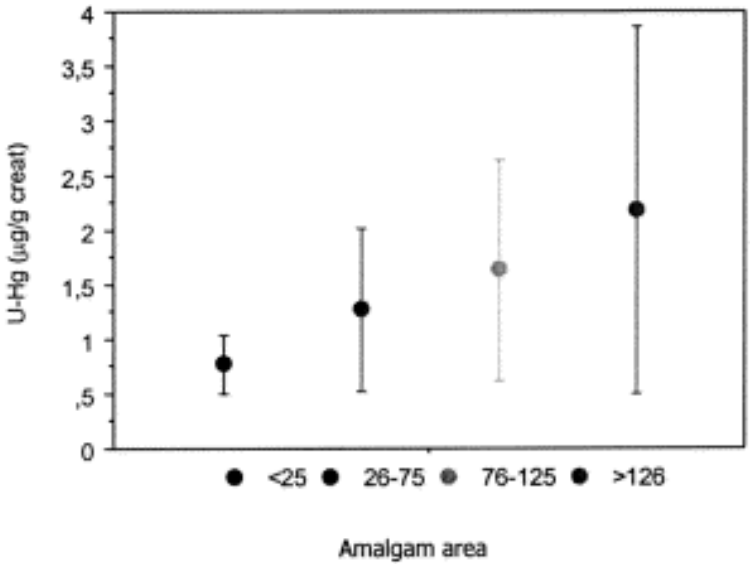
Sources of Mercury

- Average exposure in non-industrial populations
  - Amalgams: 10 ug/d
  - Fish: 2.3 ug/d
  - Water: 0.3 ug/d
  - Air
  - Vaccinations
- Industrial

Vimy, M.J., and Lorscheider, F.L (1990) Dental amalgam mercury daily dose estimated from intra-oral vapor measurements: A predictor of mercury accumulation in human tissues.]. Trace Elem. Exp. Med 3, 111-123

Amalgams

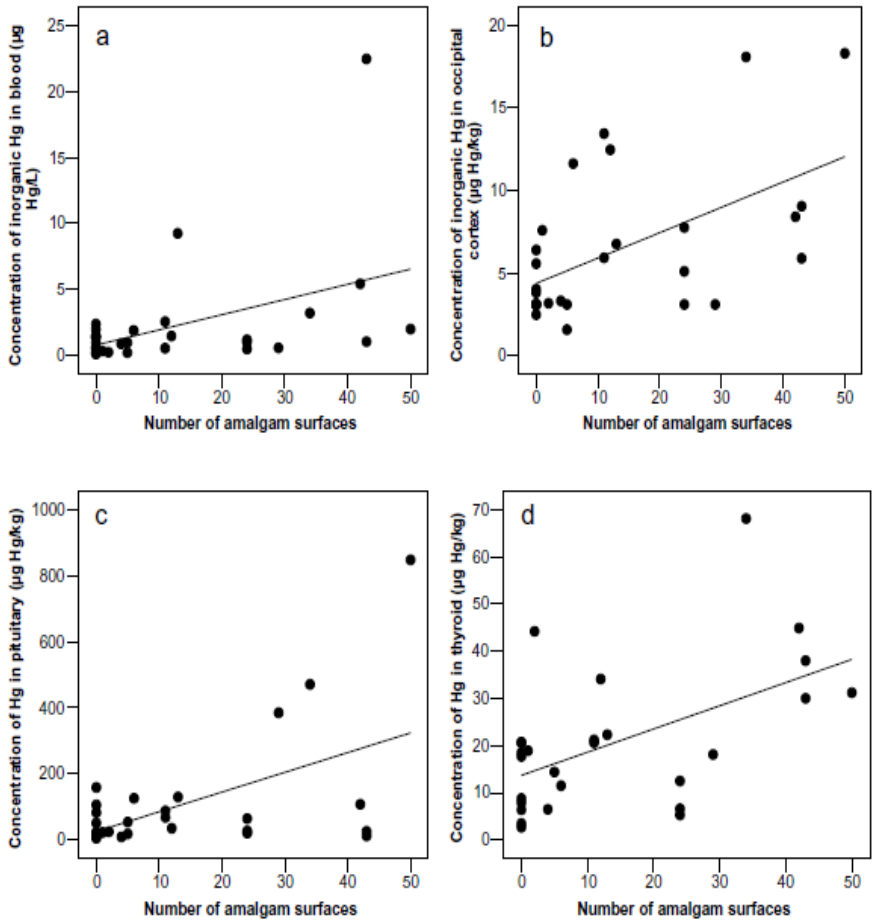
- Typical amalgam is 55% Hg
  - = 400 mg/filling
- Release 10 ug/d
- Hg excretion proportional to surface area (poorer correlation with count)
- Release elemental Hg which is methylated by bacteria in gut and absorbed



Lorscheider FL, Vimy MJ, Summer O. Mercury exposure from “silver” tooth fillings: emerging evidence questions a traditional dental paradigm. FASEBJ. 9,504-508(1995)
Apostoli P, ICortesi I, Mangili A, et al. Assessment of reference values for mercury in urine: the results of an Italian polycentric study. The Science of the Total Environment 289 (2002)13-24

What Autopsies Tell Us

- Mercury accumulates in the brain in proportion to surface area
- Study of 18 cadavers
  - Hg in brain, thyroid and kidneys proportional to the number of amalgam surfaces
  - For those with more than 12, Hg in brain disproportionately higher
  - Suggests that at higher levels of exposure the brain's mercury excretion pathways become overloaded.



J.W. Reinhardt. Side-Effects: Mercury Contribution to Body Burden From Dental Amalgam. Adv. Dent. Res. 1992; 6; 110

Guzzi G, et al. Dental amalgam and mercury levels in autopsy tissues. Am J Forensic Med Pathol. 2006 Mar;27(1):42-5

What Live Tissues Tell Us

- Donated kidneys for transplant
- R = 0.62 correlation with number of amalgam surfaces
- 6% increase in kidney Hg per amalgam surface

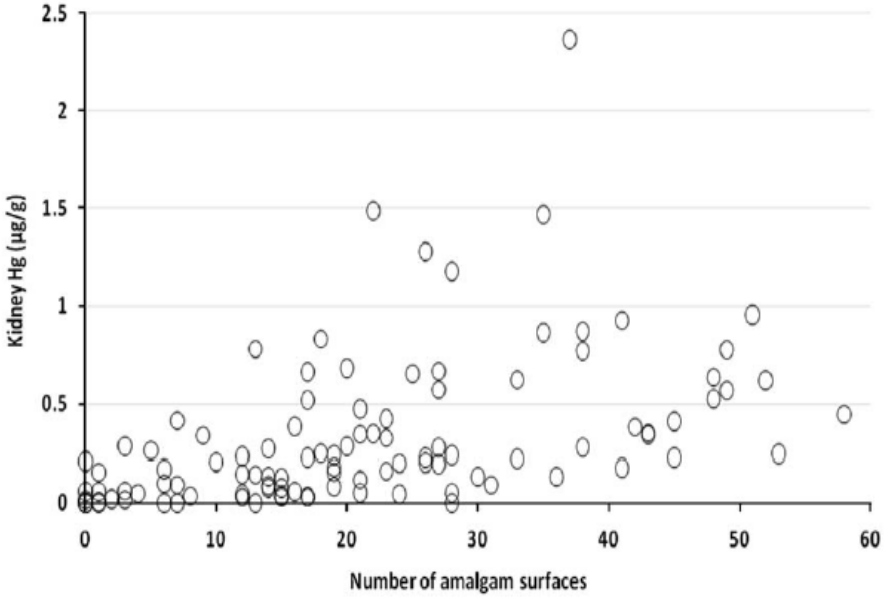


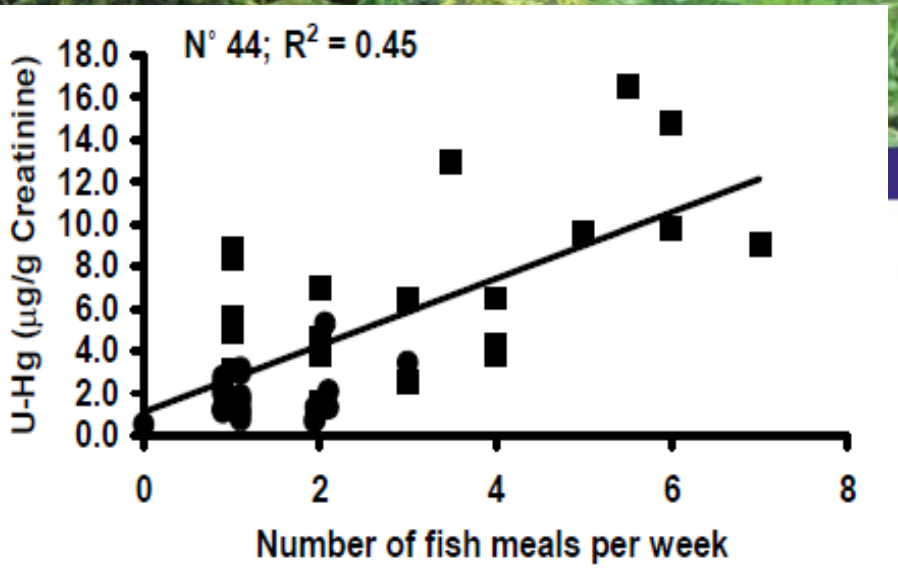
Fig. 3. Kidney mercury levels (µg/g wet weight) in living kidney donors vs. number of amalgam surfaces.

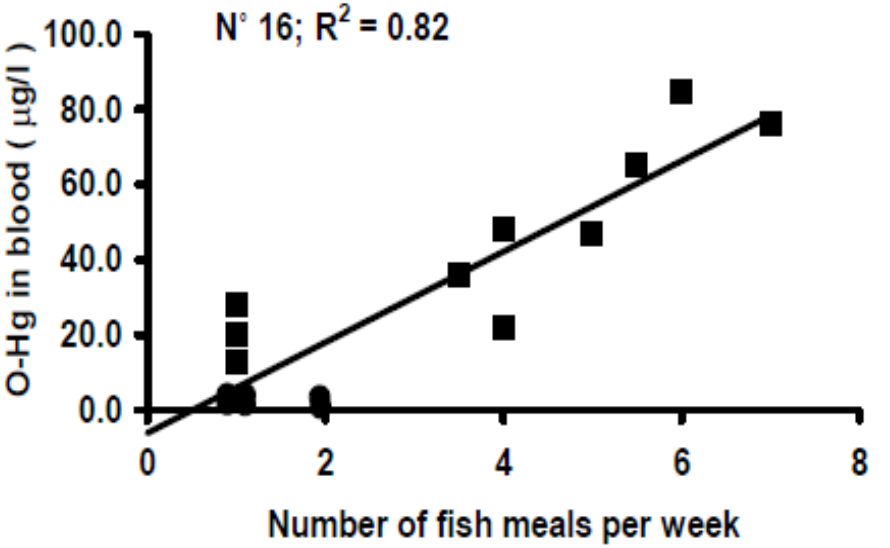
Barregard 2010

Barregard L, et al. Cadmium, mercury, and lead in kidney cortex of living kidney donors: Impact of different exposure sources. Environ Res. 2010 Jan;110(1):47-54

Hg From Fish

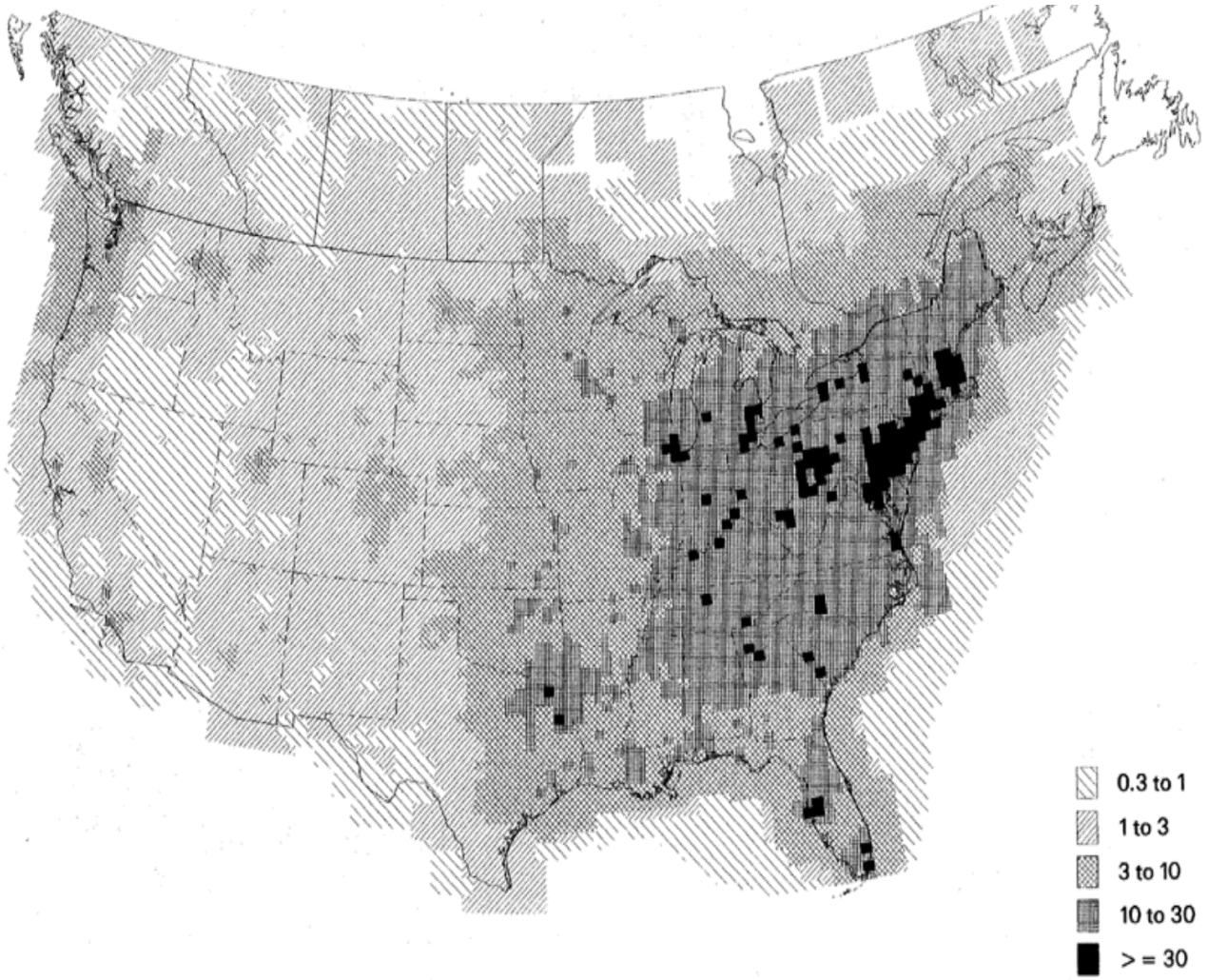
- Total Hg urinary excretion proportional to amount of fish eaten
- Impaired psychomotor performance
  - R = 0.38 blood
  - R = 0.77 urine





Apostoli P, ICortesi I, Mangili A, et al. Assessment of reference values for mercury in urine: the results of an Italian polycentric study. The Science of the Total Environment 289 (2002)13-24
Carta P, et al. Sub-clinical neurobehavioral abnormalities associated with low level of mercury exposure through fish consumption. NeuroToxicology 24 (2003) 617–623

Mercury in the Air



Hg Concentrates in Fetus

- Both MeHg and elemental Hg
- MeHg 100% higher in cord blood
- Cord blood Hg correlates with # of maternal amalgams, r = 0.46
- Fetal brain 40% higher than maternal brain AND more sensitive to damage

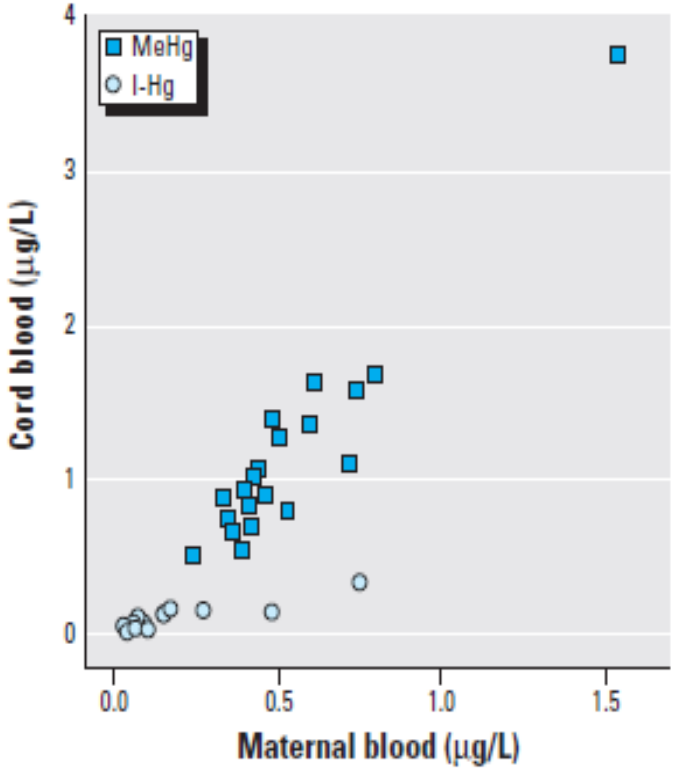


Figure 2. The associations between concentrations in cord blood and maternal blood for MeHg ($r = 0.95$; $p < 0.001$) and I-Hg ($r_S = 0.77$; $p < 0.001$).

Björnberg 2005

Palkovicova L, et al. Maternal amalgam dental fillings as the source of mercury exposure in developing fetus and newborn. J Expo Sci Environ Epidemiol. 2008 May;18(3):326-31

Björnberg KA, et al. Transport of methylmercury and inorganic mercury to the fetus and breast-fed infant. Environ Health Perspect. 2005 Oct;113(10):1381-5

Mercury Distribution In the Body

- Except immediately after exposure, mercury in the tissues is at a higher concentration than in the blood.
- Methyl mercury easily crosses blood-brain-barrier
- Typical issue distribution ratios:
  - Blood = 1 (~5% of body burden)
  - Brain = 2-13
  - Liver = 5
  - Kidney = 33
  - Bone = 100
- Most is bound to sulfur compounds

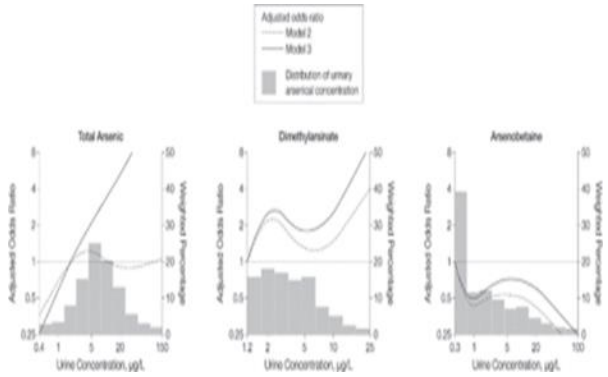
Arsenic Exposure

- Arsenic – main exposure through diet & water
- 13 million in US exposed to public water which exceeds EPA limit of 10ug/L
- Seafood, rice, mushrooms and poultry are main food sources, with seafood primarily arsenobetaine (organic form, considered less toxic)
  - Organic rice recently found to be risk for inorganic exposure
- Inorganic considered much more toxic than organic
- Toxic to the majority of organ systems, the most sensitive target organs being the kidney & liver

Jomova K, et al. Arsenic: toxicity, oxidative stress and human disease. J Appl Toxicol. 2011 Mar;31(2):95-107.
Holtcamp W 2012. Suspect Sweetener: Arsenic Detected in Organic Brown Rice Syrup. Environ Health Perspect 120:a204-a204.

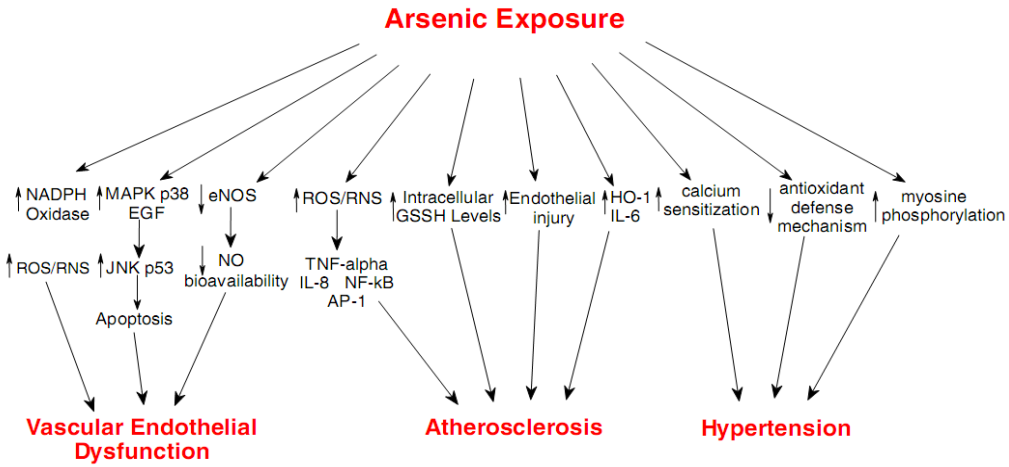
Arsenic Clinical Consequences

- Inorganic organic associated with risk for diabetes, with no obvious threshold for safety



Navas-Acien 2008

- Arsenic linked to increased CVD, cancer, dermal disease, and gastrointestinal disease



Jomova 2011

Navas-Acien A, et al. Arsenic exposure and prevalence of type 2 diabetes in US adults. JAMA. 2008
Jomova K, et al. Arsenic: toxicity, oxidative stress and human disease. J Appl Toxicol. 2011 Mar;31(2):95-107.

Arsenic – High exposure

- Bangladesh
  - Nearly 12,000 men and women
  - Dose-response between arsenic in well-water and mortality from ischemic heart disease and other heart disease
  - Synergistic effect with smoking on heart disease

Chen Y, et al. Arsenic exposure from drinking water and mortality from cardiovascular disease in Bangladesh: prospective cohort study. BMJ. 2011 May 5;342:d2431.

Arsenic and Cancer

- Associated with multiple cancer types
  - Population with low/moderate exposure
    - ~3-5 fold risk for lung cancer (small cell & sqaumous carcinoma) in those with higher levels of toenail arsenic
  - Also evidence for bladder, renal, and liver cancer
- Trivalent arsenicals appear to be much more toxic than pentavalent
  - Detoxification routes not only methylate arsenic, but in the process create trivalent forms – potential problem

Heck JE, et al. Lung cancer in a U.S. population with low to moderate arsenic exposure. Environ Health Perspect. 2009 Nov;117(11):1718-23.

Cadmium

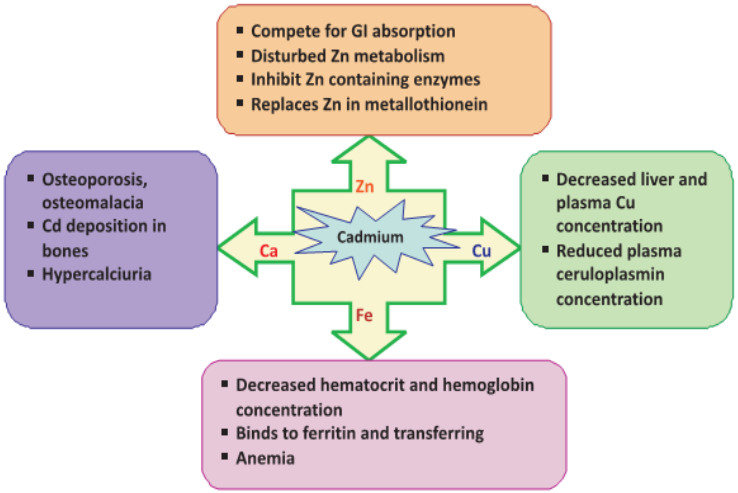
- 73% of U.S. women age 50+ have levels of cadmium > 0.50 ug/g creatinine, a level associated with increased risk for osteoporosis (43% greater if 0.5-1.0 than if <0.50)
- Same data found that dietary cadmium (not cadmium from smoking) is the source of Cd related osteoporosis
- Recent analysis by Fred Hutchinson found tofu/soy to be greatest dietary source among premenopausal women
- Crustaceans, mollusks and cephalopods also considered to be high sources

Gallagher CM, et al. Urinary cadmium and osteoporosis in U.S. Women >or= 50 years of age: NHANES 1988-1994 and 1999-2004. Environ Health Perspect. 2008

Adams SV, et al. Sources of cadmium exposure among healthy premenopausal women. Sci Total Environ. 2011 Apr 1;409(9):1632-7.

Cadmium and MI

- Same level of cadmium exposure which increases osteoporosis risk also increases MI risk 80% (in women only)

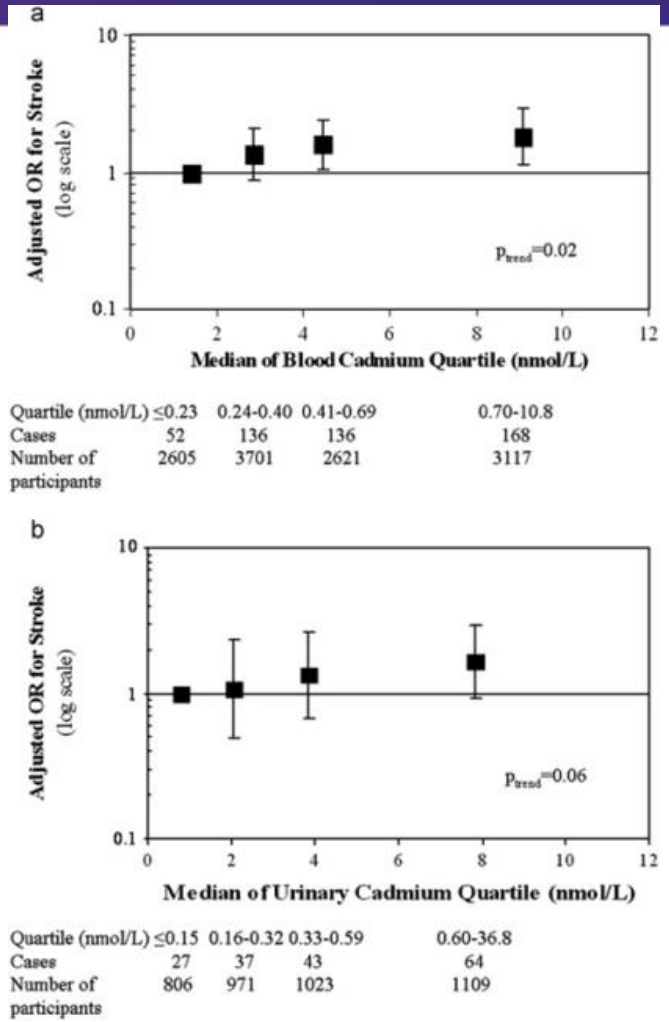


Flora 2008

Everett CJ, et al. Association of urinary cadmium and myocardial infarction. Environ Res. 2008 Feb;106(2):284-6.

Cadmium and CVD

- Higher blood & urinary cadmium recently linked to a higher stroke & heart failure prevalence
  - A 50% increase in blood cadmium was associated with a 35% increase in stroke prevalence and a 48% increase in HF prevalence
  - A 50% increase in urinary cadmium was associated with a 9% and 12% increase in prevalent stroke and HF

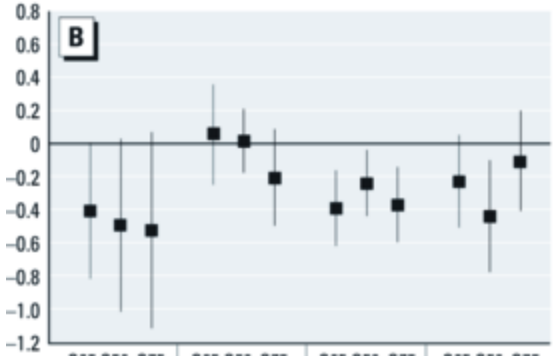


Peters 2010

Peters JL, et al. Cadmium exposure in association with history of stroke and heart failure. Environ Res. 2010 Feb;110(2):199-206.

Cadmium and Fetal Development

- Prospective study with large sample size
- Inverse association between maternal Cd exposure during pregnancy and infant size at birth
- Especially head circumference and birth weight
- Effect limited to girls



Kippler 2012

Kippler M, et al. Maternal cadmium exposure during pregnancy and size at birth: a prospective cohort study. Environ Health Perspect. 2012 Feb;120(2):284-9.

Toxin Synergy

- Effects of low-levels of multiple chemicals unknown
- Synergism between toxins often greater than additive effects
  - Parkinson's disease – synergistic effect of metals and pesticides. "the total brain load of pesticides and metals, rather than individual levels, is a very important contributor to the potential effect on α-synuclein fibrillation"

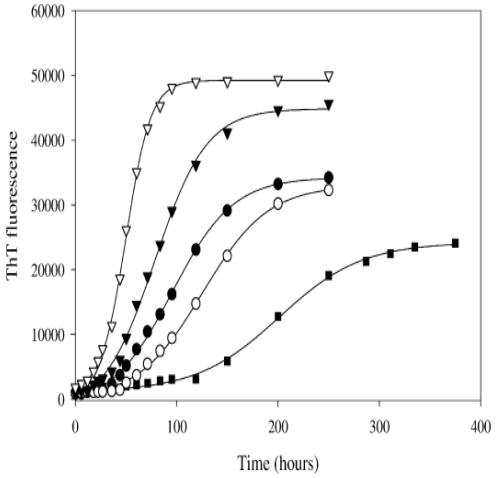


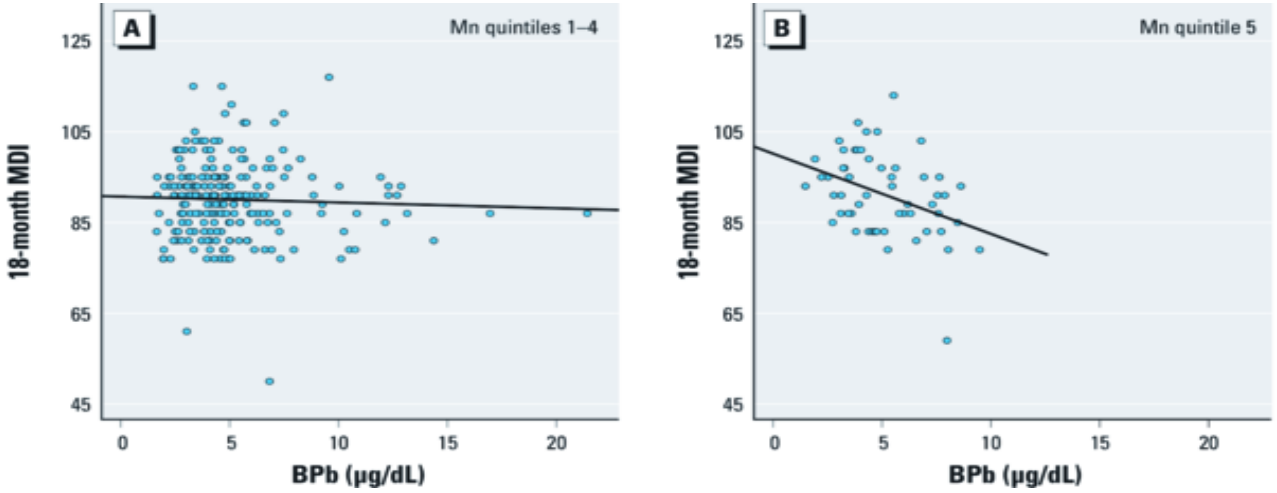
Fig. 5. Synergistic interactions between pesticide and metal in the stimulation of α-synuclein fibril formation. The kinetics of fibril formation were monitored as in the legend to Fig. 1. α-Synuclein (28 μM) alone (■); with 100 μM DDC (○); with 4 mM $AlCl_3$ (●); with DDC (100 μM) and $AlCl_3$ (4 mM) added in that order (▼); and with $AlCl_3$ (4 mM) and DDC (100 μM) added in that order (▽).

Uversky 2002

Uversky VN Synergistic effects of pesticides and metals on the fibrillation of alpha-synuclein: implications for Parkinson's disease. Neurotoxicology. 2002

Metal Synergy

- Prospective study in children (n=455)
- Evaluated effect of manganese & lead on mental and psychomotor development
- Greater harm of Pb with high Mn exposure than Pb alone
- Synergism highlights risk of mixed exposures



Claus Henn B, et al. Associations of early childhood manganese and lead coexposure with neurodevelopment. Environ Health Perspect. 2012 Jan;120(1):126-31.

Multiple toxins– e.g. NAFLD

- ALT (proxy marker) elevation in 10.4% (not including viral hepatitis, hemochromatosis, or alcoholic liver disease) of NHANES 03-04 subset
- Risk of elevated ALT increased dose-dependently with lead, mercury, *and* PCB exposure
- 100% of individuals had detectable PCBs, 92.5% mercury, and 99.6% had detectable lead
- In 2005-08, prevalence of NAFLD in US was 11%, a growing cause of chronic liver disease.

Cave M, et al. Polychlorinated biphenyls, lead, and mercury are associated with liver disease in American adults: NHANES 2003-2004. Environ Health Perspect. 2010 Dec;118(12):1735-42.
Younossi ZM et al. Changes in the prevalence of the most common causes of chronic liver diseases in the United States from 1988 to 2008. Clin Gastroenterol Hepatol. 2011 Jun;9(6):524-530.e1;

Assessment

- Both clinical and laboratory
- Often no gold standard for testing
- Must differentiate between acute exposure and body load
- Serum, whole blood, hair, urine, feces, nails, and adipose
- In general, serum levels represent acute exposure,
  - E.g. Lead, mercury - blood levels and urine (Hg) represent acute exposure, not chronic or body burden
- Testing reveals exposure, not necessarily toxicity

DeVito MJ, Comparisons of estimated human body burdens of dioxinlike chemicals and TCDD body burdens in experimentally exposed animals. Environ Health Perspect. 1995
Rooney JP. The role of thiols, dithiols, nutritional factors and interacting ligands in the toxicology of mercury. Toxicology. 2007

Sample Questions for Heavy Metal Exposure

1. Has the patient knowingly been exposed to metals?
2. What is patient's occupation (dentist, welder, ship builder, etc.)?
3. How frequently does the patient eat tuna, swordfish or shark?
4. Does the patient have mercury amalgam fillings?
5. If the patient is taking any dietary supplements, do they have certificates of analysis that they are free of contaminants?
6. Is the patient taking any Ayurvedic or traditional Chinese medicine dietary supplements?
7. Do patients experience a metallic taste in their mouth *and* have not recently been taking medications documented to cause metallic taste?
8. Do the patient have a history of smoking (particularly high in cadmium)?

Neustadt J, Pieczenik S. Mercury—an example of heavy metal toxicity. IMCJ 2007;6:1

Heavy Metal Signs and Symptoms

Behavioural changes
Cognitive changes
Depression
Fatigue
Headache
Learning deficits
Memory loss
Irritability
Tremor

Alzheimer's disease
Anemia
Cancer
Chronic renal failure
Gingivitis
Gout
Hypertension
Hyperuricemia
Male infertility
Multiple sclerosis
Osteodystrophies

From Peter Bennet, ND: IM Conference Miami 2004

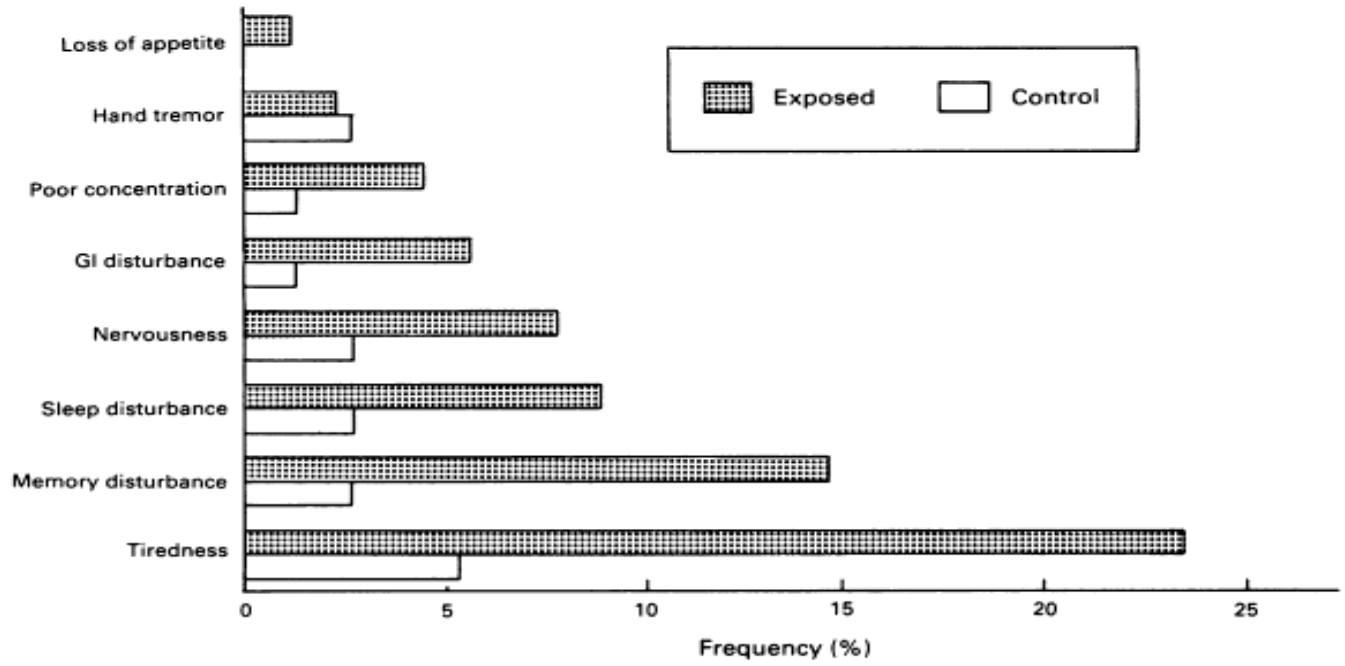
Laboratory Evaluation of Heavy Metals

- Blood and urine typically represent acute exposure
  - Lead
    - Blood levels widely accepted to represent acute exposure, but bone lead (chronic exposure) better predictor of disease
    - Prospective trial of ~1000 men found bone lead to be associated with all cause (HR 2.52) and cardiovascular mortality (HR 5.63) in a population with low blood lead levels
  - Mercury
    - Metallic mercury has a short ½ life, thus 24-hour urine preferred unless testing within 3 days of exposure (for blood)
    - Ethyl/methyl mercury – whole blood is primary indicator of exposure
    - **No gold standard**

Weisskopf MG, A prospective study of bone lead concentration and death from all causes, cardiovascular diseases, and cancer in the Department of Veterans Affairs Normative Aging Study. Circulation. 2009
Risher et al. Mercury exposure: evaluation and intervention the inappropriate use of chelating agents in the diagnosis and treatment of putative mercury poisoning, *Neurotoxicology* 2005

Mercury Neurological Symptoms

Effects of occupational exposure to mercury vapour on the central nervous system 549



S Langworth, O Almkvist, E Söderman, and B O Wikström. Effects of occupational exposure to mercury vapour on the central nervous system. Br J Ind Med. 1992 August; 49(8): 545–555

Most common Symptoms of Hg

Symptom	Frequency
Depression	73%
Memory loss	70%
Anxiety	69%
Unintentionally dropping things	60%
Headache	56%
Moody	45%
Shakiness in hands	44%
Stomach problems	43%
Fatigue	39%
Confusion	35%
Change in sense smell or taste	29%
Parasthesia	26%
Sleep disturbance	25%
Coordination problems	20%
Muscle weakness	16%

Pizzorno J. The mercury epidemic. IMCJ 2009; 8:1

Mercury - No Gold Standard For Body Load

- Poor correlation between the measures
- Huge inter-person and inter-test variations
- Best measure of Hg from fish is whole blood/plasma methyl mercury/hair (only excretes organic)
- Best measure of mercury from amalgams is whole blood/plasma inorganic mercury and urinary inorganic Hg.

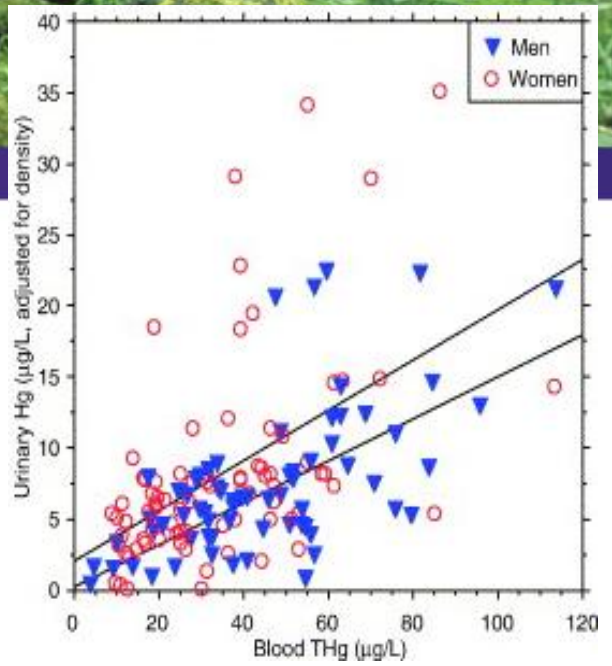
Table 4: The Spearman correlation coefficients between mercury species in different media and exposure vavariables. Spearman correlation coefficients of inorganic mercury (IHg) and organic mercury (OHg) species in whole blood (B; μg/L), red blood cells (RBC; μg/L), plasma (P; μg/L) and urine (U: μg/L, adjusted to density 1.019) and IHg, OHg and total mercury (THg) in hair (H; mg/kg) and the exposure variables fish consumption (number of meals per month) and number of dental amalgam fillings. The number of samples are 25–28. The significance level is indicated as * $p < 0.05$; ** $p < 0.01$; *** $p < 0.001$.

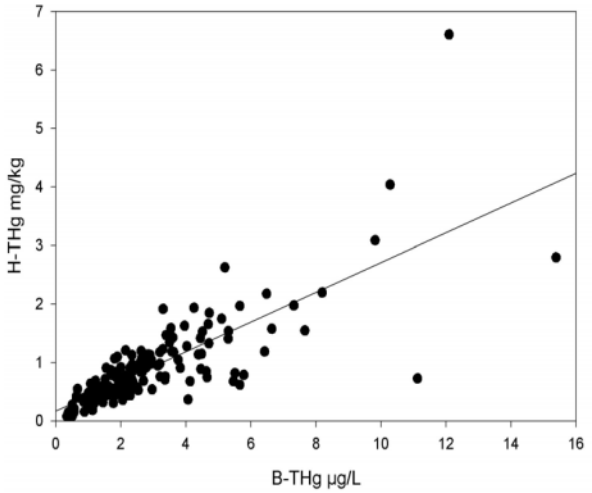
	B-OHg	RBC-IHg	RBC-OHg	P-IHg	P-OHg	H-THg	H-IHg	H-OHg	U-IHg	U-OHg	Fish	Amalgam
B-IHg	0.19	0.83 ***	0.25	0.91 ***	0.05	0.28	0.29	0.27	0.81 ***	-0.11	0.07	0.48 *
B-OHg		0.38	0.96 ***	0.07	0.82 ***	0.87 ***	0.79 ***	0.87 ***	-0.07	0.27	0.82 ***	0.09
RBC-IHg			0.45 *	0.70 ***	0.34	0.46 *	0.42 *	0.43 *	0.73 ***	0.04	0.37	0.27
RBC-OHg				0.13	0.77 ***	0.82 ***	0.81 ***	0.81 ***	0.03	0.22	0.76 ***	0.14
P-IHg					-0.13	0.16	0.16	0.14	0.74 ***	-0.14	-0.04	0.49 *
P-OHg						0.77 ***	0.74 ***	0.75 ***	-0.003	0.29	0.82 ***	0.06
H-THg							0.86 ***	0.99 ***	0.18	0.32	0.75 ***	0.28
H-IHg								0.83 ***	0.28	0.28	0.63 ***	0.32
H-OHg									0.17	0.31	0.74 ***	0.30
U-IHg										0.05	-0.03	0.49 **
U-OHg											0.24	-0.007
Fish												0.13

Berglund M, et al. Inter-individual variations of human mercury exposure biomarkers: a cross-sectional assessment. Environ Health. 2005 Oct 3;4:20

Poor Hg Inter-Test Correlation

- Poor correlation between blood and urine , r = 0.30
- Better correlation between blood and hair, r = 0.56





Zimmera H, et al. Determination of mercury in blood, urine and saliva for the biological monitoring of an exposure from amalgam fillings in a group with self-reported adverse health effects. Int. J. Hyg. Environ. Health 2002;205(3):205-211
Berglund M, et al. Inter-individual variations of human mercury exposure biomarkers: a cross-sectional assessment. Environ Health. 2005 Oct 3;4:20

Evaluation of Mercury Exposure

- Hair Hg >5 ppm indicative of toxicity
  - However, poor detoxifiers will have false negative
  - Not good estimate of inorganic mercury, better for methylmercury
  - Decrease in IQ of 0.18 points/ppm increase in maternal hair Hg
- Fecal Hg
  - 80-90% of Hg is excreted via bile (enterohepatic recirculation)
  - Fecal Hg correlates with # amalgams
  - No pharmaceutical provocation agent required
- Urine
  - Unprovoked urine has reference range established for US population, represents acute exposure
  - Provoked (DMPS) urine probably better measure of body load

Katz SA, et al. Use of hair analysis for evaluating mercury intoxication of the human body: a review. J Appl Toxicol. 1992

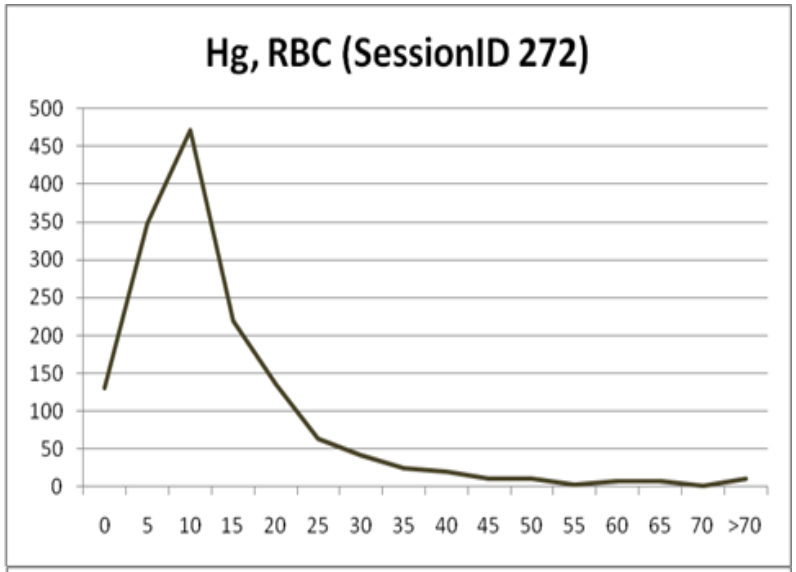
Axelrad DA, et al. Dose-response relationship of prenatal mercury exposure and IQ: an integrative analysis of epidemiologic data. Environ Health Perspect. 2007

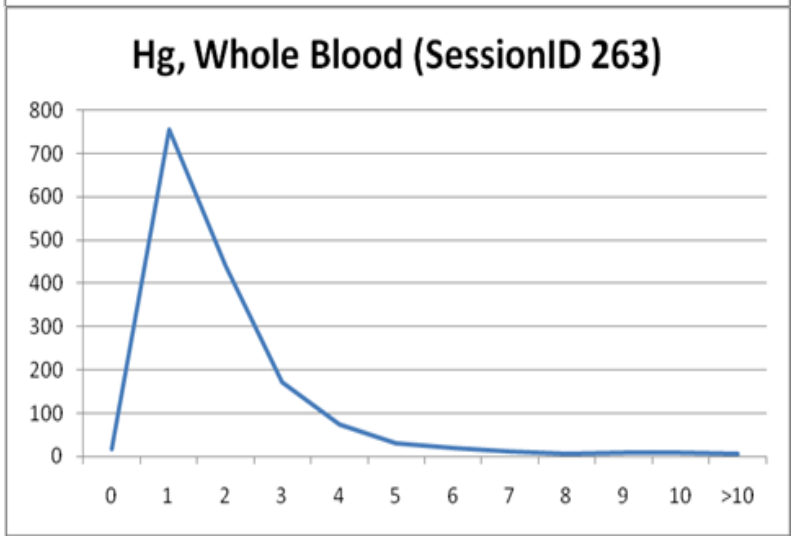
Marques RC, Dórea JG, Fonseca MF, et al. Hair mercury in breast-fed infants exposed to thimerosal-preserved vaccines. Eur J Pediatr. 2007

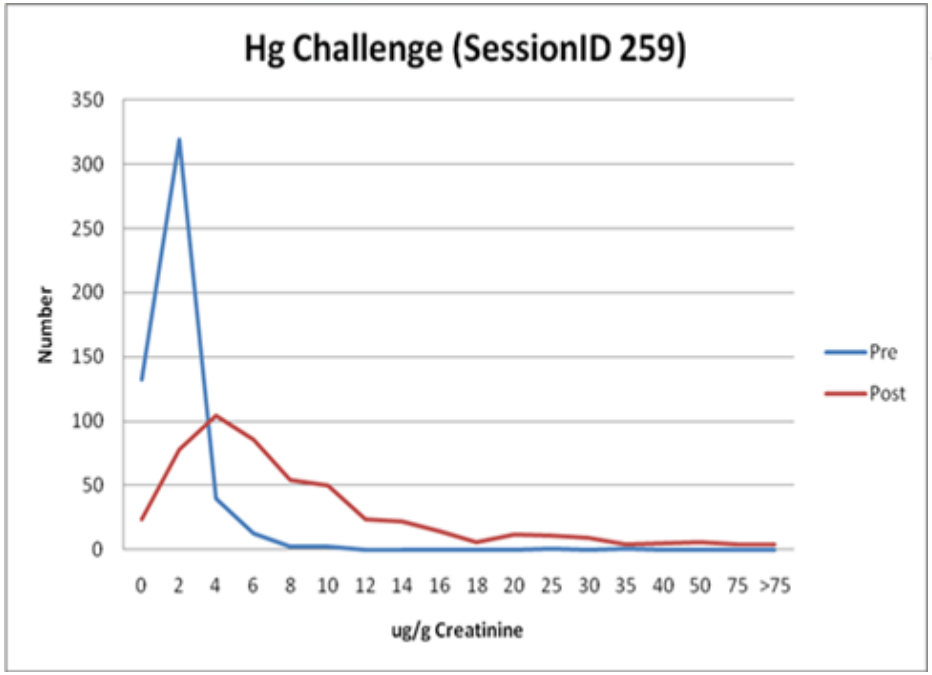
Berglund M, Lind B, Björnberg KA, et al. Inter-individual variations of human mercury exposure biomarkers: a cross-sectional assessment. Environ Health. 2005

Risher JF, De Rosa CT. Inorganic: the other mercury. J Environ Health. 2007

What We Found In Canada



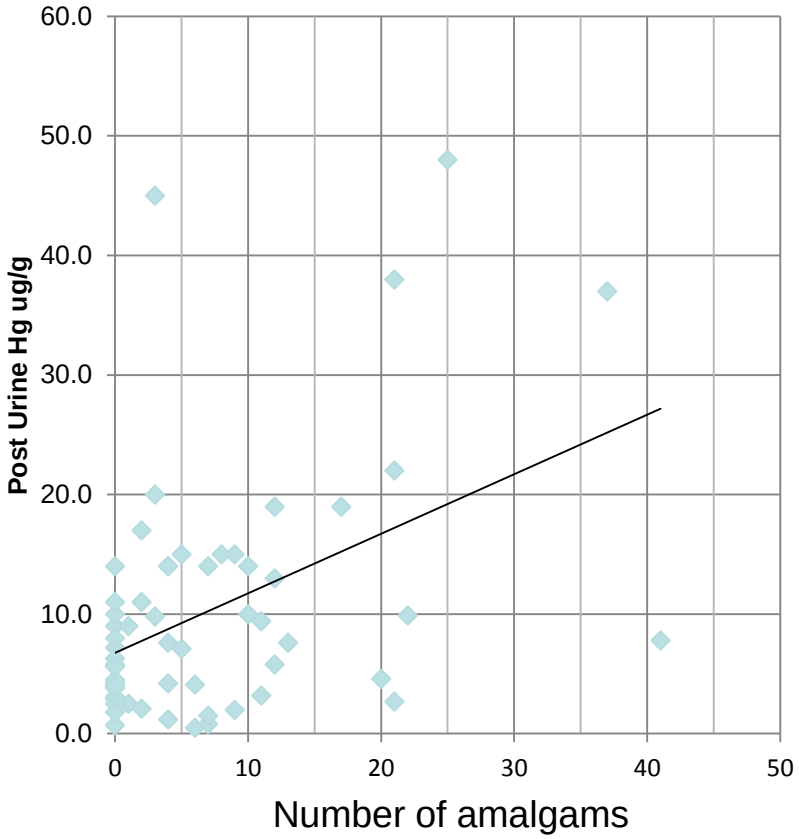




- Deviations from the mean of 14%, 29% and 91% respectively
- DMPS is spreading distribution, suggesting that it is better at differentiating mercury body load
- Some VERY high

Assessment Correlations

- Extensive measurements in 65
  - Whole blood Hg
  - Oral DMPS challenge
  - Amalgam surfaces
- Correlations
  - Whole blood w pre urine: r = 0.40
  - Whole blood w post urine: r = 0.57
  - Pre urine w post urine: r = 0.68
  - Amalgams w pre urine: r = 0.26
  - Amalgams w whole blood: r = 0.36
  - Amalgams with post urine: 0.44
- Clear documentation that challenge testing is better



Lead Assessment - Blood Lead Levels?

- Lead in blood has a half-life of approximately 30 days, indicating recent exposure
- Vast majority of lead is stored in bone, and is a better indicator of cumulative exposure, i.e. chronic toxicity. ½ life is 5-19 years.
- Bone lead stronger predictor than blood levels for hypertension, ECG disturbances, pulse pressure, renal function, cognition, and cataracts. Should replace blood levels as more relevant biomarker

Weisskopf MG, et al. A prospective study of bone lead concentration and death from all causes, cardiovascular diseases, and cancer in the Department of Veterans Affairs Normative Aging Study. Circulation. 2009 Sep 22;120(12):1056-64.

Lead Assessment

- Blood levels limited to acute toxicity, but symptoms are related to degree of elevation

Gracia 2007, 17189579

Level of Toxicity	Blood Lead Concentration (μg/dL)	Clinical Presentation[a]	
		Children	Adults
Asymptomatic or impaired abilities	<10	Decreased learning and memory, decreased verbal ability, impaired fine motor coordination, signs of ADHD or hyperactivity, lower IQ, impaired speech and hearing	. . .[b]
Mild	10–39	Myalgia or parasthesia, irritability, mild fatigue/lethargy, occasional abdominal discomfort	. . .
Moderate	>40–50	Arthralgia, difficulty concentrating, general fatigue, headache, muscular exhaustibility, tremor, weight loss, vomiting, constipation, diffuse abdominal pain	Fatigue, somnolence, moodiness, lessened leisure interest, impaired psychometrics, chronic hypertensive effects, reproductive effects
Severe	>70–80	Lead lines (blueish black appearance on gingival tissue), colic (intermittent, severe cramps), parasthesia or paralysis, encephalopathy	Headache, memory loss, decreased libido, insomnia, metallic taste, abdominal pain, constipation, myalgia/arthralgia, nephropathy
Severe, acute	>100–150	Encephalopathy, seizures, anemia, nephropathy	Encephalopathy, various CNS effects, anemia, nephropathy

Provoked Urine for Chronic Lead

- Superior to blood for chronic exposure - more than 90% of body lead stored in bones, not detected in blood
- Provoked lead reflects toxicologically active fraction of the total lead body burden
- In individuals with previous lead exposure but low recent exposure, blood lead may be only slightly increased whereas the mobilizable pool is significantly increased
- DMSA 4hr found to be highly correlated to 24hr urine collection

Hoet P, Clinical evaluation of a lead mobilization test using the chelating agent dimercaptosuccinic acid. Clin Chem. 2006

Cadmium

- Blood cadmium - a marker of current exposure but may also reflect body burden from long-term retention of cadmium in the liver and kidney
  - Assessed as whole blood
- Urinary cadmium is thought to more specifically be a marker of cumulative exposure

Järup L, Akesson A. et al. Current status of cadmium as an environmental health problem. Toxicol Appl Pharmacol. 2009 Aug 1;238(3):201-8.

Cadmium - Urinary

- Urinary cadmium is mainly influenced by the body burden of cadmium and is proportional to the concentration in the kidney
- Cadmium is efficiently retained mainly in the kidney with a biological half-time of around 10–30 years
- Cd excretion in 24-h urine
- 0.5 µg Cd /g creatinine or greater may be reasonable cut-off

Järup L, Akesson A. et al. Current status of cadmium as an environmental health problem. Toxicol Appl Pharmacol. 2009 Aug 1;238(3):201-8.

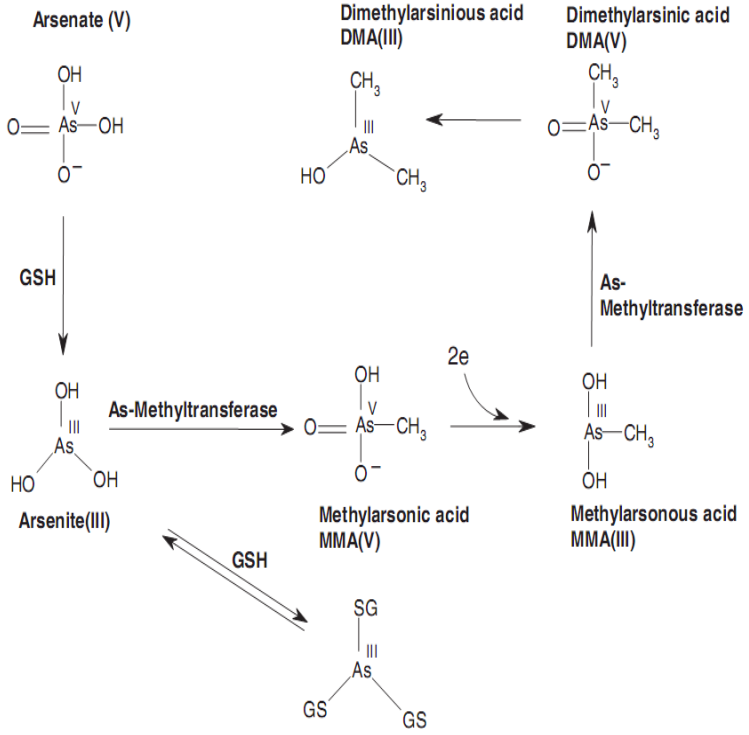
Arsenic Evaluation

- Blood level of arsenic is not a good marker for long term exposure
- Additionally, it may not be a sensitive marker for acute exposure
- Urinary arsenic is often used as a marker for acute exposure
  - Variety of arsenic compounds in urine, may reflect toxicity
- Urinary levels also used for chronic exposure, but may only be relevant if exposure has stayed constant (and still present)
- Other tissues (hair, nails) may reflect chronic exposure
  - Hair & toenails do reflect past exposure, but susceptible to external contamination and lack standard ranges

Orloff K, et al. Biomonitoring for environmental exposures to arsenic. J Toxicol Environ Health B Crit Rev. 2009 Aug;12(7):509-24.

Arsenic Methylation

- Arsenic methylation was previously believed to be a simple arsenic-detoxification reaction.
- However, it is actually a complex metabolic process which may determine arsenic toxicity, because the toxicological profiles of arsenic metabolites vary
- MMAIII and DMAIII have consistently been reported to be more toxic than any other As metabolite
- Variation in methylation capacity may thus determine individual susceptibility to arsenic – many contributing factors, such as cystathionine-β-synthase SNP



Jomova K, 2011 (21321970)

Gomez-Rubio P et al. Association between body mass index and arsenic methylation efficiency in adult women from southwest U.S. and northwest Mexico. Toxicol Appl Pharmacol. 2011 Apr 15;252(2):176-82.

Evaluation of Heavy Metal Exposure – Provocation

- Provocation – the use of a chelating agent – before urine collection often done clinically, but several limitations
  - No reference range for provoked urine
  - Most chelating agents do not extract metals from all tissues, thus does not necessarily represent total body burden
    - Example: Mercury
      - Brain is one of the main target organs for both elemental and organic mercury, yet agents do not chelate brain mercury
- Despite limitations, widely used and advocated by clinicians, in part to see efficacy of chelating agent as a guide to treatment, and based on empirical evidence

Rooney JP. The role of thiols, dithiols, nutritional factors and interacting ligands in the toxicology of mercury. Toxicology. 2007

Toxic Metal Assessment Recommendation

- First morning urine
  - Acute exposure
- 300 mg DMPS + 250mg of DMSA
  - 6 hour collection
  - Body load
- DMPS Hg and DMSA forPb and Cd

Treatment

- Decrease Exposure!!
- Organic, mostly plant-based diet
- Heavy metal chelation if indicated
- Increase glutathione production
- Supportive therapies
  - Antioxidant support
  - Detoxification support
- Specific therapies
- Systemic detoxification
  - Sauna
  - Fasting
  - Hydrotherapy

Increase Glutathione Production

- Silymarin
  - Standardized extract, 100 mg tid
- NAC
  - Also directly binds methyl-Hg
  - 300-500 mg bid
- Whey powder
  - 15 g bid
- Alpha lipoic acid (decreases depletion)
  - R form preferred: 250 mg bid

Soltan-Sharifi MS, et al. Improvement by N-acetylcysteine of acute respiratory distress syndrome through increasing intracellular glutathione. Hum Exp Toxicol. 2007;26(9):697-703

Micke P, et al. Oral supplementation with whey proteins increases plasma glutathione levels of HIV-infected patients. Eur J Clin Invest. 2001;31(2):171-8

Jariwalla RJ, et al. Restoration of blood total glutathione status and lymphocyte function following alpha-lipoic acid supplementation in patients with HIV infection. J Alt Comp Med. 2008;14(2):139-46

Intervention For Mercury

- Avoidance
  - Choose lower Hg fish
  - Amalgam removal
- Decrease damage
- Provide competing minerals
- Facilitate body’s excretion processes
- Directly remove

Interventions We Used In Canada

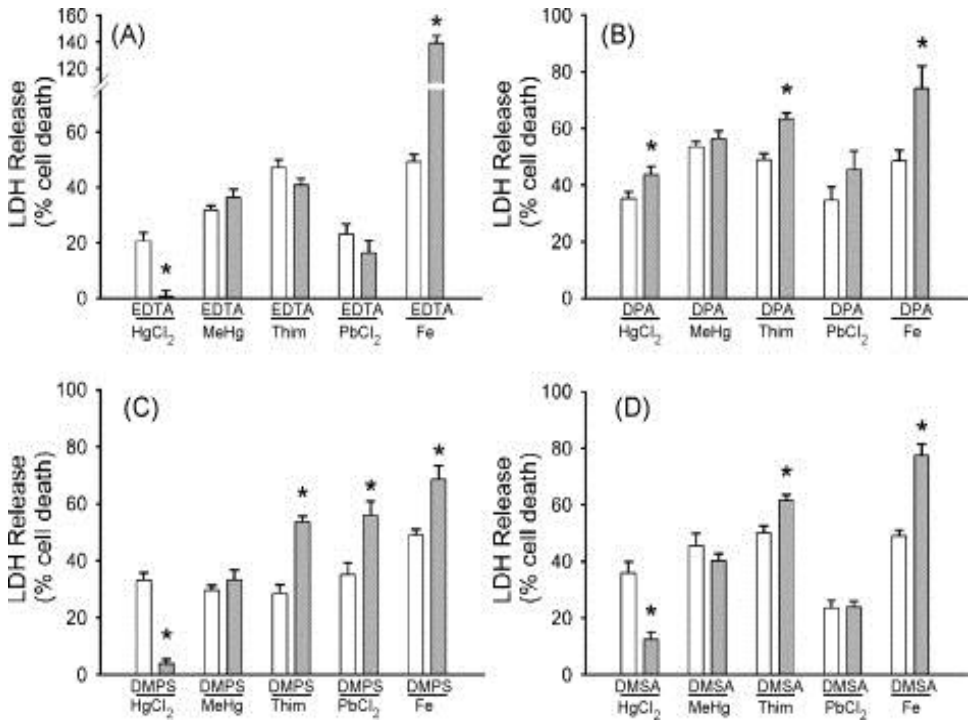
- Removal of amalgams—must use ecological dentist!!
- IV DMPS
  - Stopped because of excessive adverse events
  - “Brain fog”
- DMSA
  - 250 mg x 3 days, 11 days off
- NAC
  - 600 mg bid
- Fiber
  - PGX: 2.25 g tid
- Supportive nutrients
  - Multivitamin designed to promote glutathione production
  - Ca/Mg/Zn until custom multivitamin available

DMPS Brain Fog

- Asserted to be due to:
  - Trace mineral loss
  - Hypoglycemia
- My opinion:
  - Transient increase in mercury (and lead) blood levels
  - Neurotoxicity of DMPS
    - Does not cross intact blood-brain-barrier?
    - BBB more permeable than we were taught in medical school:
      - Hyperinsulinism
      - Mercury toxicity
      - Food allergies (likely anything that increases gut permeability)

Neurotoxicity of Chelating Agents

- In vitro cortical culture:
  - * Much higher dosages than achieved clinically
  - Increase metal toxicity
  - Increase toxicity of iron
    - High Fe levels common in men

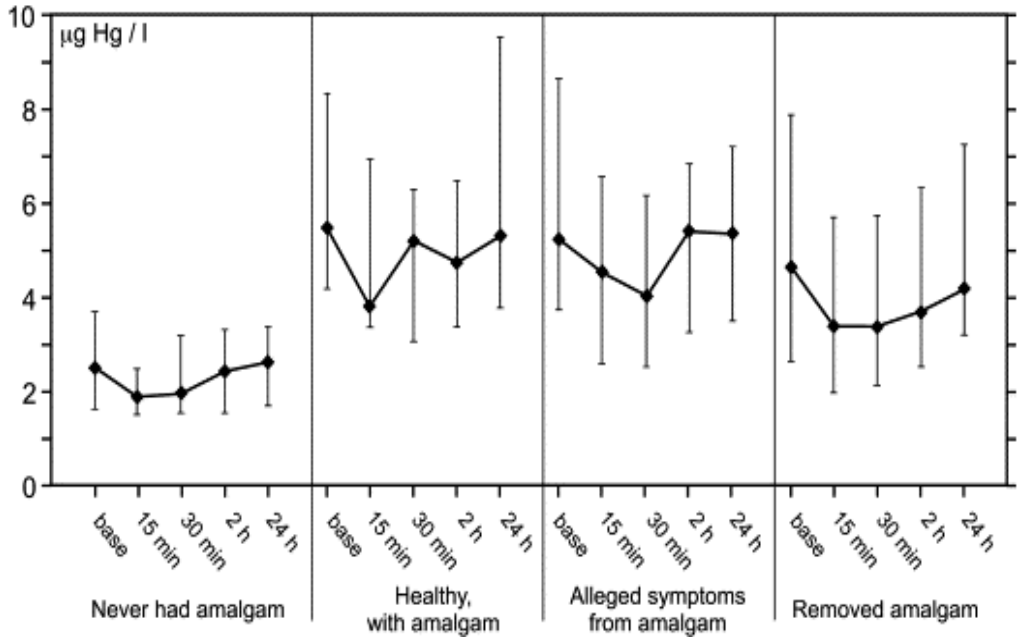


Clear is metal alone, gray is metal + chelate

Rush T, et al. Effects of chelators on mercury, iron, and lead neurotoxicity in cortical culture. Neurotoxicology. 2009;30(1):47-51

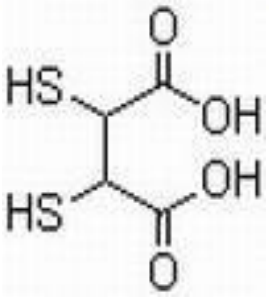
Blood Levels After IV DMPS

- Single dose IV DMPS 2 mg/kg
- Higher blood levels in those with amalgams
- Rebound
- Some experience elevation due to binding of Hg in kidneys and release into blood
- Concluded DMPS not clinically effective!!



Vamnes JS, et al. Blood mercury following DMPS administration to subjects with and without dental amalgam. Sci Total Environ. 2003 Jun 1;308(1-3):63-71

DMSA



- 2,3-Dimercaptosuccinic acid
- SH-containing, water-soluble, low-toxicity, oral (IV toxic)
- Developed in 1950s as alternative to more toxic chelating agents
- 10-20% of oral dose absorbed
- Chelates all forms of mercury (more effective for Pb)
- ½ through urine, ½ through bile
- Amount of Hg bound: ~7.5 ug/g of oral DMSA
- Increases glutathione production
- ½ life in blood 2-3 hours

Ruha AM, Curry SC, Gerkin RD, et al. Urine mercury excretion following meso-dimercaptosuccinic acid challenge in fish eaters. Arch Pathol Lab Med. 2009 Jan;133(1):87-92

Roels HA, Boeckx M, Ceulemans E, Lauwerys RR. Urinary excretion of mercury after occupational exposure to mercury vapour and influence of the chelating agent meso-2,3-dimercaptosuccinic acid (DMSA). Br J Ind Med. 1991 Apr;48(4):247-53

DMSA

- Nutrients to improve efficacy
  - Alpha lipoic acid
  - NAC
  - Probiotics
  - Fibre
- Research studies use 30 mg/kg/day
  - 7 days on, 7 off
  - Not recommended
- Protocol we used:
  - 50 mg trial dose; if no reaction within 2 hours:
    - 250 mg qd for 3 days then off for 11 days, or
    - 250 mg every 3rd day before bed

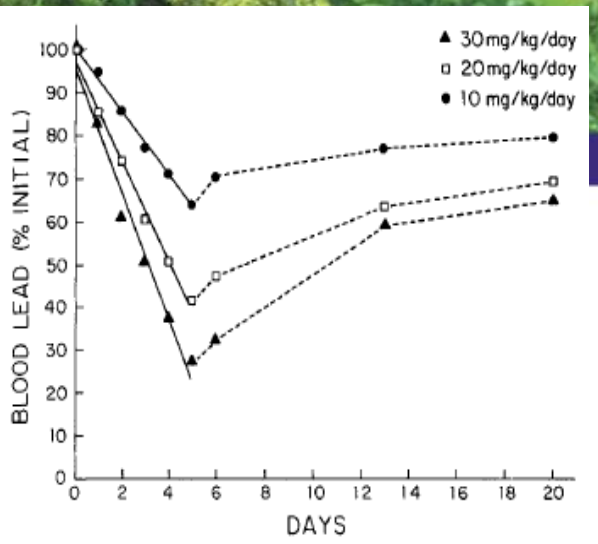
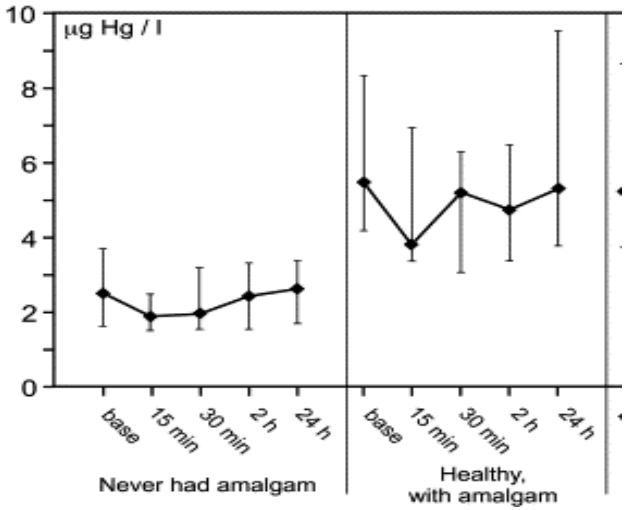


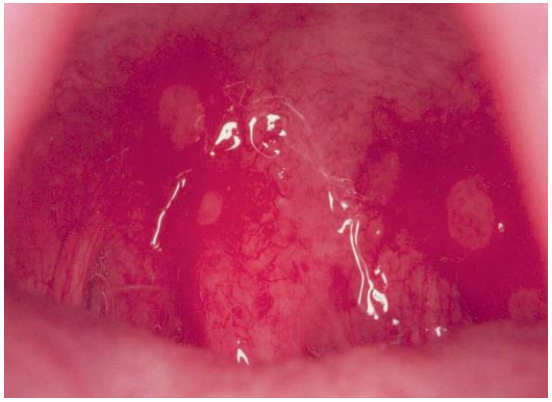
Fig. 1. Mean BPb concentration (expressed as percentage of pretreatment value) after 5 days of DMSA therapy.



Graziano JH, et al. 2,3-Dimercaptosuccinic acid as an antidote for lead intoxication. Clin Pharmacol Ther. 1985;37(4):431-8

DMSA

- At high dosage (30 mg/kg/day):
  - 14% elevated ALT
  - Mucositis
  - 50% increased loss of Zn
- At low dose
  - Primary adverse event is allergy, typically skin rash
  - No apparent drug interactions
- Not recommended in pregnant women (no research)
  - Animal research: removes MeHg in blood, brain and kidneys of fetus

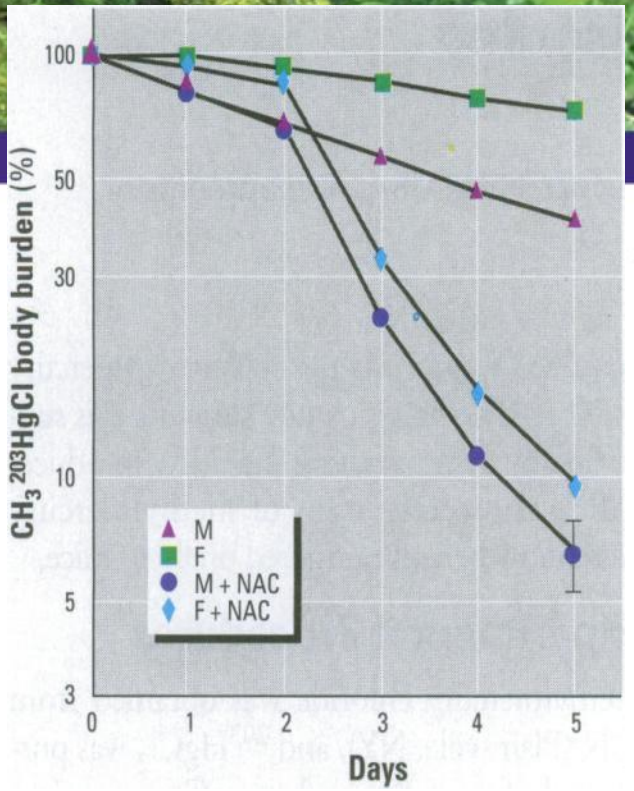


Bradberry S, et al. Use of oral dimercaptosuccinic acid (succimer) in adult patients with inorganic lead poisoning. QJM. 2009 Oct;102(10):721-32

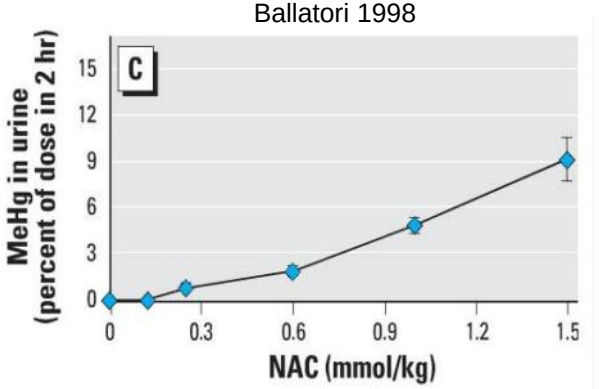
C.C. Bridges, L. Joshee, R.K. Zalups. Effect of DMPS and DMSA on the placental and fetal disposition of methylmercury. Placenta 30 (2009) 800–805

NAC

- Most research animal and human cell lines
- Multiple benefits:
  - Increases production of glutathione
  - Protects human neurological cells from Hg toxicity
  - Reverses damage to human pancreatic cells from Hg
  - Directly binds to Hg, esp. MeHg, and excrete through kidneys



Ballatori 1998

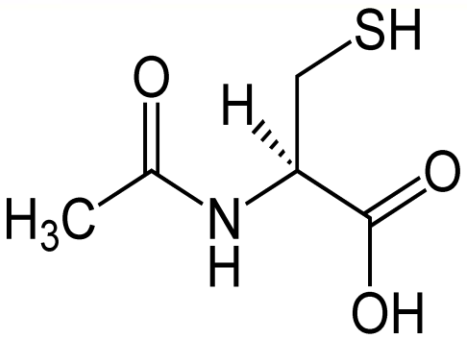


Aremu 2008

Aremu DA, et al. N-acetylcysteine as a potential antidote and biomonitoring agent of methylmercury exposure. Environ Health Perspect. 2008 Jan;116:26-31

Ballatori N, et al. N-acetylcysteine as an antidote in methylmercury poisoning. Environ Health Perspect. 1998 May;106:267-71

NAC



- IV
  - Treatment of acute acetaminophen poisoning
  - 150 mg/kg body weight given over 15-60 minutes
  - Effective but high incidence of adverse events—ER only!!
- Oral
  - Safe: No serious adverse events in review of 4,000 patients
  - 500 mg: 1-2 times a day

Atkuri KR, et al. N-Acetylcysteine--a safe antidote for cysteine/glutathione deficiency. Curr Opin Pharmacol. 2007 Aug;7(4):355-9

Fibre

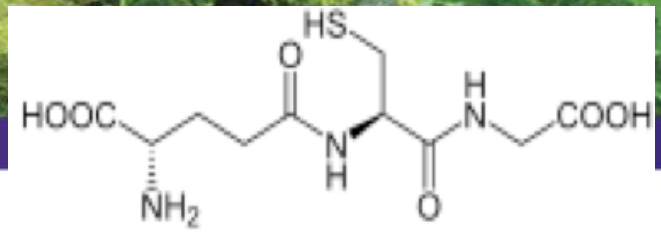
- Decrease enterohepatic recirculation
- No significant research on fibre
- PGX
  - Research support for improving insulin sensitivity and weight loss
  - 2.25 g tid

Selenium

- Dietary selenium (Se) status is inversely related to vulnerability to methylmercury (MeHg) toxicity
  - Directly binds MeHg
  - Prevents oxidative damage
  - Helps protect selenoenzymes which are particularly susceptible to MeHg
  - High Hg fish also rich in Se are less toxic to fetal brain (probably due to maintenance of thyroid function)
  - Required for glutathione production

Ralston NV, Raymond LJ. Dietary selenium's protective effects against methylmercury toxicity. Toxicology. 2010 Nov 28;278(1):112-23

Glutathione: Critical

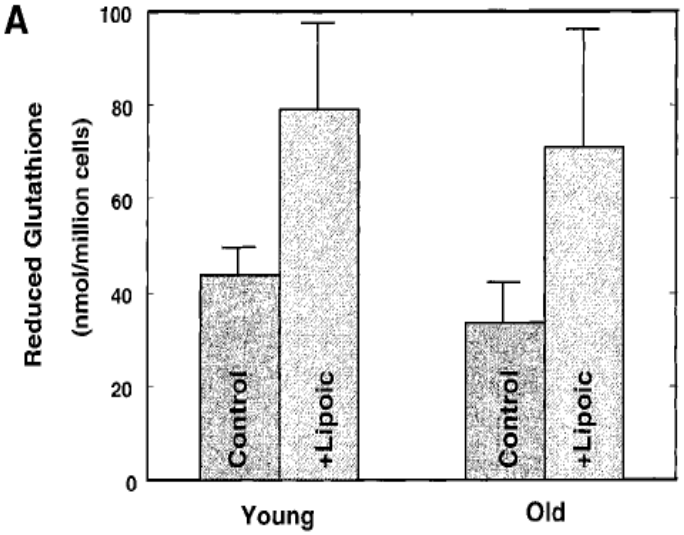


- Difficult to overstate its importance
- Most important intracellular and intra-mitochondrial antioxidant
- Binds and transports mercury out of cells
- Binds and transports mercury out of the brain
- Irreversibly(?) binds to mercury in the brain
- Neutralizes oxidative damage from mercury
- Depleted by oxidative stress, metals, alcohol
- Even predictor of healthy aging!

Baker, SM. The Metaphor of Oceanic Disease. IMCJ February, 2008;7:1.
Mosharov, E., Cranford, M.R., Baneriee, R. The Quantitatively Important Relationship between Homocysteine Metabolism and Glutathione Synthesis by the Transsulfuration Pathway and Its Regulation by Redox Changes. Biochemistry. 2000 Sept;39:13005-13011.

Glutathione: Decrease Depletion

- Decrease utilization
  - Decrease toxic exposure, esp alcohol
- Decrease oxidative stress
  - Decrease oxidative markers, increase GSH
  - Alpha lipoic acid for mitochondria
  - Vitamin D for brain
  - Melatonin for brain



Addolorato G, et al. Effects of short-term moderate alcohol administration on oxidative stress and nutritional status in healthy males. Appetite. 2008 Jan;50(1):50-6
Liu J. The effects and mechanisms of mitochondrial nutrient alpha-lipoic acid on improving age-associated mitochondrial and cognitive dysfunction: overview. Neurochem Res 2008;33:194-203
Garcion E, et al. New clues about vitamin D functions in the nervous system. Trends Endocrinol Metab. 2002 Apr;13(3):100-5
Herrera J,. Melatonin prevents oxidative stress resulting from iron and erythropoietin administration. Am J Kidney Dis. 2001 Apr;37(4):750-7

Glutathione: Direct Administration

- Oral glutathione
  - Inconsistent research; 3 g did not work in humans
- Oral liposomal glutathione
  - Early promising research
- IV glutathione
  - Very effective, but may increase Hg transport into brain
- Intranasal glutathione
  - Intriguing, does not transport Hg from blood
  - Only lung absorption documented (very effective)

Witschi A, et al. The systemic availability of oral glutathione. Eur. J. Clin. Pharmacol 1992;43(6): 667–9
Cooke RW, Drury JA. Reduction of oxidative stress marker in lung fluid of preterm infants after administration of intra-tracheal liposomal glutathione. Biol Neonate. 2005;87(3):178-80
Buhl R, et al. Augmentation of glutathione in the fluid lining the epithelium of the lower respiratory tract by directly administering glutathione aerosol. Proc Natl Acad Sci USA 1990;87:4063–7

Glutathione: Support Production

- Supply cysteine—primary rate limiting step
- Whey protein
- NAC
  - Also facilitates excretion of mercury
  - 300 mg bid
- SAMe
  - Not methionine as it also increases homocysteine

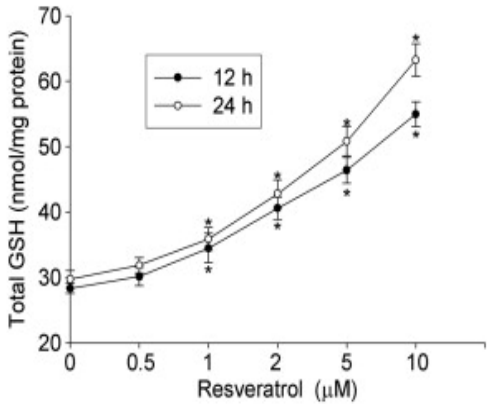
Micke P, et l. Oral supplementation with whey proteins increases plasma glutathione levels of HIV-infected patients. Eur J Clin Invest. 2001;31(2):171-8

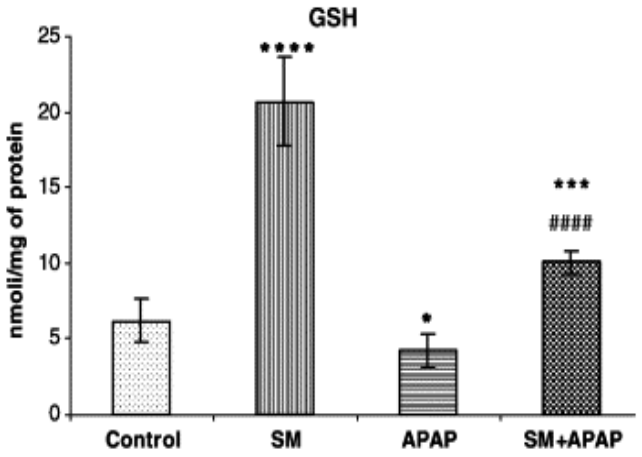
Soltan-Sharifi MS, et al. Improvement by N-acetylcysteine of acute respiratory distress syndrome through increasing intracellular glutathione, and extracellular thiol molecules and anti-oxidant power: evidence for underlying toxicological mechanisms. Hum Exp Toxicol. 2007;26(9):697-703

Liber CS, Packer L (November 2002). "S-Adenosylmethionine: molecular, biological, and clinical aspects—an introduction". Am J Clin Nutr. 76 (5): 1148S–50S

Glutathione: Stimulate Production

- Resveratrol
- Milk thistle/Silymarin

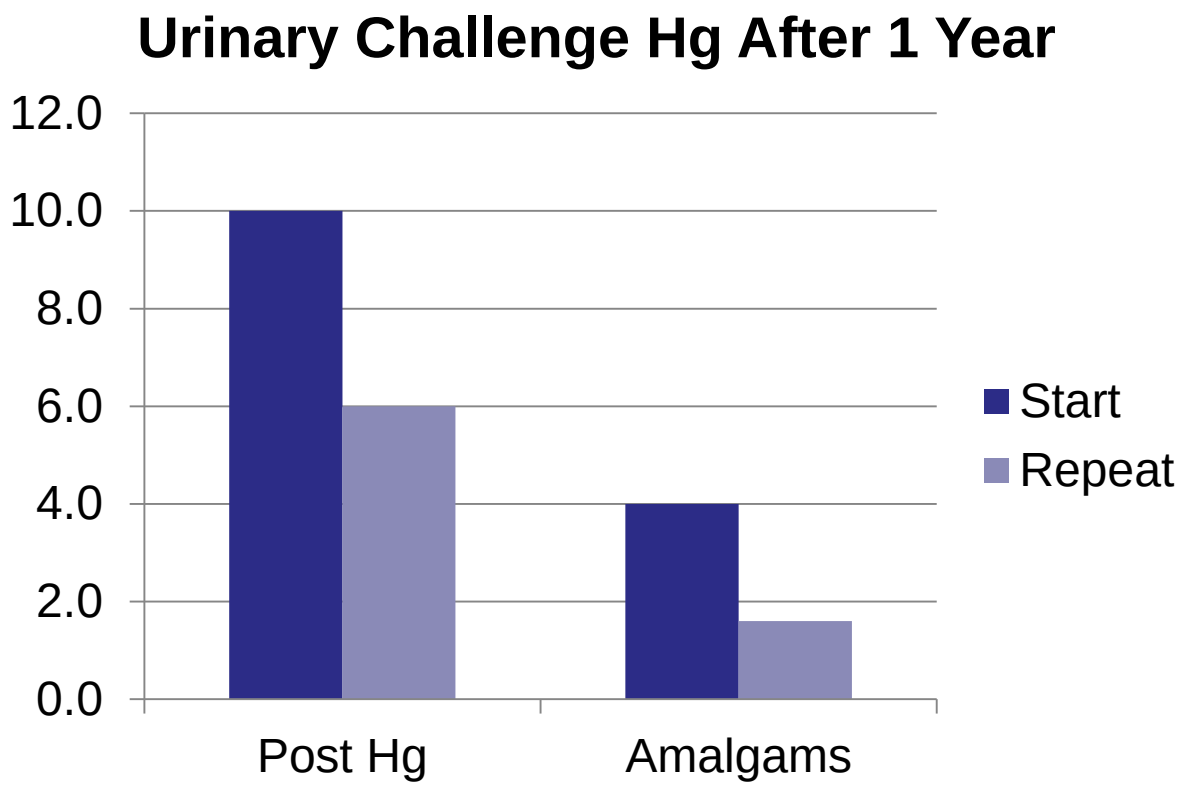




Kode A, et al. Resveratrol induces glutathione synthesis by activation of Nrf2 and protects against cigarette smoke-mediated oxidative stress in human lung epithelial cells. Am J Physiol Lung Cell Mol Physiol. 2008 Mar;294(3):L478-88
Nencini C, et al. Protective effect of silymarin on oxidative stress in rat brain. Phytomedicine. 2007 Feb;14(2-3):129-35

Results of Intervention

- DMPS challenge test, ~ 1 year apart



40% reduction!

Lead Chelation

- Chelators: DMPS, DMSA, EDTA, d-penicillamine (DPA)
  - Long history of EDTA use, most often used IV
  - EDTA also depletes Zn, Cu, Fe, Co, and Mn
  - **Oral DMSA as effective as IV EDTA**
  - Not clear if DMSA removes lead from bone, but does reduce hippocampal lead
  - Combination of EDTA and DMSA increase amount excreted

Bradberry, S et al. A comparison of sodium calcium edetate (edetate calcium disodium) and succimer (DMSA) in the treatment of inorganic lead poisoning. Clinical Toxicology 2009
Bradberry Use of oral DMSA in adult patients with inorganic lead poisoning. QJM. 2009
Lee BK, Provocative chelation with DMSA and EDTA: evidence for differential access to lead storage sites. Occup Environ Med. 1995

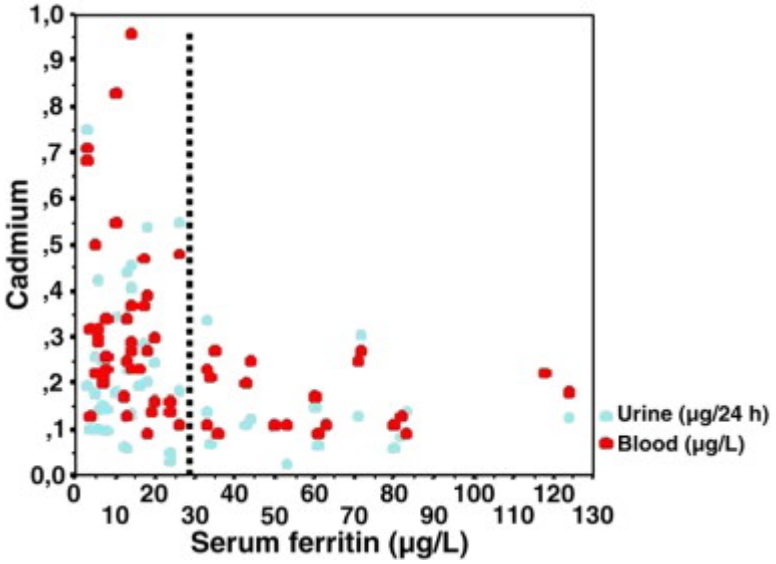
Lead Chelation

- Chelation causes a rapid fall in blood lead levels within the first few days of therapy
- Recheck 1-3 weeks after chelation for rebound (if BLL was elevated, rebounds to 70% of pretreatment in two weeks following DMSA)
- DMSA dosed at 350 mg/m^2 and administered three times daily for 5 days, then decreased to twice daily for 14 days. The dosage for adults and children also can be expressed as 10 mg/kg per dose using the same regimen

Gracia RC, et al. Lead toxicity and chelation therapy. Am J Health Syst Pharm. 2007 Jan 1;64(1):45-53.

Cadmium Absorption and Iron

- Iron supplementation if low ferritin
- Cadmium absorbed much more efficiently if low in iron



Järup 2009 (19409405)

Cadmium Chelation

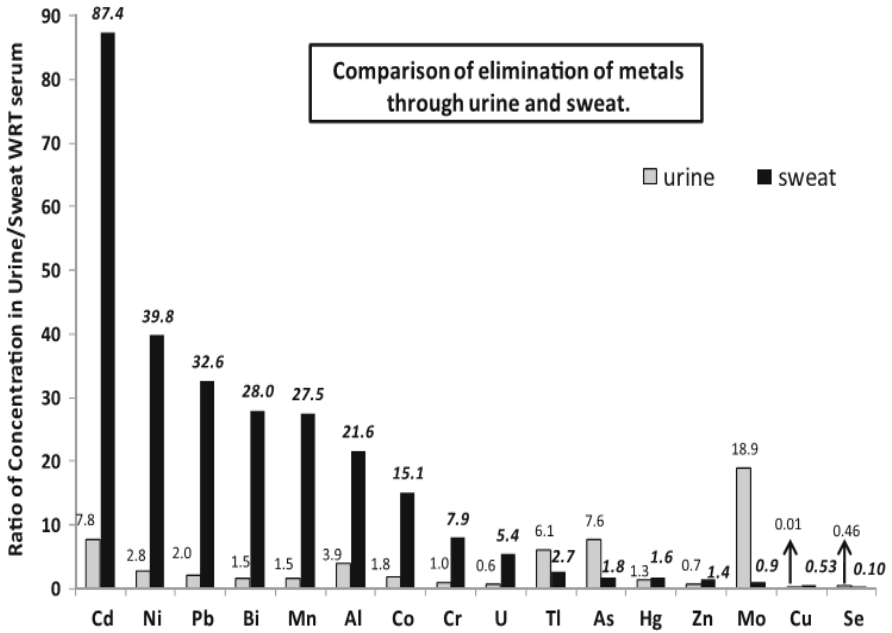
- Little data for chelation, but EDTA primarily used
- DMSA will chelate some
- May redistribute cadmium and increase its toxicity
- In a case study, glutathione was used with EDTA, and appeared to increase both blood cadmium and renal excretion of cadmium
- In workers with high exposure, a 14 year study found if urinary levels were initially > 10 microg/g Cr, renal damage was irreversible with EDTA
- Extreme care as easily concentrates in kidneys

Gil HW, et al. Effect of glutathione on the cadmium chelation of EDTA in a patient with cadmium intoxication. Hum Exp Toxicol. 2011 Jan;30(1):79-83.

Wu X, et al. Lack of reversal effect of EDTA treatment on cadmium induced renal dysfunction: a fourteen-year follow-up. Biometals. 2004 Aug;17(4):435-41.

Cadmium – Sweat it Out

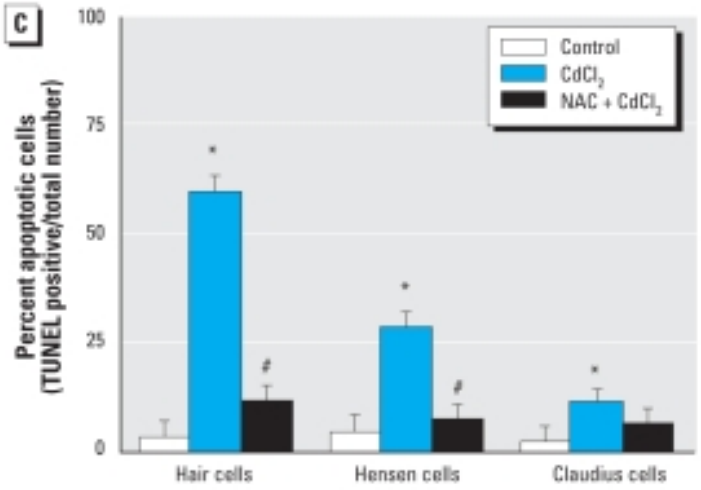
- Cadmium appears to be eliminated efficiently through sweat
- 20 individuals sweat via exercise, steam or infrared sauna
- Cadmium found in sweat in those with undetectable serum levels, suggesting it could be used for assessment of burden
- Elimination of other minerals (Cu, Mn) suggests need replenishment during induced sweat



Genuis SJ, et al. Blood, Urine, and Sweat (BUS) Study: Monitoring and Elimination of Bioaccumulated Toxic Elements. Arch Environ Contam Toxicol. 2011 Aug;61(2):344-57

Cadmium - Support

- Antioxidants have been shown to reduce cadmium toxicity
  - NAC reduced ototoxicity in animal studies near to control level, and prevented apoptosis
  - Quercetin also reduced cadmium induced oxidant damage



Kim 2008

Kim SJ, et al. The protective mechanism of antioxidants in cadmium-induced ototoxicity in vitro and in vivo. Environ Health Perspect. 2008 Jul;116(7):854-62.
Morales AI, Protective effect of quercetin on experimental chronic cadmium nephrotoxicity in rats is based on its antioxidant properties. Food Chem Toxicol. 2006 Dec;44(12):2092-100.

Arsenic Chelation

- Randomized trial of IV DMPS for chronic arsenicosis found significant reduction in symptoms compared to placebo
  - Dose: 100mg capsules orally, qid x 1 week. Repeat on weeks 3, 5, and 7.
- Monoisoamyl dimercaptosuccinic acid (MiADMSA) removes from blood and soft tissue when given with DMSA, animal studies only
- Spirulina and zinc given together also had significant benefit compared to placebo

Guha Mazumder DN, et al. Randomized placebo-controlled trial of 2,3-dimercapto-1-propanesulfonate (DMPS) in therapy of chronic arsenicosis due to drinking arsenic-contaminated water. J Toxicol Clin Toxicol. 2001;39(7):665-74.
Misbahuddin M, et al. Efficacy of spirulina extract plus zinc in patients of chronic arsenic poisoning: a randomized placebo-controlled study. Clin Toxicol (Phila). 2006;44(2):135-41.
Flora SJ et al. Arsenic and lead induced free radical generation and their reversibility following chelation. Cell Mol Biol (Noisy-le-grand). 2007
Bhadauria S, et al. Response of arsenic-induced oxidative stress, DNA damage, and metal imbalance to combined administration of DMSA and monoisoamyl-DMSA during chronic arsenic poisoning in rats. Cell Biol Toxicol. 2007

Arsenic Methylation

- In general, supporting methylation pathways seems logical
  - Increased urinary MMA^{V} in arsenic-exposed subjects suggests an inefficient methylation and probably an increased concentration of the highly toxic MMA^{III} at cellular level
  - Dietary intake and serum concentration of cysteine, methionine, choline, selenium, zinc, folate, niacin, vitamin B_{12}, ferritin, may all modify the metabolism, retention, and toxicity of arsenic
  - Arsenic related skin conditions are more common in those with low folate status
  - 400ug folate per day in those with low plasma folate increased urinary DMA, and lowered blood MMA, which would seem likely to reduce disease risk

Gamble MV, et al. Folic acid supplementation lowers blood arsenic. Am J Clin Nutr. 2007 Oct;86(4):1202-9.

Arsenic & B12?

- Somewhat surprisingly, B12 may not be desirable
- Study of ~800 individuals in Bangladesh, in which low B12 oversampled
  - Plasma cobalamin was inversely associated with %iAs and positively associated with %MMA in urine
  - It did not influence %DMA – thus it may increase the speed of the 1st step to MMA (more toxic), but not the next step to DMA (less toxic).
  - Awaits further evaluation

Hall MN, et al. Influence of cobalamin on arsenic metabolism in Bangladesh. Environ Health Perspect. 2009 Nov;117(11):1724-9.

Arsenic – GSH & Antioxidant support

- GSH depletion due to utilization during arsenic metabolism may be crucial in arsenic-induced oxidative stress
  - NAC supplementation appears to lower arsenic's toxicity
- ALA, vitamins C &E, quercetin, taurine all associated with reduced arsenic toxicity
- Zinc and selenium interfere with arsenic
- Turmeric/curcumin appear to block angiogenesis induced by arsenic species

Han YH et al. Suppression of arsenic trioxide-induced apoptosis in HeLa cells by N-acetylcysteine. Mol Cells. 2008 Jul 31;26(1):18-25.
Pantazis P, et al. Curcumin and turmeric attenuate arsenic-induced angiogenesis in ovo. Altern Ther Health Med. 2010 Mar-Apr;16(2):12-4.
Flora SJ. Arsenic-induced oxidative stress and its reversibility. Free Radic Biol Med. 2011 Jul 15;51(2):257-81

Supportive Therapies: Antioxidants

- N-acetyl-cysteine
  - Animal studies support use as antioxidant for lead, arsenic, and cadmium toxicity, and assists in Hg removal
- Lipoic acid
  - Inhibits neuronal Hg damage and increases excretion, and has shown protection against cadmium induced hepatotoxicity
- Vitamins C & E
  - Protective against oxidative damage, and human study showed small reduction in lead retention

Wang L et al. Protective effect of N-acetylcysteine on experimental chronic cadmium nephrotoxicity in immature female rats. Hum Exp Toxicol. 2009

Wang L Protective effect of N-acetylcysteine on experimental chronic lead nephrotoxicity in immature female rats. Hum Exp Toxicol. 2010

Kim SJ, et al. The protective mechanism of antioxidants in cadmium-induced ototoxicity in vitro and in vivo. Environ Health Perspect. 2008

Flora SJ Heavy metal induced oxidative stress & its reversal by chelation therapy. Indian J Med Res. 2008

Supportive Therapies: Antioxidants

- Melatonin
  - Excellent antioxidant, several animal studies demonstrated protective effect for lead, cadmium and arsenic toxicity
  - Also induces antioxidant and detoxification enzymes
- Beta-carotene
  - Significant dose-response relationship was observed for arsenic-related ischemic heart disease and serum level of alpha- and beta-carotene

Pal S, et al. Possible Benefcial Effects of Melatonin Supplementation on Arsenic-Induced Oxidative Stress in
Wistar Rats. Drug Chem Toxicol 2006
Hsueh YM, Low serum carotene level and increased risk of ischemic heart disease related to long-term arsenic exposure. Atherosclerosis. 1998
Kim YO, et al. Infuence of melatonin on immunotoxicity of lead. Int J Immunopharmacol 2000
Kotler M, et al. Melatonin increases gene expression for antioxidant
enzymes in rat brain cortex. J Pineal Res 1998

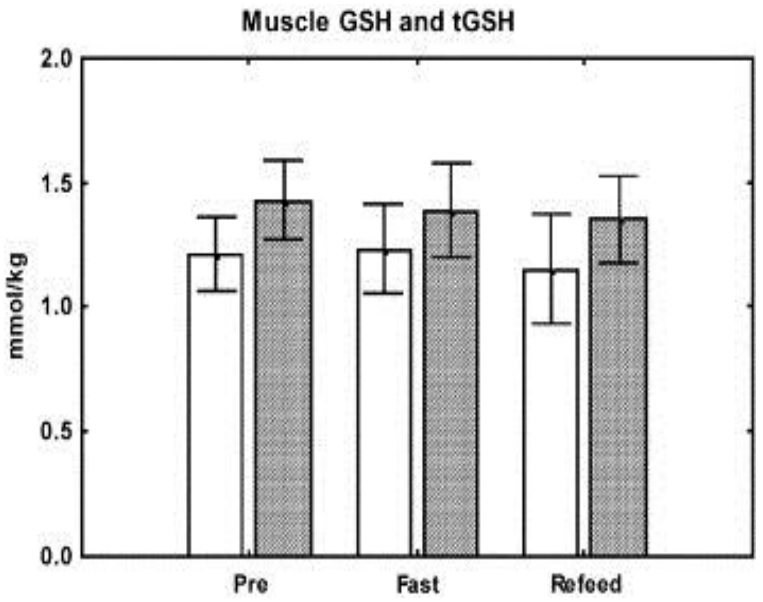
Sauna
(Heat Chamber Depuration)

- Extended time: 1-2 hours
- Modest temperature: 150-170^{o}F
- Increases excretion of:
  - Heavy metals: cadmium, lead
  - Chemicals: PCBs, PBBs, and HCBs
  - Essential trace minerals
- Increases:
  - Lipolysis
  - Growth hormone

Schnare DW, et al: Evaluation of detoxification for fat stored xenobiotics. Med Hyp 1982
Schnare DW, et al: Body burden reductions of PCBs, PBBs, and chlorinated pesticides in human subjects. Ambio, 1984
Tretjak Z, et al: PCB reduction & clinical improvement by detoxification: and unexploited approach? Hum Exp Toxicol, 1990
Cohn JR, et al: The excretion of trace metals in human sweat. Ann Clin Lab Sci 1978
Lammintausta T, et al: Change in hormones reflecting sympathetic activity in Finnish sauna. Ann Clin Res, 1976

Fasting

- Increases detoxification of:
  - PCBs, DDT
  - Circulating immune complexes
  - Food allergies
- Depletes glutathione?
  - Not short term



Imamura M, Tung T: A trial of fasting cure for PCB poisoned patients in Taiwan. Am J Ind Med 5:147-53, 1984
Shakman RA: Nutritional influences on the toxicity of environmental pollutants: A review. Arch Env Health 28:105-33, 1974
Hammarqvist F, et al. Free amino acid and glutathione concentrations in muscle during short-term starvation and refeeding. Clin Nutr. 2005;24:236-43

Hydrotherapy

- Bath General Hospital
  - Lead poisoning (colica pictonum)
  - 120 years of records analyzed
  - 3,377 patients with lead poisoning
  - 45.4% cured; 93% improved
- Treatment
  - 1+ hour full body (standing) immersion at 35oC
  - 3 times per week; average stay 150 days
- Physiological research
  - Standing full immersion:
    - Increases cardiac output 50%
    - Increases excretion of lead 250%
    - Peak excretion at 2.5 hours

Heywood A: A trial of Bath waters: The treatment of Pb poisoning. Med Hist Supl 10:82-101, 1990

Summary

- Metal body load substantial
- Body load at levels associated with increased incidence of a wide range of diseases
- Avoidance works, but exposure not avoidable
- Nutrients, botanicals, hydrotherapy and drugs work to decrease body load