Clearance half life of mercury in urine after the cessation of long term occupational exposure: influence of a chelating agent (DMPS) on excretion of mercury in urine

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Abstract

The elimination of mercury (Hg) in urine was investigated in 12 former chloralkali workers exposed to metallic Hg vapour for two to 18 (median five) years. Morning urine samples were taken on several (median 9) occasions after change of employment or retirement. The median follow up time was 28 months. The decrease in concentration of Hg in urine (U-Hg) was well characterised by a one compartment model. Three different regression methods were used; non-linear least squares regression (NLSR), weighted non-linear least squares regression (WNLSR), and linear least squares regression (LLSR) after log transformation of the U-Hg data. The median half life from the WNLSR method was 55 days. There were no large differences in the half life estimates given by the WNLSR or the NLSR methods, but for five subjects the LLSR method gave poor fits. There was a non-significant tendency towards longer half lives with higher initial U-Hg. About three years after the cessation of occupational exposure a mobilisation test with 2,3-dimercaptopropane-1-sulphonate (DMPS) was performed on seven subjects. Excretion of Hg, copper (Cu), and zinc (Zn) in urine was estimated before and after the ingestion of 300 mg of DMPS. Treatment with DMPS increased 24 hour urinary excretion by a factor of 7.6 for Hg, 12 for Cu, and 1.5 for Zn. The relative increase in U-Hg was not significantly higher than that obtained in a previous study of an occupationally unexposed group. A major proportion (62%) of Hg excreted during 24 hours after DMPS appeared in the first six hours. For Hg and Zn, but not for Cu, the amounts excreted before and after DMPS were highly correlated. The excretion of Hg in urine probably reflects the amount of Hg stored in the kidneys, and the use of a single dose of DMPS gives no further information about the size of that pool.

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When an individual has been exposed to inorganic mercury (Hg), urine and faeces are the principal routes of elimination.^{1,2} In volunteers exposed to radioactive Hg vapour, faecal excretion dominated in the first week.³ After

long term exposure, however, urinary excretion seems to predominate.² The kinetic pattern of urinary Hg excretion has been studied after short term^{4,5} and long term⁶⁻⁸ occupational exposure. The half life for elimination of Hg in urine was 40-60 days after both short term high^{4,5} and long term low level exposure.⁶ After long term high exposure it was 70-90 days.^{7,8} A similar result was found in a mixed group of workers exposed both short term and long term.⁹ In two of the studies,^{4,7} the data indicated that elimination could be described by a two compartment model. As the total number of subjects studied was small, further studies on the elimination kinetics of U-Hg were considered desirable.

The main sites of deposition after inhalation of Hg vapour are the kidneys, the liver, and the brain.^{1,2} Chelating agents have been used for many years for treatment of metal poisoning.^{10,11} In rats exposed to inorganic Hg the amount of Hg excreted in urine after a single dose of 2,3-dimercaptopropane-1-sulphonate (DMPS) or 2,3-dimercaptosuccinic acid (DMSA) is a good indicator of the renal burden of mercury.^{12,13} These two chelators also increased the excretion of copper (Cu) and zinc (Zn)¹⁰ and have been used for the mobilisation of Hg in workers with current exposure to inorganic Hg^{8,14} and in persons with and without amalgam fillings.¹⁴⁻¹⁷ If, in workers previously exposed long term, the increase in Hg excretion induced by chelating agents a long time after the end of mercury exposure, is much higher than in other subjects with the same baseline Hg excretion, this could indicate the existence of compartment(s) with slow turnover rates. Such data are scarce, however.^{8,18} In the present study, a mobilisation test with DMPS was performed in workers about three years after they ceased occupational exposure. Besides Hg, Cu and Zn excretion in urine were also estimated.

Subjects and methods

ESTIMATION OF MERCURY ELIMINATION HALF LIVES
Twelve workers from two different chloralkali plants, all exposed to Hg vapour, volunteered for multiple consecutive urine sampling, in conjunction with change of employment or retirement. The workers were recruited during a four year period. They had been working in the chloralkali industry for two to 18 (median five) years, and were 22 to 65 years of age at the start of investigation. They were all healthy and had low or moderate alcohol consumption. Table 1 shows their ages, expo-

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Table 1 Previous exposure and background factors in the study group of 12 former chloralkali workers exposed to Hg vapour

Subject No	Age	Exposure time (y)	Cumulative exposure index* (nmol.y.l ⁻¹)	Fish consumption (meals/week)	Smoking	No of amalgam surfaces	Mobilisation test with DMPS
1	57	2	130	<1	No	12	No
2	28	6	350	1	Yes	31	Yes
3	65	18	830	1	Yes	0	No
4	26	3	200	1	No	28	Yes
5	31	12	920	<1	Yes	36	No
6	31	13	950	1	Yes	34	Yes
7	27	4	140	1	No	14	No
8	23	2.5	320	1	No	17	Yes
9	22	2	170	2	Yes	15	Yes
10	33	4	410	2	Yes	22	Yes
11	43	10	1010	1	Yes	35	No
12	27	7	780	<1	Yes	26	Yes

*Integrating B-Hg as a function of time.

sure times, smoking habits, fish consumption, and number of amalgam surfaces. The first sampling took place within the first week after the end of exposure for five of the subjects (Nos 4, 5, 7, 9, and 10), within the first three weeks for four subjects (Nos 1, 2, 6, and 8), and after 1.5 to two months for the remaining three subjects (Nos 3, 11, and 12).

First morning urine samples, generally on two or three consecutive days, were taken at several (median nine, range 5–15) occasions during a period of four to 68 (median 28) months. One person was followed for four months only (subject No 5), as he was re-employed at the chloralkali factory after that period. The total number of urine samples collected from each subject varied between 12 and 29.

The urine samples were collected at home in polyethylene bottles (with a small amount of sulphamic acid added) that had previously been washed in RBS 25 detergent. The samples were stored, firstly, in refrigerators for no more than three days, and then at -25°C until analysis. In urine, bacterial growth can cause evaporation of metallic Hg,¹⁹ but addition of sulphamic acid produces stable urine samples for at least one month even at room temperature.²⁰ In urine samples stored at low temperatures, Hg is concentrated in the precipitate, and urine samples were therefore homogenised by vigorous shaking before analysis. From our experience, no loss of Hg occurs in urine samples refrigerated for several months.

Urinary Hg concentrations (U-Hg) were determined by the cold vapour atomic absorption technique.^{20,21} The detection limit was 1 nmol/l. Each sample was analysed in duplicate. Precision was about 95% for U-Hg in the range 5–500 nmol/l. The accuracy was checked by analysing external reference samples (Lanorm metals 1, Behring Institute, Behringwerke AB, Marburg and Seronorm batch 108, Nycomed, Oslo, Norway) together with the test samples. The results (46 nmol/l (SD 2.6, $n = 14$) and 252 nmol/l (SD 7.3, $n = 10$)) were in accordance with the recommended values of 48 nmol/l and 254 nmol/l respectively. Concentration of Hg in urine was expressed per mmol creatinine to correct for differences in urinary flow rate. Creatinine was determined with a modified kinetic Jaffé

method. Precision, as calculated from duplicate analyses, was greater than 98%.

A cumulative exposure index (table 1) was calculated for each subject from previous concentrations of Hg in blood (B-Hg), measured in the period between 1970 and the end of exposure, by integrating B-Hg as a function of exposure time.

In each subject, models with one or two compartments were fitted to the decrease in U-Hg, assuming an exponential decrease, by NLSR (non-linear least squares regression). This was done with the NLIN procedure in the SAS statistical program.²² Also, all 12 individual curves were analysed simultaneously, calculating the best fit, on the assumption that all subjects had a common half life. This was done with a special version of the EXPFIT program,²³ EXPGRF17. These different models were compared statistically with the F test for differences in sums of squares.²³ For the one compartment model, we also used a weighted, non-linear least squares (WNLSR) method,²⁴ with the assumption that the variances are proportional to the concentration of U-Hg (applicable for U-Hg above 1 nmol/mmol creatinine). The data were also fitted to a linear least squares regression (LLSR) method after log transformation of the U-Hg data (REG procedure in SAS).

When calculating the half lives, a baseline concentration was subtracted from each U-Hg. The baseline values were from the average concentration after at least one year of follow up for 10 of the subjects. If the half life is about two months for U-Hg elimination, then a one year period would be enough to reach a baseline concentration. The low concentrations (median 0.8 (range 0.3–1.6) nmol/mmol creatinine) in comparison with other occupationally unexposed groups in Sweden, indicate that they had reached their baseline. For two subjects (Nos 1 and 5), who were followed up for four and 10 months only (presumably too short to reach baseline concentrations), we used the median U-Hg found in an occupationally unexposed reference group from one of the plants, 1.7 nmol/mmol creatinine ($n = 44$). A reduction of the baseline concentration by 50% for these two subjects only slightly increased the point estimate of the half life for the group. For correlations between two variables, Pearson's correlation

coefficient, r_p (after log transformation) was calculated.

MOBILISATION TEST WITH DMPS

Seven men in the U-Hg elimination study (table 1) volunteered for an Hg mobilisation test with DMPS 18–56 (median 34) months after exposure had ceased. All participants were in good health and had no renal disease. Their body weights varied between 66 and 96 kg. The protocol of the DMPS study was approved by the Board for Medical Ethics of the University of Göteborg and by the National Board of Health and Welfare, Department of Drugs.

One morning sample and two consecutive 24 hour urine samples were collected in metal-free polyethylene bottles. After the first morning urine sample on the first day (m, pre), all urine excreted during the next 24 hours (24h, pre) was collected. After the first 24 hour collection period, the volunteers ingested 300 mg of DMPS before breakfast, and started to collect urine for the second 24 hour period (24h). Urine excreted during the first six hours (6h) after DMPS was collected in a separate bottle. One subject (No 10) misunderstood the instructions and ingested DMPS after the first morning sample. His baseline excretion of Hg, Cu, and Zn during 24h before the mobilisation test was therefore calculated from the excretion rate in the first morning sample.

For the fixed term samples, the volume and the time limits were registered. Storage and determination of U-Hg and creatinine were the same as described earlier. Urinary Zn was analysed by flame atomic absorption. One ml 0.3 M nitric acid was added to one ml urine, and absorbance was measured at 215 nm. Urinary Cu was analysed by graphite furnace atomic absorption at 324.8 nm. Urine samples were diluted (1:5) with Triton solution including ammonium nitrate (0.12 mol/l) as a modifier. Urine, spiked with Zn or Cu, was used for calibration. Each sample was

analysed in duplicate. The detection limit for Cu was 0.1 $\mu\text{mol/l}$, and for Zn 1.0 $\mu\text{mol/l}$. Precision was above 95% for U-Zn concentrations in the range 3–30 $\mu\text{mol/l}$ and about 95% for U-Cu in the range 0.1–5 $\mu\text{mol/l}$. Quality control with a reference sample of lyophilised urine (Seronom batch 108, Nycomed, Oslo, Norway) measured together with the samples, showed good accuracy. The results for U-Zn (9.9 $\mu\text{mol/l}$ (SD 0.2, $n = 14$) and U-Cu (721 nmol/l (SD = 40, $n = 18$)), accorded with the certified values of 10 $\mu\text{mol/l}$ and 709 nmol/l.

For correlations between two variables Pearson's correlation coefficient r_p (after log transformation) was calculated.

Results

MERCURY ELIMINATION HALF LIVES

Table 2 shows the results from fitting a one compartment model to individual U-Hg data with different regression methods. When the NLSR method was used for each subject, the median half life was 59 days. From a model with a common half life (EXPFIT), the point estimate was 69 days. For four subjects this model gave a skewed distribution of residuals over time. The model with individual half lives was statistically better (F test, $p = 0.02$) than the model with a shared half life.

The weighted non-linear method (WNLSR) with variances assumed proportional to concentration, resulted in R^2 values (the fraction of the variance explained by the model) similar to those obtained with the NLSR method, whereas the LLSR method gave a low R^2 in several subjects. When the estimated values from the different regression models were visually compared with the data points, the equations from WNLSR for a few subjects seemed to fit the data better than the corresponding equations from NLSR. For most subjects, however, NLSR and WNLSR were equally good. The first fitted the data better for high concentrations and the second better for moderate concentrations. The

Table 2 Kinetics of Hg in urine (U-Hg) in 12 men after occupational exposure

Subject No	NLSR			WNLSR			LLSR		
	$T_{1/2}$ (95% CI) (days)	Y_0 (nmol/mmol creatinine)	R^2 (%)	$T_{1/2}$ (95% CI) (days)	Y_0 (nmol/mmol creatinine)	R^2 (%)	$T_{1/2}$ (95% CI) (days)	Y_0 (nmol/mmol creatinine)	R^2 (%)
1	58 (47–77)	14.9	98	57 (48–71)	14.8	97	57 (50–67)	14.9	94
2	51 (45–59)	22.0	99	46 (41–52)	22.9	97	128 (92–210)	6.9	63
3	46 (39–55)	20.1	99	47 (41–54)	19.4	99	49 (44–56)	18.1	96
4	83 (66–111)	13.1	95	82 (71–99)	12.4	94	95 (87–105)	11.4	95
5	52 (41–74)	14.3	98	48 (39–61)	14.5	98	46 (39–56)	15.1	91
6	53 (40–75)	14.5	93	52 (45–63)	13.5	93	61 (55–68)	11.8	95
7	41 (34–51)	6.1	97	40 (35–46)	6.0	97	37 (33–43)	6.4	95
8	78 (67–93)	24.5	98	63 (55–74)	26.9	95	77 (61–104)	18.6	76
9	59 (45–87)	37.6	95	63 (53–76)	35.2	95	56 (51–61)	40.5	98
10	88 (76–104)	26.4	97	79 (68–93)	26.7	93	126 (103–161)	15.6	77
11	66 (51–96)	16.2	96	59 (47–77)	17.1	95	325 (203–743)	4.3	52
12	67 (58–78)	32.8	98	54 (46–66)	39.8	91	226 (134–722)	3.4	40
Median	59 (51–78)			55 (47–63)*			69 (49–128)*		
Mean	62			57			—		
Model using common half lives	69 (64–74)								

* 96% CI (binomial distribution).³³

Results from one compartment models using a non-linear least-squares regression method (NLSR), a weighted non-linear least-squares regression method (WNLSR), and a linear least-squares regression method (LLSR). After subtraction of the estimated baseline level, the following equations were fitted: $\text{U-Hg} = Y_0 \cdot e^{-kt}$ (NLSR and WNLSR) and $\ln(\text{U-Hg}) = \ln(Y_0) - kt$ (LLSR). The half lines ($T_{1/2}$) are derived from: $T_{1/2} = \ln 2/b$. R^2 is the fraction of the variance in U-Hg explained by the model. Confidence intervals (95% CI) are calculated as ± 2 SE (asymptotic standard error).

Elimination of Hg in urine after long term exposure to Hg vapour (subject No 2). The observed data are compared with the predicted one compartment equations from different regression methods. (—) NLSR (non-linear least squares regression); (---) WNLSR (weighted non-linear least squares regression); (-.-) LLSR (linear least squares regression) after log transformation.

median half life with the WNLSR method, 55 days, was somewhat lower compared with that obtained with the NLSR method. The median point estimate for the half life with the LLSR method was 69 days. The LLSR method gave very poor estimates of the half lives and intercepts (Y_0) for five subjects (Nos 2, 8, 10, 11 and 12). The figure shows the poor fit to the observed values with the LLSR method for subject No 2.

There were no significant correlations between the half life estimates from the one compartment model (NLSR) on the one hand and exposure time, cumulative exposure index, or the calculated U-Hg (Y_0) at the end of exposure on the other. There was, however, a tendency towards longer half lives with higher intercepts ($r_p = 0.46$) and shorter exposure time ($r_p = -0.41$). The results were similar when WNLSR half life estimates were used.

When the data were fitted to a two compartment model, a fast phase was discerned in three of the subjects. The half life estimates for the fast and slow phases were 1.6, 3.2, and 8.9 days and 53, 83, and 66 days respectively. For these subjects, the two compartment model was not significantly better than the corresponding one compartment model. No second compartment could be shown with the

common half life model (EXPFIT).

The average intraindividual variation of U-Hg in morning samples on consecutive days was 36% (coefficient of variation for morning samples corrected for creatinine, 19% for 0.1–2 nmol/mmol creatinine, and 13% for 10–25 nmol/mmol creatinine).

MOBILISATION TEST WITH DMPS

Table 3 shows U-Hg values in urine before and after the DMPS mobilisation test. After the ingestion of DMPS (dose 3.0–4.5 mg/kg), the excretion of U-Hg increased. Of the amount of mercury excreted during 24 hours after DMPS most appeared in the first 6 hour sample (mean 62%, range 36%–78%). The average of the individual ratios U-Hg(24h)/U-Hg (m, pre) and U-Hg(24h)/U-Hg(24, pre) were 6.8 and 7.6 respectively. The ratio was expressed in these two ways to make comparisons with other studies^{8,14–17} possible. The U-Hg (24h) was significantly correlated with U-Hg (m, pre). The Pearson correlation coefficient was 0.79. There was also a high correlation between the U-Hg (24 h) (in μg) before and after the DMPS test ($r_p = 0.86$).

The rate of urinary excretion of Cu and Zn also increased (table 4). The average ratios between the amounts excreted in the 24 hour sample after and before the ingestion of DMPS respectively, was 12 for Cu and 1.5 for Zn (one outlier excluded, see table 4). The proportion of the amount excreted during the first six hours was 51% for Cu and 42% for Zn. There were no significant correlations between the Cu excretion before and after DMPS. Both U-Zn (6h) and U-Zn (24h) correlated significantly ($p < 0.001$) with the amount excreted 24 hours before the DMPS test ($r_p = 0.96$ and 0.99 respectively).

About a fourfold increase in 24 hour albumin excretion was seen in one subject after the ingestion of DMPS. The concentration, however, returned to normal on the next day. In the other six subjects no such effect was seen. Two subjects reported headaches after the ingestion of DMPS.

Discussion

KINETICS OF MERCURY IN URINE

The elimination of Hg in urine was well characterised by a one compartment model. Our point estimate for the half life was 55 days

Table 3 Hg concentrations determined in morning urine (U-Hg (m, pre)) and 24 hour urine before (U-Hg (24h, pre)), and urine 0–6 hours (U-Hg (6h)), and 0–24 hours (U-Hg (24h)) after ingestion of 300 mg DMPS

Subject No	U-Hg(m,pre) nmol/mmol creatinine	U-Hg(6h) nmol/mmol creatinine	U-Hg(24h) nmol/mmol creatinine	U-Hg(24h) U-Hg (m, pre) *	U-Hg (24h,pre) (μg)	U-Hg(6h) (μg)	U-Hg(24h) (μg)	U-Hg(6h) U-Hg (24h (%)) *	U-Hg(24h) U-Hg (24h, pre) *
2	1.5	27	12	8.4	3.4	24	36	68	10
4	1.5	13	6.3	4.4	3.8	11	18	62	4.7
6	3.6	67	26	7.4	8.9	65	82	79	9.2
8	1.7	37	15	9.1	5.8	31	44	70	7.5
9	1.2	44	14	12	3.0	30	38	78	13
10	1.4	8.0	5.3	3.8	3.4†	6.6	15	43	4.5
12	0.9	2.5	2.6	2.9	1.7	2.6	7.3	36	4.2
Mean	1.7	28	12	6.8	4.3	24	34	62	7.6

*The ratio was calculated from original data.

†The 24 hour excretion was calculated from a presample with shorter sampling time.

Table 4 Cu and Zn concentrations in urine as determined before (U-Cu/Zn(24h,pre)) and 0-6 hours (U-Cu/Zn(6h)) or 0-24 hours (U-Cu/Zn(24h)) after ingestion of 300 mg DMPS

Subject No	U-Cu(24h, pre) (µg)	U-Cu (6h) (µg)	U U-Cu (24h) (µg)	U-Cu (24h) U-Cu (24h, pre)*	U-Zn (24h,pre) (µg)	U-Zn(6h) (µg)	U-Zn(24h) (µg)	U-Zn(24h) U-Zn (24h, pre)*
2	14	173	330	24	759	456	1222	1.6
4	21	48	111	5.4	466	311	744	1.6
6	13	90	148	11	904	631	1324	1.5
8	16	94	169	11	926	620	1361	1.5
9	22	95	158	7.3	830	501	1163	1.4
10	14†	87	159	12	216†	180	1303	(6.0)‡
12	13	46	138	11	493	279	805	1.6
Mean	16	90	173	12	657	426	1132	1.5

*The ratio was calculated from original data.

†The 24hour excretion was calculated from a presample with shorter sampling time.

‡Value in parentheses is not included in the average.

(median, WNLSR method). This point estimate is longer than the median half life reported among long term, low level exposed dental personnel before and after a vacation (41 days).⁶ Three studies of long term,^{7,8} or mixed⁹ high level exposed workers, have shown longer half lives, of about 70 to 90 days. There is, however, large interindividual variation in all studies.

In the present study, there was a tendency towards longer half lives with higher initial U-Hg concentrations (Y_0). This tendency was more obvious when our data were compared with the half life estimates in other studies of long term exposed workers. In a study of dental personnel, the starting values were about 3 µg/g creatinine, and the half life 41 days.⁶ In workers from an alkaline battery factory, the initial concentrations were about 200 µg/g creatinine and the half life was 90 days.⁸ In the present study, the initial concentrations were about 35 µg/g creatinine (20 nmol/mmol creatinine) and the half life 55 days.

We found no significant correlations between the half life estimates and exposure time or the cumulative exposure index. As only one or two B-Hg samples were taken each year and B-Hg is influenced by recent exposure, our exposure index is a relatively crude estimate. There was a tendency towards longer half lives with shorter exposure time. An induction of a higher metabolic rate after a longer exposure time would result in such an association, but there is no evidence of such an effect.

The indications of a fast compartment in a few subjects were relatively weak. Nor was a fast phase for U-Hg seen in a previous study of chloralkali workers during a vacation period.²⁵ Piotrowski *et al*⁷ reported a fast elimination phase of about two days in three subjects, but the methods were crude. We have found two elimination phases after brief exposure,⁴ but the peak U-Hg, in accordance with the results of another recent study,²⁶ occurred several weeks after the end of exposure. The excretion pattern after short term exposure seems to be different from that after long term exposure (when uptake and elimination have reached a steady state).

Some data indicate that the Hg concentrations in the kidneys and brains of workers formerly exposed to Hg are still substantially raised many years after the end of exposure.²⁷⁻³⁰ If this were the case in our subjects, the reason we did not see a slower elimination

phase is probably that there is a rather limited amount of Hg in these pools or a very slow elimination rate, or both.

There were no large differences in the half life estimates given by the WNLSR or the NLSR methods, although the first seems to fit data better for a few subjects. Calculation of the variances in different concentration intervals indicates a concentration dependent variance. Therefore, in our case, the WNLSR method is the method of choice from a theoretical point of view.²⁴ The LLSR method resulted in models with bad fits for five subjects. The problems with LLSR arise mainly when subjects are followed up over such a long period that they reached very low concentrations. The LLSR method tends to give too much weight to slight absolute differences (but high differences in log transformed values) between observed and predicted concentrations.

METAL EXCRETION AFTER DMPS TEST

It was hoped that the mobilisation test with DMPS would give some information on the compartmentalisation of Hg. This did not happen. The relative increase in U-Hg after the mobilisation test, 6.8 (SD 3.2), was in agreement ($p = 0.20$, Student's t test) with the ratio of 5.3 (SD 2.4, $n = 18$) found in a previous study of an occupationally unexposed control group.¹⁴ The same result was obtained when the doses in mg per kg body weight were used in the calculation. This indicates that if a slow compartment exists, this must be very small, or that a single dose of DMPS cannot mobilise Hg from pools with a slow turnover rate.

The high proportion of the total amount of Hg excreted in urine during the first six hours (62%) accords with results presented previously.¹⁴ Similar results have also been reported in humans after a single dose of DMSA.⁸ As in other studies with DMSA after occupational exposure had stopped,^{5,8} or with DMPS during ongoing exposure,^{14,17} a high correlation was found between the excretion of Hg in urine before and after a single dose. In summary, the excretion of Hg in urine probably reflects the amount of Hg stored in the kidneys, and the use of a single dose of chelating agents, such as DMPS or DMSA, gives no further information about the size of that pool. This conclusion has also been reached by others.^{8,14,17} The extra Hg excreted after a single dose of DMPS is equivalent to

the amount normally excreted during a week.

In rats, the rate of removal from the kidneys was higher after DMPS than after an equimolar dose of DMSA.¹³ This also seems to be true for humans, because a dose of 300 mg DMPS caused a fivefold to eightfold increase in U-Hg, both in previously occupationally exposed subjects (this study) and in occupationally unexposed groups,^{14 15 17} whereas only about a twofold increase was obtained after 2 g DMSA.⁸

The increased excretion of Cu and Zn in urine after a single dose of DMPS accords with results from animal experiments.¹⁰ The greatest effect seems to be on Cu excretion, where a 13-fold increase has been reported after two days of treatment of Hg exposed workers with DMPS.¹⁰ In animals, the effect on Cu and Zn is dose dependent and returns to normal if the drugs are withdrawn.¹⁰ Excretion of Zn after DMPS in humans has not been reported previously. In humans, the elimination of Cu is mainly via the bile, and only a few % is found in the urine, usually about 20 µg/day.³¹ In our group, the average excretion of Cu before DMPS was 16 µg/day. The major route of elimination of Zn is via the gastrointestinal tract (75%), and the rest via urine.³² The excretion in humans is about 0.5 mg/day, which is similar to the average 0.7 mg/day found in our group. The extra loss of Cu and Zn after a single dose of DMPS seems to be small compared with the total normal elimination.

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- 1 World Health Organisation. *Environmental health criteria 118. Inorganic mercury*. Geneva: WHO, 1991.
- 2 Clarkson TW, Hursh JB, Sager PR, Syversen TLM. Mercury. In: Clarkson TW, Friberg L, Nordberg GF, Sager PR, eds. *Biological monitoring of toxic metals*. New York, NY: Plenum Press 1988:199-246.
- 3 Cherian MG, Hursh JB, Clarkson TW, Allen J. Radioactive mercury distribution in biological fluids and excretion in human subjects after inhalation of mercury vapour. *Arch Environ Health* 1978;33:109-14.
- 4 Barregård L, Sällsten G, Schütz A, Attewell R, Skerfving S, Järholm B. Kinetics of mercury in blood and urine after brief occupational exposure. *Arch Environ Health* 1992;47:176-84.
- 5 Bluhm R, Bobbitt R, Welch L, Wood AJJ, Bonfiglio JF, Sarzen C, et al. Elemental mercury vapour toxicity, treatment, and prognosis after acute, intensive exposure in chloralkali plant workers. Part I: History, neuropsychological findings and chelator effects. *Hum Exp Toxicol* 1992;11:201-10.
- 6 Skare I, Engqvist A. Urinary mercury clearance of dental personnel after a long term intermission in occupational exposure. *Sued Dent J* 1990;14:255-9.
- 7 Piotrowski J, Trojanowska B, Mozilnicka EM. Excretion kinetics and variability of urinary mercury in workers exposed to mercury vapor. *Int Arch Occup Environ Health* 1975;35:245-56.
- 8 Roels HA, Boeckx M, Ceulemans E, Lauwerys RR. Urinary excretion of mercury after occupational exposure to mercury vapour and influence of the chelating agent meso-2,3-dimercaptosuccinic acid (DMSA). *Br J Ind Med* 1991;48:247-53.
- 9 Ellingsen D, Thomassen Y, Kjuus H. Urinutskilling av kvikksolv etter opphørt eksponering for kvikksolvdamp i en kloralkali fabrikk. (In Norwegian). Abstract. 41 Nordiska Arbetsmiljökonferensen 1992:42.
- 10 Aposhian V. DMSA and DMPS—water soluble antidotes for heavy metal poisoning. *Ann Rev Pharmacol Toxicol* 1983;23:193-215.
- 11 Aaseth J. Recent advances in therapy of metal poisonings with chelating agents. *Human Toxicology* 1983;2:257-72.
- 12 Cherian MG, Miles EF, Clarkson TW, Cox C. Estimation of mercury burdens in rats by chelation with dimercaptopropionate. *J Pharmacol Exp Ther* 1988;245:479-84.
- 13 Buchet JP, Lauwerys RR. Influence of 2,3 dimercaptopropionate-1-sulfonate and dimercaptosuccinic acid on the mobilization of mercury from tissues of rats pretreated with mercuric chloride, phenylmercury acetate or mercury vapors. *Toxicology* 1989;54:323-33.
- 14 Molin M, Schütz A, Skerfving S, Sällsten G. Mobilized mercury in subjects with varying exposure to elemental mercury vapour. *Int Arch Occup Environ Health* 1991;63:187-92.
- 15 Hickel R, Meier C, Schiele R, Raab W, Petschelt A. Nebenwirkungen von amalgam? Eine interdisziplinäre Studie. *Dtsch Zahn Mund Kieferheilkd Zentralb* 1991;46:542-4.
- 16 Aposhian HV, Bruce DC, Alter W, et al. Urinary mercury after administration of 2,3-dimercaptopropionate-1-sulfonic acid: correlation with dental amalgam score. *FASEB J* 1992;6:2472-6.
- 17 Zander D, Ewers U, Freier I, Blockhaus A. Untersuchungen zur Quecksilberbelastung der Bevölkerung III. Quicksilbermobilisation durch DMPS (Dimaval®) bei Personen mit und ohne Amalgamfüllungen. *Zentralbl Hyg Umweltmed* 1992;192:447-54.
- 18 He FS, Zhou XR, Lin BX, Xiong YP, Chen SY, Zhang SL, Ru JU, Deng MH. Prognosis of mercury poisoning in mercury refinery workers. *Annals of the Academy of Medicine Singapore* 1984;13(suppl):389-93.
- 19 World Health Organisation. *Environmental health criteria 1: Mercury*. Geneva: WHO, 1976.
- 20 Skare I. Microdetermination of mercury in biological samples. Part III: Automated determination of mercury in urine, fish and blood samples. *Analyst* 1972;97:148-55.
- 21 Einarsson Ö, Lindstedt G, Bergström T. A computerized automatic apparatus for determination of mercury in biological samples. *Journal of Automatic Chemistry* 1984;6:74-9.
- 22 SAS Institute Inc. *SAS/STAT Guide for personal computers, version 6 edition*. Cary, NC: SAS Institute Inc, 1987: 675-712.
- 23 Guardabasso V, Munson PJ, Rodbard D. EXPFIT: a program for simultaneous analysis of families of exponential decay curves. *Computer Methods and Programs in Biomedicine* 1988;27:55-63.
- 24 Bailer AJ, Portier CJ. A note on fitting one-compartment models: Non-linear least squares versus linear least squares using transformed data. *J Appl Toxicology* 1990;10:303-6.
- 25 Sällsten G, Barregård L, Schütz A. Decrease in mercury concentration in blood after long term exposure: a kinetic study of chloralkali workers. *Br J Ind Med* 1993;50:814-21.
- 26 Molin M, Bergman B, Marklund SL, Schütz A. Mercury, selenium, and glutathione peroxidase before and after amalgam removal in man. *Acta Odontol Scand* 1990;48:109-22.
- 27 Kosta L, Byrne AR, Zelenko V. Correlation between selenium and mercury in man following exposure to inorganic mercury. *Nature* 1975;254:238-9.
- 28 Hargreaves RJ, Evans JG, Janota I, Magos L, Cavanagh JB. Persistent mercury in nerve cells 16 years after metallic mercury poisoning. *Neuropathol Appl Neurobiol* 1988;14:443-52.
- 29 Nylander M, Weiner J. Mercury and selenium concentrations and their inter-relationships in organs from dental staff and the general population. *Br J Ind Med* 1991;48:729-34.
- 30 Takahata N, Hideo H, Watanabe S, Anso T. Accumulation of mercury in the brains of two autopsy cases with chronic inorganic mercury poisoning. *Folia Psychiatrica et Neurologica Japonica* 1970;24:59-69.
- 31 Aaseth J, Norseth T. Copper. In: Friberg L, Nordberg GF, Vouk V, eds. *Handbook on the toxicology of metals*, 2nd ed. Amsterdam: Elsevier, 1986:233-54.
- 32 Elinder C-G, Zinc. In: Friberg L, Nordberg GF, Vouk K, eds. *Handbook on the toxicology of metals*, 2nd ed. Amsterdam: Elsevier 1986:664-79.
- 33 Gardner MJ, Altman DG. *Statistics with confidence*. London: British Medical Journal, 1989.