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Maternal occupational risk factors for oral clefts

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Objectives This study investigated the role of maternal exposures at work during pregnancy in the occurrence of oral clefts.

Methods The occupational exposures of 851 women (100 mothers of babies with oral clefts and 751 mothers of healthy referents) who worked during the first trimester of pregnancy were studied. All the women were part of a multicenter European case-referent study conducted using 6 congenital malformation registers between 1989 and 1992. In each center, the mother's occupational history, obtained from an interview, was reviewed by industrial hygienists who were blinded to the subject's status and who assessed the presence of chemicals and the probability of exposure. Odds ratios (OR) were estimated by a multivariate analysis including maternal occupation or occupational exposures during the first trimester of pregnancy and possible confounding factors such as center of recruitment, maternal age, urbanization, socioeconomic status, and country of origin.

Results After adjustment for confounding factors, cleft palate only was significantly associated with maternal occupation in services such as hairdressing [OR 5.1, 95% confidence interval (95% CI) 1.0—26.0] and housekeeping (OR 2.8, 95% CI 1.1—7.2). The analysis suggests that the following occupational exposures are associated with orofacial clefts: aliphatic aldehydes (OR 2.1, 95% CI 0.8—5.9) and glycol ethers (OR 1.7, 95% CI 0.9—3.3) for cleft lip with or without cleft palate and lead compounds (OR 4.0, 95% CI 1.3—12.2), biocides (OR 2.5, 95% CI 1.0—6.0), antineoplastic drugs (OR 5.0, 95% CI 0.8—34.0), trichloroethylene (OR 6.7, 95% CI 0.9—49.7), and aliphatic acids (OR 6.0, 95% CI 1.5—22.8) for cleft palate only.

Conclusions Due to the limited number of subjects, these results must be interpreted with caution. However, they point out some chemicals already known or suspected as reproductive toxins.

Key terms epidemiology, occupational exposures.

Oral clefts are among the most frequent congenital anomalies, with a prevalence of approximately 1 per 700 births in Europe (1). Investigators agree that oral clefts are multifactorial in origin and are caused by both genetic and environmental factors. Many genetic (risk of recurrence) and epidemiologic (sex ratio, prevalence)

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characteristics tend to suggest that cleft lip with or without cleft palate [CL(P)] and cleft palate only (CP) are etiologically distinct, although most early studies in environmental risk factors have considered them a group. Some of the environmental factors implicated in the causation of nonsyndromic oral clefts include tobacco use [for all types of clefts (2—5) and also for CL(P) (3, 4)], antiepileptic drugs (6, 7), and possibly alcohol consumption [for CL(P)] (8, 9). Debate continues as to whether multivitamin supplements, especially folic acid, can prevent oral clefts (10—12).

Various occupations and exposures have been associated with reproductive risks (13—17). For oral clefts, the occupations include those in the agricultural (18, 19) and health care fields (13). Maternal exposure to solvents has also been associated with clefts (20—22). Nonetheless, not enough is yet known about the occupational risk factors related to orofacial clefts. The present analysis is a part of a larger study; our objective here is to investigate the role of maternal workplace exposures during pregnancy in the occurrence of oral clefts.

Subjects and methods

Data for this analysis were obtained from a multicenter European case-referent study conducted by 6 European congenital malformation registries, all members of EUROCAT (European Registration of Congenital Anomalies): 2 in France (Paris and Bouches du Rhône), 1 in the United Kingdom (Glasgow), 2 in Italy (Emilia Romagna and Tuscany), and 1 in The Netherlands (Groningen). The methods used in this investigation have been described in detail in a previous publication (23).

Cases were defined as any product of conception (live or stillborn child or fetus from a therapeutic abortion performed because of the malformation) with a major congenital malformation diagnosed prenatally or during the perinatal period (0 to 6 days). Cases were identified between 1989 and 1992 by the 6 registries. For practical reasons, the registries in France and Italy recruited cases from only some of their hospitals. Each malformation was coded locally according to the British Paediatric Association Classification of Diseases (BPACD) (24). Coding and inclusion criteria were then verified centrally.

A healthy reference baby, without malformations, was recruited for each case in every center except Glasgow, where 2 referents were recruited for each case. For the hospital-based cases, the referent was the next child born without malformations. For the cases recruited from a general population (Glasgow and Groningen), the referent was a child born on the same date and in the same town.

The medical file provided information about the baby: date of birth, gender, birthweight, gestational age, description of the malformation, status (liveborn, stillborn, abortion).

Specially trained investigators used a standardized questionnaire to interview mothers. The same investigator saw both mothers of a case-referent pair, and all the interviews took place in the hospital during the week following the birth or abortion for the hospital-based centers or at home and during the month after birth for the centers that recruited referents from the general population. The interview provided information about the parents' sociodemographic characteristics, age, residence, and country of origin, as well as the mother's medical and obstetric history, alcohol, tobacco and drug use, and occupation and hobbies, both before conception and during each trimester of the pregnancy. The interviews elicited a detailed description of occupations before and during pregnancy — industrial activity and specific occupation. It included a description of tasks, products handled, frequency of use, and period (1 month before conception and 1st, 2nd or 3rd trimester). There were also supplemental questionnaires for typical job categories (cleaners and janitors, hairdressers and beauticians, cooks, waiters, and teachers) and for some jobs especially common at specific centers (eg, leather work, ceramics, and plastics manufacturing). All the interviewers had all

Table 1. Distribution of the cases and referents by center and type of malformation (working mothers only).

Center	Cases						Referents		
	Cleft lip with or without cleft palate			Cleft palate only			Matched	Unmatched	Total
	Isolated	Multiple	Total	Isolated	Multiple	Total			
Paris	10	7	17	7	1	8	24	253	277
Bouches du Rhône	10	-	10	5	2	7	15	74	59
Emilia Romagna and Tuscany	4	-	4	8	-	8	13	111	124
Groningen	24	3	27	7	1	8	37	116	153
Glasgow	6	-	6	3	2	5	26	164	138
Total	54	10	64	30	6	36	115	636	751

the questionnaires and used them when relevant jobs were reported, at any center.

Despite efforts at exhaustiveness, only 63% of the eligible cases of oral cleft could be interviewed, mostly because the mother left the hospital before the interview or because the mother or her physician refused to participate. Refusals were rare among the hospital referents (less than 10% in Paris). In the population-based studies, however, more of the referents did not participate. In Groningen, about 150 of the referenece mothers contacted did not respond to the request for participation and were replaced by the next child meeting the same criteria; in Glasgow, 39 referents (15 refused, 24 not traced) had to be replaced. In all, between 1989 and 1992, a total of 984 cases of malformation, including 161 oral clefts (BPACD code 749.01 to 749.29), and 1134 referents were included in this study.

One hundred cases and 751 referents (66% of the total) worked during pregnancy (table 1) and were included in the present analysis. Most of the cases were live-born babies (98.5%). Due to the small number of subjects, the Italian centers (Tuscany and Emilia Romagna) were combined in subsequent analyses. More than 80% of the malformations were isolated rather than syndromic forms.

Because our analysis concerned only cases of oral clefts, we had 2 types of referents available, those matched with the cases of oral clefts, whom we will refer to as matched referents (N=183), and those referents matched with the other cases of malformations, called the unmatched referents (N=951). These 2 categories of referents did not differ significantly for characteristics such as maternal age, socioeconomic status, country of origin (maternal and paternal), urbanization (residence in a municipality with <200 000 inhabitants; ≥200 000 inhabitants), and mother's employment during pregnancy. To increase the power of the analysis, therefore, we chose to consider the overall reference group (N=1134).

The working mothers of the cases and referents did not differ notably for either sociodemographic variables or for obstetric history, except for place of residence [mothers of CL(P) cases came from less urban backgrounds than their referents] and mother's age [older for CL(P) cases] (table 2). Moreover, no relevant differences were observed for the paternal sociodemographic variables.

The coding of occupations and industrial activities followed the code of the International Standard Classification of all Economic Activities (25) for industrial activity and the code of the International Standard Classification of Occupations (26) for occupations. In each center, an industrial hygiene expert blinded to the case-referent status interpreted the description of jobs during pregnancy and identified each potential workplace exposure (from a prepared list of 314 exposures) and the period of pregnancy when the exposure took place. Each exposure was defined by the following 4 parameters: (i) route of exposure: inhalation, cutaneous, both; (ii) level: low, medium, high; (iii) frequency: <5%, 5—50%, >50% of worktime; (iv) reliability of the assessment: possible, probable, or certain exposure. All occupational codes and center-specific exposures were centrally reviewed and standardized.

The analysis of occupational exposures was restricted to women who worked during pregnancy (100 cases and 751 referents). The association between occupation, occupational exposures, and orofacial clefts was studied by calculating the Mantel-Haenszel odds ratio (OR) and its 95% confidence interval (95% CI), separately for each type of cleft [CL(P) and CP]. The reference group for the odds ratios for each occupation were all women

Table 2. Sociodemographic characteristics of the working mothers. [CL(P) = cleft lip with or without cleft palate, CP = cleft palate only]

Characteristic	Cases: CL(P) (N=36) (%)	Cases: CP (N=64) (%)	Referents (N=751) (%)
Mother's socioeconomic status (last job before delivery)			
Scientific, technical, professional, managerial, student	25.7	31.3	38.3
Administrative, sales, services	68.6	56.2	54.7
Agricultural, production workers	5.7	12.5	7.0
Mother's country of origin			
Same as child's	91.7	84.3	88.2
Foreign	8.3	15.6	11.8
Mother's age			
≤24 years	22.2	4.7	14.7
25—29 years	33.3	59.4	39.2
30—34 years	25.0	25.0	31.6
≥35 years	19.4	10.9	14.5
Mother's residence			
Municipality of ≤200 000 inhabitants	61.1	78.1	63.8
Municipality of >200 000 inhabitants	38.9	21.9	36.2
Previous medical abortion			
Yes	0	3.2	4.3
No	100	96.8	95.7
Previous spontaneous abortion			
Yes	22.2	22.2	20.9
No	77.8	77.8	79.1
Previous stillbirth			
Yes	2.8	0	1.7
No	97.2	100	98.3
Parity			
Primiparous	58.3	49.2	56.6
Multiparous	41.7	50.8	43.4
Tobacco smoking during 1st trimester of pregnancy			
Yes	30.0	38.3	30.5
No	70.0	61.7	69.5
Alcohol drinking during 1st trimester of pregnancy			
Yes	34.5	21.0	22.0
No	65.5	79.0	78.0

working during pregnancy in any occupation except that under study. To minimize the possible effects of selection, which might be related, for example, to hospital recruitment, we adjusted these odds ratios for center, mother's socioeconomic status (professional, clerical and student, sales and service, production or agriculture), urbanization (<200 000 habitants; ≥200 000 habitants), and country of origin. Moreover, because maternal age has been suggested as a possible risk factor for oral clefts (27—29), it was taken into account in the adjustment (4 age classes: ≤24 years, 25—29 years, 30—34 years, ≥35 years).

The occupational exposures considered for the analysis were those reported by the experts for more than 10% (N≥8, cases and referents combined) of working mothers for the first trimester of pregnancy. Women were considered exposed, regardless of the frequency or probability of exposure, as long as neither was zero. For each product, the "unexposed" category comprised all women not exposed to that product, regardless of their exposure to any other product.

Because most women had been exposed simultaneously to several chemicals, our goal — in addition to estimating individual risk — was to identify, at the end of the process, a limited number of chemicals independently associated with an increased risk of orofacial clefts. Many of these exposures were highly correlated, either because of our study design (ie, exposure to formaldehyde automatically entailed exposure to "aliphatic aldehydes") or because of the work environments represented in our sample (ie, bleaching agents and ammonia were considered present almost exclusively for hairdressers and almost always together). We decided in the first situation to consider only the broader exposure, representative of the chemical family, and in the second situation to consider only 1 exposure to be representative of hairdressers.

The adjusted odds ratios for each of these exposures were estimated for CL(P) and CP. To estimate the independent effects of these exposures, we selected for further analysis those associated with an odds ratio for which the P-value was ≤20%. We used a backward

Table 3. Odds ratios associated with maternal occupation in the first trimester of pregnancy (subcategories reported only when at least 10% of all subjects were employed in that category). [CL(P) = cleft lip with or without cleft palate, CP = cleft palate only, 95%CI = 95% confidence interval]

Maternal occupation	CL(P) (N=64)	CP (N=36)	Referents (N=751)		Odds ratio CL(P)[a]	95% CI CL(P)	Odds ratio CP[a]	95% CI CP
			N	%				
Professional, technical and related workers	18	9	267	36	0.69	0.38—1.25	0.68	0.30—1.53
Medical, dental, veterinarians, pharmacists	3	1	52	.	0.76	0.22—2.60	0.47	0.06—3.56
Nurses, midwives, medical X-ray technicians	4	1	64	.	0.73	0.25—2.14	0.35	0.05—2.61
Architects, engineers and related technicians	2	-	12	.	2.43	0.47—12.5	.	.
Statisticians, mathematicians, system analysts	-	-	8	.	.	.	.	.
Teachers	4	2	73	.	0.52	0.18—1.53	0.55	0.13—2.42
Social workers	1	1	17	.	0.42	0.05—3.43	1.14	0.14—9.49
Others professional and technical workers	4	4	41	.	1.51	0.49—4.64	2.43	0.75—7.87
Students	-	-	9	1	.	.	.	.
Administrative, managerial workers	2	-	11	2	2.78	0.53—14.6	.	.
Clerical and related workers	15	8	227	30	0.70	0.37—1.30	0.73	0.32—1.65
Stenographers, typists	2	2	46	.	0.42	0.09—1.90	0.94	0.21—4.33
Bookkeepers, cashiers	5	2	73	.	1.00	0.37—2.68	0.51	0.12—2.22
Computing machine operators	-	1	9	.	.	.	3.91	0.44—35.0
Other clerical and related workers	8	3	99	.	0.83	0.37—1.86	0.71	0.21—2.42
Sales workers	6	2	75	10	1.0	0.40—2.46	0.56	0.13—2.41
Technical salesmen, commercial travellers	1	-	13	.	1.15	0.14—9.67	.	.
Salesmen, shop assistant	5	2	45	.	1.43	0.51—3.99	0.90	0.21—3.98
Other sales workers	-	-	17	.	.	.	.	.
Service workers	16	14	106	14	1.71	0.90—3.24	3.92	1.83—8.38
Housekeeping workers	6	7	52	.	1.16	0.45—2.97	2.80	1.08—7.24
Nurses' aides	3	2	14	.	1.68	0.44—6.36	2.91	0.58—14.6
Hairdressers, beauticians	2	2	9	.	1.86	0.36—9.65	5.10	1.01—25.9
Cooks, waiters	2	2	17	.	1.74	0.35—8.70	3.28	0.67—16.1
Other service workers	3	1	14	.	2.43	0.64—9.22	1.57	0.19—12.9
Agricultural workers	1	-	6	1	1.37	0.14—13.2	.	.
Production workers	6	2	46	6	2.51	0.94—6.72	0.78	0.17—3.52
Textile workers	1	1	12	.	1.80	0.20—16.2	1.65	0.19—14.5
Leather workers	-	-	10	.	.	.	.	.
Other production workers	5	1	24	.	3.17	1.06—9.51	0.95	0.12—7.51

[a] Adjusted for center, maternal age, mother's socioeconomic status, urbanization, and country of origin.

stepwise logistic regression starting with a full model including all the exposures selected at the previous step and all the sociodemographic variables already discussed to obtain a final set of exposures independently associated with oral clefts.

Results

Most of the working mothers had administrative and professional or technical jobs. Only 14% worked in service industries, and 6% were in production (table 3). The odds ratios were estimated for each type of cleft and were highest for service occupations. Within this group, the odds ratios were higher for CP than for CL(P) and statistically significant for CP for only 2 occupations: housekeepers (OR 2.80, 95% CI 1.08—7.24) and hairdressers (OR 5.10 95% CI 1.01—25.9). For production workers, the elevated odds ratios primarily concerned CL(P).

Of the prepared list of 314 exposures, 96 chemicals, chemical groups, and end-use products were assessed as present in the workplaces of more than 10% of the subjects. Odds ratios adjusted for the potential confounders already discussed were estimated for each of these 96 exposures and for each type of cleft. Table 4 lists those products for which the P-value was ≤20% for at least 1 type of cleft. Odds ratios significantly different from 1 ($P<0.05$) were observed for aliphatic aldehydes, glycol ethers, cleaning agents, products used for duplicating processes, and formaldehyde for the CL(P) group and for hair dust, fluorocarbons, lead compounds, aliphatic alcohols, toluene, hydrogen peroxide, trichloroethylene, alkanes (C1-C4), aliphatic acids, biocides, antineoplastic drugs, ammonia, bleaching agents, and spray gases for the CP group.

Table 4. Adjusted odds ratios for occupational exposures in the 1st trimester in association with oral clefts (presented for exposures to which at least 10% of all the subjects were exposed and P ≤20% for at least one type of cleft). [CL(P) = cleft lip with or without cleft palate, CP = cleft palate only, 95%CI = 95% confidence interval]

Exposure	CL(P) (N=64)	CP (N=36)	Referents (N=751) (%)	Odds ratio CL(P)[a]	95% CI CL(P)	Odds ratio CP[a]	95% CI CP
Hair dust	2	2	6	2.67	0.46—15.6	6.87	1.21—39.2
Nitrogen oxides	10	7	78	1.50	0.71—3.19	2.20	0.90—5.38
Fluorocarbons	6	5	27	2.07	0.77—5.57	4.10	1.38—12.2
Lead compounds	6	5	45	1.66	0.63—4.33	3.03	1.07—8.57
Aliphatic aldehydes	7	4	32	2.69	1.01—7.21	2.29	0.71—7.41
Aliphatic alcohols	15	10	101	1.67	0.86—3.26	2.51	1.13—5.59
Toluene	1	2	7	1.61	0.15—17.7	6.73	1.19—38.0
Monocyclic aromatic hydrocarbons	5	4	32	1.79	0.62—5.16	3.02	0.93—9.84
Alkalis and caustics	8	6	47	1.49	0.62—3.59	2.67	0.97—7.38
Hydrogen peroxide	3	3	12	1.99	0.50—7.88	4.62	1.12—19.0
Trichlorethylene	2	2	5	3.21	0.49—20.9	6.47	1.02—40.9
Blood and by-products	5	5	59	0.97	0.35—2.68	2.42	0.80—7.29
Polish	3	3	12	2.25	0.52—9.81	3.29	0.79—13.7
Mineral oils	4	3	25	1.12	0.33—3.78	4.14	0.95—18.1
Alkanes C1-C4	4	4	22	1.55	0.49—4.97	3.55	1.08—11.7
Aliphatic acids	2	4	12	1.50	0.31—7.39	8.17	2.31—28.9
Aliphatic amines	2	2	9	1.79	0.33—9.60	3.77	0.69—20.5
Glycol ethers	23	11	137	2.10	1.14—3.88	1.82	0.82—4.03
Pharmaceutical products	7	6	85	1.05	0.44—2.55	2.24	0.80—6.29
Laboratory products	1	2	13	0.68	0.08—5.61	3.30	0.65—16.7
Biocides	20	13	135	1.73	0.95—3.17	2.99	1.37—6.51
Antineoplastic drugs	1	2	7	3.35	0.37—3.12	11.20	1.98—63.7
Microbiological contaminants	11	7	81	1.45	0.67—3.12	2.47	0.93—6.59
House dust	14	3	68	1.99	0.97—4.09	0.57	0.15—2.08
Ammoniac	3	2	7	3.08	0.66—14.4	6.29	1.13—35.2
Adhesives	4	3	67	0.47	0.16—1.42	0.85	0.24—3.05
Inorganic acids	4	1	9	2.92	0.79—10.9	1.80	0.20—16.1
Cleaning agents	26	11	162	1.92	1.05—3.51	1.50	0.67—3.37
Duplicating process	10	10	201	0.40	0.19—0.84	1.08	0.48—2.42
Polyvinyl acetate	2	2	9	2.20	0.40—11.9	5.14	0.96—27.4
Engine emission	5	4	37	1.87	0.67—5.22	2.78	0.90—8.61
Aromatic amines	2	2	7	2.40	0.43—13.3	5.27	0.95—29.2
Bleaching agents	2	7	2	2.29	0.41—12.7	6.17	1.12—33.9
Spray gases	4	4	11	2.94	0.81—10.7	5.62	1.54—20.6
Formaldehyde	7	4	28	3.06	1.13—8.24	2.70	0.83—8.73
Ethanol	14	8	90	1.77	0.89—3.51	2.12	0.90—5.02
Methanol	4	2	8	3.61	0.91—14.4	3.77	0.65—21.8

[a] Adjusted for center, maternal age, mother's socioeconomic status, urbanization, and country of origin.

We then selected for multivariate analysis the exposures associated with an odds ratio for which the P-value was 20% or less: 15 for CL(P) and 32 for CP (table 4).

Some of the exposures were highly correlated, and we therefore made some arbitrary decisions. Of the chemical products or end use products associated only with hairdressers (hair dust, polyvinyl acetate, ammonia, aromatic amines, and bleaching agents), we chose only 1 (hair dust) to be representative of hairdressers. Some exposures were hierarchically organized; that is, for example, formaldehyde represented more than 95% of the aliphatic aldehydes. Ethanol and methanol were similarly hierarchically related to aliphatic alcohols. In these situations we considered the exposure that was representative of the chemical family (ie, aliphatic aldehydes, aliphatic alcohols). Spray gases and engine emissions (gasoline) were considered as possible end-use products for fluorocarbons and lead compounds, respectively. In our sample, all the women exposed to spray gases or engine emission were also coded as exposed to fluorocarbons or lead compounds. Only 50% of the fluorocarbons were used as spray gases, however, and 82% of the lead compounds resulted from engine emissions. We therefore selected the chemical products (fluorocarbons and lead compounds) instead of the end-use products. At the end of this process, we kept 11 exposures for CL(P) and 22 for CP.

For each type of cleft, the exposures were included in a backward stepwise logistic regression model with the adjustment variables presented earlier. Three exposures were retained for CL(P); 2 of these — aliphatic aldehydes and glycol ethers — were associated with an excess risk (table 5). The 3rd, which involved exposure to the duplicating process, showed an inverse relation with CL(P). At the end of the logistic regression, 5 exposures remained in the global CP model (table 6): lead compounds, trichlorethylene, aliphatic acids, biocides, and antineoplastic drugs. Forward or backward stepwise procedures gave the same results. Adjusting for tobacco use and alcohol consumption during the first trimester of pregnancy did not alter these results (table 5—6).

We also compared the results obtained by estimating risk for individual exposures separately (the univariate analysis) and by simultaneous (multivariate) evaluation. Four occupational exposures were associated with an odds ratio that was statistically different from 1 ($P<0.05$) for CL(P) in the estimation of individual risks (table 4): aliphatic aldehydes, glycol ethers, cleaning agents, and the duplicating process. After the competitive selection of 11 exposures with P-values of ≤ 0.20, 3 of these remained associated with the risk of CL(P). The end-use product group of cleaning agents was no longer included in the model, but much of its information was already included, with exposure to aliphatic aldehydes and glycol ethers (70% of exposure to glycol ethers occurred through the use of cleaning agents).

In the CP group, 14 exposures were individually associated with a statistically significant increased risk ($P<0.05$). After we eliminated structurally related exposures, 11 statistically significant associations remained. After competitive selection, only 5 exposures remained significantly associated with the risk of CP.

Table 7 summarizes the primary occupations of the mothers exposed to substances found to be significantly associated with an increase in oral clefts. Some exposures

Table 5. Last step of the global model, including 11 significant exposures (P≤20%), for cleft lip with or without cleft palate.

Exposures	Referents (N=751)	Cases (N=64)	Odds ratio[a]	95% CI	P-value	Odds ratio[b]	95% CI	P-value
Aliphatic aldehydes	32	7	2.1	0.8—5.9	0.16	4.4	1.3—14.4	0.02
Glycol ethers	137	23	1.7	0.9—3.3	0.13	1.5	0.6—3.5	0.40
Duplicating process	201	10	0.5	0.2—1.1	0.08	0.4	0.1—1.1	0.06

[a] Adjusted for center, maternal age, mother's socioeconomic status, urbanization, and country of origin.
[b] Adjusted for center, maternal age, mother's socioeconomic status, urbanization, country of origin, and tobacco and alcohol consumption.

Table 6. Last step of global model, including 22 significant exposures (P≤20%), for cleft palate only.

Exposures	Referents (N=751)	Cases (N=36)	Odds ratio[a]	95% CI	P-value	Odds ratio[b]	95% CI	P-value
Lead compounds	45	5	4.0	1.3—12.2	0.03	4.9	1.2—19.2	0.04
Trichlorethylene	5	2	6.7	0.9—49.7	0.09	7.8	0.8—71.8	0.10
Aliphatic acids	12	4	5.9	1.5—22.8	0.02	7.6	1.3—42.6	0.04
Biocides	135	13	2.5	1.0—5.95	0.05	1.9	0.6—6.4	0.29
Antineoplastic drugs	7	2	5.1	0.8—34.0	0.13	4.4	0.3—73.5	0.34

[a] Adjusted for center, maternal age, mother's socioeconomic status, urbanization, and country of origin.
[b] Adjusted for center, maternal age, mother's socioeconomic status, urbanization, country of origin, and tobacco and alcohol consumption.

Table 7. Principal occupations (%) of women exposed to substances found to be significantly associated with the risk of oral clefts.

Occupation	Lead compounds (N=56)	Trichloro-ethylene (N=9)	Aliphatic acids (N=18)	Biocides (N=168)	Antineo-plastic drugs (N=10)	Aliphatic aldehydes (N=43)	Glycol ethers (N=171)
Professional, technical workers	*42.9*	*22.2*	*33.4*	*55.4*	*70.0*	*32.7*	*13.0*
Medical doctors, dental, veterinarians, pharmacist	1.8	0	16.7	13.1	10.0	14.0	0.6
Nurses, midwives, medical X-ray technicians	8.9	0	0	33.3	60.0	14.0	2.3
Teachers	7.1	0	5.6	2.4	0	0	1.8
Architects, engineers and related technicians	3.6	11.1	0	0	0	0	1.2
Social workers	16.1	0	0	1.2	0	0	1.2
Other professional and technical workers	5.4	11.1	11.1	5.4	0	4.7	5.9
Administrative, managerial workers	*1.8*	*0*	*0*	*0*	*0*	*0*	*1.8*
Clerical workers	10.7	22.2	0	4.2	0	0	9.4
Sales workers	26.8	0	0	4.2	0	2.3	20.5
Service workers	5.4	22.2	66.8	34.5	30.0	48.8	48.5
Housekeeping workers	*0*	*0*	*0*	*19.6*	*0*	*7.0*	*24.6*
Nurses' aides	1.8	0	5.6	8.9	20.0	20.9	4.1
Hairdressers	0	0	55.6	1.8	0	20.9	7.0
Cook, waiters	1.8	0	0	1.8	0	0	6.4
Other service workers	1.8	22.2	5.6	2.4	10.0	0	6.4
Agricultural workers	*0*	*0*	*0*	*1.2*	*0*	*0*	*0*
Production workers	*12.5*	*33.3*	*0*	*0.6*	*0*	*16.3*	*7.1*
Textile workers	1.8	11.1	0	0	0	4.7	0
Leather workers	0	11.1	0	0	0	9.3	1.2
Other production workers	10.7	11.1	0	0.6	0	2.3	5.9
Total	*100*	*100*	*100*	*100*	*100*	*100*	*100*

were specific to particular occupations, for example, antineoplastic drugs and health care workers. Other exposures, such as to lead compounds, were more widespread.

A more-detailed analysis of the exposure variables of the level, frequency, and reliability of exposure could be performed only when enough subjects were exposed to each product. This analysis showed that, for glycol ethers among isolated CL(P) cases, the risk increased with the level, frequency, and reliability of exposure and therfore confirmed the results of a previous publication (23). For trichloroethylene exposure among the CP patients, it also showed that risk increased with the level and frequency of exposure (ie, for frequency: odds ratio low 6.6, 95% CL 0.6—79; odds ratio medium 13.9, 95% CI 1.1—186). This analysis did not allow us to observe any increase in risk with the level, frequency, or reliability of any of the other exposures selected by the final model; this result, however, was sometimes due to a lack of variability among the exposure indicators. For example, all exposure to antineoplastic drugs was low-level, low-frequency, and certain.

Discussion

Determining the role of chemical exposures in the occurrence of congenital malformations in humans is an important challenge. Most of our knowledge about the effects of chemical exposures on reproductive outcomes comes from animal data. Because the reproductive processes of each species seem unique, extrapolation from animal data is always uncertain. It becomes all the more difficult if we presume, as appears to be the case, that humans are at least as sensitive as the most sensitive animal species tested (30). This study attempts to obtain some information about reproductive toxins in the workplace.

Our analysis suggests that occupational exposure to some chemicals can present a hazard to the developing embryo that leads to an orofacial cleft. These chemicals include lead compounds, biocides, antineoplastic drugs, trichloroethylene and aliphatic acids for CP and aliphatic aldehydes and glycol ethers for CL(P). An important advantage of this investigation was that the exposure assessment was made by industrial hygiene experts. It helped to reduce possible recall bias and to standardize the assessments.

Some of the limitations of this work are due to the population's occupational distribution. Conclusions are necessarily limited to chemicals present in the occupations represented. For instance, because of the paucity of agricultural workers, we could not study pesticide exposures. Service and production workers were the 2 occupational groups in our population that were specifically associated with an increased risk. These results may be conservative, however, because overadjustment may have resulted from the adjustment for the mother's socioeconomic status. The only occupations with an odds ratio significantly greater than 1 were housekeeping and hairdressing. Reproductive disorders, including spontaneous abortions (31, 32) and major malformations (32), have previously been observed among hairdressers, but not to a statistically significant degree. It has been suggested that these effects are related to several specific chemicals to which this occupational group is exposed (33). A few studies have associated housekeeping workers with an increased risk of oral clefts (21, 34). Janitors, who perform essentially the same tasks as housekeeping workers, with the same chemicals, have also been reported to have reproductive disorders (preterm deliveries and stillbirths) (35). These different reproductive disorders may not all have causes relevant to the etiology of oral clefts, but they do indicate that the work environment in these occupations is harmful to the reproductive process.

As table 7 shows, some of the 7 products selected at the end are independent indicators of tasks, such as cleaning and disinfection, that might on the whole increase the risk of CL(P) or CP. These particular chemical groups were selected at the end of the multivariate analysis, a finding that may have resulted from chance. The plausibility of these specific associations must therefore be evaluated together with additional evidence. Other products (such as lead compounds, aliphatic aldehydes, glycol ethers) are ubiquitous and not associated uniquely with 1 type of occupation or task. In these cases, an association with the specific product selected is more credible. It must be added that for most of these 7 exposures, the reliability of the exposures was rated as at least probable or certain.

Applying the selection process to occupational exposures resulted in multiple comparisons, and we cannot exclude the possibility that some results are due to chance. Nevertheless, this process gave us the opportunity to take into account the correlation between exposures. Obtaining the same results with the backward and forward procedures indicates that the procedure was robust. In addition, most of the exposures selected are biologically plausible. Animal experiments have suggested that all the exposures selected by the logistic regression model may be reproductive toxins (36); some epidemiologic evidence suggests that they have a similar effect on humans.

Indeed, antineoplastic drugs are among the most potent teratogens known, as both animal studies and human observations have shown (36, 37). They have also been linked to congenital malformations in epidemiologic studies (38, 39). Lead compounds are generally teratogenic in animal studies. Lead compounds may induce stillbirth and spontaneous abortion in humans (36, 40, 41). One study found prenatal exposure to lead to be associated with minor anomalies (42). Maternal occupational exposure to solvents (which may include trichloroethylene and glycol ethers) has been related to oral clefts (20—22). Moreover, solvents have been indirectly incriminated by studies that have found an excess risk of orofacial clefts among leather workers (43, 44).

The limited number of exposed subjects prevents us from drawing any firm conclusions. These results nonetheless suggest that further evaluation of the effects of maternal occupational exposures on orofacial clefts may lead to useful findings.

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References

1. Institute of Hygiene and Epidemiology. Rapport EUROCAT no 6. Surveillance of congenital anomalies in Europe 1980—1992. Brussels: Institute of Hygiene and Epidemiology, 1995.
2. Andrews J, Mc Garry JM. A community study of smoking in pregnancy. J Obstet Gynaecol Br Common 1972;79:1057—73.
3. Ericson A, Källen B, Westerholm P. Cigarette smoking as an etiologic factor in cleft lip and palate. Am J Obstet Gynecol 1979;135:348—51.
4. Källen K. Maternal smoking and orofacial clefts. Cleft Palate Craniofacial J 1997;34:11—6.
5. Khoury MJ, Gomez-Farias M, Mulinare J. Does maternal cigarette smoking during pregnancy cause cleft lip and palate in offspring? Am J Dis Child 1989;143:333—7.
6. Dravet C, Julian C, Legras A, Magaudda A, Guerrini R, Genton P, et al. Epilepsy, antiepileptic drugs, and malformations in children of women with epilepsy: a French prospective cohort study. Neurology 1992;42 suppl 5:75—82.
7. Abrishamchian J, Khoury MJ and Calle EE. The contribution of maternal epilepsy and its treatment to the etiology of oral clefts: a population-based case-control study. Genet Epidemiol 1994;11:343—51.
8. Werler MM, Lammer EJ, Rosenberg L and Mitchell A. Maternal alcohol use in relation to selected birth defects. Am J Epidemiol 1991;134:691—8.
9. Munger RG, Romitti PA, Daack-Hirsh S, Burns TL, Murray JC, Hanson J. Maternal alcohol use and risk of orofacial cleft birth defects. Teratology 1996;54:27—33.
10. Toralova M, Haris J. Reduced recurrence of orofacial clefts after periconceptional supplementation with high-dose folic acid and multivitamins. Teratology 1995;51:71—8.

11. Shaw G, Lammer E, Wasserman C, O'Malley C, Toralova M. Risks of orofacial clefts in children born to women using multivitamins containing folic acid periconceptionally. Lancet 1998;346:393—6.
12. Hayes C, Werler M, Willet W, Mitchell C. Case-control study of periconceptional folic acid supplementation and oral clefts. Am J Epidemiol 1996;143:1229—34.
13. Erickson JD, Cochran WM, Anderson CE. Parental occupation and birth defects. Contrib Epidemiol Biostat 1979; 1:107—17.
14. Hemminki, Mutanen P, Saloniemi I and Luoma K. Congenital malformations and maternal occupation in Finland: multivariate analysis. J Epidemiol Community Health 1981;35:5—10.
15. Mc Donald AD, Mc Donald JC, Armstrong B, Cherry NM, Coté R, Lavoie J. Congenital defects and work in pregnancy. Br J Ind Med 1988;45:581—8.
16. Taskinen HK. Effect of parental occupational exposures on spontaneous abortion and congenital malformation (review). Scand J Work Environ Health 1990;16:297—314.
17. Savitz DA, Olshan AF and Gallagher K. Maternal occupation and pregnancy outcome. Epidemiol 1996;7:269—74.
18. Thomas DC, Pettiti DB, Goldhaber M, Swan SH, Rappaport EB, Hertz-Picciotto I. Reproductive outcomes in relation to Malathion spraying in the San Francisco Bay Area, 1981—1982. Epidemiology 1992;3:32—9.
19. Nurminen T, Rantala K, Kurppa K, Holmberg PC. Agricultural work during pregnancy and selected structural malformations in Finland. Epidemiology 1994;6:23—30.
20. Holmberg PC, Hernberg S, Kurppa K, Rantala R, Riala R. Oral clefts and organic solvent exposure during pregnancy. Int Arch Occup Environ Health 1982;50:371—6.
21. Cordier S, Ha MC, Ayme S, Goujard J. Maternal occupational exposure and congenital malformations. Scand J Work Environ Health 1992;18:11—7.
22. Laumon B, Martin JL, Bertucat I, Vernet M, Robert E. Exposure to organic solvents during pregnancy and oral clefts: a case-control study. Reprod Toxicol 1996;10:15—29.
23. Cordier S, Bergeret A, Goujard J, Ha MC, Aymé S, Bianchi F, et al. Congenital malformations and maternal occupational exposure to glycol ethers. Epidemiology 1997;8:355—63.
24. British Paediatric Association. Classification of Diseases. 2nd ed. London: British Paediatric Association, 1987.
25. United Nations. International Standard Industrial Classification of all Economic Activities. New York (NY): United Nations, 1971.
26. International Labor Office. International Standard Classification of Occupations. Geneva: International Labor Office, 1968.
27. Saxen I. Cleft lip and palate in Finland: parental histories, course of pregnancy and selected environmental factors. Int J Epidemiol 1974;3:263—70.
28. Shaw GM, Croen LA, Curry CJ. Isolated oral cleft malformations: associations with maternal and infant characteristics in a California population. Teratology 1991;43:225—8.
29. Womersley J, Stone DH. Epidemiology of facial clefts. Arch Dis Child 1987;62:717—20.
30. US Environmental Protection Agency. Guidelines for reproductive toxicity risk assessment part II. Fed Regist 1996; 61(212).
31. John EM, Savitz DA, Shy CM. Spontaneous abortion among cosmetologists. Epidemiology 1994;5:147—54.
32. Kersemaekers WM, Roeleved N, Zielhuis GA. Reproductive disorders among hairdressers. Epidemiology 1997;8:396—401.
33. Kersemaekers WM, Roeleved N, Zielhuis GA. Reproductive disorders due to chemical exposure among hairdressers (review). Scand J Work Environ Health 1995;21:325—34.
34. Holmberg P, Hernberg S. Congenital defects and occupational factors: a comparison of different methodological approaches. Scand J Work Environ Health 1979;5:328—32.
35. Savitz DA, Olshan A and Gallakher K. Maternal occupation and pregnancy outcome. Epidemiology 1996;7:269—74.
36. Shardein JL. Chemically induced birth defects. 2nd ed. New York (NY): Marcel Dekker, 1993.
37. Kline J. Maternal occupation: effect on spontaneous abortions and malformations. Occup Med 1986;1:381—403.
38. Hemminki K, Kyyrönen P, Lindbohm ML. Spontaneous abortions and malformations in the offspring of nurses exposed to anaethesic gases, cytostatic drugs and other potential hazards in hospitals, based on registered information of outcome. J Epidemiol Community Health 1985;313:141—7.
39. Ahlborg G, Hemminki K. Reproductive effects of chemical exposures in health professions. J Occup Environ Med 1995;37:957—61.
40. Savitz DA, Whelan EA, Kleckner RC. Effect of parents' occupational exposures on risk of stillbirth, preterm delivery, and small-for-gestational-age infants. Am J Epidemiol 1989;129:1201—18.
41. Antilla A, Sallmen M. Effects of parental occupational exposure to lead and other metals on spontaneous abortion. J Occup Environ Med 1995;37:915—21.
42. Needlman HL, Rabinowitz M, Leviton Md, Linn S, Shoenbaum S. The relationship between prenatal exposure to lead and congenital anomalies. JAMA 1984;251:2956—9.
43. Bianchi F, Cianciulli D, Pierini A, Seniori Constantini A. Congenital malformations and maternal occupation: a registry based case-control study. Occup Environ Med 1997;54:223—8.
44. Garcia A, Fletcher T. Maternal occupation in the leather industry and selected congenital malformations. Occup Environ Med 1998;55:284—6.

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