Occupational Exposure to Solvents and Cognitive Performance in the GAZEL Cohort: Preliminary Results.

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Abstract

Background: The impact of occupational exposure to solvents on cognitive ageing remains unclear. We examined whether long-term occupational exposure is associated with poor cognitive performance in late midlife.

Methods: Participants of the GAZEL cohort, set up 1989, are employees of the French national Electricity and Gas Company. Data on the working environment was used to create measures of cumulative exposures to solvents using a job-exposure matrix. Cognitive performance was assessed using the Digit Symbol Substitution Test (DSST) and the MMSE assessed in 2002-4 on 5,242 participants, aged 55-65.

Results: In cross-sectional analysis using multiple logistic regression, there was greater risk of poor cognitive performance (score DSST < 25th percentile) among those with high exposure to benzene (Odds Ratio (OR)=1.58; 95% CI 1.31-1.90) and the grouped categories of chlorinated (OR=1.39; 95% CI 1.3-2.3), aromatic (OR=1.76; 95% CI 1.08-2.87) and petroleum solvents (OR=1.50; 95% CI 1.23-1.81).

Conclusions: These results suggest that occupational exposures to solvents may be associated later in life with cognitive impairment even after taking into account effects of education, employment grade and numerous health factors.

Introduction

It remains unclear whether occupational exposure during working life affects cognitive functioning later in life [1]. Some [2] but not all studies [3] suggest greater risk of dementia among manual workers. This inconsistency may be due to the multifaceted nature of occupational position, namely as an indicator of environmental exposures, of material deprivation, of access to medical care and attitudes to health or a surrogate marker of premorbid intelligence or cognitive abilities. Our focus here is on the impact of chemical exposures at work on cognitive ageing, an area that has not yet been sufficiently investigated.

Chronic exposure to organic solvents induces central nervous system (CNS) damage, usually called chronic solvent-induced encephalopathy [4]. It typically results in CNS depression and psychomotor or attentional deficits. The acute effects often resolve after cessation or decrease in exposure, except for extremely high exposure [5]. Some findings also suggest residual CNS dysfunction, persisting years after the end of exposure, particularly with long term exposure to organic solvents [6]. Neuropsychological changes associated with acute and chronic exposure to organic solvents have been well documented in cross sectional and longitudinal studies in those still at work or less than 60 years old [4,7,8]. Neuro-imaging results also appear to support these findings [9]. Results obtained in studies using the case-control design for dementia [10-12] are limited due to the retrospective determination of exposures. A recent review [13], highlighted the need for further studies with rigorous exposure description, adjustment for important confounders and cognitive tests sensitive for the detection of poor performance. The GAZEL cohort

allowed us to examine whether long-term occupational exposure to solvents is associated with poor cognitive performance on two tests in late midlife.

Population and Methods

Population

The Gazel cohort was initiated in 1989 among the employees of the French national electricity and gas company, Electricité de France - Gaz de France (EDF-GDF), the only utility company in France at that time. In January 1989, after an information campaign in the company and union newsletters, an invitation was sent to all male employees then aged 40-50 years and all female employees then aged 35- 50 years [14]. At baseline, 20,625 individuals agreed to participate and these have been followed using an annual self-reported questionnaire. In 2002-2004, the GAZEL study undertook a medical examination by inviting participants to one of the 54 Health Screening Centres (“Centres d’examens de santé”) of the French social security located all over France. However, the cognitive measures were added to the study after the start of the medical examination campaign. Thus, only a sub-sample of the cohort (N=14,751) was eligible for cognitive testing. A decision was made to invite only participants aged 55 years or more (N=10,537) to the cognitive testing. The present study is based on subjects who participated in these cognitive tests (N= 5242, 49.7% of the target population).

Occupational exposure

From recruitment into the company and onwards until 1998, data on the workforce’s working environment were collected systematically [15]. Assessment of various physical

and chemical exposures (n=29) is based on a job-exposure matrix (JEM) specific to the company (MATEX) developed from expert judgment using a standardized procedure in order to study cumulative exposure to occupational chemicals [16,17]. In the present analysis we focused on the most frequent solvent exposure with eight specific solvent species (Toluylene disocyanate (TDI), Hydrazine, Tetrachloromethane, Trichloroethylene, Perchloroethylene, Dichloromethane, Trichloroethane, benzene). Besides, benzene, these can be regrouped into 3 categories of solvents: chlorinated, aromatic and petroleum solvents[18].

Solvents were reported in the matrix as semiquantitative exposure indices with time-weighted average exposures. Cumulative doses were calculated taking into account the level of exposure in each episode together with the probability of exposure. Finally, for each solvent, the subjects were classified into three exposure categories: unexposed / moderate (exposed with level lower than the median of exposition) / high exposure (exposed with level equal or above the median). For exposure to tetrachloromethane, present only in 0.6% of subjects, we considered two classes, unexposed and moderate exposure.

Cognitive function

Cognitive function was assessed in 2002-2004 using two tests, the French version of the 30-point Mini-Mental-State-Examination (MMSE) [19] and the Digit Symbol Substitution Test (DSST) [20]. DSST is generally thought to be more sensitive in non-demented elderly populations than the widely used Mini-Mental Status Exam. It requires response speed, sustained attention, visual spatial skills, associative learning, and memory. For these reasons it has been chosen in the NHANES study in 2005 (see

http://www.cdc.gov/nchs/data/nhanes/nhanes_01_02/cfq_b_doc.pdf).The DSST is a subtest of the Weschler Adult Intelligence Scale-Revised, a timed paper- and pencil-task requiring translation of numbers to symbols using a key provided at the top of the test form. The score is the number of correct symbols drawn within 90 s for a maximum score of 93. For both tests, poor cognitive performance was defined by a score below or equal to the 25th percentile.

Covariates

Covariates included in the analysis were socio-demographic factors: sex, age (in years), education (finished secondary school (baccalaureate) yes/no), and employment grade at age 35 (unskilled/skilled/manager); lifestyle factors: smoking (current smoker /no) and alcohol consumption (no alcohol consumption;/moderate defined as 1-20 drinks/week for women and 1-27 for men /heavy drinker defined for more than 20 drink/week for women and 27 for men); and health factors, via medical interview for hypertension, asthma, and other respiratory symptoms. Depression symptoms were assessed by the Center for Epidemiological Studies-Depression (CESD) scale using a score of 17 for men and 23 for women to define depressive symptomatology [21]. We also adjusted for the geographical location of the screening center (Paris and suburb/ other). For descriptive purpose, we examined the association with retirement status (Yes/no) at time of medical screening.

Statistical analysis

Analysis was performed on the 5242 subjects with data on occupational exposure and the DSST. For MMSE, the analyses were restricted to a sub-set of 4904 participants with MMSE data.

In the main analysis on the DSST, missing data for education (n=89) and grade at age 35 (107) were replaced by the modal value. For three factors, with a greater proportion of missing data, a missing data category was used in the analysis; this was the case for alcohol (n=437), tobacco (n=562) and the CESD (n=1084). Finally as 718 subjects had no data on their medical history, a dummy variable “missing data on health” was used in the analysis.

We first examined the bivariate associations between all the covariates and poor cognitive performance using logistic regression. Multivariable logistic regression analysis was performed for all solvents that were found to have a robust association ($p<0.05$) in the bivariate analysis. These analyses were adjusted for covariates in two steps. Model 1 included socio-demographic factors (sex, age, education, and grade at age 35); model 2 additionally included screening center, lifestyle and health factors selected according to their association with major occupational exposures. The Wald test of significance was examined for each exposure. All analyses were performed using the SAS software, version 9.1.

Results

DSST was completed by 5,242 participants, 90.7 % of them were retired at the time of cognitive examination. Characteristics of the study population are shown in Table 1. Eighty four percent of subjects were men and the mean age was 59 years (range, 55-65 years). Less than a quarter of the participants had completed secondary school and, at age 35, 62.7% were skilled workers and 16.7% managers. Depressive symptomatology was observed in 13.2 % of the participants. Among those with data on health measures, the prevalence was: hypertension 28.1 %, history of vascular disease 6.1%, asthma 5.8 %, and other respiratory diseases 15.7%.

Mean DSST score was 48.4 with an interquartile range from 42 to 55. Mean MMSE score was 28.7 with an interquartile range from 28 to 30. Poor cognitive performance was defined by a score below or equal to the 25^{th} percentile, corresponding to a value of 41 for DSST and 27 for the MMSE. Due to a skewed distribution, poor performance on the MMSE corresponds to 18.8% (n=920) of the 4904 subjects with MMSE score.

In this population, 69.0% of subjects were unexposed to the eight specific solvent types examined, 14.7% were exposed to one solvent, 8.7% to two and 7.6% to more than three solvent types. Exposure to TDI, hydrazine and tetrachloromethane was present in less than 10 % of the sample while exposure to trichloroethylene, perchloroethylene and benzene was recorded for more than 20%. Exposure to dichloromethane and trichloroethane was observed respectively for 16.0% and 11.4% of the population. Exposures to the three overall categories of solvents (chlorinated, aromatic and petroleum, excluding benzene) was respectively 31.8 %, 2.8% and 24.1%.

Table 2 shows the bivariate association between the covariates and poor cognitive performance. When using the DSST score, we observed expected associations with age, education, employment grade at age 35. Women performed better than men and so did those who were seen at the screening center located in Paris or its suburbs. Smokers, participants with cardiovascular disease or respiratory symptoms other than asthma and those with depressive symptoms had poorer cognitive performance. With the MMSE, these associations were not observed for age, sex, smoking habits, and depressive symptomatology. The bivariate analysis showed poorer cognitive performance, both for the DSST and the MMSE, in workers with the highest estimated cumulative exposure to TDI, Trichloroethylene, Perchloroethylene, Dichloromethane, Trichloroethane and Benzene. There was no association with exposure to hydrazine or tetrachloromethane.

Table 3a presents results on the multiple regression analysis using the DSST. Model 1 was adjusted for socio demographic characteristics (sex, age, education and grade at age 35). Significant trends were observed for all exposure except TDI, Hydrazine and tetrachloromethane. Additional adjustment on screening center, lifestyle and health factors (Model 2) did not substantially change the associations. As compared to unexposed individuals, high exposure groups (above median of exposure in subjects exposed) had a greater risk of poor cognitive performance: an odds ratio of 1.33, 95% CI (1.10,1.60) for Trichloroethylene, 1.36 (1.11,1.68) for Perchlorethylene, 1.54 (1.22,1.96) for Dichloromethane, 1.52 (1.18,1.96) for Trichloroethane, 1.58 (1.31,1.90) for benzene. The moderate exposure category suggested no robust effects.

Table 3b shows similar results using the MMSE as the outcome. As compared to unexposed individuals, high exposure groups had a greater risk of poor cognitive performance: an odds ratio of 1.32, 95% CI (1.07, 1.63) for Trichloroethylene, 1.41 (1.12, 1.78) for Perchlorethylene, 1.36 (1.04, 1.77) for Dichloromethane, 1.53 (1.15, 2.02) for Trichloroethane, 1.28 (1.03, 1.59) for benzene. Furthermore, moderate exposition to perchlorethylene (OR=1.40 (1.10-1.77)) and to benzene (OR=1.39, (1.12-1.74)) were also associated with poor MMSE performance.

Discussion

This paper is one of the first to document the relationship between chronic exposure to solvents and cognitive performance in a large sample of 55-65 year-old, most of who were retired. Participants whose cumulative exposure to solvents was above the median exposure had an elevated risk for cognitive impairment compared to the non-exposed individuals. The risk was greater in workers with the highest estimated cumulative exposure to chlorinated solvents and to the three types of chlorates studied, to petroleum solvents but also to aromatic solvents and benzene.

The data used in the present analysis were collected for a pilot medical screening in this cohort. Thus, only a short cross-sectional cognitive evaluation was proposed and we have no previous evaluation on pre-morbid IQ. The MMSE is often used as a screening tool for dementia in the elderly but is less appropriate for exploring cognitive performance in younger age-groups such as our population aged 55-65 years. The DSST has a large inter individual range in this age-group and is relatively unaffected by intellectual ability,

memory, or learning. It is also more a more sensitive test at higher levels of cognitive function than the MMSE [22]. It requires response speed, sustained attention, visual spatial skills, associative learning, and memory. The DSST score has been linked to dementia [23] and to mortality [24]. Overall it showed good metrological properties in this population. This test has also been shown to be sensitive to cognitive change linked with chronic exposure to both lead and solvents [25,26].

The GAZEL cohort, like all other longitudinal studies relies on the willingness of the participants to continue to take part in the study and as such is subject to potential selection biases. Lower occupational position is associated with lower response rates over the follow-up [27]. If exposure to solvents is greater in the lower employment grades then the current analysis is likely to exclude those most exposed to solvents. Nevertheless, the measure of cumulative exposure for most of the solvents in this cohort was such that dose-effect associations could be examined. Our measure of cumulative exposure integrates full employment history because, in most cases, participants started working for the Electricity and Gas companies on which GAZEL is based in their 20’s and continued till retirement. Furthermore, the GAZEL cohort has a full spectrum of participants, across all occupational categories from manual labourers to executives.

Most studies on aging are based on elderly subjects and do not have the opportunity of documenting detailed occupational exposure over the working life. Furthermore, exposure assessments are most often restricted to job titles. One of the unique features of this study is the detailed history of exposures alongside data on

numerous potential confounding factors. Literature on aging increasingly points to the effects of long-term exposure [28] which is difficult to document retrospectively.

Since the 1970s, beginning with several reports from Scandinavia, various studies have suggested that chronic low level occupational exposure to organic solvents may have a negative impact on cognitive and psychological functioning [4,29]. Indeed, a cluster of clinical symptoms, alternatively named ‘chronic painter’s syndrome’, ‘solvent syndrome’, or ‘chronic toxic encephalopathy’ have been reported among exposed workers. This cluster included headache, fatigue, difficulties with memory and concentration, irritability, depression and personality changes.

However, most studies were performed during active life using a cross sectional design. They were often based on small selected samples and comparisons have often lacked suitable control groups. Exposure assessment was retrospective and potential confounders were not fully taken into account. Furthermore, as neuropsychological tests vary between studies, comparisons of results may be limited [6]. Residual effects on cognitive functioning, years after the cessation of neurotoxin exposure have been the target of very few previous studies. In 89 retired male workers with previous long term exposure to solvents assessed retrospectively [30], a lower mean scores on test measures of motor, memory and reasoning ability has been described. The study with the longest follow-up was performed in Sweden [8,31], Nilson et al followed 41 floor layers exposed to organic solvents (solvent based glues) and 40 carpenters using ten neuropsychological tests at baseline and then again at a 18 year-follow-up. This study assessed exposures extensively and found that among the oldest subjects higher cumulative exposure was

associated with decrements in visual episodic memory, perceptual speed and attention and visiospatial skill with significant dose-effect associations. There was also evidence of an effect on neuropsychiatric functioning indicating that general well-being later in life is affected in floor layers with past heavy solvent exposure, strengthening the evidence that long-term heavy occupational solvent exposure may negatively impact the normal ageing process [32]. In the 1947 Scottish Mental Survey[26] on 336 subjects, aged 67, with low lifetime exposures there was no clear evidence of an association between organic solvent exposure and cognitive function.

These results suggest that occupational exposure to solvents may interact with the normal aging process, primarily in the most heavily exposed individuals. The effects are quite similar for all solvents and evident in this study on mostly retired workers, suggesting a potential long term residual effect of solvents. It could be hypothesised that chronic exposure to various organic solvents or other exposures would lead to different patterns of cognitive disturbance. This hypothesis could not be tested in the present study but we hope, in the near future, to add measures of memory, language, attention and concentration capacities to this cohort.

Several hundred million tons of organic solvents are still used worldwide per year, although regulatory pressure and concerns for the environment are gradually leading to a reduction in use [33]. Occupational exposures are clearly modifiable factors. The solvents examined in our study have been extensively linked to cancer, with fraction of all cancers attributable to occupational exposure being at least 5% [34,35]. Their importance to cognitive aging and risk of dementia needs to be more completely evaluated in future studies.

Table 1: Characteristics of participants (n= 5,242): mean±SD, median or n (percent)

	Total sample N=5242	Median	
Age (y)	59.03 ± 2.77	59	
Female sex	835 (15.9)		
Baccalaureate (Secondary High School)	1256 (24.0)		
Grade at age 35			
Unskilled	1,076 (20.5)		
Skilled	3,289 (62.7)		
Manager	877 (16.7)		
Retired	4,754 (90.7)		
Screening center (Paris and suburb)	1,196 (22.8)		
Alcohol*			
Abstinent	442 (8.4)		
Moderate	3,609 (68.8)		
Heavy	754 (14.4)		
Smoker*	515 (9.8)		
Missing data on health	718 (13.7)		
Hypertension	1,471 (28.1)		
History of vascular disease	320 (6.1)		
Asthma	302 (5.8)		
Other respiratory symptoms	821 (15.7)		
Depressive symptomatology*	693 (13.2)		
Digit Symbol Substitution Test	48.42 ± 9.85,	48	
MMSE*	28.67 ± 1.57	29	
Solvents	% unexposed	% exposed	median**
Toluylene diisocyanate (time weighted average)	93.0	7.0	0.21

Hydrazine	93.9	6.1	0.05
Tetrachloromethane	99.4	0.6	0.01
Trichloroethylene	71.3	28.7	0.35
Perchloroethylene	77.9	22.1	0.21
Dichloromethane	84.0	16.0	0.10
Trichloroethane	88.6	11.4	0.50
Benzene	74. 5	25.5	11.9
Solvent Category			
Chlorinated solvents	68.2	31.8	0.50
Aromatic solvents	97.2	2.8	0.35
Petroleum solvents	95.9	24.1	0.37

* Missing data: alcohol (n=437), smoker (n=562), depressive symptomatology (n=1084), MMSE (n= 338)

** Median among exposed participants

Expressed in ppm-years for benzene and in hours/week-years for the other occupational exposures

Table 2: Bivariate association between poor cognitive performance (score below the 25th percentile for DSST or MMSE) and socio-demographic factors, lifestyle, health factors and exposure to solvents.

	DSST		**MMSE**	
	OR	**95% CI**	**OR**	**95% CI**
Sociodemographic factors				
Age (≥ 60 years/<60*)	1.73	1.52, 1.96	1.07	0.93, 1.24
Female sex	0.39	0.31, 0.48	1.11	0.92, 1.35
Baccalaureate (Higher secondary school)	0.40	0.33, 0.48	0.46	0.38, 0.56
Grade (/ unskilled*)				
Skilled	0.55	0.47, 0.63	0.62	0.53, 0.74
Manager	0.24	0.18, 0.63	0.32	0.25, 0.41
Screening center (/ no Paris*)	0.59	0.50, 0.69	1.77	1.51, 2.07
Lifestyle and Health Factors				
Alcohol (/ moderate*)				
Abstinent	1.19	0.95, 1.50	0.83	0.63, 1.10
Heavy	1.16	0.96, 1.39	0.94	0.76, 1.16
Unknown	1.46	1.17, 1.82	1.16	0.90, 1.49
Smoker (/ never*)	1.64	1.34, 2.01	0.77	0.59, 1.00
Missing data on Health (/no*)	0.99	0.82, 1.19	1.11	0.91, 1.36
Hypertension (/no*)	1.14	0.99, 1.31	1.09	0.93, 1.28
Vascular disease (/ no*)	1.56	1.22, 2.0	1.35	1.02, 1.78
Asthma (/ no*)	0.85	0.64, 1.13	1.12	0.84, 1.51
Other respiratory symptoms (/no*)	1.34	1.15, 1.55	1.14	0.96, 1.35
Depressive symptomatology (/no*)				
Present	1.59	1.32, 1.91	1.14	0.92, 1.42
Unknown	1.63	1.40, 1.91	1.30	1.10, 1.55
Solvents* *				
Toluylene diisocyanate				
Moderate	1.92	1.42, 2.61	1.67	1.18, 2.37
High	2.33	1.72, 3.16	2.01	1.43, 2.83
Hydrazine				
Moderate	0.84	0.56, 1.26	0.96	0.62, 1.49

High	1.32	0.94, 1.85	1.45	1.00, 2.11
Tetrachloromethane				
Moderate	1.99	0.94, 4.23	1.03	0.39, 2.74
Trichloroethylene				
Moderate	1.73	1.45, 2.06	1.34	1.10, 1.64
High	2.11	1.78, 2.50	1.51	1.24, 1.84
Perchloroethylene				
Moderate	1.69	1.40, 2.05	1.60	1.29, 1.98
High	2.19	1.82, 2.64	1.70	1.38, 2.10
Dichloromethane				
Moderate	1.82	1.48, 2.25	1.53	1.21, 1.94
High	2.50	2.01, 3.1	1.74	1.36, 2.23
Trichloroethane				
Moderate	2.21	1.72, 2.84	1.61	1.20, 2.16
High	2.34	1.85, 2.96	1.90	1.46, 2.47
Benzene				
Moderate	1.53	1.27, 1.84	1.48	1.20, 1.81
High	2.28	1.92, 2.72	1.40	1.14, 1.73
Solvent category*				
Chlorinated solvents				
Moderate	1.75	1.48, 2.08	1.25	1.29, 1.88
High	2.30	1.95, 2.71	1.56	1.03, 1.53
Aromatic solvents				
Moderate	1.18	0.70, 2.01	1.19	0.66, 2.17
High	2.73	1.71, 4.35	1.13	0.61, 2.09
Petroleum solvents				
Moderate	1.48	1.22, 1.79	1.22	0.98, 1.52
High	2.19	1.83, 2.62	1.31	1.06, 1.62

* reference for OR is indicated after/
**reference for solvents= no exposure

Table 3a- Multiple regression associations between poor DSST performance (<25th percentile of distribution) and exposure to solvents

	Model 1				Model 2			
	No Exposure	Moderate Exposure*	High Exposure*		No Exposure	Moderate Exposure*	High Exposure*	
		OR (95% CI)	OR (95% CI)	**p value**		OR (95% CI)	OR (95% CI)	**p value**
Toluylene diisocyanate	ref	1.21 (0.88, 1.67)	1.19 (0.86, 1.65)	**0.32**	ref	1.19 (0.86, 1.64)	1.15 (0.82, 1.59)	**0.45**
Hydrazine	ref	0.95 (0.63, 1.43)	1.24 (0.88, 1.77)	**0.45**	ref	0.94 (0.62, 1.44)	1.19 (0.83, 1.69)	**0.61**
Tetrachloromethane	ref	1.11 (0.51, 2.40)		**0.79**	ref	1.00 (0.46, 2.19)		**0.99**
Trichloroethylene	ref	1.12 (0.92, 1.35)	1.34 (1.12, 1.61)	**0.007**	ref	1.13 (0.93, 1.37)	1.33 (1.10, 1.60)	**0.01**
Perchlorethylene	ref	1.03 (0.84, 1.27)	1.38 (1.13, 1.70)	**0.007**	ref	1.02 (0.83, 1.26)	1.36 (1.11, 1.68)	**0.01**
Dichloromethane	ref	1.10 (0.88, 1.38)	1.59 (1.26, 2.01)	**0.0005**	ref	1.06 (0.84, 1.33)	1.54 (1.22, 1.96)	**0.002**
Trichloroethane	ref	1.25 (0.96, 1.64)	1.59 (1.23, 2.04)	**0.0009**	ref	1.20 (0.91, 1.57)	1.52 (1.18, 1.96)	**0.004**
Benzene (PPM)	ref	1.16 (0.95, 1.41)	1.59 (1.32, 1.92)	**<0.0001**	ref	1.16 (0.95, 1.42)	1.58 (1.31, 1.90)	**<0.0001**
Solvent category					ref			
Chlorinated solvents	ref	1.14 (0.95, 1.38)	1.41 (1.18, 1.69)	**0.0010**	ref	1.15 (0.95, 1.38)	1.39 (1.16, 1.67)	**0.002**
Aromatic Solvents	ref	1.01 (0.58, 1.74)	1.85 (1.14, 2.99)	**0.047**	ref	1.00 (0.57, 1.74)	1.76 (1.08, 2.87)	**0.08**
Petroleum solvents	ref	1.15 (0.94, 1.40)	1.50 (1.24, 1.82)	**0.0001**	ref	1.15 (0.94, 1.41)	1.50 (1.23, 1.81)	**0.0002**

Model 1: Logistic regression models adjusted for sex,age, education and grade at age 35
Model 2: model 1 plus additional adjustment for screening center, tobacco, alcohol, missing health data, hypertension, asthma, respiratory symptoms and depressive symptomatology.

Table 3b- Multiple regression associations between poor MMSE performance (<25th percentile of distribution) and exposure to solvents

	Model 1				Model 2			
	No Exposure	Moderate Exposure*	High Exposure*		No Exposure	Moderate Exposure*	High Exposure*	
		OR (95% CI)	OR (95% CI)	p value		OR (95% CI)	OR (95% CI)	p value
Toluylene diisocyanate	ref	1.33 (0.93,1.89)	1.42 (0.99,2.03)	**0.06**	ref	1.30 (0.90,1.86)	1.42 (0.99,2.05)	**0.08**
Hydrazine	ref	1.12 (0.72,1.76)	1.46 (1.00,2.14)	**0.13**	ref	1.16 (0.73,1.82)	1.54 (1.05,2.27)	**0.08**
Tetrachloromethane	ref	0.90 (0.33,2.41)		**0.83**	ref	1.02 (0.38,2.78)		**0.96**
Trichloroethylene	ref	1.12 (0.90,1.39)	1.26 (1.02,1.55)	**0.09**	ref	1.15 (0.92,1.43)	1.32 (1.07,1.63)	**0.03**
Perchlorethylene	ref	1.31 (1.04,1.65)	1.39 (1.10,1.74)	**0.005**	ref	1.40 (1.10,1.77)	1.41 (1.12,1.78)	**0.002**
Dichloromethane	ref	1.19 (0.93,1.54)	1.36 (1.05,1.78)	**0.048**	ref	1.24 (0.96,1.61)	1.36 (1.04,1.77)	**0.04**
Trichloroethane	ref	1.22 (0.90,1.66)	1.51 (1.14,1.99)	**0.01**	ref	1.26 (0.92,1.72)	1.53 (1.15,2.02)	**0.008**
Benzene (PPM)	ref	1.39 (1.12,1.72)	1.23 (0.99,1.53)	**0.006**	ref	1.39 (1.12,1.74)	1.28 (1.03,1.59)	**0.004**
Solvent category					ref			
Chlorinated solvents	ref	1.06 (0.85,1.31)	1.24 (1.01,1.53)	**0.12**	ref	1.10 (0.88,1.37)	1.29 (1.05,1.60)	**0.056**
Aromatic Solvents	ref	1.15 (0.63,2.10)	0.95 (0.51,1.77)	**0.89**	ref	1.16 (0.63,2.15)	0.95 (0.50,1.77)	**0.87**
Petroleum solvents	ref	1.15 (0.92,1.44)	1.13 (0.91,1.41)	**0.33**	ref	1.18 (0.94,1.48)	1.18 (0.94,1.48)	**0.19**

Model 1: Logistic regression models adjusted for sex, age, education and grade at age 35

Model 2: model 1 plus additional adjustment for screening center, tobacco, alcohol, missing health data, hypertension, asthma, respiratory symptoms and depressive symptomatology

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