Investigation of dose related neurobehavioural effects in paintmakers exposed to low levels of solvents

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Abstract

A cross sectional study was carried out to compare 110 paintmakers exposed to solvents with 110 age matched controls for outcome measures designed to assess cognitive performance and mental health. Hygiene data available for the paintmakers allowed the development of individual indices of solvent exposure and the analyses of health effects in relation to both duration and intensity of exposure. No effects on cognitive functioning or mental health were found in the paintmakers. For most of their period of employment the exposure of the paintmakers had been below current occupational exposure limits. The results are therefore interpreted as providing support for the view that long term exposure at or below current compliance levels does not result in damage to the central nervous system.

(*Occup Environ Med* 1994;51:626-630)

Keywords: solvent exposure, paintmakers, neurobehavioural tests, mental health.

Evidence that long term exposure to organic solvents may damage the central nervous system has been accumulating for many years. In more recent investigations the effects found have tended to be much less severe than those reported in earlier studies and much more subtle in nature, represented by small decrements in performance on neurobehavioural tests.¹⁻³ Although methodological improvements in research may partly account for these differences a further explanation may lie in the reduction of exposure levels that has occurred in many workplaces during the past 30 years. Although the study of solvent related effects has always been a controversial area the neurotoxic potential of many solvents is now generally accepted and much of the present debate therefore seems to centre on the question of the precise level or duration of exposure likely to be associated with health effects. Most current occupational exposure limits, which take into account neurotoxicity, relate only to acute effects as the establishment of a no-effect level is in the short term much less problematic from a scientific point of view than in situations where long term effects are under consideration. The problems of developing valid retrospective indices of

exposure in long term studies to investigate dose-effect relations have been well documented⁴ and few investigations have successfully overcome this problem. Nevertheless there is now increasing recognition that more information about the levels at which chronic effects occur will be required if future limits, which take into account long term as well as acute effects, are to be set with any degree of confidence.

Prospective studies of chronic effects are expensive, logistically difficult, and by their very nature unable to provide information for many years. An alternative means of approaching this question is to focus on groups of workers where more detailed information on earlier exposure is available. Most reported studies have been concerned with end product users, in particular brush and spray painters. This is understandable as it is among these workers that the problem has most often been manifest.²⁻⁷ Such individuals frequently work in uncontrolled conditions and are exposed periodically to high levels of solvent vapour that result in acute effects such as headache, nausea, and dizziness. Regular hygiene monitoring is often absent due to the varied nature and conditions of the work. Although such studies have been able to provide evidence of the existence of long term effects under certain working conditions, information about the effects has necessarily been limited. By contrast, workers involved in paint manufacture usually work in conditions of greater control where exposure are likely to be somewhat lower than those experienced by many product users. Most importantly, large industrial concerns have tended to carry out regular environmental monitoring and thus have accumulated a bank of hygiene data that may extend over many years. A recent study of paintmakers in the United States was able to make use of this type of data to define more precisely the levels at which neurobehavioural effects might be found.⁸ Our study adopted a similar approach in that the population under investigation was drawn from paintmakers employed at two large manufacturing plants, where regular hygiene monitoring had been carried out for many years. The objectives of the investigation therefore were to establish whether long term health effects in the form of impairment of cognitive functioning or mental health were evident in workers manufacturing paint and, if so, whether such effects were related to the extent of solvent exposure as determined by reference to pre-existing hygiene data.

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Accepted 23 May 1994

Materials and methods

STUDY DESIGN AND POPULATION

A cross sectional design was adopted to compare a group of workers exposed to solvents with a group of unexposed controls on a range of outcome measures selected to assess cognitive functioning, mental health state, and symptoms in relation to solvent exposure. As well as whole group comparisons, the availability of data on past exposure permitted the division of the exposed population into groups and hence allowed the investigation of any dose-effect relations. The exposed population consisted of 110 male paintmakers employed on two sites by a large paint manufacturing company. Potential subjects were selected at random from staff lists of those currently employed in areas of the plant where there was regular solvent exposure. The control population consisted of 110 male workers employed at a plant belonging to the same company manufacturing nylon fibre and with no known neurotoxic exposure. Controls were individually age matched, within three years, to exposed subjects. A series of exclusion criteria was applied to both exposed subjects and controls namely, (a) specified previous or existing diseases likely to affect the nervous system, (b) previous head injury involving loss of consciousness, (c) previous or existing alcohol or other drug dependency, and (d) a non-English first language. Also, controls were excluded if they had current or previous notable exposure to solvents in the course of a job or hobby, "notable" being defined as >16 h of solvent handling per month for >3 y. This was deemed to represent greater exposure than would occur in the normal population in the course of everyday life. All participants received overtime payment for the period of their participation, which was outside normal working hours and before work after the week end.

MEASURES

Assessment of cognitive functioning was carried out under standardised conditions with a range of tests selected from the computer administered neurobehavioural evaluation system.⁹ Those selected were symbol-digit substitution, hand-eye coordination, digit span, associate learning, pattern memory, colour word vigilance, continuous performance, and associate recall. Mental health state was evaluated with the standardised 12 item version of the general health questionnaire (GHQ).¹⁰ The GHQ was developed as a screening tool to assess the prevalence of psychiatric symptoms in community based and occupational samples. As well as conventional scoring to compare groups the questionnaire provides threshold "caseness" scores, which identify those at risk of developing psychiatric illness.

The prevalence of symptoms associated with exposure to solvents was assessed with the Orebro 16 item questionnaire (Q16)¹¹ developed to identify neurotoxic effects in occupationally exposed populations.

As well as these measures information was collected on factors having the potential to influence outcomes. These included (a) information collected with a purpose developed questionnaire on smoking and alcohol consumption, computer experience, recent sleep loss, viral infection, and medication, (b) two measures of premorbid ability, namely the national adult reading test (NART)¹² and the neurobehavioural evaluation system (NES) vocabulary test, and (c) a measure of job satisfaction.¹³

EXPOSURE ASSESSMENT

The primary objective of the exposure assessment was to divide the exposed subjects, on the basis of their past and current exposure, into reasonably homogenous and defensible groups, to show any dose-effect relation. This was carried out with reference to occupational exposure monitoring data generated from past records of the company. Details of the methods are described elsewhere.¹⁴ Three different retrospective exposure indices for individual subjects were calculated: (a) duration of exposure (y); (b) cumulative exposure representing the sum of the mean daily exposure (8 h time weighted average (TWA)) to solvents (ppm) by years of exposure; (c) intensity of exposure represented by cumulative exposure, divided by duration (y). These indices formed the basis of the exposure groupings used to carry out analyses of dose-effect relations of the various outcome measures.

PROCEDURE

Participants completed questionnaires and neurobehavioural tests on a single session that took place in a room on site immediately before starting the afternoon (2 pm–10 pm) shift. All participants were employed on rotating 8 h shifts and the immediate and long term effects of shift work were therefore standardised across subjects and controls. Exposed subjects had an exposure free period of at least 12 h before testing and it was ascertained that controls had no recent (previous 12 h) exposure as a result of activities such as home decorating. All participants were tested for breath alcohol with an alcometer. These results were uniformly negative. The experimenter remained with participants throughout the procedure in case assistance was needed. Most participants completed the tests and questionnaires unaided after initial instructions delivered in a standardised format.

Results

RESPONSE RATES

Response rates on the two paintmaking sites were rather low (43% and 42%) raising concerns that this may have produced a bias in the study population—that is, either a healthier group (with no health concerns) or a particularly unhealthy group (with greater than average health concerns)—electing to participate. To investigate this, follow up letters were sent to non-participants requesting the reason for

their non-participation. Of the 50% of those who replied, 30% stated that they had decided not to participate because they had no health worries. Of the rest only two individuals gave health worries as their reason for not taking part, the main reasons being shift changes, annual leave, or general lack of interest in research. This gave support to the view that any bias in the exposed population was likely to be of over representation of the less healthy members thus increasing the likelihood of finding a positive relation between exposure to solvents and outcome measures.

CHARACTERISTICS OF THE POPULATION

The exposed and control groups were compared on a number of factors with the potential to influence outcome measures. There was no difference between the two groups in terms of: educational level (Wilcoxon test $P = 0.36$); computer experience (Wilcoxon test $P = 0.21$); current smoking (Wilcoxon test $P = 0.39$); current units of alcohol per week (paired t test $P = 0.72$); and lifetime units of alcohol consumed (paired t test $P = 0.69$). A similar number in each group reported use of spectacles for reading (45.5% of painters *v* 40.9% of controls). No subjects reported difficulties in reading the computer screen. A similar percentage in each group reported left handedness (10.0% of painters *v* 10.9% of controls), which is similar to figures reported for the general population of between 8% and 11%.¹⁵ Job satisfaction was assessed at all three sites and compared with analysis of variance. There were no significant differences between groups ($P = 0.89$).

Premorbid ability assessed with both the NART and NES vocabulary test showed no significant differences between the groups. (NART paired t test $P = 0.13$; NES vocabulary paired t test $P = 0.36$).

The reported occurrence of other factors assessed, namely recent sleep loss, viral infection, and use of medication was very low in both the exposed and control populations.

EXPOSURE LEVELS

Details of exposures in the two plants are provided elsewhere.¹⁴ Workers were exposed to a mixture containing predominantly white spirit, toluene, xylene, methyl ethyl ketone and methyl isobutyl ketone. Other substances present were acetone, isobutyl alcohol, n-butyl acetone, and n-butyl alcohol.

The American Conference of Government Industrial Hygienists (ACGIH) "mixtures formula" was applied to data collected during 1980 and between 1985 and 1990—that is, the measured concentration of each solvent was divided by the relevant exposure limit and the fractions were summed. If the sum was < 1 then compliance was deemed to have been achieved. In the two plants levels were typically well below compliance levels in most of the 15 areas where the study participants worked. In eight areas no readings were > 1 . In six areas $< 6\%$ of the readings were > 1 . Highest levels were recorded in the one remaining area where 11% of readings were > 1 . Here the maximum was 6.0 with an arithmetic mean of 0.48.

GROUP EFFECTS (MENTAL HEALTH AND SYMPTOMS)

Comparison of the GHQ scores for exposed subjects and controls showed no significant differences in terms of either total scores (mean (SD) 1.1 (2.1) *v* 0.9 (2.0)) or the percentage of each group falling above the defined caseness threshold (16.3% *v* 15.4%). The numbers falling above the threshold were similar to those reported by Goldberg for community samples.¹⁰

Scores on the Q16 were not significantly different in the two groups (paired t test $P = 0.36$); mean (SD) scores (paintmakers 3.2 (2.6) *v* controls 2.9 (2.8)) were low compared with those reported by Hogstedt *et al.*¹¹ but very similar to those obtained in a previous British sample of workers exposed to solvents.³

DOSE-EFFECT RELATION (NEUROBEHAVIOURAL TESTS)

The exposed group was subdivided in terms of the three alternative assessments of long-term exposure: duration in years; cumulative exposure; intensity of exposure¹⁴; and analysis was carried out in each case for neurobehavioural outcomes to assess possible dose-effect relations. Also those factors judged logically to be likely to exert the most significant influence on results were adjusted for at this stage. Although, at group level, painters and controls had been shown to be well matched for potential confounders or modifying factors, this adjustment was carried out to increase the precision of the analysis. These factors were premorbid ability (NART error

Table 1 Mean differences in test outcomes between painters and their age matched controls by duration of exposure, adjustment for NART, computer experience, and life time alcohol consumption

Test	< 11 y (n = 39)	11–20 y (n = 43)	21–30 y (n = 17)	> 30 y (n = 11)
	Coefficient (95% CI)	Coefficient (95% CI)	Coefficient (95% CI)	Coefficient (95% CI)
Paired associate learning	-0.04 (-0.76 to 0.69)	0.20 (-0.52 to 0.91)	0.03 (-1.02 to 1.08)	0.54 (-0.83 to 1.91)
Hand-eye coordination	0.01 (-0.16 to 0.18)	0.05 (-0.13 to 0.22)	0.11 (-0.14 to 0.36)	0.02 (-0.30 to 0.35)
Symbol-digit substitution	0.09 (-0.09 to 0.26)	0.06 (-0.11 to 0.23)	-0.20 (-0.45 to 0.05)	-0.25 (-0.58 to 0.08)
Digit span†	-0.06 (-0.81 to 0.69)	0.05 (-0.68 to 0.79)	0.14 (-0.94 to 1.22)	1.00 (-0.41 to 2.40)
Pattern memory	-0.39 (-1.22 to 0.45)	0.02 (-0.80 to 0.84)	0.22 (-0.98 to 1.43)	0.94 (-0.63 to 2.51)
Continuous performance	-8.58 (-26.41 to 9.26)	-10.00 (-27.56 to 7.57)	-31.01* (-56.70 to -5.31)	-8.58 (-42.12 to 24.97)
Colour word vigilance	-2.68 (-33.34 to 27.97)	-44.84* (-75.10 to -14.69)	-40.26 (-85.53 to 5.01)	-40.89 (-95.12 to 13.25)
Associate recall	0.11 (-0.79 to 1.02)	0.21 (-0.69 to 1.10)	0.03 (-1.27 to 1.34)	-0.32 (-2.02 to 1.39)

* $P < 0.05$. Performance of exposed subjects better than that of controls.

†Difference between forwards and backwards span.

NART = national adult reading test.

Table 2 Mean differences in test outcomes between paintmakers and their age matched controls by cumulative exposure, adjustment for NART, computer experience, and lifetime alcohol consumption

Test	Low <300 ppm-y (n = 42) Coefficient (95%CI)	Medium 300-600 ppm-y (n = 37) Coefficient (95%CI)	High >600 ppm-y (n = 25) Coefficient (95%CI)
Paired associate learning	0.20 (-0.50 to 0.90)	-0.04 (-0.77 to 0.70)	0.30 (-0.61 to 1.20)
Hand-eye coordination	0.11 (-0.06 to 0.28)	-0.01 (-0.19 to 0.16)	0.30 (-0.19 to 0.24)
Symbol-digit substitution	0.14 (-0.03 to 0.31)	-0.06 (-0.23 to 0.12)	-0.22 (-0.44 to 0.01)
Digit span†	0.23 (-0.49 to 0.94)	-0.43 (-0.18 to 0.32)	0.55 (-0.38 to 1.47)
Pattern memory	-0.67 (-1.46 to 0.11)	0.52 (-0.30 to 1.34)	0.45 (-0.56 to 1.46)
Continuous performance	-2.88 (-19.77 to 14.00)	-20.35 (-37.96 to 2.75)	-22.13* (-43.87 to -0.39)
Colour word vigilance	1.18 (-25.53 to 27.89)	-51.48* (-79.36 to -23.60)	-52.86* (-87.53 to -18.18)
Associate recall	0.44 (-0.44 to 1.31)	-0.02 (-0.93 to 0.89)	-0.09 (-0.21 to 1.04)

Footnotes as for table 1. Total n < 110 as detailed exposure data were not available for all subjects.

scores), computer experience (subject rating), and lifetime alcohol consumption. Results show analysis of covariance for the different test outcome measures; duration of exposure (table 1), cumulative exposure (table 2) and intensity of exposure (table 3). Duration (table 1) was expressed in terms of the number of years working in a part of the factory where solvent exposure occurred. The range was 3–42 y and this was divided into four groups (see table 1). Table 2 shows that cumulative exposures were calculated for individual subjects. These represented mean daily exposure (8 h TWA) to solvent mixtures (ppm) by years of exposure. The range was from 12–1800 ppm and this was subsequently divided into three groups, low, medium, and high. Individual exposure intensities (table 3) were calculated by dividing cumulative exposure by years of exposure, giving a range of 2.6–60 ppm as a yearly mean 8 h TWA. These were similarly divided into low, medium, and high groups.

Results of these analyses gave no indication of dose-effect relations of any of the three retrospective solvent exposure indices. A significant difference in performance between paintmakers and controls on the continuous performance and colour word vigilance tests was noted in some medium and high exposure groups. As poorer performance occurred in the control group this is unlikely to be a solvent related effect unless one advances the unlikely hypothesis that solvent exposure may enhance performance on tasks with a high attentional loading.

Discussion

The objective of the study was to determine whether workers employed in paint manufac-

turing showed similar signs of cognitive impairment and mental health problems to those identified in some product users. A particular feature of this investigation was the availability of exposure data that enabled the development of individual retrospective exposure indices. This allowed us to be more precise about the levels of exposure under consideration and to carry out an assessment of possible dose-effect relations with more confidence than in earlier investigations. Exposure indices were constructed, which took into account both the duration and intensity of solvent exposure.

The exposure data indicated that although workers in these factories were occasionally exposed to levels above current occupational exposure limits, average exposures were usually below compliance levels. As the performance of the exposed subjects was not inferior to that of the controls on any neurobehavioural outcomes, either in the highest (>40 ppm) or longest duration (>30 y) exposure groups, these results strongly suggest that workers with moderate levels of exposure (below current occupational exposure limits) do not experience effects on the nervous system even when such exposure takes place over many years.

The study had a number of strengths in that subjects and controls were shown to be well matched in terms of factors such as pre-morbid ability, educational level, drinking and smoking habits, and familiarity with computers. Possible influences of time of day and shift system were controlled for and there seemed to be no difference in the general level of job satisfaction of the two groups. Some concern may be expressed about the rather low response rate, which had the potential to produce a population bias as well as that

Table 3 Mean differences in test outcomes between paintmakers and their age matched controls by intensity of exposure, adjustment for NART, computer experience, and lifetime alcohol consumption

Test	Low <20 ppm (n = 31) Coefficient (95% CI)	Medium 20–40 ppm (n = 47) Coefficient (95% CI)	High >40 ppm (n = 26) Coefficient (95% CI)
Paired associate learning	-0.13 (-0.93 to 0.67)	0.40 (-0.24 to 1.05)	-0.05 (-0.95 to 0.85)
Hand-eye coordination	0.29* (0.11 to 0.47)	-0.12 (-0.26 to 0.03)	0.06 (-0.14 to 0.26)
Symbol or digit substitution	0.15 (-0.04 to 0.34)	-0.05 (-0.21 to 0.11)	-0.16 (-0.38 to 0.06)
Digit span†	0.21 (-0.62 to 1.04)	-0.04 (-0.71 to 0.64)	0.09 (-0.85 to 1.02)
Pattern memory	-0.22 (-1.14 to 0.70)	0.04 (-0.70 to 0.78)	0.26 (-0.78 to 1.30)
Continuous performance	0.05 (-19.17 to 19.21)	-19.00 (-34.57 to -3.42)	-20.50 (-42.23 to 1.23)
Colour word vigilance	6.20 (-23.92 to 36.30)	-48.46* (-73.20 to -23.72)	-39.27* (-74.78 to -3.75)
Associate recall	0.21 (-0.79 to 1.21)	0.06 (-0.75 to 0.87)	0.27 (-0.86 to 1.40)

Footnotes as for table 2.

which may result from the "survivor" effect, which is an inherent problem in cross sectional studies. One cannot discount the possibility that those who were more seriously affected had either left the workforce or were reluctant to take part. The results of the follow up of non-responders suggested that it was more likely to be the healthier workers who refused to participate, thus the probability of effects being concentrated in the exposed population is increased. Also, the effects under investigation are subtle and preclinical and are likely therefore to be present in workers who are still part of the workforce and to all outward appearances healthy.

The finding that the performance of the control group was significantly poorer in two tests was curious and difficult to explain. This was found in both whole group and dose-effect analysis. In the dose-effect analysis it is important to emphasise that "dose" in this context referred to the exposed group and did not necessarily correlate with, for example, years of employment of the controls. In examining possible differences not related to solvents in the working conditions of the two groups only one factor emerged as possibly significant, namely that controls were exposed to higher levels of continuous noise. Some evidence from laboratory based and non-occupational studies suggests that exposure to continuous noise at levels below that likely to impair hearing may reduce the ability to sustain attention, and that this effect may persist after removal from exposure.^{16 17} This is, however, speculative in terms of an explanation and represents an area that might need further investigation. In relation to the objectives of our study it seems reasonable simply to conclude that this difference in performance is not related to exposure to solvents.

As well as an assessment of cognitive performance consideration was given to the mental health (vulnerability to problems of anxiety and depression) of the exposed group. The measures used are sensitive to earlier and more subtle difficulties of the type that would not necessarily come to the attention of the medical department or result in withdrawal from the workplace. There was no indication from our results that the mental health of the exposed group was poorer than that of the controls or in any way unusual compared with that of samples drawn from other working populations. This is perhaps not unexpected in the light of previous evidence that even where some subtle impairments of cognitive function were found in users of solvent based products there was no increased prevalence of mental health problems.³ Similarly the number of symptoms reported, as assessed by a questionnaire that has been used as a screening tool amongst Swedish workers, did not indi-

cate an excess of symptoms related to neurotoxic agents in these paintmakers. Again this result is consistent with that found in our previous investigation where we found very low symptoms reported by painters and other solvent users.³

In conclusion, therefore, our study has provided some evidence to support the view that adherence to current United Kingdom occupational exposure standards may as well as preventing the acute pre-narcotic effects of solvents, also provide protection from the putative cumulative effects of long term exposure.

We gratefully acknowledge the support of ICI Paints Division in funding this investigation. In particular we would like to thank Dr Frank Rose, Dr Geoff Paddle, and members of the medical department of ICI Paints, Mr John Clark and members of the hygiene department of ICI Paints, and Dr Steve Jones and members of the medical and personnel departments of ICI Fibres. Thanks are also due to Karen Sweet who helped collect the data, to Janet Bailey who typed the final manuscript and above all to the willing study participants.

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