ORIGINAL ARTICLE

Occupational exposure to organic solvent mixtures during pregnancy and the risk of non-syndromic oral clefts

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Objectives: To examine the association between maternal occupational exposure to mixtures of organic solvents during pregnancy and the risk of non-syndromic oral clefts.

Methods: A case-control study (164 cleft lip with/without cleft palate (CL/P), 76 cleft palate (CP), 236 controls) was conducted in France to investigate the role of maternal occupational exposure to organic solvents at the beginning of pregnancy in the risk of non-syndromic oral clefts. An expert chemist, guided by a detailed description of the women's occupational tasks, assessed exposure for each. Analysis of the findings used logistic regression.

Results: In the control group, 39% of the women who reported working during pregnancy were exposed to at least one type of organic solvent. The risk of oral clefts was associated with oxygenated (for CL/P: OR = 1.8, 95% CI 1.1 to 2.9; and for CP, OR = 1.4, 95% CI 0.7 to 2.7), chlorinated (OR = 9.4, 95% CI 2.5 to 35.3; OR = 3.8, 95% CI 0.7 to 20.7), and petroleum (OR = 3.6, 95% CI 1.5 to 8.8; OR = 1.2, 95% CI 0.3 to 4.9) solvents. The risk of oral clefts increased linearly with level of exposure within the three subgroups of oxygenated solvents we considered (aliphatic alcohols, glycol ethers, and other oxygenated solvents, including esters, ketones, and aliphatic aldehydes).

Conclusions: Results suggest that maternal occupational exposure to organic solvents during pregnancy may play a role in the aetiology of oral clefts. The limited number of subjects and the problem of multiple exposures require that these results be interpreted cautiously.

Organic solvents are chemicals ubiquitous in women's occupational and domestic environments. The teratogenicity of some of these chemical agents has been shown in animal experiments, but their impact on human reproduction is unclear. Exposure to some glycol ethers is associated with male infertility, but very few studies have examined their effects on female fertility.¹ Several epidemiological studies associate maternal occupational exposure to solvents with an excess risk of spontaneous abortion and with an increased risk of several major congenital anomalies, the most studied of which are oral clefts, neural tube defects, and congenital cardiovascular anomalies.^{2–9} Other papers focus on paternal occupational exposure to solvents and report inconclusive results.^{10–13}

The difficulty in drawing conclusions from these epidemiological studies may stem from the heterogeneity of their methods, particularly their exposure assessments, and from the standard biases. Other factors preventing clarification of an association between parental occupational exposure to solvents and the risk of adverse reproductive outcome include the multiplicity of occupational exposures to chemical substances, the failure of epidemiological studies to report exposure–response relations, and possible publication bias.

Non-syndromic oral clefts are among the most common congenital anomalies. Their aetiology is known to be complex, involving both environmental and genetic risk factors. Several studies report an increased risk of oral clefts associated with maternal occupational exposure to organic solvents,^{4,5,7,14,15} including glycol ethers. Two others show an increased risk associated with mothers who work in the leather industry,^{16,17} and the authors noted the likely role of occupational exposure to some types of solvents, such as toluene and aliphatic hydrocarbons.

This study, conducted in France between 1998 and 2001, assessed occupational solvent exposure individually to examine the association between maternal occupational exposure to organic solvents and the risk of non-syndromic oral clefts. Simultaneous exposures to organic solvents in the workplace were identified, and exposure–response relations assessed.

METHODS

Data collection

Data come from a case-control study conducted in France between 1998 and 2001 at seven hospitals (five in Lyon and Grenoble in the Rhône-Alpes region, one in Paris, and one in Clermont-Ferrand in the Auvergne region). A case patient was defined as a child diagnosed with cleft lip and/or cleft palate. They were recruited during their initial hospitalisation for surgery in the maxillofacial surgery department. Syndromic cases of oral clefts ($n = 23$), including children with Pierre Robin sequence, were excluded. Parental refusal or communication difficulties (non-French speaking families) prevented inclusion of 37 cases. Finally, the study included a total of 240 non-syndromic case children (164 cleft lip with/without cleft palate (CL/P), and 76 cleft palate only (CP)).

Control children were recruited in the same hospitals as the cases, among children with no birth defect, cancer, or genetic disease but hospitalised for treatment of some other disorder, most often infections (respiratory or urinary system) or need for minor surgery (naevus, fractures). They were frequency matched with case children for sex, age

Abbreviations: CL/P, cleft lip with/without cleft palate; CP, cleft palate only

(± 1 month), mother's geographic origin (European/other), and residence (in/outside the hospital region). Because of the small number of children meeting the study criteria in hospital departments in Paris, control recruitment ($n = 80$) was extended to two neighbouring maternity hospitals. Twenty five control mothers refused to participate, and the study finally included 236 controls.

Mothers of cases and controls were interviewed in the hospital with a standardised questionnaire that collected data about sociodemographic information (parental age, education, country of origin, municipality of residence), mother's medical and obstetrical history, family history of oral clefts and other congenital anomalies, exposure to x rays and surgery during pregnancy, as well as infectious diseases, drug and vitamin intake (during the month preceding conception and each trimester of pregnancy), alcohol and tobacco consumption (for the month preceding conception and each trimester of pregnancy), passive smoking, parental occupations (maximum two), occupational tasks, and some domestic activities involving chemical exposures (for the month preceding conception and each trimester of pregnancy). Folate intake in the mother's usual diet was assessed with a validated questionnaire.

Occupational exposure assessment

Because facial development takes place early in embryogenesis, we assessed occupational exposure according to mother's work during the first trimester (for the 13 mothers with two jobs during the first trimester, the exposure assessment considered the highest levels). Interviewers asked mothers to describe their occupational tasks in detail, and a supplemental model-questionnaire was used for several job categories (nurses, house cleaners, hairdressers, beauticians, teachers, cooks, waiters, and leather workers). An expert chemist (BD), blinded to case-control status, assessed each mother's exposure to 22 classes of agents, including organic solvents, lead compounds, and non-ionising and ionising radiations. Organic solvents were separated into three chemical classes: oxygenated solvents (for which we separately considered aliphatic alcohols, aliphatic aldehydes, aliphatic esters, aliphatic ketones, and glycol ethers); chlorinated solvents (alkanes and alkenes); and petroleum products (aromatic hydrocarbons, mineral spirits, and fuel). The assessment rated three parameters of exposure: intensity, frequency, and reliability of exposure (from 0 to 2). Then, as reported in Cordier *et al*, we combined this information to construct a global exposure index:³ no exposure (intensity, frequency, and reliability are all rated zero), very low exposure (intensity $\times$ frequency = 1 and reliability = 1), low exposure (intensity $\times$ frequency = 1 and reliability ≥ 2), and medium to high exposure (intensity $\times$ frequency ≥ 2 and reliability ≥ 2); these levels of exposure were rated from 0 to 3.

This study considered all three chemical classes of organic solvents and some of their subgroups, when enough women were exposed to these subgroups. When too few subjects had very low or medium-high exposure, we rated them with the intermediate level of "low exposure".

Statistical analysis

Estimates of oral cleft risk were computed from an unconditional logistic regression adjusted for major matching criteria: centre (Rhône-Alpes region, Paris, Auvergne region), child's sex, and mother's geographic origin (European, other). We computed odds ratios (OR), reported here with their 95% confidence intervals (95% CI).

Analysis of occupational exposure to organic solvents was restricted to women who reported an occupational activity at the beginning of their pregnancy, and separate analyses were

conducted for CL/P and CP groups. Potential risk factors of oral clefts, such as maternal age, socioeconomic status, maternal smoking and alcohol consumption during pregnancy, and dietary folate intake were retained in the adjustment combination if they provided a "change-in-the-estimate" of 10%. The working mothers with no report of solvent exposure (114 control mothers, 55 CL/P mothers, and 28 CP mothers) served as the reference group for all exposures studied.

Each exposure was examined in the model in turn, as a dichotomous variable. The significance of the exposure-response relation was assessed by a linear trend test for categorical variables.¹⁸ It consisted of two likelihood ratio tests: (1) between models, including the exposure level as quantitative or qualitative variable to verify the validity of a constant change in estimates between each supplementary unit of exposure level; and (2) between the model including the categorical exposure level as a quantitative variable and the model without the exposure level, to assess the statistical significance of this one-point change. We reported the p value of the latter test as the p trend after verifying the linearity assumption in the first step.

Because occupational exposure most often involves several solvents simultaneously, we attempted to identify the most frequent combinations of multiple solvent exposures.

The association of maternal non-occupational activities with oral cleft risk was evaluated with logistic regression when enough subjects reported the activity. We were able to examine the use of hair dyes or hair colour removers and the activity of painting or varnishing by mothers during the first trimester.

RESULTS

As planned in the study design, case and control families were similar with regard to centre, child's sex, and mother's geographic origin (table 1). Boys predominated among the CL/P (70%) cases, and the sex ratio was balanced in the CP group. Most mothers (84%) were of European origin. Overall, control children were recruited slightly younger on average than case children, but the hospital controls were enrolled at about the same age (around 7 months). The mothers' average age was approximately 29.5 years in both groups. More mothers of controls than of cases were categorised in the highest occupational categories and highest educational level. Risk of oral clefts increased as maternal folate intake decreased.

Description of mothers' occupations

Table 2 lists the occupations of mothers exposed to organic solvents in the workplace during the first trimester of pregnancy. Simultaneous exposure to all three chemical classes of organic solvents occurred for mothers in the following occupational categories: hairdresser-beautician, industrial worker, packaging worker, engineer-laboratory technician, office worker-secretary, cashier, and sales worker. The highest levels of exposure to chlorinated and to petroleum solvents were observed principally among industrial workers and packers. A medium or high level of chlorinated solvent exposure was also observed among hairdressers-beauticians. Exposure to oxygenated solvents occurred mainly among women working in cleaning and nursing. Most of them were also exposed to aliphatic alcohols at a medium or high level, as were hairdressers-beauticians. Exposure to glycol ethers was reported mostly among cleaners and sales workers, and the highest levels of exposure were observed essentially among hairdressers-beauticians and cleaning workers.

Table 1 Description of non-syndromic oral cleft case and control populations

	Case families				Control families (n = 236)		Among the overall cases	
	CL/P (n = 164)		CP (n = 76)		n	%	OR‡	95% CI
	n	%	n	%				
Centre								
Rhône-Alpes region	90	54.9	50	65.8	126	53.4		
Paris	56	34.1	16	21.1	80	33.9		
Auvergne region	18	11.0	10	13.2	30	12.7		
Child's sex								
Female	50	30.5	38	50.0	98	41.5		
Male	114	69.5	38	50.0	138	58.5		
Child's age at the interview								
Missing	2	—	—	—	1	—		
≤ 2 months	3	1.9	0	0	94	40.0		
2–6 months	92	56.8	26	34.2	51	21.7		
> 6 months	67	41.4	50	65.8	90	38.3		
Mean	5.2		7.9		4.7			
Mother's geographic origin								
Sub-Saharan Africa	5	3.0	2	2.6	7	3.0		
North Africa	12	7.3	6	7.9	17	7.2		
Europe	136	82.9	64	84.2	200	84.7		
Other	11	6.7	4	5.3	12	5.1		
Maternal age at birth (years)								
≤ 30 years	93	56.7	47	61.8	139	58.9	ref	
30–35 years	52	31.7	21	27.6	71	30.1	1.0	0.7 to 1.5
> 35 years	19	11.6	8	10.5	26	11.0	1.1	0.6 to 1.9
Mean	29.6		29.1		29.7			
Maternal occupation categories during the first trimester								
Unemployed or missing	48	—	19	—	49	—	1.9	1.1 to 3.3
Scientific, professional, managerial	33	28.4	17	29.8	70	37.4	ref	
Administrative	28	24.1	16	28.1	66	35.3	0.9	0.5 to 1.6
Sales	10	8.6	3	5.3	12	6.4	1.5	0.6 to 3.6
Services	25	21.6	16	28.1	32	17.1	1.8	1.0 to 3.3
Agricultural, production work	20	17.2	5	8.8	7	3.7	5.0	2.0 to 12.3
Maternal education level								
Missing	—	—	1	—	2	—		
Primary–secondary level	45	27.4	19	25.3	45	19.2	2.2	1.4 to 3.7
Technical schooling	59	36.0	29	38.7	57	24.4	2.3	1.5 to 3.6
University level	60	36.6	27	36.0	132	56.4	ref	
Maternal alcohol consumption during the first trimester of pregnancy*								
No	132	80.5	67	88.2	206	87.3	ref	
Yes	32	19.5	9	11.8	30	12.7	1.4	0.9 to 2.4
Maternal smoking during the first trimester of pregnancy†								
No	119	72.6	54	71.1	167	70.8	ref	
Yes	45	27.4	22	28.9	69	29.2	0.9	0.6 to 1.4
Maternal dietary folate intake (µg/day)								
Missing	2	—	1	—	1	—		
>301 µg/day	45	27.8	14	18.7	78	33.2	ref	
217–301 µg/day	42	25.9	25	33.3	79	33.6	1.1	0.7 to 1.8
≤ 217 µg/day	75	46.3	36	48.0	78	33.2	1.9	1.2 to 3.0
Mean	252		234		270			
Family history of oral clefts								
In siblings, parents or grandparents	14	8.5	9	11.8	0	0		

*Mothers are considered to have consumed alcohol during the first trimester of pregnancy if they reported at least one drink per week during this period.

†Mothers are considered to have smoked during the first trimester of pregnancy if they reported regular smoking during this period.

‡Logistic regression adjusted for centre (Rhône-Alpes, Paris, Auvergne), child's sex, and maternal ethnic origin (Europe, other).

CL/P, cleft lip with or without cleft palate; CP, cleft palate only.

n, number; OR, odds ratio; 95% CI, 95% confidence interval.

Solvent exposure

Table 3 shows that maternal occupational exposure to each of the three solvent classes (oxygenated, chlorinated, and petroleum) was associated with an increased risk of CL/P or CP. Risks were also increased for each of the three subclasses of oxygenated solvents (aliphatic alcohols, glycol ethers, and aliphatic aldehydes, ketones, and esters). These associations were statistically significant for the CL/P group. Significant increasing linear trends were observed for the CL/P risk and level of exposure to aliphatic alcohols (p trend = 0.02), glycol

ethers (p trend = 0.009), some types of aliphatic aldehydes, ketones, or esters (p trend = 0.02), and petroleum solvents (p trend = 0.005). We observed similar but not significant trends in the CP group when there were enough subjects.

Adjustment for maternal smoking status, alcohol consumption, and dietary folate intake during the first trimester did not substantially alter these associations. Maternal education appeared to modify the effect rather than confound the relation between maternal exposure to oxygenated and oral cleft risks: to act as an effect modifier than as

Table 2 Occupations of mothers exposed to organic solvents during the first trimester of pregnancy

Occupation	Exposures % (n total–n with medium or high level)					
	Oxygenated solvents					
	Aliphatic alcohols (n = 136)	Glycol ethers (n = 96)	Aldehydes esters, ketones (aliphatic) (n = 130)	At least one type* (n = 157)	Chlorinated solvents (n = 20)	Petroleum solvents (n = 30)
Physician, dentist, veterinarian, pharmacist	10.3 (14–5)	0	10.8 (14–0)	8.9	0	0
Nurse, nursing aids	19.1 (26–22)	4.2 (4–0)	20.0 (26–0)	16.6	0	0
Engineer, laboratory technician	4.4 (6–3)	5.2 (5–2)	6.9 (9–0)	7.0	10.0 (2–1)	16.7 (5–0)
Teacher	2.9 (4–1)	5.2 (5–1)	5.4 (7–0)	5.1	0	3.3 (1–0)
Book editor	0	0	0.8 (1–0)	0.6	0	0
Office worker, secretary	4.4 (6–4)	2.1 (2–0)	2.3 (3–0)	4.5	10.0 (2–0)	10.0 (3–1)
Cashier	4.4 (6–0)	6.3 (6–0)	0.8 (1–0)	3.8	5.0 (1–0)	6.7 (2–0)
Sales worker	10.3 (14–0)	15.6 (15–1)	6.9 (9–0)	9.6	5.0 (1–0)	13.3 (4–1)
Cleaning worker	21.3 (29–9)	29.2 (28–4)	22.3 (29–0)	18.5	0	0
Childcare worker	3.7 (5–0)	5.2 (5–0)	0	3.2	0	0
Hairdresser, beautician	5.9 (8–8)	8.3 (8–5)	6.2 (8–0)	5.1	20.0 (4–4)	13.3 (4–1)
Waiter, cook	5.9 (8–0)	8.3 (8–0)	6.2 (8–0)	5.1	0	0
Other service worker	1.5 (2–1)	2.1 (2–0)	0.8 (1–0)	1.3	0	3.3 (1–1)
Industrial worker	2.2 (3–2)	3.1 (3–0)	5.4 (7–0)	5.1	35.0 (7–3)	20.0 (6–4)
Packaging worker	3.7 (5–2)	5.2 (5–1)	3.1 (4–0)	3.8	15.0 (3–2)	13.3 (4–2)
Agricultural worker	0	0	2.3 (3–0)	1.9	0	0

*At least one type of oxygenated solvent.

n, number.

Note: 21.3% of women exposed to aliphatic alcohols were cleaning workers, which constituted a group of 29 women among which 9 women were exposed with a medium-high level.

Table 3 Risks of non-syndromic oral clefts associated with maternal occupational exposures to organic solvents and to non-occupational activities involving use of products containing solvents

	Controls n	CL/P n	OR†	95% CI	CP n	OR†	95% CI
Maternal occupational exposure to organic solvents, among women with an occupational activity during the first trimester (187 controls, 116 CL/P, 57 CP)							
Unexposed mothers*	114	55	ref		28	ref	
Oxygenated solvents	71	58	1.76	1.1 to 2.9	28	1.42	0.7 to 2.7
Aliphatic alcohols	61	49	1.76	1.0 to 3.1	26	1.56	0.8 to 3.0
Very low–low	39	27	1.53	0.8 to 2.8	13	1.20	0.5 to 2.6
Medium–high	22	22	2.14	1.1 to 4.3	13	2.20	1.0 to 5.1
p trend				p=0.02			p=0.10
Glycol ethers	41	37	1.88	1.1 to 3.5	18	1.50	0.7 to 3.2
Very low	16	10	1.30	0.5 to 3.1	2	0.40	0.1 to 1.9
Low	22	20	1.88	0.9 to 3.8	12	1.83	0.8 to 4.4
Medium–high	3	7	4.77	1.2 to 19.5	4	4.06	0.8 to 20.3
p trend				p<0.01			p=0.06
Aliphatic aldehydes, esters, and ketones	56	46	1.74	1.0 to 2.9	28	1.82	1.0 to 3.5
Very low	54	42	1.66	1.0 to 2.8	28		
Low–medium–high	2	4	4.41	0.7 to 26.8	0		
p trend				p=0.02			
Chlorinated solvents	3	14	9.45	2.5 to 35.3	3	3.78	0.7 to 20.7
Petroleum solvents	10	17	3.64	1.5 to 8.8	3	1.21	0.3 to 4.9
Very low–low	7	10	3.21	1.1 to 9.3	3		
Medium–high	3	7	4.60	1.1 to 19.2	0		
p trend				p<0.01			
Extra professional activities of the mother (during the first trimester of pregnancy), among all women (236 controls, 164 CL/P, 76 CP)							
Hair dyes and bleaching products							
No reported use	217	145	ref		63	ref	
Use	19	17	1.26	0.6 to 2.5	12	2.29	1.0 to 5.1
Painting or varnishing activities							
No reported activity	223	151	ref		71	ref	
Yes	13	13	1.57	0.7 to 3.5	4	1.00	0.3 to 3.2

*Unexposed mothers are women who reported an occupational activity during the first trimester for which the expert assessed no exposure to any the three chemical classes of organic solvents (oxygenated, chlorinated, and petroleum).

†Logistic regression adjusted for centre (Rhône-Alpes, Paris, Auvergne), child's sex, and mother's geographic origin (Europe, other).

CL/P, cleft lip with/without cleft palate; CP, cleft palate.

n, number; OR, odds ratio; 95% CI, 95% confidence interval.

p trend = p value of the likelihood ratio test between models with and without the categorical level of exposure included as continuous variable. For each reported p trend, the test of the linearity assumption based on the comparison between the model including the exposure level as categorical and continuous variable, has not been rejected.

a confounder. Among both the women with a university education and those with only primary or secondary schooling, we observed an increased risk of non-syndromic oral clefts associated with maternal occupational exposure to each of three solvent classes (for oxygenated solvents: among university level stratum, OR = 1.60, 95% CI 0.8 to 3.2; and among primary–secondary level stratum, OR = 1.85, 95% CI 0.6 to 5.5). Mothers with technical schooling did not have increased risk of having an affected child associated with exposure to oxygenated solvents (OR = 0.85, 95% CI 0.3 to 2.0); increased risks were maintained for exposures to chlorinated and petroleum solvents.

Finally, although analyses with conditional logistic models are restricted to the matched pairs for which both mothers of the case and the control have an occupational activity, unconditional and conditional (results not shown) models have provided comparable results.

Simultaneous exposure to several classes of solvents

When women exposed to chlorinated or petroleum solvents were excluded from the analyses ($n = 33$), the risks associated with exposure to oxygenated solvents alone remained elevated but no longer significant (for CL/P and CP, respectively: OR = 1.44, 95% CI 0.8 to 2.4 and OR = 1.47, 95% CI 0.8 to 2.8). In this group ($n = 130$), 91% were simultaneously exposed to some type of aliphatic alcohol and at least one other subgroup of oxygenated solvents. We considered separately the women exposed to glycol ethers (knowing that 76/78 were also exposed to aliphatic alcohols) and those exposed to other types of oxygenated solvents (42/52 were also exposed to aliphatic alcohols). The impact of these separately considered exposures on the risk of CL/P and CP was similar and relatively minor (exposure to glycol ethers: for CL/P, OR = 1.33, 95% CI 0.7 to 2.5, for CP, OR = 1.38, 95% CI 0.6 to 3.0; exposure to all other oxygenated solvents: for CL/P, OR = 1.49, 95% CI 0.7 to 3.0, for CP, OR = 1.49, 95% CI 0.6 to 3.5). The estimates of the exposure–response relations revealed linear trends that increased with levels of exposure to glycol ethers and to aliphatic alcohols, but they were not statistically significant (results not shown). When we pooled the CL/P and CP groups, the linear trend of the risk according to glycol ether exposure was of borderline significance (OR_{VeryLow} = 0.72, 95% CI 0.3 to 1.7; OR_{Low} = 1.45, 95% CI 0.7 to 2.9; OR_{MediumHigh} = 5.26, 95% CI 1.1 to 25.6; p trend = 0.05).

Mothers' non-occupational activities involving solvents

Maternal use of hair dyes or colour-strippers and painting or varnishing at home during the first trimester of pregnancy appeared to increase the risk of CL/P slightly (table 3). Use of these hair products significantly increased the risk of CP, doubling it. Additional adjustment for dietary folate intake changed the estimates of the associations with painting or varnishing by the mother: for CL/P, OR = 1.75, 95% CI 0.8 to 4.0; for CP, OR = 0.84, 95% CI 0.2 to 2.7.

Additional adjustment for these non-occupational activities did not modify the association between the mother's occupational exposure to organic solvents and the risk of oral clefts, as shown in table 3.

DISCUSSION

This study indicates that maternal occupational exposure to organic solvents appears to be associated with the risk of CL/P and CP.

We recruited the cases during their initial surgery in hospital maxillofacial surgery departments, where most children affected by non-syndromic oral cleft (95%) are treated.¹⁹ This recruitment process did exclude minimal cases

of oral clefts (those not in need of surgery). Our case group is composed of one third CP and two thirds CL/P, the expected proportion. The male predominance among the CL/P patients in our study was expected and the sex ratio observed in our CP group was not statistically different from the slight predominance expected for girls in European populations. Causes of hospitalisation for controls were multiple (infections, fractures, naevus) and had no a priori link with solvent exposure.

The lower socioeconomic status observed in this study for the case mothers is consistent with evidence in previous studies that a low socioeconomic status is associated with risk factors for oral clefts.²⁰ We cannot rule out the possibility that this difference between controls and cases could indicate a selection bias, despite our efforts to match case and control groups for some socioeconomic determinants (centre, residence location). Nonetheless, the risk of non-syndromic oral clefts associated with maternal occupational exposure to solvents remained increased among women with the highest educational level.

The association between maternal exposure to oxygenated solvents and oral cleft risk varied slightly between strata of maternal education, even though the overlapping confidence intervals indicate that the heterogeneity of the specific stratum effects was limited. We therefore could not include the education level in the adjustment combination of the corresponding models. We have no explanation other than chance for this situation.

In the present study, our rationale for excluding non-working women was to prevent potential confounding linked to working status. For example, we observed in our control group that 88% of working women were European compared with 73% of the non-working women, and 27% of the working women reported regular smoking compared with 37% of the non-working women. We are aware that these restricted analyses, limited to working women, focus on a healthier population (healthy worker selection bias). Additional analyses including non-working women (in the unexposed group) reported comparable conclusions: we observed increased risks for maternal exposures to oxygenated (all subclasses), chlorinated, and petroleum solvents, as well as similar increasing “exposure–response” relations; although at lower magnitudes of association.

The strategy of expert assessment of maternal occupational exposure is now considered standard in retrospective assessments.²¹ Of the control mothers employed during the first trimester of pregnancy in our study, approximately 22% were exposed to glycol ethers and 33% to some type of aliphatic alcohols. Previous studies reported that respectively 18% and 13% of a European population of working women were exposed to these substances from 1989 to 1992.^{5,7} A Californian study from 1989 to 1991 found that 15% of the control mothers were exposed to glycol ethers and 29% to some type of aliphatic alcohols, from either occupational or hobby activities.⁶ Differences between studies (including this one) for the proportion of exposed subjects may indicate different distributions of maternal occupations or differences in the sensitivity of exposure assessment. The previous European study⁷ and the Californian study⁶ evaluated a large number of chemical compounds: 314 and 74 chemical, respectively, compared with 22 in this study. We can thus suppose that this study had great sensitivity in assessment of glycol ether and aliphatic alcohol exposure. In any case, exposure was assessed blinded to case-control status in all three studies.

Increased risks of CL/P and CP were associated with maternal occupational exposure to chlorinated and to petroleum solvents. Although these results are limited by the small numbers concerned, they are consistent with

previous reports. For example, Lorente *et al* reported an increased risk of CP associated with maternal exposure to trichloroethylene,⁷ Wennborg *et al* an excess of risk of craniofacial anomalies associated with maternal occupation exposure to benzene,²² and Bove *et al* a relation between oral cleft risk and maternal ingestion of water contaminated by organic solvents (such as tetrachloroethylene, dichloroethane, and benzene).²³

Very few mothers ($n = 3$) were exposed only to petroleum solvents, and mothers exposed to chlorinated solvents were always also exposed to either a petroleum or oxygenated solvent. Thus estimates for these exposures are based on low numbers: only 20 mothers were exposed to chlorinated solvents and 30 to petroleum solvents (17 to both simultaneously). The risk may thus be due to the simultaneous exposure to both types of organic solvents, chlorinated and petroleum.

Previous studies suggested that maternal occupational exposure to some types of oxygenated solvents is associated with the risk of oral clefts.^{4 5 7 14 15} This exposure, however, has rarely been studied separately from occupational exposures to other classes of organic solvents. In our study, exposure to oxygenated solvents alone was associated only moderately (and not statistically significantly) with the risk of bearing a child with CL/P or CP. Most of this group (91%) was exposed to aliphatic alcohols. Lorente *et al* attempted to consider some of simultaneous exposures among 96 chemical products through multivariate modelling.⁷ Their results found an excess (but not significant) risk of CL/P associated with oxygenated solvents, and no risk of CP.

Cordier *et al* observed a positive exposure-response relation between the level of the mother's occupational exposure to glycol ethers and risk of CL/P.⁵ This finding is reproduced in our study for both the CL/P and CP groups, even when we exclude mothers exposed to either chlorinated or petroleum solvents. Nine of the ten women with the highest glycol ether exposure were also the most highly exposed to aliphatic alcohols. Finally, in this study, exposure to glycol ethers could not be effectively separated from exposures to the other oxygenated solvents, such as aliphatic alcohols, aliphatic aldehydes, esters, or ketones.

Our results show that domestic use of hair dyes or colour strippers at the beginning of pregnancy is associated with a slightly increased risk of CL/P and with a significantly increased risk of CP. Of the 48 mothers who used these products, 46% (8 CL/P, 4 CP, and 10 controls) were also exposed to organic solvents at work. Because only five women were hairdressers (3 CL/P and 2 controls, all but 1 reported use of these products), we could not assess the association between the occupation of hairdresser and risk of having an affected child. Assessment of this domestic exposure was imprecise in this study: the frequency of use was not available, nor were the specific products and their chemical composition recorded. However, these suggestive results may deserve specific attention since it is already known that hairdresser products contained a variety of chemical substances that are potentially toxic for reproductive functions: some studies report that women hairdressers have an increased risk of spontaneous abortion²⁴ and of bearing children with intrauterine growth retardation or congenital anomalies,²⁵ particularly CP.⁷

Several solvents are known to be teratogenic in animal experiments. Their reproductive toxicity varies according to exposure route (inhalation, ingestion, dermal), concentrations, species, and substance.²⁶ Chlorinated solvents, specifically trichloroethylene and dichloroethylene, have been associated with cardiac anomalies in animal experiments.²⁷ Many petroleum solvents, including benzene, toluene,

xylene, fuel gas, and gasoline additives, are teratogenic in laboratory animals, and some of them induce CP in mice.²⁶

Several aliphatic alcohols are reported to be teratogenic when inhaled in animal models.²⁶ Glycol ethers are a family of organic solvents that have for several decades been ubiquitous in the human home and workplace. Some have been identified as possibly toxic for human reproduction, suspected of acting on child development without affecting the mother's health.¹ Our study could not distinguish subfamilies of glycol ethers.

Solvents are found as mixtures both at work and in the home, so that identification of the agent responsible for specific reproductive outcome is difficult. Epidemiological studies dealing with occupational exposure need to improve the objectivity of exposure measurement; the use of biomarkers may be promising, including investigation of specific metabolic pathways with genetic polymorphisms.^{15 28} Finally, solvents are potential teratogens. This study shows evidence of the risks associated with them in occupational and domestic settings. They are widely used and much too common. This issue requires serious consideration since experimentation shows that a brief exposure during the critical period of embryogenesis appears sufficient to induce adverse pregnancy outcomes.

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