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Delayed manifestations of CNS effects in formerly exposed printers - a 20-year follow-up

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ABSTRACT

Whether long-term occupational exposure to organic solvents may affect mental and cognitive functioning later in life, remains unclear. In this study, twelve rotogravure printers formerly exposed to toluene and 19 referents, all initially examined in the mid-1980s, were reexamined after twenty years, applying neuropsychological tests, symptoms and social interaction questionnaires, medical examination, and exposure assessment of each individual's cumulative exposure. By far the most extensive exposure, mainly toluene, had occurred before 1985.

The printers were found to have deteriorated more than their referents in cognitive functioning affecting reasoning and associative learning. No relevant additional exposure during the lengthy time period between assessments could explain this discrepancy. In addition, printers performed significantly worse than the referents in verbal memory and sustained attention at follow-up, where also a dose-effect relationship was noted for reasoning. While the printers did not report more subjective cognitive complaints than the referents, a slightly higher depression score was noted for the printers.

The findings of significantly worse deteriorations in cognitive functioning in previously toluene-exposed printers are in line with our hypothesis that sub clinical deficits during the working life may become manifest later in life, indicating that exposure may in fact interact with ageing. However, considering the small study groups the results must be interpreted with caution.

Keywords: solvents, cognitive, long-term, follow-up, toluene

1. Introduction

The question whether long-term occupational exposure to organic solvents may affect mental and cognitive functioning later in life has been a subject of speculation rather than study, although some indications of delayed CNS effects after earlier neurotoxic exposure can be found. Even after controlling for exposure time, workers exposed to organic solvents as well as lead displayed larger age-related cognitive impairments than unexposed controls, and more pronounced age-related neurological abnormalities were seen in workers with high past mercury exposure than in a referent group, especially in the oldest individuals, in spite of insignificant exposure differences between the younger and the older persons [9, 3].

There is a possibility that signs of cognitive dysfunction may appear earlier than normal in previously exposed individuals as a result of diminishing reserve capacity due to an increased rate of neuronal loss caused by the neurotoxic exposure in combination with normal, age-related neuronal attrition. Findings to support this hypothesis were reported in a long-term, follow-up study of a group of floor layers with past exposure to solvent-based glues, who were found to have deteriorated more than the referents in cognitive functions 18 years after the first assessment, in spite of the fact that the exposure dated back 30 years [45]. Some additional support for the possibility of delayed manifestations has been forwarded by Schwartz et al. who reported associations between deteriorations in cognitive functioning and past exposure to lead in 40–76-year-old industrial workers long after cessation of the exposure [54].

In a study in the mid-1980s of rotogravure printers exposed to toluene and an unexposed referent group, no group differences in the cognitive tests applied were found after adjusting for differences in verbal ability [47]. In contrast, higher cumulative exposure was associated with somewhat lower results in a few tests. The occupational setting of these printers was characterized by high past mean toluene exposure and the median exposure duration was 29 years.

Neurotoxic effects of toluene exposure are well documented in animal studies and in humans following long-term and/or intensive exposure with evidence of central nervous system (CNS) damage [8, 21]. Evidence of acute and chronic encephalopathy in toluene abusers as well as diffuse cerebral, cerebellar and brainstem atrophy has been reported recurrently [21, 35]. Chamber studies have demonstrated effects mainly on reaction time at exposure levels above 100 ppm (380 mg/m^3) while at lower levels, 80 ppm (300 mg/m^3), no effect has been reported [32, 4, 11]. Occupational exposure has been associated with neurasthenic complaints and, more rarely, with cognitive decrements [36, 10, 28, 20].

The aim of the present study was to clarify the long-term effects of occupational exposure to organic solvents by means of a longitudinal follow-up of a group of previously toluene-exposed printers and their referents initially examined in the mid-1980s [47]. Specifically, the following questions were addressed: does long-term occupational exposure to toluene lead to aggravated cognitive impairment later in life? More specifically, will printers with long-term exposure to toluene before 1980 be found to have deteriorated more in their cognitive performance than their unexposed referents when re-examined 20 years later?

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An additional aim was to examine whether printers would report more complaints of cognitive dysfunction and mood disturbances, and poorer social adjustment compared with the referents.

2. Methods

2.1 Subjects

The initial study in 1983/1984 included 30 male rotogravure printers and a reference group of 50 sugar refinery workers and 22 railway carriage repair shop workers, employed and active at work when examined [47]. All subjects still alive in 2003 were approached with a letter of invitation, followed by a personal telephone call to each printer and to referents of similar age. Exclusion criteria were (a) present or past exposure to organic solvents in referents (to a greater extent than is usually seen among these workers); and (b) diagnosed disease that markedly affects CNS functions, e.g. cerebrovascular disorders, brain tumour, multiple sclerosis, Parkinson's disease, Alzheimer's disease, long-term severe epileptic disease, sleep apnoea and high alcohol intake.

Seven printers and 14 referents had died; one printer and two referents could not be located; eight printers and 20 referents declined participation because of poor somatic health (six printers and four referents) or for unspecified reasons; two printers and seven referents were excluded because of CNS disease (stroke, Alzheimer's disease, Parkinson's disease and sleep apnoea). Of the available referents only individuals at an equivalent age range were included in the examinations. This was motivated by the wish to avoid statistical adjustment for the cofactor age on the presumed not linear detrimental effects of the previous exposure. Altogether 12 rotogravure printers and 19 referents participated in

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the follow-up study; response rates were 55 % of the available printers and 41 % of the available referents of similar age.

Age varied from 59 to 80 years (mean 70, standard deviation (SD) 6.8) among the printers and from 57 to 84 years (mean 67, SD 7.3) among the referents. The majority of subjects (nine printers, 14 referents) had retired, one printer and five referents were still occupationally active and two printers were unemployed. School education averaged 9 and 11 years, respectively, for printers and referents. All subjects gave their informed consent prior to their participation in the study. The study was approved by the Ethics Committee of Lund University (LU 423-03).

Printers participating in the follow-up study did not differ significantly from referents in any aspect of cognitive performance at baseline. For raw scores, see Table 2.

2.2 Exposure

Working conditions for the printers had been thoroughly investigated in the mid-1980s, including assessment of present and past solvent exposure for printers, mainly to toluene, and for the referents in the early 1980s [47]. The exposure situation since then was followed up. Semi-structured interviews by a senior occupational hygienist on telephone or during personal meetings with all subjects focused on work tasks, chemical handling and the general working environment during the person's whole working life. Possible exposure during leisure time was explored as well. The information collected at the present interviews and the data from the 1980s were used to calculate each individual's cumulative exposure to solvents and other potentially neurotoxic exposure. The time-

weighted average (TWA) exposure was estimated from measurement reports and information on preventive measures at the different workplaces. The hygienic effect (HE) - the quota of the estimated TWA solvent exposure and the occupational exposure limit of the given solvent - was used when calculating total solvent exposure (Swedish OELs 2000 were used) [60, 38]. The cumulative solvent exposure was calculated as the sum of the estimated HE from solvent exposure during each year, multiplied by the time actually having worked in contact with the solvent. The cumulative exposure of lead, the only other chemical with a neurotoxic effect present, was assessed in the same way.

The rotogravure printers had been exposed mainly to toluene. By far the most extensive exposure to toluene or any other solvent among the printers occurred before 1985 (Figure 1 and Table 1). Past mean toluene exposure was estimated to around 1,500 mg/m^3 during the 1950s and the early 1960s. The exposure level was gradually reduced by preventive measures, and towards the end of these printers' working life (mid-1980s) the mean levels of toluene were 43 and 157 mg/m^3, respectively, at two printing shops. Neither toluene nor any other volatile solvent was involved in any exposure during the follow-up period. Only four printers had been exposed after 1992. No relevant exposure to solvents, none to toluene, was found in the referent group during the follow-up period or in the past. Neither printers nor referents had engaged in any activity during their leisure time that had resulted in any solvent exposure exceeding that of the general population.

A short period (2 years in the late 1930s) of low level lead exposure when sealing packages was noted for one printer and likewise low level or infrequent lead exposure was noted for three referents (plumbing up to 1968 and using lead-containing paint in the mid-1940s).

[Figure 1]   [Table 1]

2.3 Medical Examination

At the site visit all participants were examined by a specialist in occupational and environmental medicine. The medical interview and clinical examination concerned general health status and focused specifically on signs of somatic disease with known negative CNS effect, psychiatric disorder and alcohol or drug overuse [56]. Where needed, and with the subject's written consent, additional information on a subject's diagnosis was obtained from hospital records.

The medical interview was structured in accordance with London School of Hygiene cardiovascular, dyspnoea and respiratory questionnaires. The structured neurological interview had special focus on cerebrovascular symptoms. Finally, the interview included questions about alcohol, smoking habits and drug use.

The subjects were examined physically, with special attention given to the cardiovascular system, according to World Health Organization (WHO) recommendations [51]. They also underwent thorough neurological examination. The medical examination was completed by blood tests screening for diabetes, inflammation, malabsorption, and thyroid, liver and kidney function as well as alcohol consumption. Analyses were made of

haemoglobin, differential white cell count, glycosylated haemoglobin (HBA1c) in blood, creatinine, C-reactive protein (CRP), calcium, thyroid-stimulating hormone (TSH), free thyroxine (fT4) and homocysteine in plasma and, finally, carbohydrate-deficient transferrin (CDT), a marker of alcohol consumption, in serum.

A total of twelve printers and 19 referents underwent a complete medical examination. None of the participants had diagnoses or clinical signs of cerebrovascular disease. There were nine printers and eight referents with cardiovascular disease (mild hypertension or ischaemic heart disease). Three printers and two referents had minor deviations in their blood tests, none of which could affect the cognitive tests. All participants had normal values of CDT. Except for two printers with a former diagnosis of chronic toxic encephalopathy, we found no diseases or discrepancies in the medical examinations of relevance for cognitive function. There were four smokers and six ex-smokers in the printer group, and two smokers and ten ex-smokers among the referents. No excessive drinking habits were reported in either of the examined groups.

2.4 Questionnaires

Two main dimensions, symptoms and social interaction, were assessed as self-reports by the following three questionnaires:

The Symptom Checklist (SCL-35); an abridged version of the SCL-90 for assessment of psychosomatic and emotional distress comprising the 35 items which form the three subscales of somatization, depression and anxiety [15]. Respondents are asked to indicate to what extent they have been distressed by each symptom during the last week on a 5-point Likert scale. Scale scores are computed as the average of the item scores.

Euroquest-9; a subscale of the Euroquest questionnaire, measuring recent subjective cognitive functioning problems [12]. Respondents are asked to indicate how often during the last month they have experienced each of nine items concerning cognitive problems (e.g. forgetfulness and inattention), on a 4-point frequency scale. Scale scores are computed as the average of the item scores.

Interview Schedule for Social Interaction (ISSI); a questionnaire measuring the availability and perceived adequacy of facets of social relationships, such as the respondent's availability of and satisfaction with close affective relationships and also the relationship with friends, workmates and acquaintances [29, 61, 19]. In the present study a 30-item version was used. The items have varying response format, and are dichotomized in line with standard guidelines. Four subscales are computed: availability of social integration (AVSI), adequacy of social integration (ADSI), availability of attachment (AVAT) and adequacy of attachment (ADAT). Scale scores are computed as the average of the item scores. The scores range from 0 to 1, a higher score indicating a higher degree of social interaction.

2.5 Neurospychological Tests

We used the same eight neuropsychological tests that were used in the initial study, mostly derived from the Swedish TUFF battery and covering the following functional domains: verbal functions, concept formation and reasoning, construction, attention, memory and motor performance, and included the following tests: Synonyms, a vocabulary test, Figure Classification, assessing inductive reasoning, and Kohs' Block Design for visuospatial skill, all from the Swedish D-S battery; the WAIS Digit Symbol

test, the Dot cancellation test and Cylinder Board for perceptual and motor speed from the TUFF battery; the Revised Visual Retention Test, Benton form C, and the Cronholm-Molander Paired associates task, assessing verbal memory [16, 18, 63, 14]. We used a local version of the Dot cancelation test, where four aspects were evaluated, namely speed (total time), accuracy (number of errors), performance variability in speed, and a weighted score taking both speed and accuracy into account (time x error score) [48]. The number of correct reproductions and the total number of errors were evaluated on the Benton test. The last test, based on associative learning, includes immediate and delayed recall.

Some additional tests, known to be sensitive to the influence of ageing, were also administered at follow-up. The Trail Making Test, assessing attention and visuomotor tracking in part A, adding flexibility by shifting the course of an ongoing activity in part B. Completion under paced conditions and increasing complexity is demanded [37]. The Stroop Colour Word Test, assessing inhibitory functions, attention, and speed of processing [58, 39]. Colour words, such as yellow and blue, are printed in incongruent combinations of colour and word. The task involves naming the colour of the words as quickly as possible, while ignoring the meaning of the words. Following a baseline test, the incongruent test was repeated three times with a 1-minute interval between trials. The time taken to perform each task was measured and the participants were instructed to correct any perceived error. Memory tasks: Episodic verbal memory was assessed using two word lists of 15 words each [6]. One of the lists included semantically unrelated words and the other list included words organizable into five categories, tested with free recall immediately after presentation of each list. Following the completion of free recall of the organizable words, cued recall was tested providing category names as retrieval

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cues. The number of categories recalled was registered. For further details on the additional tests, see Nordling Nilson et al. 2003 [43].

Alternating between printers and referents, all subjects were examined by the same two experienced test leaders with tests presented in a standardized order including a 45-minute break for lunch and a shorter break for coffee or tea. The test leaders were aware of the subjects' occupations but not of the degree of exposure.

2.6 Statistical methods

The test results were analysed using a 2 (exposure group: printers, referents) x 2 (age group: oldest (70–84 years), less old (57–69 years)) x 2 (time: baseline, follow-up) mixed ANOVA with repeated measures on the last factor. Multiple linear regression analyses including exposure indices, and, for the analyses over time, also previous test results, were performed for all tests for evaluations of potential dose-effect relationships. The limit for statistical significance was set at $p \leq 0.05$. All calculations were done using the SAS, version 9.1, software package (SAS Institute, Cary, NC, USA). For questionnaire data, between-group comparisons were carried out with Mann-Whitney U-test as the responses on a number of the scales had a skewed distribution. Here the software package SPSS, version 15.0 (SPSS Inc., Chicago, IL, USA), was used.

3. Results

Group mean test scores on the repeated tests are presented in Table 2. As expected, deterioration over time in test performance from baseline to follow-up, regardless of occupation (main effect of time), was seen in all but one of the tests. For synonyms

assessing verbal understanding identical results were seen at baseline and follow-up. Otherwise, the decrements were significant for the majority of the tests (Block design, Digit symbol, Dots speed, Dots time fluctuation, Dots speed x accuracy, Cylinder board, Benton errors, Paired associates) but did not reach significance for reasoning, Benton correct, and Dots accuracy.

[Table 2]

The main finding with reference to our hypothesis was a more pronounced deterioration over time in printers than in referents (exposure group x time) in reasoning and associative learning (paired associates), see Table 2. In fact, only printers deteriorated in reasoning where the referents displayed a stable result. A closer inspection of the data revealed that the printers also displayed a more pronounced average deterioration between baseline and follow-up compared with the referents in Dots speed (total time), performance variability (time fluctuations) and the weighted score taking both speed and accuracy into account (time x errors), see table 2. However, the within-group variability was large particularly at follow-up, which may explain the fact that these interactions did not reach statistical significance. No dose-effect relationships were seen in cognitive changes over time.

Group comparisons of test results at baseline revealed slightly although not significantly lower scores in verbal understanding among the printers (Table 2). In view of this fact, analyses including synonyms test scores at baseline as covariate were also performed but did not change the results. Also, the results remained stable whether or not interactions between age group and group were included in the analyses.

At follow-up printers performed significantly more poorly compared with the referents in associative learning (paired associates), variability in sustained attention (Dots time fluctuation), and in verbal episodic memory, displayed in the number of categories involved in cued recall of organizable words (Table 3). A dose-effect relationship, i.e. poorer performance with increasing cumulative exposure, was seen only for reasoning [$F (1, 8) = 6.99$, $p=0.03$] at follow-up.

[Table 3]

The individual test profiles indicated deteriorations and/or deficits in 75% of the printers, as contrasted with 25% of the referents, affecting mainly memory and attention.

3.1 Symptoms and social interaction

Questionnaire results on symptoms and social interaction are presented in Table 4. Contrary to expectations, the printers did not report more subjective cognitive complaints (Euroquest-9) than the referents ($p=0.29$). On the SCL subscales assessing psychosomatic and emotional distress the printers reported a slightly higher depression score compared with the referents ($p=0.05$), whereas no significant group differences were found on the ISSI subscales exploring social relationships.

[Table 4]

4. Discussion

In this 20-year follow-up of workers with long-term past exposure mainly to toluene, rotogravure printers were found to have deteriorated more than unexposed referents in cognitive functioning affecting reasoning and associative learning. No relevant additional

exposure between assessments could explain the discrepancy. The findings are in line with our hypothesis that sub-clinical deficits during the working life may become manifest later in life, when the reserve capacity of the brain is diminished and compensation for an acquired impairment may be reduced [7, 24]. In addition, printers performed significantly poorer than did referents in associate learning, verbal memory and sustained attention at follow-up, where also a dose-effect relationship was noted for reasoning. The decrements were associated with exposure to solvents, mainly toluene, for an average of 35 years with high levels (approximately 1,500 mg/m^3) during the 1950s and 1960s [59].

The present results of decrements in cognitive functioning are in agreement with the findings of a previous long-term follow-up study in which floor layers with past exposure to solvent-based glues had deteriorated significantly more in cognitive functioning than their referents [45]. Domains affected were episodic memory, perceptual speed and attention, and visuospatial skill. Just as in the present study, the major exposure had dated 30 years back.

A follow-up study with four repeated measurements over 5 years in employees from several different rotogravure printing plants presented no evidence for affected cognitive performance at toluene exposure below 50 ppm (equivalent to 190 mg/m^3) [55]. Negative findings have also been reported in a multi-centre field trial evaluating effects after long-term toluene exposure, and Zupanic et al. found no evidence of affected psychomotor performance at low-level toluene exposure [23, 65]. Reduction of information processing velocity and attention was reported for workers with higher solvent exposure in the past in a two years follow-up study [31]. In CTE subjects with a history of occupational mixed-

solvent exposure, followed up at 5 years or more after the CTE diagnosis, no cognitive deterioration was found [49, 17]. It is noteworthy that the follow-up periods in all these studies were markedly shorter, hence including younger subjects.

Affected cognitive domains of attention and episodic memory are in line with previous findings in cross-sectional studies of workers exposed to toluene and workers exposed to organic solvent mixtures as well as in groups of toluene abusers [20, 13, 22, 42, 27, 50, 49, 30, 64]. Reasoning has not been as frequently assessed in epidemiological and patient studies in the field as have the other domains studied, recently confirmed in a meta-analysis [40]. However, reasoning has been found to discriminate between currently employed exposed and unexposed subjects [26]. In the present study, the deterioration over time in reasoning was seen only in printers and poorer performance at follow-up was associated with increasing cumulative exposure lending support to the hypothesis of an interaction between age and previous exposure.

The findings of decrements over time as a general effect of ageing were expected considering the 20-year-long follow-up period. Typically, performance tests such as reasoning, block design and digit symbol tests, where efficiency of current processing is crucial, reveal a gradual decline from early to late adulthood whereas verbal comprehension, strongly influenced by education, remains relatively stable over life [34, 53]. The identical results in verbal understanding at baseline and 20 years later adhere to these findings; the synonyms test, assessing verbal comprehension, appears to be a fairly robust test in the long run, suggesting that it may well be used as a hold test.

At follow-up, the printer group was three years older in average than the referents, a non-significant difference. School education was two years shorter in average in the printer group than among the referents. Although the magnitude of the association of age with cognitive performance is relatively larger than for other predictors, age constitutes a relatively small proportion of the total variance in cognitive performance [53]. The age-related differences in cognitive performance are in fact small taking the total range of individual differences into account. Education exercises a strong influence mainly on tests of verbal comprehension and general knowledge while performance tests are largely uninfluenced by education [34]. The test battery used for retest in the present study includes only one test of the former type. Thus, the differences between groups in age and education are not likely to have had any crucial influence on the results.

The printers showed a slightly higher score on the SCL depression subscale than did the referents, which is congruent with previous findings among solvent-exposed subjects diagnosed with CTE showing higher depression scores than unexposed referents [1, 2, 33]. However, in the present printer group the level of the depression scores was lower (i.e. the printers were less depressed) than in CTE groups referred to above and was, furthermore, within the normal range, which is to be expected in a non-patient sample [15]. In a 7-year follow-up of a patient group participating in a brief rehabilitation programme shortly after being diagnosed with CTE, their global symptom load (GSI) on the symptom checklist (SCL-90) was clearly reduced at follow-up [1]. In contrast, depressive mood was found to have increased over an 18-year follow-up period in the most exposed of a sample of re-examined floor layers and to be more prevalent at follow-up in the floor layers than in their referents [44]. Contrary to expectations, the printers in

the present study did not differ in self-reported cognitive dysfunction. This may indicate that their cognitive dysfunction was not large enough to be experienced as disturbing. In previous studies subjects diagnosed with CTE have reported low availability of social integration, although perceived as adequate [1, 2]. In the present study there was a similar tendency, but no significant differences between the groups.

Not all persons who participated in the first examination were present at follow-up. There is a tendency among the exposed that those who participate in the follow-up were those who had the highest cognitive scores at baseline. The same tendency was seen in the referents although to a somewhat lower extent. This means that there is a risk of "regression to the mean" which means that even if there was no true change in cognitive performance from baseline to follow-up, it is likely that those who scored highest at baseline will have lower values at follow-up owing to random variation. Thus, the effect of the exposure could be overestimated. However, if there is a similar selection among the controls (mainly those who scored highest at baseline participate in the follow-up tests), the effect of the exposure will not be overestimated (because then both exposed and controls display a change over time which is slightly too large).

The major draw-back of the present study is the small study group available for the follow-up in the end. We have reason to believe that advancing age and related progressing poor health accounted for a large proportion of the loss of participants among the printers but only a smaller part of the referents. Therefore, it may well be that the examined printers are the more healthy of that group. Six of the eight printers who declined participation referred to poor somatic health, in some cases volunteering

(telephone) information about concentration difficulties, memory deficits, fatigue and anxiety – complaints that are compatible with adverse sequels from long-term exposure to organic solvents. This healthy "worker" effect may underestimate the detrimental influence from exposure on cognitive functioning. The low response rate of the referents is partly accounted for by the fact that the available referents were younger than the available printers and that we chose to include only those of similar age, as motivated in the method section.

Although the groups examined were small in number, the exposure and working conditions of the printer group may be considered to be representative of conditions in rotogravure printing in Sweden and other Western countries during the 1950s–1970s. At baseline all subjects were employed and on regular working schedules. None had ever sought psychiatric help. We find the present group to be fairly representative of their generation of workers and, accordingly, the results to be credible. Nevertheless, the generalizability of the results is limited by the small number, particularly in the printer group, and the low response rate, particularly in the referent group. As age and verbal comprehension were included as covariates in the statistical models, there is no reason to expect residual confounding due to minor (non-significant) differences between the groups in age and formal education in their youth.

The analyses include multiple comparisons. However, we chose not to do formal tests for adjustment but, rather, to inspect the overall pattern of the outcome [52]. Each association on its own should be interpreted with caution, but when all the associations from the different analyses are taken into account (changes over time, differences between groups

at follow-up, and the dose-effect analyses), the results indicate impairment in the same cognitive domains. Given this concordance we consider it unlikely that these deficits reflect the number of comparisons made.

Follow-up studies of long-term adverse sequelae following occupational exposure to organic solvents are few. Moreover, most of the published follow-ups are focused on patients diagnosed with chronic toxic encephalopathy [1, 5, 17, 41, 46]. Although these contribute in the clarification of the progress and prognosis of individuals with clinical manifestations following exposure, these subjects constitute a selected group, possibly with a particular vulnerability with respect to neurotoxic exposure. Other studies have focused on symptoms or accidental intoxication or have so far had too short follow-up and exposure time periods to be of major relevance for the long-term perspective [25, 57, 62]. In view of this, non clinical samples of workers exposed in the past for a lengthy time period (more than 10 years) would be preferable in the study of long-term effects. The present study and a previous long-term follow-up of formerly exposed floor layers based on re-examinations after 18-20 years, with the main exposure dating back 30 years, have attempted to meet up with these requirements.

The present findings of significantly worse deteriorations in cognitive functioning in previously toluene-exposed rotogravure printers add to similar findings in floor layers formerly exposed to solvent-based glues containing toluene [45]. They indicate that exposure may in fact interact with ageing, disclosing sub-clinical deficits presumably acquired during exposure earlier in the working life. In addition, indications of a higher prevalence of depressive mood were seen in both samples of formerly exposed, ageing

subjects. However, considering the small study groups and the low response rates in the present study, the results must be interpreted with caution. Nevertheless, this potentially far-reaching detrimental influence of occupational solvent exposure should be taken into consideration in evaluating deficits appearing many years after cessation of the exposure. Considering the limited size of the present study, the need for more longitudinal studies including no longer occupationally active, formerly solvent-exposed professional groups remains vital.

Acknowledgements

Conflict of Interest Statement

The authors declare that there are no conflicts of interest.

Figure legend

Fig. 1. Estimated retrospective exposure levels (mg/m^3) for toluene at the two rotogravure printing plants. At plant A the printing technique used was letterpress printing up to 1956. The solvent used during that period was mixed Stoddard solvent.

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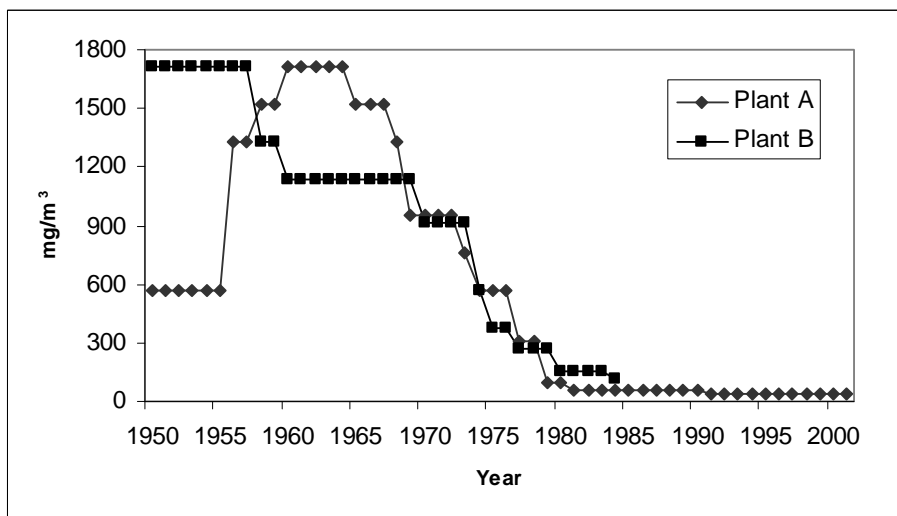
Fig. 1. Estimated retrospective exposure levels for toluene at the two rotogravure printing plants. At plant A the printing technique used was letterpress printing up to 1956. The solvent used during that period was mixed Stoddard solvent.

Table1_Exposure_data.xls / 2007-05-31

Table 1
Exposure data for all subjects

	Printers	Referents
Years with solvent exposure; range	16-43	0-25
(median, average)	(36.5; 34.8)	(0, 4.8)
Cumulative solvent exposure (year*hygienic effect);	5.2 – 162	0 – 8
range (median, average)	(102; 92)	(0; 1.2)
Cumulative exposure since previous investigation		
(year*hygienic effect); range	0-9.5	0 – 0.2
(median, average)	(1.6; 2.4)	(0, 0)
Cumulative lead exposure; numbers of individuals	1 (1)	3 (0.4-2.7)
(year*hygienic effect; range)		
Leisure time exposure	not found	not found

Table 2
Group mean test scores - baseline data and at follow-up - and p-values from analyses of time effect and differences between groups in delevopment of cognitive performance between baseline and follow-up

	Printers (*n* = 12)				Referents (*n* = 19)				Time[a]	Time x group[b]
	Baseline		Follow-up		Baseline		Follow-up			
	Mean	SD	Mean	SD	Mean	SD	Mean	SD	p[c]	p[c]
Age	50.2	6.8	70.2	6.8	44.9	7.8	67	7.3		
Synonyms	20.5	5.5	20.6	5.5	23.1	4.5	23.2	4.3	0.9420	0.4492
Reasoning	21.3	4.1	18.7	3.8	20.9	4.4	21.0	4.1	0.0550	0.0258
Block design	25.0	6.4	21.5	5.3	28.4	5.2	24.2	5.2	<0.0001	0.3501
Digit symbol	43.8	10.6	39.8	10.5	54.2	15.4	47.3	13.2	0.0012	0.3292
Dots speed	415	52.2	469	87.6	404	75	427	90.3	0.0047	0.2528
Dots accuracy	13.0	10.2	17.7	10.2	12.5	7.9	15.6	11.8	0.0751	0.6030
Dots time fluctuation	20.5	6.8	27.2	11.8	18.9	5.7	19.8	6.2	0.0431	0.1474
Dots speed x accuracy	5369	4215	8239	4497	5181	3198	6513	4951	0.0108	0.2904
Cylinder board[d]	80.8	6.8	73.3	7.5	-	-	77.2	8.8	0.0016	-
Benton correct	7.1	1.1	6.3	1.6	7.3	1.4	7.1	1.3	0.0680	0.2896
Benton errors	4.3	2.3	5.8	2.6	3.8	2.2	4.8	2.6	0.0027	0.5385
Paired associates	20.6	4.5	15.5	5.1	21.6	4.7	18.6	4.5	0.0001	0.0126

[a] Main effect of time   [c] ANOVA with repeated measure
[b] Interaction effect of time and group   [d] Only printers performed Cylinder board at baseline

Table 3
Group mean test scores at follow-up including the additional age sensitive tests and
p-values from the analyses of group differences

	Printers (n = 12)		Referents (n = 19)		
	Mean	SD	Mean	SD	p*
Age	70.2	6.8	67	7.3	
Repeated tests					
Synonyms	20.6	5.5	23.2	4.3	0.1192
Reasoning	18.7	3.8	21.0	4.1	0.2809
Block design	21.5	5.3	24.2	5.2	0.2731
Digit symbol	39.8	10.5	47.3	13.2	0.1925
Dots speed	469	87.6	427	90.3	0.2909
Dots accuracy	17.7	10.2	15.6	11.8	0.8199
Dots time fluctuation	27.2	11.8	19.8	6.2	0.0497
Dots speed x accuracy	8239	4497	6513	4951	0.5377
Cylinder board	73.3	7.5	77.2	8.8	0.4696
Benton correct	6.3	1.6	7.1	1.3	0.3372
Benton errors	5.8	2.6	4.8	2.6	0.6069
Paired associates	15.5	5.1	18.6	4.7	0.0460
Additional tests					
Trailmaking A	40.3	13.8	34.6	10.6	0.4309
Trailmaking B	120.0	54.9	93.6	42.9	0.3311
Stroop baseline	84.8	15.2	77.1	17.2	0.3216
Stroop incongruent 1	142.6	32.8	129.6	28.6	0.3701
Stroop incongruent 2	132.5	30.3	120.9	26.8	0.4031
Stroop incongruent 3	126.9	24.4	112.7	21.8	0.1900
Free recall, random words					
correct	5.9	2.1	6.9	1.9	0.2971
error	0.17	0.38	0.32	0.48	0.2907
Free recall, organizable words					
correct	7.6	3.0	9.2	2.4	0.2246
error	0.25	0.45	0.58	0.77	0.1763
Cued recall, organizable words	8.9	3.0	9.8	2.6	0.5468
categories involved	3.8	1.3	4.6	0.6	0.0541

* ANOVA

Table4_Symptoms_rev090616.xls / 2007-12-20

Table 4

Self-rated symptoms and social network[a]

	Printers (n=12)		Referents (n=19)		M-W
	Md	Q1 - Q3[b]	Md	Q1 - Q3	p
Euroquest-9	1.78	1.44 - 2.22	1.67	1.44 - 1.89	0.29
SCL					
Somatization	0.29	0.02 - 0.65	0.17	0.00 - 0.42	0.37
Depression	0.42	0.19 - 0.88	0.23	0.00 - 0.33	0.05
Anxiety	0.20	0.10 - 0.53	0.10	0.10 - 0.40	0.39
ISSI[c] total score	0.79	0.76 - 0.83	0.85	0.75 - 0.92	0.27
AVAT[d]	1.00	0.67 - 1.00	1.00	0.83 - 1.00	0.64
ADAT[e]	1.00	0.93 - 1.00	1.00	0.80 - 1.00	0.31
AVSI[f]	0.33	0.33 - 0.63	0.50	0.33 - 0.83	0.08
ADSI[g]	1.00	1.00 - 1.00	1.00	0.88 - 1.00	0.54

[a] Groups were compared with Mann-Whitney U Test (M-W).

[b] Q1-Q3 = items 1-3 from the Euroquest-9

[c] ISSI = Interview schedule of social integration

[d] AVAT = Availability of attachment, [e] ADAT=Adequacy of attachment,

[f] AVSI = Availability of social integration, [g] ADSI = Adequacy of social integration