Congenital malformations and maternal occupation: a registry based case-control study

Fabrizio Bianchi, Domenico Cianciumi, Anna Pierini, Adele Seniori Costantini

Abstract

Objectives—To investigate the relations between congenital malformations and maternal occupation during pregnancy with a registry based case-control study.

Methods—Analysis was performed on data derived from the Florence Eurocat registry surveillance programme. The study included cases with isolated conditions, including chromosomal anomalies (n = 1351), cases with multiple anomalies registered during the 1980–91 period (n = 440), and babies with no congenital malformations recognised at birth who were born from 1982 to 1989 and selected as controls (n = 3223). 11 categories were defined, 10 including cases with isolated malformations and one for cases with multiple congenital anomalies. Four categories of maternal occupation were selected for the study. Odds ratio (OR) values were adjusted for maternal origin, maternal and paternal education, number of previous live births, illness during pregnancy, and maternal age when the group of chromosomal anomalies was analysed.

Results—A notable and significant association between oral clefts and mothers involved in leather and shoe manufacturing was found (adjusted OR 3.9; 99% confidence interval [99% CI] 1.5 to 9.8) and the risk consistently increased when considering cases with isolated cleft palate separately (OR 5.4; 95% CI 1.8 to 13.4). Moreover, a significant risk was identified for the association between multiple anomalies and textile dye workers (adjusted OR 1.9; 99% CI 1.0 to 3.8).

Conclusions—This study indicates a notable, significant relation between maternal occupation as a pelt or leather worker and orofacial clefts in offspring. This finding is in agreement with the suggested inheritance models. The dilution effect due to studying large and heterogeneous groups of workers and occupations limits the value of the study; but it provides a good example of the use of a large database to search for teratogenic risk with the aid of malformation registries.

The association between maternal occupation and congenital malformations in offspring has been repeatedly described by registry based case-control studies, and other important results on occupational exposure have been obtained from epidemiological studies. From case-control investigations, major anomalies of the central nervous system have been reported in association with the maternal occupation “sales worker” during the first trimester and oral clefts have been associated with health service carers, clerical workers, and the repair services industry.1

Among women involved in healthcare work, a relation between maternal exposure to anaesthetic gas and various malformations has been described several times with postal questionnaires: however, the only study performed in Sweden with medical records did not suggest increases in risk.2 A significant association was found among cases with birth defects whose mothers had been exposed, as nurses, to cytostatic drugs, but no specific pattern of defects was identified.3 For exposure to anaesthetic gases, evidence of increased risk of congenital malformations was considered inconclusive.4

In epidemiological studies focused on hairdressers, associations were found with menstrual disorders and spontaneous abortions, as well as other inconsistent results probably due to methodological problems.5

For leather workers a relevant reproductive risk has been reported of perinatal mortality due to all causes (and particularly to congenital malformations)6, fetal mortality (but not for congenital malformations)7, and subfecundity.8

Another study, conducted in Norway, found an odds ratio (OR) of 0.77 for congenital malformations and occupation in textile and leather industries.9

Evidence on the risk of oral cleft in offspring of mothers exposed to solvents during pregnancy has sometimes been described.10–12 Recently, a significant association (OR 1.9) for orofacial cleft and agricultural work during pregnancy has been identified by a case-control study based on the Finnish register of congenital malformations, but exposure to solvents did not explain the association found.13

The aim of the present registry based case-control study was to explore associations among selected groups of congenital anomalies and four groups of maternal occupations during pregnancy.

Keywords: congenital malformations; maternal occupation; case-control; orofacial cleft
Materials and methods

Since 1979 the Province of Florence (Italy) has been part of the Eurocat concerted action project. Between 1982 and 1989 a case-control surveillance was carried out with the primary aim of preparing a database to describe and investigate relationships between congenital malformations and hypothetical risk factors. The present study includes 1146 births and induced abortions for isolated conditions, 205 with chromosomal anomalies and 440 with multiple anomalies, registered in eight maternity units during the 1980–91 period, as well as 3223 controls, normal at birth, registered in the same hospitals from 1982 to 1989. Cases were selected among all births and induced abortions with congenital malformations collected according to the Eurocat guidelines. One out of 20 normal live or stillbirths, resident in the study area, was included in the control group. In effect, every normal birth occurring after 19 consecutive births was selected as a control in each maternity unit (the subsequent normal birth was selected as a control when the 20th had malformations); this selection was performed basically for organisational reasons at the maternity units. The sampling fraction of 1/20 was chosen to build up a control group of at least double the size of the group of cases, assuming 2–5 per 100 to be the prevalence of congenital malformations among the births. The control group did not include abortions due to causes other than congenital malformations.

In each maternity unit, mothers of cases and controls were interviewed (not blindly) by the same neonatologist, involved in the Eurocat Registry. A standardised questionnaire, based on the Eurocat form, was used to collect information about both cases and controls.

Specific questions on the maternal occupation and branch of activity during pregnancy were asked. An unstructured section was provided for the specific job title and possible risk agents, even if a reduced level of completeness and reliability was expected. Neither previous working periods nor duration of exposure during the present pregnancy were investigated by the questionnaire. However, the interviewers were instructed to ask specific questions about any “moonlighting” jobs.

Coding of maternal occupation was performed by the central staff of the Florence Eurocat registry according to the three digit ISTAT classification of occupations. To select groups of occupations for analysis, three inclusion or exclusion criteria were used: (a) occupation in which at least 10 women were exposed when all malformations were considered; (b) an existing interest on the basis of the scientific literature; (c) exclusion of groups with generically defined occupations—for example, mechanical worker.

With the above criteria, four groups of occupations were selected: health service carriers (ISTAT code 1·4x), hairdressers (ISTAT code 9·4x), textile dye workers (ISTAT code 5·3x), and leather workers (ISTAT code 5·5x). (See table 6 for some occupational titles of interest compared with the ISCO-88 code.)

Coding of congenital malformations was carried out with the British Paediatric Association classification of diseases and grouping by the Eurocat schedule.

In the present study, 10 classes of isolated congenital malformations and one class of multiple conditions (two or more major congenital malformations) were considered (table 1). Some groups of isolated anomalies were excluded due to the small numbers, such as eye (n = 13), ear (n = 15), respiratory (n = 8), metabolic (n = 10), other major congenital malformations (n = 18), and a miscellaneous group of other minor isolated or associated anomalies (n = 41).

Malformation sequences—such as Potter’s sequence—were considered to be a single anomaly, whereas anomalies of known environmental origin—for example, fetal alcohol syndrome, toxoplasmosis—or monogenic syndromes were excluded: this left 73/1969 cases (3·7%), a percentage comparable with many other registries.

An assessment of the diagnosis reported at the local level is routinely performed by medical geneticists at the central level, taking into account the reported environmental exposure. Nevertheless, the possibility that some unrecognised syndromes were included among the multiple anomalies cannot be ruled out.

Crude ORs (95% confidence intervals (95%
CIs) were calculated for case-control associations with the sociodemographic variables (table 2), the obstetric history variables (table 3), and the lifestyle variables (table 4), with EPI Info software. To study the associations among 11 groups of malformations and the four occupations selected (table 5), adjusted ORs were calculated for those variables that accounted for significant differences between cases and controls and that were potentially associated with maternal occupation.

When the chromosomal anomalies group was analysed, the adjustment variables were: maternal place of birth (foreign or in Italy), particularly as an indirect indicator of the socioeconomic status; maternal and paternal education (primary, other levels); previous live births (0, 1, >1); illness during pregnancy (no, yes); and maternal age (≥ 35, < 35). Maternal alcohol consumption was not considered for the adjustment owing to its weak reliability. None of the other potential confounding variables reached significance when tested against employment or unemployment.

To minimise the possibility of producing significant results by chance, adjusted ORs with 99% CIs were calculated by means of unconditional logistic regression, with EGRET software. When subgroups of leather workers and oral clefts were compared, crude ORs with 95% CIs were reported (table 6), owing to the few cases.

The number of cases gathered in the subgroups of malformations, with 0-05 first type error and 0-20 second type error (power 80%), will allow detection of ORs from 1-5 when the frequency of cases and the percentages of exposures are high—for example, association of multiple congenital anomalies with health service carers—to 3-2 for the associations with fewer subjects—for example, teguments anomalies with hairdressers.

### Results

During the 1982–9 period, 3223 births without congenital malformations were collected as controls out of 70 214 births resident in the study area, compared with 3511 expected on the basis of the 1/20 sampling fraction. Underreporting was partly expected as the selection of controls was from the total births minus the malformed babies, and some organisational difficulties were thought likely to be responsible for other missing data. The actual underestimation (about 8%) was thought uniformly distributed among the participating hospitals.

All 1969 malformed babies and induced abortions after prenatal diagnosis registered between 1980 and 1991 out of the 106 074 total births (prevalence 18-6 per 1000 births) made up the group of cases, as there seemed to be no contraindication to limiting case selection to the same period as that considered for controls.

No significant changes in the pattern of women's employment were found either for cases during the 1980–91 period or for controls over the 1982–9 period. Table 1 shows

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### Table 2 Distribution of sociodemographic variables for cases and controls

<table>
<thead>
<tr>
<th>Variable</th>
<th>Cases (n = 1791)</th>
<th>Controls (n = 3223)</th>
<th>OR (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mother's alcohol use:</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>&lt; 35</td>
<td>1337 (98-6)</td>
<td>2877 (89-9)</td>
<td>1-0 r</td>
</tr>
<tr>
<td>≥ 35</td>
<td>178 (11-4)</td>
<td>327 (10-2)</td>
<td>1-1 (0-9 to 1-4)</td>
</tr>
<tr>
<td>Unknown</td>
<td>31</td>
<td>19</td>
<td></td>
</tr>
</tbody>
</table>

### Table 3 Distribution of variables of obstetric history for cases and controls

<table>
<thead>
<tr>
<th>Variable</th>
<th>Cases (n = 1791)</th>
<th>Controls (n = 3223)</th>
<th>OR (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Previous live births:</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>0</td>
<td>1058 (60-2)</td>
<td>1817 (57-2)</td>
<td>1-0 r</td>
</tr>
<tr>
<td>1</td>
<td>548 (31-2)</td>
<td>1104 (39-9)</td>
<td>0-9 (0-8 to 1-0)</td>
</tr>
<tr>
<td>&gt; 1</td>
<td>151 (8-6)</td>
<td>249 (7-8)</td>
<td>1-0 (0-8 to 1-3)</td>
</tr>
<tr>
<td>Unknown</td>
<td>34</td>
<td>48</td>
<td></td>
</tr>
</tbody>
</table>

### Table 4 Distribution of lifestyle variables during pregnancy for cases and controls

<table>
<thead>
<tr>
<th>Variable</th>
<th>Cases (n = 1791)</th>
<th>Controls (n = 3223)</th>
<th>OR (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mother's drug use:</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Yes</td>
<td>958 (55-0)</td>
<td>1763 (55-7)</td>
<td>1-0 (0-9 to 1-1)</td>
</tr>
<tr>
<td>No</td>
<td>783 (45-0)</td>
<td>1401 (44-3)</td>
<td>1-0 r</td>
</tr>
<tr>
<td>Unknown</td>
<td>50</td>
<td>59</td>
<td></td>
</tr>
</tbody>
</table>

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|r = reference value.
the frequency of cases included in the study, by group of anomalies and status upon registration. Induced abortions made up 6-4% of multiple and 8-4% of isolated anomalies, 38.7% of anomalies of the nervous system, and 29-3% of chromosomal anomalies, and for the other groups a small or zero percentage was found.

Table 2 shows the sociodemographic characteristics of cases and controls. No significant difference was found for maternal age between cases and controls when chromosomal anomalies, with an established association with maternal age, were excluded. Within this group, however, the number of subjects with maternal age ≥ 35 years was significantly higher among cases than controls, as expected. No significant differences were found for the mother’s place of birth among cases and controls for the three Italian areas (north, centre including Florence, and south including islands), whereas foreign origin was significantly more frequent among cases. More mothers were employed during pregnancy among the cases, although this difference was not significant. Among cases, maternal education to primary level and paternal absence of schooling were significantly different from controls, both parents of cases tended to have had no schooling or schooling to only primary level, but there were no other differences in schooling from the reference high school level.

Table 3 shows data about history of previous pregnancies. There was a slight but significant excess of one previous live birth among the controls, but no difference between still births or abortions, spontaneous or therapeutic. Nevertheless, the high ORs for one or more than one previous still birth are noteworthy (OR 1.5 and 1.8, respectively).

Table 4 shows variables related to lifestyle. The proportion of mothers reporting either drug misuse or tobacco smoking during pregnancy was similar in cases and controls; alcohol consumption was significantly more frequent in controls (probably underreported because of a more frequent recall bias among the cases). Among the cases a significant excess of infections or illnesses during pregnancy was found.

There was a low rate of non-response for all the categorical variables already described. Maximum values for missing data were 1-9% among cases and 1-5% among controls when simple questions were investigated (maternal age and obstetric history variables), whereas for the other variables “not known” answers were reported in < 5-0% among cases and < 3-5% among controls.

Table 5 shows the ORs (99% CIs) corresponding to the association between four groups of maternal occupations and the different groups of congenital malformations. A significant relation between maternal occupation in the pelt or leather industry and overall oral cleft in offspring was identified (crude OR 3-7; 99% CI 1-5 to 9-3; adjusted OR 3-9; 99% CI 1-5 to 9-8).

A risk of multiple abnormalities was also associated with textile dye workers (crude OR 1-8; 99% CI 0-9 to 3-4; adjusted OR 1-9; 99% CI 1-0 to 3-8).

Table 6 shows the analysis for oral cleft, isolated cleft palate, and cleft lip with or without cleft palate, by subclassification of the pelt or leather group into tanners and leather dyers (ISTAT code = 5-51), shoemakers and related workers (ISTAT code = 5-52), and

### Table 5 Maternal occupation during pregnancy for cases and controls, by groups of anomalies

<table>
<thead>
<tr>
<th>Group of anomalies</th>
<th>Total (Controls = 3223) n</th>
<th>Health service 1/2 (Controls = 141) n</th>
<th>Hairdresser 1/2 (Controls = 52) n</th>
<th>Textile dye work 1/2 (Controls = 84) n</th>
<th>Pelt or leather work 1/2 (Controls = 120) n</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Cases</td>
<td>OR (95% CI)</td>
<td>Cases</td>
<td>OR (95% CI)</td>
<td>Cases</td>
</tr>
<tr>
<td>Nervous system</td>
<td>106</td>
<td>0.2 (0.0 to 2.5)</td>
<td>2</td>
<td>1.2 (0.2 to 8.1)</td>
<td>2</td>
</tr>
<tr>
<td>Cardiovascular</td>
<td>296</td>
<td>0.6 (0.2 to 1.5)</td>
<td>7</td>
<td>1.0 (0.5 to 4.6)</td>
<td>7</td>
</tr>
<tr>
<td>Oral cleft</td>
<td>79</td>
<td>0.3 (0.0 to 3.6)</td>
<td>3</td>
<td>2.2 (0.4 to 10.7)</td>
<td>4</td>
</tr>
<tr>
<td>Digestive</td>
<td>90</td>
<td>1.2 (0.3 to 3.9)</td>
<td>1</td>
<td>0.4 (0.0 to 6.0)</td>
<td>3</td>
</tr>
<tr>
<td>External genital</td>
<td>123</td>
<td>1.8 (0.7 to 4.4)</td>
<td>1</td>
<td>0.4 (0.0 to 6.0)</td>
<td>5</td>
</tr>
<tr>
<td>Internal urogenital</td>
<td>83</td>
<td>1.0 (0.3 to 3.8)</td>
<td>2</td>
<td>1.0 (0.1 to 6.4)</td>
<td>1</td>
</tr>
<tr>
<td>Limbs</td>
<td>237</td>
<td>0.6 (0.2 to 1.7)</td>
<td>8</td>
<td>2.2 (0.8 to 6.1)</td>
<td>8</td>
</tr>
<tr>
<td>Musculoskeletal</td>
<td>67</td>
<td>0.3 (0.0 to 4.3)</td>
<td>1</td>
<td>0.0 (0.0 to 9.1)</td>
<td>3</td>
</tr>
<tr>
<td>Segments</td>
<td>65</td>
<td>1.4 (0.4 to 5.6)</td>
<td>1</td>
<td>0.9 (0.1 to 12.9)</td>
<td>34</td>
</tr>
<tr>
<td>Total isolated</td>
<td>1146</td>
<td>0.8 (0.5 to 1.2)</td>
<td>22</td>
<td>1.2 (0.6 to 2.4)</td>
<td>34</td>
</tr>
<tr>
<td>Chromosomal anomalies</td>
<td>205</td>
<td>0.9 (0.3 to 2.6)</td>
<td>3</td>
<td>1.0 (0.2 to 5.4)</td>
<td>6</td>
</tr>
<tr>
<td>Multiple</td>
<td>440</td>
<td>0.5 (0.2 to 1.2)</td>
<td>11</td>
<td>1.7 (0.7 to 4.0)</td>
<td>20</td>
</tr>
</tbody>
</table>

*Odds ratio adjusted for maternal country of birth, maternal and paternal education, previous live births, illness in pregnancy.
†Odds ratio adjusted for maternal country of birth, maternal and paternal education, previous live births, illness in pregnancy, and maternal age.

### Table 6 Maternal occupation during pregnancy in pelt or leather industry for controls and cases with isolated oral cleft, cleft palate, and cleft lip with or without palate

<table>
<thead>
<tr>
<th>Occupation</th>
<th>Controls (n = 3223) n</th>
<th>Total oral cleft (n = 79) OR (95% CI)</th>
<th>Cleft palate (n = 35) OR (95% CI)</th>
<th>Cleft lip ± palate (n = 44) OR (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Tanner or leather dyer</td>
<td>11</td>
<td>3.7 (0.1 to 26.3)</td>
<td>1</td>
<td>8-6 (0.2 to 62.1)</td>
</tr>
<tr>
<td>(ISTAT code = 5-51, ISCO-88 = 7441)</td>
<td>12</td>
<td>3-0 (0-3 to 12)</td>
<td>1</td>
<td>3-0 (0-1 to 21)</td>
</tr>
<tr>
<td>Shoemaker and related workers (ISTAT code = 5-52, ISCO-88 = 7442)</td>
<td>28</td>
<td>3.0 (0-3 to 12)</td>
<td>1</td>
<td>2-6 (0-1 to 16)</td>
</tr>
<tr>
<td>Leather goods makers</td>
<td>81</td>
<td>3.8 (1-4 to 8-5)</td>
<td>4</td>
<td>5-0 (1-2 to 14-6)</td>
</tr>
<tr>
<td>(ISTAT code = 5-53, ISCO-88 = 7442)</td>
<td>81</td>
<td>3-8 (1-4 to 8-5)</td>
<td>4</td>
<td>2-8 (0-5 to 9-2)</td>
</tr>
<tr>
<td>Total pelt or leather workers (ISTAT code = 5-5, ISCO-88 = 744)</td>
<td>120</td>
<td>3-7 (1-7 to 7-6)</td>
<td>6</td>
<td>5-4 (1-8 to 13-4)</td>
</tr>
</tbody>
</table>

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leather goods makers (ISTAT code = 5-53).

Of the 35 cases with isolated cleft palate, six had mothers who were leather or shoe workers, resulting in an increased crude OR (OR 5-4; 95% CI 1-8-13-4), whereas for cleft lip with or without cleft palate the association between the four mothers employed in the leather trade among 44 total cases was weaker and not significant (OR 2-6; 95% CI 0-7-7-3).

Discussion

There are limitations inherent to this study.

(1) The power of the study is weak, despite its overall size, as only a few cases were present for analysis of selected occupations with groups of anomalies, and so identification of small excesses of risk was reduced.

(2) As the interviews were not performed blindly, a related bias cannot be ruled out, although the interviewers were specifically trained to investigate moonlighting occupations.

(3) Organisational difficulties may have caused underreporting from controls, mainly due to some discontinuities in coverage by the neonatologist involved in the registration, but this is unlikely to have caused notable anomalies.

(4) Unmatched selection of controls was performed, although it was decided to include only those controls resident in the study area. On checking for heterogeneity in notification among eight hospitals, we found only one, in the centre of Florence, which reported anomalies (particularly congenital heart defects) more than the others.

(5) Maternal occupations were grouped loosely to achieve adequately sized groups. Thus, consideration of the type of declared occupation rather than the type of exposure may have resulted in a limitation of the recall bias.

There were also advantages in our study.

(1) The inclusion of induced abortions due to a prenatal diagnosis of congenital malformations represents an important feature.

(2) No significant differences in ratios of isolated or multiple anomalies existed among hospitals, probably because of a good standardisation between neonatologists.

(3) The frequency of "unknown" answers obtained for the maternal and paternal variables was low. Some of the few that there were could be due to difficulties in submitting the questionnaires, especially for the cases.

(4) The answers to questionnaire studies tend not to be specific possibly because of the structure of the study.

In general, as substantial differences exist in risk factors associated with employment related to pregnancy, with working women generally having more favourable demographic and behavioural characteristics and less favourable reproductive histories, it is essential when a case-control study is performed, to be aware of the most important potential confounding factors that distinguish employed women from unemployed women.22

Some methodological studies have shown that even although reporting bias for maternal occupation cannot be ruled out, concerns about recall bias are likely to be overrated in studies of birth defects, and that the use of normal controls is acceptable unless evidence of substantial recall bias exists.23 The results obtained for the sociodemographic, obstetric, and lifestyle factors included in the study showed considerable agreement with other data reported, particularly in recent publications.12 A higher alcohol consumption during pregnancy was reported among the controls than among the cases. However, the uncertainty about the timing and amount of consumption was considered to be an indication for the exclusion of these data from the adjustment variables. Other sociodemographic and obstetric history variables are routinely collected for the birth medical record, and both are easier to obtain by questionnaire, so they are more likely to be reliable.

Maternal age was significantly higher among the cases only if chromosomal anomalies were pooled with the other groups considered. Maternal foreign origin was in excess among the cases, but the frequency was small.

This study indicates a significant relation between maternal occupation as a pelt or leather worker and orofacial clefts in offspring.

Maternal age is higher, as well as more significant, when considering cases with isolated cleft palate separately (table 6). It is noteworthy that none of the 10 newborn cases had a family history of congenital malformations (including third degree relatives) whereas among the 59 cases in whom mothers were otherwise employed we found a family history in three cases of cleft lip and palate (two cases with the same defect in a third degree relative of both mother and father and one case with a cleft palate in the sister).

Table 6 shows significant ORs for makers of leather goods for both total oral clefts and cleft palate only. Moreover, a non-significant risk of cleft palate was also associated with tanners or leather dyers and shoemakers, and the sample size was small. These findings are in agreement with the inheritance models recently suggested for cleft palate and cleft lip.24-27

A specific relation between employment as a leather worker and birth defects has not yet been proved, but the few observational studies performed in this field should be taken into account. In our experience, in the manufacturing cycle of pelt or leather factories, such as tanneries and shoe and leather goods factories, employees can be reasonably assumed to be exposed to organic solvents.28-29 Although no assumptions can be made about intensity, degree, and duration of this exposure, it is relevant to report that aliphatic hydrocarbons are often used, as well as chlorinated hydrocarbons and aromatic solvents other than benzene.29

No association between defects of the nervous system and maternal occupation as a leather worker was found in our analysis, although such a relation has been previously described.30 On the other hand, there is a small amount of evidence that structural or func-
tional defects of the central nervous system are
due to parental exposure, even though the few
studies and the wide range of different com-
ounds considered as organic solvents limit the
considerations.11 When the nervous system
and chromosomal anomalies groups are
analysed, the high percentages of induced abortions among the cases must be taken into
account.

There was no evidence of an association
between maternal occupation and urinary tract
defects. This is in agreement with the
findings of Cordier et al., although a definite
excess due to exposure to aromatic solvents
has been described.20

The relation between multiple anomalies and
textile dyeworkers approached signific-
cance, increasing the interest in this group
of defects.17 Identification of new multiple
congenital anomalies combined with exposure
evaluation is considered to be a powerful
research technique for discovering human ter-
atogens and mutagens.34 Among the 20 cases
with multiple malformations occurring in
textile dyeworkers some associations seem to be noteworthy: hydro-
cephaly and cleft palate; hydrocephaly, and
cleft lip and palate; cleft palate, absence of
diaphragm, and low set ears; cleft palate, com-
mon mesentry, and talipes equinovarus;
spina bifida and congenital heart diseases; in
another three cases (congenital heart diseases,
absence of auditory canal, and polydactyly;
ventricular septal defect, oesophageal atresia,
common mesentry, and absence of
diaphragm; cleft palate, pterygium colli, poly-
dactyly, and other oesophageal anomalies) a
supplementary investigation on diagnosis and
family history is in progress to check for recog-
nised conditions. Among the other cases no
particular pattern of associations was found.

The dilution effect due to studying large
and heterogeneous groups of anomalies and
occupations for exploratory and descriptive
purposes limits the value of this type of study.
Nevertheless, it provides a good example of
the use of a large database to search for terato-
getic risk with the aid of malformation reg-
istrari.35

Additional analytical studies are required
as well as to the ongoing case-control surveil-
lance programme, to improve evaluation of
occupational exposures and identification of
specific patterns of defects and prevent occupa-
tional risks during pregnancy.

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