Porphyrins

Interpretive Guide

Tox*fx* Toxic Effects℠
Porphyrins Profile

Metametrix®
Clinical Laboratory

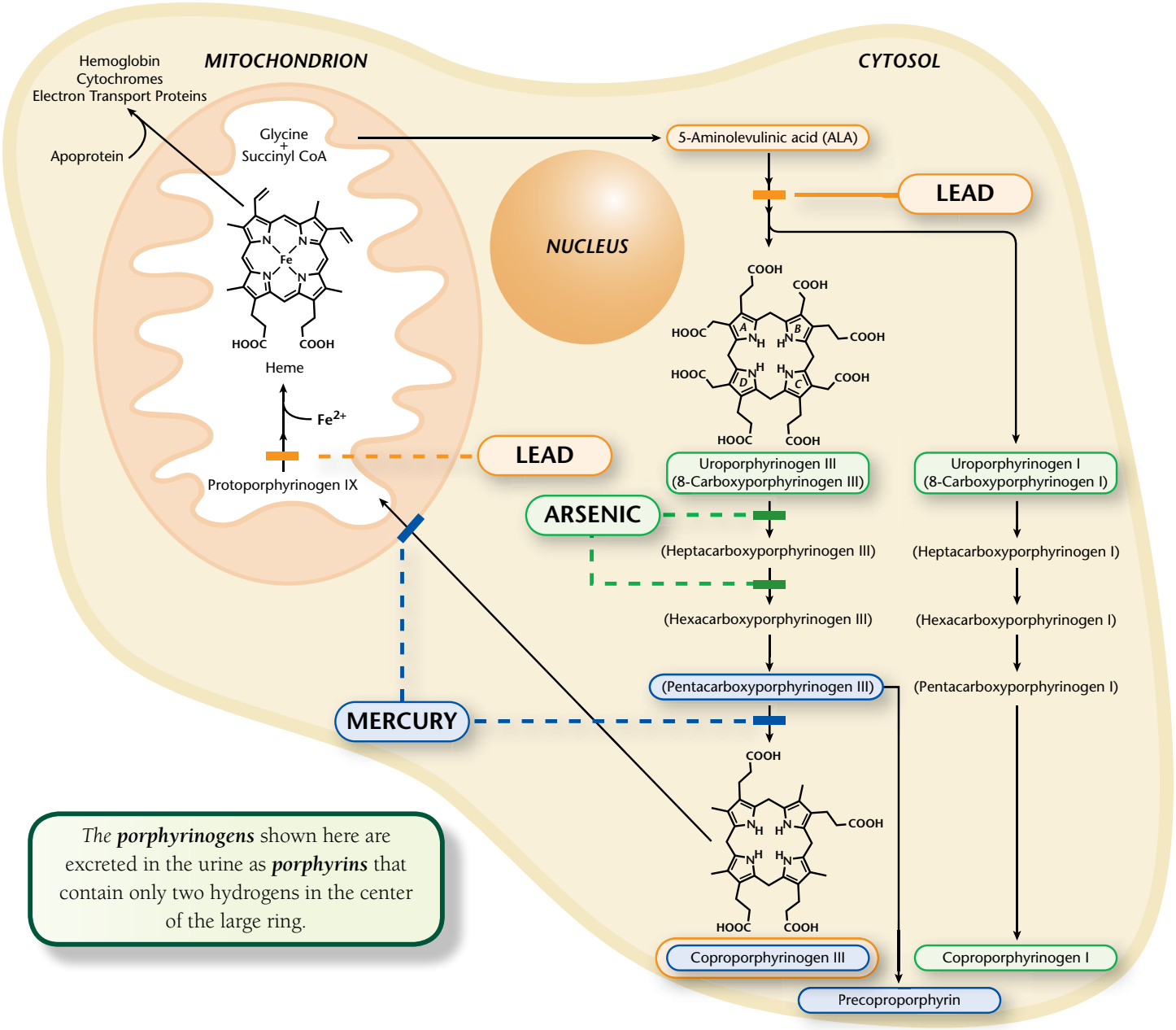

Figure 1: The Heme Pathway

The highly regulated heme pathway consists of eight enzyme-driven reactions. Reactions begin and end inside the mitochondria, with intervening steps carried out in the cytosol. When porphyrinogens build up, they are easily oxidized to porphyrins that appear in urine. Toxicants like heavy metals and organic xenobiotics bind to one or more enzymes to produce specific patterns of urinary porphyrin elevation. Oxidized porphyrins that accumulate in the body become additional toxicants that cause further tissue degradation. The blockages also slow down the production of the heme-requiring proteins listed at the upper left.

Uroporphyrinogen I is produced in a non-enzymatic reaction that leads to the inactive by-product coproporphyrin I. Some toxicants (especially arsenic) slow the metabolism of uroporphyrinogen III, causing diversion to coproporphyrinogen I, so the copro I/III ratio becomes elevated.

Porphyrins appear elevated in urine when the cellular pathway for heme synthesis is blocked by natural or man-made toxicants or when genetic disorders that affect the enzymes of the porphyrin pathway are present. When confounding variables are absent, the analytes and ratios of the Metametrix Porphyrin Profile allow discrimination of certain types of toxic effects. Table 1A summarizes some of the most frequently encountered environmental abnormalities. Table 1B shows inherited factors (see below).

Environmental Toxin-induced Porphyrinurias

	Heavy Metals					Organotoxins						
Analytes	Aluminum	Arsenic	Mercury	Lead		Hexachlorobenzene	Methyl chloride	Dioxin	Polyvinylchloride	Polybrominated biphenyl	Alcohol (chronic hepatic porphyria - early)	Alcohol (chronic hepatic porphyria - late)
Uroporphyrin I & III	+	+				+		+		+		++*
Heptacarboxyporphyrin		(+)				(+)		(+)		(+)		+
Hexacarboxyporphyrin		(+)				(+)		(+)		(+)		+
Pentacarboxyporphyrin		(+)	+									
Precoproporphyrin			++									
Coproporphyrin I		+		+			+		+	+	+	
Coproporphyrin III	+		+	+			+		+	+	++	
Precopro/Uro I & III†			+									
Copro I/Copro III‡		+										

Table 1A: Effects of toxins on urinary porphyrin levels

The green pluses (+) show the typical pattern of elevated porphyrins. The double pluses (++) show dominant elevations. Pluses enclosed in parathesises indicate alternate patterns that may appear. Calculated total porphyrins levels are generally elevated in the severe types of any condition that produce porphyrias. Aminolevulinic acid (ALA) and zinc protoporphyrin are other porphyrin pathway intermediates elevated in lead toxicity and iron deficiency, respectively.

* *Hepatic degeneration due to porphyrin accumulation in the liver is found in these conditions.*

Inheirited Porphyrinurias

Analytes	Acute intermittent porphyria (AIP)	Congenital erythropoietic porphyria	Porphyria cutanea tarda (PCT) and hepatoerythropoeitic porphyria (HEP)	Hereditary coproporphyria	Variegate porphyria
Uroporphyrin I & III	+	+	++		
Heptacarboxyporphyrin			+		
Hexacarboxyporphyrin			+		
Coproporphyrin I		++		+	+
Precopro/Urocopro I & III†		+		++	+

Table 1B: Effects of inherited disorders on urinary porphyrin

† If Precopro is very high, then mercury effects are always suspected. Slight elevations, however might be overlooked. High Precopro with lower Uro I & III will elevate the Precopro/Uro I & III ratio, drawing attention to a specific mercury effect. On the other hand, high Uro I & III with a normal Precopro/Uro I & III ratio is indicative of pathway stimulation rather than mercury-specific effects.

‡ Elevation of the Copro I/III ratio lets you spot the potential arsenic-specific effects. Arsenic causes a diversion away from the enzymatic product (Copro III) to the non-enzymatic one (Copro I). This effect is rarely dramatic, so the ratio is useful.

Toxicity can be a component of...

- Multiple chemical sensitivity
- Behavioral and learning disorders
- Immune dysfunctions
- Chronic fatigue
- Neurological and mental/emotional disorders

Porphyrias, which can be inherited or acquired, are often diagnosed with the aid of information regarding the distribution profile of individual porphyrin intermediates in urine.[5] Porphyrins are particularly well suited as biomarkers for two reasons. First, the pathway is highly active, so any disturbance tends to cause rapid and relatively large accumulations of intermediates. Second, the enzymes of the porphyrin-producing pathway are widely distributed in human tissues and some of them are highly sensitive to the presence of various toxins.

Table 2: Symptoms Associated with Porphyrinopathies

Chronic elevation of porphyrins causes tissue degeneration due to their secondary toxic effects. However, many conditions that manifest as less severe patterns of elevation may not be associated with such direct porphyrin toxicity. Symptoms in patients with these conditions are highly variable. Chronic mercury-induced porphyria may be a factor in autism and the alcohol-associated porphyria may contribute to the transient nausea following excessive alcohol intake.

	Primary Complaints	Associated Symptoms	Condition Exacerbated by
Acute porphyrias	Neurologic presentations due to hepatic accumulations: • Acute abdominal pain • Nausea • Vomiting • Constipation • Seizures	• Headaches • Difficulty in concentration; • Personality changes; • Weakness • Muscle and joint aches; • Unsteady gait • Poor coordination • Numbness • Tingling of arms and legs; • Fluid retention; • Rapid heart rate; • High blood pressure; • Increased sweating; • Intermittent fever	• Low carbohydrate diets (skipped meals); • Intake of alcoholic beverages; • Medications, including sulfa-drug antibiotics, barbiturates, estrogen, birth control pills; • Exposure to toxic chemicals
Non-acute porphyrias	• Cutaneous presentations (photosensitivity) due to bone marrow accumulations: • Pigmentation • Changes in facial hair • Fragile skin • Rashes • Blistering	• Dark-colored urine (especially after its exposure to sunlight), and above symptoms may be present	• All of the above • Skin symptoms made worse by exposure to sunlight. Copper or brass jewelry exacerbates reaction

Table 3: Other Conditions That Can Cause Elevation of Total Porphyrins (Generally due to uroporphyrin and coproporphyrin elevation.)	
Genetic Disorders	
Hereditary hyperbilirubinemias	• Dubin–Johnson syndrome • Rotor's syndrome
Bronze baby syndrome	
Erythrohepatic protoporphyria	
Hereditary tyrosinemia	
Metabolic Disturbances	
Diabetes mellitus	
Myocardial infarction	
Hematologic diseases	• Hemolytic, sideroachrestic, sideroblastic and aplastic anemias • Ineffective erythropoiesis (intramedullary hemolysis) • Pernicious anemia • Thalassemia • Leukemia • Erythroblastosis
Disturbance of iron metabolism	• Hemosiderosis • Idiopathic and secondary • Iron deficiency anemia
Diseases	
Infectious diseases	• Mononucleosis • Acute poliomyelitis
Liver diseases	• Cirrhosis • Active chronic hepatitis • Toxic and infectious hepatitis • Fatty liver • Alcoholic liver syndromes • Drug injury • Cholestasis • Cholangitis • Biliary cirrhosis
Malignancies	• Hepatocellular tumors • Hepatic metastases • Pancreatic carcinoma • Lymphomatosis
Other Conditions	
Pregnancy	
Carbohydrate fasting	

"Patterns of specific porphyrin elevations in urine may serve as functional fingerprints of toxicity due to specific toxins."

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Alterations of porphyrin synthesis that are not due to hereditary or toxic disturbances of porphyrin metabolism are adaptive responses. Such responses caused by alcohol or other drugs (see Table 4) may not lead to clinical consequences. However, these disturbances often initiate biochemical and clinical manifestation of genetic porphyrias that previously may have been latent. Once initiated, the symptoms may be long-lasting, especially if the offending toxicant is not identified and removed or avoided.

Numerous toxic porphyrias are precipitated by environmental mediators (see Table 5). Exposure to the fungicide hexachlorobenzene used in some provinces of Turkey to treat wheat in 1956 resulted in thousands of adult cases of cutaneous photosensitivity and porphyrinuria. Many of these cases are thought to represent latent genetic enzyme polymorphisms. Multiple environmental and nutritional factors can cause additive effects. For example, hexachlorobenzene-induced porphyria is accentuated by estrogens and attenuated by vitamin C. The estrogen effect increases the susceptibility of women to porphyrias.

Aluminum inhibits some heme synthetic enzymes and has been implicated in causing porphyria in chronic hemodialysis patients, whom are often aluminum overloaded. Lead intoxication causes signs and symptoms similar to acute intermittent porphyria including abdominal pain, constipation and vomiting. However, anemia which is often found with lead intoxication may be absent in lower lead exposures that generate porphyria, indicating that the overall flux through the porphyrin pathway is not strongly reduced even though significant amounts of intermediates are spilled, due to the toxicant effect.

Table 4: Some Drugs That Cause or Exacerbate Porphyria (Elevation of Total Porphyrins)	
• Antipyrine	• Amidopyrine
• Aminoglutethimide	• Barbiturates
• Carbamazepine	• Carbromal
• Chloropropramide	• Chloral hydrate
• Danazol	• Dapsone
• Diclofenac	• Diphenylhydantoin
• Ergot preparations	• Ethanol (acute)
• Ethclorvynol	• Ethinamate
• Glutethimide	• Griseofulvin
• Isopropylmeprobamate	• Mephenyltoin
• Meprobamate	• Methylprylon
• N-butylscopolammaonium bromide	• Nitrous oxide
• Novobiocin	• Phenylbutazone
• Primadone	• Pyrazolone preparations
• Succinimides	• Sulfonamide antibiotics
• Sulfonthylmethane	• Sulfonmethane
• Synthetic estrogens, progestins	• Tolazamide
• Tolbutamide	• Trimethadone
• Valproic acid	

Table 5: Environmental Mediators of Toxic Porphyrias That May Cause Hepta-, Hexa-, or Pentacarboxyporphyrinurias.	
Hexachlorobenzene exposure in adults results in cutaneous photosensitivity and porphyrinuria. However, in infants, exposure results in high mortality and neurotoxicity (convulsions) without porphyrinuria. Aluminum inhibits some heme synthetic enzymes and has been implicated in causing porphyria in chronic hemodialysis patients, whom are often aluminum overloaded. Lead intoxication causes signs and symptoms similar to acute intermittent porphyria including abdominal pain, constipation and vomiting. However, anemia which is often found with lead intoxication is virtually absent in porphyria. http://database.healthandenvironment.org	
Hexachlorobenzene	PAHs
PCBs	2,4,5-T
2,4-D	Carbon tetrachloride
Chlordane	Chloroform
DDT/DDE	Diazinon
Dioxins/TCDD	Formaldehyde
Halothane	Methyl chloride
Organochlorine pesticides	Organophosphates
Paint fumes	Pesticides
Phenoxyacetic herbicides	Solvents such as xylene
Vinyl chloride	

Follow up testing:

Whenever porphyrinurias are found on an initial investigation, follow up testing of toxic metals, organotoxins or genetic enzyme defects may need to be done to determine the exact cause. Then, treatments may be designed to deal with specific causes and efficacy of treatment can be indicted by correction of the porphyrinuria.

Quintile range limit significance

The quintile limits allow a systematic way of indicating a reasonable point of concern. Based on a general outpatient population, eighty percent of people in our toxicant-exposed society are better off than a patient with a value above the 5th quintile limit. Most practitioners of environmental medicine agree that results greater than the 5th quintile limit should be considered to be at risk of toxic consequences.

References

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