Parental occupational exposure to organic solvents and anencephaly in Mexico

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ABSTRACT

Objective: To assess the relationship between parental occupational exposure to organic solvents, and the risk of anencephaly in Mexico.

Methods: A case-control study was conducted based on the registers of the Epidemiological Surveillance System for Neural Tube Defects in Mexico; 151 cases of anencephaly of ≥20 weeks’ gestation were included. A control, born alive and without any apparent congenital malformations at birth, was selected for each case in the same maternity service in which the case was born. Information on occupational exposures, lifestyle habits, reproductive history, use of medicines, supplementation of folic acid and other B vitamins. Occupational exposure to organic solvents was based on job title as a proxy for exposure and analysed considering two critical periods around conception.

Results: In logistic regression analysis, the odds of having a child with anencephaly was higher if the mother or the father was occupationally exposed to organic solvents during the periconceptional period, or when both parents or at least one of them were occupationally exposed during this period with an adjusted odds ratio of 2.97 (95% CI 1.36 to 6.52).

Conclusions: The results support the hypothesis that both maternal and paternal occupational exposure to organic solvents can increase the probability of having a child with anencephaly.

The organic solvents are a group of diverse volatile liquids of low molecular weight, which belong to a structurally diverse group, including aliphatic hydrocarbons (varnishes and kerosene), aromatic hydrocarbons (benzene, toluene and xylene) and their halogenated derivatives, halogenated hydrocarbons (carbon tetrachloride, trichloroethylene), aliphatic alcohols (methanol), glycols (ethylene glycol and glycol ether) and methoxy-ethanol.1 Owing to their ability to dissolve organic substances, such as high molecular weight lipids and compounds, they are generally used in the industrial, occupational and domestic setting.2

Occupational exposure to organic solvents usually occurs during the preparation, use and manipulation of solvents, treatment with natural and synthetic resins, use of varnishes and paints, enamels, adhesives, lacquers and putty, production of colorants and explosives, production of natural and synthetic rubber, in the leather and shoe industry, in the graphics industry, in dry cleaning, production of polymers and also during the cleaning and degreasing of industrial machinery.1 2

There is experimental evidence of the teratogenic effects of some organic solvents3; nevertheless, there is not consistency in the findings of epidemiological studies that have evaluated the exposure to organic solvents and the occurrence of adverse reproductive effects such as spontaneous abortion,4–9 neural tube defects (NTDs) such as spina bifida10–12 and anencephaly.3 4

In a recent meta-analysis of epidemiological studies that evaluated the association between maternal exposure to organic solvents and pregnancy outcomes, McMartin et al. (1988),7 assert that although there is evidence of fetal damage from exposure of pregnant women to non-toxic levels of organic solvents, there are inconsistencies in this respect in the medical literature.

In a recent meta-analysis of the effects of parental exposure to organic solvents and their adverse effects on reproduction, 47 publications on the exposure to organic solvents and its effects on reproductive health were analysed, and the authors concluded that there was association between parental exposure to organic solvents and the risk for any NTD (odds ratio (OR) 1.86 (95% CI 1.40 to 2.46)), for anencephaly (OR 2.18 (95% CI 1.52 to 3.11)) and for spina bifida (OR 1.59 (95% CI 0.99 to 2.56)).8

What this paper adds

► In a recent meta-analysis the authors concluded that the odds of having a child with anencephaly was higher if the fathers were exposed to organic solvents, although they do not specify the period around conception in which the exposure occurred.

► Nevertheless, previous studies evaluating the relationship between maternal exposure to organic solvents and neural tube defects are scarce and their results are inconclusive.

► This study evaluates the association between anencephaly and the occupational exposure to organic solvents of both parents during different critical periods around conception.

► The results support the hypothesis that both maternal and paternal occupational exposure to organic solvents during the periconceptional period (3 months before and 1 month after the date of the last menstruation) can increase the probability of having a child with anencephaly.
Hooiveld et al. (2006), observed an increased risk of congenital malformations in offspring of workers employed as painters exposed to organic solvents compared with carpenters not exposed to organic solvents (OR 6.2 (95% CI 1.4 to 27.9)), with a positive significant exposure–response trend.

One of the major limitations of the aforementioned epidemiological studies is that they evaluate the isolated exposure of the mother or the father. Nevertheless, in all studies that evaluate the aetiology of adverse reproductive effects it is necessary to consider the exposure of both parents as well as the critical periods of risk, such as the cycles of spermatogenesis (with a duration of about 74 days) and part of organogenesis (approximately 28 days after conception for closure of the neural tube).14–16

The NTDs constitute a public health problem of multifactorial aetiology and despite having been intensively studied their aetiology is not well understood and their pathogenesis is uncertain.17 Anencephaly, one of the NTDs, is one of the most important health problems that affect the development of the central nervous system (CNS) and is also one of the most frequent NTDs.18 According to the World Health Organization (WHO), in the year 2000, the prevalence of anencephaly in Mexico was one of the highest in the world with 8.05 cases per 10,000 births.19 Considering that in Mexico NTDs display a wide range of temporal and geographic variation, eight of every 10 cases are found in the states of the central region of the country—the State of Mexico and Puebla had 40% of all the cases of anencephaly identified in the entire country.20

This study evaluated the association between maternal and paternal occupational exposure to organic solvents in the critical risk periods and the presence of anencephaly in three states in the central region of Mexico.

MATERIALS AND METHODS

Design and selection of the cases and controls

A case-control study was conducted, paired (1:1) for maternity service, birth date, and federal entity in three states in the central region of Mexico: Puebla, State of Mexico and Guerrero; and based on the register of the Epidemiological Surveillance System for Neural Tube Defects (ESSNTD) in Mexico. The above three states were selected because of the regular functioning of the ESSNTD there in the last few years as well as the high prevalence of anencephaly. Detailed information about the operation of the ESSNTD in Mexico, design and population of the study has been previously published by our research group.21 22

All the cases with ≥20 weeks’ gestation (born alive or fetal death) are identified in maternity hospitals and prenatal clinics and reported to the local ESSNTD in each of the three states included in the study. Cases notified between 1 March 2000 and 28 February 2001 were selected. A control was selected for each case that participated in the study and was the next live born infant in the same maternity service in which the case was born and that was not diagnosed with anencephaly or any other apparent major congenital malformation at birth. Mothers of cases and controls had to be resident in the same state of delivery for at least 1 year before the birth of the affected child and in order to be included in the study, they had to be contacted during the first 5 months after the end of pregnancy.

During the period of study 252 cases of anencephaly were identified in the three states. One hundred and eighty-nine cases fulfilled all the inclusion criteria. Fifty-seven were excluded because the mother was not contacted within the 3-month period after birth, generally due to delays in case notification. Six more cases were excluded because the families emigrated, leaving 189 cases that fulfilled all the inclusion criteria. Of these, 157 mothers (83%) agreed to participate in the study, while 32 (17%) did not agree; 26 mothers of cases did not have partners or for some reason did not live with the fathers of their children. Of the 163 fathers of cases who could be contacted, 129 (79%) agreed to participate in the study, and 34 (21%) did not accept.

One hundred and sixty mothers of controls were contacted and 151 (94%) agreed to participate. Complete information was obtained for 110 (79%) fathers of controls as 11 mothers were not living with the fathers of their children, and another 30 fathers of controls did not want to participate in the study. It was impossible to find a control that fulfilled all the inclusion criteria for six of the cases, and these cases were not included in the analysis.

The study was approved by the research, ethics and biosafety committees of the National Institute of Public Health of Mexico. All the participating mothers and fathers signed informed consent.

Data collection

A general questionnaire (a specific one for the mother and another for the father) was applied to the participating parents in order to elicit information on variables of interest and potential confounders: sociodemographic characteristics (age, education, income and marital status), habits (smoking and alcohol consumption in the periconceptional period and throughout life), pathological antecedents, use of medication and multivitamin supplements in the periconceptional period, reproductive history of the mother (number of pregnancies, history of stillbirths, abortions, premature births and children with malformations), antenatal care during the pregnancy, family reproductive history, occupational history, exposure to chemical agents in the home and in the residential area during the periconceptional period.

An 85-item food frequency standardised questionnaire was applied to the mothers to evaluate the intake of folate in the diet. This instrument was developed by Willett and validated for its use in epidemiological studies in Mexican populations.21

A short questionnaire applied to those parents who did not agree to participate in the study elicited summarised information on the principal variables of interest (occupational history, socioeconomic level, and reproductive history).

Interviews were conducted by previously trained nurses at cases and controls parents’ home. Before the start of the interview the interviewers knew if interviewees were cases or controls’ parents, but interviewers did not know the principal hypothesis of the study. The interviewers helped the mothers to relate relevant exposures to the periods of interest in accordance with the risk periods defined for anencephaly.22 Although the periconceptional period was considered to be the period of greatest risk (3 months before and 1 month after the date of the last menstruation), many pathogenic mechanisms are still not well known and we thought that it would be interesting to evaluate the risks associated with exposure before this period.23

Occupational exposure assessment to organic solvents

Participants were asked about their occupational history over the previous 5 years, information was obtained about the start and end dates of each job, and the activity of the company. The occupations exposed to organic solvents were defined based on occupational title, job activity or substances that participants

were exposed to in each of the jobs. Dichotomous occupational exposure (yes/no) to organic solvents was established if the workers reported using an organic solvent in their job or if the occupation was linked to exposure to organic solvents in the available literature. In our sample, the following occupations were considered as being exposed to organic solvents: shoemakers, workers in shoe factories, house painters, spray painters, carpenters, mechanics, welders, artisans, tile layers, workers in cable and electrical material factories, industrial engineers, and drivers.

Two relevant periods were defined from the date of the last menstrual period of the mother and the same period was assigned to the father: the acute risk period (ARP), defined as 3 months before and one after the date of the last menstruation and the non-acute risk period (NARP) when the exposure was before the ARP. If the exposure occurred in both periods, the person was considered to be exposed in the ARP.

Statistical analysis

The association between maternal exposure to organic solvents and anencephaly was evaluated by means of conditional logistic regression. Paternal exposure was evaluated by non-conditional logistic regression, given that 69 women did not live with the father of their child and that it was not possible to obtain information on the father. In these cases, the effect of the potential confounding of the matched variables was evaluated (date of birth and place of birth where the child was born).

The association between the exposure to organic solvents of one or the other parent and anencephaly was evaluated by non-conditional logistic regression, comparing couples non-exposed to solvents at work with couples in which at least one of the partners had been exposed at work.

In order to assess the father’s exposure or the exposure of at least one parent to organic solvents, three models that considered three exposure periods of interest (some time during the last 5 years, ARP and NARP) were constructed. Nevertheless, to evaluate the exposure of the mother, we constructed two models that took into account exposure in the NARP and at some time during the last 5 years. It was not possible to construct a model for exposure in the ARP as none of the women in the control group had been exposed to organic solvents at work during this period.

All the variables associated with anencephaly in the bivariate models were selected to evaluate the presence of confounding. Multivariate models were constructed adding the previously selected variables one by one, including all those that modified the OR of the association between exposure to organic solvents and anencephaly by at least 10%.

RESULTS

According to data already published, there were no significant differences between the participating mothers’ cases and the non-participants in terms of age, education, family income, reproductive history, maternal and paternal occupation.

The distribution of some characteristics of the mothers and fathers of cases and controls, are presented in Table 1, where we can observe an increase in the OR as educational level of the parents and family income decreases. Multiparous women with adverse reproductive antecedents had a significantly higher probability to have a child with anencephaly than primiparous women.

A daily intake of folate of <600 μg/day was associated with an increase in the odds of anencephaly (crude OR 1.91; 95% CI 0.93 to 3.11). It is important to note that 15 women used multivitamin supplements with folic acid during pregnancy, but only three (two cases and one control) used them during the ARP.

Women who reported the burning of wood, coal or tires in their home for cooking or heating had twice the odds of having a child with anencephaly compared with women not using this kind of combustible (crude OR 2.04; 95% CI 1.29 to 3.23).

Table 2 shows the results of the bivariate and multivariate models for occupational exposure to organic solvents, for the mother, the father, and the effect of exposure of at least one parent.

In our study very few women (n = 17) had occupational exposure to organic solvents at some time in their lives, and of these, eight mothers of cases and none from the control group had been exposed during the ARP, for which reason it was not possible to estimate the magnitude of the association for this period. Nevertheless, a mother with occupational exposure to organic solvents at some time during the last 5 years demonstrated a significant increase in the odds of having a child with anencephaly (adjusted OR 9.22; 95% CI 1.97 to 43.17). When we analysed the exposure during the NARP, the OR was 1.69 (95% CI 0.25 to 11.41).

The odds of having a child with anencephaly was higher if the fathers were exposed to organic solvents during the ARP (adjusted OR 2.08; 95% CI 0.93 to 4.60) or at some time during the last 5 years (adjusted OR 2.16; 95% CI 1.08 to 5.32). We did not calculate the adjusted OR in the NARP because only one father in the control group was exposed to organic solvents at work in this period.

By means of a variable that combined occupational exposure to organic solvents in both parents, the couples in which at least one of the parents was occupationally exposed to organic solvents compared with couples in which none of the parents were exposed, demonstrated a statistically significant increase in the odds of anencephaly when the exposure was during the periconceptional period (ARP) (adjusted OR 2.97; 95% CI 1.36 to 6.52) or when the exposure was at some time during the last 5 years (adjusted OR 2.77; 95% CI 1.35 to 5.70).

DISCUSSION

This study found a significant increased probability of having a child with anencephaly when the mother reported having been occupationally exposed to organic solvents at some time during the last 5 years before the birth of their child. Although, it is not possible to calculate the magnitude of the association for maternal exposure in the ARP, it must be emphasised that eight mothers of cases and none in the control group were exposed in the periconceptional period. This increased OR to have an anencephalic child was also observed if the father was exposed to organic solvents at work in the ARP.

In the same way, the couples in which at least one of the partners was occupationally exposed to solvents in the periconceptional period demonstrated a statistically significant increase in the odds of anencephaly.

The neural tube closes during the first 4 months of gestation. When this does not occur, which is not very frequent, various types of NTD may be present (eg, spina bifida: when closure of the caudal neuropore is affected, or anencephaly when the lesion affects the cephalic neuropore). This is also the period of maximum fetal vulnerability, and if this period is not considered, it is not possible to detect an existing association.

Previous studies have demonstrated fetal susceptibility to environmental exposures in terms of time period of exposure
with respect to gestational age of the fetus; in which the exposure can have a teratogenic effect.\textsuperscript{17–22,28,29} Our results in relation to maternal occupational exposure to organic solvents are consistent with this hypothesis, around a window period of susceptibility.

The greater probability to have a child with anencephaly observed in this study when the father has an occupational exposure to organic solvents, in both ARP or at some time during the last 5 years before the birth of the child, is consistent with the modalities in which paternal occupational exposure, acute and chronic, to chemical agents can affect reproductive health in the critical risk periods because of the mechanisms of action of these chemical agents. The acute effects of paternal exposure during the ARP may be due to mutations in the germinal cells and the susceptibility.

El-Zein\textit{et al} 2002\textsuperscript{39} showed that the exposure in utero to ethylene glycol methyl ether (EGME) is associated with the development of specific congenital anomalies and with chromosomal aberrations in humans; and that the exposure to organic solvents produces specific congenital anomalies in the development of specific congenital anomalies and with chromosomal aberrations in humans; and that the exposure to organic solvents produces specific congenital anomalies and with chromosomal aberrations in humans; and that the exposure to organic solvents produces specific congenital anomalies and with chromosomal aberrations in humans; and that the exposure to organic solvents produces specific congenital anomalies and with chromosomal aberrations in humans; and that the exposure to organic solvents produces specific congenital anomalies and with chromosomal aberrations in humans; and that the exposure to organic solvents produces specific congenital anomalies and with chromosomal aberrations in humans; and that the exposure to organic solvents produces specific congenital anomalies and with chromosomal aberrations in humans; and that the exposure to organic solvents produces specific congenital anomalies and with chromosomal aberrations in humans; and that the exposure to organic solvents produces specific congenital anomalies and with chromosomal aberrations in humans; and that the exposure to organic solvents produces specific congenital anomalies and with chromosomal aberrations in humans; and that the exposure to organic solvents produces specific congenital anomalies and with chromosomal aberrations in humans; and that the exposure to organic solvents produces specific congenital anomalies and with chromosomal aberrations in humans; and that

\begin{table}[h]
\centering
\caption{Characteristics of the cases and controls' parents} \label{table:1}
\begin{tabular}{|c|c|c|c|}
\hline
Variables & Cases (n = 151) & Controls (n = 151) & OR (95\% CI) \\
\hline
Maternal age (years) & & & \\
< 35 & 135 (89.40) & 144 (95.36) & 1 \\
> 35 & 16 (10.60) & 7 (4.64) & 2.44 (0.97 to 6.10) \\
Paternal age (years) & & & \\
< 40 & 116 (94.31) & 106 (96.36) & 1 \\
> 40 & 7 (5.69) & 4 (3.64) & 1.60 (0.46 to 5.62) \\
Family monthly income and maternal education & & & \\
> 1000 pesos and > 9 years of school & 24 (16.44) & 46 (31.29) & 1 \\
< 1000 pesos and > 9 years of school & 8 (5.48) & 13 (8.84) & 1.18 (0.43 to 3.24) \\
> 1000 pesos and < 9 years of school & 47 (32.19) & 51 (34.69) & 1.77 (0.94 to 3.33) \\
< 1000 pesos and < 9 years of school & 67 (45.89) & 37 (25.17) & 3.47 (1.84 to 6.56) \\
Adverse reproductive antecedents in previous pregnancies* & & & \\
Multiparous without antecedents & 52 (35.14) & 55 (38.19) & 1 \\
Multiparous with antecedents & 46 (31.08) & 20 (13.89) & 2.12 (1.12 to 4.02) \\
Primiparous & 50 (33.78) & 69 (47.92) & 0.71 (0.40 to 1.27) \\
Periconceptional dietary intake of folic acid (\textmu g/day)\textsuperscript{+} & & & \\
> 600 \textmu g/day & 21 (14.58) & 32 (21.92) & 1 \\
< 600 \textmu g/day & 123 (89.04) & 114 (78.08) & 1.91 (0.93 to 3.11) \\
Maternal tobacco smoke during ARP & & & \\
No & 145 (96.03) & 141 (94.0) & 1 \\
Yes & 6 (4.0) & 9 (6.0) & 0.7 (0.20 to 1.91) \\
Maternal alcohol consumption during ARP & & & \\
No & 138 (91.39) & 134 (88.74) & 1 \\
Yes & 13 (8.61) & 15 (9.93) & 0.84 (0.36 to 1.96) \\
Residential use of organic solvents during the ARP & & & \\
No & 139 (92.05) & 139 (92.67) & 1 \\
Yes & 11 (7.28) & 12 (7.35) & 0.92 (0.39 to 2.15) \\
To cook with wood, coal or tires & & & \\
No & 58 (38.41) & 84 (55.63) & 1 \\
Yes & 67 (45.89) & 66 (43.71) & 2.04 (1.29 to 3.23) \\
\hline
\end{tabular}
\end{table}

The sum of cases and controls is not necessarily equal to the total owing to missing values.

*Includes stillbirths, premature births, malformations and miscarriages.

\textsuperscript{+}Limits selected in accordance with current daily recommendations for folic intake by pregnant women.\textsuperscript{35}

ARP, acute risk period; OR, odds ratio.
have evaluated NTD as a group, despite the fact that the different types of NTD are aetiopathologically different. 36 A further strength is that the critical periods of exposure and the potential confounders were evaluated for the fathers as well as for the mothers. These have been the principal limitations of previous studies that evaluated occupational and environmental exposures as risk factors for NTD.

This study does, however, have limitations, and one of the most important limitations is the methodology employed to evaluate exposure, as this is based exclusively on the information available from an occupational title. This is similar to how one would construct a matrix of employment exposure in which only the absence/presence of the exposure for different occupations would be evaluated. Nevertheless, if some degree of error exists in the classification of exposure to solvents based on parental occupation it would be non-differential since there is no reason why parents involved in such cases would have a better memory of jobs related to the use of solvents than parents in the control group. In fact, parents of the cases in this study did not associate any occupational exposure to solvents with having a newborn with anencephaly. When parents were asked about any health effects that could be associated with occupational exposure, they only mentioned nausea and headaches. Therefore, they never associated exposure to solvents with any adverse reproductive event. In this respect there were no differences between cases and controls. Hence, we consider the magnitude of the associations observed in this study could be underestimated.

The occupations of mothers and fathers of the cases who refused to participate in the study (34 and 32, respectively) do not differ from those of parents who did participate. 21 22 Therefore, we believe that the possibility of selection bias due to non-participation is minimal. The main reason parents refused to participate in the study was because, in addition to responding to the questionnaire, they were also asked to give a blood sample. Nevertheless, in both the cases and controls, information could not be gathered on fathers who were not living with the mothers at the time of the interview. Therefore, if the occupations of those men differed from the occupation of the men who were actually interviewed, a selection bias cannot be completely ruled out. In that case, we can’t predict the direction of the bias.

The high magnitude of association observed might largely be due to the small sample size, which reduces the power of the study, and wide confidence intervals, due to the sparseness of data in some of the categories analysed, especially ones concerning the evaluation of paternal exposure to organic solvents. Therefore, the results are suggestive but have to be carefully considered and corroborated with those from other studies as well as in future studies.

### Variables

<table>
<thead>
<tr>
<th>Variables</th>
<th>Cases</th>
<th>Controls</th>
<th>Crude OR (95% CI)</th>
<th>Adjusted OR (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Mother</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Some time during the last 5 years</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Not exposed</td>
<td>138 (91.39)</td>
<td>147 (97.35)</td>
<td>1</td>
<td>1</td>
</tr>
<tr>
<td>Exposed</td>
<td>13 (8.61)</td>
<td>4 (2.65)</td>
<td>3 (0.97 to 9.30)</td>
<td>9.22 (1.97 to 43.17)</td>
</tr>
<tr>
<td>ARP</td>
<td></td>
<td></td>
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<td></td>
</tr>
<tr>
<td>Not exposed</td>
<td>138 (94.52)</td>
<td>147 (100)</td>
<td>1</td>
<td>1</td>
</tr>
<tr>
<td>Exposed</td>
<td>8 (5.48)</td>
<td>0 (0)</td>
<td>–</td>
<td>–</td>
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<tr>
<td>NARP</td>
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<td></td>
<td></td>
</tr>
<tr>
<td>Not exposed</td>
<td>138 (96.50)</td>
<td>147 (97.35)</td>
<td>1</td>
<td>1</td>
</tr>
<tr>
<td>Exposed</td>
<td>5 (3.50)</td>
<td>4 (2.65)</td>
<td>1.33 (0.28 to 6.85)</td>
<td>1.69 (0.25 to 11.41)</td>
</tr>
<tr>
<td><strong>Father</strong></td>
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<td></td>
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<tr>
<td>Some time during the last 5 years</td>
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<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Not exposed</td>
<td>104 (80.62)</td>
<td>95 (86.38)</td>
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<td>1</td>
</tr>
<tr>
<td>Exposed</td>
<td>25 (19.38)</td>
<td>15 (13.64)</td>
<td>1.52 (0.76 to 3.06)</td>
<td>2.16 (1.08 to 5.32)</td>
</tr>
<tr>
<td>ARP</td>
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<tr>
<td>Not exposed</td>
<td>104 (82.54)</td>
<td>95 (87.16)</td>
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<td>1</td>
</tr>
<tr>
<td>Exposed</td>
<td>22 (17.46)</td>
<td>14 (12.84)</td>
<td>1.44 (0.702.97)</td>
<td>2.08 (0.93 to 4.60)</td>
</tr>
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<td>NARP</td>
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<td></td>
<td></td>
</tr>
<tr>
<td>Not exposed</td>
<td>104 (97.20)</td>
<td>95 (98.96)</td>
<td>1</td>
<td>1</td>
</tr>
<tr>
<td>Exposed</td>
<td>3 (2.80)</td>
<td>1 (1.04)</td>
<td>2.74 (0.25 to 69.57)</td>
<td>–</td>
</tr>
<tr>
<td>The father and/or the mother</td>
<td></td>
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<td></td>
<td></td>
</tr>
<tr>
<td>Some time during the last 5 years</td>
<td></td>
<td></td>
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<td></td>
</tr>
<tr>
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<td>1</td>
</tr>
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<td>33 (24.81)</td>
<td>19 (17.12)</td>
<td>1.6 (0.85 to 3.01)</td>
<td>2.77 (1.35 to 5.70)</td>
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<td>ARP</td>
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<td></td>
</tr>
<tr>
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<td>100 (78.74)</td>
<td>92 (86.79)</td>
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<td>1</td>
</tr>
<tr>
<td>Exposed</td>
<td>27 (21.26)</td>
<td>14 (13.21)</td>
<td>1.77 (0.883.59)</td>
<td>2.97 (1.36 to 6.52)</td>
</tr>
<tr>
<td>NARP</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Not exposed</td>
<td>100 (87.72)</td>
<td>92 (86.79)</td>
<td>1</td>
<td>1</td>
</tr>
<tr>
<td>Exposed</td>
<td>6 (12.28)</td>
<td>5 (5.15)</td>
<td>1.10 (0.29 to 4.34)</td>
<td>1.40 (0.26 to 7.23)</td>
</tr>
</tbody>
</table>

The multivariate model was adjusted for the mothers by: age of the mother, socioeconomic level (family income and education of the mother), adverse reproductive history in previous pregnancies, daily ingestion of folic acid and total calories of the mother, cooking with wood, coal or tires. For the fathers it was adjusted by: age of the mother, socioeconomic level (family income and education of the mother), adverse reproductive history in previous pregnancies, cooking with wood, coal or tires. For the fathers it was adjusted by: age of the mother, socioeconomic level (family income and education of the mother), adverse reproductive history in previous pregnancies, cooking with wood, coal or tires.

The sum of cases and controls is not necessarily equal to the total owing to missing values.

ARP, acute risk period; NARP, non-acute risk period.
Only products of conception with a gestational age of >20 weeks were included in the study and spontaneous and induced abortions were excluded. This prenatal selection could have affected the estimate of the association, if the probability of attaining 20 weeks of gestation is associated with exposure to organic solvents and with the presence of anencephaly. We could not evaluate if exposure to organic solvents increases the risk of early loss in affected foetuses because of the design of the study, but the available studies did not find a significant association between exposure to organic solvents and spontaneous abortion.1, 3

It is possible that the interviewers introduced differential information bias to the study given that they knew which of the participants were cases and which ones were controls; nevertheless, they did not know the hypothesis of the study and they were carefully trained to apply the questionnaire in the same manner to both the cases and the controls.

It is necessary to conduct multicentric studies with the aim to increase the sample size, which will allow to evaluate specific compounds with the intention of identifying chemicals that have highly toxic reproductive health effects. It is important to note that the proportion of women who are exposed to different chemical products during pregnancy in the workplace is increasing and that this situation varies from country to country. Moreover, in developing countries the use of personal protective equipment is rare or absent, owing to the fact that this is normally imported and is not designed for the anthropometric characteristics of the population nor the climatic conditions in these countries. This situation can be of major concern because of the limited capacity at these sites to regulate levels of occupational exposure and to implement control regulations for occupational exposure. In addition, with globalisation, the most dangerous industries are operating in developing countries where they pose a grave threat to public health.

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Parental occupational exposure to organic solvents and anencephaly in Mexico

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