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A 30-year follow-up of residual effects on New Zealand School Dental Nurses, from occupational mercury exposure

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This paper reports possible residual adverse effects from occupational mercury exposure in dentistry, Thirty years ago, the all-women exposed group worked with both silver and copper amalgam filling material without protective gloves or a ventilation system, resulting in chronic mercury exposure. The aim of the study was to test the null hypothesis in a survey of general and reproductive health, and a battery of nine neurobehavioral tests. The population was the 115 graduates of one school for dental nurses from 1968 to 1971. The sample was 43 mercury-exposed women and 32 matched controls. Statistical comparisons revealed that the two groups were equivalent on cognitive tasks and four of the six mood subscales. Significant between-group differences were found in current health symptom experience and reproductive health, especially early hysterectomy experience. Reporting of Occupational Overuse Syndrome was strongly positively correlated with years of work. In general, the study suggests that acute symptoms from mercury exposure may be reversible, while some residual health effects may be becoming more of a concern with the women's increasing age. *Human & Experimental Toxicology* (2007) **26,** *367–374*

Key words: dentistry; mercury poisoning; neurobehavioral test battery; reproductive health; women

Introduction

There is empirical evidence that occupational mercury exposure may result in deficits or changes in affect, cognitive skills, psychomotor skills and sensory function, and psychosomatic illness experience. Ratcliffe *et al.*[1] critically assessed the methodology and analysis of 164 mercury exposure studies and conclude 'the evidence for association between neurologic effects and inorganic mercury is irrefutable' (p. 238). More recently, meta-analysis of mercury studies has suggested that there are exposure and test performance relationships for different domains with common neurobehavioural tests.[2,3]

Studies specifically in dentistry have found adverse neurobehavioral effects from chronic low-level mercury exposure.[4–7] Despite this, some uncertainty remains on the long-term consequences of occupational mercury exposure, as there are few longitudinal studies. While some research has demonstrated that there can be residual effects from occupational mercury exposure, and in particular with chloralkali factory workers,[8–11] long-term effects are not empirically established for dental personnel. In other industries the possibility has been raised that some deficits are reversible once exposure ceases.[12]

Women have little profile in neurobehavioral studies of occupational mercury exposure. There are three reports specifically of women and occupational mercury exposure, and a limited number of studies that include both genders in the samples.[7,13,14] From these studies, there does not appear to be a gender difference in the range of adverse neurobehavioral responses to mercury exposure, but the studies have not included data specifically on women's health and reproduction.

Studies of the impact of occupational exposure to mercury and fertility or pregnancy outcomes have also failed to generate a clear relationship, such as unfavorable odds ratios for normal births,[15–20]

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despite various animal and human models demonstrating that there is the potential for reproductive harm. [21–29] Recent reviews[30, 31] conclude that adverse reproductive outcomes are possible but largely unproven; yet neither have safe mercury exposure levels for fecund women been established.

The present study focused on a unique women-only occupation, the New Zealand (NZ) School Dental Nurse. These women were trained by the state to provide dental treatment for children, from diagnosis to drilling and filling, local anesthetics and tooth extractions. All NZ primary schools had a dental clinic, usually staffed by one woman. Clinics had no ventilation or air conditioning systems, and protective gloves were not supplied or worn.

Until 1975, copper amalgam (CuAm) pellets and silver amalgam (AgAm), as alloy and mercury, were the materials supplied for fillings. There was no routine biological monitoring for mercury exposure, but in 1974 all workers were urine tested in a one-off assessment. Records of this event were not archived but the pattern of high urine mercury levels prompted the state to withdraw CuAm and introduce encapsulated AgAm. Retrospectively, the assumption that mercury exposure levels for the women were high can be deduced from a secondary analysis of work output data. State records show that in 1974 the 1356 school dental nurses mixed and inserted 2,589,019 amalgam fillings (M = 1909 amalgams per woman),[32] which equates to each woman heating and handling mercury 9–10 times per day.

Frykholm[33] described a series of experiments on mercury from dental materials like those used in NZ. He demonstrated that when a pellet of CuAm was heated, the ambient air in a dental clinic environment could reach peak levels of 3000 $\mu g\,Hg/m^3$ air. In describing the practice of heating CuAm over an open flame, as was the practice for School Dental Nurses until 1975, Frykholm said, 'In order to avoid too much mercury vapor being released, the CuAm should not be prepared in this way, but preferably under a ventilated hood with good exhaustion' (p. 76). Frykholm's experiments also described exposure from AgAm, reporting 400 $\mu g\,Hg/m^3$ in the air above the mix.

Of the few long-term studies of mercury-exposed workers, Letz *et al.*[10] and Frumkin *et al.*[8] found significantly poorer general health in exposed workers than controls. Langolf and colleagues,[34, 35] in several studies, demonstrate that there are memory deficits in mercury-exposed workers compared with non-exposed controls, and suggest that it has not been established that memory deficits assessed during occupational exposure, are reversible. Gonzalez-Ramirez *et al.*,[36] comparing 19 mercury exposed and 20 unexposed dentists, found a significant dose–response relationship between urinary mercury and emotional lability. Powell,[9] who assessed workers from a mercury processing plant five years after their exposure, found that the most frequently recorded symptoms were those known to be linked to mercury poisoning, including body tremor, sweating, gingivitis, skin problems, memory and concentration problems, headache, fatigue and emotional ability.

A study of NZ School Dental Nurses, 30 years on from the commencement of their work with CuAm and unencapsulated AgAm, could contribute to the scant knowledge of long-term effects of chronic occupational mercury exposure, particularly in dentistry and specifically in women. The aim of the present study then was to test the null hypothesis: that there are no differences in health survey and neurobehavioral assessments between women who worked in the NZ School Dental Service before the withdrawal of CuAm or introduction of encapsulated silver, and matched women who were never occupationally exposed to mercury. This paper reports the cognitive, mood, general health and reproductive health findings. Psychomotor findings will be reported elsewhere.

Methods

Sample

A total population sampling method was used on a four-year cohort (1968–1971) of 115 graduates from the Willis Street School for Dental Nurses, Wellington, NZ. The sample had the youngest women who, before the withdrawal of CuAm, had had time to work through a three-year 'moral bond'. This was a point before which few women resigned but after which many did.

Participants were 75 women: 43 ex-School Dental Service employees in a mercury-exposed group and 32 matched controls. The response rate was a 40.2%. Of 32 women control group participants, 13 were sisters and 19 were friends of the exposed group. Groups were very closely matched for alcohol intake, tobacco intake and self-reported general health (Table 1).

Materials

The preliminary questionnaire This questionnaire surveyed physical injuries, health, work history and environmental influences on health. Health was rated first as a global measure,[37] and then as two sets of symptom data 'in the past' and 'in the present' on

Table 1 Matched variables: exposed and control participants

	Exposed group		*Control group*	
	M	*SD*	*M*	*SD*
Age in years	52.19	1.20	51.39	4.54
Alcohol intak (on a 4-point scale where 0 = none and 3 = very frequent)	1.76	0.95	1.78	0.75
Tobacco smoking (scale as above)	0.32	0.82	0.30	0.87
State of health (1 = very poor to 7 = excellent)	6.05	0.83	6.03	0.81

a 5-point scale. Reproductive health questions included experiences from fertility to childbirth and infants' health. Participants were asked to record either 'yes' or 'no' to a checklist of items. Environmental influences were quantified on a nine-category table of toxins and chemicals in relation to the one-year period prior to the survey. The mercury-exposed group was asked open-ended questions about their memory of the mercury-poisoning episode and work history.

A neurobehavioral test battery (NBTB) This was based on an American model[38] adapted and designed for middle- aged NZ women. Test selection issues included the need for tests to have been used in other occupational mercury-exposure studies, domain coverage, the time asked of participants, the need for portable 'low-tech' tests and cultural safety.

The California Verbal Learning Test (Adult-Research Version)[39] (CVLT) assessed cognitive skills: short-delay and long-delay recall tasks, an interference task, free and cued recall and a recognition task. Test author's instructions for recording data and scoring were followed.

The Rey 15-item test was introduced as a memory test, which it is, but verbal instructions stressed that this was a difficult task (which it is not), presenting an opportunity for inadequate effort, and achieving the dual purpose of a memory and a malingering test. Interpretation is described in Spreen and Strauss.[40]

The Symbol Digit Modalities Test (SDMT)[41] assessed higher executive function, concentration and attention. Participants completed a 10-digit trial, then had 1 min by stopwatch, for the main symbol-digit exchange task. The number of correct was recorded and errors deducted to give an individual score.

The Profile of Mood States (POMS) bipolar form, developed for non-clinical population, was used to assess mood.[42] It has six subscales that measure continuums from composed–anxious, agreeable–hostile, elated–depressed, confident–unsure, energetic–tired and clearheaded–confused factors. Participants rate the 72 stimulus words for their mood in the previous week. Presentation and scoring are described by the test authors.

Other not reported assessments included simple reaction time, the Grooved Pegboard, the O'Connor Tweezer Dexterity Test, grip strength and tremor.

Procedure
Massey University Human Ethics Committee approved the protocol (PN 01/125). After pilot testing with five pseudo-participants and minor revisions, the first author of the present study undertook all data collection over the course of one year, mostly in the participants' own homes.

Results

Overview of analysis
There were multiple stages in the process of data analysis. One case from the mercury-exposed group was excluded from the analysis due to a confounding traumatic brain injury. There was no difference in the distribution of scores between the exposed and control groups, and no outliers after the single case was excluded. Reported environmental influences included hormone replacement therapy, vitamins and various but few individual drug regimens. There was no evident pattern or confound presented by the data, hence they are reported no further. Work history for the mercury-exposed group was used to calculate an approximate duration of exposure. There were few missing data. The non-completion rate was 0.03% for the exposed group and 0.02% for the control group.

General health
Self-rated global health could score a maximum of seven, based on how participants rated their health in relation to their ideal of excellent health. There was no significant difference, and most women reported very good or excellent health: exposed group (M = 6.05, SD = 0.83) and control group (M = 6.02, SD = 0.81). For physical injuries in the past year, occupational overuse syndrome (OOS) was reported by 32.5% of exposed group and 6.66% of the control group χ^2 (1, $N = 70$) = 6.80, $P < .01$. All participants from the exposed group reporting OOS had medium-to-long duration of mercury exposure (medium exposure = 2 years training, 3 years bonded employment and up to a further 10 years employment; long duration exposure = criteria for medium but more than 10 years employment, not necessarily continuously).

Illness symptoms were analysed separately by time. Symptom experience when participants were in their late teens and early twenties showed no significant between-group difference. Present symptom experience included the six months prior to the completion of the survey. Of the 33 symptoms listed, the exposed group reported greater symptom experience generally, with significant differences on seven symptoms: arthritis, bloating, dry skin, headaches, metallic taste, sleep disturbances and unsteadiness (Table 2). Thyroid problems were not significant (Mann–Whitney U test, $P < 0.07$) but were rated most consistently at the high end of the 5-point symptom experience scale.

Reproductive health

Taken either as a ratio of all categories, or as a ratio of the two most frequently recorded categories, the exposed group experienced reproductive health problems at a level of more than 2:1 in comparison with controls. Early-age hysterectomy was experienced at the rate of 4:1. Frequency data are presented in Table 3. The number of participants for each category is given, with the corresponding percentage of the group in brackets, as two exposed participants reported choosing not to have children.

The neurobehavioural test battery

There were no significant differences between the exposed and control groups on the cognitive tests: SDMT [exposed: M = 38.1, SD = 4.64; controls: M = 36.47, SD = 6.71, $t = 1.23$, $P = 0.23$ (two-tailed), df = 71]; Rey 15-item memory test [exposed: M = 13.39, SD = 1.83; controls: M = 13.47, SD = 1.98, $t = -0.175$, $P = 0.86$ (two-tailed), df = 71] and the CVLT. Typical CVLT examples were: for the total recall score of a possible 80 from five trials [exposed: M = 60.38, SD = 7.26; controls: M = 60.83, SD = 7.75, $t = -0.25$, $P = 0.81$ (two-tailed), df = 67]; immediate free recall following a distraction list of a possible score of 16 [exposed: M = 12.67, SD = 2.34; controls: M = 12.47, SD = 2.60, $t = 0.34$, $P = 0.74$ (two-tailed), df = 67] and free recall following a 20-min delay of a possible score of 16 [exposed: M = 13.18, SD = 2.14; controls: M = 12.07, SD = 2.96, $t = 1.71$, $P = 0.09$ (two-tailed), df = 67].

Mood

POMS raw scores were separated into six subscale scores. Total score per subscale was calculated using the formula: Ts = sum (p1 to p6) − sum (n1 to n6) +18, where Ts = total score, p = positive stimuli and n = negative stimuli. This gave a subscale Ts range between 0 and 36, where 0 is the lowest mood score and 36 is the highest mood score. Two subscales, the agreeable–hostile and composed–anxious, showed significant differences between groups. The exposed group was more agreeable and more anxious than the control group, as presented in Table 4.

Table 2 Reported 'present' symptoms, by group

Symptom	*Exposed (%)*	*Control (%)*	*Mann–Whitney*	*U test*
Arthritis	37.5	16.6	U = 443.5	$P < 0.05$
Bloating	55.0	26.6	U = 408.5	$P < 0.03$
Dry skin	62.5	46.6	U = 369.5	$P < 0.01$
Headaches	65.0	46.6	U = 403	$P < 0.03$
Metallic taste	32.5	10.0	U = 400	$P < 0.02$
Sleep disturbances	70.0	46.6	U = 402	$P < 0.04$
Unsteadiness	30.0	6.6	U = 427	$P < 0.03$

Discussion

Between-group results supported the acceptance of the null hypothesis in all but the survey results for seven current health symptoms, OOS and hysterectomy experience, and for all but two subscales of the mood assessment of the NBTB. There was no evidence of malingering. It was notable from the outset of analysis that the two groups of women, one of whom was occupationally mercury-exposed and the

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Table 3 Reproductive health experiences, by group

Experienced	*Exposed N = 38*	*Control N = 30*	*χ^2 sig.*
Conception difficulties	8 (21%)	2 (6.66%)	ns
Miscarriage	9 (23.68%)	4 (13.33%)	ns
Stillbirth	2 (5.26%)	0 (0%)	ns
Low birth-weight baby	4 (10.52%)	1 (3.33%)	ns
Child with birth defect	7 (18.42%)	3 (10%)	ns
Child with learning difficulties	5 (13.15%)	2 (6.66%)	ns
Child with developmental delay	2 (5.26%)	1 (3.33%)	ns
Hysterectomy	10 (25%)	2 (6.66%)	$P < 0.04$[a]
Breast cancer	1 (2.5%)	0 (0%)	ns

[a]Pearson's χ^2 (1, $N = 70$) = 4.06, $P < 0.04$.

Table 4 POMS-Bi subscale scores (0 = lowest and 36 = maximum score), by group

Subscales	*Exposed group*		*Control group*		*t*	*P (two-tailed)*
	M	*SD*	*M*	*SD*		
Agreeable–hostile	28.76	4.99	26.22	5.89	2.09	0.04*
Composed–anxious	24.61	5.86	27.72	5.78	2.26	0.03*
Elated–depressed	25.27	5.59	25.72	5.94	−0.33	0.74
Confident–unsure	24.07	6.25	25.31	6.24	−0.84	0.40
Clearheaded–confused	28.27	5.51	28.66	4.41	−0.33	0.75
Energetic–tired	22.12	6.26	20.93	6.59	0.78	0.44

*Significant $P < 0.05$ (df = 71).

other not, were equivalent on most of the measures. In addition, the women's self-assessment of overall health against a perceived ideal was that they were in equally very good health.

The finding of equivalent perceived health indicated a within- and between-group homogeneity that, in the absence of biological exposure data, and no evidence of malingering, suggests there may be a sampling bias in favor of only well women volunteering to participate. It would be useful to know how representative the exposed group were, of all the women from the four-year work cohort. If symptoms of mercury poisoning, such as erythism, including depression, shyness and social withdrawal, were experienced and are enduring, then this may have decreased the likelihood of some women responding to a mailed invitation to a 2-h neurobehavioral assessment, while those who were in good health felt able to do so. The assumption is supported by qualitative data and anecdote from participants who reported on their recollection of the 1970s mercury poisoning episode. They named their colleagues who have lived with chronic, clinical depression, and the author was aware that the named women had not volunteered. Accepting the null hypothesis then could be to make a Type-2 error when generalising to the non-responders in the population. This is a limitation of the study that should be followed up by trying to establish reasons for non-responding.

In considering the importance of a significant OOS finding, mechanical vibration must be considered as a confounding variable. While Albers and colleagues[43,44] have established that peripheral nerve damage is associated with occupational mercury exposure, and this does raise the possibility that mercury exposure may predispose a person to OOS, those with long duration exposure to mercury have also been working the longest with vibrating mechanical devices in the form of the dental drill.

Of the reported symptoms, dry skin was the only symptom to feature strongly both in the past and in the present experience for the exposed group. It was the one symptom that came close to significance in the between-groups Mann–Whitney U test on reported symptoms in the past, and of all symptoms was the least likely to have been a chance finding, with a significant between-group difference at $P < 0.01$, for present symptoms.

Dry skin is a symptom of micromercurialism and acrodynia, hence the possibility remains that there was a link to early mercury exposure. Frequent unprotected skin contact with elemental mercury, from the use of CuAm, and the manual mixing of silver amalgam, marks out the school dental nurse from other dental personnel. They did not wear gloves, excluding disposable glove material as a sensitizer, but they did use methylated spirits for cold sterilization of surfaces and would have repeated washing their hands throughout a working day. Frykholm[33] reported on 29 cases of allergy to mercury from dental amalgam, "15 (seven of them dental nurses) had skin symptoms in the form of various kinds of eczema" (p. 62). Sinclair and Thompson[45] surveyed NZ dentists on hand dermatoses and found that one-third of their respondents had experienced skin problems in the previous year. The contribution of this finding to the understanding of the present study is diminished by Sinclair *et al.* not including any measure of amalgam use in their survey.

Of the six other symptoms reported with a significant between-group differences, the pattern is that the symptoms are predictable from the literature on mercury exposure and from the medical definitions of mercury poisoning. Numbness in the extremities, unsteadiness and metallic taste are classic signs, although with mid-life women, for three symptoms at least (arthritis, bloating and headaches), these could be confounded by many other causal influences; for numbness and unsteadiness, there may be influences related to the dental work operating position. In the 1970s, School Dental Nurses operated from a standing position on patients seated upright. There is no data on the effect of standing in unnatural

positions much of a working day could have in the long term, on the musculoskeletal system.

Symptoms of thyroid dysfunction were interesting, if not significant, in that when mercury is implicated in immune system dysfunction, thyroid function is questioned. In Jones,[46] anecdotal evidence that could be supported by medical records showed hyperthyroidism in remission following deamalgamation and detoxification. With four women from the exposed group and none of the controls reporting thyroid symptoms suggests that a link between this uncommon symptom and mercury exposure may warrant further investigation.

Where health problems specifically for women were concerned, from the 'past symptoms' list, menstrual difficulties were rated more by the exposed group than controls, but this did not feature in the present symptom reporting. This raised an issue for having used a past–present symptom checklist. It was not until data were available that it became apparent that for some symptoms, for example, menstrual difficulties or carpal tunnel syndrome, a major medical intervention such as surgery might have confounded comparisons over time.

One-quarter of the exposed group had a hysterectomy. This was the only significant finding in the section on reproductive health, although being in the exposed group increased the likelihood of reporting fertility and birth problems by 2:1. Perhaps there was an important reproductive health difference from the women being in their late teenage years when high-level mercury exposure began, and the consequence was surgery. It would explain why there was no equivalent (menopausal) menstrual difficulty pattern in the present symptoms. The data from the present study were nominal level and only begin to quantify a relationship. However, when read in conjunction with existing reports and reviews of women in dentistry, or any of the methylmercury studies,[47–50] reproductive health merits further study.

The spread of scores between subscales on the POMS shows a pattern for the total sample of a homogenous group of women. The predicted results from previous mercury studies[51,52] onward, where anger, anxiety and depression were evident in mercury-exposed groups, were not found. In the present study, the exposed group was significantly more anxious on the composed–anxious subscale, but against the prediction, the exposed group was not more depressed. On the hostile–agreeable subscale, rather than being more hostile, the exposed group was significantly more agreeable.

In addition to the between-group comparison, the group mean scores can be compared to the USA norms for the POMS.[42] In the composed–anxious subscale, the norms suggest 23 as the mean T-score, so that even with the significant difference, both groups are below the mean T-score of this subscale – a positive position. Taking the same approach to the agreeable–hostile subscale, the exposed group fell on the mean of T-score 29, and the control group below it at 26. From this it could be suggested that the control group was averagely hostile, rather than the exposed group being especially agreeable.

However, there may be a third variable, linked to personality or temperament, which was influencing the data, and presumably then, the other subscales. It was the perceived wisdom of the staff of the NZ Department of Health that women applying for training for careers in the School Dental Service should appear agreeable and friendly. These were virtues that were seen to be important in a woman who would need to gain rapport and the confidence of small dental patients undergoing painful procedures (R. Ritchie, Principal Dental Officer, personal communication, 16 March, 2004).

Agreeableness has been suggested as a personality trait for dentists, when one study found that 20% of dentists in a study of toxic influences from the dental clinic environment scored highly on the clinical analysis questionnaire, a finding interpreted as a good proportion being 'warm hearted and personable' (p. 57).[53] The authors add that such extremely high scores 'may indicate an unhealthy and overriding need for approval by others' (p. 57). Furthermore, in studies of occupational stress in dentistry, it has been shown that dentists want to be liked by their patients but perceive they are disliked[54] and that this is a continuing source of occupational stress. From these findings, if further studies of dental personnel were undertaken, both current mood and some state-trait assessment, such as the State-Trait anger and anxiety inventories,[55] may generate more useful data.

Memory was a domain where the women perceived themselves to be weak, but the CVLT results did not support their subjective concerns. Previous evidence[35] suggested that there may be enduring effects on verbal memory; this has not been demonstrated in the present study. There were no extraordinary developments in delivering the CVLT and no apparent reason not to accept the null hypothesis.

The digit-symbol substitution task was straightforward to administer and score. All participants completed the test, and none displayed any difficulty in the requisite rapid visual processing skills and task switching to make rapid motor responses. Meyer-Baron (personal communication, INA conference, Helsinki, 2005) suggested that in mercury

studies, where cognition shows between-group differences, an intelligence measure such as a vocabulary test would be necessary to establish group equivalence. Although the present study did not include such a measure, cognition does not appear to be a domain with residual effects.

Conclusion

The principal finding of this study is that the sample of NZ School Dental Nurses, who were chronically exposed to high levels of mercury vapor from heating CuAm, and skin contact with elemental mercury when mixing filling material, do not appear to be neurobehaviorally compromised by their early career choice, now that they are aged in their fifties. However, while the exposed group perceived themselves to be in very good health, there were seven symptoms from a list of 33 selected from a medical definition of mercury poisoning, that were reported to a significantly greater extent than the control group. Unfavorable reproductive outcomes for the exposed group were reported at more than twice the rate of controls. Hysterectomy experience was statistically significantly higher in the exposed group, making this is a topic that warrants further investigation. The possibility of sampling bias, in favor of well women only forming the exposed group, also needs to be addressed by a follow-up survey of non-responders. Without knowing why more exposed women failed to respond, an issue of representativeness of the exposed sample, it is difficult to generalise the findings more broadly to all women who worked in dentistry, and with CuAm in particular.

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Q3 The “apostrophe” has been deleted in Table 2 under the column “control (%)”, and “control” in Table 3. Please confirm that it is correct