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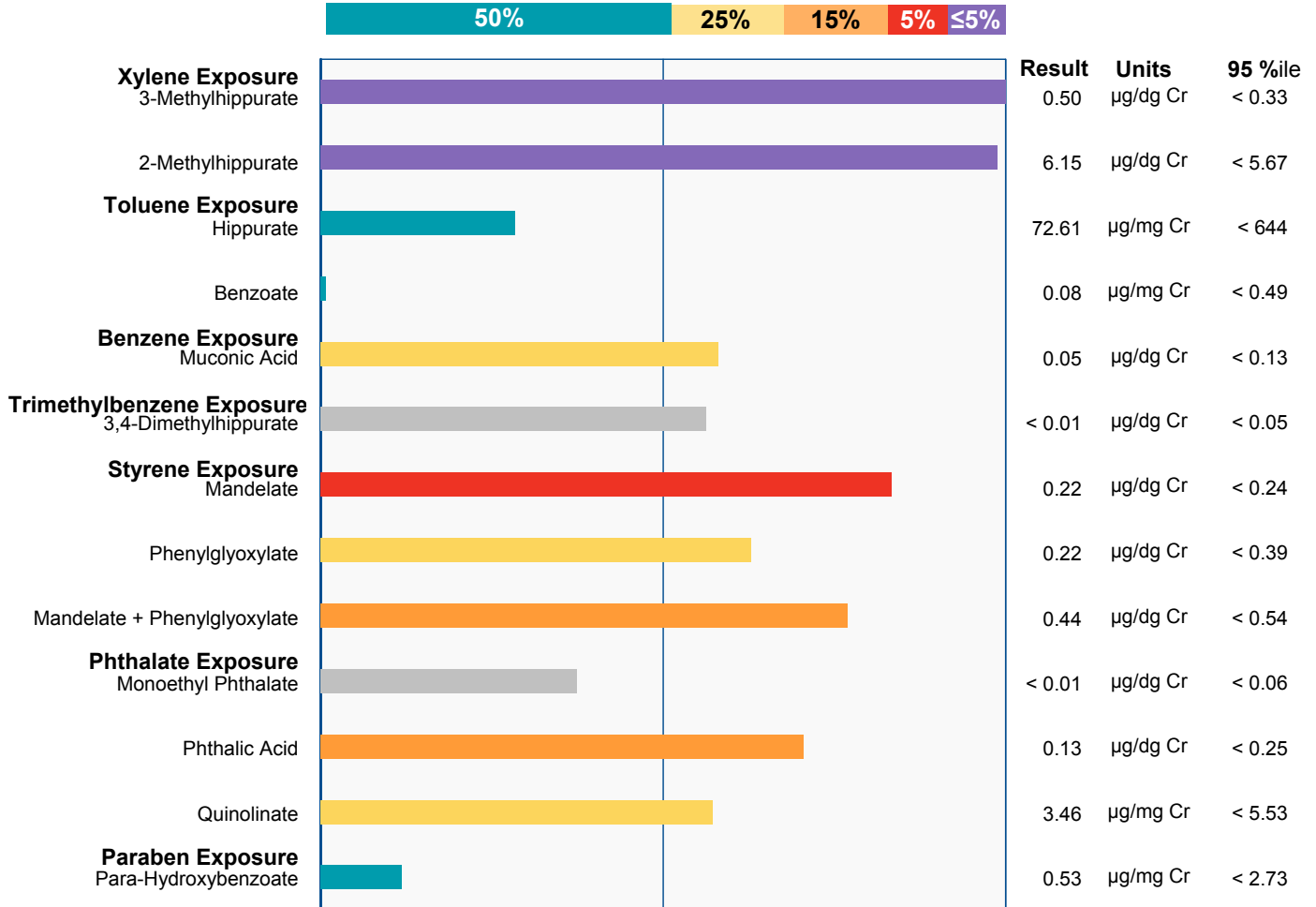
Collection Date First: 20-Feb-2013
 Collection Date Last: Urine
 Sample Received: 21-Feb-2013
 Reported On: 10-Apr-2013

Environmental Pollutants Profile **Accession Number: 361324**

Provider: **Client:** **Age:** 50
DOB:
Gender: M

Phone:
 Fax:

Percentage of asymptomatic people with a particular metabolite.



REFERENCE RANGE CHANGE

Effective January 1, 2013 the reference ranges have been changed. Benzoate ranges are still "under construction" and benzoate results will not be reported at this time. A small green bar is displayed for this analyte, even though there is no actual result.

GENERAL COMMENTS ABOUT YELLOW AND ORANGE BARS

A yellow bar for any given analyte means that approximately twenty-five out of one hundred clinically normal people who do not have industrial exposures to the compound in question, or its "parent", will have a level comparable to the patient; similarly, about fifteen people out of one hundred will have an orange bar for any given analyte. If these findings (yellow or orange bars) are accompanied by classic signs and symptoms consistent with environmental illness, the implication might be that the patient has significant loss-of-function gene polymorphisms in the relevant detox pathways. Blood testing would then be indicated. In the absence of clinical correlation, measures to identify and eliminate sources of exposure are probably not worth pursuing. No commentary is offered for analytes with yellow or orange bars.

GENERAL COMMENT ABOUT PURPLE BARS

The reference ranges for these analytes were developed by analyzing clinically normal individuals who did not have occupational exposures to any of the compounds of interest. As a result, even the very highest levels measured in normal individuals (those results having a purple bar) are still many times lower than the levels measured in people with symptomatic occupational exposure.

For example, exposure to styrene can cause impairment in the ability to sense vibration. This occurs with urinary combined styrene metabolite levels (Mandelate + Phenylglyoxylate) on the order of 20,000 times higher than the highest levels measured in clinically normal individuals.

This does not rule out the possibility that styrene exposure could still be causing problems in a person with less significantly elevated metabolite levels (e.g. 10 to 1000 times higher than the 95th percentile); any given individual might be much more sensitive to any given toxin, compared to the average person, for a wide variety of reasons.

Basically, what this says is that even a purple bar is not an automatic indication of a harmful exposure; these results have to be considered along with the clinical circumstances, as is the case with all laboratory investigations.

RED OR PURPLE BAR FOR ANY HIPPURATE "FAMILY MEMBER"

Here, one or more metabolites in the hippurate family (hippurate, 2-methylhippurate, 3-methylhippurate, 3,4-dimethylhippurate) are significantly elevated. These compounds are all formed by glycine conjugation of the parent benzoic acid/substituted benzoic acid. This takes place in the liver and also in the kidneys. If the glycine conjugation pathway was not functioning at all, none of the hippurates would appear in urine. The main reasons why this might occur would be an inborn enzyme defect, liver disease, or deficiencies in the rate-limiting nutrients: glycine and pantothenic acid (B5). (Other important nutrients include lipoic acid, cysteine, magnesium, thiamine, riboflavin and niacin.)

Although some glycination is obviously taking place in this case, there may be some situations where it would still make sense to support the glycination pathway nutritionally. If most or all of the hippurates measured here are elevated into the red or purple zone, or if one or more of the hippurates is very markedly elevated (more than 3-5 times the 95th percentile threshold), nutritional support may be warranted, especially if the patient has a clinical picture that might be consistent with toxicity from the parent environmental pollutants. With an ongoing level of exposure, there is continual demand on the glycination pathway.

Since some toxic elements (mercury, arsenic, antimony) impede some of the steps involved in glycination, it is also worthwhile making sure the patient is not carrying an excessive body burden of these elements, in order to optimize basal or supplemented ability to detoxify through glycination.

GENERAL COMMENTS ON XYLENE

Xylene refers to a mixture of three isomers: ortho, meta and para. 2-methylhippurate and 3-methylhippurate are metabolites of ortho-xylene and meta-xylene, respectively. Ortho and meta xylenes typically make up 55% to 95% of commercial xylene-containing products and therefore the 2- and 3-methylhippurates are quite representative of xylene exposure. Note that the half-life of xylenes in blood is 4 hours; urine xylene metabolites

therefore reflect exposure during the previous 24 hours.

EITHER XYLENE METABOLITE ABOVE THE 90th PERCENTILE (RED OR PURPLE BARS)

Either or both of the xylene metabolites are at or above the 90th percentile; out of one hundred clinically normal people who do not have occupational exposure to xylenes, approximately ten would have results similar to this patient, for these analytes.

The recommended upper limit for methylhippurates in urine is approximately 2000 ug/dG creatinine (American Conference of Governmental Industrial Hygienists), approximately 500 times higher than the 95th percentile limits on this report. Exposure to xylenes at 100 ppm is expected to yield urine methylhippurate levels on the order of 10,000 to 100,000 ug/dG creatinine. At very modest occupational exposure levels of 1-2 ppm xylene in air, urine xylene metabolites are on the order of 1-10 ug/dG creatinine, close to or several times above the 95th percentile limits.

The earliest adverse effects of xylene exposure are neurologic, and include dizziness, inco-ordination, impairment of reaction time and "brain fog". These effects are thought to manifest above 100 ppm xylene in air.

In summary, red or purple bars for xylene metabolites do not necessarily indicate that xylene exposure is a problem for this patient; exposures which normally cause symptoms generally result in urine levels thousands of times higher than those measured here.

RED BARS FOR MANDELATE AND/OR PHENYLGLYOXYLATE

Urinary mandelate and phenylglyoxylate are well-recognized markers for styrene exposure. Both components are displayed independently as is their sum. It is possible for either of the bars to be red (at the same level as five out of one hundred normal people), yet the total still falls below the 90th percentile (orange, yellow or green bar). The total is a better overall marker of styrene exposure.

Styrene, like trimethylbenzene, is a gasoline additive, and is also found in tobacco smoke. Styrofoam packaging and disposable cups are other sources of styrene, as is living in proximity to an open landfill site. Outgassing from new construction/carpeting may afford exposure to styrene.

Neurologic effects of chronic styrene exposure include impairment of vibration sensitivity, and ototoxicity. The former is thought to manifest along with urinary levels of MA + PGA on the order of 80,000 ug/dG creatinine (50 ppm styrene in air), and the latter is not thought to be seen when urine MA + PGA is below approximately 30,000 ug/dg creatinine (20 ppm styrene in air). As mentioned above, these levels are far in excess of the 95th% level in unexposed individuals.

GENERAL COMMENTS ON PHTHALATES

Phthalic acid was chosen as one of the analytes as it is a final common elimination pathway for various common phthalates. It is more representative of total exposure to low molecular weight phthalates. Higher molecular weight phthalates are excreted in both urine and feces, and are also excreted in other oxidized forms not measured here. Monoethyl phthalate (MEP) more specifically reflects exposure to diethyl phthalate, which is found in significant levels in personal care products (perfumes, lotions, creams). According to an analysis of the most recent NHANES survey in the United States, MEP is also associated with dietary intake of meat, total vegetable intake and specifically, the intake of tomatoes and potatoes. (Environ Health Perspect 2010;118:998-1003.

Dietary intake is associated with phthalate body burden in a nationally representative sample. Colacino JA, Harris TR, Schechter A.)

GENERAL COMMENTS FOR PARABENS

Parabens are a large family of similar molecules, widely used in skincare products, and widely added to foods and beverages. The main concern with parabens is that they can act as estrogen mimics or xenoestrogens; however, the estrogen-mimetic effect is highly dependent on the exact structure of the paraben. Para-hydroxybenzoate, measured here, is a final common pathway for a wide variety of different parabens. An elevated level of para-hydroxybenzoic acid does not automatically mean a high level of xenoestrogen activity. There is a trend toward measuring urine metabolites of the various different parabens, as a way to more accurately determine xenoestrogen effect.

Some foods naturally contain parabens. These include blueberries, carrots, olives and strawberries. Consumption of large amounts of these foods could conceivably elevate parahydroxybenzoic acid levels. Processed foods may contain up to 0.1% by weight parabens and some sources indicate that paraben exposure

via processed foods exceeds that afforded by skincare products.

URINE METABOLITES vs BLOOD LEVELS

High urine metabolite levels can be interpreted several ways. In the face of a large, one-time or infrequent exposure to the parent compounds, high urine levels of metabolites could simply mean that the patient is efficiently clearing the exposure, and does not have ongoing accumulation. On the other hand, high urine metabolite levels could also be consistent with a situation where the patient has ongoing, daily exposure, and is clearing at least some fraction of the daily load.

Conversely, low levels of metabolites in the urine are not automatically indicative of no exposure. If the patient is unable to convert the parent compounds to metabolites, then blood levels of the parent compounds will be high, and the low levels of urine metabolites will be a false negative. High clinical suspicion should take precedence over absent urine metabolites; blood levels of parent compounds are indicated when clinical suspicion is high.

Metabolite testing is useful as a screen, when there is clinical suspicion of problems clearing organic compounds from the environment. It is not a definitive test. High levels of metabolites are not an automatic indication that the parent compounds are problematic for the patient. Low levels of metabolites in the face of signs and symptoms consistent with toxicity are an indication for blood testing.

Parabens *(para-hydroxybenzoate)*

Source of Exposure

Household: Parabens are antimicrobial, preservative and flavorants in food. They are used in cosmetic and pharmaceutical formulations to increase shelf life. Cosmetics with parabens include: sprays, fragrances, conditioners, shampoos, soaps, hand sanitizers, facial masks and foundations, sunscreens, self-tanners, hair removal creams, shaving gels, nail and skin creams, baby lotion. Pharmaceuticals containing parabens include: injectable drugs, antacids, suppositories, Benadryl™ cream, topical hydrocortisone, medicated pain-relieving patches, mentholated vapor rubs, lip balms, antifungal and antibacterial preparations. Food products containing parabens include: packaged meats, fish and poultry, salad dressings, ketchup, pickles, relishes, processed fruits and vegetables, frozen dairy products, cakes, pies, pastries, icings, jellies and jams, beers and ciders, soft drinks, fruit juices, syrups,

Industry: Industrial oils, fats, glues, shoe polishes, & textiles.

Toxic Effects

- allergic contact dermatitis.
- parabens exhibit weak estrogenic activity.
- animal studies show decreased testosterone levels and sperm count.

Metabolism

- alkyl esters of para-hydroxybenzoic acid and parabens are hydrolyzed to para-hydroxybenzoate, (the main metabolite of parabens) via tissue esterases found in skin, subcutaneous fat, liver and kidney.

Phthalates *(monoethylphthalate, phthalic acid)*

Source of Exposure

Household: PVC plastics are used in vinyl flooring and tile, wall coverings, pool liners, wires & cables, garden hoses, construction materials, weather stripping, canvas tarps, upholstery, some food containers, flexible plastic medical tubing and bags, children's toys, shower curtains, faux leather, adhesives, dyes, some pharmaceutical and pesticide formulae.

Industry: Used in the manufacture of plastics to make them more flexible, widely used to make polyvinylchloride (PVC) plastics.

Workplace: Plasticizer and PVC processing plants.

Toxic Effects

- phthalates are endocrine disrupting chemicals (EDC).
- may cause developmental and morphological abnormalities, including deficits in behavior and cognition.
- phthalate esters perturb tryptophan metabolism causing accumulation of the metabolite quinolate (QA). QA in the CNS is markedly elevated after trauma or inflammation, and has been implicated in neuronal injury via activation of the NMDA receptor. In theory, the combination of toxic phthalate levels and consumption of tryptophan-rich foods could increase risk of some neurological disorders.

Metabolism

- monoethylphthalate (MEP) excreted in urine reflects exposure to diethylphthalate (DEP), with 70% being excreted in urine as its free monoester.
- DHEP (di (2-ethylhexyl)) phthalate is used in manufacture of plasticizers and is eliminated in urine as phthalic acid.
- phthalates are hydrolyzed in gut by pancreatic lipases, yielding phthalate esters.
- phthalate esters are metabolized in the liver by cytochrome p450 dependent multifunction oxidase enzymes and excreted as glucuronide derivatives.
- phthalates and metabolites accumulate in lipid depots; bioaccumulation may result from chronic exposure.

Benzene *(trans, trans-muconic acid)*

Source of Exposure

- Household:** Adhesives, paint removers/ strippers, degreasing agents, carburetor cleaner, rubber cement, some arts and crafts supplies.
- Inhalation:** Tobacco smoke (5.9-90 mcg per cigarette), wood burning.
- Outgassing:** Building materials, particleboard, carpet glue, textured carpet, liquid detergent, furniture wax.
- Industry:** Used to manufacture styrofoam, resins, synthetic fibers and rubbers, gums, lubricants, dyes, glues, paints, and markings pens. Solvent in manufacture of faux leather and rubber goods.
- Workplace:** Oil refineries, petroleum plants, tire manufacturers, paint and shoe manufacturers, gas stations, second-hand smoke.
- Waste:** Seepage from underground petroleum storage tanks, waste streams.
- Petroleum:** Automotive emissions, gas stations, poor vehicle emission control.

Toxic Effects

- skin and eye irritation
- decreased hematocrit, hemoglobin, erythrocytes, leukocytes, platelets
- bone marrow depression: aplastic anemia, leukemia, thrombocytopenia
- carcinogenic, genotoxic
- CNS depression, death

Metabolism

- most benzene is excreted as sulphate or glucuronide conjugates of phenols. About 20% is metabolized to muconaldehyde, a hemotoxic intermediate, prior to hydroxylation to muconic acid.
- following inhalation exposure, most benzene is exhaled unchanged
- benzene and benzene metabolites can accumulate in lipids.

Styrene *(mandelate, phenylglyoxalate)*

Source of Exposure

- Household:** Packaging materials (polystyrene), thermal and electrical insulation, fiberglass, foam cups and food containers.
- Workplace:** Fabrication and application of plastics: polystyrene/ styrene manufacturing, resin manufacturing, laminators, and manufacture of: synthetic rubber, boats, and automobiles.
- Waste:** Emissions from styrene production and disposal procedures: chemical spills, landfill and industrial discharges.
- Petroleum:** Automotive emissions, gas stations.
- Solvent:** Solvent used in laboratories, industrial paints, adhesives, paint removers/ strippers, degreasing agents, carburetor cleaner, rubber cements, some arts and crafts supplies.

Toxic Effects

- impaired balance and manual dexterity and reaction time; dizziness, lightheadedness, headache, drowsiness, nausea, difficulty concentrating
- major metabolic pathway involves sequential oxidation to mandelic and phenylglyoxylic acids.
- genotoxic
- CNS depression

Metabolism

- styrene is metabolized into epoxide derivatives via cytochrome p450 dependent multifunction oxidase enzymes in the liver.
- irritation of mucous membranes, dermatitis, nausea, fatigue
- styrene oxides also conjugate with glutathione
- styrene and metabolites accumulate in lipid tissues; and their slow elimination means bioaccumulation is possible with chronic exposure.
- the sum of mandelate and phenylglyoxylate in urine correlates better with styrene exposure than either metabolite alone; therefore the sum is reported as well.

Toluene *(hippurate)*

Source of Exposure

- Household:** Aerosols, spray paint cans, varnishes, shellac, rust inhibitors, solvent-based sanitizers and germicides, may be an additive in cosmetic products.
- Petroleum:** Fuel additive, automotive emissions, gas stations, poor vehicle emission control.
- Solvent:** Solvent carrier in paints, ink, thinners, coatings, adhesives, degreasers, pharmaceutical products.
- Inhalation:** Tobacco smoke (80 to 100mcg per cigarette)
- Workplace:** Painters, printers, leather finishing, rubber-coating, shoemaker.

Toxic Effects

- CNS depression or excitation
- euphoria followed by disorientation, tremulousness, labile mood, tinnitus, diplopia, hallucinations, dysarthria, ataxia, convulsions, coma
- irritation of mucous membranes (i.e. eyes, nose, throat), dizziness, taste and olfactory fatigue
- drowsiness, headache, impaired cognitive & motor function, insomnia, anorexia
- deliberate inhalation (sniffing) may lead to gross disorientation, neurological impairment and death

Metabolism

- toluene is metabolized in the liver via cytochrome p450 dependent multifunction oxidase enzymes; conjugates primarily with glycine, and is excreted in urine as hippuric acid
- some toluene conjugated with glucuronic acid
- small amounts are hydroxylated to cresols, which are excreted in urine as sulfate or glucuronide conjugates
- toluene interferes with biotransformation of other volatile solvents in liver

Trimethylbenzene *(3,4-dimethylhippurate)*

Source of Exposure

- Household:** Coatings, paint thinners, wood preservatives, cleaners, aerosols, drycleaning, degreasing, pesticides, printer inks.
- Industry:** Produced during petroleum refining.
- Workplace:** Janitors, scientific laboratories, dry cleaners, auto body repairs, construction workers, house painters, ski boot finishing, telephone cable assembly, and screen cleaning processes.
- Petroleum:** Fuel additive, automotive emissions, gas stations, poor vehicle emission control.
- Solvent:** Solvent in coatings, paint thinners, wood preservatives, cleaners, dry cleaners, degreasers, aerosols, pesticides, inks and printing. Component of white spirit, widely used solvent in paint/coating

Toxic Effects

- irritation of mucous membranes, dermatitis, dizziness, fatigue, headache, anxiety, nervousness, 'drunkenness'
- diarrhea, abdominal pains, nausea, blurred vision
- low frustration tolerance, lack of initiative, apathy, depression, irritability ("painter's syndrome")
- carcinogenicity
- glomerulonephritis, renal dysfunction
- decreased erythrocyte, leukocyte and platelet counts
- neurotoxicity
- cyanosis, cognitive and motor impairment, apnea, bursts of perspiration, cardiac arrest

Metabolism

- metabolized in the liver via cytochrome p450 dependent multifunction oxidase enzymes; conjugates with glucuronic acid, glycine or sulfates for excretion in urine
- lipophilic and therefore may accumulate in fat and fatty tissues.

Xylene *(mixed isomers)*

Source of Exposure

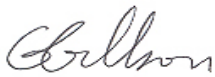
- Household:** Varnish/ polish, paint thinner, paint remover, shellac, rust inhibitors, lacquers, inks, dyes, adhesives, cleaning fluids, degreasing agents, cleaning products.
- Industry:** Used in synthesis of plasticizers and manufacture of polyester fiber, film, insecticide, formulations and perfumes.
- Inhalation:** Tobacco smoke.
- Outgassing:** Fabric and leather treatments.
- Petroleum:** Fuel additive, natural component of petroleum and coal tar, automotive emissions, gas stations, poor vehicle emission control.
- Solvent:** Solvent for rubbers, synthetic resins, gums, inks and paints.
- Waste:** Waste & landfill sites, local industrial waste/ spillage
- Workplace:** Paint and printing ink industries, automobile body and related repairs, photographic processing, rubber, leather plastics and textile industries, flooring contractor.

Toxic Effects

- irritation of mucous membranes, dermatitis, nausea, fatigue, headache, anxiety
- neuropsychological and neurophysiological dysfunction
- anemia, thrombocytopenia, renal damage
- dyspnea, cyanosis
- CNS depression

Metabolism

- xylene is metabolized in the liver by cytochrome p450 dependent multifunction oxidase enzymes; conjugates primarily with glycine
- minor amounts conjugate with sulfur and glucuronide
- excreted in urine as methylhippuric acids
- 2-methylhippurate has longer half-life, but 3-methylhippurate correlates more strongly with exposure
- xylene does not accumulate significantly in tissues



George Gillson, MD PhD
Medical Director

The Environmental Pollutants Panel is not intended to diagnose, treat, or prevent any disease or replace the medical advice and/or treatment obtained from a qualified healthcare practitioner. The College of Physicians and Surgeons of Alberta has not evaluated the interpretation comments. This test does not assess for neonatal inborn errors of metabolism and is based on stable renal function and normal renal clearance. The analytes on the panel are subject to change without notice.