Biological monitoring and exposure to mercury

H. J. Mason*, P. Hindell* and N. R. Williams†

*Health & Safety Laboratory, Broad Lane, Sheffield S3 7HQ; and †Health & Safety Executive, Field Operations Directorate, Birmingham, UK

Occupational health professionals’ interest in controlling mercury (Hg) exposure, and the use of biological monitoring in this context, has been ongoing for a number of years. Evidence from urinary Hg results in a number of UK firms who have undertaken some form of biological monitoring or occupational health surveillance suggest that exposure has decreased over the last 10–15 years. This decrease precedes the establishment in the UK of an advisory biological monitoring guidance value (HGV) for urinary Hg and the production of updated medical guidance from the Health & Safety Executive on Hg exposure (MS12 1996). This latter document recommends a urinary sampling interval for urinary Hg of between 1 and 3 months, which is consistent with the reported toxicokinetics of Hg excretion, but we highlight that urinary Hg represents integrated exposure over many previous months. Mercury is a recognized nephrotoxin and MS12 1996 mentions the use of regular dipstick protein estimations. We review our experience of investigating proteinuria and enzymuria in a large-scale cross-sectional occupational study. The incidence of Hg-induced renal disease is probably very rare at current exposure levels. Therefore acceptance of a high false-positive rate of proteinuria not related to Hg exposure needs to be considered in any urinary protein testing regime of Hg workers. The establishment of an HGV for urinary Hg has raised questions about the uncertainty associated with a urinary Hg result, including factors such as diurnal variation, whether urine correction by creatinine or specific gravity is preferable and the possibility of non-occupational sources of Hg contributing significantly towards breaching the HGV. Correction of urinary Hg results by creatinine or specific gravity and the use of a fixed sampling time, such as the beginning or end of the day, substantially reduce the uncertainty in a urinary Hg measurement. But even with good laboratory precision, an individual with a true urinary Hg excretion of 20 nmol/mmol creatinine could supply urine samples of between 14 and 26 nmol/mmol creatinine. The influence of dietary sources in the UK contributing to urinary Hg values approaching or exceeding the HGV is unlikely. The use of tribal or ethnic cosmetics and remedies needs to be considered if a urinary Hg result looks inappropriately high, as some such preparations have been found to contain Hg and can be absorbed through the skin. The ability of excessive chewers or teeth grinders who have a large number of dental amalgam fillings to breach the urinary HGV in the absence of substantial occupational Hg exposure has been reported in a few Scandinavain studies. We report here a likely case of this phenomenon. Since the establishment of the HGV, our biological monitoring Hg data from a number of industry sectors using inorganic or metallic Hg have suggested that a minority of samples (13%) are still greater than the HGV.

Key words: Biological monitoring; biological monitoring guidance value; blood; metals; urine.

Received 18 February 2000; revised 8 June 2000; accepted 23 August 2000

Correspondence to: H. J. Mason, Health & Safety Laboratory, Broad Lane, Sheffield S3 7HQ, UK.
Introduction

This paper discusses biological monitoring of mercury (Hg) exposure in the context of a recently established biological monitoring guidance value in the UK and the guidance note produced in 1996 by the Health & Safety Executive (HSE) [1]. We present our experience of routine biological monitoring and research studies in Hg-exposed subjects, together with available published data, covering the level of confidence associated with any single urinary Hg value, the toxicokinetics of Hg and implications for sampling strategies, and the recent temporal changes in urine values in various UK industry sectors. We also consider the possible influence of non-occupational Hg sources on urinary Hg levels and further discussion on Hg-induced renal effects.

Mercury has long been recognized as an occupational toxin. Not only were the psychiatric, behavioural and neurological symptoms of excessive inorganic Hg exposure understood, but the association with renal damage was also noted by early physicians who held an interest in occupational health [2]. Thus, the target organs of chronic Hg toxicity have long been known to be the central nervous system and the kidney. The setting of occupational exposure limits continues to be driven by establishing limits below which subclinical abnormalities in these target organs are not apparent.

Biological monitoring for Hg exposure has long been established. The fluid nature of elemental Hg means that undetected spillages of it have been common, which, coupled with its significant vapour pressure, can lead to unexpected exposures. The potential for skin absorption and subsequent effects by inorganic mercurials and elemental Hg is sometimes underestimated [3–5]. Blood Hg measurements have been used in acute exposures, whether accidental or deliberate, whereas urine measurements have been widely adopted for monitoring occupational exposure.

In the UK, urinary biological monitoring activity has been performed historically in the absence of a defined national biological exposure limit. Although HSE guidance MS12 1978 [6] suggested a 'potentially dangerous' level of 1000 nmol/l (~100 nmol/mmol creatinine), it was not clear about a 'safe' urinary Hg level. In the early 1980s, a number of reports were published suggesting a no-effect level at urine concentrations of ~30 nmol/mmol creatinine [7–9]. The adoption of advisory biological monitoring guidance values by the HSE [10] was promptly followed by the establishment of a health guidance value (HGV) for urinary Hg of 20 µmol/mmol creatinine (20 nmol/mmol creatinine) and establishment of a reduced atmospheric occupational exposure standard (OES) of 0.025 mg/m³ as part of an HSE review of inorganic Hg in 1995. The OES and HGV were set at levels below which no adverse health effects would be expected. An HGV is non-statutory, but may be used to show that adequate control measures and work practices are in place.

A new HSE medical guidance note on Hg (MS12) was produced in 1996 [1] clearly defining the HGV of 20 nmol/mmol creatinine, and suggesting a usual urinary sampling frequency of between 1 and 3 months, and more frequent sampling for subjects close to the HGV value. Two actions were recommended for urine results over the HGV value: examination for any symptoms of Hg toxicity with removal of those subjects with suspicion of symptoms and a review of the control measures. MS12 1996 also advised on whether to use regular dipstick urinary protein screening, with the suggestion of exclusion from further Hg exposure of those with proteinuria until the cause of the proteinuria had been investigated. However, such advice is dependent on the sort of renal impairment and symptoms caused by Hg, and the likely incidence of other non-occupational renal abnormalities.

Toxicokinetics of urinary and blood Hg

Toxicokinetic data on any chemical underpin the interpretation of any biological monitoring result in terms of the exposure it is reflecting [11]. The half-life of urinary Hg after cessation of exposure has been reported from a number of different exposure scenarios. These include studies on retired workers with histories of long-term chronic Hg exposure and individuals who have had a high acute exposure [12,13]. The half-life of urine creatinine has been reported as ~40 days in two studies with differing occupational exposure scenarios [12,14], 55 days [15], 70–90 days [16,17] and as short as 20 days [13]. We have calculated half-lives of 83 days for a worker removed from high chronic Hg vapour exposure and 76 days for a woman removed from occupational Hg vapour exposure because of nephrosis. It has been suggested that the reported variation in half-lives of urinary excretion is due to individual factors, such as induction of renal metallothionein, which binds Hg, and that higher initial urinary Hg levels may lead to longer half-lives.

Applying the single compartment, pharmacokinetic model calculation described by Droz and Fiserova-Bergerova [11] for likely half-lives of between 40 and 90 days, cumulative exposure over the prior half-year contributes ~60–70% of any urinary Hg value, whilst the last month's exposure contributes 20–25%, with the previous week's exposure contributing only 10% to the urine value. Therefore, in long-term workers, urinary Hg is an integrated marker of exposure over previous months and in new workers with <6 months occupational exposure urinary Hg results will not be a full reflection of the extent of their current occupational exposure. This analysis supports the recommended biological monitoring strategy of 3-monthly routine urine sampling, with
We had studied the within- and between-day intra-individual variation (Table 1) in two groups of workers exposed to Hg under relatively constant but high exposure conditions [25]. The method [26] used for these analyses had a precision of 5–6%. A low mean and SD of intra-individual coefficients of variation (CV) derived from multiple spot urinary Hg values in a number of individuals (Table 1) would imply that any single urine sample closely reflects the true Hg excretion in that individual. Creatinine correction of Hg concentration significantly reduced the mean intra-individual variation, both between and within day, to ~50% of the variation in uncorrected urine values. Even with creatinine correction, the mean CV_Total of ~15% with the imprecision of our method implies that two consecutive spot urine samples taken at the same time of day could statistically be ~40–50% apart ($r\sqrt{2\cdot CV_{\text{Total}}}$) and not imply any change in body burden. It has been widely accepted in clinical studies investigating Hg dose–effect relationships, as well as routine biological monitoring, have often used urinary concentrations from untimed, random samples [17,20]. There has been debate about whether creatinine or other forms of correction for urinary concentration are better in making a single spot measurement more likely to reflect the ‘true’ Hg excretion [21,22]. Diurnal variation in the metal’s excretion has also been noted [13,23,24], but had been suggested as being of no practical relevance in a biological monitoring scheme [24]. However, the mean difference between samples taken at 07:00 and 16:00 h is between 15 and 30%, and this may need to be considered in interpreting results against the uncertainty around the HGV value. It would seem prudent to use a fixed time point for sample collection to remove the effects of diurnal variation. Either pre-shift, where sample contamination is less likely, or post-shift has been suggested as a pragmatic solution, although the use of a midday sample has been suggested as being most representative of the 24 h excretion of the metal [23].

### Table 1. Mean ± SD of within- and between-day total intra-individual variation (CV_total) for urinary Hg results, uncorrected and corrected by creatinine, specific gravity (SG) and osmolality

<table>
<thead>
<tr>
<th></th>
<th>CV_total creatinine corrected (%)</th>
<th>CV_total SG (1.016) corrected (%)</th>
<th>CV_total osmolality corrected (%)</th>
<th>CV_total uncorrected (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Within day</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>(17 subjects)</td>
<td>22.4 ± 7.9</td>
<td>32.2 ± 12.3</td>
<td>36.5 ± 15.1</td>
<td>47.3 ± 22.2</td>
</tr>
<tr>
<td></td>
<td>P &lt; 0.001</td>
<td>P &lt; 0.05</td>
<td>P &gt; 0.05</td>
<td></td>
</tr>
<tr>
<td><strong>Between day</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>(10 subjects)</td>
<td>15.6 ± 7.2</td>
<td>22.0 ± 14.0</td>
<td>–</td>
<td>37.3 ± 23.6</td>
</tr>
<tr>
<td></td>
<td>P &lt; 0.05</td>
<td>P &lt; 0.05</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Within-day results were obtained from six samples obtained between 07:00 and 22:00 h in 17 subjects. Between-day results were obtained from a 10:00 h sample taken over a working week (Monday–Friday) in 10 subjects. Statistical significance is shown of corrected results compared with uncorrected results.
pathology that analytical imprecision should be less than or equal to half the average intra-individual biological variation \( (CV_{\text{Biological}}) \) \([27,28]\). This value for urinary Hg corrected for creatinine can be derived from the formula:

\[
CV_{\text{Total}}^2 = CV_{\text{Analytical}}^2 + CV_{\text{Biological}}^2
\]

and therefore the analytical precision \( (CV_{\text{Analytical}}) \) of any urinary Hg and creatinine method should be \(<7.3\%\).

The recently established HGV of 20 nmol/mmol creatinine is quoted without any qualification of the likely errors that may be associated with this number. From the data in Table 1, it is possible to calculate the statistical 95% distribution of values that may be found in a large number of theoretical urine samples collected from a worker with a ‘true’ Hg excretion of 20 nmol/mmol creatinine. This distribution depends on the inherent intra-individual biological \( (CV_{\text{Biological}}) \) variation and the laboratory-dependent analytical precision \( (CV_{\text{Analytical}}) \). With our analytical precision, which is readily achievable, the distribution of 95% of the urine values found in this hypothetical worker could be between 14 and 26 nmol/mmol creatinine. Table 2 shows the influence on this distribution of analytical precision which ranges from the best probably achievable to relatively poor.

**Table 2.** The influence of laboratory analytical precision on the distribution of urine results that could be found in a worker with a ‘true’ urinary excretion of 20 nmol/mmol creatinine

<table>
<thead>
<tr>
<th>Analytical precision of combined Hg and creatinine analyses (%)</th>
<th>Lower limit (mean – 2 SD)</th>
<th>Upper limit (mean + 2 SD)</th>
</tr>
</thead>
<tbody>
<tr>
<td>4</td>
<td>13.9</td>
<td>26.1</td>
</tr>
<tr>
<td>5.5</td>
<td>13.8</td>
<td>26.2</td>
</tr>
<tr>
<td>8</td>
<td>13.4</td>
<td>26.6</td>
</tr>
<tr>
<td>10</td>
<td>12.9</td>
<td>27.1</td>
</tr>
<tr>
<td>12</td>
<td>12.4</td>
<td>27.6</td>
</tr>
<tr>
<td>15</td>
<td>11.6</td>
<td>28.4</td>
</tr>
<tr>
<td>20</td>
<td>10.1</td>
<td>29.9</td>
</tr>
</tbody>
</table>

**Temporal changes in the levels of UK Hg exposure evidenced from biological monitoring data**

Changes in the Hg-utilizing industries over the last 15–20 years are reflected in the size of the population exposed to Hg and the degree of exposure. A 1988 HSE cross-sectional study \([29]\) of Hg and its inorganic compounds preliminarily identified 165 UK industrial premises using Hg, with additionally a large number of dental practices, educational establishments and herb-arias. Of the industrial premises, 33% were classified as involved in instrument maintenance and repair, 16% in electrical lighting equipment, 10% in petrochemicals, 6% in the manufacture of electronic components, 5% in the manufacture of pharmaceuticals, 4% in battery manufacture, 3% in the chloralkali industry, and 3% in the manufacture of soaps and toiletries. However, the number of workers employed at these premises varied widely. Of the 165 premises, 31 were investigated by the HSE using atmospheric and biological monitoring \([29,30]\). Table 3 shows the condensed results of the urinary Hg results from this study carried out in late 1987/early 1988. Twenty-two per cent of the 643 urine measurements were over the current HGV value, which had not been established at the time of that study.

Whilst not directly comparable, the Health & Safety Laboratory (HSL) has analysed 666 urinary Hg samples since January 1997 from 36 different firms or workplaces. Thirty per cent of these samples were still greater than the HGV, which had been established at the beginning of this period. The majority (70%) of the samples greater than the HGV derived from two firms involved in instrument manufacture and repair.

Six firms involved in the 1988 cross-sectional HSE study have also been studied using biological monitoring by the HSE/HSL at various times prior to and after the 1988 study. The same analytical technique and quality

**Table 3.** Results from 1988 HSE technical development survey of Hg and its inorganic compounds (data taken from \[29,30\])

<table>
<thead>
<tr>
<th>Industry type</th>
<th>Mean (range) years of exposure</th>
<th>Mean (range) urinary Hg (nmol/mmol creatinine)</th>
<th>No. (male/female)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Petrochemicals</td>
<td>3.7 (0.1–8.0)</td>
<td>7 (1–32)</td>
<td>20 (19/1)</td>
</tr>
<tr>
<td>Basic industrial chemicals</td>
<td>12.6 (0.1–23.6)</td>
<td>8 (1–58)</td>
<td>12 (11/10)</td>
</tr>
<tr>
<td>Electronic component manufacture</td>
<td>7.1 (0.7–35.0)</td>
<td>3 (1–14)</td>
<td>8 (2/6)</td>
</tr>
<tr>
<td>Battery manufacture</td>
<td>5.2 (0.1–27.0)</td>
<td>10 (1–136)</td>
<td>199 (99/100)</td>
</tr>
<tr>
<td>Metals treatment</td>
<td>–</td>
<td>3 (2–6)</td>
<td>7 (5/2)</td>
</tr>
<tr>
<td>Instrument manufacture and repair</td>
<td>8.4 (0.1–47.0)</td>
<td>9 (1–164)</td>
<td>146 (93/53)</td>
</tr>
<tr>
<td>Pharmaceutical manufacture</td>
<td>3.6 (1.0–8.4)</td>
<td>18 (2–55)</td>
<td>6 (3/3)</td>
</tr>
<tr>
<td>Soap and toiletries manufacture</td>
<td>3.3 (0.3–4.5)</td>
<td>11 (4–25)</td>
<td>6 (5/1)</td>
</tr>
<tr>
<td>Electrical lighting manufacture</td>
<td>9.6 (0.1–37.0)</td>
<td>5 (1–931)</td>
<td>189 (47/142)</td>
</tr>
<tr>
<td>Chloralkali manufacture</td>
<td>9.8 (0.2–36.0)</td>
<td>20 (4–75)</td>
<td>50 (50/0)</td>
</tr>
<tr>
<td>All</td>
<td>7.6 (0.1–47.0)</td>
<td>8 (1–931)</td>
<td>643 (325/318)</td>
</tr>
</tbody>
</table>
control procedures were used at all time points. Most of these firms were not monitored on a regular basis, but may allow for some comparison of exposure over time. However, one small firm undertaking Hg reclamation and refining has been under regular supervision by HSE occupational health professionals since January 1986.

Results for the comparison of urinary Hg levels over time are shown in Figure 1 using criteria whereby >10 workers in a firm were surveyed at any time point who had been employed at the firm for at least 1 year. Data from three firms and on at least three time points met these criteria and came from three different industry sectors, namely, instrument manufacture and repair, electrical lighting manufacture and electronic component manufacture. These data suggest that there has been a decline in urinary Hg levels over the last 15 years, including the number of subjects who breach the current HGV level.

The graphs in Figures 2 and 3 show the biological monitoring results of urinary and blood Hg obtained from a small Hg refining company, first visited by a factory inspector in January 1986. Atmospheric Hg monitoring was carried out with an atmospheric personal sampler; a level of 571 µg/m³ was measured in the room where the Hg was distilled. Two workers underwent biological monitoring, and at the initial investigation their urinary Hg levels were 403 and 241 nmol/mmol creatinine and their blood Hg levels 305 and 328 nmol/l, respectively. Subject 1 was the 50-year-old director of the company who had previously worked 50 h per week for 10 years on Hg reclamation and had no obvious health problems. Subject 2 was a 42-year-old Hg refiner with 45 h per week exposure, who had only joined the company 9 months previously to this initial visit.

**Figure 1.** Changes in urinary Hg levels (mean and range shown) over time for three firms who participated in the 1988 HSE Technical Development Study. The HGV is also shown on the graph as a dotted line at 20 nmol/mmol creatinine.

**Figure 2.** Urine measurements in the initial two workers (subject 1 is the director) and a third worker who joined in 1994.
An immediate notice to wear respiratory protective equipment and a programme of improvement to the premises, including improved extraction ventilation, containment of the Hg and control of spillages, were demanded by the HSE. Following the initial visit, a new fume extractor was installed at the working bench and a new floor was laid and sealed within 1 month. Interestingly, the decrease in urinary Hg levels over the first 18 months from the initial visit suggested a half-life decay of between 30 and 66 days, which is within the values reported for subjects removed from exposure altogether. This suggests that the initial changes in control measures removed a very substantial element of the total exposure, although in 1988 urine levels were still at 33 and 58 nmol/mmol creatinine in the two subjects, and the personal atmospheric monitoring results were 43 and 200 µg/m³, respectively. This led to further recommendations for improvements to ventilation and containment of spillages.

The workers at this firm underwent biological monitoring at monthly intervals during 1986, but at roughly every 3–4 months until the end of 1996. Monitoring frequency was increased to every 6–8 weeks from 1997 onwards, as two of the refining workers (another had joined the firm) still had urinary Hg results above the recently established HGV. Interestingly, atmospheric monitoring was only carried out on three separate occasions in 1986, 1988 and 1998.

From the beginning of 1996, urinary Hg levels remained consistently below the HGV in the director. By the middle of 1998, the increased monitoring was reflected in decreased urinary Hg levels below the HGV in the two active refiners even though the company had reported processing about three times the normal amount of Hg since the end of 1996. In May 1998, personal atmospheric sampling in the two active Hg refiners was now around the current OES of 25 µg/m³.

We suggest that the data identify a general decrease in Hg exposure where some form of biological monitoring, either regular or spasmodic, has been carried out. This reduction in exposure during the mid-1980s onwards predates the establishment of an HGV in the UK, but is contemporary with published reports and international bodies suggesting safe urine levels substantially lower than noted in the then current MS12 1978 [6]. This decrease probably reflects the input of occupational health professionals to modulating exposure. Given that, in the firms on which we have reported, biological monitoring data far outweigh the amount of personal atmospheric monitoring data, it seems reasonable to suppose that improvements may well be related to the occupational health professional using biological monitoring data in a proactive way to drive improvements in Hg containment and safe working practices. However, our current HSL data suggest that a significant minority of Hg workers are still not meeting the HGV value 2 years after its establishment and that further work still needs to be done in certain sectors.
Non-occupational exposures to Hg

As the level of acceptable occupational Hg exposure has declined, it is questioned what contribution non-occupational Hg exposure can make to urinary Hg levels that approach or exceed the HGV value. Such exposures include dietary intake, dental amalgam fillings and possible traditional, tribal medicines and cosmetics.

Average UK dietary intake of Hg has been estimated at <5 µg/day since 1976, with a 97.5 percentile of 9 µg/day [31]. Fish contained the highest mean concentration of 54 µg Hg/kg and made the highest contribution (25%) to dietary intake, but this is mainly in the form of methyl Hg, which contributes little to urinary Hg levels. However, although the gastrointestinal absorption of methyl Hg is greater than the estimates of 7–25% for inorganic Hg compounds, the UK food study data [31] suggest that dietary intake is small in comparison with allowable occupational exposure. The mean daily UK absorbed dietary dose is <1 µg, but exposure to the current 8 h OES for Hg vapour would suggest a daily absorption of ~190 µg, assuming a light activity respiration rate and a retention level of 75% Hg in the lungs.

Degradation of dental amalgam restorations remains a debated source of concern in the UK and Europe [32–34]. Dental amalgams consist of ~45–50% Hg, 25–35% Ag, 2–30% Cu and 15–30% Sn. In general, blood Hg concentrations appear not to be strongly influenced by the number of amalgam restorations, although plasma and urinary Hg values are [35,36]. A 6 nmol/l difference in blood Hg between an amalgam-free group (mean = 22 nmol/l, n = 22) and a group with >35 restorations (mean = 28 nmol/l, n = 30) was reported by Jokstad et al. [34] in a Norwegian population; the mean urinary Hg level with >35 restorations was ~3 nmol/mmol creatinine as compared with 0.5 nmol/mmol creatinine in those without fillings. Mercury in exhaled air also correlated with the number of restorations. Estimates of daily Hg absorption from amalgam were ~10–12 µg in people with >35 restored surfaces. Skare and Engqvist [37] calculated a mean increment of 0.027 nmol/mmol creatinine in urinary Hg for each filling. Begerow et al. [38] found a mean urinary Hg reduction of 0.6 nmol/mmol creatinine in 17 subjects who had between 4 and 24 fillings removed, the half-life of urinary decay after amalgam removal being 95 days.

There is evidence that Hg uptake from amalgam is significantly increased as a result of excessive chewing [39]; long-term, habitual gum chewers had mean urinary Hg levels of 6.5 nmol/mmol creatinine as compared with 1.2 nmol/mmol creatinine in non-chewers. Similarly, blood plasma Hg was increased from 4.9 to 27 nmol/l. This suggested that chewing or teeth grinding could cause significant increases in released Hg from dental amalgam. Barregard et al. [40] described three cases of people with between 34 and 42 fillings, and not occupationally exposed to Hg, with urinary Hg levels of ~20–28 nmol/mmol creatinine, i.e. greater than the HGV, and blood levels of ~60–115 nmol/l. The average values for normal blood and urinary Hg in the Swedish population were reported as 12 and 1.5 nmol/mmol creatinine, respectively, which may be slightly higher than is found in the UK. After removal of their amalgam fillings, the urine and blood values in patients reduced considerably, and they reported subjective improvement in their health.

It thus appears that in a small proportion of a population, a combination of gum chewing, teeth grinding and a high level of dental amalgam fillings could lead to a urinary Hg level approaching or exceeding the HGV. Barregard et al. [40] estimated from their Swedish studies that 1 in 100 people with amalgam fillings will have a urinary Hg of >6 nmol/mmol creatinine, 1 in 1000 >14 nmol/mmol creatinine, and between 1 in 2000 and 1 in 10 000 >28 nmol/mmol creatinine. Such values may be influenced by geographic and dietary differences between Swedish and UK populations.

A likely recent case of this phenomenon in the UK is noted briefly here. A 45-year-old female with low-level occupational exposure to Hg showed increasing urine results repeatedly above the HGV and substantially higher than her similarly exposed colleagues. She was removed to office work, but did not show any appreciable decrease in urinary Hg levels over the next 6 months. Her blood Hg levels were also repeatedly around three times the upper limit of normal. Any sources of Hg were exhaustively investigated. Her diet was normal and there was no apparent alternative environmental source of Hg, but she did have 32 amalgam restored tooth surfaces. Although not exposed occupationally to Hg for almost 2 years, her blood and urinary Hg levels remained consistently significantly elevated until she decided to have the amalgams replaced by ceramic dental fillings. Her blood and urinary Hg levels have now returned to within our reference range for blood and urinary Hg (16 and <3 nmol/mmol creatinine), which were derived from ~200 subjects without occupational exposure to heavy metals but without consideration of the number of dental amalgam fillings.

Another rare but potential source of Hg that may confound urinary Hg measurements as an indicator of occupational exposure is the use of some ‘traditional’ medicines and cosmetics. Mercury-containing beauty creams or soaps continue to be used in certain ethnic populations due to their skin-lightening properties [41, 42] and some traditional medicines have been shown to contain significant levels of Hg [43–45]. The use of Hg-containing bleaching agents has been reported to cause urinary Hg levels of >25 nmol/mmol creatinine [46,47]. Such findings may emphasize the potential for dermal absorption of inorganic and elemental Hg compounds.
In cases of inappropriately high levels of urinary Hg compared with their likely level of occupational Hg exposure, consideration should be given to the influences of chewing/teeth grinding habits in association with their number of dental amalgam fillings and the possible use of traditional or ethnic remedies and cosmetics. A diet with a high intake of fish products, not usually associated with traditional or ethnic remedies and cosmetics. A diet with a high intake of fish products, not usually associated with traditional or ethnic remedies and cosmetics.

Renal effects of Hg exposure

The kidney is an established target organ for Hg toxicity, and a number of laboratory tests of abnormality or subclinical disease are readily available. Consideration therefore has to be made of the value of any renal testing as part of health surveillance.

A clinical renal sign of excessive Hg exposure is an obvious glomerular proteinuria. Acute exposure to inorganic Hg salts has also been shown to cause severe renal tubular damage [48]. There is a rat experimental model for Hg-induced glomerular disease where the disease is related to immunological activation and autoantibody production against components of the glomerulus. In this model, the disease is self-limiting and any repeat exposure to similar doses does not precipitate the disease, i.e. it displays tolerance.

In humans, the pathology of a few cases of Hg-induced renal disease has been found to represent a membranous glomerulopathy with complete or partial recovery on withdrawal of Hg exposure [49], but there are no data on whether tolerance is bestowed against further Hg exposure. In 20 years of routine monitoring of Hg workers by the HSL, only a few cases have been brought to our attention where a glomerular type of renal disturbance of clinical significance has been linked to their occupation. These anecdotal data may suggest that Hg-induced renal disease is probably rare at UK occupational exposure levels. Kazantzis et al. [50] reported four cases in Hg-exposed males: three with nephrosis and oedema; one with gross proteinuria. These four subjects had urinary Hg levels between ~500 and 700 nmol/mmol creatinine at presentation, which is considerably more than has recently been occupationally encountered in the UK.

A number of research studies have looked at subclinical changes in excreted proteins influenced by glomerular or proximal tubular functional changes or cellular damage [8,51,52]. Studies in this area were reviewed in the HSE’s criteria document in 1995 [53]. Small increases in proteinuria and especially urine enzymes derived from proximal tubular cells, such as N-acetylglucosaminidase (NAG), were noted in many studies. A no observed adverse effect level (NOAEL) of these changes for urinary Hg was stated to be ~20 nmol/mmol creatinine. However, re-analysis of the data from the large cross-sectional study of >600 Hg workers carried out in the late 1980s by the HSE [29] suggests that NAG, which is a lysosomal enzyme, and the brush-border-associated enzyme leucine aminopeptidase (LAP) showed no threshold level (Figure 4). However, these small increases in urinary enzymes at low Hg exposure levels may reflect a normal, uprated physiological process of Hg excretion in response to the increased renal Hg burden. The metal stored within the kidney is excreted by renal cell lysosomal exocytosis through the tubular brush border into urine. Thus, the linear response in urine enzymes at low exposure levels may be distinct from an increase defining an early pathological process of cell damage in the kidney. Interestingly, the prevalence of increased albuminuria in this UK cross-sectional study [29,30] was ~3%, but there was no relationship between the prevalence of albuminuria and urinary Hg levels.

The significance of small increases in NAG, LAP and other markers of renal tubular cell function as early markers of increased risk of clinical renal disease from any aetiology is unclear, and the health significance of small increases in urine albumin, indicating glomerular permeability, is also not well defined outside the field of diabetic nephropathy. However, the non-renal causes of increased albumin excretion, such as postural and exercise-induced proteinuria, are well known. Therefore, currently there is little evidence for using any of the sophisticated laboratory-based analytical tests of glomerular or tubular damage or dysfunction as part of health surveillance for Hg workers at current exposure levels.

The use of semi-quantitative urinary protein dipstick tests will detect subjects with the relatively rare case of Hg-induced developing nephrosis. But it will have a relatively low positive predictive value due to the relatively common finding of proteinuria, whether transiently induced, constant or postural in the general population. Approximately 10% of hospital admissions [54] and 1% of healthy adult males [55] have been reported to have proteinuria, of which only a small minority were shown...
by biopsy to have any renal pathology. Therefore, in any monitoring strategy, the occupational health professional needs to balance the low likelihood of finding a developing Hg-induced nephrosis with the likelihood of other clinically relevant non-occupationally induced glomerular dysfunctions, and the even more likely discovery of benign proteinuria. This situation is reflected within the current medical guidance MS12 [1], which suggests consideration of regular dipstick protein testing, but in the light of the level of exposure control.

References