Urinary excretion of mercury after occupational exposure to mercury vapour and influence of the chelating agent meso-2,3-dimercaptosuccinic acid (DMSA)

H A Roels, M Boeckx, E Ceulemans, R R Lauwerys

Abstract

The spontaneous and chelator mediated excretion of mercury in urine was investigated in male subjects occupationally exposed to mercury vapour (alkaline battery and chloralkali plants) who did not exhibit any sign of kidney damage. The time course of the spontaneous elimination of mercury in urine was examined in seven workers (age 22–40) who had been removed from exposure to mercury vapour (average duration of exposure 4·4 years) because their urinary mercury concentrations repeatedly exceeded 100 $\mu g/g$ creatinine. The post exposure observation period started 10 to 29 days after the date of removal and lasted about 300 days (slow HgU elimination phase). For each worker, the kinetics of the spontaneous HgU decline followed a first order process; the biological half life ranged from 69 to 109 days (mean 90 days). The increased urinary excretion of mercury after a single oral administration of 2 g meso-2,3-dimercaptosuccinic acid (DMSA) was investigated in 16 control workers (group A; age 23 to 49), in 11 workers removed from exposure for at least two years (group B; age 27 to 41), and in 16 workers currently exposed to mercury vapour (group C; age 21 to 58). In group C, the DMSA experiment was repeated twice (three weeks before and three weeks after a holiday) after measures had been taken to reduce the mercury emission. The urinary mercury excretion was significantly higher during the 24 hours after DMSA administration in all groups compared with that in the 24 hours before. The bulk (50–70%) of the DMSA stimulated mercury excretion appeared within the first eight hours. In each group, the amount of mercury (μg Hg/24 h) excreted after DMSA was significantly correlated with that before administration of DMSA. The groups whose exposure had ceased, however, exhibited much higher correlation coefficients (r = 0·97 for group B and 0·86 for group C after three weeks of holiday) than those currently exposed to mercury vapour (r = 0·66 for group C before and 0·58 after reduction of exposure). The data suggest that after a few days of cessation of occupational exposure to mercury vapour the HgU before and after administration of DMSA mainly reflects the amount of mercury stored in the kidney, which represents a mercury pool with a slow turnover.

Industrial Toxicology and Occupational Medicine Unit, School of Medicine, Catholic University of Louvain, B-1200 Brussels, Belgium
H A Roels, M Boeckx, R R Lauwerys
Medi-Leuven, B-3200 Leuven, Belgium
E Ceulemans

The toxicokinetics of mercury after inhalation of metallic mercury vapour have been extensively studied in workers, volunteers, and animals (for reviews see[1-3]). The main sites of deposition are the kidneys (80% of body burden in man), the liver, and the brain. The main routes of elimination are in the faeces (partly due to biliary excretion and intestinal secretion) and the urine (accounting for about 50% of the total elimination of mercury in subjects with long term occupational exposure). Small quantities are also excreted through the salivary, lacrimal, and sweat glands, and via expired air.

In man the excretion of mercury in urine after cessation of exposure to mercury vapour has only been studied in five volunteers[4] during the first seven days after exposure to a mixture of stable and radiolabelled mercury vapour (0·1 mg Hg/m³, 14 to 24 minutes) and in a group of six subjects who were followed up for three weeks after removal from chronic occupational exposure to mercury vapour.[5] According to the last study, the kinetics of urinary

mercury excretion appear to follow a two term exponential equation: initially there may be a rather fast wash out phase ($t_{1/2}$ about two days) representing only a limited proportion (about 20%) of the amount excreted, and subsequently a slow excretion phase with a rate constant estimated at about 0.01 day^{-1}. The first phase is likely to be influenced by recent exposure as suggested by the repeated observation of a good correlation between the concentration of mercury vapour in air (Hg air) and concentration of mercury in urine (HgU) at the end of the workshift.[6-9] The results of Cherian *et al*[4] suggest that the second phase is probably more a reflection of the content of mercury in the kidney. We have attempted to better estimate the rate constant of this slow elimination phase by monitoring (repeatedly during about 300 days) the urinary concentrations of seven workers who had been removed from exposure to mercury vapour. Meso-2,3-dimercaptosuccinic acid (DMSA), a water soluble and less toxic analogue of British anti-lewisite, has been shown to be effective as an antidote for intoxication by heavy metals.[10] In man, oral administration of this chelating agent is active in accelerating the urinary elimination of arsenic[11] and lead.[12 13] Its potential usefulness for the elimination of mercury into urine was first reported in patients from China with occupational mercury poisoning.[14] Oral administration of DMSA to animals pretreated with organic (methylmercury)[15 16] or inorganic ($HgCl_2$)[16 17] mercury has shown its effectiveness in mobilising mercury from the body with a concomitant increase in its urinary excretion rate. Experimental studies have shown that after chronic exposure to mercury vapour DMSA was capable of removing mercury from peripheral tissues (liver, kidney) but had no significant effect on the amount of mercury accumulated in the brain.[18] It is likely that the same phenomenon occurs in man. It has been suggested that the amount of mercury excreted in urine after one single (oral or parenteral) administration of DMSA[18] or a closely related thiol containing chemical, 2,3-dimercaptopropane-1-sulfonate,[19] could reflect the amount of mercury mobilisable from peripheral depots (mainly the kidney). In the present study we have also examined the response of urinary mercury excretion after a single oral administration of DMSA to groups of workers who had sustained various intensities of exposure to mercury vapour.

Subjects and methods
STUDY GROUPS
The elimination half life of mercury in urine after removal from exposure to mercury vapour was determined in seven male workers who were employed on average for 4.4 (range 1–8.4) years in a plant manufacturing alkaline batteries using zinc

mercury amalgam. Their removal from exposure was justified by the repeated finding of a raised HgU (> 100 μg/g creatinine) in the preceding months. During the removal period, which lasted seven to 11 months, HgU was repeatedly measured and the first measurement took place 10 to 29 days after the date of removal. These workers were in good clinical health and did not show any biological change (in urinary excretion of albumin, β_2-microglobulin, retinol binding protein, and N-acetyl-β-glucosaminidase; see also below) suggestive of adverse mercury effects on the kidney. Their age at the time of removal ranged from 22 to 40 (mean 29.5).

The protocol of the DMSA study was approved by the Board for Medical Ethics of the Université Catholique de Louvain, and informed consent was obtained from the volunteers who participated in the study. The DMSA study was performed on three groups of male workers: (1) a control group of 16 workers occupied in a chemical plant (mean age 37.6; range 23–49) and who had never been engaged in processes with compounds containing mercury; (2) a group of 16 workers currently exposed to mercury vapour in a chloralkali plant (mean age 34.9; range 21–58) who were given DMSA on three different occasions (see below); (3) a group of 11 workers previously exposed to mercury vapour in the aforementioned alkaline battery factory (mean age 33; range 27–41) and who, at the time of the DMSA study, had been removed from exposure to mercury vapour for at least two years.

Information gathered by a questionnaire showed that all these subjects met the following criteria: (1) controls and workers exposed to mercury had never been occupationally exposed to other nephrotoxins; (2) the workers currently or previously exposed to mercury had been uninterruptedly exposed to mercury vapour for at least one year; (3) the medical history of the controls and exposed workers did not show neurological or neuropsychiatric problems, renal diseases of known causes, or current medical treatments.

Alcohol consumption was low and mainly restricted to a few glasses of beer a week. All the subjects were also submitted to a renal screening test, which did not show appreciable disturbances. The individual results of four renal markers did not exceed the upper limits of normal values—namely, 300 μg/g creatinine for β_2-microglobulin and retinol binding protein in urine, 15 mg/g creatinine for albuminuria, and 2.7 IU/g creatinine for the activity of N-acetyl-β-glucosaminidase in urine.[20]

EXPOSURE TO MERCURY AND OTHER HEAVY METALS
BEFORE THE DMSA STUDY
The exposure to mercury was evaluated during the few weeks before the DMSA study. The external exposure to inorganic mercury. (Hg air) in the

chloralkali plant was assessed by personal sampling over periods of 5·5 to 9·5 hours using hopcalite tubes as described previously.[9] In total 21 air samples were taken spread over 13 different jobs and depending on the job characteristics the Hg air ranged from 9 to 308 μg Hg/m³.

The internal exposure to mercury in the chloralkali plant workers and in the corresponding control group was assessed by measuring HgU one month and mercury in blood (HgB) 24 hours before the DMSA study. In the group of workers from the alkaline battery plant who were removed from mercury exposure, HgU and HgB were measured during the week preceding the DMSA experiment.

The exposure to cadmium (Cd) and lead (Pb) was also evaluated a few days before the DMSA experiment by analysing blood for Cd, Pb, and Zn-protoporphyrin (ZPP) concentrations, and urine for concentration of Cd. None of the subjects in each group exceeded 150 μg Pb/l for lead in blood, 2·5 μg Cd/l for Cd in blood, 2 μg/g haemoglobin for ZPP, and 1·5 μg Cd/g creatinine for Cd in urine. These results show that the current and past exposure to Cd and Pb were in the normal range (only low environmental exposure).

DESIGN OF THE DMSA EXPERIMENT

The DMSA experiment consisted of two consecutive 24 hour urine collections. On the first day at 8.00 am the workers emptied their bladders before the start of the experiment. During the next eight hours (a workshift) they came to the medical department of the plant to each collect their urine in a container A. Each time care was taken to prevent external mercury contamination. At the end of the workshift at 4.00 pm they emptied their bladders for the last time in the same container. For the next 16 hours (from 4.00 pm until 8.00 am the next day) the urine was collected at home in container B. Contamination by mercury at home is unlikely because the workers took a shower after the working day and left their working clothes in the factory. The next morning at 8.00 am they each emptied their bladders for the last time into container B at the medical department of the plant. Then a single dose of 2 g of DMSA was administered orally with a glass of water. For the next eight hours the subjects each collected their urine in a container C in the same way as described above for the first urine collection. For the subsequent 16 hours they each collected their urine in a container D at home and the bladder was emptied for the last time into this container at the medical department of the plant the next morning at 8.00 am. The selection of the single dose of 2 g DMSA was based on earlier reports dealing with DMSA treatment of occupational metal poisoning.[13 21]

The volume, the total HgU, and the creatinine concentration of the urine specimen in each container were measured. This protocol was applied to the three study groups. After measures were taken to reduce the exposure to mercury in the chloralkali plant the same workers of this plant volunteered one year later to repeat the DMSA experiment twice, the first time a few weeks before their summer holiday, and the second time two days before they resumed their normal activities after a holiday period of three weeks on average.

BIOLOGICAL ANALYSES

Standardised syringes, tubes for blood collection (containing 0·1 ml EDTA-Na₂, 10% w/v), and urine containers were previously checked for lack of heavy metal contamination. Total HgB and HgU were analysed using an automated "cold vapour" atomic absorption technique.[22] Urinary creatinine was determined according to Jaffe's picrate method.[23] The HgB is expressed as μg/l and HgU as μg/24 h or μg/g creatinine (1 μg mercury = 4·99 nmol; 1 g creatinine = 8·84 mmol). To assure the quality of the mercury analyses in blood and urine, we included as a routine procedure internal quality control samples of blood and urine in each analytical run and, furthermore, our laboratory participated in two external quality control programmes for the analysis of mercury in urine. During the present investigation our proficiency in analysing urine and blood for mercury is similar to that reported previously.[9 24]

The Cd and Pb analyses in blood and urine were performed by electrothermal atomic absorption spectrometry with stabilised temperature-platform-furnace techniques coupled with a Zeeman effect background correction system (Perkin-Elmer Zeeman 3030). The method of external standard line in whole blood matrix was used for the analysis of blood, whereas for urine the method of standard addition was used. Measurement of ZPP concentration was carried out with a haematofluorimeter (Aviv Associates, Lakewood, NJ). The urinary concentration of β_2-microglobulin, retinol binding protein, and albumin was determined by a latex immunoassay,[25] and a fluorimetric method[26] was used for the determination of N-acetyl-β-glucosaminidase activity in urine.

STATISTICAL ANALYSIS

Student's *t* test (two tailed) for unpaired data was used to compare group means. A paired *t* test was used to compare the mercury excretion in urine before and after administering DMSA. Pearson correlation coefficients and regression equations were calculated to assess the association between HgU before and after DMSA in the different groups.

Results

BIOLOGICAL HALF LIFE OF MERCURY IN URINE

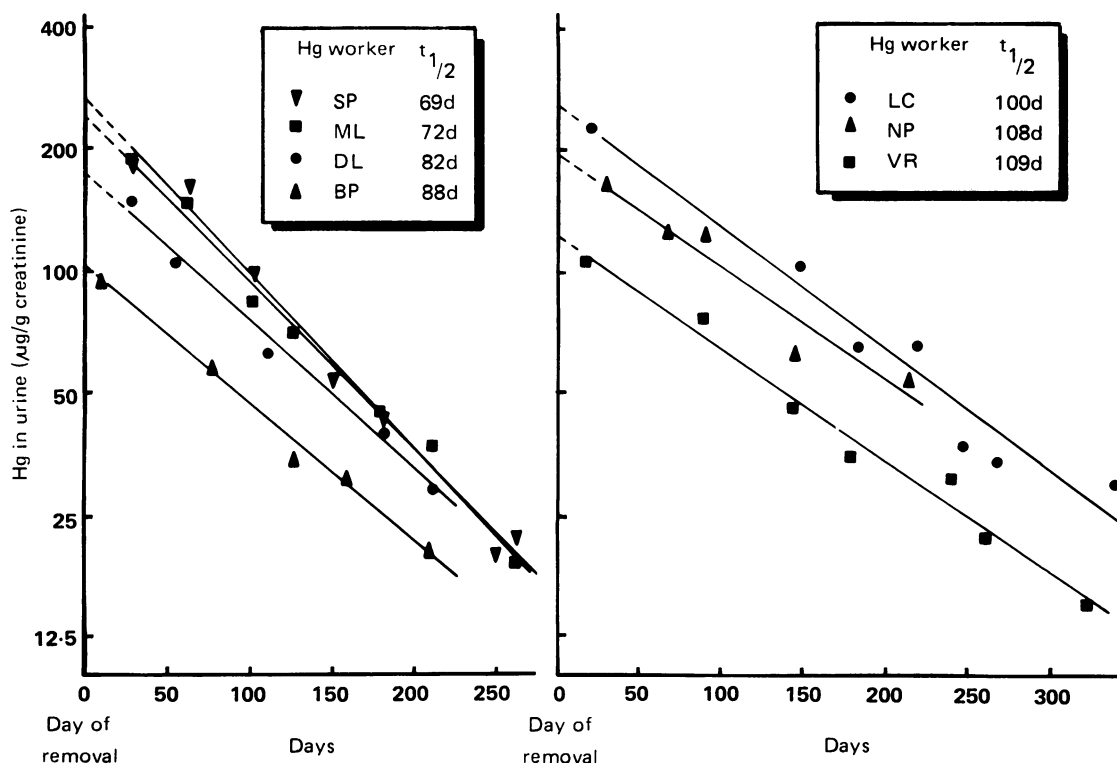Concentration of mercury in urine was monitored

Figure 1   First order kinetics of the spontaneous disappearance of mercury from urine in seven alkaline battery workers after discontinuation of chronic exposure to mercury vapour (first HgU monitoring not earlier than 10 days after the date of removal). The least squares method was used to determine the best fitting straight lines (r = −0·960 to −0·995, p < 0·01).

during several months in the seven workers removed from exposure. The first HgU measurement took place not earlier than 10 days after the date of removal. Figure 1 shows the time course of HgU for each worker. The rate of decline of urinary mercury during the observation period seems to follow a single first order process with a mean elimination half life of 90 days (range 69 to 109 days) and a mean disappearance rate constant of 0·008 day^{-1} (range 0·006 to 0·010 day^{-1}).

It is interesting that about one year after the end of

the first removal period one subject (ML) was again removed from exposure because of the repeated finding of a raised HgU (mean 160 μg/g creatinine); the urinary elimination half life measured during the second removal period (77 days) agrees well with the first one (72 days).

EFFECT OF A SINGLE ADMINISTRATION OF DMSA ON URINARY MERCURY EXCRETION

Table 1 summarises the characteristics of the exposure to mercury in the different study groups

Table 1   Exposure to mercury in different study groups before DMSA experiment

	Control (n = 16) Mean (SEM)	Removed from exposure (n = 11; battery plant) Mean (SEM)	Currently exposed* (n = 16; chloralkali plant) Mean (SEM)
Years of exposure to Hg vapour	—	3·5 (0·5) (1·0–6·5)†	7·0 (1·1) (2·3–15)
Years of removal from exposure	—	4·5 (0·6) (2·4–9·4)	—
Hg air (μg/m^3)	—	—	110‡ (18) (9–308)
HgB (μg/l)	1·6 (0·3) (1·0–6·5)	2·8 § (0·3) (1·2–4·3)	25·6 (3·5) (8·3–51·4)
HgU (μg/g creatinine)	2·1 (0·2) (1·4–3·7)	6·9§ (1·1) (3·0–13·3)	119 (10·1) (49–200)

SEM = Standard error of the mean.
*Before implementation of technical prevention measures in the chloralkali plant.
†Range.
‡Average of 21 personal samples.
§Significantly higher than in control group.

Table 2   Concentrations of mercury in 24 hour urine samples before and after a single oral administration of 2 g DMSA in groups of workers differently exposed to mercury vapour

			Chloralkali plant (currently exposed)*		
				After reduction of exposure	
	Control group (n = 16)	Alkaline battery plant (removed from exposure) (n = 11)	Before reduction of exposure (n = 16)	Before holiday (n = 16)	After holiday (n = 16)
HgU (µg Hg/24 h)					
Before DMSA:					
Mean	4·1	10·4	184	78	66
SEM	0·3	1·5	15	8	6
Range	2·1–5·3	4·3–19·1	93–293	24–136	24–134
After DMSA:†					
Mean	8·3	31·1	793	257	174
SEM	0·4	5·2	66	23	20
Range	5·3–10·8	13·4–66·1	416–1269	106–459	49–324

SEM = Standard error of the mean.
*The same subjects were examined at three different occasions (for details, see Subjects and methods).
†Significant increases of the urinary mercury levels after DMSA administration in all the groups (paired t test; p < 0·001).

before the DMSA experiment. After an average removal period from exposure to mercury of 4·5 years the battery plant group still showed slightly but statistically significant higher mean values for HgB (p < 0·05) and HgU (p < 0·001) than the control group. The Hg air (personal samplers) in the chloralkali plant fluctuated widely and was rather high before technical measures was applied to reduce the emission. On a group basis the ratio Hg air (µg/ m³):HgU (µg/g creatinine) equals 1:1·1, which agrees with our previously[9] reported data in workers exposed to much lower (about three times) and less fluctuating Hg air in an alkaline battery plant.

Immediately after the first DMSA experiment several measures were taken in the chloralkali plant to reduce the exposure to mercury. One year later, the current mercury exposure had dropped considerably as reflected by HgB and HgU measured a few weeks before the summer holiday (mean HgB = 17·7 µg/l, range 7–38·4; mean HgU = 48 µg/g creatinine, range 29–73). After the holiday period (mean 19 days) the mean HgB in the

group had dropped further by about 60% and HgU by about 15%.

Table 2 compares the amounts of mercury excreted in urine during 24 hours before and 24 hours after a single oral administration of DMSA (2 g) on a group basis. Figure 2 shows the data for individual subjects. On average 50 to 70% of the amount of mercury excreted in 24 hours is eliminated in urine during the first eight hours after DMSA administration (results not shown). Each study group showed significantly higher HgU in urine after DMSA administration than before (paired t test, p < 0·001) (fig 2). The administration of a single dose of 2 g DMSA did not influence the diuresis or the renal markers in the different groups. The relation between the amount of mercury in the 24 hour urine specimens before (x axis) and after (y axis) administration of DMSA was examined. Table 3 shows that both parameters were highly associated in all the groups. In the chloralkali workers currently exposed to mercury, however, the correlation coefficients were lower (r = 0·66 and 0·58) than in the

Table 3   Correlation between amount (µg) of mercury excreted in urine during 24 hours before (x axis) and after (y axis) a single oral administration of 2 g DMSA

			Regression equation		
Groups	No of subjects	Pearson correlation coefficient	Intercept	Slope	p Value
Control	16	0·80	3·5	1·17	<0·001
Workers removed from Hg exposure*	11	0·97	−2·9	3·27	<0·001
Workers currently exposed to Hg:†					
Before reduction of exposure	16	0·66	263	2·88	<0·01
After reduction of exposure					
Before holiday	16	0·58	120	1·75	<0·025
After holiday	16	0·86	2·4	2·60	<0·001

*Alkaline battery plant.
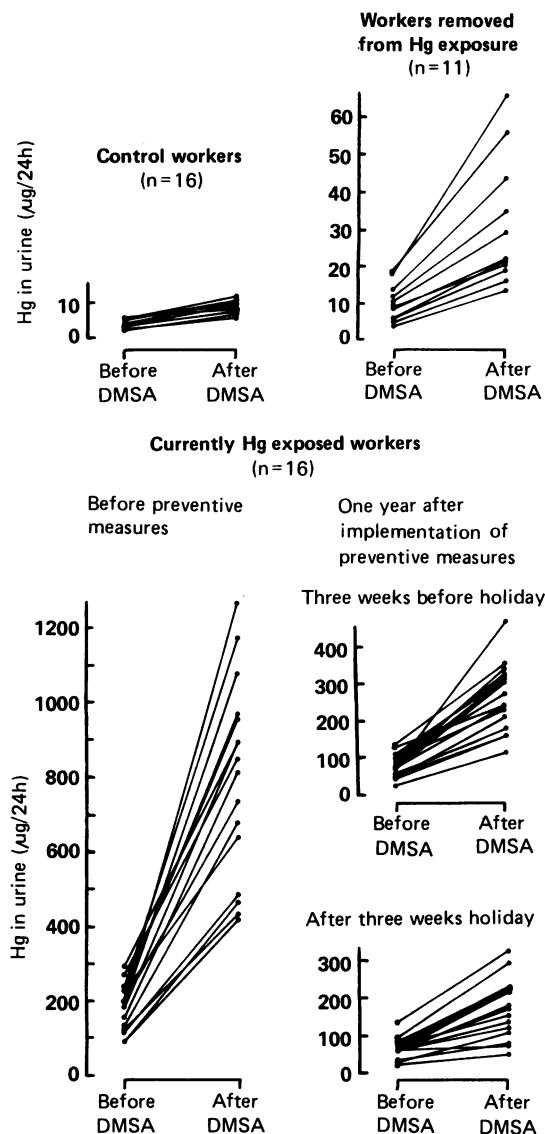†Chloralkali plant: same subjects examined at three different occasions.

Figure 2 Excretion of mercury in urine 24 hours before and after a single oral administration of 2 g meso-2,3-dimercaptosuccinic acid (DMSA) in different groups of male workers—that is, controls, alkaline battery workers removed from mercury vapour exposure for at least two years, and chloralkali workers currently exposed to mercury vapour (studied at three different occasions). In all groups p < 0·001 (paired t test).

control group (r = 0·80) and the other groups not recently exposed to inorganic mercury at the time of the test (r = 0·97 and 0·86).

Discussion

This study is the first one during which the urinary excretion of mercury in workers removed from

occupational exposure to mercury vapour was followed up during a long period (about 300 days). It indicates that in the absence of kidney lesions the slow component of the elimination of mercury in urine shows the characteristics of a one compartment open model with a biological half life of about three months (range 69 to 109 days). During this phase the rate constant of disappearance of mercury from the urine was 0·008 day^{-1} on average and this agrees well with the results of Piotrowski et al.[5] It is also interesting to mention the results of Hursh et al[27] who studied the clearance of radioactive mercury isotopes in five volunteers immediately after a short term inhalation exposure to a mixture of stable and radioactive mercury vapour (0·1 mg Hg/m^3 during about 20 minutes). The post exposure observation period lasted about 40 days and within this interval the loss of radioactivity from the kidney region occurred with a half life of 64 days on average (range 47 to 83 days). These observations support the suggestion that a few days after discontinuation of chronic occupational exposure to mercury vapour the HgU is mainly influenced by the amount of mercury stored in the kidney.

In all the groups studied DMSA significantly stimulates the urinary excretion of mercury. In view of the results of animal experiments[18] it is likely that DMSA chiefly removes mercury from its main peripheral site of deposition (kidney). In this regard it is interesting that in subjects not currently exposed to mercury (workers removed from exposure on the average for 4·5 years and subjects returning from a three week holiday period) the correlation coefficient between the amount of mercury excreted during 24 hours before and 24 hours after DMSA is greater than 0·85 confirming that under these conditions mercury in urine before administration of the chelator is mainly a reflection of the amount stored in the kidney. The correlation coefficient is much lower when the DMSA experiment is carried out during the exposure period because under these conditions the basal excretion of mercury is greatly influenced by recent exposure. Because during steady state occupational exposure to mercury vapour the intensity of external exposure to the metal and the amount stored in the kidneys are probably related, it is not surprising that a weak but statistically significant correlation is also found between the amount of mercury excreted in urine before and after administering DMSA.

Our previous studies[28 29] have shown that after exposure to mercury vapour it is unlikely that signs of renal dysfunction will be detected in workers usually excreting less than 50 μg Hg/g creatinine (or about 75 μg/24 h). As this biological exposure threshold has been established for workers currently exposed to mercury vapour, it should be lowered by about 20% when considering urine samples collected a few days

after exposure has ceased. The present study suggests that an HgU of 40 µg/g creatinine (or about 60 µg/24 h) corresponds to a quantity of mercury accumulated in the kidneys that after DMSA administration (2 g orally a few days after removal from exposure) would lead to a 24 hour urinary excretion of about 160 µg mercury (95% confidence interval 68–251 µg). Further studies would be useful to confirm that direct toxic effects of exposure to mercury vapour on the kidney are unlikely to occur when this mobilisable pool of mercury is never exceeded.

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