



# ELEMENTS

## INTERPRETIVE GUIDE

BLOOD, HAIR & URINE



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## HOW TO NAVIGATE THIS INTERPRETIVE GUIDE

This **interpretive Guide** contains information from all our Element Profiles. At any time you can navigate to a specific element for the precise information you need to consult with your patient.

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In the **Table of Contents** simply click on the name of the element, the table or the figure you wish to explore and you will go directly there. To **return** to the Table of Contents just click on the **Home** symbol found at the top right of each page. To navigate **forward** and **backwards** between pages click on the corresponding arrow symbols.

Element Profile Comparisons	Hair	Whole Blood Toxic Metals	Whole Blood/ Erythrocyte	6-8hr Urine Nutrient & Toxic Elements	6-8hr Urine Toxic Metals	24hr Urine Nutrient & Toxic Elements	24hr Urine Toxic Metals
Profile Number	0020 <sup>1</sup>	0026/0039 <sup>1</sup>	0022/0037 <sup>1</sup>	0052/0055 <sup>1</sup>	0152/0155 <sup>1</sup>	0058/0059 <sup>1</sup>	0158/0159 <sup>1</sup>
Nutrient Elements	✓		✓	✓		✓	
Toxic Elements	✓	✓	✓	✓	✓	✓	✓
Potentially Toxic and Rare Earth Elements	✓			✓	✓	✓	✓
Elements of Unknown Human Requirement	✓			✓	✓	✓	✓

<sup>1</sup> Not available in New York

For more information concerning Individual Element Profiles, please visit [www.metametrix.com/elements](http://www.metametrix.com/elements)



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**Table 1. Symptoms and Treatments Associated with Nutrient Element Abnormalities**

Element	Status	Associated Symptoms and Diseases	Treatment		
			Children 2-12 yrs.	Adult Male	Adult Female
<b>Calcium (erythrocyte)</b>	H	Hypertension, oxidative damage, cell membrane permeability Not indicative of dietary calcium status	Magnesium, omega 3 fatty acids, antioxidants		
<b>Magnesium</b>	L	Muscle cramping, twitching, depression, hypertension, cardiovascular disease, and diabetes	200–600 mg	350–750 mg	300–700 mg
	L	Advanced aging due to glutathione insufficiency	NAC 200-500 mg 1000-1500 mg		
<b>Potassium</b>	L	Hypertension, stroke, kidney stones, osteoporosis, low bone density	50–150 mg	150–300 mg	150–300 mg
<b>Iron</b>	L	Fatigue, delay in growth or cognitive development, weakness, arthralgias, organ damage	10–20 mg IDA: 5 mg/kg	10–30 mg IDA: 90–200 mg	18–50 mg IDA: 90–200 mg
	H	Vomiting, abdominal pain, bloody diarrhea, shock, lethargy and dyspnea	ascorbic acid and red meats Phlebotomy, decrease iron, increase phytates (whole grains)		
<b>Zinc</b>	L	Depressed growth, poor immune function, alopecia, eye and skin lesions, diarrhea	8–30 mg	15–65 mg	15–65 mg
	H	Cancer metastasis, hypertension or renal failure See low copper below	Avoid supplemental zinc		
<b>Copper</b>	L	Refractory anemia, depigmentation, impaired glucose tolerance, cardiac-related problems, elevated cholesterol Zinc supplementation without adequate copper can decrease copper levels.	1.0–5 mg	2.0–10 mg	2.0–10 mg
	H	Nausea, vomiting and diarrhea, hepatic cirrhosis, neurodegenerative conditions, heart disease, retinal degeneration	Zinc supplementation can reduce copper, Decrease exposure to copper cookware or copper pipes, copper-binding drugs such as tetrathiomolybdate, penicillamine, and trientine		
<b>Manganese</b>	L	Increased oxidative activity	1–10 mg	5–13 mg	5–13 mg
	H	Neurotoxicity, including parkinsonism	Decrease intake, EDTA chelation therapy		
<b>Selenium</b>	L	Compromised immunity, male & female reproductive health, cardiovascular health, inflammation regulation in asthma and thyroid hormone metabolism	50–150 µg	50–400 µg	50–400 µg
	H	Garlic breath odor, brittle fingernails and hair, neurological complaints, swelling	Support methylation for clearance (Vitamin B12, B6, and folic acid, betaine or dimethylglycine)		
<b>Molybdenum</b>	L	Sulfite intolerance, copper toxicity	20–200 µg	50–400 µg	50–400 µg
<b>Chromium</b>	L	Blood sugar dysregulatory conditions	50–500 µg	200–1000 µg	200–1000 µg
	H	Dermatitis; exposure to paint, metals, cement, detergents	Balance gut microflora, phytates		
<b>Cobalt</b>	L	B12 deficiency or pernicious anemia	Vitamin B12 1000 µg		
<b>Boron</b>	L	Steroid hormone modulation, bone health, prostate cancer	N/A	1–6 mg	
<b>Nickel</b>	H	Carcinogenic, dermatitis, asthma, rhinitis, sinusitis	Reduce stainless steel cookware and nickel jewelry		

<b>Lithium</b>	L	Psychosis, depression, violence, learning disabilities	N/A	400–1000 µg
	H	Persistent cognitive and neurological impairment, thyroid suppression, alopecia	Reduce exposure	
<b>Vanadium</b>	L	Insulin insensitivity, abnormal blood lipids, hypertension	N/A	9 µg–125 mg (as vanadyl sulfate)
	H	Respiratory disorders, green tongue, neurological impairment	Reduce exposure	
<b>Strontium</b>	L	Osteopenia, osteoporosis	N/A	125–680 mg

See the individual element sections for other interpretations (i.e. hair or urine abnormalities). Amounts shown are daily oral doses of bioavailable element salts commonly used in research and clinical settings. The percentage of element present in a given element chelate may vary depending on form. In pregnant or lactating women: Calcium up to 2000 mg, magnesium 600 mg, zinc 50 mg. Daily iron requirements during pregnancy may be 30 to 60 mg but revert to non-pregnant amounts 2 to 3 months after delivery, even if lactating.  
*NOTE: Calcium and magnesium have different interpretations in blood, hair and urine.*

## INTERPRETATION OF NUTRIENT AND TOXIC ELEMENTS IN BLOOD, HAIR, & URINE

In routine clinical practice, results from element profiles can identify chronic deficiencies as well as diagnose toxicities or imbalances that impair tissue functions. Most individuals consuming a standard western diet have significant risk of one or more nutrient element deficiencies. The most widely occurring of these are magnesium, potassium and iron.

Elements can be measured in whole blood, erythrocytes, challenged or unchallenged urine, and hair. There is no single best specimen for simultaneous, optimal status assessment of nutrient and toxic elements. Single specimen profiles can reveal potential weaknesses and exposures, but testing of multiple specimen types is the preferred evaluation because it can provide a more complete picture of elemental status, especially when aggressive supplementation regimes are employed. Each element has unique physiological properties, so the most sensitive and specific tests for evaluating a patient vary according to the element. Once an abnormality in element status is identified in a patient, treatment is required and follow-up testing 3-6 months later is recommended to show whether imbalances in nutrient and toxic elements have been resolved or if continued interventions are needed. Low levels of nutrient elements should be augmented with foods rich in those minerals and/or supplements (Table 1 and Table 2). High levels of toxic elements may be treated by reducing exposure, giving protective nutrients, and employing procedures that enhance elimination and detoxification (See Toxic Elements).

### Blood- Whole Blood and Erythrocyte

**Whole blood** or **red blood cell (RBC)** are the most broadly recognized specimens for assessing total body status

of nutrient elements. Low levels of nutrient elements in blood can indicate low nutritional status and need for supplementation. High levels of nutrient elements are unusual but may be due to excessive supplementation or abnormal cellular homeostasis. Nutrient elements in blood should routinely be monitored in patients undergoing chelation therapies that increase rates of excretion.

**Whole blood** is commonly used for baseline, non-challenged toxic element assessment. A flowchart based on initial decisions regarding the need for toxic metal assessment is presented in Fig. 1. High levels of toxic elements in whole blood indicate chronic or acute exposures. Low levels imply that the toxic element is not high in the patient's immediate environment or that their body efficiently eliminates the toxic element. Low levels in blood do not guarantee that toxic elements are uninvolved in the patient's symptoms because certain elements (esp., mercury) may be sequestered in tissues.

**Erythrocyte** essential element testing is a valuable assessment tool for evaluating long term element status. The average

### Definitions

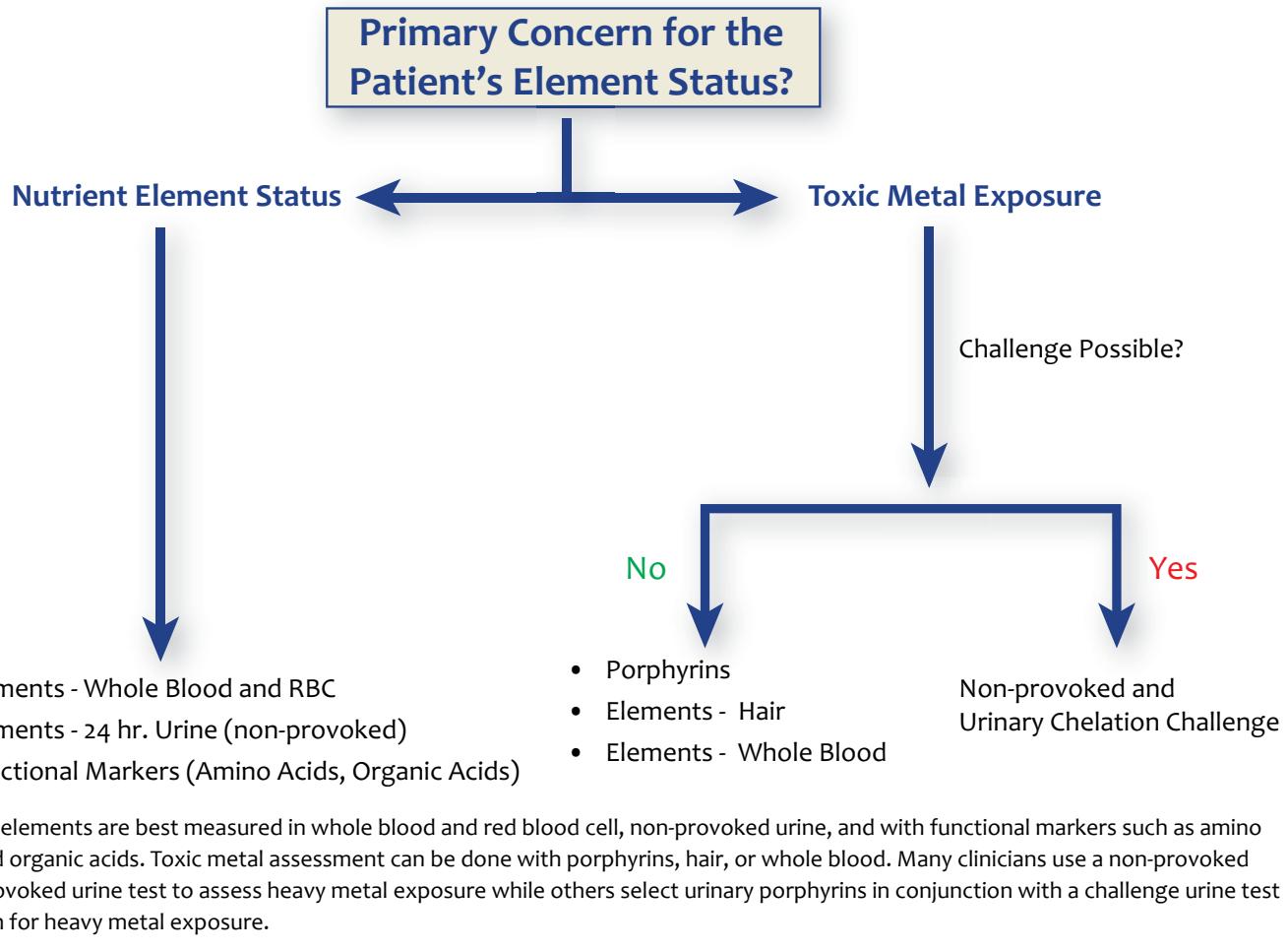
#### Minerals

Compounds such as iron oxide found in the crust of the earth and generally not found in animal tissues

#### Elements

Element implies “chemical element” as used herein, denoting the forms of those entities that are found in the human body, usually complexed with proteins or other biological macromolecules

Figure 1. Specimens for Element Status Testing



erythrocyte population turnover is four months, so they represent average long-term elemental status. Erythrocyte levels tend to reflect elemental tissue levels.

#### Hair

Hair specimens can be useful in routine screening for toxic element exposure. A specimen composed of one and one half inches of hair closest to the scalp gives information about the past three months of exposure. Keratin, which is rich in sulfur-containing cysteine residues, is the major component of hair. When elements circulating in blood reach the hair follicle, they bind with high affinity to keratin, becoming trapped in the extruded shaft of hair. Hair concentrates toxic metals at least 10-fold above concentrations found in blood. When exogenous metal contamination is excluded, hair is described in toxicology textbooks as a very useful specimen for assessing many toxic elements.

Levels of toxic elements in hair indicate exposure to toxic elements in the last three months. Low levels of toxic

elements imply that the toxic element is not high in the person's immediate environment. However, low levels in hair do not guarantee that toxic elements are uninvolved in the patient's symptoms because toxic elements can be stored in tissues. High levels of nutrient elements found in hair may be due to supplementation or abnormal homeostasis. High levels of some nutrient elements, such as calcium and magnesium, can suggest bone resorption due to chronic negative element balance. Hair element levels can be affected by exogenous contaminants such as hair treatments, shampoos, and dust.

#### Urine (Non-Provoked)

Urine elements give useful information about patient status of certain nutrient and toxic elements. Urinary element excretion can vary with recent dietary intake and exposure. Thus, for individuals whose day-to-day dietary intake is relatively constant, urine elements can be useful for detecting nutrient insufficiency. Normal levels of urinary zinc and chromium can reflect nutritional adequacy for these elements, since urine is the main route of excretion. On the other hand, for individuals

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with large daily variations in diet and exposure, urinary levels are more difficult to interpret.

Low levels of nutrient elements in non-provoked urine points to possible dietary deficiency. However, this does not tell the clinician overall body status. High levels of nutrient elements are sometimes found in urine due to recent intake of foods or supplements rich in those elements. Likewise, high levels of toxic elements in non-provoked urine can indicate recent exposures.

Low levels of toxic elements imply that toxic elements are not high in the person's immediate environment. Low levels in urine do not guarantee that toxic elements are uninvolved in the patient's symptoms due to tissue sequestration effects. Thus, many practitioners prefer combining a non-provoked urine with a provoked urine test (see "Chelation Challenge Tests").

**Twenty-four-hour urine** specimens are commonly used in research, although accurate results rely on the patient's ability to reliably collect their urine for 24 hours and measure the volume accurately. Results are reported as amount excreted in 24 hours (mg/d). **Six to eight hour urine** collections are considerably more convenient, and chelation-challenged element concentrations are generally higher because their excretion rates decrease 6 hours after taking the provoking agent. The results must be expressed as amount per milligram of creatinine.

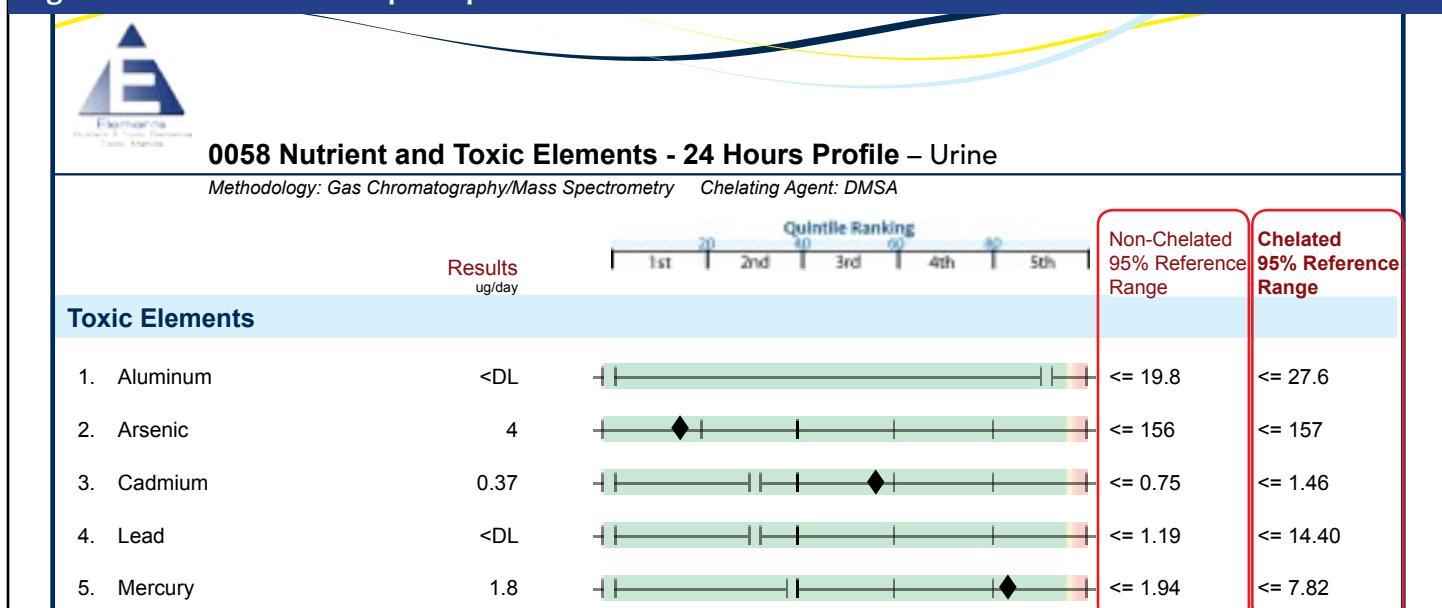
### Chelation Challenge ("Provocation") Tests

Chelation challenge tests offer a way to assess total-body burden of toxic metals or for assessing a patient whose toxic metal exposure occurred much earlier in life. Typically, a challenge consisting of an oral or IV dose of a chelating agent is administered. Urine is collected for the next 6 to 8 or 24 hours and analyzed for toxic metals. The more convenient 6- to 8-hour collection is effective because a large percentage of the chelating agents are cleared into the urine in the first few hours after administration.

It is desirable to evaluate toxic and essential elements by comparing the results of a baseline (pre-challenge) and a chelation (post-challenge) test. An elevation in one or more toxic metals in the post-challenge urine, when compared with baseline, may confirm the diagnosis of elevated toxic metal body burden with potential toxic consequences. Rules such as a four-fold increase over unchallenged levels have been proposed for judging clinically significant effects from a single oral chelator challenge.

Due to the ubiquitous presence of toxic metals in the environment, any chelation-challenged specimen is expected to yield toxic metal levels higher than non-chelated specimens. Some clinicians prefer to compare chelated ranges against the non-chelated referenced ranges, and believe the unprovoked ranges provide a comparison as to what should be considered normal. Metametrix provides both chelated and unchelated ranges for provocation tests. If clinical symptomatology is not compelling, further testing for functional evidence of a toxic burden, such as a urinary porphyrin profile, may be considered

Figure 2. Toxic Elements Sample Report



prior to initiating aggressive treatment for metal toxicity. Further information on chelation and metal detoxification can be found at the American Board of Clinical Metal Toxicology and the American College for Advancement in Medicine.

## NUTRIENT ELEMENTS

Across all demographic strata in industrialized nations, nutrient element, or mineral, deficiencies are recognized as being involved in the pathogenesis of many health conditions, including heart disease, hypertension and cancer. Populations such as the elderly, pregnant women, small children, and immunocompromised patients are particularly vulnerable to nutrient element deficiencies. In the United States the recommended dietary allowance (RDA) is not met by diet alone in most population groups for magnesium, calcium, and potassium. Supply is lowered by depleted soil, toxic element interference, poor food choices, and compromised digestion, including iatrogenic-induced gastric acid reduction. The major roles of essential elements in biological systems are (1) electron acceptors in oxidative/reductive homeodynamics; (2) enzyme cofactors; (3) crystalline structures, especially in bone; and (4) ionic migrations necessary for nerve signal transmission or cell regulatory responses.

### Calcium (Ca)

Calcium is essential for bones and teeth, heart, nerves, muscles, and blood clotting. Calcium's actions are as wide ranging as neuronal excitation, neurotransmitter release, innate immunity, hormonal secretion, and tone of smooth muscle cells in the vasculature, airways, uterus, gastrointestinal (GI) tract, and urinary bladder. Calcium deficiency can lead to osteoporosis. Other symptoms include musculoskeletal pain, muscle cramps, and tetany. Optimum calcium status can help prevent lead toxicity.

Because calcium is high outside of the cell, calcium levels in **erythrocytes** are not a measurement of total body calcium status, but instead are a measure of cell membrane permeability. Erythrocyte calcium is a useful marker in the management of patients with hypertension and arrhythmias, renal failure, and even pre-menstrual syndrome. Treatment for high intracellular calcium includes magnesium, anti-oxidants, and fatty acids (to improve the integrity of the cell membrane).

**Table 2. Food Sources of Nutrient Elements**

	Common Food Sources Of Nutrient Elements
<b>Calcium</b>	Dark green vegetables, whole grains, nuts, milk
<b>Magnesium</b>	Whole grains, nuts, legumes, molasses, brewer's yeast
<b>Potassium</b>	Avocado, banana, mango, corn on the cob, dried beans, potatoes, tomatoes
<b>Phosphorus</b>	Processed food, sodas
<b>Iron</b>	Organ meats, brewer's yeast, wheat germ, egg yolk, oyster, dried beans, and some fruits
<b>Zinc</b>	Red meat, oysters, whole grains
<b>Copper</b>	Liver, cashews, black-eyed peas, sunflower seeds
<b>Manganese</b>	Tea, whole grains, legumes, nuts, green vegetables
<b>Iodine</b>	Seaweed, shellfish, marine fish, iodized salt
<b>Selenium</b>	Garlic, onions, broccoli, Brazil nuts, brewer's yeast
<b>Molybdenum</b>	Beans, nuts, grains, green leafy vegetables
<b>Chromium</b>	Whole grains, legumes, nuts, yeast, meats
<b>Cobalt</b>	Organ meats, nuts, yeast extract
<b>Boron</b>	Apples, soy, grapes, nuts
<b>Nickel</b>	Foods cooked in stainless steel cookware, canned foods, oatmeal, dried fruits, dried peas and beans, nuts, chocolate
<b>Lithium</b>	Vegetables, grains
<b>Vanadium</b>	Buckwheat, parsley, soybeans, safflower oil
<b>Strontium</b>	Green leafy vegetables, Brazil nuts

Calcium accumulation in **hair** can reflect the end result of the process of chronic mobilization from bone. Thus, high levels are associated with calcium loss, which may indicate early signs of osteoporosis, especially in females in the age range of 30-50 yrs. High hair calcium in younger women may, by inference, indicate calcium loss that has not yet shown as bone density decrease. Low hair calcium may indicate increased risk of myocardial infarction with increased associated aortic calcium concentrations. However, low hair calcium in children reflects calcium distribution and is not directly related to dietary intake of calcium. Low hair calcium accompanied by other low element levels such as chromium, cobalt, magnesium, and manganese may suggest malabsorption. Hair treatments such as permanent solutions, bleach, or dyes may contain calcium and cause high hair calcium levels.

Kidney stone formers are characterized by high **urinary** calcium, and potassium appears to decrease stone formation by decreasing urinary calcium levels. Conversely, low

potassium intake results in higher calcium urinary levels. Other tests that may be helpful when calcium is abnormal are: bone density analysis, vitamin D, deoxypyridinoline (DPD), and parathyroid hormone.

### Magnesium (Mg)

One of the most abundant elements on earth, magnesium (Mg) is the fourth most plentiful cation in mammals, and it is the dominant intracellular cation. Magnesium plays a key role in more than 350 enzymes, primarily as Mg-ATP complex in energy-dependent activities. Deficiency of magnesium can cause a wide variety of problems including muscle cramping, twitching, depression, hypertension, cardiovascular disease, and diabetes. Magnesium glycinate has been recommended to prevent aluminum toxicity.

The magnesium content of **red blood cells** is a good indicator of short-term magnesium status and low levels indicate magnesium insufficiency.

Magnesium and calcium are associated in many ways in the body, and this strong relation is seen in **hair** also. The association is primarily established in bone, where they are jointly used to form the mineral matrix of bone tissue. High magnesium and high calcium may be seen elevated in tandem under conditions of bone loss. Malabsorption should be investigated if low hair magnesium is detected.

### Potassium (K)

Potassium is the most abundant intracellular cation in eukaryotic cells. Only 2% of total-body potassium is extracellular. Potassium insufficiency has been implicated in stroke, cardiac dysfunction, hypertension, renal stone formation, hypercalciuria, and postmenopausal osteoporosis. Potassium is important in maintaining acid-base equilibrium and in insulin sensitivity, and it has been suggested to play a role in neurological complaints (including schizophrenia and brain injury), and gastroesophageal reflux disorder (GERD).

**Red blood cells** may be the best specimen for assessing total body potassium status, as they reflect intracellular levels of potassium over the erythrocyte life cycle.

**Hair** potassium levels decrease after prolonged alcoholism, apparently showing chronic deprivation of hair follicles during their active growth phase. Low values are frequently found

in highly trained athletes and may indicate proper intake and utilization of this element. High hair potassium may suggest imbalanced whole body homeostasis of potassium, such as that seen in adrenocortical insufficiency. Abnormal potassium balance should be further investigated with blood and/or urine measurements of potassium. Certain shampoos can contaminate hair with potassium.

Unpublished studies conducted at Metametrix have shown an association between elevated **hair** potassium and increased risk factors of atherosclerosis. For example, the well-known risk factor, LDL/HDL cholesterol, is greater in individuals with high hair potassium. Studies with cystic fibrosis indicate that when there is normal potassium retention by the soft tissues, hair potassium remains normal or low. Only when potassium retention becomes elevated does hair potassium show abnormal high values.

If renal failure is not present, **urinary** potassium excretion accurately reflects potassium intake (likely from fruits and vegetables) on the day the specimen was collected. Some epidemiologic studies have shown that urinary potassium is significantly less in African-Americans, whether on random or controlled diets. Urinary potassium correlates with bone density at femoral, neck and lumbar spine as well as total-body bone density in children.

### Sodium (Na)

Sodium deficiency is rarely considered outside of unusual circumstances in losses due to vomiting and diarrhea or sweating. Excessive sodium intake is widely considered to be a risk factor for hypertension in salt-sensitive individuals. Frequent monitoring with 24-hour urinary sodium measurements is recommended to help educate patients who need to lower sodium intake. Magnesium deficiency has been demonstrated to impact electrolytes, including sodium, potassium, and calcium.

High **hair** sodium indicates potential for impaired renal function. Electrolyte balance may be disturbed, causing excessive retention of sodium and accumulation in hair. Some evidence points to an association of chronic stress reaction with decreased hair sodium and/or potassium, possibly due to inadequate renal response to adrenal hormones. Adrenocortical hyperactivity may result in high hair sodium. Further testing for sodium balance can be done with blood testing of sodium and electrolyte levels.

## Phosphorus (P)

**Blood** and **urine** specimens are used to evaluate phosphorus status as part of profiles to diagnose parathyroid, bone and calcium disorders, vitamin D imbalances, and kidney abnormalities. Little is known about the significance of **hair** phosphorus above reference range values, and should be interpreted together with other phosphorus measurements.

## Iron (Fe)

Ferritin and transferrin saturation are some of the best **blood** markers of iron status. Ferritin is an excellent measure of iron stores in patients who do not have an underlying inflammatory process. Transferrin saturation is a good marker of iron overload.

The iron in **hair** is unrelated to the major iron pool in the pathways of hemoglobin. Conditions of iron accumulation, such as hemochromatosis or hemosiderosis, do not manifest as elevated hair iron. Long term chronic iron deficiency has been associated with low hair iron.

## Zinc (Zn)

Zinc is necessary for growth and development of all living organisms due to its role in numerous catalytic and regulatory enzymes and in protein folding and receptor binding. It is a cofactor for more than three hundred known enzymes. Symptoms of mild and severe zinc deficiency include depressed growth, teratogenesis, poor carbohydrate metabolism, altered cognition, poor immune function, alopecia, impotence, eye and skin lesions, and diarrhea. Causes of zinc deficiency include: maldigestion and malabsorption, chelation, low dietary zinc, extensive use of diuretics, metallothionein dysfunction, high alcohol intake, surgery, and burns.

Zinc is vital to the normal healing of wounds and skin disorders and is required for normal immune function. To date, there is no generally accepted standard index for zinc status, although levels of zinc in whole blood, plasma, blood cells, and urine tend to fall in severe zinc depletion. Ultimately, gathering multiple measurements of zinc status is ideal in an effort to put together the puzzle of a patient's total-body zinc status. Zinc can help prevent cadmium toxicity.

**Erythrocyte** zinc levels become low in zinc depletion. Erythrocyte zinc analysis is useful primarily due to high concentration of zinc in enzymes such as carbonic anhydrase.

Additionally, since red blood cells remain in the circulation for 110 to 120 days, RBC zinc levels reflect long-term zinc stores. Low zinc in RBCs was seen in 1 of 3 cystic fibrosis patients ( $n = 51$ ). High erythrocyte zinc has been found in cases of cancer metastasis, hypertension and renal failure.

**Urinary** zinc has also been shown to be a useful biomarker of zinc status, and correlates with plasma zinc levels. Low urinary zinc indicates zinc deficiency. Urinary zinc levels are high in muscle protein catabolism precipitated by starvation or trauma. Some studies show that in zinc depletion, urinary zinc decreases, and in zinc excess, urinary zinc increases, indicating a renal mechanism in regulating total-body zinc. Urinary zinc, but not copper, was found significantly higher in stone formers than in controls.

Nutritional zinc deficiency has been associated with low **hair** zinc levels. Elevations of hair zinc have been reported only during the special metabolic needs of pregnancy, where the high values were present together with evidence of zinc deficiency. Such a "false" high value in a tissue like hair is not indicative of systemic elevation, but possibly of the system depletion. Chemical treatments of hair using bleaches, dyes, or permanent solutions can result in low hair zinc. Some denture adhesives, ointments and shampoos (Table 3) contain zinc and may cause high levels of zinc in hair.

## Copper (Cu)

Copper is required for over 30 metalloproteins involved in oxidation-reduction reactions; neurotransmitter, energy, myelin, and bone or connective tissue production; immune function; and hematopoiesis.

**Table 3. Shampoos Containing Zinc or Selenium**

	Shampoo
Zinc-containing shampoos	Head & Shoulders® Zincon® Dandrex® Subulon DHS Zinc ZNP Bar Theraplex Z
Selenium-containing shampoos	Selsun Blue® Head & Shoulders Intensive Treatment® Selenium sulfide 1% Selseb Selsun 2.5% Exsel 2.5% Selenium sulfide 2.5%

An extensive body of evidence exists for copper deficiency associated with cardiovascular disease: aortic fissures and rupture, arterial foam cells and smooth muscle migration, cardiac enlargement and rupture, coronary artery thrombosis, and myocardial infarction. Mild copper deficiency can also contribute to elevated cholesterol, impaired glucose tolerance, and erythropoietin and iron resistant normocytic anemias, as well as neutropenia, thrombocytopenia, peripheral neuropathy, defective elastin, and bone demineralization. A type of myeloneuropathy similar to that seen in vitamin B12 deficiency, but responding to copper supplementation, has also been reported. Menke's disease is a copper deficiency condition.

Dietary deficiency of copper is seen as low levels of **erythrocyte** copper even in early stages of copper depletion. Chronically elevated **plasma copper** may result in elevation of erythrocyte copper levels as well, although the two specimens represent different copper utilization. Approximately 80% of erythrocyte copper is associated with superoxide dismutase (SOD), while most plasma copper is bound to ceruloplasmin. RBC copper appears to be closely associated with hepatic copper utilization.

Chronic copper exposure via copper piping or copper cooking utensils can lead to poisoning. Environmental and occupational exposures and excess supplementation can also lead to high copper. Symptoms include nausea, vomiting, and diarrhea. High levels of copper can result in depression, irritability, muscle and joint pain, tremor, learning disabilities, behavioral disorders, and hemolytic anemia. Long term exposure to elevated copper can result in hepatic cirrhosis. Biliary obstruction is sometimes seen with high copper due to difficulty excreting copper. Renal dysfunction may be associated with high copper levels.

High blood levels of copper have been seen in Wilson's disease and in the elderly. Autistic children have been shown to have high serum copper-zinc ratio and low ceruloplasmin. Copper dysregulation is present in some neurodegenerative conditions such as amyotrophic lateral sclerosis (ALS), Parkinson's disease, Down's syndrome, and idiopathic seizure disorder.

Low **hair** copper offers evidence that either dietary copper is low or other conditions have diminished tissue copper supply. Excess dietary copper can lead to elevated hair levels.

However, in copper loading diseases, such as Wilson's disease, high hair copper is not detected. Exogenous contamination of the hair with copper (hair treatments, public pools or hot tubs, bathing water transported through copper pipes) can be misleading about the patient's total body copper status.

Although **urinary** copper is occasionally used to assess body status, it is primarily useful for diagnosis of copper toxicity, such as in Wilson's disease, where excretion is significantly elevated.

### Manganese (Mn)

Manganese is a cofactor for enzymes involved in metabolism of amino acids, lipids, and carbohydrates. Physiological activities include immune function, regulation of blood sugar and cellular energy, reproduction, digestion, bone growth, and protection from oxidative challenge. Manganese with vitamin K supports blood clotting and hemostasis.

Toxic effects of inhaled manganese present in dust or aerosols have been reported from occupational exposure in welding or steel alloy production. Toxicity via ingestion, primarily from water sources, has also been reported. Frank manganese toxicity, "manganese madness," presents similarly to schizophrenia. Symptoms include compulsive or violent behavior, emotional instability, hallucinations, fatigue, and sexual dysfunction.

**RBCs** are best associated with long-term levels and are considered to be a good index of manganese status. RBC manganese demonstrates a high correlation with magnetic resonance imaging (MRI) ( $r = 0.55, p = 0.02$ ) in manganese-exposed workers prior to onset of clinical symptoms. RBC and MRI manganese assessment also correlated in liver cirrhosis patients.

**Hair** manganese is a valid indicator of toxicity in cases of manganese excess, but there is controversy over its use for deficiency states. Neurological disorders, such as epilepsy and Down Syndrome, are extreme conditions that have been associated with low hair manganese.

### Selenium (Se)

Due to the role of selenoproteins in glutathione peroxidase (GPx), thioredoxin reductase, and iodothyronine deiodinase, it is not surprising that selenium deficiency affects most

physiologic systems, including endocrine and reproductive, hepatic, cardiovascular, immunological, gastrointestinal, and musculoskeletal systems. Symptoms of selenium deficiency are: alopecia, weight loss, increased inflammatory response or depressed immune function, malaise, stunted growth, skeletal and muscular dysfunction. Selenium is widely recognized as a key nutrient in cancer prevention and treatment. Selenium has been shown to inversely correlate heart disease and asthma. Selenium can help protect from mercury toxicity and is a cofactor in deiodination of T4 to T3. It has also been suggested to protect from arsenic toxicity.

Frank selenium toxicity, called selenosis, is rare in humans. However, cases have been noted, primarily caused by contaminated soil. Symptoms of selenosis include garlic breath odor, thick brittle fingernails, dry, brittle hair, red swollen skin of the hands and feet, and nervous system complaints including numbness, convulsions, or paralysis.

**Erythrocytes** can be useful to establish selenium status, as selenium is present in high concentrations in erythrocyte glutathione peroxidase. However, of all the selenoproteins, GPx has the lowest threshold for selenium saturation. Therefore, a patient may have high or normal RBC Se levels (due to GPx), while other tissues are still low in Se. In clinical settings, **whole-blood** selenium is widely used to assess selenium status. Also, large studies evaluating selenium in cancer and other diseases have relied on plasma and serum levels. Whole blood selenium may be more reflective of long term selenium status than plasma selenium.

When exogenous selenium exposure, especially from shampoos, can be ruled-out (see Table 3), **hair** selenium may accurately reflect selenium status. Selenium is readily accumulated in the cysteine-rich residues of hair, and hair selenium can reflect dietary intake in both animal and human studies. Low levels of hair selenium may be associated with poor dietary intake or cardiovascular disorders.

### Molybdenum (Mo)

Molybdenum supplementation has been shown to reduce sulfite sensitivity, a condition marked by asthma, shortness of breath, edema, dermatitis, and possible anaphylaxis by increasing sulfite oxidase activity, in patients with low blood molybdenum. Frank molybdenum deficiency states are largely relegated to those on total parenteral nutrition, with symptoms including mental disturbance and coma. **Blood**

and **urine** specimens have been used for direct molybdenum measurement, but they are mainly reflective of intake and have not been adequately evaluated.

Given the cysteine-rich composition of hair, and molybdenum's ability to complex with sulfur, **hair** should concentrate molybdenum more effectively than other tissues. Indeed, a few studies show correlation of hair molybdenum with disease conditions. One study showed low molybdenum in patients with severe motor disabilities on enteral nutrition. An additional study showed correlation with water and hair molybdenum levels.

### Chromium (Cr)

Unlike most essential elements that have multiple metabolic functions, the only known role for chromium (Cr) is in potentiating insulin receptor tyrosine kinase. This nutrient impacts sugar metabolism through its role in uptake of insulin. High chromium in urine is related to increased mobilization and in response, frequent blood sugar peaks. Given the difficulties with interpretation of direct chromium concentration measurements, functional evidence for dysglycemia, such as elevated blood glucose and insulin levels, or an abnormal glucose-insulin tolerance test can provide additional evidence of chromium insufficiency. Thus far, the reversal of dysglycemia with chromium supplementation is currently the only generally accepted diagnosis of chromium deficiency.

Occupational or hobbyist exposure to chromium through paints, metalwork, cement, or chemical use can cause elevation. Chromium may also be present in detergents and bleaches. Exposure may cause dermatitis as chromium is a common skin irritant in allergic eczema. Forms of chromium (i.e., hexavalent) are highly toxic, but acute exposure to such compounds is rare outside of the chemical industry.

**Erythrocyte** chromium has been used to assess excessive levels of exposure in workers exposed to chromate.

When external chromium contamination from shampoos or water is ruled out, **hair** continues to be a viable specimen option for establishing long-term chromium status. Elevated chromium in hair is an unusual finding.

Since chromium is excreted as the insulin-stimulated metalloprotein chromodulin, **urinary** chromium presents

a special situation, where levels may provide a type of functional assessment because of the high percentage that is excreted in the form of chromodulin. Further research into the interpretation of fasting and non-fasting urinary chromium levels is warranted.

Measures of poor blood sugar regulation such as high blood glucose, high insulin, and high hemoglobin A1c could be used to help determine chromium need.

### Cobalt (Co)

Cobalt (Co) is an essential trace element due to its well-known role in vitamin B12, important in hematopoiesis and thyroid function. The consequences of B12 deficiency are well known, including central nervous system complaints, pernicious anemia, and potentially fatal macrocytic anemia. Ingested cobalt is largely excreted in urine. Whole-blood cobalt was detected at approximately 0.17 µg/L in patients awaiting surgery. Toxicity may occur at cobalt intakes above 300 mg/d, although even therapeutic doses at 29.5 mg/d have been associated with toxicity, including goiter, hypothyroidism, and heart failure.

Very little data is available on clinical indications of high hair cobalt and we observe that multiple abnormal values for several elements are present most of the time when cobalt elevation is seen. Low hair cobalt may indicate B12 deficiency, but further research is needed to substantiate this claim.

### ELEMENTS OF UNCERTAIN HUMAN REQUIREMENT

#### Boron (B)

Boron is best known for its role in bone and joint health because of the effects on steroid hormones including estrogen, testosterone, DHEA, and 1,25 dihydroxy-cholecalciferol. Boron also affects nutrient element metabolism. Boron markedly reduces urinary calcium and magnesium loss, as well as increases calcium absorption. In human studies, when compared with healthy bone, arthritic bone was associated with almost a 20-fold decrease in boron content. The bone, spleen, and thyroid have the highest contents of boron. Average boron intake has been estimated at 1 – 4 mg/day in the U.S.

Boron toxicity has been shown to cause testicular atrophy, decreased seminal volume, decreased sexual activity, and

stunted growth. Boron can be found in water and in foods such as nuts, leafy vegetables, non-citrus fruits, legumes, cider, wine, or beer. Other sources of boron are sodium borate and boric acid. Borax (meaning boron-containing compounds) and boric acid are well-known antimicrobials, and each has been used in laundry detergent and medicinals. Boron may also be found in ceramics, glass, and cement. Excessive intake of boron can cause riboflavinuria.

**Serum** and **urine** boron measurements have been employed to establish supplementation efficacy, rates of excretion, and dietary intake. **Hair** has been used to screen for boron deficiency. However, as with any hair analysis, one must carefully consider external contamination; since many commonly used hygiene products contain boron, including shampoos and soaps.

#### Nickel (Ni)

Deficiency of nickel is associated with poor growth and reproductive dysfunction. Nickel has been shown to work in a cooperative way with calcium, iron, and zinc.

Chronic exposure to some forms of nickel via inhalation is carcinogenic. Mucosal tissue irritation associated with nickel can manifest as asthma, rhinitis and sinusitis. Pulmonary inflammation may arise after breathing in nickel in the form of dust or smoke. Nickel toxicity may result in liver necrosis or carcinoma.

Hypersensitivity reactions may occur with chronic nickel exposure. Dermatitis is also associated with nickel worn as jewelry. Other sources of nickel include stainless steel, tobacco smoke, industrial exhaust fumes, batteries, as well as electronic and plating and mining industries. **Urine** and **plasma** have been used for assessing nickel exposure, although only acute exposure is revealed because nickel is rapidly cleared from blood. **Hair** nickel has been measured for assessment of nickel status, and may prove a useful biomarker for past exposure. However, hair can be contaminated with nickel from hair dyes or hair treatments. Hair nickel levels were shown to be elevated relative to controls in 71 nickel-sensitive women. D-penicillamine and EDTA are thought to mobilize nickel.

#### Lithium (Li)

**Urine** has been used to establish lithium deficiency. Research

has found urine lithium levels showed significant inverse correlation with neurosis, schizophrenia, psychiatric admissions, and violence, in decreasing order of magnitude.

**Hair** lithium levels have been shown to correlate with total body content. Numerous studies have shown that lower lithium values correlate with increased violent criminality, learning disabilities and heart disease. Students in high academic standing had greater hair lithium levels than average students. Low hair lithium was demonstrated in young children with autism.

At the supraphysiologic doses used to treat psychosis, lithium has a narrow therapeutic range, and toxicity may occur. Lithium toxicity may be life threatening or result in persistent cognitive and neurological impairment. **Serum** lithium must therefore be closely monitored.

### Vanadium (V)

Some studies suggest vanadium has a role in glucose and lipid metabolism, red blood cell formation, and thyroid function. Vanadium assessment and treatment may be indicated in cases of metabolic syndrome or non-insulin-dependent diabetes mellitus due to vanadium's role in insulin sensitization. Symptoms that appear to be associated with excessive vanadium are hypertension, decreased coenzymes A and Q10, bipolar disorder, and disruption of energy metabolism.

Exposure to vanadium in air or water is of concern for those exposed to vanadium industrial plants. Symptoms may include respiratory disorders, green tongue, high urinary excretion of vanadium, and reduced neurobehavioral abilities. **Urine** vanadium is traditionally used to assess occupational exposure. **Whole blood** vanadium has been shown to significantly differentiate children with vanadium exposure from non-exposed children but authors stated that **hair** levels of vanadium did not significantly correlate with vanadium exposure. This may have to do with distinction of acute versus chronic exposure.

### Strontium (Sr)

Strontium incorporates into hydroxyl crystal lattice of bone, stimulates new cortical and cancellous bone formation, and decreases bone resorption by inhibiting osteoclastic activity. There are a number of stable isotopes of strontium,

including  $84\text{Sr}$ ,  $86\text{Sr}$ ,  $87\text{Sr}$ , and  $88\text{Sr}$ . Radioactive strontium,  $90\text{Sr}$ , is a nuclear waste product and a human carcinogen. **Serum** strontium levels have been evaluated during therapy to establish GI absorption. Strontium has been shown to concentrate in **hair** with increased environmental exposure. Like calcium and magnesium, strontium is deposited in bone. Conversely, it is mobilized from bone when blood calcium levels fall. Elevated levels in hair may signal negative calcium balance and provides a valuable marker for the risk of bone loss.



## TOXIC ELEMENTS

### General Mechanisms of Metal Toxicity

Toxic metals tend to accumulate undetected in the body over time. They are virtually indestructible and can affect membrane or structural proteins, enzymes, membrane lipids, or DNA. The toxic element may displace an essential element from its binding site and thereby disrupting protein function or it may cause neurotoxicity by: (1) inorganic element transformation to an organic species, (2) sulphydryl group binding, and/or, (3) free radical generation. Unchecked formation of free radicals leads to lipid peroxidation, cellular membrane degeneration, and ultimately cell death.

### Causes of high toxic elements in blood, hair, or urine are:

- Environmental food, water, or airborne particulate exposure
- Work-related exposure
- Use of toxic element-containing products
- Increased intestinal uptake (exacerbated with essential element deficiencies)
- Poor elimination (gut, liver, kidney dysfunction)
- Exogenous contamination (hair)

**Table 4. Symptoms, Sources, Treatments in Toxic Element Elevations**

Elevated Toxic Element	Associated Symptoms and Diseases	Sources	Protective Measures	Chelating Agents
Aluminum	Abnormal speech, myoclonic jerks, osteomalacia, progressive encephalopathy, Alzheimer's disease, Parkinson's disease	Aluminum cookware, antacids, drinking water, tobacco, and cannabis smoke	Adequate iron (check ferritin), glycine, calcium, phosphorus (lowers intestinal absorption)	DFO, DMHP
Arsenic	Peripheral arteriosclerosis ("blackfoot disease") "rice-water" stools, proteinuria, hyperkeratosis, "milk and roses" hyperpigmentation, garlic breath odor, stomatitis	Metal foundry, drinking water, seafood, glues, industrial exposure, contaminated wine, contaminated herbal supplements, cigarette smoke, arsenic-treated wood	Selenium, <i>Emblica officinalis</i> , sulfur amino acids, glutathione	DMSA, DMPS, DMPA
Cadmium	Femoral pain, lumbago, osteopenia, renal dysfunction, hypertension, vascular disease	Industry, spray paint, tobacco smoke, car emissions, plants grown in cadmium-rich soil	Zinc, iron, antioxidants	EDTA; DMSA and NAC (experimental)
Lead	Microcytic hypochromic anemia, renal dysfunction, hypertension, anorexia, muscle discomfort, constipation, metallic taste, low IQ (children)	Certain supplements, paint, contaminated soils (and plants grown in them), plumbing	Alpha lipoic acid-protection against toxicity, iron (reduces intestinal absorption)	Ca –EDTA
Mercury	Mental symptoms (erethism, insomnia, fatigue, poor short- term memory), tremor, stomatitis, gingivitis, GI and renal disturbances, decreased immunity	Dental amalgams, fish consumption, preservatives (esp. thimerosal), industrial release effects	Selenium (protects against cellular toxicity)	DMSA, DMPS

**Table 5. Commonly Used Chelating Agents**

Name	Abbreviation	Administration	Metals Bound
2,3-Dimercapto-1-propane sulfonic acid	DMPS	IV, Oral	Arsenic, lead, mercury
Meso-2,3-dimercaptosuccinic acid or succimer	DMSA	IV, Oral	Arsenic, copper, lead, mercury
Dimercaprol (British anti-Lewisite)	BAL	IV	Arsenic, copper, lead, mercury
D-Penicillamine (Cuprimine, Depen)	DPA	IV	Arsenic, copper, lead, mercury
Desferoxamine	DFO	IV	Aluminum, iron
Calcium disodium ethylenediaminetetraacetic acid	CaNa <sub>2</sub> -EDTA	IV, rectal suppositories	Cadmium, lead, manganese

**Table 6. Commonly Used Conversions in Toxic Metal Assessment**

ppb = ng/ml

ppm =  $\mu$ g/mL or mg/L

ppb/10 =  $\mu$ g/dL (primarily used for lead assessment)

1ppb = 0.001 ppm

Table 7. Sources of Toxic Elements

Aluminum	Cadmium	Lead	Mercury	Arsenic
Aluminum cooking utensils	Drinking water	Some red lipsticks and painted toys	Dental amalgams	Rat poisons
Baking powder (Al sulfate)	Soft water (from galvanized pipes)	Leaded house paint	Broken thermometers and barometers	Automobile exhaust
Antacids (certain brands, see labels)	Soft drinks from dispensing devices with galvanized plumbing	Drinking water from lead plumbing	Grain seeds treated with methylmercury fungicide	Household detergents
Antiperspirants	Refined wheat flour	Vegetables grown in Pb-contaminated soil	Predator fish, certain lake fish	Wood preservatives
Aluminum cans	Canned evaporated milk	Canned fruit and juices, canned evaporated milk, boxed wines	Mercuric chloride Thimerosal (Ethylmercurithiosalicylic acid sodium salt)	Insecticide residues on fruits and vegetables
Drinking water (alum used as bactericide)	Processed foods	Certain Chinese and Ayurvedic herbal preparations	Calomel (body powder, talc, laxatives)	Wine (if arsenic in pesticides used)
Milk and milk products (from equipment)	Oysters, kidney, liver	Milk from animals grazing on Pb-contaminated land	Cosmetics (check labels if possible)	Colored chalk
Alum in pickled foods (check labels)	Cigarette smoke, tobacco products	Bone meal	Latex and solvent-thinned paints	Wallpaper dye and plaster
Nasal spray	Superphosphate fertilizers	Organ meats such as liver	Hemorrhoid suppositories	Drinking water, seawater, well water
Toothpaste	Dental appliances	Lead-arsenate pesticides	Mercurochrome, merthiolate	Sewage disposal
Ceramics (made from Al 203 clay)	Ceramic glazes	Leaded caps on wine bottles	Fabric softeners	Seafood (source of non-toxic arsenic)
Dental amalgams	Paint pigments	Rainwater and snow	Floor waxes and polishes	Chicken
Cigarette filters and tobacco smoke	Electroplating	Improperly glazed pottery	Air conditioner filters	
Automotive exhausts	Silver polish	Painted glassware	Wood preservatives	
Pesticides	Polyvinyl plastics	Painted pencils	Certain batteries	
FD&C color additives	Rubber carpet backing	Toothpaste	Fungicides for lawns and shrubs	
Vanilla powder	Nickel-Cadmium batteries	Newsprint	Leather tanning products	
Table salt, seasonings	Rust-proofing materials	Colored printed materials	Thimerosal-preserved immunization fluids	
Bleached flour		Eating utensils	Adhesives	
American cheese		Curtain weights	Skin-lightening creams	
Medications containing kaolin (Al silicate)		Putty	Certain ointments to treat psoriasis	
Sutures with wound-healing coatings		Car batteries	Photoengraving	
Rat poisons		Cigarette ash, tobacco	Tattooing	
		Lead shot, firing ranges	Sewage sludge used as fertilizer	

### Managing Patients with Metal Toxicities:

1. Identify and avoid exposure to the toxic element
  - a. Test water
  - b. Evaluate cooking utensils
  - c. Evaluate building materials in the home
  - d. Diet: eat organic fruits and vegetables, consider seafood as a source of toxic elements
  - e. Evaluate source of herbal supplements for contamination
  - f. See Tables 4 and 7 for sources of toxic elements
2. Increase elimination by improving GI, liver, and kidney function
  - a. Methionine - 3,000 mg/d, vitamin B12 - 1,000 µg/d, and folate - 800 µg/d
  - b. N-Acetylcysteine at 3-4 g/day (high doses have been associated with pulmonary hypertension)
  - c. Sauna
  - d. Reduce intestinal absorption
    - i. Total dietary fiber intake to 30-40 g/day, hydration: drink 60 - 90 oz. clean water daily
    - ii. Bentonite
    - iii. Beans, cooked vegetables, whole grain breads
    - iv. Whole grain cereals, especially oatmeal
    - v. Fresh fruits, especially apples
3. Protect against damage
  - a. Anti-oxidants including vitamin C at 3 g/day or more; lipoic acid 200 mg TID
  - b. Give protective agents such as nutrient elements or elements that compete for binding sites
4. Consider oral or intravenous chelation if warranted by clinical symptoms and test data
5. See Table 5 for commonly used chelating agents

### Aluminum (Al)

The major tissue sites of aluminum toxicity are the nervous system, immune system, bone, liver, and red blood cells. Aluminum may also interfere with heme (porphyrin) synthesis. Consequences of aluminum toxicity are encephalopathy and abnormal speech, myoclonic jerks, convulsions, and a predisposition to osteomalacic fractures.

Exposure to aluminum is ubiquitous via food, water, air and soil. Aluminum is used to produce beverage cans, cooking pots, siding, roofing, aluminum foil and airplanes. Further, it is found in antacids, buffered aspirin, food additives (especially in grains and cheeses), astringents, vaccinations,

cat litter, antiperspirants, infant formula, and baking soda. Aluminum has been detected in calcium, magnesium, and phosphate salts used in parenteral solutions, and it has been found high in lung tissue as a result of tobacco and cannabis smoke inhalation. When aluminum is used in water treatment facilities, concentration in community water supplies can reach 93 µmol/L (2,500 µg/L).

Though not proven as a causative agent, it is striking that the neurofibrillary tangles of neurons that characterize the brains of Alzheimer's patients (as well as in patients with amyotrophic lateral sclerosis and Parkinson's and Huntington's diseases) accumulate aluminum. A study group with aluminum exposure had higher vanillylmandelic and homovanillic acids in urine and were significantly different from controls on neurobehavioral tests. Aluminum replaces calcium in bone, disrupting normal osteoid formation and mineralization.

Iron deficiency predisposes laboratory animals to higher aluminum absorption and, conversely, aluminum decreases absorption and uptake of iron. Aluminum concentration was found high in the liver and kidney and distribution of essential minerals, in tissues such as bone, brain, liver, and kidney, were altered in aluminum-treated rats. Assessing copper, zinc, and iron status helps to determine a patient's vulnerability to the toxic effects of aluminum, and appropriate elemental treatments may help to overcome aluminum toxicity. Testing for anemia is indicated in patients with high RBC, plasma, or serum aluminum. Higher plasma aluminum is seen in infants fed soy formula compared with breast-fed infants.

**Serum, erythrocyte, and plasma** aluminum levels appear to correlate. Serum aluminum levels above 5 µmol/L (135 µg/L) are predictive of aluminum toxicity. Testing for anemia is indicated in patients with high blood levels of aluminum. High hair aluminum has been shown in aluminum toxicity and therefore, a high value in hair likely reflects a regular source of exposure and should be eliminated. **Urinary** aluminum can provide information about aluminum intake and has been used to monitor humans exposed to dangerous amounts of aluminum. Because aluminum is ubiquitous in the environment, contamination of a patient's specimen with aluminum is possible when collection containers are opened in living and work environments.

Desferrioxamine (DFO) is a chelator of aluminum and iron that has been used to treat acute aluminum toxicity. In fact, cases of aluminum toxicity are managed similarly to iron toxicity. DFO decreased RBC and plasma aluminum and improved hemoglobin, hematocrit, and mean cell volume in 13 patients. Chelation treatment with desferrioxamine should be handled conservatively due to the risk of inadvertently mobilizing large amounts of aluminum to the brain, which may enhance encephalopathy or a chemical interaction. The chelator, L1 (1,2-dimethyl-1,3-hydroxypyrid-4-one deferiprone or DMHP) has also been used to lower aluminum total-body burden. Ascorbate combined with DFO has been used to remove aluminum from human brain cells. Glycine has been used to help mobilize aluminum. As discussed above, it is important to assure adequate status of essential elements (calcium, iron, copper, zinc). Silicon is an antagonist of aluminum. Further testing of an aluminum-toxic patient might involve measurement of bone resorption, urinary catecholamines, oxidative stress, and even vitamin D.

### Arsenic (As)

Exposure to arsenic-laden drinking water can induce symptoms of gastroenteritis and lead to cancer, diabetes, and neurological and vascular dysfunction. Long-term arsenic exposure in drinking water shows a dose-response relationship to carotid atherosclerosis. The mechanism involves the induction of expression of genes coding inflammatory mediators. Arsenic has also been linked to dermatosis and cancers of the skin, bladder, and lung. Dietary arsenic is contributed by various foods including cereals and breads, 18.1%; starchy vegetables, 14.9%; and meats and fish, 32.1% of total average daily intake.

Arsenic exposure is associated with the following clinical symptoms:

- **Neurological:** Central depression with visual effects, headache and high fever
- **Hematological:** Abnormal RBC counts, increased megalocytes and microcytes
- **GI tract:** Increased peristalsis with “rice water” stools
- **Skin:** “Milk and roses” complexion from vasodilation, darkening and degeneration

Laboratory values of arsenic represent both the toxic form of arsenic and the non-toxic form of arsenic. Because seafood is rich in the non-toxic form of arsenic, the clinician should rule out ingestion of seafood in cases of borderline or moderate

arsenic elevation before implementing aggressive therapy.

**Urinary** arsenic is most commonly measured to screen for arsenic exposure. Urine reflects arsenic exposure in the few days prior to specimen collection. To eliminate the contribution of seafood to total arsenic levels, avoid seafood 72 hours before test.

**Hair, nail** and urinary arsenic levels have been shown to be comparable. Hair or nail arsenic represents several months of exposure prior to taking the specimen. Hair arsenic greater than 1  $\mu\text{g/g}$  dry weight has been taken to indicate excessive exposure.

Since elevated arsenic in the **serum** drops within 6 to 10 hours, serum is not the best specimen for determining chronic arsenic exposure. **Whole blood** is suitable for identifying acute exposure to arsenic, and high levels should be addressed immediately.

When arsenic toxicity is suspected, arsenic levels in drinking water should be measured. Support clearance of arsenic with B vitamins, especially folate. Give sulfur amino acids, antioxidants, as well as essential elements. *Emblica officinalis*, a medicinal plant, has shown promising results in animal studies.

### Cadmium (Cd)

The principal organs most vulnerable to cadmium toxicity are kidney and lung. Environmental cadmium exposure is associated with renal tubular damage and high blood pressure. Cadmium toxicity impacts the kidney, where damage to proximal tubules has been described. Also, cadmium compounds are classified as carcinogenic to humans.

Associated conditions include:

- **Renal:** hypertension, kidney failure
- **Neurological:** loss of coordination, numbness of limbs, loss of hearing

**Whole blood** cadmium is indicative of recent exposure, and is therefore not reflective of total-body burden. Normal concentration of whole blood cadmium is up to 1  $\mu\text{g/L}$  for non-smokers, and up to 4  $\mu\text{g/L}$  for smokers. Whole blood levels of 10  $\mu\text{g/L}$  have been associated with renal dysfunction.

**Urinary** cadmium may be reflective of total-body burden, although recent exposure will increase levels. Monitoring

urinary output of cadmium is an excellent means of assessing exposure, given normal renal function. Daily output of cadmium of 2 to 4 µg per 24-hour urine indicates toxicity (approximately 1–3 µg/g creatinine).

High **hair** cadmium is an indication of increased body burden. Elevated hair cadmium has been demonstrated in smokers. When a combination of high cadmium and low zinc is found, potential toxic effects may result because zinc competes for some protein binding sites that are sensitive to cadmium.

The toxic effects of cadmium may be reduced by specific dietary components or supplements such as vitamins E and C and carotenoids, as well as the botanical black cumin seeds, and if indicated, vitamin D. Repletion in iron and the amino acids comprising the glutathione tripeptide is recommended. Supplementation with zinc and selenium salts also can reverse inhibitory effects of cadmium on human peripheral blood mononuclear cell proliferation and cytokine release. Chelating agents used in cadmium toxicity include EDTA, DMSA, and N-acetylcysteine.

### Lead (Pb)

Lead toxicity causes paralysis and pain in the extremities due to effects on demyelination, axonal degeneration, and presynaptic block. Lead toxicity commonly affects sensory, visual, auditory, and cerebellar (coordination) functions, reflecting its impact on the nervous system. Normocytic, sideroblastic anemia is the consequence of lead's inhibiting effects on enzymes in the heme biosynthesis pathway. Other clinical signs associated with lead toxicity are kidney damage, epigastric pain and nausea, and male and female reproductive failure.

Hyperactivity, anorexia, decreased play activity, low intelligence quotient and poor school performance have been observed in children with high lead levels. Sources of lead include lead pipes, painted toys, some red lipsticks, lead paint or its dust, soil around old cars, old homes, or highways (past leaded gasoline contamination). Other sources are found in Table 7.

**Hair** lead is a sensitive measure of lead exposure. For those in apparent steady-state lead balance, hair levels were well correlated with blood lead. Normally, hair lead content is < 5 µg/g. Lead levels > 25 µg/g indicate severe lead exposure. Some hair darkening products contain lead acetate and may

elevate lead levels in hair.

**Whole blood** is concentrated about 75-fold greater than that of serum or plasma and it has the highest correlation with toxicity. For this reason, whole blood lead is defined by the CDC as the preferred test for detecting lead exposure. The World Health Organization has defined high whole-blood lead levels as > 20 µg/dL in adults and > 10 µg/dL in children. As of 2007, the CDC acceptable level of whole blood lead was 10 µg/dL. Some have proposed to lower reference values for whole blood lead.

**Urinary** lead concentrations increase with lead poisoning, although urinary elimination of lead is a process that occurs for many days after a single exposure.

Prevention continues to be the best route for reducing toxic effects of lead. Nutritional and adjunctive support for the lead-toxic patient includes promoting gastrointestinal integrity and supplementing with calcium, magnesium, iron, and vitamins C and D. Carotenoids have also been found to be lower in lead-exposed workers. Nutrients with demonstrated benefit when used with or without chelating agents include alpha lipoic acid, zinc, taurine, selenium—which is able to bind lead directly—and N-acetylcysteine.

**Table 8. Potentially Toxic Elements and Rare Earth Elements: Summary of Sources, Symptoms, and Treatments**

	<b>Sources</b>	<b>Symptoms</b>	<b>Treatment</b>
<b>Antimony</b>	Flame retardant in draperies, wall coverings, carpets Cosmetics, food, gunpowder, cigarette smoke Batteries, semiconductors, solder, paints, bearing metals, glass, ceramics, alloys, synthetic fabrics Some anti-helminthic drugs	Fatigue, muscle weakness, headaches, low back pain, myopathy and metallic taste Nausea, vomiting, abdominal pain, hematuria, hemolytic anemia, myoglobinuria, renal failure	Avoidance BAL, DMSA, glutathione, or N-acetylcysteine
<b>Barium</b>	X-ray contrast media, enema salts, foods	Gastrointestinal complaints, muscle weakness, facial numbness, and hypotension	Oral sodium sulfate, treat hypokalemia if present
<b>Bismuth</b>	Alloys, catalysts, ceramics cosmetics, magnets, paints, pharmaceuticals, semiconductors, x-ray contrast media	Nausea, vomiting, diarrhea Possible renal, neurological and hematological problems	BAL or penicillamine for chelation
<b>Cerium</b>	Food (collard or turnip greens), Ceramics, dental compositions, some zirconia-based products, steel manufacturing, coloring and polishing of glass, flat screen televisions, low-energy light bulbs, alloys Red pigmentation of toys, household items and crates	Itching, sensitivity to heat, skin lesions	Avoidance and treat for symptoms and conditions
<b>Cesium</b>	Rocks, soil and dust Photoelectric cells, photo emitter devices, scintillation counters, atomic clocks Released into the air from pollucite mining, energy and electronic production, fly ash	Mild toxicity: gastrointestinal distress, hypotension, loss of consciousness, numbness or tingling of lips High levels: severe hypokalemia, hypomagnesaemia, ventricular tachycardia, cardiac arrest	Avoidance and treat for symptoms and conditions
<b>Europium</b>	Rarely encountered Genetic disease testing Nuclear control rods, laser material, television screens	Skin and lung irritation	Avoidance and treat for symptoms and conditions
<b>Holmium</b>	“Getter” in vacuum tubes Alloyed with other metals Spectroscopy Magnets	N/A	Avoidance and treat for symptoms and conditions
<b>Indium</b>	By-product of zinc smelting and lead sulfide ores Alloys, bearings, metal surfaces, mirror surfaces, nuclear reactors, sodium vapor lamps Diagnostic nuclear medicine	Inhalation – lung inflammation Mild reproductive effects May have negative effects on heart, liver, and kidney tissues	Avoidance and treat for symptoms and conditions
<b>Niobium</b>	High temperature-resistant alloys and stainless steel, jewelry, joint replacements, dental implants, super magnets	Possible lung irritation Possible skin sensitization Possible cytotoxicity Renal injury	Avoidance and treat for symptoms and conditions

Table 8. continued

Palladium	Mobile phones, wide screen TVs, computers and electrical appliances White gold jewelry Petroleum production catalyst, metalizing ceramics, dental alloys Food	Possible lung inflammation Skin sensitization Allergic reaction	Avoidance and treat for symptoms and conditions
Platinum	Jewelry Surgical tools Laboratory utensils Electrical resistance wires Automobile catalytic converters Liquid crystal display glass Dental restorations Chemotherapy drugs Silicone breast implants	Contact dermatitis, urticaria Respiratory symptoms	Avoidance and treat for symptoms and conditions
Rubidium	Soil, food Photocells, vacuum tubes, glass and ceramics, fireworks, ion engines, vapor turbines, “getter” in vacuum tubes	Chemical burns of eyes and skin, failure to gain weight, ataxia, skin ulcers, nervousness Potassium imbalance	Avoidance and treat for symptoms and conditions
Samarium	Catalyst in organic reactions, production of synthetic products, nuclear reactor control rods, cobalt alloys Industrial sources	Skin and eye irritation, GI symptoms, CNS symptoms, cardiac dysfunction	Avoidance and treat for symptoms and conditions
Tantalum	Capacitors, rectifiers, tools, dental and surgical implants, pen parts, furnaces, aircraft, nuclear reactors Industrial sources	Skin and eye irritation Lung irritation and lung disease	Avoidance and treat for symptoms and conditions
Tellurium	Food Ceramics, steel, cast iron, copper Alloys chemicals catalysts in the petroleum industry Production of rubber	Garlic odor on breath or sweat, alopecia after dietary intake (in rats)	Avoidance Nutrients supporting methylation pathways BAL Eliminate exposure
Terbium	Lasers, semiconductor devices, phosphors in color television tubes Solid-state devices	Eye and skin irritant, digestive tract irritation, respiratory tract irritation	Avoidance and treat for symptoms and conditions
Thorium	Naturally occurring in rocks, soil, water, plants, animals Production of gas mantles for lanterns, crucibles, tungsten wire coating, camera lenses, welding rods, light bulb filaments Nuclear energy fuel	Lung disease Increased lung, prostate, bone, and blood cancers Skin irritation	Avoidance and treat for symptoms and conditions
Thulium	Industrial sources Ceramic magnetic materials in microwave equipment Doping agent in lasers	Irritation to respiratory tract; GI tract, skin, or eyes Lung damage Asthma	Avoidance and treat for symptoms and conditions
Tin	PVC, glass coverings, silicone and wood preservative, paints, biocides and pesticides, and medicines Food, cosmetics, dental amalgams, pewter, bronze, preservatives, food and beverage containers, and anticorrosive platings	High levels: neurotoxic, immunogenic, or carcinogenic conditions Eye, skin, and GI irritation as well as testicular degeneration, anemia, and muscle weakness	Avoidance Treatment with selenium may protect against the effects of tin

**Table 8. continued**

<b>Tungsten</b>	Filaments for electric lamps, electron and television tubes, and for metal evaporation work Electrical contact points for car distributors X-ray targets Windings and heating elements for electrical furnaces Missile and high-temperature applications	Pulmonary fibrosis, lung cancer and neurosensory and cognitive deficits Reproductive, neurological and developmental effects	Avoidance and treat for symptoms and conditions
<b>Uranium</b>	Widespread use in military and industry as well as nuclear power	Renal damage Lung cancer	Avoidance IV sodium bicarbonate Inositol hexaphosphate (animal studies)
<b>Zirconium</b>	Gemstone, steel alloy, surgical appliances, light bulbs, poison ivy lotion, lenses, ceramic glazes and enamels	Skin and pulmonic granulomas, reddish-brown papules on abraded skin	Avoidance

## Mercury (Hg)

Mercury intoxication is associated with a triad of symptoms: (1) mental changes, (2) spontaneous tremor and deficits in psychomotor performance, and (3) stomatitis and gingivitis. The toxic effects of mercury have been associated with neurological dysfunction, dementia, and autoimmune diseases. Although research suggests that the etiology of autism is multifactorial, numerous reports demonstrate that aspects of mercury toxicity appear similar to autism symptomatology. According to the CDC, mercury released from amalgams may comprise up to 75% of an individual's mercury exposure. Methylmercury from seafood is considered to be the most important source of non-occupational human mercury exposure.

**Blood** mercury has revealed low level chronic and acute exposure from work environments. Significant exposure is evident when whole blood alkyl mercury is greater than 50 µg/L, or when inorganic mercury (Hg<sup>2+</sup>) exposure is greater than 200 µg/L. Children's reference values for whole blood mercury from 1.5 to 1.0 µg/L have been proposed. Risk of Attention Deficit Hyperactivity Disorder (ADHD) was found to be nearly 10 times higher when blood mercury was above 29 nmol/L. The quantity of mercury assayed in blood and hair, but not urine, correlates with the severity of toxicity symptoms.

**Hair** has been a frequently used specimen by CDC and the Environmental Protection Agency (EPA) for accurately assessing mercury exposure in selected populations. Levels of mercury greater than 1 µg/g also indicate mercury toxicity. A positive correlation of blood pressure with levels of hair mercury has been seen.

The level of mercury in **urine** is a reliable way to assess exposure to inorganic mercury. Daily urinary levels greater than 50 µg indicate a Hg<sup>2+</sup> overload.

Sulfur-containing agents, such as N-acetyl cysteine and dimercaptosuccinic acid (DMSA), can be effective agents for removing mercury from tissues. Research has shown that N-acetyl cysteine and glutathione can protect cells from mercury toxicity. Some antioxidants such as alpha-lipoic acid and glutathione may also possess chelative effects. Dietary selenium has been found to reduce the toxic effects of mercury. Potential sources of mercury include dental amalgams, broken thermometers, cosmetics, and predator or fresh water fish.

## Thallium (Th)

Severe, painful neurological and gastrointestinal symptoms occur from thallium poisoning; alopecia is the most characteristic sign, as it is coupled with a black pigment at the hair root. Nausea, vomiting, and diarrhea have been reported. Thallium exposure may occur due to soil contamination with thallium-containing pesticides although they have been banned since 1972. Specimens used for thallium detection include **urine**, which is the main route of excretion, and **hair**. **Blood** levels have been measured, but thallium is rapidly cleared, so exposure must be acute to achieve accurate results. Treatment for high thallium levels include Prussian blue, DMSA, or activated charcoal for ingested thallium. BAL, D-penicillamine and EDTA are contraindicated.

### POTENTIALLY TOXIC AND RARE EARTH ELEMENTS

These elements have no known function in human physiology, although they are present in the environment as airborne particles as well as in water and food. There are various reports of toxic effects when these elements accumulate, especially in the presence of specific disorders.

### RARE EARTH ELEMENTS

Europium • Holmium • Niobium • Samarium • Terbium • Thulium

Rare earth elements are not actually rare. The name refers to the great difficulty in extracting rare earth elements from the metal ores in the earth's crust. China mines approximately 95% of the rare earth metals. These metals are used in electronic devices such as mobile phones, hybrid cars, batteries, compact fluorescent light bulbs, magnets, lasers, capacitors, superconductors, and phosphors.

The physical, chemical, and toxicological properties of the rare earth elements have not been fully investigated and reported. It is thought that rare earth elements are not absorbed through the skin and are poorly absorbed from the gastrointestinal tract. Skin contact should be avoided, especially if skin diseases or abrasions are present. Rare earth dusts or fumes can be especially dangerous to those with lung disease or decreased pulmonary function. Two cases were documented involving occupational exposure to rare earth elements which caused interstitial lung disease and pneumoconiosis. These elements can be slowly absorbed into the body through the lungs and can cause irritation and ulcers on abraded skin. If a wound is contaminated with a rare earth element, it should be cleaned well and the patient should be removed from the exposure source. There is no specific therapy for exposure to rare earth elements other than avoidance and treating the individual disease conditions that result. According to a material safety data sheet, rare earth element toxicity can cause symptoms of writhing, ataxia, labored respiration, walking on the toes with arched back, and sedation.

### Antimony (Sb)

Antimony-based compounds are used as a flame retardant material in draperies, wall coverings, and carpets. Antimony is present in cosmetic products, food, gunpowder, and cigarette smoke. Antimony is used in the production of batteries,

semiconductors, solder, paints, bearing metals, glass, and ceramics. Some antihelminthic drugs and antiparasitic drugs contain antimony. Other materials containing antimony include alloys, ceramics, glass, plastic, and synthetic fabrics.

A number of studies have associated significantly elevated antimony in both **hair** and liver samples of children who died from SIDS, although other work has challenged the validity of the findings.

Excess antimony exposure can result in fatigue, muscle weakness, headaches, low back pain, myopathy, and metallic taste. Antimony toxicity presents with nausea, vomiting, abdominal pain, hematuria, hemolytic anemia, myoglobinuria, and renal failure. Skin antimony exposure can result in, "antimony spots," which look like chicken pox.

Because **whole-blood** antimony is cleared from the blood slowly over months, it best reflects chronic exposure. **Urine** has shown good correlation with acute antimony exposure. **Hair** antimony can reflect long-term exposure. External exposure from cigarette smoke or gunpowder can result in high hair levels. Treatments for high antimony levels include BAL, DMSA, glutathione, or N-acetyl cysteine. Antimony is conjugated with glutathione and can deplete glutathione levels.

### Barium (Ba)

Barium is used in X-ray contrast media and in some salts for enemas. It is not a highly toxic element, so transient high levels in **hair** may be of small clinical significance. Many foods contain small concentrations of barium, and it responds somewhat like calcium, magnesium, and strontium to physiological controls. Symptoms of high barium include gastrointestinal complaints, muscle weakness, facial numbness, and hypotension. Treatments for high barium include oral sodium sulfate. Serum potassium levels should also be checked and treat hypokalemia, if present.

### Bismuth (Bi)

Bismuth is found in alloys, catalysts, cosmetics, paints, magnets, ceramics, pharmaceuticals, x-ray contrast media, and semiconductors. Bismuth is generally non-toxic, although very high levels may cause nausea, vomiting, and diarrhea. Renal, neurological, and hematological problems have been associated with bismuth toxicity. **Hair** is not a sensitive specimen for bismuth toxicity; **blood** and **urine** are most commonly used.

### Cerium (Ce)

Cerium has no known biological function and is considered to have low to moderate toxicity. Symptoms observed in workers exposed to cerium are: itching, sensitivity to heat, and skin lesions. Toxicity studies in rats caused cardiovascular collapse. It has been detected (within referenced daily intake amounts) in collard greens or turnip greens from neighborhood gardens. Cerium may be found in ceramics and dental compositions. It is sometimes used in zirconia-based products as a stabilizer and in steel manufacturing. It is used in the coloring and polishing of glass. Cerium is used in flat-screen televisions and in low-energy light bulbs. It has been used in aluminum and steel alloys. Cerium has been suggested to replace cadmium compounds for red pigmentation of toys, household items, and crates.

### Cesium (Cs)

Cesium is a naturally occurring element found combined with other elements in rocks, soil, and dust in low amounts. It is used in photoelectric cells, photo emitter devices, scintillation counters, and atomic clocks. Cesium is released into the environment in pollucite mining and production of energy and electronics. Fly ash from coal burning power plants contains cesium. Cesium salts are used as an alternative method of cancer treatment to raise the pH of the cell.

Exposure to low levels of stable or radioactive cesium can occur by breathing air, drinking water, or eating food containing cesium. It is thought that the average person would not come in contact with enough cesium to cause negative health effects. **Blood**, feces, saliva, and **urine** have been used to measure levels of cesium in the body. Radioactive cesium is not measured on the Metametrix Elements Profiles. If cesium is present, it is likely the result of exposure to stable cesium.

Cesium can be easily absorbed through the skin, GI, and lungs at which point it is distributed through the body and concentrates in muscles. It has been said that, “cesium mimics potassium for cellular transport.” Mild toxicity symptoms from cesium include gastrointestinal distress, hypotension, loss of consciousness, and numbness or tingling of the lips. Total cesium intakes of 6 g/day or more can cause severe hypokalemia, hypomagnesemia, ventricular tachycardia, and cardiac arrest. Studies on experimental animals suggested that cesium would pose an acute health hazard only when ingested in large quantities.

### Europium (Eu)

Europium compounds are rarely encountered by most people. Europium is used in television screens to produce a red color. It is also found in nuclear control rods and is used in doped plastic as a laser material. Europium and terbium phosphors (luminescent compounds) are used to test for polycystic kidney disease and other genetic diseases. Europium can enter the body through gastrointestinal absorption and inhalation, although only about 0.05% is absorbed into the bloodstream through the digestive tract.

Until further studies are conducted, europium is viewed as a highly toxic substance, although initial studies suggest that the danger is low. The metal dust presents a fire and explosion hazard. Toxicity studies with rats given high doses of oral europium chloride showed accumulation of europium in liver, spleen, femurs, and kidneys. The rats lost weight as a result of reduced food intake and there appeared to be irritation of the GI tract. Total iron binding capacity increased while iron levels in the spleen decreased. Bone strontium levels decreased.

### Holmium (Ho)

Holmium is used as a “getter” in vacuum tubes and in spectroscopy. It is also used in alloys. Holmium has been used to create the highest known magnetic fields.

Exposure to holmium is rare. Holmium may be highly toxic even though initial research indicates that it is not extremely dangerous. It has low acute inhalation toxicity and oral toxicity and is essentially non-irritating to the skin. A radioactive form of holmium is used in the treatment of bone-only breast cancer metastasis with minimal toxicity. However, radioactive holmium is not measured on the Metametrix Elements Profiles.

### Indium (In)

Because indium has no known biological role and little research has been done on its effects in humans, some sources suggest that it should be regarded as toxic. Pure indium is considered non-toxic but indium compounds have been shown to be toxic in animal studies (i.e. indium trichloride or indium phosphide). Inhalation of indium has resulted in dramatic lung inflammation and mild reproductive effects in experimental animals. Indium exposure may have negative effects on heart, liver, and kidney tissues. Indium may be used in alloys, bearings, metal surfaces, mirror surfaces that resist corrosion, in nuclear reactors, in sodium vapor lamps and in diagnostic nuclear medicine, especially as a radiolabeled monoclonal antibody used in the localization of tumors. Indium is produced as a by-product of smelting zinc and lead sulfide ores. Urinary excretion of indium is low.

**Blood or serum** levels of indium may be better than **urine** for assessment of exposure.

### Niobium (Nb)

Niobium is a transition metal that is used for the production of high temperature-resistant alloys and special stainless steels. Small amounts of niobium are used to increase the strength of other metals, especially those that are exposed to low temperatures. Niobium is used in stainless steel alloys for nuclear reactors, jets, missiles, cutting tools, pipelines, super magnets, and welding rods.

Niobium and some niobium alloys are physiologically inert and hypoallergenic. For this reason, niobium is found in many medical devices such as pacemakers and jewelry.

Niobium dust causes eye and skin irritation. When inhaled, niobium resides mainly in the lungs, and secondarily in the bones. It can interfere with calcium pathways. A recent study showed that metals display different levels of cytotoxicity depending on their form (bulk or powdered). The study showed that niobium showed definite cytotoxicity in the powdered form, but was biocompatible in the bulk form. New titanium alloys for biomedical applications (dental and orthopedic), frequently contain niobium produced by powder metallurgy. The cytotoxicity is tied to the ion release from the metals. Another study speculated the possibility that debris from joint replacement materials, which sometimes include niobium, can be toxic to osteoblast-like cells, fibroblasts, and lymphocytes.

Toxicology studies in rats showed that high dose intravenous niobium salts resulted in renal injury or death while 1% niobium in the diet ingested for seven weeks showed no toxic effect. When the salts were complexed with ascorbic acid prior to injection, the nephrotoxic action was not observed.

### Palladium (Pd)

Palladium is usually found with platinum, nickel, copper, and mercury ores. It is used in alloys for telecommunication equipment, as a catalyst in petroleum production, for metalizing ceramics and for mixing with gold to make “white gold” jewelry. Palladium is now the main “ingredient” in automobile catalytic converters. It is being used more frequently in mobile phones, wide screen TVs, computers, and electrical appliances.

Palladium is a possible skin sensitizer. Occupational asthma has been reported at a low incidence. Primary exposure to palladium is through dental alloys, jewelry, food, and emissions from automobile catalytic converters. Palladium dust can possibly cause lung inflammation. The metallic form is relatively inert and has showed little or no toxicity, but the soluble halide salt is very reactive and can cause an allergic reaction in susceptible individuals. Palladium levels can be detected in **blood** and **urine**. As a member of the platinum group elements (platinum, palladium, and rhodium), these elements are now believed to pose a greater health risk than previously believed. Dusts emitted from these elements can be solubilized by various compounds and made more bioavailable. The presence of chloride in pulmonary fluids can lead to the formation of complexes that are more likely to produce cellular damage.

Studies with rats and rabbits showed high-dose palladium salts caused decreased desire for food and water, ataxia, tip-toe gait, peritonitis, cardiovascular effects, clonic and tonic convulsions, biochemical changes (i.e. to liver enzymes), changes to the kidney, and hemorrhages of lung and small intestine. Short term exposure resulted in weight loss, sluggishness, hematoma, or exudations. Ingestion of palladium salts was the least toxic route of exposure.

### Platinum (Pt)

Platinum and platinum alloys are used in surgical tools, laboratory utensils, dentistry, jewelry, silicone breast implants, electrical resistance wires, automobile catalytic converters, optical fibers, and liquid crystal display glass, especially for laptops. It is believed that automotive catalytic converters release platinum to the roadside environment. Platinum is used in some chemotherapy drugs, such as cisplatin, which is used to treat ovarian cancer. Workers in the following areas show the highest platinum levels: roadside maintenance, refineries, oncology wards, electronics plants, chemical plants, and jewelry production. Women with silicone breast implants have platinum exposure. One study showed a significant uptake of platinum from platinum-containing dental alloy restorations. The general population is at increasing risk of exposure to platinum because of the widespread use of catalytic converters and growing applications for platinum in various sectors of the economy.

Symptoms of platinum salt hypersensitivity are urticaria, contact dermatitis, respiratory disorders including sneezing, shortness of breath, cyanosis, and/or severe asthma. Symptoms usually abate when exposure is removed. A history of atopy, respiratory disease, or smoking may predispose an individual to developing platinum salt hypersensitivity. Platinum as a pure metal is thought to be non-allergenic.

**Blood** levels of platinum in the general population have been recorded at 0.1-2.8 µg/L while occupational exposure resulted in serum platinum levels of 150-440 µg/L. It is thought that little platinum is absorbed in the lungs and GI tract. When ingested or inhaled by experimental animals, platinum is cleared via the lungs, feces, and a small portion is cleared in the urine. Platinum is concentrated in the kidneys, liver, spleen, and adrenals in animal studies.

### Rubidium (Rb)

Rubidium and its salts have few commercial uses. The metal is used in the manufacture of photocells. Rubidium salts are used in glass and ceramics and in fireworks to give them a purple color. Potential uses are in ion engines, vapor turbines, and as a “getter” in vacuum tubes. Rubidium isotopes have been used as tracers in medical tests to observe blood flow in the heart, brain, and kidney. Foods found to contain up to 200 ppm rubidium include tomatoes, beef, soybean, and coffee. Rubidium has no known biological role but has a slight

stimulatory effect on metabolism, probably because of its similarity to potassium. The two elements are found together in minerals and soils, although potassium is much more abundant than rubidium. Rubidium enters the food chain and so contributes to a daily intake of between 1 and 5 mg. It is moderately toxic by ingestion. Rubidium reacts readily with moisture on the skin and forms rubidium hydroxide which can cause chemical burns of the eyes and skin. Overexposure to rubidium can cause failure to gain weight, ataxia, skin ulcers, and extreme nervousness. Since rubidium and potassium have similar properties, potassium imbalance can occur when replaced with rubidium in the body.

Rubidium can be tested in human **erythrocytes, plasma, or urine**. **Hair** levels are thought to indicate rubidium exposure. Rubidium has been used in alternative cancer treatments to raise pH.

Toxicity studies in rats showed that rubidium chloride resulted in decreased growth, anemia, and changes to liver cells, kidney cells, brain enzymes, and hepatic lipid composition. Ascorbic acid supplementation appeared to prevent the rubidium-induced liver and kidney effects. Studies on experimental animals suggested that rubidium would pose an acute health hazard only when it is ingested in large quantities.

Rubidium toxicology has not been fully investigated. It appears to displace potassium in rats, with symptoms of hyperirritability, neuromuscular effects, and muscle spasms. There have not been reports of industrial exposure leading to injury. However, in one small human study, rubidium replaced 10-15% of the body's potassium and the subjects showed no symptoms of toxicity. Exposure could lead to irritation, burns, or ulceration.

### Samarium (Sm)

Samarium is used in some organic reactions as a catalyst. Sm<sub>2</sub> is used in organic chemistry research. It is used in control rods in nuclear reactors, as well as in cobalt alloys to make strong permanent magnets.

Samarium toxicity has not been fully investigated. Safety sheets on samarium suggest the following possible health effects: eye irritation, tearing, photophobia, blurred vision, damage to the cornea, or chemical conjunctivitis. Ingestion may cause digestive irritation, cardiac disturbance, central nervous system abnormalities, nausea, vomiting, increased

salivation, and abdominal pain. Inhalation of samarium may cause respiratory tract irritation, olfactory fatigue, and/or delayed pulmonary edema. Symptoms pertaining to the central nervous system may include abnormal fatigue, memory difficulties, and dizziness.

### Tantalum (Ta)

Tantalum is used to make capacitors, rectifiers, chemical- and heat-resistant equipment, tools, dental and surgical implants, pen parts, parts for furnaces, aircraft, and nuclear reactors.

Metallic tantalum has a low solubility, making its toxicity low. Tantalum implants in the form of wire mesh and rods for bone repair have not shown any adverse tissue reactions in humans overall, although some allergic reactions may be due to this metal. Tantalum dust exposure has been shown to be toxic in industrial workers, causing lung disease. Chronic tantalum inhalation may have caused a mild fibrosis and rhinitis in workers exposed to the metal. This might have played a role in the development of “hard metal pneumoconiosis.”

Tantalum dust can cause eye and skin irritation and is irritating to the mucous membranes and upper respiratory tract. When given intravenously, tantalum has an anticoagulant effect. Animal studies suggest that tantalum may be absorbed by the oral route.

### Tellurium (Te)

Tellurium has no known biological role and is considered mildly to moderately toxic. Acute poisoning is rare. Tellurium can be inhaled. Symptoms of tellurium toxicity include garlic breath odor, nausea, vomiting, metallic taste, blackened oral mucosa and skin (especially after topical contact), and inhibition of sweating. Garlic odor on breath or sweat can persist for months after exposure. A rat study showed alopecia after dietary tellurium intake. Tellurium sources include ceramics, steel, cast iron, and copper. Tellurium alloys are used in machines and tellurium is used to make chemicals and catalysts used in the petroleum industry and in the production of rubber. Plants grown in tellurium-rich soils have been shown to have concentrations of 2-25 ppm but tellurium levels in garlic and onions have been reported as high as 300 ppm. Studies of tellurium exposure have been carried out on **whole blood** and **urine**.

Treatment for tellurium toxicity is to eliminate exposure, at

which time symptoms resolve. Some have treated tellurium toxicity with BAL. Ascorbic acid may reduce garlic breath odor but is not commonly recommended. Tellurium shares many characteristics with selenium, including comparable final methylated products. Therefore tellurium toxicity may be approached similarly to selenium toxicity. Nutrients supporting methylation pathways may help to eliminate tellurium.

### Terbium (Tb)

Terbium is rare and expensive, so it has few commercial uses. Some minor uses are in lasers, semiconductor devices, and phosphors in color television tubes. It is also used in solid-state devices.

Terbium may be mildly toxic if ingested. Terbium powder and compounds are very irritating to the skin and the eyes. Its toxicity has not been investigated in detail. It is suspected that ingestion would likely result in digestive tract irritation and inhalation would result in respiratory tract irritation. A study of systemic terbium toxicity in mice indicated that pulmonary lipid peroxidation may be an early result of terbium exposure.

### Thorium (Th)

Thorium is a naturally occurring, radioactive substance that is present in rocks, soil, water, plants, and animals. Some rocks in underground mines contain thorium in a more concentrated form. It is used to make mantles for gas lanterns; it is also used in crucibles, tungsten wire coating for electronic components, camera lenses, welding rods, and light bulb filaments. Thorium can also be used as a fuel for generating nuclear energy.

Thorium can enter the body by eating food, drinking water, or breathing air. Most exposure to the general public is through gastrointestinal absorption of food and water. Thorium is not considered to be a radiation hazard because it emits only a small amount of gamma radiation.

Exposure to thorium can occur if a person breathes air near facilities where uranium, phosphate, or tin ore are processed, or by handling these products. Breathing high levels of thorium dust can result in an increased chance of getting lung disease. Smokers who were exposed to radon gas and thorium had increased rates of lung, pancreas, and blood cancers. Thorium has been measured in **blood**, **urine**, and **feces**. Urinary thorium was used to monitor inhaled thorium exposure in gas mantle manufacture workers.

Thorium is thought to accumulate in the liver, spleen, and femurs. In mice, thorium exposure resulted in oxidative damage (in the liver, spleen, and femurs) and altered liver function. A calcium salt of diethylenetriamine pentaacetate was reported to protect the mice from the effects of thorium. Because thorium can accumulate in bone and can be stored for a long time, bone cancer can result. Animals ingesting large doses of thorium in drinking water (1,000 ppm) died from metal poisoning. High levels of thorium may indicate exposure to thorium radioactive decay products such as radium and thoron (isotope of radon).

### Thulium (Tm)

Thulium is the least abundant of the rare earth metals. It has possible uses as an energy source, in ceramic magnetic materials in microwave equipment, and as a doping agent in lasers.

The toxic properties of thulium have not been fully investigated. It is thought that ingestion could cause irritation to the gastrointestinal tract while direct contact with skin or eyes would also cause irritation. The soluble salts of thulium are considered to be slightly toxic in large amounts. Thulium dust may cause irritation to the respiratory tract and mucous membranes, damage to the lungs, and may cause asthma attacks. Rats fed high-dose thulium chloride showed growth inhibition and depression of all systems studied, with death resulting from cardiovascular collapse and respiratory failure.

### Tin (Sn)

Tin is used in PVC, glass coverings, silicone and wood preservative, paints, biocides and pesticides, and medicines, including Ayurvedic treatments. Tin is found in food, cosmetics, dental amalgams, pewter, bronze, preservatives, food and beverage containers, and anticorrosive platings.

Specimens used for assessment of tin exposure include **urine** and **blood**, which may be useful for both acute and chronic exposure. Hair tin may correlate with environmental exposure. Inorganic tin appears to be less harmful than organic tin.

High tin levels may induce neurotoxic, immunogenic, or carcinogenic conditions. Tin can also cause eye, skin, and GI irritation as well as testicular degeneration, anemia, and muscle weakness. Selenium was protective against the high incidence of lung cancer in tin miners shown to be selenium

deficient. Therefore, treatment with 200-400 µg/d of selenium may protect against the effects of tin.

### Tungsten (W)

Tungsten is found in electric lamps, television tubes, car distributors, electrical furnaces, and x-ray targets. It is used in metal evaporation work. Inhaled tungsten has been associated with pulmonary fibrosis, lung cancer, and neurosensory and cognitive deficits. Oral exposure is suspected to cause reproductive, neurological, and developmental effects. **Hair** and nails have been used to identify toxicity. **Blood, urine**, and stool are also used for assessment.

### Uranium (U)

Uranium (U) is an abundant element on earth. Its widespread use in military and industry, including nuclear power, has increased human exposure. Uranium can be ingested or inhaled and is cleared in urine rapidly, although some will pool in bone and kidney tissues. Uranium toxicity in humans leads to renal damage. Lung cancer is commonly associated with inhaled uranium. **Urine** can be a sensitive specimen for uranium exposure, but assessment should be undertaken promptly. Intravenous sodium bicarbonate 1.4% has been used to treat uranium toxicity and inositol hexaphosphate has been used in animal studies.

### Zirconium (Zr)

Topical and inhaled exposures have been associated with skin and pulmonic granulomas, respectively. Acute exposure has resulted in small reddish-brown papules in streaks on abraded skin. Chronic exposure to zirconium can result in pulmonic granulomas. No specimen has been endorsed for routine biological monitoring but hair has been used to assess exposure. Possible sources of zirconium include: the gemstone itself, steel alloy, surgical appliances, photoflash bulbs, light bulb filaments, poison ivy lotion (combined with urushiol), superconductive magnets, laboratory crucibles, lenses, ceramic glazes and enamels, metal industries, and silicon rubber. It is used in the glass and ceramic industries. When investigating exposure sources, also consider other zirconium compounds such as zirconium acetate, zirconium carbide, zirconium chloride, or others. Eliminating zirconium exposure is the mode of treatment.