



**HAL**  
open science

## Association Between Occupational Exposure to Formaldehyde and Cognitive Impairment

Noemie Letellier, Laure-Anne Gutierrez, Corinne Pilorget, Fanny Artaud, Alexis Descatha, Anna Ozguler, Marcel Goldberg, Marie Zins, Alexis Elbaz, Claudine Berr

► **To cite this version:**

Noemie Letellier, Laure-Anne Gutierrez, Corinne Pilorget, Fanny Artaud, Alexis Descatha, et al.. Association Between Occupational Exposure to Formaldehyde and Cognitive Impairment. *Neurology*, 2022, 98 (6), pp.e633-e640. 10.1212/WNL.0000000000013146 . hal-03512810

**HAL Id: hal-03512810**

**<https://hal.science/hal-03512810>**

Submitted on 28 Jan 2022

**HAL** is a multi-disciplinary open access archive for the deposit and dissemination of scientific research documents, whether they are published or not. The documents may come from teaching and research institutions in France or abroad, or from public or private research centers.

L'archive ouverte pluridisciplinaire **HAL**, est destinée au dépôt et à la diffusion de documents scientifiques de niveau recherche, publiés ou non, émanant des établissements d'enseignement et de recherche français ou étrangers, des laboratoires publics ou privés.

## **Association between occupational exposure to formaldehyde and cognitive impairment**

Noémie Letellier<sup>a</sup>, Laure-Anne Gutierrez<sup>a</sup>, Corinne Pilorget<sup>b</sup>, Fanny Artaud<sup>c</sup>, Alexis Descatha<sup>d,e,f</sup>, Anna Ozguler<sup>d</sup>, Marcel Goldberg<sup>d,g</sup>, Marie Zins<sup>d,e,g</sup>, Alexis Elbaz<sup>c</sup>, Claudine Berr<sup>a,h</sup>

<sup>a</sup>Univ Montpellier, INSERM, INM (Institute for Neurosciences of Montpellier) Montpellier, France

<sup>b</sup>Santé Publique France, Lyon, France

<sup>c</sup>Paris-Saclay University, UVSQ, Inserm, Gustave Roussy, "Exposome and Heredity" team, CESP, 94807, Villejuif, France

<sup>d</sup>INSERM, Population-Based Epidemiological Cohorts Research Unit, UMS 011, Villejuif, France

<sup>e</sup>UVSQ, INSERM, VIMA; Aging and chronic diseases, U1168, Villejuif, France

<sup>f</sup>UNIV Angers, CHU Angers, Univ Rennes, Inserm, EHESP, Irset (Institut de recherche en santé, environnement et travail) - UMR\_S1085 ; CHU Angers, Poisoning Control Center-Clinical Data Center ; Angers, France

<sup>g</sup>Université de Paris, Paris, France

<sup>h</sup>Memory Research and Resources Center, Department of Neurology, Montpellier University Hospital Gui de Chauliac, Montpellier, France

### **Corresponding author:**

Noémie Letellier

INSERM Unité 1298, Equipe NEUROPEPS

Institut des Neurosciences de Montpellier, BP 74103

80, rue Augustin Fliche | 34091 Montpellier Cedex 5 – France

Phone: (33) 4 99 61 45 60; Fax: (33) 4 99 61 45 79

Email address: nletellier@ucsd.edu

**Search terms:** Cognition; Occupational exposure; Formaldehyde; Working conditions

## **Author Contributions**

NL performed the statistical analysis, interpreted the results and edited the first draft of the manuscript. LG and FA contributed to the data management and statistical analysis. CP provided the French Job Exposure Matrix of *Santé Publique France*. MG, MZ, AO and AD acquired the data. CB designed the study, contributed data and helped to write the manuscript. CB and AE developed study hypotheses. All authors critically revised the manuscript.

## **Study funding**

The CONSTANCES Cohort Study was supported and funded by the Caisse nationale d'assurance maladie des travailleurs salariés (CNAMTS). The CONSTANCES Cohort Study is an “Infrastructure nationale en Biologie et Santé” and benefits from a grant from Agence Nationale de la Recherche (ANR-11-INBS-0002). CONSTANCES is also partly funded by MSD, AstraZeneca, Lundbeck and L'Oréal.

The present analyses were supported by a grant from the French Agency for Food, Environmental and Occupational Health & Safety (ANSES, EST – N°2016/1/102).

These funding sources had no role in the study design, collection, analysis or interpretation of the data, writing the manuscript, or the decision to submit the paper for publication.

## **Disclosure**

The author declares that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

## **Acknowledgments**

We thank Laurène Delabre and Loïc Garras for providing the formaldehyde job-exposure matrix.

## ABSTRACT

**Objective:** To our knowledge, no study has investigated the effect of exposure to formaldehyde on cognition in the general population. Our objective was to examine the association between occupational exposure to formaldehyde and cognitive impairment in middle-aged and young-old adults ( $\geq 45$  years).

**Methods:** In the French CONSTANCES cohort, cognitive function was assessed with a standardized battery of seven cognitive tests to evaluate global cognitive function, episodic verbal memory, language abilities and executive functions (e.g., Digit Symbol Substitution Test, DSST). A global cognitive score was created using principal component analysis. Cognitive impairment was assessed in reference to norms of neuropsychological battery according to age, sex and education. Lifetime exposure to formaldehyde was assessed using a French job-exposure matrix created in the framework of the Matg n  project. After performing multiple imputation, separate modified Poisson regression models were used to evaluate the association between cognitive impairment ( $< 25^{\text{th}}$  percentile) and formaldehyde exposure (exposed/never exposed), exposure duration, cumulative exposure index (CEI), and combination of CEI and time of last exposure.

**Results:** Among 75 322 participants (median age: 57.5 years, women: 53%), 8% were exposed to formaldehyde during their professional life. These participants were at higher risk of global cognitive impairment (for global cognitive score: adjusted relative risk, aRR, 1.17, 95% confidence interval, CI: 1.11-1.23), after adjusting for confounders (age, sex, education, income, solvent exposure, Effort–Reward Imbalance, night-shift, repetitive, and noisy work). They were at higher risk of cognitive impairment for all cognitive domains explored. Longer exposure duration and high CEI were associated with cognitive impairment, with a dose-effect relationship for exposure duration. Recent exposure was associated with impairment in all cognitive domains. Time did not fully attenuate formaldehyde-associated cognitive deficits especially in highly exposed individuals (for DSST: high past exposure aRR 1.23, 95% CI: 1.11-1.36; high recent exposure: aRR 1.24, 95% CI: 1.13-1.35).

**Conclusion:** Our findings highlight the long-term detrimental effect of formaldehyde exposure on cognitive health in a relatively young population.

## **INTRODUCTION**

Until recently, formaldehyde has been widely used as disinfectant, biocide, fixative or binder in many industries (e.g., chemical industry), agriculture, specialized construction, and human health activities, before its decline due to new knowledge on its toxicity. Formaldehyde was classified as carcinogenic for humans by the International Agency for Research on Cancer, based on sufficient evidence that it causes nasopharyngeal cancer in 2004 (1), and leukemia in 2012 (2).

Moreover, excessive exogenous exposure to formaldehyde can lead to cognitive impairment in animals (3). Experimental animal exposure to formaldehyde induces neuropsychiatric symptoms, such as aggression, depression, locomotor activity decline, spatial memory deficits, learning and memory impairment, a decrease in the number of hippocampal neurons, and memory decline (4–10).

To our knowledge, only few studies investigated the cognitive effects of exogenous formaldehyde exposure in humans (11–15). A study on 305 women aged 23 to 78 years, working as histology technicians, showed an association between the number of hours of occupational exposure to formaldehyde per day and lower performance in tests to assess memory, dexterity, balance, coordination and reaction time (11). Another study showed that four employees (three histology technicians and one railway worker) exposed to formaldehyde for 13 to 30 years presented impaired balance, color discrimination, intellectual performance, and memory (12). A study on the relationship between cholinergic neurotransmitter and formaldehyde exposure in 35 formaldehyde-exposed workers and 32 control employees found that formaldehyde occupational exposure affected the activity of acetylcholinesterase, an enzyme needed for normal functioning of the nervous system (15). Nevertheless, the effects of exogenous formaldehyde on cognitive performance have been under-investigated. Surprisingly very few studies assessed the impact of formaldehyde on mental health, given its use in many activity sectors involving many employees and the potential neurotoxic effect observed in animal studies, in addition to the known carcinogenic effect (16).

Therefore, the objective of this study was to examine the association between occupational exposure to formaldehyde and cognitive impairment in a large French cohort of middle-aged and young old adults from the general population.

## **METHODS**

### Population

This study used the baseline data from the CONSTANCES cohort, a randomly selected sample of the French adult population (18-to 69-year-old) that includes individuals who represent a broad range of socioeconomic and occupation conditions. Participants were randomly selected among members of the French national Caisse Nationale d'Assurance Maladie (CNAM) health insurance that covers salaried workers, unemployed and retired, and their family (more than 85% of the French population). Agricultural and self-employed workers are excluded. More than 215,000 participants were recruited during the 2012-2020 period and attended an interview and examination by a study physician at one of the 21 Health Screening Centers located in different regions of France. Baseline health and occupational exposure data were collected using self-administered questionnaires. Detailed information on the CONSTANCES cohort is available elsewhere (17). The present analysis was restricted to  $\geq 45$ -year-old participants who underwent a standardized cognitive assessment by trained neuropsychologists at baseline (18). The analyses for this study are based on data available in February 2021.

#### Standard Protocol Approvals, Registrations

In agreement with French regulations, the CONSTANCES study was authorized by the National Data Protection Authority (Commission Nationale de l'Informatique et des Libertés, CNIL-#910486) and approved by the Institution Review Board of the National Institute for Medical Research (INSERM, #01-011). All participants signed a written informed consent.

#### Assessment of formaldehyde exposure

Lifetime formaldehyde exposure was assessed using a Job-Exposure Matrix (JEM) developed for the French population in the context of the Matgéne project by *Santé Publique France* (19). This JEM assesses occupational formaldehyde exposure (all job types) in France from 1950 to 2018. Lifetime occupational history was collected from all participants with a description of the sector and occupation and the corresponding dates. Then, the job types were coded according to two French nomenclatures that provide information on the occupation and activity sector: *Professions et Catégories Socioprofessionnelles* (PCS) and *Nomenclature d'Activité Française* (NAF). For each combination of PCS and NAF codes, three exposure indices were provided by the JEM: (i) probability of exposure (percentage of exposed workers); (ii) intensity of exposure (mean exposure dose during tasks); and (iii) frequency of exposure (percentage of working time performing tasks with exposure). Exposure indices were provided for different calendar periods to consider variations due to changes in exposure over time.

Based on these three JEM indices, formaldehyde exposure was evaluated in the CONSTANCES cohort using four different indicators: formaldehyde exposure (exposed/never exposed), life-time exposure duration (in years), cumulative exposure index (CEI), and combination of CEI and time since last exposure. Life-time exposure duration was categorized in tertiles: never exposed, low ( $\leq 6$  years), medium (7 to 21 years) and high ( $\geq 22$  years). CEI represents the cumulative exposure over the entire working life (the sum of the product of probability, intensity, and frequency for each year of exposure). CEI was categorized in four categories: never exposed, and low, medium and high exposure according to the tertiles of the distribution among exposed participants. Finally, an indicator was created by combining the total lifetime dose (i.e., CEI) and time (i.e., date of last exposure) that was then divided into four categories: ‘moderate past’, ‘moderate recent’, ‘high past’, and ‘high recent’. To construct this indicator, exposed participants were dichotomized into “moderate” exposure (total lifetime dose below the sample median) and “high” exposure (lifetime dose at or above the median), and as a function of the time since last exposure: 1962–2001 (“past”) or 2002–2017 (“recent”).

### Cognitive Function

As described previously (20), cognitive function was assessed by trained neuropsychologists using a standardized battery of cognitive tests to evaluate global cognitive function, episodic verbal memory, language abilities, and executive functions (25). This cognitive battery was administered to a subset of the CONSTANCES cohort that was 45 years or older at the time of the baseline exam. The French version of the Mini Mental State Examination (MMSE) (22) was used to assess the global cognitive function. The Digit Symbol Substitution Test (DSST) is a subtest of the Wechsler Adult Intelligence Scale-Revised (23,24) that explores attention, psychomotor speed, and reasoning. Episodic verbal memory was assessed with the Free and Cued Selective Reminding Test (FCSRT) (25); for this study, the total recall score (the sum of free and cued recall) was considered. Language abilities were evaluated with the Verbal Fluency Tasks (VFT) (26,27), by counting the number of words named in one minute (semantic and phonemic fluency tasks). The two parts of the Trail Making Test (TMT-A and -B, coded as time in seconds) assessed executive function and shifting abilities (28,29). For all tests, cognitive impairment was defined as a score  $\leq 25$ th percentile of the distribution ( $\geq 75$ th percentile for the TMT) according to age, sex and level of education.

A global cognitive score was created using principal component analysis (PCA). It was defined as the first axis of the PCA of the DSST, FCRST, VFT (semantic and phonemic), TMT -A and -B scores. The first axis explained 47% of the variance. It was characterized by positive scores

and high weights for DSST, FCSRT and VFT (semantic and phonemic), and by negative scores for TMT-A and -B. The participants' position on this axis defines their degree of global cognitive performance: lower scores correspond to worse cognitive performance. Global cognitive impairment was defined by a global cognitive score  $\leq$ 25th percentile of the distribution.

### Covariates

Individual covariates included sociodemographic factors: age (in years), years of education (5 years, 5 to 11 years, 11 to 13 years, 14 to 16 years, and  $\geq$ 17 years) and income. For the working environment, the following variables were used to characterize lifetime professional exposures: solvent exposure (number of solvent types [gasoline for hand washing, trichloroethylene, white spirit, cellulosic thinner] to which participants were exposed: 0, 1 or  $\geq$ 2), psychosocial work environment 'measured with the short version of the Effort–Reward Imbalance (ERI) questionnaire), night-shift work (shift work with alternating hours or working hours and travel time often requiring not to sleep during the night at least 50 days/year), repetitive work (under time constraints), and noisy work (working in an atmosphere that sometimes requires raising one's voice to speak to a neighbor/interlocutor within 2/3 meters, or working with/near noisy tools, machines or vehicles).

### Statistical analyses

For all cognitive tests dichotomized at the 25th percentile (75th percentile for the TMT), a modified Poisson regression with a robust error variance (30) was used to estimate the relative risk (RR) and 95% confidence interval (CI). Separate models were considered for each combination of formaldehyde exposure (exposed/never exposed, exposure duration, CEI, and combination of CEI and time of last exposure) and cognitive test scores. Covariates included in the multivariate analysis were selected based on previous identified confounders and Directed Acyclic Graph. All models were adjusted for sociodemographic characteristics (age, education level, income) and occupational exposures (solvent exposure, ERI, nightshift, repetitive, and noisy work). Interactions between formaldehyde exposure and sex and age were tested.

Multiple imputation was performed to handle missing data for covariates (percentage of missing data: 1.5% for income, 10.2% for solvent exposure, 4.5% for nightshift, 3.2% for repetitive and 4.3% for noisy work) with ten imputed data sets using PROC MI in SAS.

All analyses were performed using SAS version 9.4.



### Data availability

Anonymized data will be shared on request to the CONSTANCES scientific committee (<https://www.constances.fr/conduct-project-ongoing.php>).

## **RESULTS**

### Study population

Among the 83 892 volunteers aged  $\geq 45$  years, analyses were restricted to subjects who spoke French and with completed and reliable cognitive tests ( $n = 77\,461$ ). Participants with outlier scores for cognitive tests [TMT A and B  $< 10$ s or  $> 130$ s (A) and 300s (B), and fluency tasks = 0] and missing data for education level, which were needed to create the variable “cognitive impairment”, were also excluded. Finally, the analytical sample included 75 322 subjects with at least one cognitive test completed (median age: 57.5 years, 53% of women).

Approximately 8% ( $n = 6\,047$ ) of participants were exposed to formaldehyde during their working life (median age = 57.5 and 68% female). Among these participants, 1 936 (2.6%) were men and 4 111 (5.5%) were women. The median age (IQR) of the exposed and non-exposed groups was 57.5 (52-63) and 58 (51.5-64) years. The main occupational groups exposed to formaldehyde were general care nurses, caregivers, medical technicians, and to a lesser degree, unskilled production workers (e.g., textile, chemistry, metal industries), carpenters, and cleaners. The characteristics of the study sample, divided in formaldehyde exposed and non-exposed, are shown in table 1. Participants exposed to formaldehyde were more often exposed to other solvents, repetitive work, noisy work, and particularly night-shift work (52% vs 17% for non-exposed). Cognitive performances in the exposed and non-exposed group were described in table 2. For example, the DSST median scores (IQR) were 63 (54-73) and 66 (57-76) in the exposed and non-exposed group, respectively.

### Formaldehyde occupational exposure and cognitive impairment

Analysis of associations between exposure to formaldehyde and risk of cognitive impairment (each test score and global cognitive score) (table 3) highlighted that formaldehyde exposure was associated with impairment for all cognitive functions tested, independently of socioeconomic factors and working conditions. Compared with the non-exposed group, the exposed group was at greater risk of global cognitive impairment (adjusted RR (aRR): 1.17; 95% CI: 1.11-1.23).

High lifetime exposure duration to formaldehyde was also significantly associated with the risk of cognitive impairment. Compared with the non-exposed group, participants exposed to formaldehyde for  $\geq 22$  years had higher risk of DSST (aRR: 1.26; 95% CI: 1.16-1.38), fluency task (e.g., phonemic fluency, aRR: 1.22; 95% CI: 1.12-1.34), TMT-B (aRR: 1.21; 95% CI: 1.11-1.32) and global cognitive score (aRR: 1.21; 95% CI: 1.11-1.32) impairment. Moreover, for the cognitive functions assessed by the DSST, phonemic fluency and TMT-B, the risk of cognitive impairment increased with exposure duration, independently of socioeconomic factors and working conditions. For instance, the risk of DSST impairment increased with the exposure duration, with aRR of 1.15 (95% CI: 1.06-1.24) for exposure duration  $< 6$  years, of 1.22 (95% CI: 1.12-1.32) for exposure duration between 7 and 21 years, and of 1.26 (95% CI: 1.16-1.38) for exposure duration  $> 22$  years.

For most tests (except MMSE and TMT-A), high cumulative exposure to formaldehyde (high CEI) was significantly associated with the risk of cognitive impairment (for DSST aRR: 1.25; 95% CI: 1.15 -1.35).

Finally, analysis using the indicator that combines total lifetime dose (i.e., CEI) and time since last exposure showed that participants with high recent exposure were at higher risk of semantic and phonemic fluency impairment (Figure 1). Recent exposure was significantly associated with increased risk of DSST, semantic fluency, phonemic fluency, TMT-B and global cognitive score impairment. Indeed, within the four groups, risk was consistently higher for the most recently exposed participants (i.e., exposure after 2002) than the past exposure groups. Overall, our results suggest that for some specific cognitive domains (DSST, FCRST and phonemic fluency), time may not fully attenuate the risk when lifetime exposure to formaldehyde has been high (DSST: high past exposure: aRR 1.23, 95% CI: 1.11-1.36; high recent exposure: aRR 1.24, 95% CI: 1.13-1.35; phonemic fluency: high past exposure aRR 1.23, 95% CI: 1.11-1.37; high recent exposure: aRR 1.26, 95% CI: 1.15-1.39). Similar results were obtained for global cognitive impairment (high distal exposure aRR 1.15, 95% CI: 1.04-1.27; high recent exposure: aRR 1.20, 95% CI: 1.09-1.31). Moreover, for the DSST and global cognitive scores, the association between exposure and risk of impairment remained significant even for participants with past and moderate life-time formaldehyde exposure (for global cognitive score: moderate past exposure aRR 1.12, 95% CI: 1.02-1.23; moderate recent exposure: aRR 1.26, 95% CI: 1.12-1.41).

Sex and age did not show any interaction with formaldehyde exposure.

## DISCUSSION

Using data from the large French CONSTANCES cohort, we examined the association between occupational exposure to formaldehyde and cognitive impairment in middle-aged and young-old adults ( $\geq 45$  years). Among 75 322 participants, those exposed to formaldehyde during their professional life were at higher risk of global cognitive impairment and for all cognitive domains explored. High exposure duration and high life-time dose (CEI) were associated with worse cognitive impairment, with a dose-effect relationship for exposure duration. Although participants with recent exposure showed higher cognitive impairment, time may not fully attenuate formaldehyde-associated cognitive deficits, especially in highly exposed but also in moderately exposed workers.

The detrimental effect of formaldehyde on brain has been previously shown mainly in animal experiments and in few human studies in restricted occupational settings, including case reports and studies with limited numbers of participants (31). Some potential mechanisms and contributors to neurodegeneration have been proposed to explain formaldehyde effect on brain including energy crisis, cerebral acidosis, oxidative stress, and excitotoxicity (31). However, more studies are required to determine whether and how such mechanisms are involved.

In this study, longer exposure was associated with higher risk of cognitive impairment. Moreover, participants who were exposed in the past (i.e. exposure before 2001) had a lower risk of cognitive impairment compared with those recently exposed (i.e. exposure after 2002), suggesting a potential reversibility of the effect of formaldehyde exposure on cognitive performance, as shown in a previous work on occupational solvent exposure in the CONSTANCES cohort (32). However, our findings also suggest that cognitive deficits associated with formaldehyde persist after occupational exposure, even for moderate lifetime exposure. These findings are in line with previous results in men from the French GAZEL occupational cohort showing that cognitive changes due to solvent exposure can persist after retirement (33).

We highlighted consistent associations with different cognitive domains, including global cognitive function, language abilities, and especially executive functions (DSST, TMT-B). We observed the highest risk of impairment for the DSST, a test that requires sustained attention, processing speed, and visual spatial skills. This sensitive cognitive test might be particularly appropriate to examine cognitive performance in middle-aged adults (34).

Our study has some limitations. First, these results should be confirmed in longitudinal analyses on cognitive change over time. Second, we assessed formaldehyde exposure with a JEM. Although JEM limit recall bias compared to self-reported exposures, the assessment is dependent on previously constructed nomenclatures and therefore, present specific limitations. The nomenclature codes may group together heterogeneous occupations or activities with a potentially different exposure assessment, making it necessary to define a mean exposure for each code, which may lead to underestimate exposure for some occupations that are underrepresented in the nomenclature. This exposure misclassification is non-differential, and therefore would lead to attenuation of the associations. Third, the CONSTANCES cohort does not include agricultural and self-employed workers. Fourth, we did not consider other non-occupational sources of exposure to formaldehyde (e.g., polluted atmosphere, domestic air). Indeed, we could not take into account home exposure to formaldehyde, although it can be important in domestic air. This could have underestimated the individual exposure. Finally, formaldehyde might also be a proxy for an exposure related found in some jobs. Further analyses will need to consider such possible pathways as other possible interactions with such other potential neurotoxicants.

Our study has also strengths. For the first time, we highlighted the detrimental effect of formaldehyde on cognition in a large sample from the general population, both in men and women. We could evaluate, in the same study, people working in many different sectors and with very different formaldehyde exposures. One of the main strengths was the assessment of cognitive performance using a cognitive test battery administered by neuropsychologists in standardized conditions. We also took into account sex, age and education level when constructing norms for cognitive impairment (21). We considered exposure to formaldehyde in several ways, including exposure duration, time since last exposure, and dose, using a CEI. This index has been widely used to estimate long-term exposure in occupational settings (35). It can flexibly represent exposure over time and consider exposures that may come from different routes. In addition, the JEM takes into account formaldehyde exposure variations due to changes in exposure over time, including changes due to new regulation or the implementation of protection equipment that may vary among occupations, company size, and period. Finally, we adjusted for multiple confounders, including working conditions and solvent exposure.

The number of workers exposed to formaldehyde has decreased in France and in Europe through successive regulations since the 1980s, particularly for women's jobs, explained notably by the interdiction as biocides in 2012 in the healthy centers for disinfection of materials

and surfaces and by the reduction of use of formaldehyde resins in the textile activity, who are more usually realized by female workers. However, some sectors remain particularly exposed, such as agriculture, specialized construction work, human health activities (histopathology), funeral care sector, and some industries that still use formaldehyde (19). Moreover, formaldehyde is commonly used around the world. Precautions can and must be taken to decrease and prevent its neurotoxic effects.

In a large sample of the middle-aged and young-old French adults ( $\geq 45$  years of age), we provided evidence that being or have been occupationally exposed to formaldehyde can affect cognitive performance. Higher level and longer duration of exposure were associated with cognitive impairment after controlling for socioeconomic factors and life-time occupational conditions. The risk of cognitive impairment was higher for recent exposure; however, time may not fully attenuate the formaldehyde-associated cognitive deficits. These results provide new evidence to further limit formaldehyde use and to target prevention efforts to the identified occupational groups.

Table 1. Population characteristics according to the presence/absence of occupational formaldehyde exposure (N=75 322)

	Not exposed to formaldehyde (n=69 275) N (%)	Exposed to formaldehyde (n=6 047) N (%)
<b>Socioeconomic characteristics</b>		
Age*	58 (51.5 - 64)	57.5 (52 - 63)
Women	35 739 (51.6)	4 111 (68.0)
Years of education		
<5	2 295 (3.3)	240 (4.0)
5 to 11	5 635 (8.1)	697 (11.5)
11 to 13	26 509 (38.3)	2473 (40.9)
14 to 16	21 759 (31.4)	2188 (36.2)
≥17	13 077 (18.9)	449 (7.4)
Income (euros)		
< 1000	1 783 (2.6)	202 (3.3)
1000 to 1500	3 857 (5.6)	516 (8.5)
1500 to 2100	6 959 (10.1)	811 (13.4)
2100 to 2800	10 358 (15.0)	1 095 (18.1)
2800 to 4200	20 148 (29.1)	1 858 (30.7)
> 4200	22 126 (31.9)	1 215 (20.1)
Do not know or do not want to answer	4 044 (5.8)	350 (5.8)
<b>Lifetime working conditions covariates</b>		
Solvent exposure		
Exposed to one solvent type	4 545 (6.6)	494 (8.2)
Exposed to two or more solvent types	2 604 (3.8)	255 (4.2)
Night-shift work	12 033 (17.4)	3 152 (52.1)
Repetitive work	5 212 (7.5)	876 (14.5)
Noisy work	20 042 (28.9)	2 059 (34.1)
ERI ≥1	19 665 (28.4)	1 737 (28.7)

\*Median (Interquartile range)

ERI: Effort–Reward Imbalance

The distribution of income, solvent exposure, night-shift, repetitive and noisy work was described after multiple imputation.

Table 2. Cognitive performance according to the presence/absence of occupational formaldehyde exposure

Cognitive tests	Total	Not exposed to formaldehyde				Exposed to formaldehyde			
	N	N	Min	Median (IQR*)	Max	N	Min	Median (IQR*)	Max
MMSE (0-30)	71 323	65 624	14	29 (27-30)	30	5 699	14	28 (27-29)	30
DSST (0-135)	72 450	66 619	0	66 (57-76)	135	5 831	4	63 (54-73)	135
FCRST (total free recall 0-48)	70 594	64 853	3	33 (29-36)	48	5 741	7	33 (29-36)	48
Semantic fluency (words in 1 min)	72 490	66 640	0	23 (20-28)	56	5 850	0	23 (19-27)	55
Phonemic fluency (words in 1 min)	72 687	66 827	0	15 (12-18)	45	5 860	0	14 (11-18)	32
TMT-A (max 180 seconds)	72 325	66 533	10	32 (25-39)	129	5 792	10	32 (26-41)	126
TMT-B (max 180 seconds)	71 280	65 563	12	60 (48-77)	300	5 717	24	64 (51-81)	300
Global cognitive score**	65 771	60 432	-10.8	0.15 (-0.1-1.2)	6.1	5 339	-8.9	-0.14 (-1.3-0.9)	5.3

\*Interquartile range

\*\* The global cognitive score was calculated using principal component analysis based on six cognitive tests: DSST, FCRST, VFT (semantic and phonemic), and TMT-A and -B.

Table 3. Association between formaldehyde exposure (yes/no, duration of exposure, and CEI) and cognitive impairment\*

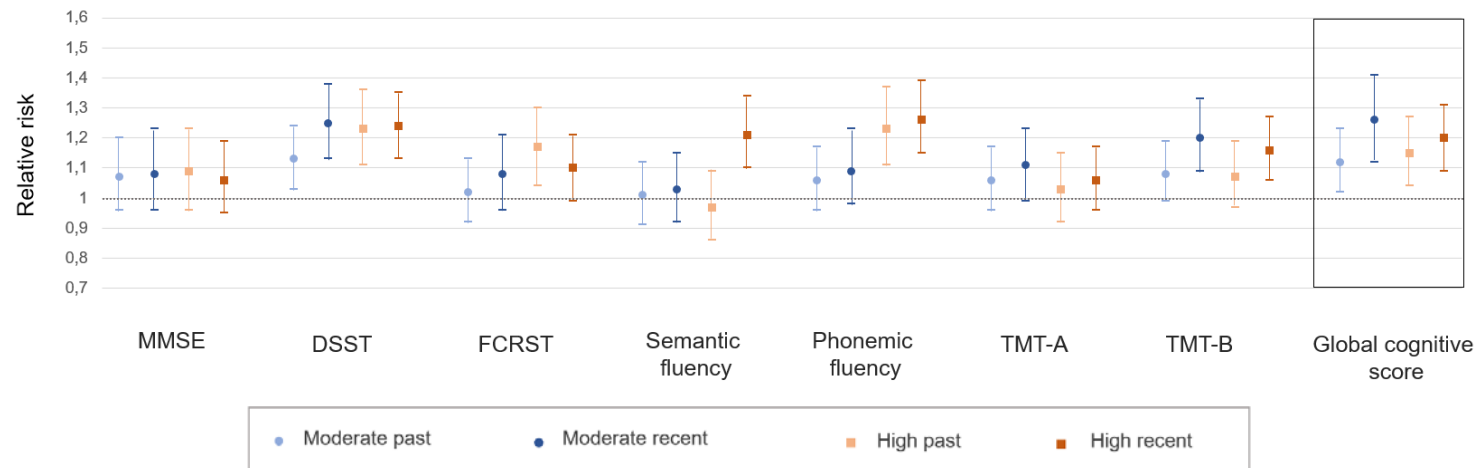
Ref. unexposed	MMSE		DSST		FCSRT		Semantic fluency		Phonemic fluency		TMT-A		TMT-B		Global cognitive score	
	RR	[95% CI]	RR	[95% CI]	RR	[95% CI]	RR	[95% CI]	RR	[95% CI]	RR	[95% CI]	RR	[95% CI]	RR	[95% CI]
Exposed	1.08	[1.01-1.14]	1.21	[1.15-1.27]	1.09	[1.03-1.15]	1.06	[1.00-1.12]	1.16	[1.10-1.23]	1.06	[1.01-1.12]	1.13	[1.07-1.19]	1.17	[1.11-1.23]
Duration of exposure																
Low ( $\leq 6$ )	1.12	[1.01-1.23]	1.15	[1.06-1.24]	1.07	[0.99-1.17]	1.04	[0.95-1.14]	1.12	[1.03-1.23]	1.05	[0.96-1.14]	1.06	[0.98-1.16]	1.16	[1.07-1.26]
Middle (7 to 21)	1.05	[0.95-1.17]	1.22	[1.12-1.32]	1.10	[1.00-1.21]	0.99	[0.90-1.09]	1.15	[1.05-1.26]	1.08	[0.98-1.18]	1.12	[1.03-1.23]	1.14	[1.04-1.26]
High ( $\geq 22$ )	1.05	[0.94-1.17]	1.26	[1.16-1.38]	1.08	[0.98-1.19]	1.15	[1.05-1.26]	1.22	[1.12-1.34]	1.07	[0.97-1.17]	1.21	[1.11-1.32]	1.21	[1.11-1.32]
CEI**																
Low	1.08	[0.97-1.19]	1.22	[1.13-1.32]	1.03	[0.94-1.13]	1.05	[0.96-1.15]	1.06	[0.97-1.17]	1.09	[0.99-1.19]	1.11	[1.01-1.20]	1.17	[1.08-1.28]
Middle	1.07	[0.96-1.19]	1.14	[1.05-1.25]	1.07	[0.98-1.18]	0.97	[0.88-1.07]	1.15	[1.05-1.26]	1.06	[0.97-1.16]	1.17	[1.07-1.27]	1.15	[1.04-1.27]
High	1.08	[0.98-1.20]	1.25	[1.15-1.35]	1.15	[1.05-1.26]	1.16	[1.06-1.27]	1.28	[1.17-1.39]	1.04	[0.95-1.14]	1.12	[1.02-1.22]	1.19	[1.09-1.28]

\*Cognitive impairment was defined as a score  $\leq 25$ th percentile ( $\geq 75$ th percentile for TMT) of the distribution according to age, sex and level of education

\*\*CEI= Cumulative Exposure Index

RR, Relative Risk adjusted for age, sex, education, income, solvent exposure, ERI, night-shift, repetitive, and noisy work.





Relative risk adjusted for age, sex, education, income, solvent exposure, ERI, nightshift, repetitive, and noisy work.

Figure 1. Association between the indicator that combines total lifetime dose (i.e., CEI) and time since last exposure and cognitive impairment

## **Glossary**

**CI** = Confidence Interval; **CEI** = Cumulative Exposure Index; **DSST** = Digit Symbol Substitution Test; **ERI** = Effort-Reward Imbalance; **FCRST** = Free and Cued Selective Reminding Test; **JEM** = Job Exposure Matrix; **MMSE** = Mini Mental State Examination; **PCA** = Principal Component Analysis; **RR** = Relative Risks; **SD** = Standard Deviation; **TMT** = Trail Making Test; **VFT** = Verbal Fluency Tasks

## REFERENCES

1. International Agency for Research on Cancer. IARC Mono-graphs on the Evaluation of Carcinogenic Risks to Humans. Formaldehyde, 2-Butoxyethanol and 1-tert-Butoxypropan-2-ol. Lyon: IARC. 2006;88:1-478
2. International Agency for Research on Cancer. IARC Mono-graphs on the Evaluation of Carcinogenic Risks to Humans. Chemical agents and related occupations. Lyon: IARC. 2012;100F. 628 p
3. Songur A, Ozen OA, Sarsilmaz M. The toxic effects of formaldehyde on the nervous system. *Rev Environ Contam Toxicol*. 2010;203:105-18.
4. Liu Y, Ye Z, Luo H, Sun M, Li M, Fan D, et al. Inhalative formaldehyde exposure enhances aggressive behavior and disturbs monoamines in frontal cortex synaptosome of male rats. *Neurosci Lett*. 2009;464(2):113-6.
5. Malek FA, Möritz KU, Fanghänel J. Formaldehyde inhalation & open field behaviour in rats. *Indian J Med Res*. 2003;118:90-6.
6. Malek FA, Möritz KU, Fanghänel J. A study on the effect of inhalative formaldehyde exposure on water labyrinth test performance in rats. *Ann Anat*. 2003;185(3):277-85.
7. Tong Z, Han C, Luo W, Wang X, Li H, Luo H, et al. Accumulated hippocampal formaldehyde induces age-dependent memory decline. *AGE*. 2013;35(3):583-96.
8. Pitten FA, Kramer A, Herrmann K, Bremer J, Koch S. Formaldehyde neurotoxicity in animal experiments. *Pathol Res Pract*. 2000;196(3):193-8.
9. Tong Z, Han C, Luo W, Li H, Luo H, Qiang M, et al. Aging-associated excess formaldehyde leads to spatial memory deficits. *Sci Rep*. 2013;3(1):1-9.
10. Li Y, Song Z, Ding Y, Xin Y, Wu T, Su T, et al. Effects of formaldehyde exposure on anxiety-like and depression-like behavior, cognition, central levels of glucocorticoid receptor and tyrosine hydroxylase in mice. *Chemosphere*. 2016;144:2004-12.
11. Kilburn KH, Warshaw R, Thornton JC. Formaldehyde impairs memory, equilibrium, and dexterity in histology technicians: effects which persist for days after exposure. *Arch Environ Health*. 1987;42(2):117-20.
12. Kilburn KH, Warshaw RH. Neurobehavioral effects of formaldehyde and solvents on histology technicians: repeated testing across time. *Environ Res*. 1992;58(2):134-46.
13. LoSasso GL, Rapport LJ, Axelrod BN. Neuropsychological symptoms associated with low-level exposure to solvents and (meth)acrylates among nail technicians. *Neuropsychiatry Neuropsychol Behav Neurol*. 2001;14(3):183-9.
14. Bach B, Pedersen OF, Mølhøve L. Human performance during experimental formaldehyde exposure. *Environ Int*. 1990;16(2):105-13.
15. Zendehdel R, Fazli Z, Mazinani M. Neurotoxicity effect of formaldehyde on occupational exposure and influence of individual susceptibility to some metabolism parameters. *Environ Monit Assess*. 2016;188(11):648.
16. Nielsen GD, Larsen ST, Wolkoff P. Re-evaluation of the WHO (2010) formaldehyde indoor air quality guideline for cancer risk assessment. *Arch Toxicol*. 2017;91(1):35-61.

17. Zins M, Goldberg M. The French CONSTANCES population-based cohort: design, inclusion and follow-up. *Eur J Epidemiol*. 2015;30:1317-28.
18. Goldberg M, Carton M, Descatha A, Leclerc A, Roquelaure Y, Santin G, Zins M; CONSTANCES team. CONSTANCES: a general prospective population-based cohort for occupational and environmental epidemiology – Cohort profile. *Occup Environ Med* 2017;74(1):66–71. .
19. Delabre L, Garras L, Houot M, Pilorget C. Occupational exposure to formaldehyde in France in 2015 and trends of exposure prevalence since 1982. Results from the job-exposure matrix of the Matgéne programme. *Bull Epidémiol Hebd*. 2019;(33):679-86.
20. Ouvrard C, Berr C, Meillon C, Ribet C, Goldberg M, Zins M, et al. Norms for standard neuropsychological tests from the French CONSTANCES cohort. *Eur J Neurol*. 2019;26(5):786-93.
21. Mura T, Amieva H, Goldberg M, Dartigues J-F, Ankri J, Zins M, et al. Effect size for the main cognitive function determinants in a large cross-sectional study. *Eur J Neurol*. 2016;23(11):1614-26.
22. Folstein MF, Folstein SE, McHugh PR. « Mini-mental state ». A practical method for grading the cognitive state of patients for the clinician. *J Psychiatr Res*. 1975;12(3):189-98.
23. Wechsler D. WAIS-R manual: Wechsler adult intelligence Scale-Revised. New York Psychological Corporation, 1981.
24. Lezak MD, Howieson DB, Bigler ED, Tranel D. Neuropsychological Assessment. Oxford, New York: Oxford University Press; 2012. 1200 p.
25. Grober E, Buschke H, Crystal H, Bang S, Dresner R. Screening for dementia by memory testing. *Neurology*. 1988;38(6):900-3.
26. Borkowski JG, Benton AL, Spreen O. Word fluency and brain damage. *Neuropsychologia*. 1967;5(2):135-40.
27. Cardebat D, Doyon B, Puel M, Goulet P, Joannette Y. Formal and semantic lexical evocation in normal subjects. Performance and dynamics of production as a function of sex, age and educational level. *Acta Neurol Belg*. 1990;90(4):207-17.
28. Boll TJ, Reitan RM. Effect of age on performance of the Trail Making Test. *Percept Mot Skills*. 1973;36(3):691-4.
29. Miner T, Ferraro FR. The Role of Speed of Processing, Inhibitory Mechanisms, and Presentation Order in Trail-Making Test Performance. *Brain Cogn*. 1998;38(2):246-53.
30. Zou G. A modified poisson regression approach to prospective studies with binary data. *Am J Epidemiol* 2004;159:702–6.
31. Zhang L. Formaldehyde: Exposure, Toxicity and Health Effects. Royal Society of Chemistry; 2018. 414 p.
32. Letellier N, Choron G, Artaud F, Descatha A, Goldberg M, Zins M, et al. Association between occupational solvent exposure and cognitive performance in the French CONSTANCES study. *Occup Environ Med*. 2020;77(4):223-30.

33. Sabbath EL, Gutierrez L-A, Okechukwu CA, Singh-Manoux A, Amieva H, Goldberg M, et al. Time may not fully attenuate solvent-associated cognitive deficits in highly exposed workers. *Neurology*. 2014;82(19):1716-23.
34. Proust-Lima C, Amieva H, Dartigues J-F, Jacqmin-Gadda H. Sensitivity of four psychometric tests to measure cognitive changes in brain aging-population-based studies. *Am J Epidemiol*. 2007;165(3):344-50.
35. Rolle-McFarland D, Liu Y, Zhou J, Mostafaei F, Zhou Y, Li Y, et al. Development of a Cumulative Exposure Index (CEI) for Manganese and Comparison with Bone Manganese and Other Biomarkers of Manganese Exposure. *Int J Environ Res Public Health*. 2018; 15(7):1341.