Effects of occupational exposure to elemental mercury on short term memory

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ABSTRACT Previous studies have indicated that exposure to elemental mercury is associated with increased short term memory scanning time. In an effort to provide converging evidence that short term memory is one locus of the neurotoxic effect of mercury, two measures of short term memory capacity were used in this study. The first measure, the Wechsler digit span forward, was too imprecise and unreliable to detect any adverse effects. The second measure, an estimate of the worker's 50% threshold for correct serial recall, was more satisfactory and provided evidence of a statistically significant decrease in short term memory capacity associated with increasing exposure to elemental mercury (based on a group of 26 workers, urinary mercury average 0·20 mg/l, range 0·0–0·51 mg/l). A replication study of another group of 60 workers was performed to confirm this apparent mercury related effect. Despite lower urinary mercury concentrations in this second group (0·11 mg/l average), a statistical association was again observed relating urine mercury to reduced short term memory capacity.

In recent years it has been suggested that industrial exposures to neurotoxic substances may result in subclinical effects that go undetected in standard medical examinations. The concern over the detection of these subclinical effects is twofold. Firstly, a small decrement in functioning may be a precursor of more significant impairment if exposure to the neurotoxin continues over a long period. Secondly, when a gross performance measure is used to test for a deficit, as in a standard medical examination, the worker may be able to conceal a sizeable, selective impairment of a single cognitive process or function by reorganising his or her behaviour so as to bypass or reduce demands on the weakened system.[1]

This paper describes a precise measure of short term memory (STM) span that is able to detect subclinical effects resulting from exposure to elemental mercury. A test of STM capacity was selected for this study because Smith and Langolf[2] have previously shown that the STM scanning time[3] is slowed with increasing levels of mercury exposure. Since Smith[4] has presented evidence suggesting that the STM scanning time and the STM capacity[5] measure a common underlying ability, it was predicted that the STM capacity should also be adversely affected by exposure to mercury. This study was conducted to test this prediction and to provide converging evidence that one locus of the neurotoxic effect of mercury is short term memory.

Two alternative measures of STM capacity were evaluated under field study conditions. The first, the Wechsler digit span forward,[6] was included because it is the test of STM span that has traditionally been used in behavioural toxicology studies.[7]

A second, more extensive test of STM span was also evaluated because it has been suggested that the Wechsler digit span test taken alone "is not sufficiently discriminating to detect significant differences in intellectual (that is, retention) functioning."[8] This second test entails estimating an individual's 50% threshold for serial recall—that is, the number of digits that can be correctly recalled 50% of the time, in serial order.

The reliability and precision of these two tests were assessed within the context of evaluating the effects of chronic exposure to elemental mercury on STM. This provided an opportunity to study the performance of a heterogeneous population (mercury cell chlor-alkali workers) and to illustrate the usefulness of precise behavioural measures in assessing the neurotoxic effects of chronic exposure to elemental mercury.

Received 25 February 1982
Accepted 8 November 1982

Experiment I: Wechsler digit span forward

In this first study the test-retest correlation and precision of the digit span forward test[6] were evaluated. The dose response relationship between urine mercury concentrations and digit span forward was also studied.

In the digit span forward test the worker is presented with a list of single digit numbers (randomly selected with no repetitions—for example 3-7-1-4) at a rate of one digit per second. The worker then attempts to repeat this list in serial order.

The first list presented contains three digits, the second four digits, and so on up to 10 digits, assuming that no errors are made by the worker. If at some list length the worker fails to recite the list correctly a second list of the same length is presented by the experimenter. If the worker recites this second list correctly the test continues with a list one item longer. If the worker makes an error on the second list the test is halted. The worker's digit span forward is the length of the last list that is correctly recalled (on either the first or second attempt at that list length). This measure will be referred to as the "Wechsler digit span."

MATERIAL AND METHODS

The workers were tested twice, with an interval of three months between sessions. The Wechsler digit span was then studied as a function of session and level of mercury exposure.

Subjects

Twenty eight male volunteers employed in two mercury cell chlor-alkali plants were tested; table 1 shows the characteristics of this group. This relatively small sample for the pilot study of experiment I was selected so that subjects' ages, educational levels, and urinary mercury concentrations were representative of the whole plant population of hourly payroll workers. Specifically, this smaller group was selected from the larger group of 98 workers studied by Langolf *et al.*[9] The volunteer rate for the earlier study was over 70% at each of the two plants.

In the earlier, larger group study the mean and standard deviation of subjects' ages at plant I were 42·1 ± 13·4 years. The smaller sample of this experiment was representative at 43·0 ± 14·7 years (table 1). At plant II, the subject's age in the larger study was 33·5 ± 11·6 years, which compares favourably with that (35·0 ± 11·6 years) in the present study. (The slightly greater mean age of subjects in the present study is undoubtedly related to the time elapsed between the two studies.)

Using the group of the past study as a comparison, the urinary mercury concentrations of subjects in experiment I were representative of the larger group. Earlier, the total group of 98 workers had mean urinary mercury concentrations of 0·14 ± 0·14 mg/l compared with 0·18 mg/l ± 0·17 mg/l in the present group of 28 subjects. (Urinary mercury concentrations are the average of three samples per worker obtained over the three months before testing.)

Table 1 *Population characteristics for workers in experiment*

	Plant I (n = 13)		*Plant II (n = 13)*	
	Mean	*SD*	*Mean*	*SD*
Age (years)	43	14·7	35	11·6
Education (years)	10·2	3·4	11·2	2·8

Apparatus

A microcomputer controlled the visual presentation of digits, which were presented at a rate of one digit/second. Response sheets showing the correct response (lists of digits) were prepared for use by the experimenter in scoring the workers' verbal responses.

Urinary mercury indices

Urinary mercury indices were determined using monthly measurements of urinary mercury concentrations in samples collected by plant medical personnel. The analytical method has been described by Henderson *et al.*[10] The four urinary mercury indices determined for each subject were the average urinary mercury concentrations for three, six, 12, and 24 months before testing (Avg3, Avg6, Avg12, Avg24, respectively); see table 2.

Design

Each worker was tested twice (the sessions were about three months apart) and the lists of digits were the same for all workers. The specific lists differed for the test and retest sessions and the lists used in the first session at one plant were used in the second session at the other, and vice versa.

RESULTS

The group mean Wechsler digit spans for the two sessions were 5·6 and 5·4 digits, respectively. The effect of session was not significant ($p > 0·2$) and the estimated within-subject variance was 1·0 digits-squared (assuming no subject × session interaction). The test-retest reliability was rather low with a correlation of $r = 0·36$ as shown in fig 1.

Stepwise regressions were run using the Wechsler

Table 2 *Urinary mercury indices in experiment I (n = 28)*

	Mean	*Range*
Avg3 (mg/l)	0·175	0·020–0·535
Avg6 (mg/l)	0·164	0·020–0·500
Avg12 (mg/l)	0·139	0·015–0·395
Avg24 (mg/l)	0·119	0·005–0·300

digit span* as the dependant variable, and allowing biographical indices (see table 1) to enter as covariates. There was a significant difference in digit span between the two plants. None of the biographical indices and none of the mercury exposure indices was significantly related to the Wechsler digit span forward ($p > 0{\cdot}10$). (Both linear and quadratic relationship were non-significant.)

The failure to find any statistically significant relationships between the Wechsler digit span and the mercury exposure indices is not surprising, given the low reliability of this performance measure.

Experiment II: precise measurement of the STM span—the 50% threshold

The purpose of this second study was to evaluate and apply a more extensive test of STM span. This test uses a statistical technique known as probit analysis[11 12] to provide a maximum likelihood estimator of a worker's 50% threshold for serial recall (fig 2). The true 50% threshold span is defined to be the length of a list of digits that the worker can correctly recall in serial order on 50% of experimental trials.

*The performance and exposure measures used were averages of the two session scores.

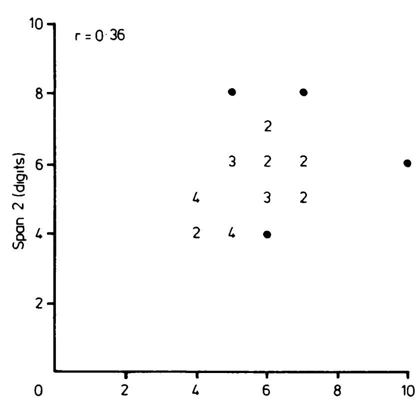

Fig 1 *Test-retest correlation of the Wechsler digit span test. Numbers in figure refer to number of observations at each point.*

METHOD

Each worker was tested twice, with the test sessions three months apart and the 50% threshold spans were evaluated as a function of session and urinary mercury concentrations.

Subjects

Twenty six male volunteers employed in two mercury cell chlor-alkali plants were studied; table 3 describes the population in terms of age, education, and plant. This group of subjects was a subset of those studied in experiment I whose selection has been described above.

Apparatus

A microcomputer system controlled the presentation of digits on a video display. Responses were scored as correct (recalled correctly in serial order) or incorrect by comparing the subjects' verbal responses with recording sheets containing the preselected lists of digits.

Stimuli

Digits were presented singly at a rate of one per per second. The members of each list were randomly selected from the set 0–9 and were further constrained so that:

(1) a digit was repeated once at most;

(2) a digit was not immediately followed by the same digit;

(3) ascending or descending sequences of digits (consisting or either consecutive digits or of every other digit) longer than two digits were not allowed; and

(4) repeated sequences of digits were not allowed—for example, 0313 would be allowed but not 0303.

The purpose of these restrictions on randomness was to make the lists more homogeneous in terms of

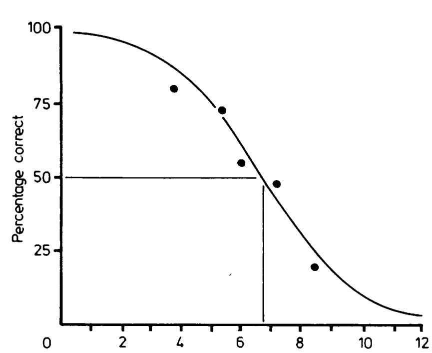

Fig 2 *Illustration of probit analysis to estimate a subject's 50% threshold span.*

Table 3 *Population characteristics for workers in experiment II*

	Plant I (n = 12)		Plant II (n = 14)	
	Mean	*SD*	*Mean*	*SD*
Age (years)	41·3	13·8	33·7	13·0
Education (years)	10·3	2·2	12·1	2·8

difficulty, thereby reducing the within-subject variability.

Urinary mercury indices

Urinary mercury indices were computed as in experiment I, see table 4.

Procedure

Each trial consisted of the following sequence:

(1) informing the worker that a new trial was beginning (two second visual display);

(2) informing the worker of the length of the list about to be presented (two second visual display);

(3) showing the digits one at a time (one second visual display for each digit); and

(4) showing the worker a set of question marks (?????) indicating the end of the list.

Thus a trial might have consisted of the following display (one line on the screen at a time):

New trial
List length three
1
7
4
?????

The workers were instructed to memorise the list of digits and then to recite the list in the same order when the question marks appeared. The experimenter compared the worker's responses with the correct responses (given on the response recording sheet). A trial was scored as correct only if no errors were made (all the digits recalled in the correct order), otherwise, it was scored as incorrect.

The testing sequence consisted of two blocks of trials. The first block served two purposes: (1) to provide practice on the task; and (2) to determine the length of lists to be used in the actual testing.

Table 4 *Urinary mercury concentrations in experiment II*

	Mean	*Range*
Avg3 (mg/l)	0·195	0·011–0·510
Avg6 (mg/l)	0·192	0·013–0·448
Avg12 (mg/l)	0·182	0·015–0·419
Avg24 (mg/l)	0·143	0·016–0·358

The data from the second block were used to estimate the worker's 50% threshold span.

The first block of trials began testing at list length 6. A simple algorithm was then used to determine the list lengths of the following trials:

(1) if the preceding trial was at list length n, and it was scored as correct, then the next trial would use list length n + 1; and

(2) if the preceding trial was at list length n, and it was scored as incorrect, then the next trial would use list length n − 1.

The first block was terminated as soon as the worker was correct a total of three times at one of the list lengths (call this length n*).

The second block consisted of 40 trials. The list lengths used were n* − 1, n*, n* + 1, n* + 2, and n* + 3. The order of the lengths used in testing was random, within the constraint that eight trials were run at each of the five list lengths.

RESULTS

For the two sessions, the group mean 50% threshold spans were 5·8 and 6 digits, respectively. The effect of session was significant ($p < 0·005$), indicating a significant between-session learning effect. The estimated within-subject variance, assuming no subject X session interaction, was 0·15 digits-squared and the test-retest correlation was 0·85 ($p < 0·01$), see fig 3.

Stepwise regressions showed a significant linear relationship ($p < 0·01$) between subjects' 50% threshold spans* and their 12 month average urinary mercury concentrations (Avg12). The regression equation for the relationship between the 50% threshold span and Avg12 was:

50% threshold span = 5·6 + 0·009 (years of education)* −0·0003 (age in years)* −2·3 (Avg12)*

*The measures used in the regression analysis were averages of the two session scores.

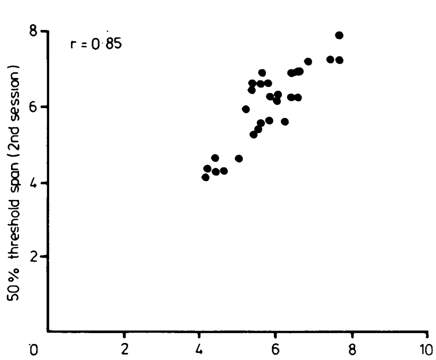

Fig 3 *Test-retest correlation for more precise 50% threshold span measure.*

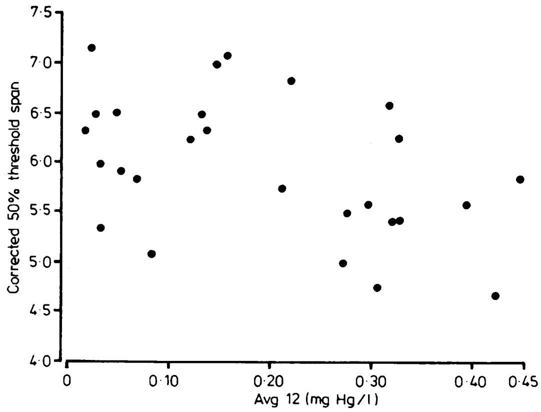

Fig 4 *Relationship between 12 month average urinary mercury and 50% threshold span.*

Note that as mercury exposure levels increase, 50% threshold spans decrease (fig 4). Also note that the subjects' 50% threshold spans shown in fig 4 vary over a roughly normal range of five to seven digits with none far outside the normal range. The trend toward lower spans as a function of urinary mercury is still substantial, however. A moderate concentration of urinary mercury of 0·2 mg/l (12 month average) would result in an expected loss of span of 0·46 digits (using the coefficient of 2·3 digits/mg Hg per litre of urine estimated in the regression equation above).

Two of the other mercury exposure indices, Avg6 and Avg24, also showed marginally significant decreases in 50% threshold span with increasing urinary mercury concentrations. Avg6 showed a linear relationship with a partial correlation of -0.32 ($p < 0.06$), while Avg24 showed a linear relationship with a partial correlation of -0.27 ($p < 0.09$).

Experiment III: replication study

Since the results in experiment II indicated a decrease in STM capacity with increasing levels of mercury exposure, a replication study was conducted with a larger group of workers.

METHOD

Each worker was tested once using the same testing procedure as was described in experiment II and urinary mercury indices were measured in the same way as in experiment II.

Subjects

Sixty male volunteers employed in two mercury cell chlor-alkali plants were studied. These chlor-alkali plants differed from those studied in experiment II. The age, education, and plant of the subjects are shown in table 5 while table 6 shows urinary mercury indices. Note that the urinary mercury concentrations at these plants were subsequently lower than those observed in the plants studied in experiment II.

Volunteers for experiment III were obtained by posting notices of the study followed by personal contact with the workers by supervisory and medical personnel. To obtain a homogeneous sample, the population from which volunteers were obtained was restricted to hourly workers who were part of the urinary mercury hygiene control programme. Office, supervisory, and technical workers were therefore excluded from the population of potential volunteers. Women were also excluded because they represented too small a percentage of chlor-alkali workers to allow for statistical correction of sex related differences in memory test performance.

At plant III, 25 male employees who had urinary mercury records volunteered for the test, and 27 did not. Workers with the highest urinary mercury were especially encouraged to participate in order to obtain the largest possible range for the independent variable of interest for regression analysis. The 25 volunteers had mean urinary mercury concentrations of 0·09 mg/l (average of previous three months) with a range from 0·00–0·26 mg/l. The non-volunteers, on the other hand, had a mean concentration of 0·06 mg/l, range 0·00–0·14 mg/l. Comparing ages, the volunteers' mean age was 33·4, range 18–61; whereas the non-volunteers' mean age was 34·33 (range 21–58) (this was not significantly different). Although other quantitative descriptive data were not available, it was not believed that the volunteers differed from the non-volunteers with respect to variables such as educational level or

Table 5 *Population characteristics for workers in experiment III*

	Plant III (n = 25)		*Plant IV (n = 35)*	
	Mean	*SD*	*Mean*	*SD*
Age (years)	33·4	10·6	33·9	3·9
Education (years)	11·9	0·9	12·9	1·4

Table 6 *Urinary mercury concentrations in experiment III*

	Mean	*Range*
Avg3 (mg/l)	0·108	0·0–0·314
Avg6 (mg/l)	0·102	0·0–0·301
Avg12 (mg/l)	0·102	0·0–0·258
Avg24 (mg/l)	0·093	0·0–0·228

socioeconomic background, because of the homogeneity of the target population.

In summary, the only known bias in subject selection was the effort to include workers with the highest urinary mercury concentrations. This resulted in a higher mean and a larger range of urinary mercury concentrations in the volunteer group. This bias would certainly result in overestimation of the *rate* of incidence of subclinical effects in the entire population. The objective of this experiment, however, was not to estimate incidence rates, but to determine if there was an *association* between subjects' urinary mercury concentrations and their short term memory spans. Including individuals with the highest urinary mercury concentrations was intended to enhance the power of the regression analysis in detecting such an association.

At plant IV, the volunteer participation rate was much higher. Of the 60 male workers with urinary mercury records available, 46 volunteered for the study. As shown in fig 5, however, the volunteer group showed a negative correlation ($r = -0·35$) between age and urinary mercury concentration. This correlation could seriously bias the estimated relationship between subjects' urinary mercury concentration and memory span. If younger subjects have larger memory spans than older subjects as found by Friedman,[13] any reduction in memory span due to mercury could be offset and masked, because the subjects with highest urinary mercury tended to be younger. To remove this potential bias, the two subjects with the highest urinary mercury in the 20–30 year age range were removed from the sample as were subjects in the 43–60 age range (who had uniformly low urinary mercury) (fig 5). This was done without knowledge of any subject's performance in memory testing. The remaining plant IV group then showed an effectively homogenous urinary mercury (AVE12) as a function of age ($r = -0·16$, $p > 0·10$).

Fig 5 Negative correlation between subjects' ages and urinary mercury at plant IV.

Both age and educational level may be related to memory span performance. While both of these attributes can be used as covariates in multiple regression analysis, they should be uncorrelated with subjects' urinary mercury concentrations to avoid confusing age and education effects with mercury effects. Table 7 shows the correlations between age, educational level, and urinary mercury for the combined subject samples of plants III and IV. There is little evidence for significant correlations between educational levels and urinary mercury concentrations, although at plant IV, despite the prior filtering of subjects, there is a consistent weak negative correlation between subjects' ages and their urinary mercury indices, and the correlation coefficient relating age and AVE6 is statistically significant. These negative correlations are due to the tendency for younger employees to be assigned to jobs with the highest potential exposure to mercury, and cannot be easily avoided in field studies of chlor-alkali workers. As mentioned earlier, the negative correlation between age and urinary mercury could tend to reduce the magnitude of estimated mercury related memory span effects, since the subjects with highest urinary mercury have the advantage that they are generally younger. Therefore, the dose response regression equations shown below must be interpreted with care; the size and significance of potential mercury related reductions in memory span may be underestimated.

RESULTS

The 50% threshold span was significantly related to Avg12 ($p = 0·014$) and Avg24 ($p = 0·044$), and marginally related to Avg3 ($p = 0·066$) and Avg6 ($p = 0·07$). The estimated relationship between the 50% threshold span and Avg12 is:

$$50\%\ \text{threshold span} = 5·97 + 0·91\ (\text{plant}) - 17·4\ (\text{Avg12})^2$$

where plant = 0 for plant III and 1 for plant IV.

The plant variable probably accounts for the differences between the two plants that are not adquately

Table 7 *Correlation coefficients relating urinary mercury, age, and educational level for plants III and IV combined*

Urine mercury index	*Age*	*Educational level*
AVE3	−0·22	−0·11
AVE6	−0·34*	−0·12
AVE12	−0·23	−0·14
AVE24	−0·10	−0·11

*Significant, $p < 0·05$.

described by age and years of education. Note that these results suggest that an Avg12 of 0·20 mg/l would result in an expected decrease in the 50% threshold span of 0·70 digits. This is of the same order of magnitude as the expected reduction of 0·46 digits predicted from experiment II's results.

Discussion

The results of the first experiment indicate that the Wechler digit span forward test, used as a measure of STM span, is a rather imprecise measure. The within-subject variance (1·0 digits-squared) is high, especially when it is noted that the observed range was from four to 10 digits. Thus it would not be advisable to use this test when relatively small differences in memory span are of interest unless a very large population were available for testing.

The second experiment, however, shows that a more extensive testing procedure can improve the precision with which the memory span (50% threshold) may be estimated. This threshold measure reduced the within-subject variance to 0·15 digits-squared.

There was no significant relationship between the Wechsler digit span and level of mercury exposure as estimated by urinary mercury concentration. Given the imprecision of the performance measure, however, this failure to attain significance is not surprising.

There was a significant relationship between the more precise 50% threshold span and Avg12 (experiment II). Short term memory span was found to decrease substantially as mercury exposure levels increased and this effect was observed in a different population in experiment III. The magnitude of this effect may be assessed by comparing it with the decrements in STM span which result from aging. Using the regression coefficients obtained in experiment II for the relationships between the 50% threshold span and Avg12 and between the 50% threshold span and age, an exposure equivalent to an Avg12 of 0·20 mg/l has the same effect on a worker's 50% threshold span as increasing that worker's age from 20 to 44. An essential question for further research concerns the question of reversibility of STM effects after cessation of exposure to mercury; no such study using quantitative measurements has as yet been attempted.

These results, combined with the finding of Smith and Langolf[2] that STM scanning times are slowed by chronic exposure to mercury, provide converging evidence that STM is affected by elemental mercury. They also serve to illustrate the value of precise behavioural measures in assessing the risks associated with exposure to a neurotoxin.

This paper is the result of research sponsored by the National Institute for Occupational Safety and Health, under Grant No R01-0H00707-04. It summarises portions of PJS's PhD dissertation at the University of Michigan. Appreciation is expressed to Professors David Krantz, Robert Pachella, and Stephen Pollock for their help during this work, and to James Foulke for his work in providing test instrumentation. Special appreciation is extended to Dr Richard Henderson for his long term encouragement and advice.

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