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Effects of occupational exposure to mercury vapour on the central nervous system

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Abstract

Possible effects of mercury on the central nervous system (CNS) were examined in a group of chloralkali workers exposed to mercury (n = 89) and compared with a control group (n = 75), by registration of subjective symptoms, personality changes, forearm tremor, and performance on six computerised psychometric tests in the two groups. The groups were similar in age, education, verbal comprehension, and work tasks. In the chloralkali group, median blood mercury concentration (B-Hg) was 55 nmol/l, serum mercury concentration (S-Hg) 45 nmol/l, and urine mercury concentration (U-Hg) 14·3 nmol/mmol creatinine (25·4 μg/g creatinine). Corresponding concentrations in the control group were 15 nmol/l, 4 nmol/l, and 1·1 nmol/mmol creatinine (1·9 μg/g creatinine) respectively. The number of self reported symptoms, the scores for tiredness and confusion in the profile of mood states (POMS), and the degree of neuroticism in the Eysenck personality inventory (EPI), were significantly higher in the mercury exposed group compared with the controls. Performance on the psychometric tests and tremor frequency spectra did not differ significantly between the two groups. Dose-response calculations showed weak but statistically significant relations between symptom prevalence and current mercury concentrations in both blood and urine. The performance on three of the psychometric tests was negatively correlated with earlier peak exposures. The findings indicate a slight mercury induced effect on the CNS among the chloralkali workers.

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The central nervous system (CNS) is the critical organ for exposure to mercury (Hg) vapour[1] and occupational exposure exceeding 100 μg Hg/m^3 air may cause clinical symptoms such as fatigue, anxiety, shyness, insomnia, loss of appetite, weight loss, and tremor.[1 2] Studies of workers with low exposure have shown both increased frequency of symptoms and disturbances in various psychological tests related to the degree of exposure to mercury.[3–5] The studies are, however, difficult to compare, because of discrepancies in study design (for example, selection of exposure indicators, test types, etc). Thus a safe threshold, below which effects on the CNS can be excluded, has not yet been established. In 1980, the World Health Organisation Study Group recommended an exposure limit of 25 μg Hg/m^3 air (time weighted average, TWA) for long term occupational exposure to mercury vapour, and a biological threshold concentration of 50 μg Hg/g creatinine in urine.[6]

In Sweden, the exposure limit (TWA) for mercury vapour is 50 μg Hg/m^3 air. The average exposure in the Swedish chloralkali industry has decreased considerably during the past decades[7] and is today about 25 μg Hg/m^3 air. Cases of chronic mercury poisoning are rare. Despite this, there has been debate concerning possible effects on the CNS of long term, low exposure to inorganic mercury, and the exposure limit (50 μg/m^3) has been questioned. The purpose of the present study was to examine health effects of long term, low level exposure to mercury vapour. We describe a survey of possible effects on the CNS of mercury exposure among Swedish chloralkali workers, examined by registration of subjective symptoms, personality changes, forearm tremor, and performance on psychometric tests. Renal and immunological effects of the workers' exposure to mercury were described in an earlier publication.[8]

Material and methods

SUBJECTS

A group of 96 chloralkali workers exposed to mercury and from five plants located in three different geographic regions in Sweden (the west coast, the central region, and the east coast) and a control group of 80 industrial workers from two chemical industries, from a paper factory, and from a saw mill located in the same regions were requested to participate in the study on a voluntary basis.

As the major objective of the study was to detect possible health effects of exposure to mercury, chloralkali workers with repeatedly raised blood mercury concentrations (>75 nmol/l) on routine tests during the past three years were selected together with workers judged to have high current exposure to mercury. Only workers with a minimum of one year of employment at the plants were included. Workers from nearby industries as similar as possible in age, educational level, and type of work were selected as controls. Criteria for exclusion from the study were exposure to other heavy metals (for example, lead, cadmium, manganese) or organic solvents, chronic neurological or renal disease, and excessive alcohol intake. Selection and rejection of subjects were based on the judgement of the company physicians and one of us (SL).

Due to sick leave that was not related to exposure to mercury (four cases) and to unwillingness to participate (three cases), the final mercury exposed group included 89 workers. Their duration of exposure varied from one to 45 years (mean 13·5 (SD 8·7) years). Because of sick leave (two cases), unwillingness to participate (two cases), and suspected previous exposure to mercury (one case), the final control group numbered 75 workers. There were 25 shift workers in the mercury exposed group and 27 in the control group. Table 1 presents the data concerning the workers age, education, verbal comprehension, alcohol consumption, and smoking.

STUDY DESIGN AND METHODS

A cross sectional study was performed during the period 1985–6. All examinations were carried out at the factories during ordinary work days. About eight persons were examined each day. All subjects underwent a clinical examination by a physician (SL), including an interview that focused on history of exposure, previous health state, and current symptoms.

Special attention was paid to previous neurological diseases including concussion of the brain. Data on smoking (smoker or non-smoker), alcohol intake (average weekly intake of beer, wine, and spirits) and fish consumption (number of meals per week and type of fish) were registered by means of a questionnaire and then checked at the interview. The current use of medicines was also registered. Odontological state was recorded by a dentist. The total number of amalgam fillings and the number of amalgam surfaces (each tooth was taken to constitute zero to five surfaces covered with amalgam) were registered. The clinical examination also included collection of venous blood samples for mercury analyses.

Immediately after clinical examination the subjects were instructed to complete questionnaires concerning subjective symptoms, mood state, and personality. A test of verbal comprehension (synonyms) was included to assess the premorbid intelligence of the workers.[9] This was followed by registration of forearm tremor, and finally a computer administered psychometric test in the presence of a psychologist (OA).

REGISTRATION OF SYMPTOMS, MOOD STATE, AND PERSONALITY

As well as the interview, three self administered questionnaires: (1) questionnaire 16 (Q16), (2) profile of mood state (POMS), and (3) Eysenck personality inventory (EPI), were used to survey the prevalence of subjective symptoms, current mood state, and personality changes. Questionnaire Q16 is a symptom questionnaire developed as a screening instrument for symptoms among workers exposed to solvents; it has been used in many epidemiological studies.[10] A higher proportion of positive answers in Q16 has been related to decreased psychometric test performance in groups exposed to lead[11] and organic solvents.[10 12]

The mood state questionnaire was based on the profile of mood states described by McNair *et al*,[13] and was adapted from a computer administered mood questionnaire.[14] The 25 items were translated into Swedish by one of us (OA), and were used to measure the degree of tiredness, depression, anger, tension, and confusion.

The Eysenck personality inventory was used to evaluate the grade of neuroticism and extroversion or introversion.[15] This questionnaire is widely used, and has been validated on groups exposed to mercury vapour.[16]

Table 1 Background characteristics of the mercury exposed and control workers

	Exposed (n=89)		*Controls (n=75)*	
	Median	*Range*	*Median*	*Range*
Age (y)	42	22–64	43	21–64
Education (y)	8	4–13	8	6–14
Synonyms (score)	21	1–29	19	0–28
Alcohol (cl/week)	10	0–100	10	0–75
Fish (meals/week)	1	0–3	1	0–3
Amalgam (surfaces)	21	0–46	28	0–54
Smoking (frequency)	44%		40%	

PSYCHOMETRIC TEST BATTERY

Psychomotor performance, attention, and short term memory were tested using six computerised tests, which were selected and adapted from the neurobehavioural evaluation system.[14 17] A personal computer equipped with a joystick and a special button panel was used. All test sessions were performed in a quiet room under guidance of the same test leader (OA). The test conditions were standardised as much as possible. Exposed subjects and controls were tested in a randomised order, and could not be identified by the test leader. In all tests the first trial was a practice run. The six tests are:

(1) *Hand-eye coordination (HEC)*—This is a visual motor coordination test executed with a joystick. The task was to move a cursor as close as possible to a curved line on the screen. The average deviation from the line (mean absolute error based on a graphic measure) during five tests was used as test parameter.

(2) *Finger tapping*—Motor speed function was tested by finger tapping with (a) dominant hand, (b) non-dominant hand, and (c) alternating hands. The subjects were instructed to tap a button with the index finger as fast as possible for 10 seconds. The average number of taps during five trials for each condition was used as test parameter.

(3) *Simple reaction time*—In this attention test the subjects were required to press a button with the index finger of the preferred hand as quickly as possible when a symbol (a large "0") appeared on the display. Twelve stimuli were presented per minute with randomised time intervals between 2·5 and five seconds. The average reaction time (ms) and standard deviation (SD) during six minutes were calculated and used as test parameters.

(4) *Symbol-digit*—In this test of perceptual speed the task was to combine symbols with corresponding digits presented in random order in a row. The key to this coding was given by a row with paired symbols and digits from one to nine. Each trial consisted of nine pairs of symbols and digits and a total of five trials were presented. The average answering time (s) was used as test parameter.

(5) *Digit span*—This is a traditional test of short term memory capacity. Series from three to nine digits were presented on the screen and the task was to reproduce the series on the key board. Depending on the correctness of the answer, the number of digits in the next series either increased or decreased. Five trials were performed, and each trial started with a series of three digits and was terminated after five incorrect answers. The average maximum level (longest digit span) in the five trials was used as test parameter.

(6) *The Sternberg task*—This is another short term memory test. A set of two, three, or four randomly selected digits was presented on the display and the test subject was asked to remember this set. A digit was then displayed on the screen and the subject was ordered to respond with a yes button if the digit was included in the previous set (positive), or with a no button if the digit was not included (negative). Each set of digits was tested twice and in total 12 positive and 12 negative presentations were made for each condition. The regression coefficients for positive and negative answers were calculated according to Sternberg's theory of processing time.[18]

REGISTRATION OF FOREARM TREMOR

The frequency spectrum of the physiological forearm tremor was investigated with an accelerometer using the technique described by Fawer *et al*.[19] The subject was seated with the right elbow resting on the arm of the chair and with a 90° elbow angle, the forearm unsupported and the hand supine. An accelerometer (Brüel and Kjaer 4384, weight 10 g) was tightly fixed on the dorsum of the wrist with a cuff. The electrical signals were amplified (Brüel and Kjaer 2626) and recorded on an FM tape recorder (Tandberg 100). Measurements were carried out first without load during 90 seconds, and then with a load of 1000 g attached to the hand for 90 seconds. The signals were continuously controlled on an oscilloscope. Tremor spectra were analysed with a spectrum analyser (Brüel and Kjaer 2032). Two peak frequencies and corresponding accelerations were registered in each spectrum. The middle 60 second periods were used for the spectra analyses.

EXPOSURE INDICATORS

The exposure indicators used in the chloralkali group were: (1) current concentration of mercury in whole blood (B-Hg), serum (S-Hg), and urine (U-Hg); (2) average B-Hg during the past five years (samples collected at each factory and analysed at the same laboratory as the current samples); (3) duration of employment (number of years worked at the chloralkali plant); (4) intensity of exposure (based on the subjects' type of work, their exposure to mercury was graded as low, medium, or high, as judged by one of the researchers together with the company physicians); (5) peak exposures (relative frequency of B-Hg values $\geqslant$ 150 nmol/l during the past five years). The relative frequency was used as a control blood sample was always requested for subjects with B-Hg above 150 nmol/l at the routine controls. Subjects with B-Hg persistently above 150 nmol/l were suspended from mercury exposed work for two or three weeks and a new blood sample was taken after this period.

In the control group, current concentrations of mercury in whole blood, serum, and urine were used as measures of current exposure to mercury. In both groups, fish consumption and amalgam burden were used as indicators of background exposure to methylmercury and inorganic mercury respectively.

Table 2 Current B-Hg, S-Hg, and U-Hg among chloralkali workers and controls

	Exposed (n=89)		Controls (n=75)	
	Median	Range	Median	Range
B-Hg (nmol/l)	55	15 –299	15	1–65
S-Hg (nmol/l)	45	1 –255	4	1–25
U-Hg (nmol/mmol creatinine)	14·3	0·3– 46·9	1·1	0– 4·3

Samples for B-Hg analyses were collected in metal free, heparinised, Venoject tubes (Terumo Europe NV, Leuven, Belgium); samples for S-Hg analyses were collected in metal free Venoject tubes and centrifuged to separate the blood cells. Morning urine samples were collected at home by each subject in 250 ml acid washed, polyethylene bottles and immediately delivered to the company's health care units. The B-Hg, S-Hg, and U-Hg were analysed in the laboratory of the Division of Medical Chemistry at the Swedish National Institute of Occupational Health. A version of the cold vapour atomic absorption spectrophotometry (CVAAS) technique described by Einarson *et al*[20] was used. The accuracy of the mercury analyses had earlier been tested and found to be comparable with that obtained in other laboratories using CVAAS and neutron activation analyses (NAA). Standard blood and urine samples with known concentrations of mercury were analysed in every analytical series. For details relating to quality control of the mercury analyses see Langworth *et al*.[21] The U-Hg was adjusted for creatinine excretion measured with Jaffe's method using picric acid.

STATISTICAL ANALYSIS

Background data, clinical parameters, test parameters (from questionnaires, psychometric tests, and tremor registrations), and mercury concentrations in the biological samples were compared between the exposed and the control groups with Student's *t* test, Mann-Whitney's U test, or the χ^2 test (smoking). Two sided p values are given throughout.

In both groups dose-effect relations were studied using Pearson's correlation coefficient, Spearman's rank correlation coefficient (for skewed parameters), and multiple regression. The influence of background factors such as age, smoking, and alcohol consumption was tested in both groups.

The 90th percentiles of the test parameters in the control group were regarded as upper normal values, and values above these among the exposed subjects were considered abnormal. The prevalence of abnormal values of test parameters in the chloralkali group was then related to the exposure parameters mentioned previously and to three levels of current U-Hg: (a) low (<10 nmol Hg/mmol creatinine); (b) middle (10–25 nmol Hg/mmol creatinine); and (c) high (> 25 nmol Hg/mmol creatinine). The prevalence of abnormal test parameters in the subgroups was then compared by χ^2 test or with Fisher's exact test. Minitab data analyses software, release 7.2, Minitab Inc, USA, were used for all analyses except Fisher's test.

Results

We found no significant differences between the two groups for age, years of education, performance on the verbal test (synonyms), smoking, alcohol consumption (cl of liquor per week), or fish intake (table 1). The average number of amalgam surfaces was slightly higher in the control group (table 1), but the group difference was not statistically significant (p = 0·09).

The interviews showed that 14 chloralkali workers and 10 controls had experienced earlier mild concussion of the brain. Eight chloralkali workers and seven controls were on regular medication because of hypertension. Two chloralkali workers and one control worker took tablets for diabetes. One chloralkali worker was taking a neuroleptic drug because of sleep disturbances and anxiety. None of the subjects used tranquillisers regularly.

The physical examination showed that 17 chloralkali workers and 13 controls had slight finger tremor (17 of 89 *v* 13 of 75, non-significant). Five chloralkali workers and three controls had slightly impaired tactile sensibility in feet or hands. There were no notable group differences in either systolic or diastolic blood pressure.

Table 2 presents results for current B-Hg, S-Hg, and U-Hg for the two groups. Table 3 presents the figures for the other indicators of exposure used in the chloralkali group. Mercury concentrations in the biological media were significantly higher in the

Table 3 Characteristics of some of the exposure indicators used in the chloralkali group

	No	Mean (SD)	Median	Range
Duration (y)	89	13·5 (8·7)	12	1– 45
B-Hg1 (nmol/l)	89	79 (34)	75	25–176
B-Hg5 (nmol/l)	65	81 (37)	77	28–182
B-Hg peaks (%)	89	24 (24)	20	0– 96

Duration = number of years worked at the plant, B-Hg1 = mean B-Hg during the past year, B-Hg5 = mean B-Hg during the past five years, B-Hg peaks = frequency of B-Hg peaks ⩾ 150 nmol/l during the past five years.

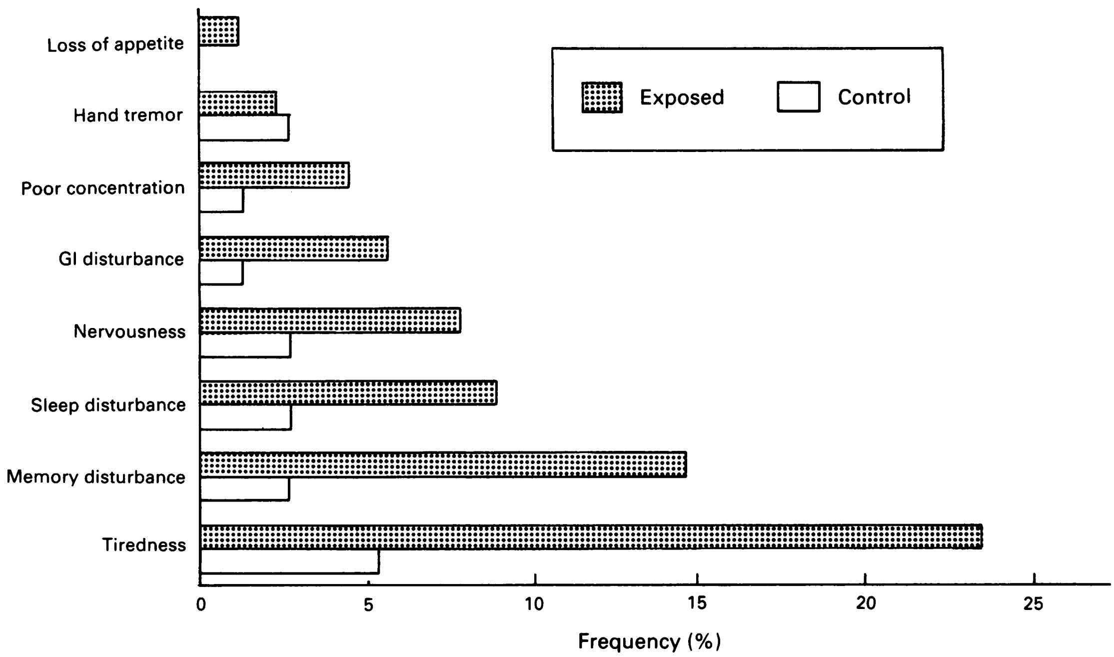


Figure 1 Symptom frequency in exposed and control groups.

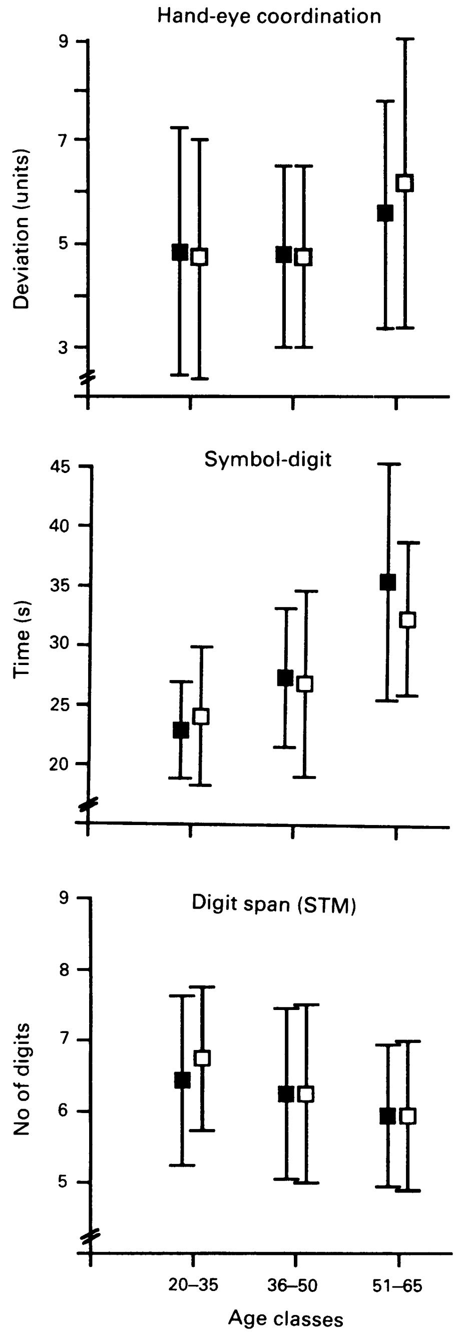
mercury exposed group than in the control group. The concentrations were significantly related to estimated intensity of exposure but not to duration of employment. In the control group the strongest predictor for B-Hg and S-Hg was fish consumption, whereas the number of amalgam surfaces was the best predictor for U-Hg (see Langworth *et al*[21]).

The number of symptoms reported at interview was significantly higher in the mercury exposed group compared with the control group ($p < 0·001$). Figure 1 shows the frequency of the eight most reported symptoms (relevant to effects of mercury on the CNS) in the two study groups. All symptoms except hand tremor were more frequent in the exposed group, and statistically significant higher frequencies were seen for tiredness ($p = 0·002$) and memory disturbance ($p = 0·013$). Within the mercury exposed group there were no significant differences in frequency of symptoms between day time workers and shift workers. Dose-effect calculations showed weak but statistically significant relations between the total number of symptoms and current B-Hg ($r = 0·25$, $p = 0·02$), current U-Hg/creatinine ($r = 0·24$, $p = 0·04$), average B-Hg during the past year ($r = 0·32$, $p = 0·003$), and average B-Hg during the past five years ($r = 0·28$, $p = 0·02$). Furthermore, the frequency of all symptoms except hand tremor and loss of appetite was higher in the subgroup with estimated high exposure to mercury than in the subgroup with estimated low exposure.

Table 4 Questionnaire scores in the chloralkali and control groups

	Exposed group		*Control group*		*p-Value (two-sided)*
	Mean	*SD*	*Mean*	*SD*	
Q16 (n = 89)	3·03	2·85	1·63	1·84	0·0002
POMS (n = 88)*					
Tiredness	2·70	0·88	2·40	0·75	0·018
Confusion	2·40	0·62	2·18	0·55	0·045
Depression	1·62	0·52	1·64	0·61	0·82
Anger	1·60	0·59	1·50	0·58	0·30
Tension	2·11	0·80	2·01	0·80	0·44
EPI-N (n = 87)†	6·55	3·88	4·99	3·42	0·007

Two sample *t* test was used for group comparisons.
*One subject and †two subjects were excluded because of incomplete answers.



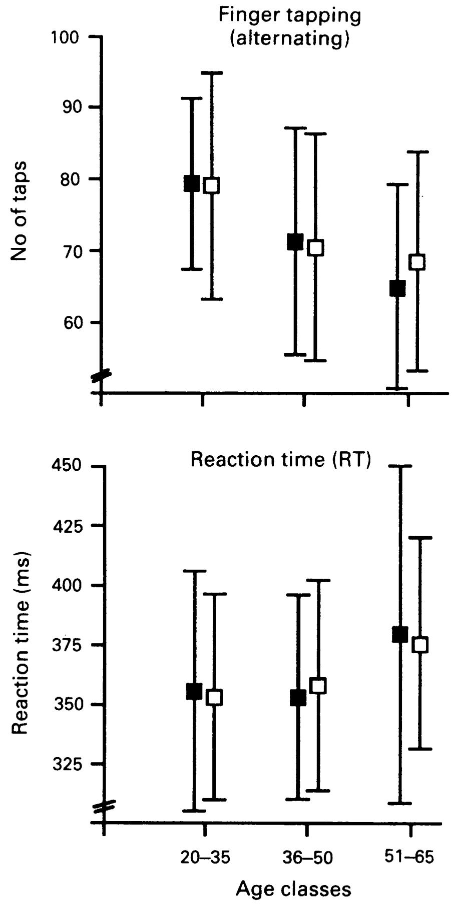


Figure 2 Psychometric test performance in exposed (■) and control groups (□). Mean values and SDs are indicated.

This increase was statistically significant for tiredness ($p = 0.013$) and nervousness ($p = 0.008$). In neither of the two groups was earlier concussion or current medication correlated to prevalence of symptoms.

Table 4 shows the scores for the questionnaires (Q16, POMS, and EPI). The number of yes answers in the Q16 was significantly higher in the chloralkali group than in the control group, and the prevalence of five or more yes answers (regarded as the upper limit in a normal population) was also significantly higher among exposed workers than among controls ($p = 0.02$, χ^2 test). Scores for tiredness and confusion in the POMS were significantly higher in the chloralkali group than in the control group, as was the score for neuroticism in EPI (EPI-N), whereas the degree of extroversion or introversion did not differ between the two groups.

The relations between the questionnaire scores and different exposure indicators (used in the chloralkali group) were weak. Only the score for neuroticism in EPI showed a statistically significant relation with average B-Hg during the past year ($r = 0.24$, $p = 0.026$).

Figure 2 gives the results of the psychometric tests

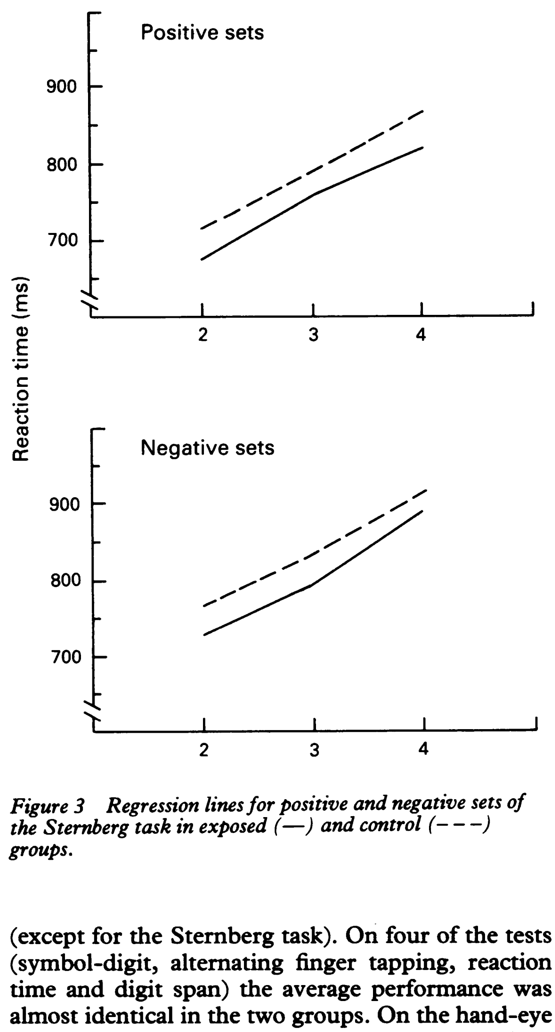


Figure 3 Regression lines for positive and negative sets of the Sternberg task in exposed (—) and control (- - -) groups.

(except for the Sternberg task). On four of the tests (symbol-digit, alternating finger tapping, reaction time and digit span) the average performance was almost identical in the two groups. On the hand-eye coordination test the mercury exposed workers showed slightly better results than the controls ($p = 0.08$). The test performance was age dependent, particularly in the symbol-digit test and in alternating finger tapping. Test performance was not correlated with earlier concussion or with current medication in either group.

Figure 3 shows the regression lines for the positive and negative sets in the Sternberg test. The mercury exposed workers performed slightly better than the controls.

In the chloralkali group the performance of the hand-eye coordination test, alternating finger tapping, and the Sternberg task for negative sets (the regression coefficient for negative sets), showed a statistically significant negative correlation with the relative number of B-Hg peaks ($\geqslant 150$ nmol/l) during the past five years ($r = 0.24$, $p = 0.022$; $r = -0.28$, $p = 0.009$; $r = 0.25$, $p = 0.017$ respectively). The regression coefficient for negative sets on the Sternberg task was also correlated with the current S-Hg and U-Hg ($r = 0.35$, $p = 0.001$; $r = 0.28$, $p = 0.009$ respectively).

The prevalence of abnormal results for the psychometric tests (poorer performance than the 90th percentile of the control group) was compared for different subgroups of the mercury exposed group (different exposure indicators were tested). No notable dose-response relations were found. Neither was there any significant correlation between fish consumption or amalgam burden and performance of the psychometric tests.

We found a large variance in the tremor frequency spectra. Four people in the chloralkali group and six controls were excluded due to large divergences in the spectra. Figure 4 summarises the results of the tremor registrations. At rest (without load), a high peak frequency (HPF, the frequency corresponding to the highest acceleration) of about 6 Hz was found in both groups. In 31 exposed subjects and in 27 controls a second HPF of about 10 Hz was seen. During load (1000 g) a first HPF was seen at about 4 Hz and a second HPF (for 85 exposed subjects and 72 controls) at about 10 Hz. The exposed subjects tended to have higher acceleration amplitudes compared with the controls, but the differences were not statistically significant.

In both groups, a statistically significant negative correlation existed between age and the second HPF during load ($p < 0.01$). Alcohol consumption and smoking did not significantly affect the tremor parameters.

Finally, the relations between the different effect parameters were tested. These calculations showed significant ($p < 0.001$) correlations between the number of self reported symptoms and the scores in both Q16 and POMS (except for anger). The scores in POMS (except for confusion) were also correlated ($p < 0.05$) with the grade of neuroticism in EPI. Performance on the psychometric tests did not correlate significantly with the other effect parameters.

Discussion

Several investigations have shown that occupational exposure to high concentrations of mercury vapour may cause effects on both the CNS and the peripheral nervous system. In 1970, Smith *et al*[2] reported a dose related increase in frequency of symptoms among 567 chloralkali workers, particularly in subgroups with exposure concentrations exceeding 100 μg Hg/m^3 air. Miller *et al*[3] found raised prevalences of neurological signs, alterations in forearm tremor frequency, and impaired performance on psychomotor tests in a group of mercury exposed chloralkali workers with raised U-Hg (>50 μg/l).

In more recent studies, increased prevalence of

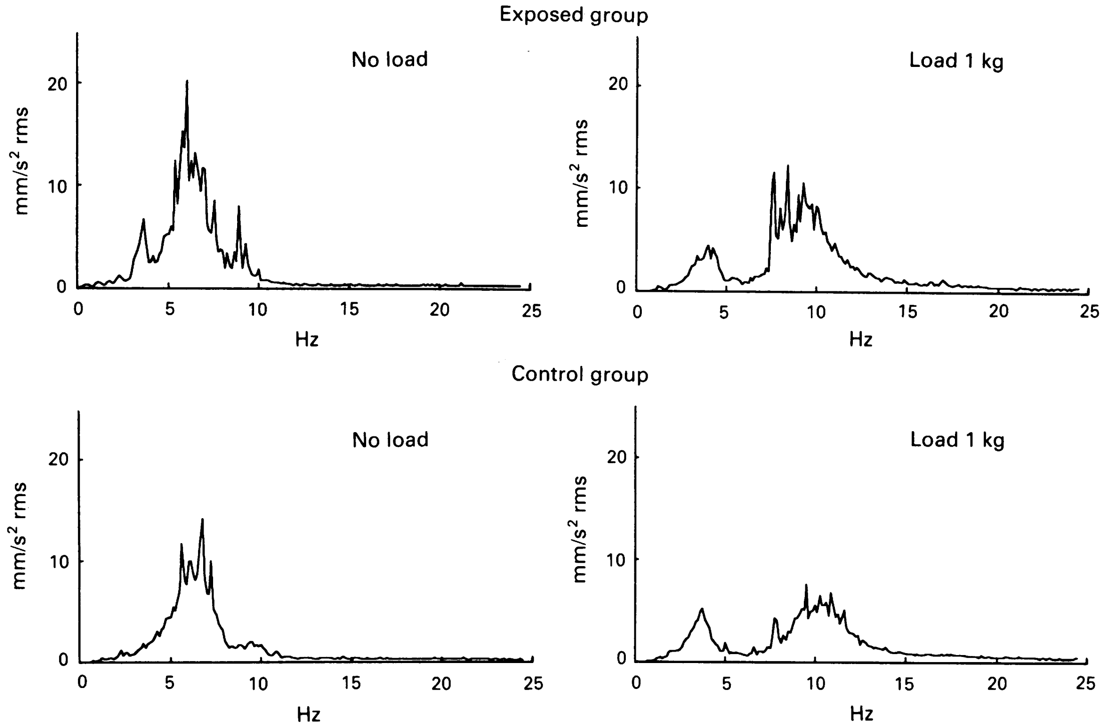


Figure 4 Mean tremor spectra in exposed group (n = 85) and control group (n = 69).

subjective symptoms and impairment of cognitive functions have been shown at lower mercury exposure. Smith *et al*[22] reported a dose related mercury effect on short term memory (assessed by 50% threshold for correct serial recall on the digit span test) in two groups of chloralkali workers with an average U-Hg during the past 12 months of 195 μg/l and 108 μg/l respectively. In a study by Roels and co-workers[4] a dose related effect of mercury was seen on both psychomotor tests (eye-hand coordination, arm-hand steadiness) and on parameters of renal dysfunction, among mercury exposed workers with an average U-Hg of 96 μg/g creatinine and an average B-Hg of 29 μg/l. A Finnish study[23] showed reduced performance on the Santa Ana coordination test among 36 chloralkali workers compared with matched controls. Average U-Hg in the chloralkali group was about 58 μg/l and average B-Hg was about 20 μg/l. In a later study, Roels and co-workers,[24] reported an increased prevalence of subjective symptoms, but normal performance on various psychological tests (simple reaction time, critical flicker fusion, colour discrimination, short term memory) among mercury exposed workers compared with controls. The authors judged the registered increase in symptom prevalence as possible overreporting, however, due to expected adverse effects among the mercury exposed workers. Rosenman *et al*[25] reported increased prevalence of symptoms correlated with U-Hg in a mercury exposed group of workers with average U-Hg between 28 and 50 μg/l and average B-Hg between 100 and 150 μg/l. A number of studies were negative. Schuckmann *et al*[26] did not find any significant group differences in finger tremor, hand-eye coordination, or reaction time for 39 controls and 39 chloralkali workers with a mean U-Hg of 108 μg/l and a mean B-Hg of 20 μg/l. Bunn and co-workers[27] examined 101 chloralkali workers and nine controls over a period of several years. Mercury concentrations in air varied from 50 μg to about 100 μg/m^3. The researchers found no signs indicative of chronic mercury intoxication. In a recent study, Piikivi and Hänninen[28] found no impairment of performance in psychological tests, but an increase in self reported memory disturbance in a group of 60 Finnish chloralkali workers with a mean U-Hg of 17 μg/l and a mean B-Hg of about 10 μg/l. The memory disturbance correlated strongest with shift work.

Alterations of hand or forearm tremor spectra induced by mercury have been described by several authors.[3 19 29] Fawer *et al*[19] reported a subclinical increase in forearm tremor frequency at an average exposure of about 26 μg Hg/m^3 air (TWA), and recently Chapman and co-workers described alterations in finger tremor in otherwise asymptomatic mercury exposed workers.[30]

In summary, many studies show effects on the CNS among mercury exposed workers; however, the reports are difficult to compare as different estimates of exposure and various types of effect parameters have been used. No clearly established thresholds exist below which effects of exposure to mercury on the CNS can be safely excluded. Results from some of the most reliable studies indicate that chronic exposure to mercury concentrations below 50 $\mu g/m^3$ air seldom lead to increased prevalence of subjective symptoms or impaired test performance. The most important indicator of biological exposure seems to be U-Hg, and the biological threshold of 50 $\mu g/g$ creatinine (corresponding to about 28 nmol/mmol creatinine) proposed by Roels and co-workers[24] appears, from these other studies, to be reasonable.

In our current study, efforts were made to obtain two groups as similar as possible for background data such as age, education, and type of work. The equivalent results on the synonym test suggest that verbal knowledge within the two groups was similar, a fact that may have been underestimated in some of the other studies mentioned.

Our chosen indicators of exposure were a combination of current and long term estimates. Peak exposure was included because correlations between peak exposures of mercury and effects on the CNS have been described in earlier studies.[22 31] This was the only estimate of exposure that correlated with impaired performance in some of the psychological tests. Theoretically, repeated peak exposures may be more dangerous for the CNS than chronic low exposure, because concentrations of free mercury vapour in blood become much higher at peak exposures, and the amount of mercury that passes the blood brain barrier is dependent on the concentration of unoxidized mercury vapour in the blood.[1]

During the past decades, technical improvements and encouragement of personal hygiene at work have significantly reduced the exposure to mercury in Swedish chloralkali factories.[7] At the time of this study the average mercury concentration in air was estimated to be about 25 $\mu g/m^3$ based on measurements made by the company's health care units and by our own random measurements performed with a goldfilm sniffer (model Jerome 411, Jerome Inc, USA). The random samples showed large fluctuations in concentration, however, with peaks up to 150 $\mu g/m^3$ air.

The selection of symptom questionnaires and psychological tests was also an object of discussion. It is well known that symptom questionnaires may lead to overreporting of subjective symptoms. To prevent this, our symptom questionnaire (Q16) was combined with an interview and two questionnaires aimed to detect early changes in mood state and personality (POMS and EPI). The last two questionnaires are regarded as less sensitive to overreporting than a common symptom questionnaire.

The raised prevalence of symptoms in the chloralkali group may still be a result of overreporting. The concomitant increase in the scores for tiredness, confusion (POMS), and neuroticism (EPI), together with the registered correlation between the prevalence of symptoms and questionnaire scores, mitigates against this, however. Furthermore, the dose-effect relations seen in all three questionnaires, although weak, indicate that a real effect of mercury on subjective wellbeing exists, at least among the workers with highest exposure to mercury.

The selection of psychometric tests was based on experiences from earlier studies of effects on the CNS caused by mercury and various neurotoxic agents. The computerised test battery developed by Baker and co-workers,[17] has shown high stability over time and strong correlations with other standardised tests.[14]

Our test battery did not show any significant differences in performance between the two groups, and dose-effect relations were weak. We found a tendency toward poorer performance among subjects with increased frequency of earlier peak exposures, whereas a long term indicator such as duration of employment did not correlate with test performance. The strong correlation between age and test performance indicates that the selected tests were sensitive for the detection of effects on the CNS.

Our findings are in agreement with earlier studies in which exposures were also low.[23 24 28] The lack of decreased performance on the psychometric tests, together with increase in prevalence of symptoms (Q16, POMS) and degree of neuroticism (EPI) registered in the chloralkali group, points to symptoms as more sensitive indicators of effects of mercury on the CNS than the psychometric tests.

The choice of tremor registration was based on the report by Fawer *et al*,[19] in which alterations in tremor spectra (higher HPFs related to exposure duration) were described at comparatively low exposure. These results are supported by newly published findings of Chapman *et al*.[30] In a recent study, however, Roels *et al*[32] compared three different methods of hand tremor registration (accelerometer registration, hand-eye coordination, and hand steadiness), without finding any significant differences between a mercury exposed group (with median U-Hg 63 $\mu g/g$ creatinine and median B-Hg 24 $\mu g/l$) and a control group.

Our results showed tendencies towards higher HPF and higher accelerations, especially during load, in the chloralkali group, but group differences were not statistically significant.

The amount of mercury released from dental amalgam fillings is normally low,[33 34] far lower than occupational exposure to mercury in the chloralkali industry. Despite this, there has been debate concerning possible toxic effects of mercury released from dental fillings. We therefore tested the relation between the number of amalgam surfaces and some of the effect parameters. These calculations showed no significant correlations between the number of amalgam surfaces and questionnaire scores or performance on the psychometric tests in either group.

We regard our results as representative for mercury exposed chloralkali workers in Sweden. Eighty nine out of a total of about 250 exposed workers were examined. The selection criteria selected mainly workers subjected to high exposure, thus the risk of underestimating the adverse effects of the workers' exposure seems to have been small.

Conclusions

Our results suggest a slight effect on the CNS due to the present low mercury exposure. The registered dose-effect relations, although weak, indicate that this effect is best related to current exposure to mercury and to earlier peak exposures. None of the parameters of effect were related to duration of employment. The finding of suspected effects on the CNS at this low exposure suggests that the Swedish exposure limit for metallic mercury vapour of 50 μg Hg/m^3 air is too high. The exposure limit of 25 $\mu g/m^3$ (TWA) recommended by the World Health organisation[6] seems more accurate.

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2 Soter NA, Wasserman SI, Austen KF. Cold urticaria: release into the circulation of histamine and eosino-phil chemotactic factor of anaphylaxis during cold challenge. *N Engl J Med* 1976;**294**:687–90.
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