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Doc, can you test me for “toxic metals”? Challenges of testing for toxicants in patients with environmental concerns

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Abstract

Laboratory testing is an important tool to assist clinicians in evaluation of patients with potential environmentally-related illness, however, it can be challenging to select or interpret the appropriate toxicological tests. Recent advances in analytical techniques and expanded consumer access to environmental laboratories led to a rise in laboratory testing for various environmental toxicants, including metals. However, most environmental tests have scant clinical evidence and are not validated for clinical use. While the tests themselves may not present direct harm to the patients, the results of inappropriately selected tests may lead to significant patient stress and unnecessary follow-up or treatment. Given the lack of environmental health content in medical training, pediatricians may feel ill-equipped to address most environmental issues they encounter in practice, including the interpretation of environmental toxicant lab results. This article provides an overview of how to approach a child and family with environmental health concerns about “toxic metals”, select appropriate metal tests if indicated, and enlist the assistance of the Pediatric Environmental Health Specialty Units (PEHSU) for further management guidance.

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Introduction

Laboratory testing is an important tool to assist clinicians in evaluating patients with potential environmentally-related illness, however, it can be challenging to select or interpret the appropriate toxicological tests. The choice of appropriate environmental testing should follow evidence-based medicine guidance on appropriate clinical laboratory testing in general. Providers should select the tests with reliable diagnostic accuracy and whose results will influence diagnostic thinking, patient management, or outcomes.[1] Inappropriate laboratory testing is common across various medical settings and clinical specialties.[2] Although limited data exist on the prevalence of inappropriate environmental testing specifically, one study found 9% of patients at an environmental/occupational medicine clinic had inappropriate or unvalidated environmental tests done prior to the clinic visit; the most commonly ordered inappropriate tests were metal testing and hair analysis.[3] In most cases, inappropriately-ordered laboratory tests themselves do not pose direct harm to the patient; however, the results may lead to high levels of stress and anxiety. Further, acting on the results of inappropriate tests may lead to significant health-related costs due to associated treatments and procedures and in pediatric patients this may be particularly problematic.[2–4]

Environmental concerns may be especially prone to inappropriate testing due to recent advances in, and expanded consumer access to, environmental laboratory tests that may not yet be validated for clinical use. Increased media attention on environmental issues and heightened parental awareness about environmental exposures may prompt families to request unusual tests to determine if their child has been exposed to toxicants. Parents may also seek the etiology of their child's diagnosis (e.g., autism spectrum disorders) to determine if a specific environmental exposure "caused" the condition. Metals are a common type of environmental toxicant often linked to inappropriate testing.

Metals are a large class of elements widely found in the environment from natural (e.g, naturally-occurring in soil, plants) or industrial sources (e.g., fossil fuel combustion, smelting, pesticides).[5] Some metals such as iron, copper, manganese, and zinc are essential to healthy physiologic functioning. Both deficiency and excess levels of these essential elements can lead to health effects.[6] Other metals such as lead, mercury, and arsenic (sometimes called "heavy metals" due to their specific gravity in relation to water) do not have physiologic roles and can be toxic to various organ systems (Table 1). The health effects from exposure to these toxic metals depend on factors such as the dose, route of exposure, genetics, underlying medical conditions, nutritional status, and age.[5]

Aside from environmental testing for metal exposure, parents may also seek treatments to "detoxify" their child from detectable levels of metals identified on a non-clinically validated test or to use chelation therapy as a treatment for neurodevelopmental issues. Anecdotally, the PEHSU network has observed a notable rise in inquiries from parents pursuing non-clinically validated tests or treatments and from pediatricians seeking advice on the interpretation of non-clinically validated test results that patients bring to clinic appointments. Pediatricians may feel ill-equipped to address many environmental health issues they encounter in practice,[7,8] due to the lack of environmental health curriculum in medical training.[9] This article will provide guidance on 1) approaching a pediatric patient with a history of an environmental exposure or an environmentally-related illness, and 2) responding to questions about environmental testing options for metals.

Approach to the Patient with Environmental Concerns

Targeted environmental laboratory testing may be warranted in a patient based on the findings of a thorough environmental history (Table 2) and physical exam, but should not include a “shotgun” approach for a variety of toxicants. Results of carefully-selected tests can help determine appropriate management (Table 3). Environmental tests that may be useful in patients with a history of exposure to certain metals (e.g., urine mercury level in a patient exposed to an elemental mercury spill in the home) or symptoms consistent with metal exposure (e.g., blood lead level in a child with abdominal pain and irritability and a history of pica). There are multiple resources to assist physicians with taking environmental histories, ordering appropriate tests, directing proper treatment, and counselling families on exposure reduction including the PEHSU network (www.pehsu.net). In this case, the pediatrician was unfamiliar with interpretation of the metal tests and enlisted the help of pediatric environmental health experts at the PEHSU to determine next steps. The PEHSU team conducted a thorough medical and environmental history with the family that revealed no concerning exposures, including for common metals of concern, nor symptoms suggesting a common toxidrome (a group of signs and symptoms characteristic of the toxic effects of a specific chemical).

Laboratory Testing for Environmental Exposures

Advances in laboratory analytical techniques now allow for the detection of hundreds of chemicals in human tissues. While most of these tests have limited utility in the clinical setting, well-designed biomonitoring studies provide population-level exposure surveillance and establish background levels. An important example is the United States Centers for Disease Control and Prevention (CDC)’s National Report on Human Exposure to Environmental Chemicals; the most recent report contains summary data on the levels of 352 chemicals (or their metabolites) measured in blood, serum, and urine in a representative sample of the U.S. population.[10] Pediatric data are limited because summary data on most chemicals are not available for children under 6 years. Children under 6 years of age are often at highest risk of both exposure and sequelae from environmental hazards.[11]

Commercial laboratories have adopted new analytical techniques to measure many of these chemicals and now offer a wide range of environmental tests for consumers including metals, pesticides, phthalates, and bisphenol A (BPA). For lead and a few other well-studied toxicants, a patient’s test result can help direct clinical management. However, for the vast majority of chemicals, it is not known what levels are associated with health effects; finding a measurable amount of a chemical does not mean it will cause a health problem. Overall, it is difficult to predict the impact of a chemical exposure on a specific patient given the complex influence of factors such as genetics, age, psychosocial stressors, diet, and the magnitude and duration of the exposure.[11] Further, it can be difficult to interpret the source and timeline of a exposures to common chemicals, given that some compounds are cleared rapidly from the body after an exposure, while others persist in the body for years.

The lack of clinical validation for many environmental tests, including testing for exposure to metals (e.g., hair testing, urine metal panels), means they cannot be used to reliably guide diagnosis or treatment, nor to establish the etiology of clinical conditions.[12] At most, many environmental lab test results (if done using validated techniques from a Clinical Laboratory Improvement Act (CLIA)-certified laboratory), can be compared to the baseline levels found in the CDC's National Report on Human Exposures to determine if a patient is exposed at levels consistent with background levels in the U.S. population.

Despite limitations for use in clinical care, patients may pursue tests from laboratories offering definitive toxicant testing and treatment plans based on the test results. It is important for providers to understand a family's motivation for seeking these tests and provide empathetic response to address the issue. While providing explanation about the limitations of these tests, it also is important to provide resources to help families reduce exposures of concern and referrals to medical or social service programs appropriate for the child's underlying diagnosis or stressors. This section will provide an overview of commonly requested testing modalities for metals, but is not an exhaustive list. Clinicians with questions about appropriate metal testing (selection of specimen, proper specimen collection, and interpretation of results) can contact the PEHSU, a medical toxicologist, or the Poison Control Center (especially for acute exposures).

Blood Tests—There are some cases in which blood metal testing is warranted, such as routine lead testing for all high-risk children at ages 12 and 24 months and recent international adoptees or immigrants.[13] Blood lead levels (BLLs) are also warranted in children with possible exposure (e.g., witnessed ingestion of peeling paint) and children with pica behaviors (e.g, children with autism spectrum disorder may have persistent pica behaviors through adolescence).[14] Blood testing for mercury is rarely warranted, but may be useful in situations of acute toxicity in symptomatic patients.[15] Arsenic has a very short half-life in the blood, so blood measurements are not recommended to document exposure.[16]

Urine Tests—Outside of the routine blood lead testing in young children, the diagnosis of metal poisoning requires an environmental exposure history and clinical findings consistent with exposure to that metal. An appropriately chosen test for a specific metal should be obtained if there is concern for a specific toxidrome based on history and/or physical examination findings. For example, urine mercury testing is useful to document subacute exposures to elemental mercury vapor in patients with a history and physical exam findings suggestive of mercury toxicity, such as a patient with tremors, irritability, rash, and history of elemental mercury spill in the home.[17] Urine arsenic testing may be warranted in individuals with potential exposure from contaminated well water and gastrointestinal symptoms, skin changes (dyspigmentation or hyperkeratosis), or sensorimotor peripheral neuropathy.[16] Broad testing with a urine metal panel (which may include arsenic, cadmium, cobalt, lead, mercury, thallium, zinc, others), as seen with the case, can lead to unnecessary stress and follow up testing if a metal level is outside the lab's stated reference range. The vast majority of people in the U.S. have detectable low levels of metals[10], and typically without overt clinical significance.[12]

Further, if urine metal tests are ordered incorrectly, the results can be misinterpreted and lead to stress in the family or misdiagnosis of toxicity. The results of spot urine tests with creatinine-correction (e.g., µg/g creatinine) may be higher compared to the concentration per volume (e.g., µg/L) for young children given the smaller amounts of creatinine excreted in the urine.[4] If a provider is concerned about arsenic toxicity, the urinary arsenic test should be ordered with "speciation" (rather than total arsenic) to determine if the arsenic is the "organic" or "inorganic" form. The organic form is relatively non-toxic and is found in fish and shellfish, and would be expected in detectable levels in the urine. The inorganic form is clinically important and can be toxic. Sources of exposure to inorganic arsenic include contaminated soil or water, some pressure-treated wood, and certain foods including rice (grown in arsenic-rich soils).[16] In the case, the patient's elevated arsenic levels were reported as "total" arsenic; however, a speciated arsenic result would have likely revealed the presence of organic arsenic, given that she eats fish several times per week and the environmental history revealed no exposure sources to inorganic arsenic.

Provoked Urine Testing for Metals—"Provocation" urine testing is an inappropriate environmental test that measures urinary excretion of metals after administration of a chelating agent such as 2,3-dimercaptosuccinic acid (DMSA; succimer). These tests offer no reliable diagnostic value, as there are no validated reference ranges for "provoked" urine metals in children; further, there are potential side effects from chelating agents.[18,19] Studies that have used this technique to bolster claims regarding higher urinary metal concentrations in children with a variety of conditions such as ASD are fundamentally flawed (e.g., comparing provoked metal levels in cases to non-provoked metal levels in controls).[14] Leading expert groups including American College of Medical Toxicology, American Academy of Clinical Toxicology, and the PEHSU do not recommend their use.[1920]

Hair Testing—Hair analysis for elements (including metals) is increasing in popularity and can lead to potentially misleading and/or spurious results as is the case in this patient's presentation. The results do not reliably represent the levels of metals inside the body, nor can they be correlated with conventional testing results (e.g., blood). These tests cannot distinguish if the metal is biologically deposited within the hair or externally deposited on the hair's surface from sources such as air pollution, dust, or hair treatments. In the case, the "elevated" titanium levels likely reflect the use of hair products (many personal care products such as shampoo, cosmetics, and sunscreen contain titanium compounds). Although hair analysis has been used in research studies with strict protocols, commercially available hair testing does not have validated specimen preparation and analytical protocols; there is significant variation in testing methodologies, reference ranges for individual metals, as well as the treatment recommendations made based upon the laboratory results.[21,22] With rare exceptions, hair analysis does not provide clinically useful information to determine individual will develop health effects,[21] and is not recommended.

Case Summary and Next Steps in Management

The mother in the case was concerned that her daughter's fatigue was related to "toxins" in her environment, especially given that titanium and arsenic were "elevated" in her test results. The PEHSU clinical team explained the limitations of hair and urine testing and conducted a thorough environmental history that revealed no concerning exposures. To confirm that the elevated arsenic was the organic form from her diet, a repeat urinary arsenic level was obtained with speciation, and the results came back with a slightly elevated organic arsenic levels and a non-detectable level of inorganic arsenic. The type of fish she regularly ate (cod and salmon) are typically low in mercury; however, the team provided routine anticipatory guidance on choosing safer fish choices to maximize the nutritional benefits of fish while minimizing mercury.[23] Given the mother's concerns about toxic exposures in general, the team discussed simple strategies to reduce environmental exposures in the home including optimizing ventilation, regular wet dusting/mopping, and choosing personal care products and cleaning products carefully. Finally, the PEHSU team recommended that the child visit her pediatrician for evaluation of her fatigue with a standard work-up based on the history and physical exam; especially focused on sleep-disordered breathing given her elevated body mass index and tonsillar hypertrophy. A PEHSU pediatrician communicated the assessment and the interpretation of the environmental testing results directly with the primary pediatrician who was appreciative for the assistance in understanding the limitations of the inappropriately-ordered environmental tests.

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Call Out Statements:

Targeted environmental laboratory testing may be warranted in a patient based on findings of a thorough environmental history and physical exam, but should not include a "shotgun" approach for a variety of toxicants.

Acting on the results of inappropriate tests may lead to significant health-related costs due to associated treatments and procedures, in pediatric patients this may be particularly problematic.

Case:

The mother of a 10-year-old girl with no significant past medical history contacted a Pediatric Environmental Health Specialty Unit (PEHSU) at the recommendation of her pediatrician to discuss the results of her daughter's environmental toxicant tests. Another practitioner had ordered a hair analysis and a urinary metals screening panel because the mother was concerned that "toxic metals" were the cause of her daughter's recent fatigue. The levels of titanium in the patient's hair and total arsenic in her urine were reported to be in the "elevated" range, and the pediatrician and family sought advice on the interpretation of these findings.

History and Physical Exam:

The patient's mother reported that she always appeared "sleepy", and did not feel refreshed in the morning for the past 6 months. The review of systems was negative for fever, recent infections, bruising/bleeding, nausea, vomiting, diarrhea, joint pains, muscle weakness, and skin changes. Her appetite was normal and her typical diet included fish, pasta, hamburgers, sandwiches, some fruits, milk, and orange juice. There were no new reported family or school stressors, and she did not take any medications or supplements, but occasionally took an over-the-counter pediatric multivitamin. No other family members reported similar symptoms. On physical exam, the patient's vital signs were normal for age, her body mass index was at the 95^{th} percentile, and physical exam was unremarkable except for keratosis pilaris and dry skin on her upper arms and grade 3+ tonsils bilaterally without exudates.

Table 1.

Sources, Health Effects, and Laboratory Testing For Common Metals of Public Health Significance: Arsenic, Lead, and Mercury[a]

Metal	Common Sources of Exposure in Children	Health Effects[b]	Laboratory testing for patients with history and/or physical exam symptoms consistent with metal toxicity[c]
Arsenic (inorganic)	Contaminated soil or water Pressure-treated wood containing chromated copper arsenate (CCA) Rice products (low levels)	Chronic exposure can lead to gastrointestinal upset, cytopenias, liver dysfunction, cardiac conduction disturbance, peripheral neuropathy, skin changes (hyperkeratosis and dyspigmentation)	Preferred method: Timed (or spot) urine with speciation Speciation delineates between organic arsenic (less toxic, found in seafood) and inorganic arsenic
Lead	Paint (homes built before 1978) Contaminated soil and house dust Contaminated drinking water Folk remedies Imported spices Imported cosmetics or religious powders Imported glazed ceramics Parent occupations and hobbies	Low levels of lead exposure (BLL <10 μg/dL) have been linked to cognitive deficits, behavioral issues, decreased hearing, reduced postnatal growth Moderate levels of lead exposure can lead to anemia and gastrointestinal symptoms Severely elevated BLLs (> 70 μg/dL) can lead to severe effects including seizures, coma	Blood lead level Notes: -Current reference level for further action is 5 μg/dL -Elevated capillary BLL should be confirmed with a venous level -All children aged 12 months and 24 months who are at high-risk for lead exposure should be routinely screened
Mercury	Elemental (inhalation of vapor): thermometers, sphygmomanometers, dental amalgams, certain religious/ cultural practices Inorganic: skin lightening creams and soaps Organic: large predatory fish such as shark, some tuna, tile fish, swordfish	Elemental: neurologic symptoms including tremor, insomnia, personality changes, photophobia; fever, sweating fatigue, rash (palms/soles), "Acrodynia" or "Pink Disease" Inorganic: ingestion can lead to gastrointestinal hemorrhage, acute renal toxicity Organic: neurologic toxicity	Elemental/Inorganic Mercury: Timed (24 hour) urine; spot urine also acceptable Organic: Whole blood

[a]Information in Table 3 adapted from Pediatric Environmental Health, 4th Edition (Chapters 22, 32, 33)

[b]Health effects from exposure to a toxicant depends on dose, route of exposure, genetics, underlying medical conditions, nutritional status, age, etc

[c]The Pediatric Environmental Health Specialty Unit (PEHSU) is available to assist clinicians with ordering or interpreting results of environmental toxicant testing.

BLL = Blood Lead Level

Table 2.

Basic Components of an Environmental History

Home Environment		Occupation and Hobbies
• Age and condition of home (lead paint) • Carbon monoxide and fire alarms • Tobacco smoke • Water damage / Mold	• Pests / Pesticides • Heat and cooking source • Strong odors, solvents, cleaning products • Heat and cooking sources • Radon	• Caregiver jobs (contaminant transfer from clothing, shoes) • Adolescent jobs (safety) • Hobby activities in the home (paints, chemicals, safety) • School exposures
Food and Water		**Other**
• Water source (well water vs. public system) • Fish (large predatory fish have mercury) • Rice products (arsenic)		• UV radiation and sun protection • Noise (loud toys, headphone volume) • Sources of neighborhood pollution (highways, industries)
Patient characteristics can help focus the environmental history.		
• Asthma: assess for common environmental asthma triggers such as mold, pests, dust mites, tobacco smoke, furry pets, cleaning chemicals, strong odors • Neurodevelopmental disorders: in addition to a general environmental history, assess for pica behavior and other risk factors that may increase the likelihood of exposures (e.g., lead); assess for use of alternative medications • Headaches/flu-like symptoms in family members: assess for sources of carbon monoxide • Patient age can help direct screening questions and anticipatory guidance (refer to the Pediatric Environmental Health Toolkit: https://peht.ucsf.edu/ for age-specific information)		

Environmental History forms are available (in English and Spanish) for an general environmental history and an asthma-focused environmental history: www.neefusa.org/resource/pediatric-environmental-history

Table 3.

Guidance for Selecting Environmental Laboratory Tests

1. **Take an environmental history** to determine if the health problem or symptom of concern may be related to an environmental exposure (Table 2).

2.**Characterize the potential exposure(s) of concern:**

- Is there a completed route of exposure? (opportunity for internal dose through inhalation, ingestion, or dermal absorption)
- Did the potential exposure occur before the health problem or symptom appeared?
- How long did the exposure last? Continuous or intermittent?
- What are evidence-based health effects associated with the toxicant?

3. **Characterize the symptoms in relation to potential exposure(s):**

- Do symptoms improve or worsen at a particular time? In a particular location?
- Do symptoms worsen during a particular activity?
- Are household members experiencing similar symptoms?

4. **Determine if validated laboratory tests are available that will help to accurately document the exposure** (*may require input from environmental or toxicology specialists: www.pehsu.net*).

- Will the laboratory measurements correlate with toxic effects?
- Will the results influence patient management?
- Is a certified laboratory available to analyze the specimen?
- What is the proper specimen for the exposure? (e.g., blood versus urine)
- Are there reliable and clinically-relevant reference ranges?

5. **Consider the appropriate next steps for patient:**

- May involve targeted environmental tests, or referrals to specialists (e.g., allergist)
- Referral to PEHSU network or other appropriate resource as needed for advice on diagnosis, management, or prevention of environmental concern
- Routine management of symptoms, as directed by history and physical exam

6. **Provide strategies to reduce exposures of concern**. This is desirable, even in absence of laboratory testing (www.nyscheck.org/rx; peht.ucsf.edu).