Altered porphyrin metabolism as a biomarker of mercury exposure and toxicity

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Abstract: Changes in urinary porphyrin excretion patterns (porphyrin profiles) have been described in response to a variety of drugs and chemicals. The present studies were conducted to define the specific changes in the urinary porphyrin profile associated with prolonged exposure to mercury and mercury compounds. In rats, exposure for a prolonged period to mercury as methyl mercury hydroxide was associated with urinary porphyrin changes, which were uniquely characterized by highly elevated levels of 4- and 5-carboxyl porphyrins and by the expression of an atypical porphyrin ("precoproporphyrin") not found in urine of unexposed animals. These distinct changes in urinary porphyrin concentrations were observed as early as 1–2 weeks after initiation of mercury exposure, and increased in a dose- and time-related fashion with the concentration of mercury in the kidney, a principal target organ of mercury compounds. Following cessation of mercury exposure, urinary porphyrin concentrations reverted to normal levels, consistent with renal mercury clearance. In human studies, a comparable change in the urinary porphyrin profile was observed among subjects with occupational exposure to mercury as mercury vapor sufficient to elicit urinary mercury levels greater than 20 μg/L. Urinary porphyrin profiles were also shown to correlate significantly with mercury body burden and with specific neurobehavioral deficits associated with low level mercury exposure. These findings support the utility of urinary porphyrin profiles as a useful biomarker of mercury exposure and potential health effects in human subjects.

Key words: mercury, porphyrins, biomarker, urine.

Résumé : Des variations du patron d'élimination urinaire de porphyrines (profils de prophyrines) en réponse à divers médicaments et composés chimiques ont déjà été décrites. Les présentes études ont eu pour but de déterminer celles qui, plus spécifiquement, sont associées à une exposition prolongée au mercure et aux composés de mercure. Chez les rats, l'exposition prolongée à un composé de mercure, tel l'hydroxyde de méthylmercure, a été associée à des variations urinaires de porphyrines, caractérisées par de très hauts taux de (carboxyl-4 et -5) porphyrines ainsi que par l'expression d'une porphyrine atypique («précoproporphyrine») absente dans l'urine des animaux non exposés. Ces variations ont été observées moins de 1–2 semaines après le début de l'exposition au mercure et elles ont augmenté en fonction du temps et de la dose avec la concentration de mercure contenue dans le rein, un des principaux organes cibles des composés de mercure. Une fois l'exposition terminée, les concentrations urinaires de porphyrines sont retournées à des valeurs normales concordant avec la clairance rénale de mercure. Chez les humains, une variation comparable du profil urinaire de porphyrines a été observée chez les sujets exposés au mercure par leur travail, par exemple, sous forme de vapeur de mercure suffisante pour produire des taux urinaires supérieurs à 20 μg/L. Les profils urinaires de porphyrines ont aussi montré une corrélation significative avec la charge corporelle de mercure ainsi qu'avec des déficits neurocomportementaux spécifiques associés à une exposition à une faible dose de mercure. Ces résultats confirment l'utilité de l'emploi des profils urinaires de porphyrines comme marqueurs biologiques de l'exposition au mercure et de ses effets possibles sur la santé chez les sujets humains.

Mots clés : mercure, porphyrines, marqueur biologique, urine.
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Introduction

Porphyrins, in the reduced form, porphyrinogens, are formed in mammalian tissues as intermediates in the biosynthesis of heme (Fig. 1). In most tissues, porphyrinogens with 8-, 7-, 6-, 5-, and 4-carboxylated side chains are produced in excess of that required for heme biosynthesis and are excreted as porphyrins in the urine. The pattern of porphyrin excretion in normal individuals, i.e., persons without porphyria or exposure to porphyrinogenic chemicals, is typically characterized by moderate concentrations of 8-carboxyl porphyrin (uroporphyrin) (e.g., 3–18 nmol/24 h), low concentrations of 7-, 6-, and 5-carboxyl porphyrins (e.g., 0.1–10 nmol/24 h), and relatively high concentrations of 4-carboxyl porphyrin (coproporphyrin) (e.g., 30–90 nmol/24 h) (Woods et al. 1993). In previous studies, we have described metal-specific changes in urinary porphyrin excretion patterns (porphyrin profiles) associated with prolonged exposure of animals to low levels of mercury, arsenic, lead, and other metals (reviewed in Woods 1995). The etiology of these changes is considered to involve specific effects of metals on porphyrin synthesis and porphyrin metabolism in target tissues such as liver, kidney, and blood cells. These findings support the view that urinary porphyrin

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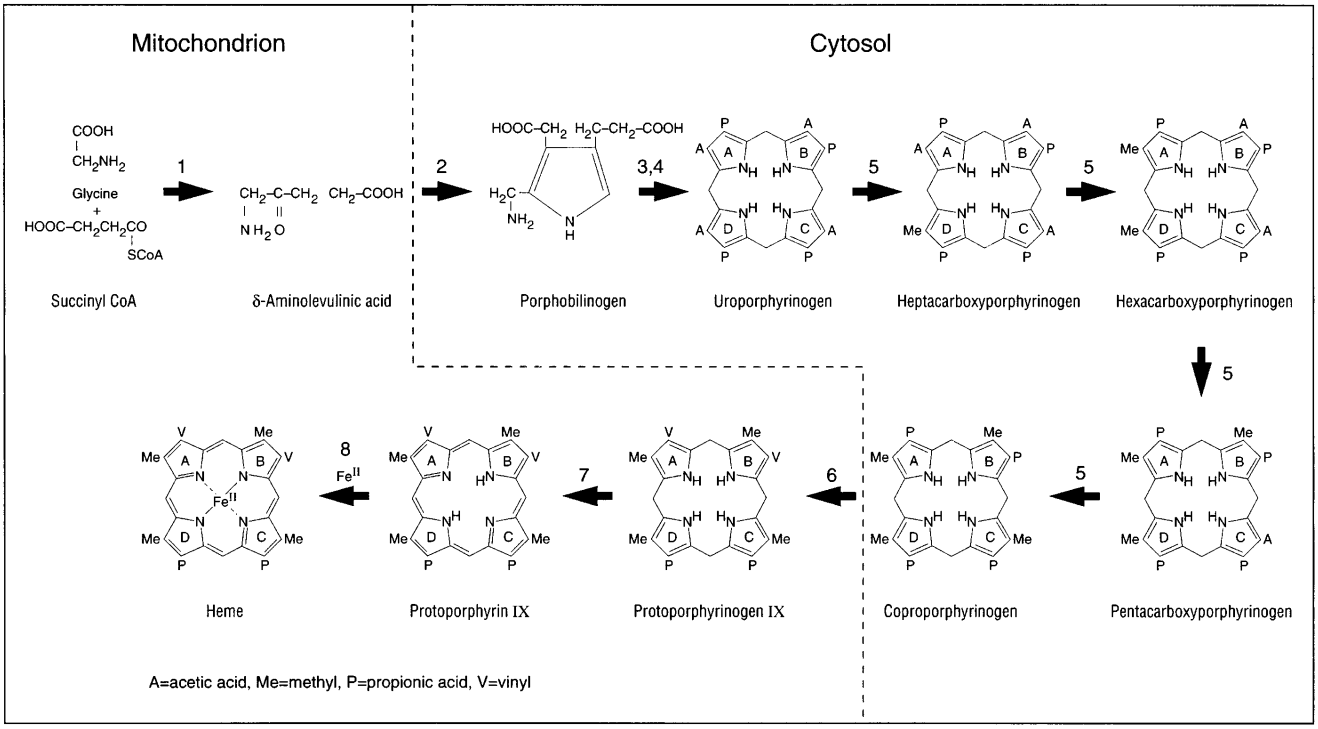
Fig. 1. Heme biosynthetic pathway. Steps are catalyzed by (1) δ-aminolevulinic acid (ALA) synthetase, (2) ALA dehydratase, (3) uroporphyrinogen I synthetase, (4) uroporphyrinogen III cosynthetase, (5) uroporphyrinogen decarboxylase, (6) coproporphyrinogen oxidase, (7) protoporphyrinogen oxidase, and (8) ferrochelatase.



profile measurements may serve as a biomarker of metal exposure and effects in human subjects (Woods 1989, 1995).

Of particular interest to the investigation of metal-induced changes in urinary porphyrin profiles are findings from studies of methyl mercury exposed rats, which have demonstrated a dramatic change in the urinary porphyrin excretion pattern due primarily to mercury-induced alterations of heme biosynthesis in the kidney (Woods and Fowler 1977; Woods et al. 1984, 1990, 1991; Miller and Woods 1993). Since the kidney is a principal target organ of mercury compounds, these observations suggest that changes in urinary porphyrin excretion patterns might serve as a specific measure of the accumulation and biological effects of mercury in the kidney during prolonged mercury exposure.

In the present article we describe the specific changes in the urinary porphyrin excretion pattern elicited during prolonged exposure to mercury as methyl mercury hydroxide (MMH) in rats. We also report findings from pilot studies designed to evaluate the efficacy of urinary porphyrin profile changes as a biomarker of mercury exposure, mercury body burden, and neurobehavioral effects related to low level mercury exposure in human subjects.

Materials and methods

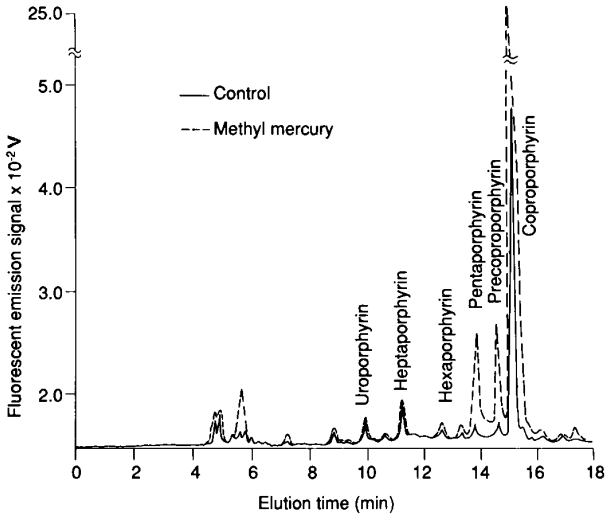
Animal studies

Animals were cared for in accordance with the principles and guidelines of the Canadian Council on Animal Care. Male Fischer 344 rats were obtained from Simonsen Labs, Gilroy, Calif., and were housed in individual wire-bottom cages with free access to food and water. After a 1-week acclimation period, all animals were placed in individual metabolism cages, and 24-h urine collections were made for baseline urinary porphyrin determinations. Rats were then divided into 3 groups of 6 animals each and were continued either on distilled water or on water containing mercury as MMH at 5 or 10 ppm (equivalent to approximately 0.6 and 1.2 $mg \cdot kg^{-1} \cdot day^{-1}$, respectively). MMH treatments were continued for up to 30 weeks, with water consumption for each rat recorded daily. At weekly intervals after the start of MMH treatment, 24-h urine collections were made from all rats for porphyrin and mercury analyses. In separate post-exposure studies rats were exposed to either distilled water or to water containing 10 ppm MMH for 8 weeks. Porphyrin profiles were monitored during exposure and subsequently for up to 40 weeks following cessation of MMH treatment, to evaluate the relationship between porphyrin excretion and renal mercury clearance. For all animal studies, urines were collected in foil-wrapped 125-mL polypropylene flasks containing 50 mg $NaHCO_3$ to maintain neutral pH. Following collection, urines either were processed immediately for porphyrin analysis or were frozen at –80°C.

Human studies

For all studies involving human subjects described herein, appropriate standards for human experimentation were followed, and the procedures employed were reviewed and approved by the appropriate institutional review boards. Subjects for urinary porphyrin profile studies and neurobehavioral assessments were drawn from among male dentists attending the 1991 American Dental Association (ADA) annual meeting in Seattle, Wash., who participated in a voluntary Health Screening Program (HSP) conducted during the meeting, as previously described (Woods et al. 1993). Approximately 1500 subjects participated in the HSP. Participants provided spot urine samples for mercury, creatinine, and porphyrin analyses. Neurobehavioral assessments were conducted on-site, as described (Echeverria et al. 1995). For mercury body burden studies, the subjects comprised dentists, dental technicians, and nondental personal who were

Fig. 2. HPLC elution profiles of urinary porphyrins from unexposed Fischer rats and from rats exposed to methyl mercury hydroxide (MMH) at 10 ppm for 5 weeks. The 24-h urine from 4 rats in each group were pooled for each determination. Porphyrin concentrations were determined as described in Materials and methods. (Reproduced with permission from Mosby-Year Book, Inc., St. Louis, Mo.).



employed in the dental profession in Monterrey, Mexico. A detailed description of this study has been published (Gonzalez-Ramirez et al. 1995).

Mercury, porphyrin, and creatinine analyses

Urinary and renal mercury concentrations were determined using a continuous-flow, cold vapor atomic absorption procedure (Atallah and Kalman 1993). Urinary porphyrins were measured as free acids by the HPLC–spectrofluorometric procedure developed in this laboratory (Woods et al. 1991; Bowers et al. 1992). Urinary creatinine content was determined using the colorimetric determination assay kit obtained from Sigma Chemical Co., St. Louis, Mo.

Statistical analyses

Analysis of significance of differences between treatment groups was determined by Student's *t* test. The level of significance was chosen at $p < 0.05$. Linear regression analyses were performed using a SYSTAT general purpose statistics package acquired from SYSTAT Inc., Evanston, Ill.

Results

The urinary porphyrin profile associated with prolonged mercury exposure is highly distinct from that of nonexposed subjects. Figure 2 illustrates the HPLC porphyrin elution patterns from 24-h urine samples of untreated (control) rats and of rats exposed to MMH at 10 ppm in the drinking water for 5 weeks. Comparison with the porphyrin profile from unexposed animals reveals that MMH exposure is associated with highly elevated concentrations of 4- and 5-carboxyl porphyrins to levels ranging from 8 to 10 times those observed in urine of untreated rats. In this respect, 4-carboxyl porphyrin (coproporphyrin) was increased from approximately 1 400 to over 15 000 pmol/24 h, whereas 5-carboxyl porphyrin increased from 39 to 320 pmol/24 h in the urine of rats exposed to MMH at 10 ppm for 5 weeks. These porphyrins increased to mean concentrations that were 31 and 17 times control levels, respectively, after 10 weeks of MMH exposure at 10 ppm. In addition, an atypical porphyrin ("precoproporphyrin"), which elutes approximately midway between 5- and 4-carboxyl porphyrins on HPLC, is also found in the urine of MMH-treated rats. The concentration of this porphyrin also varied in direct proportion to MMH exposure. In contrast, 8-, 7-, and 6-carboxyl porphyrins were largely unaffected by MMH treatment.

Rats exposed to 5 ppm MMH displayed a urinary porphyrin profile with characteristics comparable with those of rats exposed at the higher MMH dose, although the magnitude of the changes in 4- and 5-carboxyl porphyrins as well as of precoproporphyrin was approximately half those observed in the 10 ppm exposed rats. Reduction of the MMH exposure level to 1 ppm revealed a further reduction in the rate of increase in the concentrations of these three porphyrins as well as in the ultimate concentrations of each achieved (data not shown). However, significant increases in the levels of each, without changes in the concentrations of 8-, 7-, or 6-carboxyl porphyrins, were observed.

Time-course studies of the development of the urinary porphyrin profile during prolonged MMH exposure for 10 weeks showed that the concentrations of 4- and 5-carboxyl porphyrins as well as of precoproporphyrin were significantly elevated, compared with control, as early as 1 week following initiation of MMH treatment, and increased in a dose-related manner throughout the 10-week course of MMH exposure (Woods et al. 1991). Regression analysis over the 10-week exposure period demonstrated a highly significant correlation between urinary porphyrin concentrations and the concentration of mercury in the kidney at each dose level over the course of prolonged MMH treatment. Correlation coefficients for each regression ranged from 0.72 to 0.90, suggesting a close association of each of the three elevated porphyrins with renal mercury content (Woods et al. 1991). These observations suggest that urinary porphyrin profiles correspond closely to the renal mercury content over a wide range of mercury exposure. Since the kidney is the principal repository of mercury in the body, these findings support the view that urinary porphyrin profiles may serve as a biomarker of mercury body burden.

In studies designed to ascertain the efficacy of urinary porphyrin profiles as a measure of past mercury exposure (Woods et al. 1991), rats were treated either with distilled water or with water containing 10 ppm MMH for 8 weeks. Urinary porphyrin profiles as well as urinary mercury levels were measured at weekly intervals both during exposure as well as during a subsequent 40-week postexposure period. Findings from this study showed that the urinary porphyrin concentration declined rapidly following cessation of MMH exposure, but it remained significantly elevated for up to 40 weeks after treatment was terminated, consistent with the clearance rate of mercury from renal tissues during MMH exposure (Smith et al. 1994). These observations suggest that porphyrin profile measurements may be useful in assessing mercury body burden as well as the biological effects of mercury for an extended period after cessation of actual exposures.

Three pilot studies designed to evaluate the efficacy of urinary porphyrin profile measurements as a biomarker of mercury exposure and health effects in humans have been undertaken. In the initial study (Woods et al. 1993), subjects were drawn from among dentists attending the 1991 American

Table 1. Urinary porphyrin concentrations in dentists.

Porphyrin	Urinary mercury ≤1 μg/L	Urinary mercury ≥20 μg/L
Pentacarboxyl porphyrin (μg/L)	1.75 ± 0.31	3.07 ± 1.41*
Precoproporphyrin (μg/L)	1.98 ± 1.37	7.58 ± 4.55*
Coproporphyrin (μg/L)	22.97 ± 5.80	74.45 ± 8.00*

Note: Values are means ± standard deviation of individual determinations.
*Significantly different from urinary porphyrin concentrations in samples with mercury level ≤1 μg/L ($p < 0.05$).

Dental Association meeting in Seattle, Wash., who participated in a Health Screening Program at the meeting in which spot urine samples were acquired for mercury and porphyrin analyses. Subjects having urinary mercury levels ≤1 μg/L ($n = 23$) were compared with those having urinary mercury levels ≥20 μg/L ($n = 38$) with respect to urinary porphyrin concentrations. Mercury concentrations within the latter group ranged from 20.3 to 135.6 μg/L (mean 38.4 μg/L). The results, presented in Table 1, show that the mean concentrations of each of the three porphyrins which are altered by mercury exposure in animals were significantly elevated among subjects having urinary mercury in excess of 20 μg/L. These differences in urinary porphyrin concentrations between the two groups were somewhat less pronounced but remained statistically significant when expressed as μg porphyrin/g creatinine (Woods et al. 1993).

In a second study, the efficacy of urinary porphyrins as a biomarker of mercury body burden in human subjects was evaluated (Gonzales-Ramirez et al. 1995). Subjects for this study comprised dentists and dental technicians in Monterrey, Mexico, who had mercury exposure from the use of Hg° in the preparation of dental amalgams. Nondental personnel with no history of occupational mercury exposure served as controls. To assess body burden, urinary mercury and porphyrin levels were measured before and after subjects were administered the mercury-chelating agent 2,3-dimercaptopropanesulfonate (DMPS) (300 mg per subject, p.o.). Subjects were fasted overnight beginning 11 h before DMPS administration to 4 h after DMPS administration. Urine was collected for mercury and porphyrin analyses from –11 to 0 h before DMPS administration and from 0 to 6 h after DMPS administration. Since DMPS is an effective chelator both of intracellular as well as of extracellular mercury (Zalups 1993), the amount of mercury appearing in the urine subsequent to DMPS administration is highly indicative of mobilizable mercury body stores. All clinical procedures were performed as previously described (Gonzales-Ramirez et al. 1995). As shown in Table 2, mean urinary mercury levels increased from 19.8 to 275.0 μg/L among dentists; from 29.7 to 481.0 μg/L among dental technicians, and from 3.0 to 37.2 μg/L among nondental personnel following DMPS challenge. Correspondingly, the urinary concentrations of the three porphyrins that are altered by mercury in the kidney declined to 67, 65, and 49% with respect to prechallenge levels among the three groups, respectively. These findings support the view that DMPS is highly effective in reducing the mercury body burden in humans. Also, since the kidney is the principal repository of mercury in the body as well as the source of excess porphyrins that are excreted in the urine during mercury exposure (Woods et al. 1991), the

Table 2. Effects of DMPS treatment (300 mg, p.o.) on urinary mercury and porphyrin concentrations in human subjects.

	Urinary mercury (μg/L)		Urinary porphyrins (μg/L)	
	Before	After	Before	After
Dentists ($n = 5$)	19.8	275.0*	74.7	50.4*
Technicians ($n = 10$)	29.7	481.0*	41.6	27.2*
Nondental personnel ($n = 13$)	3.0	37.2*	33.6	16.5*

Note: DMPS (300 mg per subject) was administered orally as described in Materials and methods. Values are means of individual determinations. Urinary porphyrin values represent the sum of pentacarboxyl porphyrin, precoproporphyrin, and coproporphyrin concentrations.
*Significantly different from urinary mercury or porphyrin concentrations before DMPS administration ($p < 0.05$).

reduction in urinary porphyrins after DMPS administration reflects the reduction in porphyrinuria attributable to mercury in the kidney that was present before DMPS was given. Since mercury that is stored in body tissues is not readily excreted subsequent to cessation of cumulative exposure, urinary porphyrin changes may represent a more accurate measure of cumulative mercury body (renal) burden than urinary mercury levels.

A third study was conducted to evaluate urinary porphyrin profiles as a predictive measure of neurobehavioral deficits associated with prolonged mercury exposure (Echeverria et al. 1995). Subjects for this study were drawn from the same population of dental professionals participating in the ADA Health Screening Program described above. For this study, subjects with urinary mercury levels ≤1 μg/L ($n = 20$) or with urinary mercury levels ≥20 μg/L ($n = 19$) were administered a 1-h test consisting of a consent form, the Profile on Mood Scales, a symptom and medical questionnaire, and six behavioral tests, including digit span, symbol–digit substitution, simple reaction time, the ability to switch between tasks, vocabulary, and the one-hole test. Multivariate regression was used to control for the effects of age, race, gender, and alcohol consumption. Among the principal findings of this investigation, tests indicating poor concentration, emotional lability, and somatosensory irritation and mood, as well as pooled scores for cognitive and motor functions, were significantly ($p < 0.05$) associated with urinary mercury levels in the range of 25–50 μg/L. Moreover, changes in urinary porphyrins were more highly correlated than urinary mercury levels with neurobehavioral deficits that are considered to reflect cumulative mercury exposure. These findings are of particular interest with respect to the use of porphyrins as a biomarker of mercury effects, because they demonstrate a potentially significant correlation between preclinical neurologic effects and altered porphyrin levels in the range of mercury exposure associated with prolonged exposure situations.

Discussion

The findings presented in this paper describe distinctive changes, characterized by elevated 4- and 5-carboxyl porphyrin concentrations and the expression of an atypical porphyrin (precoproporphyrin) in the urinary porphyrin excretion pattern associated with prolonged exposure to mercury in both

animals and human subjects. As assessed from animal studies, changes in porphyrin excretion patterns are highly correlated with the dose and time course of mercury exposure and also with the mercury content of the kidney, the principal target organ of mercury accumulation. Urinary porphyrin profiles also reflect residual mercury body burden, as indicated by a high correlation of urinary porphyrin profiles with renal mercury content subsequent to cessation of mercury exposure (Woods et al. 1991). The predictive and diagnostic potential of urinary porphyrin profile measurements as a specific biomarker of mercury exposure and potential toxicity in human subjects is suggested from the findings of changes in porphyrin excretion patterns among humans with low level mercury exposure comparable with changes observed in mercury-treated animals.

Of interest with respect to the specificity of the change in the urinary porphyrin profile elicited during mercury exposure is the appearance of the atypical porphyrin, precoproporphyrin, which elutes on HPLC approximately midway between the 5- and 4-carboxyl porphyrins (Woods et al. 1991). The identity of this compound as a porphyrin was determined by absorption spectrophotometry; precoproporphyrin isolated from urine of mercury-exposed rats displays typical porphyrin absorption properties, including a characteristically narrow Soret peak at ~403 nm in the absorption mode and an undistorted first derivative sigmoid deflection in the derivative mode. Preliminary studies using electrospray ionizing mass spectroscopy have suggested that this porphyrin shares properties of a derivative of isocoproporphyrin, a coproporphyrin isomer excreted by humans with porphyria cutanea tarda (Stoll et al. 1973). Studies are in progress to describe the structural and biochemical characteristics of this atypical porphyrin and to define its specificity with respect to mercury exposure.

The efficacy of urinary porphyrin profile measurements as a biomarker of mercury health effects in humans has been recently demonstrated in a study of neurobehavioral deficits associated with low level occupational mercury exposure (Echeverria et al. 1995). Of particular note from this study is the finding that changes in urinary porphyrins were significantly associated with deficits in specific tests of both cognitive and motor function, in some cases more highly correlated with such changes than urinary mercury levels. Although the study from which these findings were derived involved only a small number of subjects, they are nonetheless of interest in supporting the potential utility of urinary porphyrin changes as a predictive measure of neurologic impairment associated with low level mercury exposure in humans.

The potential efficacy of urinary porphyrin measurements as a biomarker of mercury body burden in humans is supported by findings of the DMPS challenge study (Gonzales-Ramirez et al. 1995), in which porphyrin profile measurements were made in dental workers before and after treatment with the mercury chelator 2,3-dimercaptopropane-1-sulfonate (DMPS). In these studies, urinary porphyrin levels in study subjects decreased substantially following DMPS treatment, consistent with the clearance of mercury from the kidney, the source of the mercury-induced porphyrinogenic effects. Among mercury-exposed subjects, urinary porphyrin levels before DMPS treatment were found to correlate strongly with urinary mercury levels following DMPS administration, indicating a strong and significant association between urinary porphyrin concentrations and mercury body burden, as reflected in renal mercury content. These findings support the view that urinary porphyrin profile measurements might serve as a useful test of mercury body burden as well as of health effects.

In summary, we have developed and characterized a test for mercury exposure and potential toxicity based on a readily performed measurement of changes in urinary porphyrin excretion profiles. Initial studies attest to the potential efficacy of this test as a sensitive and specific biomarker of mercury exposure and toxicity among human subjects with low level exposure to mercury from occupational sources. A large scale human study is currently in progress to confirm these findings and to establish the threshold of sensitivity of porphyrin profile measurements as a predictive biomarker of a number of health effects related to low level mercury exposure.

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