URINARY PORPHYRIN PROFILES AS A BIOMARKER OF MERCURY EXPOSURE: STUDIES ON DENTISTS WITH OCCUPATIONAL EXPOSURE TO MERCURY VAPOR

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Porphyrins are formed as intermediates in the biosynthesis of heme. In humans and other mammals, porphyrins with eight, seven, six, five, and four carboxyl groups are excreted in the urine in a well-established pattern. Mercury selectively alters porphyrin metabolism in kidney proximal tubule cells, leading to an altered urinary porphyrin excretion pattern. Previous studies in rats have shown that changes in the urinary porphyrin profile during exposure to mercury as methylmercury hydroxide are uniquely characterized by highly elevated (20- to 30-fold) levels of four- and five-carboxyl porphyrins and by the excretion of an atypical porphyrin ("precoproporphyrin"), which elutes on high performance liquid chromatography (HPLC) approximately midway between penta- and coproporphyrins. Changes in the urinary porphyrin profile are highly correlated with the dose and duration of mercury exposure and persist for up to 20 wk following cessation of mercury treatment. In the present studies, the utility of urinary porphyrin profile changes as a biomarker of mercury exposure in human subjects was evaluated. Urinary porphyrin concentrations were measured in dentists participating in the Health Screening Programs conducted during the 1991 and 1992 annual meetings of the American Dental Association and compared with urinary mercury levels measured in the same subjects. Among dentists with no detectable urinary mercury, mean concentrations of urinary porphyrins were within the established normal ranges for male human subjects.

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In contrast, among dentists with urinary mercury in excess of 20 μg/L, mean urinary concentrations of four- and five-carboxyl porphyrins as well as of precoproporphyrin were elevated three to four times those of unexposed subjects. Significant differences in urinary porphyrin concentrations remained when porphyrin concentrations in spot urine samples were adjusted for creatinine levels. These findings suggest that urinary porphyrin profiles may serve as a useful biomarker of mercury exposure in clinical or epidemiologic studies of mercury-related human health risks.

INTRODUCTION

Porphyrins are formed in mammalian tissues as intermediates in the biosynthesis of heme (Fig. 1). In most tissues, porphyrins bearing side chains with eight, seven, six, five, and four carboxyl groups are produced in excess of that required for heme synthesis and are excreted in the urine in a well-established pattern (Fig. 2a). In previous studies, we described specific changes in urinary porphyrin excretion patterns (porphyrin profiles) associated with prolonged exposure of animals to low levels of mercury as methylmercury hydroxide (MMH) (Woods and Fowler, 1977; Woods et al., 1991; Bowers et al., 1992). The etiology of these changes involves both mercury-directed impairment of specific heme biosynthetic pathway enzymes in the kidney (a principal target organ of mercury compounds) and mercury-promoted oxidation of reduced porphyrins that accumulate in kidney cells because of impaired porphyrin metabolism (Woods et al., 1990a, 1990b; Woods, 1989; Miller and Woods, 1993). These observa-

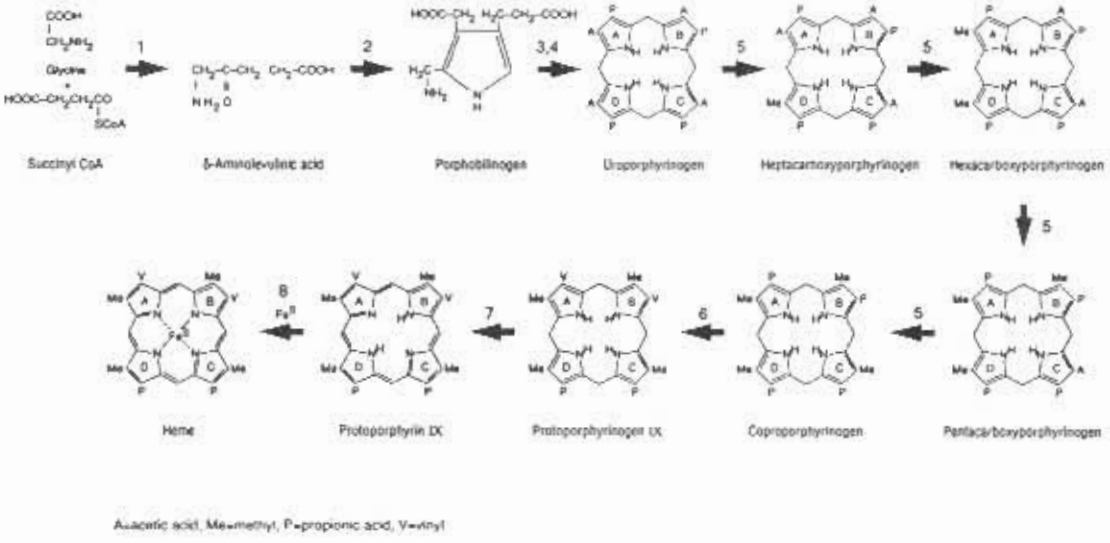

FIGURE 1. Heme biosynthetic pathway. Steps are catalyzed by (1) δ-aminolevulinic acid (ALA) synthetase, (2) ALA dehydratase, (3) uroporphyrinogen I synthetase, (4) uroporphyrinogen III cosynthetase, (5) uroporphyrinogen decarboxylase, (6) corproporphyrinogen oxidase, (7) protoporphyrinogen oxidase, and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

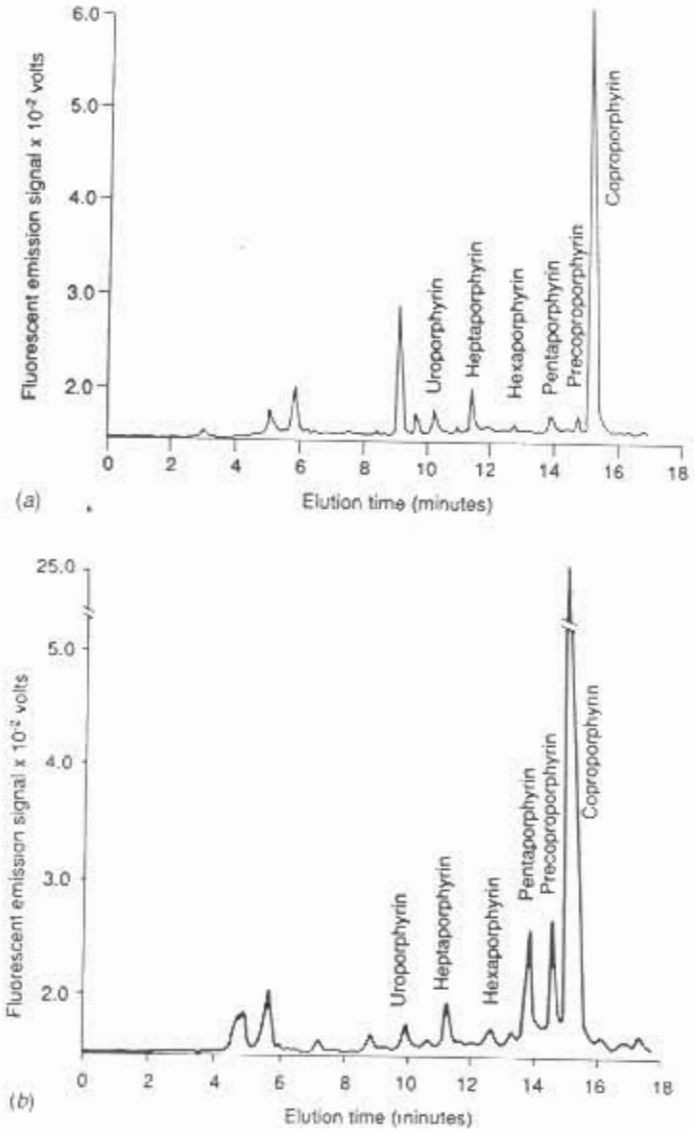

FIGURE 2. HPLC elution profiles of urinary porphyrins (a) from unexposed Fischer rats or (b) from rats exposed to methylmercury hydroxide (MMH) at 10 ppm for 5 wk. Porphyrin concentrations in this and Figure 3 were determined as described in Materials and Methods. Porphyrin concentrations (pmol/24 h, means ± SD) of untreated (control) rats were uro, 355 ± 81; hepta, 104 ± 71; hexa, 22 ± 8; penta, 39 ± 7; and copro, 1439 ± 180. Porphyrin concentrations of MMH-treated rats were uro, 362 ± 96; hepta, 117 ± 72; hexa, 21 ± 10; penta, 320 ± 83; and copro, 15,192 ± 1629. Values for penta- and coproporphyrin were significantly different from control value ($p < .05$).

tions support the suggestion that porphyrin profile measurements may serve as a biomarker of metal exposure and their effects in human subjects (Marks, 1985; Fowler et al., 1987; Woods, 1989).

Dentists and other dental professionals are subjected to chronic low-level exposure to mercury arising from the use of elemental mercury in the preparation of dental amalgam restorative material (Langan et al., 1987; Fung and Molvar, 1992). Practicing dentists have been found to have from 1.5 (Chang et al., 1987) to 2 (Mackert, 1991) times higher blood mercury levels than nondentists. The mean concentrations of urinary mercury among dentists practicing in the Health Screening Program (HSP) conducted during the American Dental Association (ADA) annual meetings from 1975 to 1983 was 14.2 μg/L (range 0–556 μg/L) (Naleway et al., 1985), whereas mean urinary mercury levels among HSP participants from the 1985 and 1986 meetings were 5.8 and 7.6 μg/L, respectively (range 0–115 μg Hg/L) (Naleway et al., 1991). Approximately 10% of HSP participants exhibited urinary mercury concentrations above 20 μg/L. The World Health Organization (1991) has set 25 μg Hg/L of urine as the upper limit of acceptable exposure.

In the present studies we measured urinary porphyrin excretion patterns among dentists participating in the Health Screening Programs conducted during the 1991 and 1992 annual meetings of the ADA, and compared these with mercury levels in urine of the same subjects. The findings are similar to those observed in experimental animal studies and support the potential utility of urinary porphyrin profile measurements in the assessment of occupational mercury exposure among human subjects.

MATERIALS AND METHODS

Study Subjects

Subjects were drawn from male dentists attending the 1991 American Dental Association (ADA) annual meeting in Seattle, Wash., and the 1992 ADA Meeting in Orlando, Fla., and who participated in a voluntary Health Screening Program (HSP) conducted during the meetings. Approximately 1500 subjects participated in the HSP at each meeting. Participants provided spot urine samples for mercury, creatinine, and porphyrin analyses and participated in a number of physiological tests, including a blood chemistry panel, electrocardiogram (EKG) and neurobehaviorial assessments. Subjects also completed a questionnaire regarding dietary and health habits, as well as dental practice characteristics.

Collection of Urine Samples

Urine collections were made in sterile 100-ml plastic cups with screw-on lids. Immediately following collection, 0.5-ml aliquots were taken for on-site mercury analysis, while 20-ml aliquots were transferred to foil-

wrapped 40-ml polypropylene vials containing 25 mg $NaHCO_3$ for porphyrin and creatinine analyses. Vials were kept refrigerated during the collection period and frozen thereafter to prevent bacterial contamination and porphyrin or creatinine decomposition.

Urinary Mercury Determination

The on-site screening for total urinary mercury was carried out using a rapid form of the conventional Hatch–Ott technique (1970), as described by Naleway et al., (1991). This technique served as a qualitative screening tool permitting on-site determination of elevated mercury exposure. All urine specimens found to contain greater than 20 μg Hg/L, as well as a randomly selected subsample (~20%) of specimens with no detectable mercury, were reanalyzed in this laboratory for total mercury content using a modification of the continuous, cold-vapor atomic absorption system described by Atallah and Kalman (1993). This method has a detection limit of approximately 0.5 μg Hg/L.

Urinary Porphyrin Analysis

Urinary porphyrin concentrations were evaluated by the HPLC-spectrofluorometric procedure developed in this laboratory, as previously described (Woods et al., 1991; Bowers et al., 1992). Porphyrin profiles were compared among 37 randomly selected urine samples from dentists with no detectable mercury in their urine and from 56 dentists whose urinary mercury levels exceeded 20 μg/L.

Urinary Creatinine Analysis

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 $p < .05$.

RESULTS

In previous studies (Woods et al., 1991; Bowers et al., 1992) we have characterized the specific changes in the urinary porphyrin excretion pattern (urinary porphyrin profile) elicited by prolonged exposure to mercury as methylmercury hydroxide (MMH) in rats. Figure 2*b* describes the HPLC porphyrin elution pattern from 24-h urine samples of rats exposed continuously to MMH at 10 ppm for 5 wk. Comparison with the control porphyrin profile (Fig. 2*a*) shows that MMH exposure is associated with highly elevated concentrations of four- and five-carboxyl porphyrins to levels ranging from 8 to 10 times those observed in urine of untreated rats. The concentrations of these porphyrins increased to 31 and 17 times controls levels, respectively,

after 10 wk of MMH exposure at 10 ppm, demonstrating the time-dependent relationship of urinary porphyrin changes with duration of mercury exposure (Woods et al., 1991). Additionally, a porphyrin with as yet unknown chemical characteristics that elutes approximately midway between five- and four-carboxyl porphyrins on HPLC ("precoproporphyrin") is observed in urine of MMH-treated rats. The concentration of this porphyrin also varies in direct proportion to duration of mercury treatment.

Changes in urinary porphyrin concentrations also vary directly in proportion to the dose of mercury administered. Animals exposed to 5 ppm MMH displayed a urinary porphyrin profile with comparable characteristics to those exposed at 10 ppm, although the magnitude of the changes in four- and five-carboxyl porphyrins, as well as in precoproporphyrin, were approximately half those observed at the higher dose level (Woods et al., 1991).

Urinary porphyrin profiles are strongly correlated with renal mercury content. Regression analyses demonstrated a highly significant correlation between urinary porphyrin concentrations and renal mercury content at each dose level over the course of prolonged MMH treatment in rats (Woods et al., 1991). Correlation coefficients for each regression ranged from .72 to .94, suggesting a close association of each of the three elevated porphyrins with renal mercury content. These observations from animal studies demonstrated that urinary porphyrin profiles are an accurate measure both of the renal mercury content and of the biological effects of mercury in the kidney over a wide range of mercury exposure.

The porphyrin profile from a healthy adult male human subject is shown in Figure 3, and mean urinary porphyrin concentrations from 24-h

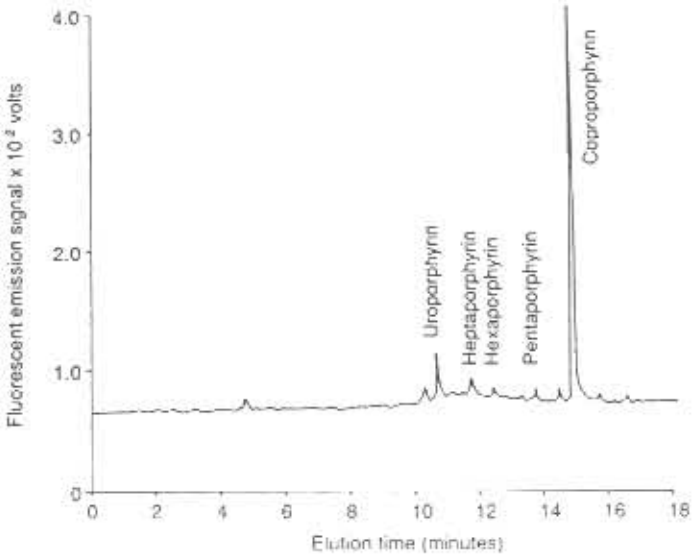

FIGURE 3. HPLC elution profile of urinary porphyrins from a healthy adult male human subject.

TABLE 1. Normal Human Urine Porphyrin Concentrations from 24-Hour and Randomly Collected (Spot) Urine Samples

	Urinary porphyrin concentration, means ± SD and (ranges)	
Porphyrin	24-h samples (nmol/24 h)	Random (spot) samples (μg/L)
Uro	6.0 ± 1.8 (3.2–18.5)	3.0 ± 1.0 (1.7–9.6)
Hepta	3.8 ± 1.5 (1.0–7.8)	3.2 ± 0.6 (0.6–5.4)
Hexa	1.0 ± 1.0 (0–3.5)	1.5 ± 1.2 (0–3.7)
Penta	3.3 ± 3.3 (0.4–15.4)	2.2 ± 1.5 (0–4.7)
Copro	52.0 ± 11.4 (29.8–92.6)	27.5 ± 16.9 (11–61)

Note. Porphyrin levels were measured in urine samples collected from healthy adult male subjects presenting to this laboratory during the period 1990–1992 for research purposes (Bowers et al., 1992). Porphyrins were analyzed as described in Materials and Methods. Values represent the means and standard deviations of 34 individual determinations for 24-h samples and 72 individual determinations for spot samples.

and randomly collected (spot) samples from a group of adult male human subjects are presented in Table 1. Porphyrins with eight, seven, six, five, and four carboxyl groups are readily measured in human urine, although are present at concentrations approximately 25 times less than those measured in rat urine. The ranges in porphyrin concentrations found in 24-h and random urine samples are also presented.

Table 2 presents the mean porphyrin concentrations in spot urine samples of dentists participating in the HSP as a comparison of those having no detectable urinary mercury with those having mercury concentrations ≥20

TABLE 2. Urinary Porphyrin Concentrations in Dentists

	Urinary porphyrin concentration (μg/l)	
	No urinary mecury	Urinary mercury >20 μg/L
Pentacarboxylporphyrin	0.76 ± 0.81	3.07 ± 1.41[a]
Precoproporphyrin	1.98 ± 1.37	7.58 ± 4.55[a]
Coproporphyrin	22.97 ± 5.80	74.45 ± 8.00[a]

Note. Porphyrin concentrations were measured in spot urine samples obtained from dentists whose urine contained no detectable mercury (n = 37) and whose urine had total mercury concentrations equal to or greater than 20 μg/l (n = 56). Urinary porphyrin and mercury concentrations were measured as described in Materials and Methods. Values represent means ± standard deviations of individual determinations.

[a]Significantly different from urinary porphyrin concentrations in samples with no detectable mercury ($p < .05$).

μg/L. The concentrations of only the three porphyrins that have been observed to be altered during mercury exposure in animal studies (i.e., pentacarboxyl-, precopro- and coproporphyrins) are presented. No changes were observed in the concentrations of eight-, seven-, or six-carboxyl porphyrins. Urinary mercury values among exposed ≥20 μg Hg/L) subjects ranged from 20.34 to 135.65 μg/L with a mean of 38.42 μg/L. Pentacarboxyl porphyrin was highly variable among unexposed subjects in the present study population, and the mean concentration was somewhat lower than that observed among the reference group (Table 1), although within the normally expected range (0–4.7). However, the mean concentrations of all 3 porphyrins were significantly elevated among dentists with urinary mercury content ≥20 μg/L, exceeding the unexposed group values by three- to four-fold.

Differences in urinary porphyrin levels among mercury-exposed and unexposed dentists were less marked when adjusted for urinary creatinine concentrations (Table 3). However, the mean concentrations of precoproporphyrin and coproporphyrin remained significantly elevated over those found in the unexposed group by 1.5- to 2-fold. When adjusted for creatinine, urinary mercury values ranged from 5.29 to 45.95 ng/mg creatinine, with a mean concentration of 22.90 ng/mg.

DISCUSSION

Previous studies from this laboratory have demonstrated that urinary porphyrin changes associated with prolonged mercury exposure meet established criteria by which an effective biomarker of toxicant exposure may be judged, as listed in Table 4. In terms of specificity, the unique change in

TABLE 3. Urinary Porphyrin Concentrations in Dentists with Adjustment for Urinary Creatinine Levels

	Urinary prophyrin concentration (ng/mg creatinine)	
Porphyrin	No urinary mercury	Urinary mercury >20 μg/L
Pentacarboxylporphyrin	0.47 ± 0.44	0.84 ± 0.54
Precoproporphyrin	2.14 ± 1.28	4.12 ± 2.27[a]
Coproporphyrin	28.16 ± 11.52	41.93 ± 18.19[a]

Note. Porphyrin concentrations were measured in urine samples obtained from dentists whose urine contained no detectable mercury (n = 23) and whose urine had total mercury concentrations equal to or greater than 20 μg/l (n = 38). Urinary porphyrin, mercury, and creatinine concentrations were measured as described in Materials and Methods. Values represent means ± standard deviations of individual determinations.

[a]Significantly different from urinary porphyrin concentrations in samples with no

TABLE 4. Criteria for an Effective Biomarker of Toxicant Exposure

1. Specific for toxicant in question.
2. Based on a biological effect of toxicant.
3. Reflects current and past exposure to toxicant.
4. Effect-related with dose and duration of toxicant exposure.

the porphyrin excretion pattern, characterized by elevated levels of five- and four-carboxyl porphyrins, as well as by the expression of the atypical porphyrin, precoproporphyrin, is, to our knowledge, unique to mercury exposure. This pattern is different from that which characterizes any of the known forms of inherited porphyria, and also differs distinctly from those elicited by exposure to other metals (Woods, 1989) or pophyrinogenic aromatic hydrocarbons (Marks, 1985). The biochemical etiology of changes in five- and four-carboxyl porphyrins observed during mercury exposure has previously been shown to occur as a result of mercuric ion- (Hg^{2+}) (or CH_3Hg^+-) directed impairment of the specific heme pathway enzymes, uroporphyrinogen decarboxylase (Woods et al., 1984) and copropophyrinogen oxidase (Woods and Southern, 1989), in kidney cells. The first-order binding constant ($k_1 > 10^{20}$) for mercaptide formation by Hg is highest for any metal, predisposing to the likely impairment of SH-dependent enzyme functions at concentrations of mercury likely to accumulate in kidney cells during low-level occupational or environmental exposures. The porphyrinogenic action of mercury is also attributable to the prooxidant property of Hg^{2+} to promote formation of H_2O_2 and other reactive oxidants (Woods et al., 1990a, 1990b; Lund et al., 1991, 1993; Miller and Woods, 1993), which facilitates the conversion of reduced porphyrins (porphyrinogens) that accumulate in kidney cells to the oxidized, readily excreted porphyrins. Since these properties of mercury may ultimately underlie cell injury and toxicity during prolonged mercury exposure, a mechanistic association between mercury-induced porphyria and toxicity involving oxidative stress reactions is suggested. The demonstration that porphyrin profiles mechanistically and quantitatively reflect a cellular response to mercury-induced oxidative stress in target tissue cells could have substantial significance in the detection, monitoring, and prevention of mercury-related toxicity in human subjects. The mechanisms underlying the expression of precoproporphyrin as a unique response to mercury exposure remain to be determined.

The criterion of an effective biomarker that it permit an assessment of past as well as current toxicant exposure is also met by the porphyrinogenic response to mercury treatment. As demonstrated in previous studies (Woods et al., 1991), urinary concentrations of five- and four-carboxyl porphyrins, as well as of precoproporphyrin, remain substantially elevated for up to 20 wk following cessation of mercury treatment, and decline at a rate consis-

tent with the clearance of organic mercury from the kidney ($t_{\frac{1}{2}} \approx 70$ d). These observations are in contrast to those pertaining to Hg levels in the urine, which decline rapidly following cessation of mercury exposure, despite potentially high residual tissue mercury levels.

Urinary porphyrin profile changes were less well correlated with urinary mercury levels when adjusted for urinary creatinine concentrations (Table 3). In the present study creatinine concentrations varied widely among individual spot urine samples, ranging from 25.0 to 410.4 mg/dl. Vestergaad and Leverett (1958) have previously reported substantial variability in creatinine excretion among individual men and women over both 24-h and shorter urine collection periods, and have concluded that creatinine should not be used to normalize or compare rates of metabolite excretion unless a preliminary assessment of individual variability in creatinine excretion is performed. The present studies, in which a substantially stronger correlation between creatinine-unadjusted porphyrin and mercury concentrations in spot urine samples is observed, support this conclusion.

Some potential applications of the urinary porphyrin profile method to the assessment of mercury exposure in human subjects are listed in Table 5. Since the change in the urinary porphyrin excretion pattern is unique to mercury exposure and occurs in subtoxic as well as potentially toxic mercury levels, the urinary porphyrin profile method could be employed in the clinical setting to indicate whether a biological response to mercury has occurred, or to monitor the effectiveness of treatment regimens for facilitating mercury clearance. The porphyrin profile method could be further used for population monitoring of current or past mercury exposure at hazardous waste sites or in the workplace. Finally, the changes in urinary porphyrin excretion patterns might be used to identify individuals or subgroups who might be uniquely susceptible to mercury toxicity or to verify biological responses to mercury predicted by risk assessment models. A positive correlation between changes in urinary porphyrin profiles and neurobehavioral test parameters among dentists with urinary mercury ≥ 20 μg/L observed in preliminary assessments of the present study population (Echeverria et al., 1993) supports this view.

In conclusion, the present studies describe characteristic changes in the

TABLE 5. Potential Applications of the Porphyrin Profile Method as a Biomarker of Human Mercury Exposure

1. Establish a biological response to occupational or environmental mercury exposure.
2. Monitor the effectiveness of treatment regimens for mercury poisoning and toxicity.
3. Population monitoring of mercury exposure at hazardous waste sites or from occupational sources.
4. Confirm past mercury exposure in clinical and epidemiologic studies and identify susceptible subgroups.
5. Verify biological responses predicted by risk assessment models.

urinary porphyrin excretion pattern among dentists with occupational mercury exposure and demonstrate that these changes are comparable to those associated with prolonged mercury exposure in animal studies. These findings suggest the predictive and diagnostic potential of urinary porphyrin profile measurements as a specific biomarker of mercury exposure and potential effects in human populations.

REFERENCES

Atallah, R. H., and Kalman, D. A. 1993. Selective determination of inorganic and methyl mercury in tissues by continuous flow and cold vapor atomic absorption spectrometry. *J. Anal. Toxicol.* 17:87–92.

Bowers, M. A., Aicher, L. D., Davis, H. A., and Woods, J. S. 1992. Quantitative determination of porphyrins in rat and human urine and evaluation of urinary porphyrin profiles during mercury and lead exposures. *J. Lab. Clin. Med.* 120:272–281.

Chang, S. B., Siew, C., and Gruninger, S. E. 1987. Examination of blood levels of mercury in practicing dentists using cold vapor atomic absorption spectroscopy. *J. Anal. Toxicol.* 11:149–153.

Echeverria, D., Heyer, N., Toutinghi, G., Ronhovde, N., and Woods, J. S. 1993. A behavioral evaluation of low level mercury vapor exposure among dentists. *Toxicologist* 13:188.

Fowler, B. A., Oskarsson, A., and Woods, J. S. 1987. Metal and metalloid-induced porphyrinurias: Relationships to cell injury. *Annu. N.Y. Acad. Sci.* 514:172–182.

Fung, Y. K., and Molvar, M. P. 1992. Toxicity of mercury from dental environment and from amalgam restorations. *Clin. Toxicol.* 31:49–61.

Hatch, W. R., and Ott, W. 1970. Determination of sub-microgram quantities of mercury by atomic absorption spectrophotometry. *Ann. Chem.* 40:2085–2087.

Langan, D. C., Fan, P. L., and Hoos, A. A. 1987. The use of mercury in dentistry: A critical review of the recent literature. *J. Am. Dent. Assoc.* 115:867–880.

Lund, B-O., Miller, D. M., and Woods, J. S. 1991. Mercury-induced H_2O_2 production and lipid peroxidation *in vitro* in rat kidney mitochondria. *Biochem. Pharmacol.* 42:S181–S187.

Lund, B-O., Miller, D. M., and Woods, J. S. 1993. Studies on Hg(II)-induced H_2O_2 formation and oxidative stress *in vivo* and *in vitro* in rat kidney mitochondria. *Biochem. Pharmacol.* 45:2017–2024.

Mackert, J. R., Jr. 1991. Dental amalgam and mercury. *J. Am. Dent. Assoc.* 122:54–61.

Marks, G. S. 1985. Exposure to toxic agents: The heme biosynthesis pathway and hemoproteins as indicator. *Crit. Rev. Toxicol.* 15:151–179.

Miller, D. M., and Woods, J. S. 1993. Redox activities of mercury-thiol complexes: Implications for mercury-induced porphyria and toxicity. *Chem. Biol. Interact.* 88:23–35.

Naleway, C., Sakaguchi, R., Mitchell, E., Muller, T., Ayer, W. A., and Hefferren, J. J. 1985. Urinary mercury levels in US dentists, 1975–1983: Review of health assessment program. *J. Am. Dent. Assoc.* 111:37–42.

Naleway, C., Chou, H.-N., Muller, I., Dabney, J., Roxe, D., and Siddiqui, F. 1991. On-site screening for urinary mercury concentrations and correlation with glomerular and renal tubular function. *J. Public Health Dent.* 51:12–17.

Vestergaad, P., and Leverett, R. 1958. Constancy of urinary creatinine excretion. *J. Lab. Clin. Med.* 51:211–218.

Woods, J. S. 1989. Mechanisms of metal-induced alterations of cellular heme metabolism. *Comments Toxicol.* 3:3–25.

Woods, J. S., and Fowler, B. A. 1977. Renal porphyrinuria during chronic methyl methyl mercury exposure. *J. Lab. Clin. Med.* 90:266–272.

Woods, J. S., and Southern, M. P. 1989. Studies on the etiology of trace metal-induced porphyria: effects of porphyrinogenic metals on coproporphyrinogen oxidase in rat liver and kidney. *Toxicol. Appl. Pharmacol.* 97:183–190.

Woods, J. S., Eaton, D. L., and Lukens, C. B. 1984. Studies on porphyrin metabolism in the kidney. Effects of trace metals and glutathione on renal uroporphyrinogen decarboxylase. *Mol. Pharmacol.* 26:336–341.

Woods, J. S., Calas, C. A., Aicher, L. D., Robinson, B. H., and Mailer, C. 1990a. Stimulation of porphyrinogen oxidation by mercuric ion. I. Evidence of free radical formation in the presence of thiols and hydrogen peroxide. *Mol. Pharmacol.* 38:253–260.

Woods, J. S., Calas, C. A., and Aicher, L. D. 1990b. Stimulation of porphyrinogen oxidation by mercuric ion. II. Promotion of oxidation from the interaction of mercuric ion, glutathione, and mitochondria-generated hydrogen peroxide. *Mol. Pharmacol.* 38:261–266.

Woods, J. S., Bowers, M. A., and Davis, H. A. 1991. Urinary porphyrin profiles as biomarkers of trace metal exposure and toxicity: studies on urinary porphyrin excretion patterns in rats during prolonged exposure to methyl mercury. *Toxicol. Appl. Pharmacol.* 110:464–476.