EDITOR'S CHOICE

Maternal occupational exposure to solvents and congenital malformations: a prospective study in the general population

R Garlantézec, C Monfort, F Rouget, S Cordier

Inserm, U625, Rennes, France

Correspondence to:
Ronan Garlantézec, Inserm U625, GERHM, Univ Rennes I, Campus de Beaulieu, Rennes F-35042, France;
ronan.garlantezec@chu-brest.fr

Accepted 5 December 2008

ABSTRACT

Objective: To study the relations between maternal occupational exposure to solvents during pregnancy and the risk of congenital malformations.

Methods: A prospective population-based cohort, specifically designed to study the impact of maternal exposure to solvents on the risk of congenital malformations, began in 2002 in three districts of Brittany (France). 3421 pregnant women were recruited until the end of 2005 by physicians before 19 weeks of gestation and followed through birth. Information on pregnancy outcomes was obtained from the hospital. Occupational exposure to solvents at the beginning of pregnancy was assessed from the women's self-reported occupational exposures at inclusion and from a job-exposure matrix (JEM). Sociodemographic characteristics, lifestyle factors, medical history, diseases during pregnancy were obtained at inclusion and from hospital records. Analyses were restricted to working women (n = 3005). Logistic regressions were used to adjust for potential confounders.

Results: 30.2% of the working women declared regular exposure to at least one product that may contain solvents. 21.3% of them were classified at least in the medium exposure category using the JEM. Occupations mainly classified as exposed by both assessment methods were hairdressers, nurses' aides, nurses and chemists/biologists. Significant associations were found between major congenital malformations and maternal occupational exposure to solvents, assessed by both self-report odds ratio (OR = 2.48, 95% CI 1.4 to 4.4 for regular exposure vs no exposure) and the JEM (OR = 3.48, 95% CI 1.4 to 8.4 for highest level of exposure vs no exposure). A significant dose–response trend was observed with both assessment methods. Several subgroups of major malformations were associated with maternal exposure to solvents (oral clefts, urinary malformations and male genital malformations).

Conclusion: This study provides further evidence of an association between exposure to solvents during pregnancy and the risk of major malformations.

Many women workers are exposed to organic solvents,[1] which are widely used in a range of industrial products including paints, varnishes, inks and cleaning agents. Solvents belong to three main chemical families: oxygenated, petroleum and chlorinated solvents. Their main routes of exposure are dermal and respiratory. Despite their widespread use, their health effects on reproduction, especially their relation to congenital malformations, remain controversial.

Several solvents have been shown to be teratogenic for animals.[2 3] In mice, for example, toluene and xylene (petroleum solvents) have been associated with the occurrence of cleft palate,[2] and ethylene glycol monomethyl ether has been associated with the occurrence of neural tube defects.[3]

In humans, malformations and cytogenetic effects have been observed among the offspring of women exposed to glycol ethers during pregnancy.[4] Some studies,[5–8] but not others,[9] report an excess risk of spontaneous abortion among women occupationally exposed to solvents. A small prospective cohort,[10] and a meta-analysis,[11] performed by the same research group both report associations between maternal occupational exposure to solvents and major malformations. Two recent occupational cohort studies of women working in laboratories suggest similar results.[12 13]

Various case-control studies have shown relations between maternal occupational exposure to solvents and some subtypes of malformations, mostly oral clefts.[14–16] Some significant associations have also been reported between maternal exposure to solvents and cardiac malformations,[14 17] and neural tube defects,[14 18] but all the studies are not consistent.[19]

Because environmental factors are suspected of responsibility for the apparent increased incidence of male genital malformations,[20] we think it is worthwhile to study their association with maternal occupational exposure to solvents.

Our prospective population-based cohort study was specifically designed to test the hypothesis of an impact of maternal exposure to solvents on the risk of congenital malformations. It sought to overcome several of the drawbacks of previous studies by using exposure data collected at the beginning of pregnancy.

METHODS

Study population

The French PELAGIE cohort (*Perturbateurs endocriniens: Étude Longitudinale sur les Anomalies de la Grossesse, l'Infertilité et l'Enfance*) began in 2002 in three districts of Brittany (north-western France): Ille-et-Vilaine, Côtes d'Armor, and Finistère. Women were recruited by gynaecologists, obstetricians or ultrasonographers at visits for prenatal care. They met the inclusion criteria if they completed the inclusion questionnaire before 19 weeks of gestation and were still pregnant at that time. The follow-up of the women included in the study began at 16 weeks of gestation and continued through the end of pregnancy. Participants provided informed consent for data

collection, and the appropriate ethics committees approved the study procedures.

In the inclusion questionnaire, women reported their social, demographic and medical characteristics: obstetrical history, educational level, present occupation, nutrition and lifestyle factors (alcohol and tobacco consumption). They returned it to our laboratory with a urine sample (the first morning void) for measurement of exposure biomarkers (results of which will be the object of further publication). Midwives, paediatricians and hospital medical records provided medical information about pregnancy outcome (delivery or medical termination, length of gestation, measurements and health status of newborn at birth).

Three thousand four hundred and twenty-one women returned the inclusion questionnaire before 19 weeks of gestation (for an estimated participation rate of 80%) between April 2002 and December 2005. Information on pregnancy outcome was available for 3399 women (99.4%). The other 22 women were lost to follow-up.

Assessment of pregnancy outcome

The presence and type of congenital malformations in liveborn infants was validated by a paediatrician based on findings at the clinical examination before discharge from the maternity ward (or neonatology or paediatric critical care unit). Malformations were determined by pathology and karyotype examinations for pregnancies that did not result in live births (medically indicated abortions or fetal deaths). Paediatricians were asked specifically about oral clefts and male genital anomalies (hypospadias, cryptorchidism and micropenis). Mention of male genital anomaly was validated by a paediatric surgeon with 2 years of follow-up. Mention of heart murmur identified at the maternity ward was sought by checking with paediatric cardiologists in the region to detect potential additional cardiac malformation.

Malformations were coded according to the International Classification of Disease (10th revision of World Health Organization 1993), and grouped according to the EUROCAT recommendations,[21] as major or minor malformations and by organ groups of malformations, in addition to genetic and chromosomal malformations considered as one group. We considered all male genital malformations that were repaired surgically, including cryptorchidism and glandular hypospadias, to be major malformations.

Solvent exposure assessment

Solvent exposure at work was defined by two independent methods: self-reported exposure to products that might contain solvents and a job-exposure matrix (JEM).

The questionnaire completed in early pregnancy asked women about the frequency of their contact (never, occasional, or regular) at work with 11 classes of products considered to contain solvents (paints, strippers, varnishes, dyes, inks, glues, gasoline, grease removers, detergents and cleaning agents, textile treatment agents, and cosmetics). Women were then classified as ''not exposed'' if they reported no exposure to any of these products. They were classified as ''occasionally exposed'' to solvents when they reported occasional exposure to at least one product and ''regularly exposed'' when they reported regular exposure to at least one product. To study malformations by organ subgroups, we have retained only two classes: ''never or occasional exposure'' and ''regular exposure''.

We also used a JEM.[22–24] This matrix assigned a probability of solvent exposure to a combination of two codes (one occupation code (International Standard Classification of Occupations of the International Labour Office 1968) and one code of industrial activity (International Standard Industrial Classification of all Economic Activities of the United Nations 1975)). This JEM originally classified exposure on five different levels: 10 — job-related exposure is not higher than for the general population; 20 — job may entail a cumulative exposure higher than for the general population; 3x — job may entail exposure to a level definitely higher than for the general population (31 — probability <1/3; 32 — probability 1/3–2/3; 33 — probability >2/3); 40 — job entails exposure to the specific agent at a level clearly higher than for the general population; and 50 — job entails exposure to the specific agent and exposure is known to be particularly high.

To have enough subjects in each category and according to the bimodal distribution of the initial levels, we combined these exposure categories into three groups: no exposure (level 10 (n = 2234)), medium exposure (levels 20 (n = 91) and 31 (n = 423)), and high exposure (levels 32 (n = 49), 33 (n = 22), 40 (n = 10) and 50 (n = 9)). For some rare outcomes, we could retain only two classes: no exposure (level 10) and exposure (levels 20, 31, 32, 33, 40 and 50).

Statistical analysis

Analyses were restricted to women who reported working at the beginning of pregnancy (n = 3005). We studied the relations between solvent exposure and congenital malformations separately for chromosomal and genetic malformations, other major malformations (excluding chromosomal and genetic), and minor malformations. Organ groups were also studied for other major malformations. We estimated odds ratios (ORs) and 95% CI with the babies with no malformations as the reference group.

Logistic regression was used to adjust for potential risk factors for congenital malformations cited in the literature. These variables were maternal age at inclusion (less than 25 years, 25–29 years, 30–34 years, 35 years and more), tobacco consumption at the beginning of pregnancy (non-smoker, at least one cigarette per day), alcohol consumption (0 drinks per week, at least one drink per week), educational level (primary or secondary, passed baccalaureate examination at the end of secondary school, 2 or more years of postsecondary education), and for studying male genital malformations, premature birth (born before 37 weeks of gestation, or at least at 37 weeks). Adjustment for these variables was made when it was possible (because of the number of cases) for studies of malformation subgroups. They were introduced into the model simultaneously and if some of them were at the origin of convergence default of the model, they were excluded from the analysis.

A trend test for categories of exposure was performed as appropriate. SAS software V8.2 was used for data analysis.

RESULTS

Population description and outcome

Of the women included in the PELAGIE study, 3005 worked at the beginning of their pregnancy (88%). Mean age at inclusion was 30.0 years (SD 5.0). An education level of at least 2 years of postsecondary education was reported by 61.4% (table 1).

Three thousand and five women represented 3041 pregnancies (36 women have twin pregnancies).

All but 33 pregnancies ended in a live birth; there were 14 elective abortions after prenatal diagnosis and 19 fetal deaths (after 16 weeks of gestation).

Table 1 Description of the 3005 working women of the PELAGIE cohort and risk factors for major malformations (chromosomal and genetic malformations excluded)

	Total	Major malformations	No malformations
	No (%)	No (%)	No (%)
Total	**3005**	**69**	**2897**
Marital status			
Alone	2946 (98.2)	68 (98.6)	2838 (98.1)
Couple	54 (1.8)	1 (1.4)	54 (1.9)
Unknown	5 (–)	–	5 (–)
Geographical origin			
European	2957 (98.8)	68 (98.6)	2849 (98.7)
Other	37 (1.2)	1 (1.4)	37 (1.3)
Unknown	11 (–)	–	11 (–)
Parity			
0	1408 (46.9)	41 (59.4)	1351 (46.7)
1	1123 (37.4)	19 (27.5)	1089 (37.7)
2 and more	469 (15.7)	9 (13.1)	452 (15.6)
Unknown	5 (–)	–	5 (–)
Maternal age (years)			
<25	311 (10.4)	8 (11.6)	298 (10.3)
25–29	1230 (40.9)	28 (40.6)	1186 (40.9)
30–34	1055 (35.1)	26 (37.7)	1018 (35.2)
⩾35	408 (13.6)	7 (10.1)	394 (13.6)
Unknown	1 (–)	–	1 (–)
Education level			
Primary or secondary education	496 (16.5)	11 (15.9)	478 (16.5)
Baccalaureate	551 (18.4)	13 (18.8)	523 (18.1)
2 years or more higher education	1954 (65.1)	45 (65.3)	1892 (65.4)
Unknown	4 (–)	–	4 (–)
Tobacco consumption periconceptional and first trimester			
Non-smoker	2131 (71.7)	52 (75.4)	2051 (71.6)
At least one cigarette per day	841 (28.3)	17 (24.6)	813 (28.4)
Unknown	33 (–)	–	33 (–)
Alcohol consumption at inclusion			
0 drinks per week	2524 (84.8)	59 (85.5)	2431 (84.7)
At least one drink per week	453 (15.2)	10 (14.5)	438 (15.3)
Unknown	28 (–)	–	38 (–)
Diabetes mellitus			
No	2833 (96.3)	64 (95.5)	2729 (96.2)
Yes	110 (3.7)	3 (4.5)	109 (3.8)
Unknown	62 (–)	2 (–)	59 (–)

Concerning the 3041 infants, 26 infants had incomplete data for physicians' examination, 2897 had no malformations and 118 infants were diagnosed with at least one congenital malformation: all 14 elective abortions and 104 of the live born babies. No malformations were diagnosed among fetal deaths. Eighty-four malformations were classified as major malformations (2.79% of the live births plus fetal deaths and elective abortions) and 34 as minor. The most frequent subgroups for major malformations involved limb (n = 20) and urinary malformations (n = 13) (table 2).

Occupational exposure to solvents

Women in the PELAGIE study cohort worked mainly in science-related (39.0%), clerical (23.2%) and service (15.6%) occupations (table 3).

Regular exposure to at least one product that may contain solvents was reported by 30.2% of our working population (table 3). Occupations entailing regular exposure were mainly hairdressers, cleaners and helpers, nurses' aides, nurses and chemists/biologists. Of the women classified by self-report as regularly exposed at work, 73.3% reported regular exposure to detergents and cleaning agents, 15.5% to glue, 12.2% to grease removers, 11.0% to inks and 10.7% to cosmetics. Moreover, 32.0% of these women had more than one regular exposure.

The JEM placed 18.1% of the working women in the medium exposure category and 3.2% in the high exposure category (table 3). The occupations most often classified as highly exposed by the JEM were chemists/biologists and non-agricultural workers. Most nurses, nurses' aides and hairdressers were assigned to the medium exposure category, whereas only 8.3% of the cleaners and helpers were assigned to this category.

Risks of congenital malformations

We found a statistically significant relation between the risk of major malformations (non-chromosomal and non-genetic malformations) and maternal solvent exposure, assessed both by self-reported exposure (OR = 2.48, 95% CI 1.4 to 4.4, for regular exposure vs no exposure) and by the JEM (OR = 3.48, 95% CI 1.4 to 8.4, for high exposure vs no exposure) (table 4). A statistically significant dose–response relation was found with each assessment method (p values for trend, respectively, p = 0.002 and p = 0.005). No significant relation was found

Table 2 Prevalence of congenital malformations by subgroup in the PELAGIE cohort

	Minor malformations	Major malformations
	No*	No† (%‡)
	34	84 (2.79)
Subgroup		
Nervous system	0	4 (0.13)
Eye	0	1 (0.03)
Ear, face and neck	10	0 (–)
Congenital heart disease	0	6 (0.20)
Periphery vascular	6	0 (–)
Respiratory	1	0 (–)
Oro-facial clefts	0	8 (0.27)
Digestive system	1	2 (0.06)
Abdominal wall defects	0	1 (0.03)
Urinary	3	13 (0.43)
Female genital	2	0 (–)
Male genital	11	12 (0.40)
Limb	3	20 (0.66)
Musculoskeletal	0	1 (0.03)
Cutaneous	0	3 (0.10)
Chromosomal	0	11 (0.36)
Genetic syndromes	0	4 (0.13)

*Three live births had two minor malformations.
†One live birth and one elective abortion had two major malformations.
‡Rate of major malformations among live births, elective late abortions and fetal deaths (n = 3015).

with either chromosomal and genetic malformations or minor malformations.

The subgroup analysis for major malformations found ORs of at least 2 for oro-facial clefts, urinary malformations, and male genital malformations with both assessment methods and statistically significant for at least one method (table 5).

DISCUSSION

Using a prospective design and two independent methods of assessing exposure to solvents during the appropriate window of susceptibility during pregnancy, we found statistically significant and dose-dependent relations between maternal exposure and the risk of major malformations. These relations were explained in part by the increased risk of several subgroups of malformations, specifically, oral clefts, urinary malformations and male genital malformations.

Our cohort was composed of pregnant women who saw one of the participating physicians and agreed to participate in our study. Although the estimated participation rate was high (80%), the need to recruit both physicians and patients resulted in selecting a highly educated population (slightly higher than the regional average), concerned by environmental problems and able to follow the instructions for completing the questionnaire and sending it back. This selection, reflected by the distribution of education level in this population, explains why the occupations classified as exposed to solvents in our population are mainly technical (nurses, chemists and biologists) or service workers rather than manufacturing labourers. These occupations may, however, account for most current women's occupations that entail solvent exposure. We can hope that this limited number of occupations will facilitate our search for the specific solvent compounds and mixtures that might explain our findings.

We successfully determined the outcomes of more than 99% of the pregnancies, independently of exposure characterisation. This rules out any differential assessment of congenital malformations.

The major malformation rates in our study are consistent with French,[25] and European registry data,[26] except for cardiac abnormalities, which were less frequent than expected (0.20% of births and abortions vs 0.58%). Cardiac malformations, which are frequently not detected until later in life,[27] were sought by checking with paediatric cardiologists in the region for babies with heart murmurs identified at the maternity ward. No additional cardiac malformations were ascertained. It is nonetheless possible that some non-symptomatic cardiac malformations without heart murmur have not been detected in our study. Other non-symptomatic and not externally visible at-birth malformations could also have not been detected in our study, for example, urinary malformations which are not detected until later in life. But, due to the performance of routine ultrasounds during pregnancy (at least three prenatal ultrasonography examinations, reimbursed by the national health insurance for all pregnancies in France) and the quality of these images, we assume that urinary malformations are now very unlikely not to be determined before delivery.[28] For other subgroups of malformations, we think that our assessment strategy is unlikely to not detect them. If some urinary or cardiac malformations were not detected at birth (which is not very probable for the urinary malformations), the misclassification would not be differential, given that the failure to detect them is unrelated to the exposure assessment conducted in early pregnancy. Consequences on the results would be on average an underestimation of the association between solvent exposure and these malformations.

Because of the well-known difficulties in recording male genital malformations in newborns,[29 30] and to limit classification error and select the most severe cases (as for other malformation subgroups), we considered only male genital malformations that were repaired surgically, including cryptorchidism and glandular hypospadias, to be major malformations.

To reduce any possible healthy worker effect, we chose before beginning our analysis, to restrict it to women who were working at the beginning of their pregnancy. The associations we found were not modified by the inclusion in the analysis of women who were not working (all of whom were classified as unexposed).

We used two indirect assessments of occupational exposure (self-report and JEM), both conducted before pregnancy outcomes were assessed. Chromosomal malformations were diagnosed by karyotype through amniocentesis (performed after 15 weeks of gestation, results available 2 weeks after), and non-chromosomal malformations were diagnosed at the second ultrasound (routinely performed in France between 20 and 23 weeks of gestation) or later during pregnancy or at birth. We could verify that in all cases, diagnosis was made after response to the inclusion questionnaire. We therefore assume that no differential recall bias is possible. Random misclassification is nonetheless possible. Self-report of the frequency of contact with compounds that may contain solvents is subjective, and JEM assessments reflect only an average of individual working circumstances. In addition, there were not enough cases to allow us to make use of the fine level of exposures originally proposed by the JEM. Solvent exposure status of some occupations may have changed since 1988 (year of this JEM publication). Classifications used to define exposure

Table 3 Description of occupational activities and solvent exposure for working mothers (n = 3005)

		Self-reported exposure			JEM-assessed exposure		
	Total	Never	Occasional	Regular	No exposure	Medium exposure	High exposure
Maternal occupation	No (%)	No (%)	No (%)	No (%)	No (%)	No (%)	No (%)
Total	**3005**	**1402 (49.7)**	**566 (20.1)**	**850 (30.2)**	**2234 (78.7)**	**514 (18.1)**	**90 (3.2)**
Professional, technical and related workers	1155 (39.0)	559 (50.9)	247 (22.5)	292 (26.6)	749 (66.7)	306 (27.2)	68 (6.1)
Medical, dental, veterinarians, pharmacists	150 (5.1)	73 (51.8)	34 (24.1)	34 (24.1)	117 (79.1)	30 (20.2)	1 (0.7)
Nurses, midwives, medical *x* ray technicians	209 (7.0)	33 (16.4)	46 (22.9)	122 (60.7)	20 (9.6)	188 (90.4)	0 (–)
Architects, engineers and related technicians	77 (2.6)	53 (70.7)	17 (22.7)	5 (6.6)	75 (100.0)	0 (–)	0 (–)
Statisticians, mathematicians, system analysts	52 (1.8)	43 (82.7)	5 (9.6)	4 (7.7)	52 (100.0)	0 (–)	0 (–)
Teachers	324 (10.9)	148 (48.2)	91 (29.7)	68 (22.1)	236 (75.4)	73 (23.3)	4 (1.3)
Social workers	59 (2.0)	36 (66.7)	11 (20.4)	7 (12.9)	55 (100.0)	0 (–)	0 (–)
Chemists, biologists and related workers	85 (2.9)	27 (33.7)	11 (13.8)	42 (52.5)	12 (14.4)	15 (18.1)	56 (67.5)
Jurists, journalists and related workers	143 (4.8)	123 (89.1)	13 (9.4)	2 (1.5)	140 (100.0)	0 (–)	0 (–)
Other professional and technical workers	56 (1.9)	23 (46.0)	19 (38.0)	8 (16.0)	42 (85.7)	0 (–)	7 (14.3)
Managerial workers	48 (1.6)	37 (82.2)	8 (17.8)	0 (–)	46 (100.0)	0 (–)	0 (–)
Clerical and related workers	689 (23.2)	476 (72.7)	121 (18.5)	58 (8.8)	657 (99.1)	6 (0.9)	0 (–)
Stenographers, typists	296 (10.0)	208 (73.7)	47 (16.7)	27 (9.6)	283 (100.0)	0 (–)	0 (–)
Bookkeepers, cashiers	212 (7.1)	139 (70.2)	42 (21.2)	17 (8.6)	200 (100.0)	0 (–)	0 (–)
Other clerical and related workers	181 (6.1)	129 (73.7)	32 (18.3)	14 (8.0)	174 (96.7)	6 (3.3)	0 (–)
Sales workers	387 (13.1)	201 (54.3)	74 (20.0)	95 (25.7)	369 (99.7)	1 (0.3)	0 (–)
Technical saleswomen, commercial travellers	83 (2.8)	62 (77.5)	11 (13.8)	7 (8.7)	80 (100.0)	0 (–)	0 (–)
Saleswomen, shop assistants	195 (6.6)	74 (40.0)	50 (27.0)	61 (33.0)	182 (99.4)	1 (0.6)	0 (–)
Other sales workers	109 (3.7)	65 (61.9)	13 (12.4)	27 (25.7)	107 (100.0)	0 (–)	0 (–)
Service workers	461 (15.6)	49 (11.5)	54 (2.6)	325 (75.9)	253 (57.5)	182 (41.4)	5 (1.1)
Cleaners and helpers	207 (7.0)	20 (10.9)	17 (9.3)	146 (79.8)	176 (91.7)	16 (8.3)	0 (–)
Nurses' aides	133 (4.5)	11 (8.6)	25 (19.5)	92 (71.9)	19 (14.4)	113 (85.6)	0 (–)
Hairdressers, beauticians	55 (1.9)	0 (–)	4 (7.4)	50 (92.6)	0 (–)	53 (100.0)	0 (–)
Other service workers	66 (2.2)	18 (28.6)	8 (12.7)	37 (58.7)	58 (92.1)	0 (–)	5 (7.9)
Agricultural workers	50 (1.7)	12 (27.3)	12 (27.3)	20 (45.4)	40 (93.0)	3 (7.0)	0 (–)
Production workers	177 (5.8)	51 (35.2)	43 (29.6)	51 (35.2)	116 (77.9)	16 (10.7)	17 (11.4)
Textile workers	13 (0.4)	3 (33.3)	5 (55.6)	1 (11.1)	11 (100.0)	0 (–)	0 (–)
Food and beverage processors	33 (1.1)	10 (33.3)	9 (30.0)	11 (36.7)	30 (100.0)	0 (–)	0 (–)
Electronic or metal processors	37 (1.2)	9 (30.0)	8 (26.7)	13 (43.3)	21 (72.4)	7 (24.1)	1 (3.5)
Material handlers and related equipment operators	37 (1.2)	12 (42.8)	8 (28.6)	8 (28.6)	31 (100.0)	0 (–)	0 (–)
Other production workers	57 (1.9)	17 (35.4)	13 (27.1)	18 (37.5)	23 (47.9)	9 (18.8)	16 (33.3)
Other or unknown occupations	38 (–)	17 (51.5)	7 (21.2)	9 (927.3)	4 (100.0)	0 (–)	0 (–)

JEM, job-exposure matrix.

for this JEM are very precise especially for service workers and production workers. These classifications may be less precise for recent technical occupations (such as information technology worker), which are not exposed a priori. Exposure situations may have changed over the past 20 years, but we think that the JEM used in our study has selected the most exposed combinations (of occupational activities and industrial sectors). Consequences of classifying truly exposed as non-exposed by this method would be on average an underestimation of the relation between solvent exposure and the occurrence of malformations. For occupations considered to be exposed, agreement between the two methods was good, except for cleaners and helpers. The kappa measure of concordance between these two methods was 0.32 (95% CI 0.28 to 0.36) with a percentage of concordance of 74%. The associations found with the two methods are very concordant but probably represent attenuated estimates of the true associations.

These two methods did not allow us to identify more specific chemical classes of solvents. "Modern" JEMs specific for chlorinated, petroleum-based and oxygenated solvents are currently under construction in France and will be applied to our data as soon as they are available. However, solvents often occur in mixtures, and identifying a single compound or class of compounds remains a challenge.

Domestic exposure to solvents has not been considered in this analysis, even though it may concern a large proportion of women from time to time and may occur during a vulnerable period. This type of exposure is hard to objectify, and we considered that it was on average less frequent and less intensive than occupational exposures.

There are very few known risk factors for congenital malformations: ethnicity, maternal age, specific diseases or medication use during pregnancy, and tobacco and alcohol use. We found associations with none of them except maternal exposure to solvents. Our population is very homogeneous in terms of both geographical origin (98.8% of European origin) and socioeconomic status, and the prevalence of risk behaviours (heavy smoking or alcohol use) is very low.

Despite the rarity of these pregnancy outcomes we found a statistically significant association between maternal exposure to solvents and the risk of major malformations, and a more specific association with the subgroups of oral clefts, urinary malformations and male genital malformations. Few prospective studies have previously been conducted in general populations. A Canadian cohort study comparing 125 women occupationally exposed to solvents with 125 women exposed at work to other non-teratogenic products found significant associations (relative risk = 13, 95% CI 1.8 to 99.5).[10] This study

Table 4 Relation between solvent exposure and the risk of malformations

	Self-reported exposure				JEM-assessed exposure			
	Never	Occasional	Regular	p Value	No exposure	Medium exposure	High exposure	p Value for trend
No malformations (n = 2897)	1358	546	810		2154	493	83	
Major malformations (chromosomal and genetic malformations excluded) (n = 69)	22	14	30		46	16	6	
OR (95% CI)	1	1.58 (0.8 to 3.1)	2.29 (1.4 to 4.0)		1	1.52 (0.9 to 2.7)	3.38 (1.4 to 8.1)	
OR* (95% CI)	1	1.66 (0.8 to 3.3)	2.48 (1.4 to 4.4)	0.002	1	1.54 (0.9 to 2.7)	3.48 (1.4 to 8.4)	0.005
Chromosomal and genetic malformations (n = 15)	6	5	4		13	2		
OR (95% CI)	1	2.07 (0.6 to 2.80	1.12 (0.6 to 3.9)		1		0.58 (0.1 to 2.6)	
OR* (95% CI)	1	2.21 (0.7 to 7.4)	1.31 (0.3 to 4.9)	0.67	1		0.54 (0.1 to 2.4)	
Minor malformations (n = 34)	13	6	13		27	5		
OR (95% CI)	1	1.15 (0.4 to 3.0)	1.68 (0.8 to 3.6)		1		0.69 (0.3 to 1.8)	
OR* (95% CI)	1	1.05 (0.4 to 2.8)	1.45 (0.6 to 3.3)	0.38	1		0.71 (0.3 to 1.9)	

*Adjusted for maternal age, tobacco and alcohol consumption and education level.
JEM, job-exposure matrix; OR, odds ratio.

has been criticised for its small size and highly selected recruitment.[31]

Two occupational cohort studies of women working in laboratories found a relation between maternal exposure to solvents and major malformations.[12 13] Wennborg *et al* found a significant relation (OR = 2.5, 95% CI 1.0 to 6.0 for solvents in general and OR = 2.1, 95% CI 0.9 to 4.9 for benzene).[12] This study has several particular limitations in its exposure assessment, including its retrospective nature and the high non-response rate (33%). Zhu *et al*,[13] using a JEM assessment for laboratory technicians (n = 991), found a non-significant association between maternal solvent exposure and major malformations (hazard ratio = 2.0, 95% CI 0.7 to 5.7). An occupational cohort study compared hairdressers with a control group in Sweden and reported a significant relation between hairdressing and major malformations (OR = 1.3, 95% CI 1.1 to 1.6).[32] But the specific association with solvent exposure has not been explored.

This is the first time, to our knowledge, that a prospective cohort in the general population has found an association

Table 5 Relation between solvent exposure and subgroups of major congenital malformations (chromosomal and genetic malformations excluded)

	Self-reported exposure		JEM-assessed exposure	
	Never or occasional	Regular	No exposure	Exposure
No malformations (n = 2897)	1904	810	2154	576
Nervous system (n = 4)	1	3	3	1
OR (95% CI)	1	7.05 (0.7 to 67.9)	1	1.25 (0.1 to 12.0)
OR* (95% CI)	1	6.58 (0.7 to 63.9)	1	1.30 (0.1 to 12.5)
Cardiac malformations (n = 6)	5	1	5	1
OR (95% CI)	1	0.47 (0.1 to 4.0)	1	0.75 (0.1 to 6.4)
OR† (95% CI)	1	0.47 (0.1 to 4.0)	1	0.75 (0.1 to 6.5)
Oro-facial clefts (n = 8)	3	5	2	6
OR (95% CI)	1	3.92 (0.9 to 16.4)	1	11.22 (2.3 to 55.7)
OR‡ (95% CI)	1	3.60 (0.8 to 16.0)	1	12.85 (2.6 to 64.7)
Urinary malformations (n = 13)	4	7	6	6
OR (95% CI)	1	4.11 (1.2 to 14.1)	1	3.74 (1.2 to 11.6)
OR§ (95% CI)	1	2.18 (0.6 to 8.0)	1	3.40 (1.1 to 10.8)
Male genital malformations¶ (n = 12)	5	7	8	4
OR (95% CI)	1	3.43 (1.1 to 10.9)	1	1.98 (0.6 to 6.6)
OR** (95% CI)	1	3.57 (1.1 to 11.4)	1	2.06 (0.6 to 6.9)
Limb malformations (n = 20)	12	7	15	5
OR (95% CI)	1	1.37 (0.5 to 3.5)	1	1.24 (0.5 to 3.4)
OR‡ (95% CI)	1	1.46 (0.6 to 3.9)	1	1.29 (0.5 to 3.6)
Other major malformations (n = 8)	7	1	8	0
OR (95% CI)	1	0.34 (0.0 to 2.7)		
OR* (95% CI)	1	0.32 (0.0 to 2.6)	–	–

*Adjusted for tobacco and alcohol consumption. †Adjusted for alcohol consumption. ‡Adjusted for maternal age, tobacco and alcohol consumption and education level. §Adjusted for maternal age, tobacco consumption and education level. ¶Analyses restricted to boys only. **Adjusted for tobacco and alcohol consumption and preterm birth.
JEM, job-exposure matrix; OR, odds ratio.

Main messages

- Occupations in the healthcare sector, as laboratory workers, beauticians, hairdressers or as cleaners, may result in significant exposure to solvents.
- This exposure during pregnancy has been associated with an increased risk of major congenital malformations in the offspring, especially oral clefts, urinary and male genital malformations.

Policy implications

- In a number of frequent female occupations, identification of potentially teratogenic compounds is required..
- In these occupations, chemical exposure during pregnancy should be avoided as early as possible.

between oral clefts and maternal solvent exposure. Testing this specific hypothesis was one of the initial objectives of this study. Our results are indeed consistent with several previous case-control studies.[14–16 33–36] All but two of those retrospective studies,[33 34] used blinded assessment by industrial hygienists to define exposure. This method allows solvent exposure to be defined more precisely.[37] Most of these studies suggested significant risk associated with oxygenated solvents,[14–16 35 36] notably glycol ethers.[14–16] Other studies have shown significant relations between maternal exposure to petroleum and chlorinated solvents and oral clefts.[14 15] Because of the multiple exposures, none of these studies could report conclusions for specific solvent exposures.

One case-control study about male genital malformations showed a non-significant relation between hypospadias or epispadias and mothers' work in leather industries (OR = 4.05, 95% CI 0.77 to 21.44).[34] The association between maternal exposure to solvents and hypospadias was not explored. A case report suggested an association between maternal exposure to ethylene glycol monomethyl ether acetate and hypospadias.[38]

Our study also suggests a relation between maternal exposure to solvents and urinary malformations. A case-control study and a case report have already suggested similar results.[39 40]

Previous case-control studies have reported associations between maternal solvent exposure and central nervous system malformations,[14 18] especially neural tube defects.[14] Another case-control study with assessment methods,[19] similar to the studies of Cordier *et al* did not find a relation with neural tube defects. In our study the slight association observed with central nervous system defects may not be related to neural tube defects: in this subgroup, one malformation is a *spina bifida* and the other three are hydrocephalus.

CONCLUSION

Our prospective population-based study provides additional evidence of an association between maternal exposure to solvents and major malformations. Exposure to solvents at the beginning of pregnancy was assessed by two independent methods and before pregnancy outcome assessment.

A large proportion of working women performed the occupational activities involved, and the exposures we considered are very likely still present in the workplace. Additional investigations are underway in order to identify the specific chemicals involved. They include measurements of urinary biomarkers of exposure to glycol ethers and chlorinated solvents (in a nested case-control study) and detailed description of products used at work for the main occupations involved. These results will be the object of subsequent publications.

Acknowledgements: We are grateful to the gynaecologists, obstetricians, ultrasonographers, midwives, paediatricians, and biochemists who participated, and to the regional medical associations (ADEPAFIN, CGMO) for their collaboration. We would like to thank in particular Professor Poulain, Professor Grall, Professor Collet, Anne Kerguelen, Dr Maheo-Kerignard, Dr Berthelot, Dr Corbel, Dr Halbout de Queiroz, Dr Van Valenberg, Dr Desagnat, Dr Millon, Dr Le Guern and Dr Le Fiblec. We wish to thank the staff of all maternity hospitals and clinics which participated in the study (Hotel Dieu and Sud Hospitals, La Sagesse Clinic, St Grégoire Clinic in Rennes, Vitré Hospital, Fougères Hospital, Redon Hospital, St Brieuc Hospital and Littoral Clinic in St Brieuc, Guingamp Hospital, Lannion Hospital, Paimpol Hospital, Brest Hospital, Keraudren Clinic and Pasteur Clinic in Brest, Pontivy Hospital, Quimper Hospital and St Michel Clinic in Quimper, Landerneau Hospital and Morlaix Hospital).
We are grateful to the participants. We thank Dr De Vigan from the Paris registry of congenital malformations for her help in classifying the congenital malformations, Veronique Villalon and Dr AH Saliou for their help, and Jo Ann Cahn for her careful revision of the manuscript.

Funding: This research was supported by grants from the National Institute for Public Health Surveillance (InVS), the Ministry of Labor, and the Regional health services (DRASS de Bretagne).

Competing interests: None.

Ethics approval: The appropriate ethics committees approved the study procedures.

Patient consent: Obtained.

REFERENCES

1. **Triollet J.** Panorama de l'utilisation des solvants en France fin 2004 (French). *Hygiène et sécurité au travail. Cahiers de notes documentaries* 2005;**199**:65–97. http://www.inrs.fr/inrs-pub/inrs01.nsf/intranetobject-accesparreference/nd%202230/$file/nd2230.pdf (accessed 24 Mar 2008).
2. **Schardein J.** Industrial solvents. In: Schardein J, ed. *Chemically induced birth defects 2nd edition, revisited and expanded*. New York, NY: Marcel Dekker, 1993:751–75.
3. **Expertise Collective INSERM.** In: Inserm eds. *Ethers de glycol: Quels risques pour la santé*? (French). Paris, FRANCE: Les éditions INSERM, 1999:131–62.
4. **El-Zein RA,** Abdel-Rahman SZ, Morris DL, *et al*. Exposure to ethylene glycol monomethyl ether: clinical and cytogenetic findings. *Arch Environ Health* 2002;**57**:371–6.
5. **Swan SH,** Beaumont JJ, Hammond SK, *et al*. Historical cohort study of spontaneous abortion among fabrication workers in the Semiconductor Health Study: agent-level analysis. *Am J Ind Med* 1995;**28**:751–69.
6. **Correa A,** Gray RH, Cohen R, *et al*. Ethylene glycol ethers and risks of spontaneous abortion and subfertility. *Am J Epidemiol* 1996;**143**:707–17.
7. **Windham GC,** Shusterman D, Swan SH, *et al*. Exposure to organic solvents and adverse pregnancy outcome. *Am J Ind Med* 1991;**20**:241–59.
8. **Lindbohm ML,** Taskinen H, Sallmen M, *et al*. Spontaneous abortions among women exposed to organic solvents. *Am J Ind Med* 1990;**17**:449–63.
9. **Elliott RC,** Jones JR, McElvenny DM, *et al*. Spontaneous abortion in the British semiconductor industry: An HSE investigation. Health and Safety Executive. *Am J Ind Med* 1999;**36**:557–72.
10. **Khattak S,** K-Moghtader G, McMartin K, *et al*. Pregnancy outcome following gestational exposure to organic solvents: a prospective controlled study. *JAMA* 1999;**281**:1106–9.
11. **McMartin KI,** Chu M, Kopecky E, *et al*. Pregnancy outcome following maternal organic solvent exposure: a meta-analysis of epidemiologic studies. *Am J Ind Med* 1998;**34**:288–92.
12. **Wennborg H,** Magnusson LL, Bonde JP, *et al*. Congenital malformations related to maternal exposure to specific agents in biomedical research laboratories. *J Occup Environ Med* 2005;**47**:11–19.
13. **Zhu JL,** Knudsen LE, Andersen AM, *et al*. Laboratory work and pregnancy outcomes: a study within the National Birth Cohort in Denmark. *Occup Environ Med* 2006;**63**:53–8.
14. **Cordier S,** Bergeret A, Goujard J, *et al*. Congenital malformation and maternal occupational exposure to glycol ethers. Occupational Exposure and Congenital Malformations Working Group. *Epidemiology* 1997;**8**:355–63.
15. **Lorente C,** Cordier S, Bergeret A, *et al*. Maternal occupational risk factors for oral clefts. Occupational Exposure and Congenital Malformation Working Group. *Scand J Work Environ Health* 2000;**26**:137–45.
16. **Chevrier C,** Dananche B, Bahuau M, *et al*. Occupational exposure to organic solvent mixtures during pregnancy and the risk of nonsyndromic oral clefts. *Occup Environ Med* 2006;**63**:617–23.
17. **Tikkanen J,** Heinonen OP. Cardiovascular malformations and organic solvent exposure during pregnancy in Finland. *Am J Ind Med* 1988;**14**:1–8.

18. **Holmberg PC.** Central-nervous-system defects in children born to mothers exposed to organic solvents during pregnancy. *Lancet* 1979;**2**:177–9.
19. **Shaw GM,** Velie EM, Katz EA, *et al*. Maternal occupational and hobby chemical exposures as risk factors for neural tube defects. *Epidemiology* 1999;**10**:124–9.
20. **Manson JM,** Carr MC. Molecular epidemiology of hypospadias: review of genetic and environmental risk factors. *Birth Defects Res A Clin Mol Teratol* 2003;**67**:825–36.
21. **Eurocat**. *Eurocat Guide 1.3 and reference documents. Instructions for the registration and the Surveillance of Congenital Anomalies*. Northern Ireland, UK: Eurocat, 2005. http://www.eurocat.ulster.ac.uk/pdf/EUROCAT-Guide-1.3.pdf (accessed 24 Mar 2008).
22. **Ferrario F,** Continenza D, Pisani P, *et al*. Description of a job-exposure matrix for sixteen agents which are or may be related to respiratory cancer. In: Hogstedt C, Reuterwall C, eds. *Progress in occupational epidemiology*. Amsterdam, Netherlands: Elsevier Science Publishers, 1988:379–82.
23. **Cordier S,** Lefeuvre B, Filippini G, *et al*. Parental occupation, occupational exposure to solvents and polycyclic aromatic hydrocarbons and risk of childhood brain tumors (Italy, France, Spain). *Cancer Causes Control* 1997;**8**:688–97.
24. **Cordier S,** Monfort C, Filippini G, *et al*. Parental exposure to polycyclic aromatic hydrocarbons and the risk of childhood brain tumors: The SEARCH International Childhood Brain Tumor Study. *Am J Epidemiol* 2004;**159**:1109–16.
25. **De Vigan C,** Khoshnood B, Lhomme A, *et al*. Prévalence et diagnostic prénatal des malformations en population parisienne: vingt ans de surveillance par le Registre des malformations congénitales de Paris (French). *J Gynecol Obstet Biol Reprod* 2005;**34**:8–16.
26. **Eurocat**. *Annual report 2003*. Northern Ireland, UK: Eurocat, 2005. http://www.eurocat.ulster.ac.uk/pdf/EUROCAT-Annual-Report-2003-for-WHO.pdf (accessed 24 Mar 2008).
27. **Acharya G,** Sitras V, Maltau JM, *et al*. Major congenital heart disease in Northern Norway: shortcomings of pre- and postnatal diagnosis. *Acta Obstet Gynecol Scand* 2004;**83**:1124–9.
28. **Wiesel A,** Queisser-Luft A, Clementi M, *et al*. Prenatal detection of congenital renal malformations by fetal ultrasonographic examination: an analysis of 709,030 births in 12 European countries. *Eur J Med Genet* 2005;**48**:131–44.
29. **Dolk H,** Vrijheid M, Scott JE, *et al*. Toward the effective surveillance of hypospadias. *Environ Health Perspect* 2004;**112**:398–402.
30. **Toppari J,** Kaleva M, Virtanen HE. Trends in the incidence of cryptorchidism and hypospadias, and methodological limitations of registry-based data. *Hum Reprod Update* 2001;**7**:282–6.
31. **Brent RL,** Chambers CD, Chernoff GF, *et al*. Pregnancy outcome following gestational exposure to organic solvents: a response. *Teratology* 1999;**60**:328–31.
32. **Rylander L,** Axmon A, Torén K, *et al*. Reproductive outcome among female hairdressers. *Occup Environ Med* 2002;**59**:517–22.
33. **Bianchi F,** Cianciulli D, Pierini A, *et al*. Congenital malformations and maternal occupation: a registry based case-control study. *Occup Environ Med* 1997;**54**:223–8.
34. **Garcia AM,** Fletcher T. Maternal occupation in the leather industry and selected congenital malformations. *Occup Environ Med* 1998;**55**:284–6.
35. **Laumon B,** Martin JL, Collet P, *et al*. Exposure to organic solvents during pregnancy and oral clefts: a case-control study. *Reprod Toxicol* 1996;**10**:15–19.
36. **Shaw GM,** Nelson V, Iovannisci DM, *et al*. Maternal occupational chemical exposures and biotransformation genotypes as risk factors for selected congenital anomalies. *Am J Epidemiol* 2003;**157**:475–84.
37. **Teschke K,** Olshan AF, Daniels JL, *et al*. Occupational exposure assessment in case-control studies: opportunities for improvement. *Occup Environ Med* 2002;**59**:575–93.
38. **Bolt HM,** Golka K. Maternal exposure to ethylene glycol monomethyl ether acetate and hypospadia in offspring: a case report. *Br J Ind Med* 1990;**47**:352–3.
39. **McDonald JC,** Lavoie J, Côté R, *et al*. Chemical exposures at work in early pregnancy and congenital defect: a case-referent study. *Br J Ind Med* 1987;**44**:527–33.
40. **Karaman MI,** Gurdal M, Ozturk M, *et al*. Maternal exposure to diethylene glycol monomethyl ether: a possible role in the etiology of retrocaval ureter. *J Pediatr Surg* 2002;**37**:E23.