Decrease in mercury concentration in blood after long term exposure: a kinetic study of chloralkali workers

Gerd Sällsten, Lars Barregård, Andrejs Schütz

Abstract

The elimination of mercury (Hg) in blood was investigated in 14 chloralkali workers exposed to metallic Hg vapour for 1-24 (median 10) years. Blood and urine samples were collected on several (median eight) occasions during a period of 17-26 days. The initial Hg concentrations were about 80 nmol/l in whole blood (B-Hg) and 17 nmol/mmol creatinine in urine (U-Hg). The decrease in Hg in whole blood, plasma (P) and erythrocytes (Ery) was best characterised by a two compartment model. In a model with a common half life for all subjects, the best fit for B-Hg was obtained with half lives of 3.8 days for a fast phase and 45 days for a slow phase. The half life of the fast phase was shorter for P-Hg than for Ery-Hg, whereas the opposite was the case for the slow phase. The half lives of the slow phases in whole blood and plasma were longer, and the relative fractions of the slow phases were higher (about 50%) after long term exposure than those (about 20%) reported after brief exposure. Slower elimination indicates higher accumulation of Hg in organs with long half lives, and possibly the presence of at least one additional, even slower compartment. The U-Hg fluctuated substantially during the sampling period, and average concentrations decreased only slightly.

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Inhaled mercury (Hg) vapour is absorbed rapidly by the blood and distributed to different organs. The dissolved Hg vapour is oxidised rapidly to

Hg²⁺ partly in the red blood cells and partly in the other tissues. Most of the Hg is then deposited in the kidneys. Urine and faeces are the main elimination routes.^{1,2} Elimination of Hg from blood has been studied in humans after single exposure in experimental studies,^{3,4} after temporary high exposure in industry,⁵ and after removal of dental amalgam.⁶ The elimination of mercury in whole blood (B-Hg) was best characterised by a two compartment model.^{5,6} The half lives reported were about three days for the fast phase and 15-30 days for the slow phase.^{2,5,6} After short term exposure, the fast phase accounts for about 80-90% of the initial B-Hg.^{2,5} In plasma (P) and erythrocytes (Ery) the half lives from one compartment models were 3.5 and 3.1 days respectively after single exposure.⁴ After brief exposure the half lives, from two compartment models for P-Hg and Ery-Hg, were one to three days for the fast phases and 10-20 days for the slow phases.⁵ Elimination from plasma was more rapid than from erythrocytes. Urinary Hg (U-Hg) excretion has been studied after short term⁵ and long term^{7,8} occupational exposure. The half life for elimination of Hg in urine was 40-60 days after short term, high exposure,⁵ as well as after long term, low exposure.⁷ After long term, high exposure it was about 90 days.⁸

To our knowledge, the elimination of Hg from blood after long term occupational exposure has previously only been reported for one single subject.² The present study reports the kinetics in chloralkali workers investigated during a vacation period.

Subjects and methods

Fifteen men from three different chloralkali plants, all exposed to Hg vapour for at least one year, volunteered for multiple consecutive biological sampling during a vacation period. Morning urine and whole blood samples were taken on several (median eight; range four to nine) occasions during a period of 17-26 days. The first blood sample was collected immediately after work on the last working day (day 0), and the first urine sample on the

Department of Occupational Medicine, Sahlgren's University Hospital, S-41266 Gothenburg, Sweden
G Sällsten, L Barregård
Department of Occupational and Environment Medicine, University Hospital, S-22185 Lund, Sweden
A Schütz

Table 1 Previous exposure and background factors in the study group of 14 chloralkali workers exposed to Hg vapour

Subject No	Age (y)	Exposure time (y)	Cumulative dose index (nmol/l* year)	Fish consumption (meals/week)	Smoking	Teeth filled with amalgam (No)
1	28	5	650	1	No	10
2	23	1	40	<1	No	8
3	29	11	920	1	Yes	14
4	21	1	40	1	No	6
5	31	12	2030	>2	Yes	14
6	39	12	1220	1	Yes	14
7	27	9	840	<1	Yes	11
8	42	24	4560	<1	No	15
9	38	20	2560	1	No	10
10	42	14	670	<1	No	18
11	22	2	210	>2	Yes	7
12	60	14	1440	>2	No	6
13	41	5	410	1	Yes	20
14	26	5	220	2	No	8

*Integrating B-Hg as a function of time.

next morning. One person was first sampled on day two and another on day three. In the same period, multiple blood and urine samples were collected from five occupationally unexposed referents.

One worker was excluded because of a clear increase in Ery-Hg (+71 nmol/l) and B-Hg (+30 nmol/l) between days 13 and 18, probably due to eating fish contaminated with methylmercury. The remaining 14 workers were 21 to 60 years of age and had been working in the chloralkali industry for 1–24 (median 10) years. They were all healthy and had low or moderate alcohol consumption. Table 1 shows their age, exposure time, smoking habits, fish consumption, and number of teeth filled with amalgam. The five referents were all healthy and all but one were non-smokers. Their age, alcohol consumption, fish consumption, and number of teeth filled with amalgam were similar to those of the 14 workers.

Blood samples (2 × 10 ml) were collected in Hg free, evacuated heparinised tubes (Venject). Urine was collected in polyethylene bottles (with a small amount of sulphamic acid added) that had been previously washed in detergent RBS 25. The blood samples were collected at the health care units and mailed to the laboratory. One of the blood samples was centrifuged, and plasma and erythrocytes were transferred into acid washed polyethylene tubes. The samples were refrigerated until analysis. Morning urine samples were collected at home and stored in refrigerators, firstly at the health care units and later at the laboratory until analysis.

Mercury was analysed by the cold vapour atomic absorption (CVAAS) technique. Blood, plasma, and erythrocytes were determined on 0.5 g samples. The samples were weighed into sintered aluminium oxide boats, placed in an oxygen gas stream in quartz tubes and gradually heated until red hot. After passing the combustion products through quartz filters at 800–900°C, the mercury vapour was absorbed in potassium permanganate

solution.⁹ Urine samples were wet digested with potassium permanganate-sulphuric acid at room temperature for at least 30 minutes. The Hg was determined after reduction of the permanganate with hydroxylamine hydrochloride and addition of stannous chloride to reduce Hg ions to elemental Hg.^{10,11} The detection limits were 2 nmol/l. Each sample was analysed in duplicate. The precision for different media and concentrations varied between 5% and 10% (coefficient of variation). Accuracy was initially tested in other samples by comparison with radiochemical neutron activation analysis, and found to be acceptable.^{9,12} Quality control with external reference samples (Seronom batch 108, Nycomed, Oslo, Norway and Lanonorm metals number 1 and 2, control blood for metals 1, Behring Institute, Behringwerke AB, Marburg, Germany) and performed together with other series of samples from the same year, showed good accuracy and precision.^{5,9} The results averaged 98% (whole blood) and 101% (urine) of the recommended values of the reference materials. The U-Hg was expressed per mmol creatinine to correct for differences in urinary flow rate. Creatinine was analysed with a modified kinetic Jaffé method.

A cumulative exposure index (table 1) was calculated for each subject from previous B-Hg, determined since 1970. Two workers exposed before 1970 had their B-Hg during the 1960s estimated from their urinary U-Hg at that time.¹³ The index was calculated by integrating B-Hg as a function of exposure time.

In each subject, models with one and two compartments were fitted to the decrease in B-Hg, P-Hg and Ery-Hg, assuming an exponential decrease and minimising the total sum of squares of the deviations from the predicted curve. This was done with the NLIN procedure in the SAS statistical program.¹⁴ For several subjects, the "best" two compartment model resulted in unrealistic inter-

Table 2 Kinetics of B-Hg after long term exposure to Hg vapour

Subject No	Initial B-Hg minus baseline (nmol/l)	One compartment model			Two compartment model					Note
		$T_{1/2}$ (95% CI) (days)	Y_0 (nmol/l)	R^2 (%)	Fast phase $T_{1/2}$ (95% CI) (days)	$Y_0(1)$ (nmol/l)	Slow phase $T_{1/2}$ (95% CI) (days)	$Y_0(2)$ (nmol/l)	R^2 (%)	
1	§	8.4 (5.0-25)	69	99	3.0 (0.1-∞)	69	14 (1.3-∞)	37	99	*
2	§	20 (15-31)	20	100	1.6 (0.6-∞)	36	26 (19-43)	17	100	*
3	55	9.2 (7.0-13)	52	99	4.6 (1.5-∞)	43	∞	13	100	*
4	41	10 (5.9-39)	34	94	1.3 (0.3-∞)	21	27 (5.5-∞)	21	98	*
5	99	15 (11-21)	98	100	7.9	73	∞	25	100	*
6	74	8.8 (7.2-11)	73	99	6.4 (1.3-∞)	64	∞	10	100	*
7	35	5.8 (3.7-13)	39	95	5.8 (3.7-13)	39	—	0	—	—
8	71	14 (9.4-25)	61	98	2.4 (1.0-∞)	34	34 (12-∞)	37	100	—
9	66	17 (12-29)	60	99	5.3 (1.7-∞)	40	∞	26	100	*
10	116	11 (7.1-26)	108	99	0.1	31	17 (14-21)	84	100	*
11	—	7.7 (4.6-24)	79	97	1.9 (0.2-∞)	61	17 (5-∞)	44	99	*
12	57	77 (44-293)	61	100	—	0	77 (44-293)	61	—	—
13	—	23 (13-79)	41	99	—	0	23 (13-79)	41	—	—
14	40	28 (19-51)	40	100	—	0	28 (19-51)	40	—	—
Median		13 (8.8-20)†			3.0 (1.6-5.8)†		28 (23-∞)‡			
Mean		18			—		—			
Model with common half lives		15 (13-18)			3.8 (3.1-5.1)		45 (28-121)			

*Sum of intercepts ($Y_0(1) + Y_0(2)$) or elimination constant ($b > 0$) restricted in the individual models.

†94% confidence interval (binomial distribution).²⁸

‡91% confidence interval (binomial distribution).

§In the first blood sample Hg was only analysed in plasma and erythrocytes.

After subtraction of the estimated baseline level, the following equations were fitted: B-Hg = $Y_0 * e^{-bt}$ (one compartment model) and B-Hg = $Y_0(1) * e^{-b(1)t} + Y_0(2) * e^{-b(2)t}$ (two compartment model), where Y_0 is the intercept on day 0. The half lives ($T_{1/2}$) are derived from $T_{1/2} = \ln 2/b$. R^2 is the fraction of the variance in B-Hg explained by the model. Confidence intervals (95% CIs) are calculated as $\pm 2SE$ (asymptotic standard error).

cepts, and in those cases, restrictions were entered into the models. Also, all 14 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,¹⁵ EXPGRF17 dimensioned for 17 curves instead of a maximum of 12 curves, as in the original PC version. The different models were

compared statistically with the F test for the difference in sums of squares.¹⁵

When calculating the half lives, a baseline value was subtracted from each Hg value. As the follow up time was limited for each subject, we could not use the last values. Therefore, as baselines, we used the following median values found in an occupationally unexposed reference group from one of the

Table 3 Kinetics of P-Hg after long term exposure to Hg vapour

Subject No	Initial P-Hg minus baseline (nmol/l)	One compartment model			Two compartment model					Note
		$T_{1/2}$ (95% CI) (days)	Y_0 (nmol/l)	R^2 (%)	Fast phase $T_{1/2}$ (95% CI) (days)	$Y_0(1)$ (nmol/l)	Slow phase $T_{1/2}$ (95% CI) (days)	$Y_0(2)$ (nmol/l)	R^2 (%)	
1	71	13 (9.8-19)	66	99	0.1	11	15 (9.9-35)	61	100	*
2	41	10 (6.7-23)	36	95	3.5 (1.0-∞)	29	∞	11	98	*
3	67	10 (6.4-23)	58	96	2.9 (1.0-∞)	45	∞	21	99	*
4	36	10 (6.0-30)	32	95	2.7 (0.7-∞)	25	∞	12	98	*
5	105	17 (9.7-59)	103	99	3.2	62	∞	43	100	*
6	115	11 (6.6-35)	92	95	0.1	52	26 (14-69)	63	100	*
7	50	7.9 (6.4-10)	48	99	5.4 (1.4-∞)	43	∞	10	99	*
8	57	16 (8.7-114)	43	93	2.1 (1.1-15)	36	∞	21	99	*
9	44	29 (21-47)	43	99	—	0	29 (21-47)	43	—	—
10	69	30 (15-900)	66	99	0.1	6	37 (2.5-∞)	62	99	*
11	—	14 (12-19)	65	100	—	0	14 (12-19)	65	—	—
12	22	267 (31-∞)	22	97	5.7 (0.1-∞)	2	∞	21	97	*
13	—	12 (7-35)	40	97	4.4 (0.4-∞)	36	∞	13	98	*
14	22	34 (9.4-∞)	19	95	1.5 (0.1-∞)	8	∞	14	97	*
Median		14 (10-29)∞			2.8 (0.1-4.4)‡		—			
Mean		—			—		—			
Model with common half lives		15 (13-18)			2.0 (1.4-3.1)		36 (25-70)			

*Sum of intercepts ($Y_0(1) + Y_0(2)$) or elimination constant ($b > 0$) restricted in the individual models.

†94% confidence interval (binomial distribution).²⁸

‡96% confidence interval (binomial distribution).

Terms are the same as explained in footnotes to table 2.

Table 4 Kinetics of Ery-Hg after long term exposure to Hg vapour

Subject No	Initial Ery-Hg minus baseline (nmol/l)	One compartment model			Two compartment model					Note
		$T_{1/2}$ (95% CI) (days)	Y_0 (nmol/l)	R^2 (%)	Fast phase $T_{1/2}$ (95% CI) (days)	Y_0 (nmol/l)	Slow phase $T_{1/2}$ (95% CI) (days)	$Y_0(2)$ (nmol/l)	R^2 (%)	
1	91	3.7 (3.1-4.4)	89	99	1.6 (0.8-∞)	42	6.0 (3.9-14)	49	100	
2	30	4.5 (2.4-41)	28	83	1.0 (0.1-∞)	22	37 (3.3-∞)	8	91	
3	48	7.9 (4.6-27)	44	93	0.1	11	9.9 (3.5-∞)	37	94	*
4	39	5.6 (2.9-115)	31	86	0.1	26	31 (6.9-∞)	13	98	*
5	89	13 (9.4-19)	88	100	0.1	27	20	59	100	*
6	43	5.8 (4.7-7.8)	43	99	5.8 (4.7-7.8)	43	—	0	—	
7	21	5.8 (3.1-82)	27	87	5.8 (3.1-82)	27	—	0	—	
8	71	11 (7.3-22)	64	96	3.1 (0.6-∞)	34	24 (4.1-∞)	37	97	
9	79	17 (13-27)	72	99	5.4 (1.9-∞)	49	∞	31	100	*
10	124	7.0 (4.6-15)	125	99	—	0	7.0 (4.6-15)	125	—	
11	—	3.8 (2.9-5.3)	111	99	2.5 (1.2-∞)	114	23 (14-69)	14	100	*
12	93	30 (17-128)	106	98	—	0	30 (17-128)	106	—	
13	—	25 (13-307)	37	98	—	0	25 (13-307)	37	—	
14	48	27 (14-447)	55	99	—	0	27 (14-447)	55	—	
Median		7.5 (5.6-17) [†]			2.1 (0.1-5.8) [‡]		25 (9.9-31) [§]			
Mean		12			—		—			
Model with common half lives		14 (11-17)			3.6 (2.7-5.3)		16 (13-23)			

*Sum of intercepts ($Y_0(1) + Y_0(2)$ or elimination constant ($b > 0$) restricted in the individual models.

[†]94% confidence interval (binomial distribution).²⁸

[‡]91% confidence interval (binomial distribution).

[§]96% confidence interval (binomial distribution).

Terms are the same as explained in footnotes to table 2.

plants: B-Hg 15 nmol/l ($n = 41$), P-Hg 7.2 nmol/l ($n = 44$), and Ery-Hg 28 nmol/l ($n = 35$). These values were lower or in the same range as the last values obtained for the subjects in the present study.

For U-Hg we could not expect a substantial decrease during a vacation period and we therefore only compared the starting values (mean of the first two samples) with the last (mean of two) values obtained, by Student's t test for paired observations.

Results

During the vacation period, B-Hg, P-Hg, and Ery-Hg decreased in all 14 workers. No declining trend could be seen in the reference group. The coefficient of variation for B-Hg, P-Hg, and Ery-Hg between days was high in these five subjects (median 17% (range 7%-33%)). Their median concentrations for B-Hg, P-Hg, and Ery-Hg were 19, 13, and 25 nmol/l respectively.

When a one compartment model for each subject was fitted to the B-Hg decay, the median half life was 13 days (table 2). From a model with a common half life, the point estimate was 15 days. For most of the subjects, a two compartment model fitted the data better, and the median point estimates for a fast and a slow phase were 3.0 and 28 days respectively. With common half lives the estimates were 3.8 and 45 days. The fast phase contributed 56% (median) to the sum of the Y axis intercepts.

For the decay in P-Hg, a one compartment model with individual or common half lives resulted in similar estimates for the half life, 14 and 15 days respectively (table 3). A two compartment model fitted the data better, but the individual half life of the slow phase could not be estimated for most of the subjects due to few observations and a limited follow up time. With common half lives, the point estimates for a fast and a slow phase were 2.0 and 36 days, with the fast phase constituting 46% (median) of the sum of intercepts.

When a one compartment model was fitted to the Ery-Hg decay, the model with individual half lives resulted in a median point estimate for the half life of 7.5 days whereas the model with a common half life showed 14 days (table 4). In a two compartment model with individual half lives the median point estimates for a fast and a slow phase were 2.1 and 25 days respectively. With common half lives, the estimates were 3.6 and 16 days, with the fast phase constituting 57% (median) of the sum of intercepts.

In general, the estimates from the individual two compartment models were uncertain, with wide confidence intervals, owing to the few data points and the short follow up time. The model with common half lives resulted in narrower limits but gave unrealistic intercepts in some cases. In all media, the two compartment models with common half lives were significantly better ($p < 0.001$) than the corresponding one compartment models. The restricted and non-restricted two compartment

Figure 1 Elimination kinetics of B-Hg, P-Hg, and Ery-Hg in 14 men after long term exposure to Hg vapour. The diagram shows the point estimates for two compartment models with common half lives.

models could not be statistically compared.

The estimates of the half lives in the two compartment models with common half lives showed a faster decay of the slow phase for Ery-Hg than for B-Hg or P-Hg, but a faster decay of the fast phase for plasma than in whole blood or erythrocytes (fig 1). There was a tendency towards

longer half lives of the slow phases in B-Hg among subjects with higher cumulative doses or longer exposure times. In plasma or erythrocytes, no such relations were found.

During the vacation period, there was no significant decrease in U-Hg in the 14 workers (fig 2). The median U-Hg concentrations were 17 nmol/mmol creatinine at the beginning and 16 nmol/mmol creatinine after 16 days (median). In seven workers, the values were higher, and in seven workers lower at the end compared with the starting values. The median U-Hg value in the five occupationally unexposed men was 1.2 nmol/mmol creatinine (range 1.0–2.1). The average intraindividual variation of U-Hg excretion among the 14 workers was 15% (coefficient of variation for creatinine corrected morning samples within subjects, range 6–34%). A similar result was obtained for the five referents namely, 14% (range 7%–22%).

Discussion

VALIDITY ASPECTS

Hg determinations

The analyses of Hg in whole blood, plasma, erythrocytes, and urine were made in a laboratory with extensive experience in this field, and quality control indicated good accuracy. All samples were stored in refrigerators until analysis. For blood samples, an experiment in our own laboratory showed no loss of Hg when stored at room temperature or in a refrigerator for several months. Storage of blood samples in a refrigerator is also recommended by the World Health Organisation.¹

Figure 2 U-Hg in 14 chloralkali workers during a vacation period. The coefficients of variation for creatinine corrected morning samples within subjects were left hand graph ∇ 20%, $\circ$ 17%, $\square$ 15%, $\blacktriangledown$ 14%, $\blacksquare$ 12%, $\triangle$ 8.4%, $\bullet$ 22%; right hand graph ∇ 18%, $\circ$ 14%, $\square$ 14%, $\blacktriangledown$ 34%, $\blacksquare$ 7.5%, $\triangle$ 5.8%, $\bullet$ 15%.

In urine, bacterial growth can cause evaporation of metallic Hg¹⁶ but this was prevented by adding sulphamic acid in the urine samples. Addition of sulphamic acid produces stable urine samples for at least one month even at room temperature.¹⁰ In urine samples stored at low temperatures, Hg is concentrated in the precipitate, and the urine samples were therefore homogenised by vigorous shaking before analysis. In our experience, no loss of Hg occurs in urine samples refrigerated for several months. The Hg concentrations found in our reference group were similar to normal reported values,¹⁷ and similar to results found among other unexposed persons from the same region (see methods). In conclusion, we consider the Hg determinations to be accurate, although we did not use external reference material in the same run at the time of this investigation.

In a previous study of kinetics of Hg after brief exposure,⁵ a discrepancy was found between the measured B-Hg and the concentration calculated from P-Hg and Ery-Hg in samples collected immediately after the end of exposure (day 0), but not in samples from subsequent days. One possible explanation was loss of Hg vapour during the process of centrifugation and pipetting plasma and erythrocytes. In this study, B-Hg, P-Hg, and Ery-Hg in the group exposed to Hg were consistent. This is in agreement with results showing that the fraction of Hg vapour in the blood of exposed workers is very small (<0.2% or not detectable)¹⁸ and thus the losses during separation ought to be negligible. Differences in exposure shortly before sampling, and the time intervals between sampling and sample separation might explain the different results.

Influence of background factors on B-Hg

In subjects occupationally exposed to Hg vapour, most of the Hg in blood is inorganic Hg, compared with about 50% in occupationally unexposed subjects from Nordic countries.¹⁹ The general population is primarily exposed to Hg through the diet and dental amalgam.¹ A correlation between B-Hg or U-Hg on the one hand, and the amount of amalgam in the teeth on the other, has been found by several authors.^{6, 20-23} After dental treatment of amalgam restorations, there was an increase in B-Hg.^{6, 20} No dental treatment was performed during the vacation period or the six weeks preceding it.

Consumption of fish is the dominant source of human exposure to methylmercury, and affects B-Hg, Ery-Hg, and P-Hg.¹⁷ The strongest influence is seen on Ery-Hg, as methylmercury in blood is mainly distributed to the erythrocytes.¹ After a meal containing contaminated fish, B-Hg rises sharply.⁶ If the consumption of fish is interrupted, B-Hg declines, the half-life of methylmercury being about 50 days.²⁵ In our study, one of the workers was

excluded because of a high increase in Ery-Hg and B-Hg during the vacation period, probably as a result of eating contaminated fish. An influence from dietary habits, primarily on Ery-Hg, cannot be ruled out among the other subjects, leading to somewhat increased or decreased values depending on their variation in fish consumption. Most of the workers, however, consumed only salt water fish, which are much less contaminated by methylmercury than are fresh water fish in Sweden. Identification and measurement of different forms of Hg instead of analysis of total Hg would have been preferable, but such methods were not in use at the time of the study.

Estimates of half lives

The baseline values used for calculation of the half lives were the median values found in an occupationally unexposed reference group from one of the plants. Individual baselines would have been preferable, but were impossible to obtain, as the follow up time was limited. The estimation of the correct baselines may be difficult, however, because of dietary influences⁶ and the relatively high variation between days, of about 10%⁶ or 17% (in our five referents). The baseline concentrations used were lower or in the same range as the last values we obtained. For some subjects, their true baselines may be lower, and in those cases our estimated elimination rates, especially for the slow phase, will be too rapid.

In our calculations we assumed an exponential decrease and fitted the values to one and two compartment models. Compartments with longer half lives probably exist.¹ The follow up time, however, was too short to detect other compartments. Whether estimates of half lives calculated from individual data or models with common half lives best represent the average kinetics in a group of subjects depends on the magnitude of the interindividual variation. Present knowledge is scant, but after brief exposure, there was no substantial variation between subjects in the elimination of Hg from whole blood.⁵

KINETICS OF HG IN BLOOD

The elimination of Hg in whole blood was best characterised by a two compartment model. Our half life for the fast phase, three to four days, is in good agreement with findings after brief occupational exposure,⁵ amalgam removal,⁶ and single low level inhalation of radioactive Hg.²⁴ The half life for the slow phase, about four to six weeks, was similar to results after amalgam removal⁶ and in one woman after cessation of occupational exposure.² After brief occupational exposure, the half life of the slow phase was shorter,⁵ two to three weeks. Figure 3 shows this comparison.

Figure 3 Elimination kinetics of B-Hg after long term (—) and brief (---) exposure to Hg vapour. The diagram shows the point estimates for two compartment models with common half lives.

In workers exposed long term, the slow phase constituted 44% of the sum of intercepts, as compared with 20% after brief exposure.⁵ This probably reflects higher accumulation of Hg in tissues with a slow Hg turnover. Not only was the fraction of the slow phase higher, but the half-life was longer in workers exposed long term. One possible explanation may be that the elimination of Hg from blood is in reality triphasic or multiphasic, and the slow phase in workers exposed long term is influenced by Hg pools in organs with the slowest elimination rates. This is supported by the tendency towards longer half lives of the slow phase seen in subjects with higher doses or longer exposure times.

The elimination of Hg from plasma and erythrocytes was also best characterised by two compartment models. The half life estimates for the fast and slow phases of Ery-Hg are similar to findings after brief occupational exposure.⁵ A similar estimate of the fast phase was also found after inhalation of radioactive Hg⁴. As found after brief exposure, the fast phase in plasma seems to be shorter than that in erythrocytes.⁵ The fast phase probably reflects the distribution of Hg to tissues, and Hg²⁺ in plasma might be more easily transferred than Hg²⁺ in erythrocytes. In plasma, the half life of the slow phase was longer after long term exposure (point estimate 36 days), compared with brief exposure, (11 days).⁵ As mentioned earlier, this could be explained by higher concentrations in organs with slow elimination rates. A difference between short term and long term exposure was seen only in plasma, where the slow phase

reflects the sum of changes in influx of Hg from organs and the redistribution from plasma to organs, as well as the excretion from the kidneys into urine. Plasma Hg²⁺ concentration mainly derives from oxidation of Hg vapour in tissues other than erythrocytes.²⁶ In erythrocytes, the half lives were similar in long term and short term exposed workers. If reduction of Hg²⁺ to Hg vapour is of minor importance, the half lives for Hg in erythrocytes should not be affected by the amount of Hg in tissues.

The elimination of Hg from whole blood is a sum of the elimination in plasma and erythrocytes. As the fraction of erythrocytes in blood is about 45%, the elimination curve for whole blood should be located between the curves for plasma and erythrocytes. This is not entirely true for the point estimates in fig 1. If confidence intervals are taken into consideration, there is, however, no significant discrepancy between the elimination in whole blood and the sum of elimination in plasma and erythrocytes.

MERCURY IN URINE

There was no significant decrease in U-Hg in the 14 workers, and in seven of them the values were even higher after a vacation. One explanation may be that the exposure in the chloralkali plant fluctuates and that some of the workers had peak exposure during the last weeks of work. After temporary exposure, the peak in U-Hg was delayed by several weeks.⁵ The elimination rates of U-Hg reported by others are relatively slow; about six to eight weeks after temporary high exposure⁵ as well as after long term low exposure,⁷ and about 13 weeks for long term workers with high exposure.⁸

The intraindividual variation in U-Hg was about 15%, both in exposed workers and referents. Similar results have been reported in other studies with morning samples corrected for specific gravity or creatinine.^{5,27}

CONSEQUENCES FOR BIOLOGICAL MONITORING

In Sweden (and in most countries) there are no governmental regulations on biological limits for Hg. The chloralkali plants, however, have their own control programme including the determination of U-Hg in morning urine at least twice a year and B-Hg once a year. If workers are suspected of having been exposed to an occasional peak of mercury vapour, this can be checked by an immediate blood sample. Workers are removed from exposure if U-Hg exceeds 60 µg/g (34 nmol/mmol) creatinine or B-Hg exceeds 150 nmol/l. The results from this study show that a decrease to half the B-Hg concentration (subtracting the baseline level) will take an average of nine days for workers exposed long term. A reduction to 25% will take 38 days,

compared with only nine days after short term exposure.⁵ For B-Hg, the possible influence from consumption of fish contaminated with methylmercury must be taken into consideration. The difference between long term and short term exposed workers is also seen in the elimination of U-Hg,^{5,7,8} where a reduction to 25% will take about six months in long term exposed workers, as compared with three to four months after brief exposure. The relatively high intraindividual variation in U-Hg (15% in the present study) makes it necessary to use the results of several measurements from one subject before a decision about removal from or return to exposure can be made.

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Requests for reprints to: Gerd Sällsten, Department of Occupational Medicine, St Sigfridsgatan 85, S-41266 Gothenburg, Sweden.

- 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 Hursh JB, Clarkson TW, Cherian MG, Vostal JV, Mallie RV. Clearance of mercury (¹⁹⁷Hg, ²⁰³Hg) vapor inhaled by human subjects. *Arch Environ Health* 1976;31:302-9.
- 4 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.
- 5 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.
- 6 Snapp KR, Boyer DB, Peterson LC, Svare CW. The contribution of dental amalgam to mercury in blood. *J Dent Res* 1989;68:780-5.
- 7 Skare I, Engqvist A. Urinary mercury clearance of dental personnel after a long term intermission in occupational exposure. *Swed Dent J* 1990;14:255-9.
- 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 Svensson BG, Björnham Å, Schütz A, Lettevall U, Nilsson A, Skerfving S. Acid deposition and human exposure to toxic metals. *Sci Total Environ* 1987;67:101-15.
- 10 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.
- 11 Einarsson O, Lindstedt G, Bergström T. A computerized automatic apparatus for determination of mercury in biological samples. *J Automatic Chemistry* 1984;6:74-9.
- 12 Barregård L, Thomassen Y, Schütz A, Marklund S. Levels of selenium and antioxidative enzymes following occupational exposure to inorganic mercury. *Sci Total Environ* 1990;99:37-47.
- 13 Roels H, Abdeladim S, Ceulemans E, Lauwerys R. Relationships between the concentrations of mercury in air and in blood or urine in workers exposed to mercury vapour. *Ann Occup Hyg* 1987;31:135-45.
- 14 SAS Institute Inc. *SAS/STAT Guide for personal computers, version 6 edition*. Cary, NC: SAS Institute Inc., 1987:675-712.
- 15 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.
- 16 World Health Organisation. *Environmental health criteria 1: mercury*. Geneva: WHO, 1976.
- 17 Brune D, Nordberg GF, Vesterberg O, Gerhardsson L, Wester PO. A review of normal concentrations of mercury in human blood. *Sci Total Environ* 1991;100:235-82.
- 18 Yoshida M. Relation of mercury exposure to elemental mercury levels in the urine and blood. *Scand J Work Environ Health* 1985;11:33-7.
- 19 Aitio A, Valkonen S, Kivistö H, Yrjänheikki E. Effect of occupational mercury exposure on plasma lysosomal hydrolases. *Int Arch Environ Health* 1983;53:139-47.
- 20 Molin M, Bergman B, Marklund SL, Schütz A, Skerfving S. Mercury, selenium and glutathione peroxidase before and after amalgam removal in man. *Acta Odontol Scand* 1990;48:189-202.
- 21 Akesson I, Schütz A, Attewell R, Skerfving S, Glantz P-O. Status of mercury and selenium in dental personnel: Impact of amalgam work and own fillings. *Arch Environ Health* 1991;46:102-9.
- 22 Olstad ML, Holland RJ, Wandel N, Hensten Pettersen A. Correlation between amalgam restorations and mercury concentrations in urine. *J Dent Res* 1987;66:1179-82.
- 23 Langworth S., Elinder C-G., Göthe C-J, Vesterberg O. Biological monitoring of environmental and occupational exposure to mercury. *Int Arch Occup Environ Health* 1991;63:161-7.
- 24 Kershaw TG, Dhahir PH, Clarkson TW. The relationship between blood levels and dose of methylmercury in man. *Arch Environ Health* 1980;35:28-36.
- 25 World Health Organisation. *Environmental health criteria 101. methylmercury*. Geneva: WHO, 1990.
- 26 Hursh JB, Greenwood MR, Clarkson TW, Allen J, Demuth S. The effect of ethanol on the fate of mercury vapor inhaled by man. *J Pharmacol Exp Ther* 1980;214:520-7.
- 27 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.
- 28 Gardner MJ, Altman DG. *Statistics with confidence*. London: British Medical Journal, 1989.

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