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# TOXICOLOGICAL HIGHLIGHT

## Porphyrinurias Induced by Mercury and Other Metals

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**The article highlighted in this issue is "Quantitative Evaluation of Urinary Porphyrins as a Measure of Kidney Mercury Content and Mercury Body Burden during Prolonged Methylmercury Exposure in Rats" by Stephanie D. Pingree, P. Lynne Simmonds, Kevin T. Rummel, and James S. Woods (pp. 234–240).**

Biomarkers for toxic agents such as methylmercury are ideally early, chemical-specific biological responses to exposure of a target cell population which can be measured in accessible biological matrices such as blood or urine. Chemical-induced alterations in the heme biosynthetic pathway are among the those biomarkers of chemical exposure/toxic cell injury that have proven themselves both useful and reliable over a number of decades. This pathway, which is essential for life, produces heme, utilized for a host of hemoproteins including hemoglobin, the cytochrome P450 family, and mitochondrial cytochromes. There are a host of biological processes of direct toxicological interest which are dependent upon the heme biosynthetic pathway. The heme pathway is also highly sensitive to inhibition by a number of inorganic agents such as lead, mercury, and arsenicals as well as organic agents such as the chlorinated benzenes and alcohol. There is also a high degree of correlation between excretion of specific porphyrins in the urine and other ultrastructural/biochemical alterations in organelles, such as the mitochondrion, which contain a number of enzymes in the heme biosynthetic pathway (Fowler *et al.*, 1987). This indicates the utility of porphyrinurias in detecting early stages of cell injury. As noted below, metal-induced disturbances in this pathway have also proven useful for examining the interactions between metals under mixture exposure conditions (Mahaffey *et al.*, 1981, Conner *et al.*, 1995). Over the years, measurement of lead-induced alterations in this pathway (e.g., blood delta-aminolevulinic acid dehydratase activity and measurement of erythrocyte zinc protoporphyrin) were used in making timely public health screening decisions for both workers and children exposed to lead-containing dust (Piomelli *et al.*, 1987). These measurements have permitted physicians to ascertain that sufficient exposure to lead had occurred to produce a disturbance in an essential biochemical pathway and that a biological threshold had been crossed.

The question of variability in individual susceptibility to alterations in the heme pathway by metals such as lead and mercury, as a function of the biologically active fraction of these metals, has remained a problem. The paper by Pingree *et al*. represents a major contribution towards addressing this question for a common organometal toxicant (methylmercury) which is of current public health concern. It examines the relationship between biological activity against the renal heme biosynthetic pathway and intracellular biological availability of $CH_3Hg^+$ and $Hg^{2+}$ as monitored by sodium 2,3-dimercapto-1-propanesulfonic acid (DMPS) mobilization from the kidney. The import of these studies in a rodent species is not trivial for humans, since the heme pathway is highly conserved across species, and previous studies (Gonzalez-Ramirez *et al.*, 1995) have shown similar findings with regard to the observed porphyrinuria pattern. Methylmercury-induced porphyrinuria of renal origin was first described in rats (Woods and Fowler, 1977) at dose levels that did not produce signs of neurological dysfunction in this species. Subsequent studies in humans exposed to mercury vapor (Gonzalez-Ramirez *et al.*, 1995) showed similar findings.

The study by Pingree and colleagues makes a substantial contribution toward a better understanding of the mechanisms underlying this unique porphyrinuria pattern. It also contributes to the field of metal toxicology in several specific areas. First, it defines a relationship between a biological effect (mercury-specific porphyrinuria pattern) and a target tissue dose of this element as measured by the relationship with the DMPS mobilizable fraction. The high degree of statistical correlation between renal mercury burden and porphyrin excretion in the urine indicates that the observed mercury-specific porphyrin excretion pattern may be reliably used as a noninvasive index of the total renal mercury burden. More specifically, the porphyrinuria pattern clarifies this relationship in terms of the biologically active fractions of $CH_3Hg^+$ and $Hg^{2+}$ as evidenced by the strong statistical relationship between DMPS chelatable fractions and alterations in the observed porphyrinuria. It is also extremely valuable to be aware of the dose-related nature of the porphyrinuria pattern across a wide range of doses, both with regard to the consistency of the

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effects and with regard to potential applicability to a wide range of exposures, such as may be encountered in human populations. These findings are also important from the pharmacological perspective since they help to delineate the fraction of these 2 mercurial species being chelated and hence provide valuable data on the pharmacological efficacy of this chelating agent. This is also of basic scientific interest since it would suggest that DMPS is capable of chelating $Hg^{2+}$ from the renal metallothionein pool normally found in rat kidney to bind zinc and copper. In addition, since the heme biosynthetic pathway is highly conserved across species, the ability to extrapolate these findings to man or other species of interest is obvious and is supported by the findings of Gonzalez-Ramirez *et al.* (1995). Finally, it should be noted that a number of studies in the last 20 years have utilized specific metal porphyrinuria patterns as biomarkers of exposure to either a single metal (Woods and Fowler, 1977, 1978) or metal mixtures (Mahaffey *et al*., 1981; Conner *et al.*, 1995). It will be of interest to determine if similar relationships exist between the biologically active fractions of these elements in their respective target tissues. It should be clear that the approach taken in the paper by Pingree *et al.* could be applied to other metal nephrotoxins which also produce relatively specific porphyrinuria patterns (e.g., for lead, using EDTA or DMSA as chelating test agents and for arsenicals, using perhaps BAL as a chelating test agent). The point here is that the approach taken in the paper by Pingree *et al.* could have broader applicability to a number of toxic metals, either alone or as mixture combinations.

In summary, the results of this paper provide further evidence of the utility of chemical-induced alterations in the heme biosynthetic pathway as a reliable class of biomarker for delineating both the total tissue burden of a toxic substance such as methyl mercury and the intracellular bioavailability of reactive chemical species of this toxic agent. It should be noted that this approach could also be applied to evaluating the efficacy of new therapeutic agents such as chelators or perhaps agents which facilitate the excretion of toxic metals from the body. It is clear that this highly useful class of biomarker may have as yet undiscovered applications in delineating both the total tissue burden of toxic metals such as mercury and the biologically available fraction of reactive chemical species.

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